Enteral Versus Parenteral Feeding: The Avoidance of Systemic Infection in the Critically Ill

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Abstract

The critically ill patient very often presents with systemic evidence of infection including tachypnea, tachycardia and hypo-hyperthermia; this may lead to sepsis syndrome and subsequent multisystem organ failure. In order to manage this clinical condition, nutritional supportive therapy is very often required. The choice between enteral and parenteral nutrition is not always straightforward. Early enteral nutrition seems to exert beneficial effects, although parenteral nutrition is often easier to administer, and thus is the treatment of choice. There are only few prospective, randomized, controlled trials

comparing the two methods of intervention therapy. Parenteral nutrition seems to be associated with mechanical, metabolic and septic complications, while enteral nutrition, which is associated with similar complications, prevents gastrointestinal mucosal atrophy, attenuates the injury stress response, maintains immunocompetence, and preserves normal gut flora. This literature review focuses on the role played by these two methods of nutritional support therapy in the development of systemic infections. This review will also analyze possible mechanisms of action and future therapeutic strategies.

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Introduction

Supportive nutritional therapy is one of the most important elements of caring for the critically ill and high-risk surgical patient [1]. Hypermetabolic states lead to a pathophysiological progressive depletion of usual energy reserves as well as to loss of body muscle mass, and results in several related complications. These include increased risk of infection, impaired wound healing, organ dysfunction and possible multiple system organ failure [2]. The goals of supportive nutritional therapy in a critically ill patient include detecting and correcting any preexisting malnutrition, preventing the progressive onset of protein calorie malnutrition, optimizing the patient's metabolic state, with the intent of decreasing the morbidity, mortality, and duration of recovery.

The decision as to whether to provide either enteral or parenteral supportive nutritional therapy is not always straightforward. Parenteral feeding is often easier to initiate and administer, but in the last few years accumulated evidence shows that enteral feeding (ENT) has many advantages over total parenteral nutrition (TPN) [3–6]. TPN is generally associated with higher costs, and with complications now recognized to include impaired gastrointestinal barrier. Traditionally, complications associated with the use of TPN have also included profound metabolic disturbances such as hyperglycemia and hypertriglyceridemia, immunosuppression by intravenous fat, and mechanical complications associated with central venous cannulation such as pneumothorax, venous thrombosis and catheter-related sepsis [7–9]. However, the latter are now recognized as not being related to TPN per se, but to the injudicious and careless use of this form of intravenous therapy. Of the former complications, systemic sepsis is one of the more

interesting because it is thought to be related to TPN-associated disuse gut atrophy [10–13].

Enteral versus Parenteral Feeding in Clinical Trials: A Difference in Septic Morbidity

A number of clinical trials have demonstrated a reduced risk of septic complications with enteral nutrition (table 1), even if it is not clear whether the observed benefits were associated with the use of ENT or the avoidance of the detrimental effects of TPN. Among these studies, there is a subset that investigated the effect of different feeding routes on normally nourished patients with major abdominal trauma.

Moore and Jones [10] randomized 75 patients with an abdominal trauma index (ATI) >15 to receive either intravenous D₅W (control group) or enteral nutrition via needle-catheter jejunostomy postoperatively. Although the overall complication rates were similar, significantly more septic complications occurred in the control group. Among patients with an ATI between 15 and 40, 26% of control versus only 4% of the ENT group developed postoperative infections.

A follow-up study comparing ENT-fed with TPN-fed patients showed similar results [11]. The incidence of major septic morbidity (defined as pneumonia or intra-abdominal abscess) was 3% for the ENT group as compared to 20% for the TPN group. Furthermore, the overall septic incidence in the TPN group was twice that of the ENT group.

A similar study compared the effect of feeding route on septic morbidity following blunt or penetrating abdominal trauma [12]. Ninety-eight patients requiring emergency laparotomy with an ATI of 15 or greater were randomized to receive TPN or ENT within

Table 1. Randomized prospective studies of enteral and parenteral feeding in patients with trauma or high surgical risk

Study	Results
Moore and Jones [10]: 75 abdominal trauma patients randomized to receive enteral nutrition (via a jejunostomy) or i.v. D ₅ W (control group)	significantly more septic complications occurred in the control group among patients with an ATI between 15 and 40, 26% of control versus only 4% of the ENT group developed postoperative infections
Moore et al. [11]: follow-up study comparing ENT-fed with TPN-fed patients following major abdominal trauma	the incidence of major septic morbidity was 3% for the ENT group compared to 20% for the TPN group
Kudsk et al. [12]: 98 patients with an ATI of 15 or greater requiring emergency laparotomy were randomized to receive TPN or ENT	enterally fed patients developed significantly fewer infections; patients with both an ATI > 24 and an ISS >20 in the TPN-fed group had a 11-fold increased risk of infection over the same subset of ENT-fed patients
Moore et al. [13]: meta-analysis of eight prospective randomized trials designed to compare ENT versus TPN nutrition in high-risk surgical patients	significantly more septic complications occurred in parenterally fed patients; the most significant differences were observed among all trauma and blunt trauma groups

24 h of injury. Enterally fed patients developed significantly fewer infections including pneumonia, abscesses and catheter sepsis as well as fewer infections per patient. Significance was reached only in patients with an ATI greater than 24 or the injury severity score (ISS) greater than 20. Patients with both an ATI >24 and an ISS >20, and who had been randomized to the TPN-fed group, had an 11-fold increased risk of infection over the same subset of ENT-fed patients.

A meta-analysis of eight prospective randomized trials designed to compare the incidence of infections in patients receiving either ENT or TPN supportive therapy in high-risk surgical patients also demonstrated similar findings [13]. This two-part analysis confirmed that significantly more septic complications occurred in parenterally fed patients. The most significant differences were ob-

served among all trauma and blunt trauma groups. Differences remained significant even after patients with catheter sepsis were excluded.

Suggested Mechanism

Bacterial translocation has recently gained increasing recognition as an important cause of septic complications. Several animal studies have suggested that enteral feeding reduces bacterial translocation, and thus by inference reduces the risk of septic morbidity. One such study compared intravenous to oral TPN in Fischer rats with a chow-fed group serving as controls [14]. A significantly greater number of culture-positive mesenteric lymph nodes were found in the parenterally fed animals. No positive nodes were found in the control

group. Translocating organisms included *Escherichia coli* and *Proteus mirabilis*. Both the oral-TPN and intravenous-TPN groups had similar and significant increases in cecal bacterial counts compared to the control group. Measurement of secretory IgA concentration in bile, however, showed that the intravenous-TPN group had a significant decrease in secretory IgA, whereas no difference was noted between the oral-TPN and control groups. The authors suggested that, despite a similar increase in cecal bacterial counts, translocation in the oral-TPN group may not have been as significant due to the maintenance of immunologic functions. In addition, they noted that the intravenous-TPN group remained healthy and gained weight throughout the study, suggesting that systemic spread of translocated bacteria may become an issue only during extreme stress and the immunosuppression which accompanies trauma, anesthesia and surgery.

As suggested by this and the other studies, the normal bowel prevents bacterial translocation by way of the barrier and the immune function. Deitch et al. [15] designed a study in which they directly assessed both these functions, utilizing in vivo and ex vivo studies of rat ileum. The magnitude of *E. coli* and phenol red transmucosal passage was significantly higher in the intravenous TPN group, indicating increased intestinal permeability and bacterial translocation. This led the authors to conclude that a loss of barrier function plays a key role in nutritionally induced bacterial translocation.

The role of mucosal atrophy as a possible cause of decreased barrier function has also received much attention [11]. The occurrence of intestinal villus atrophy after periods of parenteral feeding is well documented in rats [16] as well as normal human volunteers [17]. To investigate the role this may play in bacterial translocation, recent studies have focused

on glutamine and its essential role in gut mucosal growth. The lack of glutamine, a semiessential amino acid, in TPN solutions has been a proposed cause of the atrophy-induced bacterial translocation. A study of 12 ICU patients, randomized to receive standard TPN or Ala-glutamine-enriched TPN, showed significantly improved intestinal absorption in the patients receiving the enriched solution [18]. Furthermore, a study done in rats comparing standard TPN to glutamine-enriched TPN showed that the supplemented solution protected against bacterial translocation [19] and attenuated mucosal atrophy in TPN rats [20], although the mucosal thickness was still significantly less than that achieved with normal ENT nutrition. However, it is important to keep in mind that the relationship between atrophy and bacterial translocation remains unclear. In fact, one study on protein-malnourished mice found no correlation between the histologic appearance of the gut mucosa and the magnitude of bacterial translocation [21].

Intestinal immune response to different feeding routes has also been investigated. In a study of healthy volunteers, Fong et al. [22] investigated the hypothesis that bowel rest may enhance endotoxin translocation and thus alter the response to infection. Twelve volunteers were randomized to receive 7 days of either enteral feeding or TPN only. Serum glucagon and epinephrine, hepatic venous cachectin/tumor necrosis factor, extremity efflux of lactate and amino acids, and C-reactive protein were significantly higher in the TPN group. This suggests that TPN, in addition to increasing bacterial translocation, may enhance the response to infection by an exaggerated counterregulatory hormone response and increased production of cytokines, as initially reported from our laboratory [23]. Tumor necrosis factor, in particular, has been shown to induce the release of a number of

Table 2. Sepsis outcome in studies evaluating supplementation of enteral feeding

Study	Results
Cerra et al. [29], Bower et al. [30]: enteral diet containing increased amounts of ω -3 fatty acids, arginine and ribonucleic acids compared to a standard enteral formula diet	infectious complications and hospital lengths-of-stay were decreased in patients who received the modified formula
Moore et al. [31], Kudsk et al. [32]: enteral formula diet containing additional glutamine, arginine, nucleic acids, and ω -3 fatty acids compared to a standard amino acid-based elemental diet	less multiorgan failure and fewer major infectious complications in patients who received the modified formula
Klimberg et al. [36], Muscaritoli et al. [37]: supplementation of glutamine in experimental models and in humans following radio- and/or chemotherapy	ability of glutamine to protect gut brush border, limiting bacterial translocation, and to attenuate mucosal atrophy
Spaeth et al. [38], Wells et al. [39]: supplementation of dietary fiber in experimental models	improved intestinal barrier function and decreased incidence of bacterial translocation, even in the absence of oral nutrients
Veerabagu et al. [40]: administration of nucleosides/nucleotide in an experimental model of indomethacin-induced enterocolitis	increase in cellular proliferation and decreased small bowel ulcer length

secondary mediators such as interleukin-1, catecholamines, and cortisol, which produce, catabolic effects [24].

Moreover, during parenteral nutrition, the clearance activity of Kupffer cells is assumed to be increased. This might consequently result in a conversion of hepatic synthesis of visceral constitutive proteins (fibronectin, prealbumin, and transferrin) toward generation of acute phase proteins (C-reactive protein and α_1 -acid glycoprotein) [25, 26]. On the other hand, the presence of enteral nutrients appears to promote mucosal health, which is reflected by better maintenance of intestinal absorption capacity [27] and conserved gastrointestinal barrier function. This may result in improving visceral protein synthesis [28] as well as carbohydrate homeostasis [27].

Possible Future Therapeutic Strategies

Several studies have evaluated the effects of various enteral formulas which were supplemented with selected nutrients on clinical outcome (table 2).

Two prospective randomized clinical trials [29, 30] compared an enteral diet containing increased amounts of ω -3 fatty acids, arginine and ribonucleic acids to a standard enteral formula diet. The authors from both studies concluded that infectious complications and hospital length-of-stay were decreased in patients who received the modified formula, mainly because of the immunostimulatory properties of the supplemented formula, based on a marked stimulation of in vitro lymphocyte proliferation responses [30]. An-

other study found that patients given a modified formula diet containing additional glutamine, arginine, nucleic acids, and ω -3 fatty acids had less multiorgan failure than those given a standard amino acid-based elemental diet [31]. A recent trial comparing the modified diet with a protein-supplemented standard enteral formula found that patients who received the enriched formula had fewer major infectious complications [32].

As discussed above, researchers have focused their attention on glutamine [33–35], because of its ability in protecting gut brush border and thus limiting bacterial translocation, both in experimental models [36] and in humans [37] following a variety of stresses including bone marrow transplantation, the critically ill ICU patient, on radio- and/or chemotherapy. This is probably due to the role played by glutamine as an energy source for the enterocyte: catabolic stress markedly increases the needs for glutamine which becomes an essential substrate for damaged intestinal mucosa.

Instead of glutamine, some researchers suggest that dietary fiber alone may be one of the key elements that protects against mucosal changes and bacterial translocation [38, 39]. They found that oral administration of cellulose powder improves intestinal barrier function and decreases the incidence of bacterial translocation, even in the absence of oral nutrients.

More recently our laboratory showed that parenteral administration of nucleosides/nucleotide exerts beneficial effects on an experimental model of an indomethacin-induced enterocolitis [40]. The protective effect occurred mainly via an increase in cellular proliferation, as evidenced by increased crypt length, crypt/villous ratio, mitotic index, PCNA labeling and decreased small bowel ulcer length. A possible explanation for such an observation is that intravenous nucleoside/

nucleotide administration could overcome the limitation of purine synthesis imposed by standard amino acids currently in clinical use, and promote cellular proliferation.

Conclusion

In conclusion, the management of the critically ill septic patient very often requires nutritional support therapy. Enteral feeding compared to parenteral feeding appears to reduce the risk of septic complications in the critically ill and high-risk surgical patients. In patients with an intact and functioning gastrointestinal tract, early enteral feeding (within 48 h) should be the initial choice for supportive nutritional therapy. Evidence exists to support the benefits of enteral feeding in gut mucosa barrier function and immune status. However, the exact mechanism and contributing elements remain to be elucidated in detail.

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