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Enteral nutrition in the critically ill patient: a critical review of the evidence

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Abstract. *Objective:* To examine the relationship between enteral nutrition (EN) and infection in the critically ill.
Setting: Computerized search of published research and review of relevant reference lists.
Study selection: 151 citations were reviewed and 39 articles met selection criteria. Primary studies were included if they evaluated EN in critically ill humans and its effect on infectious morbidity and mortality.
Measurements and results: Relevant data were abstracted on the timing and impact of EN on morbidity, the optimal route of administration, composition and pH of EN, and bacterial contamination of EN. The evidence from human studies that EN, particularly early EN, results in reduced septic morbidity as compared to parenteral nutrition is limited to small, unblinded studies with non-rigorous definitions of pneumonia. There is no evidence to support a preference of feeding into the stomach versus the small bowel. The addition of fish oil, arginine, glutamine and fiber to enteral feeds has a variable impact on survival in animal models; there are no trials in critically ill patients that demonstrate a reduction in infectious morbidity and mortality. Acidification of enteral nutrition results in decreased bacterial colonization of the stomach in critically ill patients. Bacterial contamination of enteral nutrition is an important source of infection.
Conclusions: Evidence from experimental data in critically ill patients suggests that enteral nutrition may have a favourable impact on gastrointestinal immunological function and infectious morbidity.

Key words: Enteral nutrition – Total parenteral nutrition – Critical care – Cross infections – Pneumonia – Review

In the past decade, many investigators have explored the immunological role of the gastrointestinal tract and have shown that compromise of the gastrointestinal tract plays a role in the pathogenesis of infection in the critically ill patient. In health, the stomach and small bowel are essentially sterile, while the colon contains hundreds of different bacterial species in various quantities. These enteric bacteria are necessary for digestion of nutrients. However, if they pass through the gut wall and initiate a systemic immune response, the consequences for the host are serious. Compromise of this barrier and gastrointestinal overgrowth with pathogenic bacteria have been implicated in the pathogenesis of noscocomial pneumonia, multiorgan failure and sepsis, major causes of morbidity and mortality in critically ill patients [1, 2].

Thus, one of the major functions of the gastrointestinal tract is to provide an immunocompetent barrier to endogenous gut bacteria. Since the maintenance of gut mucosal barrier structure and function is augmented by intestinal stimulation from enteral nutrients [3], it is plausible that enteral nutrition may decrease infectious outcomes in the critically ill. However, EN may also be associated with gastric colonization and subsequent aspiration and pneumonia [4]. The purpose of this overview is to examine the relationship between enteral nutrition and infectious complications in the critically ill. Based on current knowledge, we present clinical recommendations and suggest a future clinical research agenda.

Methods

We conducted a computerized bibliographic search of MEDLINE from 1977 to 1992 to locate all relevant articles. The terms "cross infections, enteral nutrition (EN), total parenteral nutrition (TPN), malnutrition and critical care" were used as subject headings. Reference lists of relevant review articles were also searched. Primary studies were selected for inclusion in this overview if they met the following criteria:

I. Population – critically ill human adult subjects
II. Intervention – any form of EN deliverd via a feeding tube into the stomach or small bowel
III. Outcome – colonization, pneumonia, sepsis, organ failure, the inflammatory response associated with infection and mortality
IV. Methodology – randomized clinical trials were selected preferentially over other study designs. Where no randomized trials existed in an area, other experimental designs were included.

Table 1. Relationship between levels of evidence and grade of recommendation

Level of evidence	Grade of recommendation
Level I: Randomized controlled trials in critically ill population with low risk of error, i.e. blinded, objective criteria used	Grade A: Supported by level I evidence; does more good than harm
Level II: Randomized controlled trials in critically ill population with high risk of error, i.e., no blinding, objective criteria not used	Grade B: Supported by at least one level II study, adverse effects not ruled out
Level III A: Non-randomized trial in a critically ill population	Grade C: No support from level I or II evidence; no proven benefit in critically ill
Level III B: Randomized controlled trials in non-critically ill population	Grade C: No support from level I or II evidence; no proven benefit in critcally ill
Level IV: Non-randomized trial in a non-critically ill population	No recommendation
Level V: Animal studies	No recommendation
Level VI: Biological rational	No recommendation

The methodological qualitiy of all selected articles was assessed by considering the extent to which randomization was conducted, blinding occurred, and whether objective definitions of infectious outcomes were employed.

Critical appraisal of the evidence allows us to put forward clinical recommendations based on rules of evidence as endorsed by consensus conferences [5]. Strong clinical recommendations can be made (i.e. grade A recommendations) when supported by rigorous randomized trials in critically ill patients with a low chance of error (level I evidence). Moderately strong recommendation (grade B) can be made from randomized trials in critically ill patients with a high risk of error (level II evidence). Weaker recommendations (grade C) are based on less rigorous studies or randomized trials in different patient populations. Finally, no recommendations can be made from evidence that comes from non-randomized studies in non-critically ill patients, animal studies or studies based on biological rationale. Our version of the relationship between levels of evidence and grades of recommendations is outlined in Table 1.

Results

The MEDLINE search yielded 84 references. These articles and a search of their bibliographies produced 67 additional papers for further examination. Thirty-nine articles met the selection criteria and were included in this overview. Articles were grouped into categories addressing the following questions:

1. What is the effect of EN versus TPN on infectious outcomes?
2. How does timing of administration of EN affect infectious morbidity and mortality in critically ill patient?
3. What is the preferred method of delivering EN?
4. Does the composition of EN affect the infectious morbidity and mortality in critically ill patients?
5. What is the relationship between gastric colonization, EN and subsequent nosocomial pneumonia?
6. Is bacterial contamination of EN a source of morbidity?

1. What is the effect of EN versus TPN on infectious outcomes?

Animal studies suggest that, compared to TPN, EN results in higher levels of secretory IgA in biliary tract secretions [6], less bacterial leak through the intestinal barrier (translocation) [7], greater mucosal weight and thickness and lower secretion of catabolic hormones following a burn injury [8], and reduced mortality following a septic [9] or hypotensive insult [10].

Fong and colleagues [11] examined the metabolic response to injury in humans and found results similar to those demonstrated by Saito [8] in guinea pigs. Levels of arterial epinephrine, glucagon and hepatic venous tumor necrosis factor were significantly higher in healthy volunteers given a endotoxin load and receiving TPN compared to those receiving EN ($p<0.05$). The peripheral production of lactate and amino acid mobilization was also higher in the TPN group ($p<0.05$).

There have been a number of randomized trials in human populations comparing EN to TPN. Few trials have included infectious complications as their major outcomes. In one study, 46 multiple trauma patients were randomized to receive TPN or EN via a NCJ within 24 h or surgery [12]. The incidence of major infections (pneumonia and intra-abdominal infection) was the same in both groups. However, infectious outcomes were not defined using objective criteria and were not assessed blindly.

Cerra et al. [13] examined the impact of EN vs TPN in septic patients at high risk for multiple organ failure syndrome (MOFS) and death. A total of 66 patients were randomized 4–6 days after the onset of sepsis to receive either TPN or EN. There was no difference in the incidence of MOFS or mortality across groups. One interpretation of these results is that the beneficial effect of EN may be dependent upon very early introduction of EN, before the "motor of MOFS" [1] is initiated.

Moore et al. [14] subsequently confirmed that enteral feeding resulted in similar nitrogen balance and caloric intake compared to TPN. They also found a lower incidence of major septic morbidity in the enterally fed group. Patients ($n = 75$) undergoing emergency laparotomy for blunt trauma were randomized to TPN or EN. Objective criteria were used to define infectious outcomes although investigators and clinicians were not blinded to treatment group allocation. Sixteen patients were excluded after randomization leaving 59 evaluable subjects. Of 29 patients from the EN group 5 (17%) compared to 11 of 30 (37%) from the TPN group ($p<0.05$) developed septic complications. However, only one patient (3%) in the EN group developed an intra-abdominal abscess compared to 6 patients (20%) in the TPN group who developed major septic complications (2 = abdominal abscess, 6 = pneumonia in 6 patients, $p = 0.03$).

Kudsk et al. [15] repeated this study in trauma patients with a broader range of severity of illness. Of 51 of those patients who received enteral nutrition 9 (15.7%)

Table 2. Results and methodologic quality of trials evaluating enteral nutrition and TPN and early EN

Study	Methodology	Population (*n*)	Intervention	Outcome
Fong 1989 [11]	Randomized; no blinding	Human volunteers (12)	1) EN 2) TPN	Metabolic response to endotoxin higher in TPN group
Adams 1986 [12]	Randomized; no blinding; objective criteria not stated	Trauma patients (4()	1) EN 2) TPN	Major infections 12/23 10/23 (p = NS)
Cerra 1988 [13]	Randomized; no blinding; objective criteria used	Hypermetabolic patients, day 4–6 post sepsis (66)	1) EN 2) TPN	MOFS/mortality 7/31 (22%)/7/31 (22%) 7/35 (22%)/8/35 (23%)
Moore 1989 [14]	Randomized; no blinding; objective criteria used	Trauma patients (75)	1) EN 2) TPN	Total/major infections 5/29 (17%)/1/29 (3%)* 11/30 (37%)/6/30 (20%)*
Kudsk 1992 [15]	Randomized; no blinding; objective criteria used	Trauma patients (98)	1) EN 2) TPN	Septic complications 9/51 (15.7%) 18/45 (40%) $p<0.02$
Moore 1992 [16]	Randomized; no blinding; objective criteria not used	Aggregate of 8 studies of surg/trauma patients (230)	1) EN 2) TPN	Septic complications 19/118 (16%) 39/112 (39%) $p = 0.03$ No difference in mortality
Early enteral nutrition				
Schroeder 1991 [20]	Randomized; no blinding	Surgical patients (32)	1) Early EN 2) Routine post-op hypocaloric fluids	Early EN = improved wound healing; low indcidence of infection in both groups
Moore 1986 [21]	Randomized; no blinding; objective criteria not used	Trauma patients (75)	1) Early EN 2) Control (D5W for 5 days)	Major infections: 3/26 (9%) vs 9/27 (29%) ($p<0.025$)

MOFS, Multi-organ failure syndrome
*$p = 0.03$

developed septic complications compared to 18/45 (40%) of patients receiving TPN ($p<0.02$).

Recently, Moore and colleagues [16] aggregated the results of 8 studies, including 6 unpublished trials to evaluate EN compared to TPN in surgical and trauma patients. The unpublished trials were not blinded and septic complications were determined by a retrospective chart review without explicit criteria. Studies also varied in the nutritional formula used and the time of initiating nutritional support. When analyzed according the intention-to-treat method, the overall results showed that 19 of 118 (16%) patients receiving EN developed infectious complications compared to 39 of 112 (35%) receiving TPN ($p = 0.03$). However, the poor methodologic quality of this study weakens the inferences that can be drawn from these results.

Data suggest that there are advantages to using EN over TPN to meet the nutritional requirements of the critically ill patient. Experimental animal studies (level V evidence) demonstrate that EN maintains mucosal integrity and the immunological function of the gastrointestinal tract, decreases bacterial translocation, blunts the systemic inflammatory response to a toxin load and improves survival in experimental hemorrhage and peritonitis. Randomized controlled trials (level II evidence) in critically ill patients show comparable nutritional outcomes but only unblinded studies, some of poor methodologic quality, show a decrease in septic morbidity in enterally fed patients. No studies have shown an impact on mortality.

2. How does timing of administration of EN affect infectious morbidity and mortality in critically ill patient?

If EN is the preferred route of administration, it has been hypothesized that the sooner it is started the better [13]. Animal studies show that early EN, compared to no EN or delayed EN (>72 h), is associated with greater wound strength after abdominal surgery [17], a reduced post-surgical hypermetabolic and catabolic phase [18] and less translocation [19] after a burn injury.

A number of trials in humans (including those already described comparing EN to TPN) have shown that NCJ started early, within 24 h or surgery, is a feasible means of providing EN [12, 14, 15]. Schroder et al. [20], examined the effect of immedaite postoperative EN on body composition, muscle function and wound healing. The amount of hydroxyproline accumulating on Gortex tubes (a measure of wound healing response) was significantly higher in the fed group ($p<0.02$). Complication rates were the same in both groups, however, the incidence of infection was very low, suggesting that this population was unlike most ICU populations.

Moore and Jones [21] studied the effect of immediate NCJ feeds in patients with major abdominal trauma.

Control patients received conventional 5% glucose intravenously for 5 days followed by TPN or oral nutrition if tolerated. The enteral fed group began on an elemental diet via NCJ started 12–18 h postoperatively. Although the overall complication rate (including non-infectious complications) was similar in both groups, 9 patients in the control group developed post-operative infections compared to 3 in the EN group ($p < 0.025$). However, outcome assessors were not blinded, nor were objective criteria used to classify outcomes.

Bowel rest, as associated with TPN or delayed EN, results in gastrointestinal mucosal atrophy which compromises the integrity of the mucosal barrier and enhances exposure to bacteria and/or endotoxin. Experimental studies in animals (level V evidence) confirm that early EN is associated with a decreased catabolic response to injury, maintenance of mucosal integrity, and lower rates or translocation. One randomized controlled trial in post operative patients (level III evidence) suggests that early EN results in improved wound healing. Evidence for reduced septic morbidity comes from one unblinded study in trauma patients (level II evidence). There are no studies showing a favorable impact on mortality.

3. What is the preferred method of delivering EN?

All of the studies involving early EN in the ICU population have used a needle catheter jejunostomy (NCJ) as the method of delivering EN. However, McDonald et al. [22] have described a series of burn patients (>20% of total body surface area) who received immediate intragastric EN. A total of 82% of the patients absorbed at least a portion of their tube feeding on the first day of injury. This rose to 95% by the fourth day of admission, at which time the mean amount of EN absorbed exceeded the calories required to meet energy requirements. The most common complication was vomiting (21 episodes in 16 patients). The investigators did not report episodes of aspiration or diarrhea, nor were infectious outcomes evaluated. Early intragastric feeding may therefore be feasible in a select group of critically ill patients.

Post-operatively, return of small bowel motility occurs before gastric or colonic activity is reestablished [23]. Thus, feeding into the small bowel has been preferred over gastric feeding in the early ICU period. However, the incidence of intolerance to early jejunal feeds ranges from 13–37% [12, 13, 21, 24]. Also, NCJs have associated complications, including catheter knotting, occlusion, leaks with and without peritonitis, bowel obstruction and aspiration [24]. The theory has been that by placing the tip of the feeding tube in the small bowel, the risk of aspiration is decreased. This hypothesis has been challenged by reports in non-critically ill populations that suggest post-pyloric feeding may not prevent subsequent aspiration [25–27].

In a critically ill population, Montecalvo [28] compared intragastric feeds to endoscopically placed jejunal feeds in 38 patients. There was no statistically significant difference in the incidence of gastric colonization, pneumonia or mortality.

As there is no convincing evidence from comparative trials to support a preference for the method of delivering early EN in the critically ill patient, one is left with biologic rationale. Food bypassing the stomach may alter the digestive secretions of the upper gut [29]. These secretions play a major role in gastrointestinal mucosal defence mechanism [30]. Gastric acid secretion, the major bactericidal mechanism of the stomach, is diminished when EN is infused in the duodenum [31]. Gastrin, an important mucosal stimulant factor, may also be affected by feeds bypassing the stomach [32]. Diminished pancreatic secretions may result in malabsorption and gastrointestinal intolerance unless a more expensive elemental preparation is used [33]. It is not known whether secretory IgA, an immunoglobulin in biliary tract secretions that prevents the adherence of bacteria to mucosal cells, is also affected by feeds bypassing the stomach.

There is no evidence from comparative trials in the critical care setting to suggest a preference in the method of EN delivery. Evidence to date suggests that bypassing the stomach does not effectively reduce the risk of aspiration and pneumonia associated with EN (level II, IIIB, and IV evidence). There is a biological rationale (level VI evidence) for use of intragastric feeds. However, further clinical investigation is necessary to determine whether early, intragastric feeds are tolerated by ICU patients and whether this has a favorable impact on important clinical outcomes.

4. Does the composition of EN effect the infectious morbidity and mortality in critically ill patients?

A comparative trial of 3 different feeding products in burn patients suggests that the composition of enteral feeds affects important clinical outcomes. Fifty patients with burns ranging from 10–89% of body surface area were randomized to 3 groups comparing a modular tube feed to two other widely used EN products (Osmolite en-

Table 3. Compostion of feeding products (34)

	Osmolite with Promix[a]	Modular tube feed	Traumacal
Protein source	Whey; casein; soy	87% Whey; 9% arginine; 2% cysteine and histidine	Casein
Carbohydrate source	Cornstarch	Maltodextrin	Corn syrup; sucrose
Fat source	50% MCT oil; 40% corn oil; 10% soy oil	50% Fish oil; 50% safflower oil	70% soybean oil; 30% MCT oil

[a] Promix = source of whey protein
MCT, Medium chain tryglyceride

riched with Promix and Traumacal) [34]. As a specially designed formula, modular tube feeds differ from the other preparations by the amount and composition of protein supplement and fats (see Table 3). Patients fed the modular feed had a significant reduction in wound infections ($p<0.03$) and length of stay in the ICU ($p<0.002$). There was also a trend to a lower incidence of pneumonia ($p<0.06$), a lower number of infectious episodes ($p<0.07$), and a lower mortality ($p<0.07$) in patients receiving the modular feeds.

The composition of EN may therefore, reduce infectious morbidity and mortality in critically ill patients. Which ingredient or combination of ingredients are responsible for this beneficial effect on infection is unknown. The literature suggests that the addition of RNA, omega-3 fatty acids, arginine [35], and glutamine [36] may improve infectious morbidity and mortality in the animal model. However, there are no trials in critically ill patients evaluating the effect of these additives.

Elemental vs polymeric formula and fiber? Animal studies (level V evidence) demonstrate that elemental diets promote bacterial overgrowth and result in greater amount of bacterial translocation [37]. Fiber may be useful in reducing the amount of bacterial translocation [38]. It remains to be seen whether specific compositions of feeds results in a reduction of infectious morbidity and mortality in critically ill patients. With respect to tolerance and nutrition, elemental diets offer no advantage over the standard polymeric formulas in critically ill patients [39] or postoperative patients [40], even in the early stages of feeding.

5. What is the relationship between gastric colonization, EN and subsequent nosocomial pneumonia?

Gastric colonization with microorganisms in the critically ill patient was first described by Atherton and White in 1978 [41]. Further studies using drugs for stress ulcer prophylaxis have demonstrated that gastric bacterial growth is pH dependent: the higher the gastric pH, the greater the amount of bacterial overgrowth which may predispose to aspiration pneumonia [42, 43]. Other investigators have further defined the sequence of transmission from gastric to tracheal colonization [44–47]. A recent review [2] of the relevant literature suggests that gastric colonization plays a causal role in the development of nosocomial pneumonia, a major cause of morbidity and mortality in ICU patients.

Pingleton [4] has described a high incidence of gastric colonization and nosocomial pneumonia associated with continuous enteral feeding. Eighteen critically ill patients with respiratory failure requiring prolonged mechanical ventilation and receiving continuous enteral feeds were studied. The stomach of every patient was colonized with gram negative bacteria at some point in the study. Eleven patients (63%) developed nosocomial pneumonia. This association of enteral feeds and gastric colonization and nosocomial pneumonia maybe pH-dependent. The pH of most commercially produced formula feeds is 6.0–7.0. It has been postulated that alkalinization of stomach contents by these feeds may promote bacterial overgrowth.

In a prospective cohort study [48], 13 of 24 (54%) ventilated patients given continuous enteral feeding for more than 3 days developed pneumonia. Of 13 patients with persistently high morning gastric pH (pH > 3.5), 12 developed pneumonia, while only one of 11 patients who had a gastric pH intermittently < 3.5 developed pneumonia ($p<0.0002$).

These same investigators examined gastric pH and the incidence of pneumonia in ICU patients fed intermittent enteral nutrition (16 h on, 8 h off) [49]. Of 26 patients 23 had an intermittently low gastric pH (pH < 3.5) while receiving intermittent feeds compared to 11 of 24 patients on continuous feeds ($p<0.002$). The incidence of pneumonia in patients on intermittent feeds was 3/26 compared to 13/24 in those fed continuously ($p<0.002$). Although this unblinded study used a historical cohort form comparison purposes, it again suggests that the risk of infection correlates with increased gastric pH.

Another strategy for maintaining a low pH in the stomach is to add acid to the feeds. Heyland et al. [50] have shown that acidified enteral feeds are effective in reducing gastric colonization with microorganisms in the critically ill patient tolerating enteral alimentation. Patients indicated to receive enteral feeds were randomized to one of three groups: 1) regular feeds into the stomach, 2) regular feeds into the duodenum, and 3) acidified feeds into the stomach. Hydrochloric acid was added to a control feed (Peptamen, Clintec, pH = 6.5) to titrate the pH down to 3.5 for use as the acidified feed. Nasogastric aspirates for gastric pH and microbiological determination were obtained daily for an average of 5 days after feeding began. Colonization was based on presence of bacteria or yeast for at least one day. Outcome assessment was done by personnel blinded to treatment allocation. The mean gastric pH of the acidified group was 3.2 compared to 4.7 in the regular stomach group and 3.8 in the duodenal group ($p<0.01$). Only 1 of eight patients receiving the acidified feeds was colonized with microorganisms (bacteria or yeast) after baseline assessment compared to 10/15 of those patients receiving regular feeds ($p<0.03$). For those patients initially colonized, 4 of 4 patients receiving acidified feeds immediately developed consistently sterile gastric aspirates. Only 2 of 10 patients receiving regular feeds remained sterile ($p = 0.02$). Of all the nasogastric samples taken after baseline, 96% of those samples taken from the acid group were sterile, while only 56% from the stomach group and 45% of the aspirated samples from the duodenal group were sterile.

Respiratory tract infections are a major cause of morbidity and mortality in critically ill patients. These infections may be causally related to gastric microbial overgrowth, a pH-dependent phenomenon. Acidified feeds are effective in eliminating gastric colonization. The hypothesis that acidified feeds may reduce nosocomial infections and improve survival in the critically ill patient warrants further investigation.

6. Is bacterial contamination of EN a source of morbidity?

The association of bacterial contamination of the enteral feeding delivery system (ENS) and infection in the critically ill patient has been well described [51]. Bacterial contamination is greater in formulae that require mixing or dilution compared to sterile, commercially prepared formulae [52, 53], in conditions where tap water is used instead of sterile water [54] and where ENS is used for longer than 24 hours [55] or left unrefridgerated for prolonged periods of time [56]. Case reports have suggested that this bacterial contamination is a cause of morbidity and mortality in the hospital population [57, 58]. The strongest evidence that bacterial contamination plays a causal role in infectious illness comes from a prospective study of ICU patients receiving EN [59]. Specimens of enteral feeds from the refrigerated containers and the bags hanging in the patient's room as well nasopharyngeal and rectal cultures were obtained from each patient upon initiation of EN and serially thereafter. By antibiotic sensitivity and plasmid analysis, eight patients were found to be colonized by 11 organisms identical to those which were first isolated from ENS. Two patients subsequently developed pneumonia caused by Acinetobacter baumannii. Therefore, 8% of patients studied developed severe bacterial infections after being colonized with organisms contained in their ENS.

This evidence (level IV) suggests that aseptic technique should be used during preparation and administration of EN and quality control measures must be adopted to minimize contamination. As bacterial growth and replication is pH dependent, it is interesting to speculate whether acidified enteral feeds would prevent or minimize bacterial contamination of ENS.

Conclusion

As with many qualitative reviews, our review is open to several possible biases. Our search strategy was limited to one bibliographic database (MEDLINE), and we did not look for unpublished material. Nevertheless, the large number of studies examined makes it likely that the most relevant, methodologically adequate studies providing evidence on the effect of EN on infection in the critically ill patient were analyzed. Although they provide indirect evidence, we did not include numerous studies examining the effect of EN on immunological markers. Article selection, data extraction, and validity assessments were done by only one author. However, explicit, objective criteria for sample selection and validity assessment were used.

In this overview, our synthesis of the evidence for use of enteral feeds to reduce morbidity and mortality of critically ill patients is presented in Table 4. The quality of this synthesis is necessarily partially determined by the quality of the original data. All the primary studies were randomized, some used objective criteria to define infectious outcomes, but few were blinded. Furthermore, all studies using pneumonia as an outcome employed nonspecific criteria. This approach is an inaccurate method of diagnosis [60], thus weakening the inferences that one can draw from these studies.

We believe that sufficient data (level II evidence) suggesting benefit from early EN is available to recommend that, unless specifically contraindicated, EN should be commenced as early as possible in the course of patient's illness. We suggest beginning with a very low hourly rate of infusion (e.g 10 ml/h) which can be increased as tolerated. The goal of early EN is not to meet the critically ill patient's nutritional requirements immediately. Rather, the objective is to stimulate gut immunological function; even if only a minimal amount of EN is tolerated, it may be enough to stimulate gut mucosal integrity and function [61]. Patients can be supplemented with TPN to meet their nutritional requirements if necessary while low volumes of EN are initially tolerated.

Current evidence suggests that it is acceptable to feed patients into the stomach or the small bowel with close monitoring of gastric residuals and abdominal distension. Presently there is no evidence to suggest a preference of one formula over another, although the increased cost of an elemental formula is probably not justifiable given that polymeric formulae are equally well tolerated (level II evidence) and may result in a lower rate of bacterial overgrowth and translocation (level V evidence).

The most important unanswered clinical questions in this field include: a) Which subgroup of patients will tolerate early EN, b) Whether early EN reduces clinically important outcomes, including infections and mortality, c) Whether a gastrointestinal prokinetic agent improves

Table 4. Summary of results and clinical recommendation

Question	Level of evidence	Grade	Clinical recommendation
1) EN vs. TPN?	II	B	EN is preferred where possible
2) Early EN?	II	B	Begin within 24 h at low rates
3) Stomach or small bowel?	II	B	Either choice acceptable
4) Optimal composition?			
Fats	V	–	Not indicated; benefit not proven
Arginine	V	–	Not indicated; benefit not proven
Glutamine	V	–	Not indicated; benefit not proven
Elemental vs polymeric	II, V	B	Choose polymeric formulas
Fiber	V	–	Not indicated; benefit not proven
5) Acid feeds	–	–	Not indicated; benefit not proven

the tolerance to early EN, d) Which is the optimal method of delivering enteral feeds and e) What is the optimal composition and pH of the feed.

Strategies for optimal delivery of enteral nutrition may be a major determinant of our success in administering care to critically ill patients, and will likely be both and active and important area of investigation in the next decade.

References

1. Carnio CJ, Meakins JL, Marshall JC et al (1986) Multi-organ failure syndrome. Arch Surg 121:196–208
2. Heyland DK, Mandell LA (1992) Gastric colonization and nosocomial pneumonia: evidence for causation. Chest 101: 187–193
3. Lo CW, Walker WA (1989) Changes in the gastrointestinal tract during enteral or parenteral feeding. Nutr Rev 47 (7):193–198
4. Pingleton SK, Hinthorn DR, Liu C (1986) Enteral nutrition in patients receiving mechanical ventilation. Am J Med 80:827–832
5. Sackett DL (1989) Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 95(2):2S–4S
6. Alverdy J, Chi HS, Sheldon G (1985) The effect of parenteral nutrition on gastrointestinal immunity: the importance of enteral immunity. Ann Surg 202:681–684
7. Alverdy JC, Aoys E, Moss GS (1988) TPN promotes bacterial translocation from the gut. Surgery 104:185–90
8. Saito H, Trocki O, Alexander JW, Kopcha R, Heyd T, Joffe SN (1987) Effect of route of administration on the nutritional state, catabolic hormone secretion and gut mucosal integrity after burn injury. JPEN 11:1–7
9. Kudsk KA, Stone JM; Carpenter G, Sheldon GF (1983) Enteral and parenteral feeding influences mortality after hemoglobin. E. coli peritonitis in normal rats. J Trauma 23:605–609
10. Zaloga GP, Knowles R, Black KW, Prielipp R (1990) Total parenteral nutrition increases mortality after hemorrhage. Crit Care Med 19:54–59
11. Fong Y, Marano MA, Barber A et al (1989) TPN and bowel rest modify the metabolic response to endotoxins in humans. Ann Surg 210:449–457
12. Adams S, Dellinger EP, Wertz MJ, Orekovich MR, Simonowitz D, Johansen K (1986) Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. J Trauma 26:882–890
13. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides KM Teasley KM (1988) Enteral nutrition does not prevent multiple organ failure syndrom (MOFS) after sepsis. Surgery 104:727–33
14. Moore FA, Moore EE, Jones TN, McCroskey BL and Petersen VM (1989) TEN versus TPN following major abdominal trauma-reduced septic morbidity. J Trauma 29:916–923
15. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret A, Kuhl MR, Brown RO (1992) Enteral versus parenteral feeding. Ann Surg 215:503–513
16. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, McL Booth F, Morgenstein-Wagner TB et al (1992) Early enteral feeding, compared with parenteral, reduces septic complications – the results of a meta-analysis. Ann Surg 216:172–183
17. Zaloga GP, Bortenschlager L, Black KW, Prielipp R (1992) Immediate postoperative enteral feeding decreases weight loss and improves healing after abdominal surgery in rats. Crit Care Med 20:115
18. Mochizuki H, Trocki O, Dominioni L, Brackett KA, Joffe SN, Alexander JW (1984) Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg 200:297–308
19. Inoue S, Epstein MD, Alexander JW, Trocki O, Jacobs P, Gura P (1989) Prevention of yeast translocation across the gut by a single enteral feeding after burn injury. JPEN 13:565–571
20. Schroeder D, Gillanders L, Mahr K, Hill GL (1991) Effects of immediate postoperative enteral nutrition on body composition, muscle function, and would healing. JPEN 15:376–383
21. Moore EE, Jones TN (1986) Benefits of immediate jejunostomy feeding after major abdominal trauma – a prospective, randomized study. J Trauma 26:874–880
22. McDonald WS, Sharp CW, Deitch EA (1991) Immediate enteral feeding in burn patients is safe and effective. Ann Surg 213: 177–183
23. Noer T (1968) Roentgenological transit time through the small intestine in the immediate postoperative period. Acta Chir Scand 134:577–580
24. Jones TN, Moore FA, Moore EE, McCroskey BL (1989) Gastrointestinal symptoms attributed to jujunostomy feeding after major abdominal trauma – a critical analysis. Crit Care Med 17:1146
25. DiSario JA, Foutch PG, Sanowski RA (1990) Poor results with percutaneous endoscopic jejunostomy. Gastrointest Endosc 36: 257–260
26. Wolfsen HC, Kozarek RA, Ball TJ, Patterson DJ, Botoman VA (1990) Tube dysfunction following percutaneous endoscopic gastrostomy and jejunostomy. Gastrointest Endosc 36:261–261
27. Strong RM, Condon SC, Solinger MR, Namihas BN, Ito-Wong LA, Leuty JE (1992) Equal aspiration rates from postpylorus and intragastric-placed feeding tubes: a randomized, prospective study. JPEN 16:59–63
28. Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF et al (1992) Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. Crit Care Med 20:1377–1387
29. Christiansen J, Beck A, Fahrenkrug BJ, Holst JJ, Lauritsen K, Moody AJ, Schaffalitzky O (1979) Fat-induced jejunal inhibition of gastric acid secretion and release of pancreatic glucagon, enteroglucagon, gastric inhibitory polypeptide, and vasoactive intestinal polypeptide in Man. Scand J Gastroenterol 14:161–166
30. Hart CA (1989) Defence against colonization and infection. In: van Saene HKF, Stoutenbeek CP, Ledingham IMcA (eds) Update in intensive care and emergency medicine –infection control by selective decontamination. Springer, Berlin Heidelberg New York, pp 13–21
31. Layon AJ, Florete OG Jr, Day AL, Kilroy RA et al (1991) The effect of duodenojejunal alimentation on gastric pH and hormones in intensive care unit patients. Chest 99:695–702
32. Johnson LR, Lichtenberger LM, Copeland EM, Dudrick SJ, Castro GA (1975) Action of gastrin on gastrointestinal function. Gastroenterology 68:1184–1192
33. Hamaoui E, Lefkowitz R, Olender L, Kransnopolsky-Levine E, Favale M, Webb H, Hoover EL (1990) Enteral nutrition in the early postoperative period: a new semi-elemental formula versus total parenteral nutrition. JPEN 14:501–507
34. Gottschlich MM, Jenkins M, Warden GD, Baumer T, Havens P, Snook JT, Alexander JW (1990) Differential effects of three dietary regimens on selected outcome variables in burn patients. JPEN 14:225–236
35. Van Buren CT, Rudolph FB, Kulkarni AD (1990) Reversal of immunosuppression induced by a protein-free diet: comparison of nucleotides, fish oil and arginine. Crit Care Med 18[Suppl]: S114–S117
36. Souba WW, Klimberg VA, Hautamaki RD et al (1990) Oral glutamine reduces bacterial translocation following abdominal radiation. J Surg Res 48:1–5
37. Alverdy JC, Aoys BS, Moss GS (1990) Effect of commercially available chemically defined liquid diets on the intestinal microflora and bacterial translocation from the gut. JPEN 14:1–6
38. Spaeth G, Specian RD, Berg RD, Deitch EA (1990) Bulk prevents bacterial translocation induced by the oral administration of total parenteral nutrition solution. JPEN 14:442–447
39. Mowatt-Larssen CA; Brown RO, Wojtysiak SL, Kudsk KA (1992) Comparison of tolerance and nutritional outcome between a peptide and a standard enteral formula in critically, hypoalbuminemic patients. JPEN 16:20–24
40. Ford EG, Jull SF, Jennings M, Andrassy RJ (1992) Clinical com-

parison of tolerance to elemental or polymeric enteral feedings in the postoperative patient. J Am Coll Nutr 11:11–16
41. Atherton ST, White DJ (1978) Stomach as source of bacteria colonizing respiratory tract during artificial respiration. Lancet II:1968–269
42. Cook DJ, Laine LA, Guyatt GH, Raffin TA (1991) Nosocomial pneumonia and the role of gastric pH: a meta-analysis. Chest 100: 7–13
43. Tryba M (1991) Prophylaxis of stress ulcer bleeding: A Meta-analysis. J Clin Gastroenterol 13[Suppl. 2]:S44–S55
44. Tryba M (1987) Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate versus antacids. Am J Med 83:117–124
45. Du Moulin GC, Hedley-Whyte J, Paterson DJ, Lisbon A (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. Lancet I:242–245
46. Donowitz GL, Page ML, Mileur BL, Guenthner SH (1986) Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. Infect Control 7:23–26
47. Goularte TA, Lichtenberg DA, Craven DE (1986) Gastric colonization in patients receiving antacids and mechanical ventilation: a mechanism for pharyngeal colonization. Am J Infect Control 14:88
48. Jacobs S, Chang RWS, Lee B, Bartlett FW. Continuous Enteral Feeding (1990) A major cause of pneumonia among ventilated intensive care unit patients. JPEN 14:353–356
49. Lee B, Chang RWS, Jacobs S (1990) Intermittent nasogastric feeding: a simple and effective method to reduce pneumonia among ventilated ICU patients. Clin Intensive Care 1:100–102
50. Heyland DK, Bradley C, Mandell LA (1992) Acidified enteral feeds: effect on gastric colonization. Crit Care Med 20:1388–1394
51. Anderson KR, Norris DJ, Godfrey LB et al (1984) Bacterial contamination of tube-feeding formulas. JPEN 8:673–678
52. Bastow MD, Greaves P, Allison SP (1982) Microbial contamination of enteral feeds. Hum Nutr Appl Nutr 36A:213–217
53. Freedland CP, Roller RD, Wolfe BM, Flynn NM (1989) Microbial contamination of continuous drip feedings. JPEN 13:18–22
54. Fagerman KE, Dean RE (1984) Tap water as a source of enteral feeding contamination (Lett). Nutr Supp Serv 4:9
55. Perez SK, Brandt K (1989) Enteral feeding contamination: comparison of diluents and feeding bag usage. JPEN 13:306–308
56. Fagerman KE, Paauw JD, McCamish MA et al (1984) Effects of time, temperature, and preservative on bacterial growth in enteral nutrient solutions. Am J Hosp Pharm 41:1122–1126
57. Casewell MW, Cooper JE, Webster M (1981) Enteral feeds contaminated with *Enterobacter cloacae* as a cause of septicemia. Br Med J [Clin Res] 282:973
58. Levy J, Laethem YV, Verhaegen G, Perpete C, Butzler J, Wenzel RP (1989) Contaminated enteral nutrition solutions as a cause of nosocomial bloodstream infection: a study using plasmid fingerprinting. JPEN 13:228–234
59. Thurn J, Crossley K, Gerdts A, Maki M, Johnson J (1990) Enteral hyperalimentation as a source of nosocomial infection. J Hosp Infect 15:203–217
60. Andrews CP, Coalson JJ, Smith JD, Johanson WG Jr (1981) Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 80:254–258
61. Zaloga GP, Black KW, Prielipp R (1992) Effect of rate of enteral nutrient supply on gut mass. JPEN 16:39–42

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