# Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes

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**Malnutrition is a common comorbidity that places inpatients at risk of complications, infections, long length of stay, higher costs, and increased mortality. Thus, nutrition support has become an important therapeutic adjunctive to the care of these patients. For patients unable to feed themselves, nutrition can be delivered via the parenteral or enteral routes. The formulations used to deliver nutrients and the route of nutrient delivery, absorption, and processing differ substantially between parenteral and enteral nutrition. Over the past two decades, many randomised clinical trials have assessed the effects of parenteral versus enteral nutrition on outcomes (ie, complications, infections, length of stay, costs, mortality) in diverse inpatient populations. From a search of medical publications, studies were selected that assessed important clinical outcomes of parenteral versus enteral feeding or intravenous fluids in patients with trauma/burn injuries, surgery, cancer, pancreatic disease, inflammatory bowel disease, critical illness, liver failure, acute renal failure, and organ transplantation. Our goal was to determine the optimum route of feeding in these patient groups. The available evidence lends support to the use of enteral over parenteral feeding in inpatients with functioning gastrointestinal tracts.**

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Malnutrition is associated with increased complication rates, infections, length of stay, costs, and mortality in inpatients.[1–4] Thus, nutrition support has become a major component of the treatment of such inpatients. Many inpatients cannot sustain themselves through oral consumption of food. Through the use of nutritional formulations, many of these patients can be sustained long enough to allow recovery from their illnesses. Despite controversies about the optimum route, timing, quantity, and quality of nutrition support, morbidity and mortality are undoubtedly improved through nutritional support techniques.[5] The type and severity of disease and the duration of malnutrition clearly affect outcomes of nutritional support.

Nutrients can be delivered via the parenteral or enteral routes. In many patients, parenteral delivery of nutrients is easier than delivery via the enteral route. As a result, many clinicians place patients on parenteral nutrition despite adequate gastrointestinal function. Delivery of parenteral nutrients results in different physiological effects than when similar nutrients are delivered enterally. Data accumulated over the past two decades indicate that parenteral nutrition is less sustaining and more expensive than enteral nutrition and should be avoided in most patients with functioning gastrointestinal tracts. In this Review, I discuss the use of parenteral nutrition in adult inpatients and concentrate the discussion on important clinical outcomes. The objective is to discuss the effectiveness of parenteral nutrition; the techniques of parenteral nutrition administration, which are discussed in many textbooks and journal articles, are not discussed here. Randomised studies of patients with functional gastrointestinal tracts are reviewed. The aim of this Review is to alert the clinician to the benefits and risks of nutrition support in patients with functioning gastrointestinal tracts, so that patients can receive the optimum form of nutrition support.

## Substrate supply

Most parenteral and enteral nutrition formulas differ in their nutrient profiles (table). Macronutrients consist of proteins, lipids, carbohydrates, and nucleic acids. Proteins can be delivered to patients as intact proteins, hydrolysed proteins or peptides, and as aminoacids. Many peptides produced on digestion of dietary proteins are absorbed intact into the circulation, and many peptides are capable of modulating cellular functions.[6,7] Intact and hydrolysed protein can be delivered only in

### Search strategy and selection criteria

The best method to determine effectiveness of clinical interventions is through randomised clinical trials. Therefore, we did a computerised bibliographic search of MEDLINE and the Cochrane Library for studies from 1980 to February, 2005, to locate all articles from randomised controlled trials of adult inpatients receiving parenteral nutrition. We used the search terms "nutrition support", "enteral nutrition", "parenteral nutrition", "peripheral nutrition", "supplemental nutrition", "total parenteral nutrition", "critical care", "critical illness", "intensive care", "surgery", "perioperative", "trauma", "burn", "cancer", "pancreatitis", "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "renal failure", "liver", and "organ transplantation". Personal files, relevant review articles, and reference lists of identified articles were reviewed for additional references. Studies were selected for inclusion in the discussion if they were randomised clinical trials or meta-analysis of such trials of parenteral nutrition versus enteral nutrition or standard care. To be included in the discussion, studies had to assess one of the outcomes of interest (ie, complications, infections, length of stay, costs, or mortality).

We assessed use of parenteral nutrition in adults with diseases that could be randomised to parenteral nutrition or enteral nutrition. The patients in the trials included in this Review had functioning gastrointestinal tracts, so we did not review studies in patients with short bowel syndromes. Most trials excluded patients with severe malnutrition, but mild or moderate malnutrition was present in many of the trials. We only assessed trials in which complete parenteral nutrition was given. We did not assess trials of protein sparing nutrition that used nitrogen with a caloric source; such therapy has been analysed previously and had no overall effect on outcomes.[8] We focus on hospital inpatients and do not review home parenteral nutrition.



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| | Parenteral nutrition | Enteral nutrition |
|---|---|---|
| **Protein** | | |
| Intact | No | Yes |
| Hydrolysed | No | Yes |
| Aminoacids | Yes | Yes |
| Glutamine | No* | Yes |
| Cysteine | No | Yes |
| Arginine | Low | Normal/high |
| **Carbohydrate** | | |
| Simple | Yes | Yes |
| Complex | No | Yes |
| Nucleic acids | No | Yes |
| Lipid | High n-6 PUFA* | Balanced |
| Medium-chain triglycerides | No* | Yes |

*Intravenous glutamine is not available in the USA but is available in Europe. Intravenous fat emulsions are high in omega-6 polyunsaturated fatty acids (n-6 PUFA) in the USA. However, omega-3 polyunsaturated fatty acids (n-3 PUFA) supplemented formulations are available in Europe. Intravenous medium-chain triglycerides are not available in the USA but are available in Europe.

***Table:*** **Macronutrient profiles**

enteral formulas, whereas parenteral formulas use aminoacids. Moreover, parenteral formulas do not contain all the aminoacids. Many years ago, aminoacids were classified as essential or non-essential. Some non-essential aminoacids were not felt to be needed in nutritional formulas because they could be synthesised from the essential aminoacids. However, the liver and kidney are the main organs necessary for aminoacid synthesis, and function of these organs is impaired in many ill patients. Furthermore, patients' need for some aminoacids might be greater than their rates of synthesis (ie, during wound healing or rapid growth). Thus, we now recognise that some aminoacids are conditionally essential. They might not be needed in healthy adults, but they are needed after stress and injury. Many parenteral formulas do not contain adequate quantities of some conditionally essential aminoacids (ie, glutamine, arginine, cysteine).[9]

The dietary essential fatty acids are the omega-6 polyunsaturated fatty acid linoleic acid and the omega-3 polyunsaturated fatty acid linolenic acid. These lipids are precursors of structural and regulatory lipids. In general, omega-6 long-chain polyunsaturated fatty acids are proinflammatory, immunosuppressive, and carcinogenic. Omega-3 polyunsaturated long chain fatty acids have opposite effects. Thus, nutritional formulas should deliver adequate quantities or precursors of these two long-chain lipids. However, nutritional formulas should also deliver optimum quantities of both. Although the optimum intake of omega-3 and omega-6 polyunsaturated fatty acids remains unknown, the diet of early man is estimated to have had a ratio of about 1 to 1. Thus, many experts believe that these lipids should be delivered in the diet in a ratio close to 1 to 1. The lipid sources of parenteral and enteral formulas vary greatly in the quantities of these essential fats. In the USA, parenteral lipids are formulated from soybeans and have a high ratio of omega-6 to omega-3 polyunsaturated long-chain fatty acids (roughly 8 to 1). In Europe, some lipid formulations contain higher amounts of omega-3 polyunsaturated fatty acids, resulting in lower omega-6 to omega-3 lipid ratios. Some (but not all) enteral formulas have omega-6/omega-3 lipid ratios that approach 1 to 1. Some of these formulas use fish oils rich in omega-3 fatty acids.

Parenteral formulas deliver carbohydrate in the form of simple sugars whereas enteral formulae use both simple and complex carbohydrates. Complex carbohydrates are known to have many beneficial effects on disease development and progression. Some such effects result from short-chain fatty acids that are produced by gut bacteria during metabolism of complex carbohydrates. Finally, parenteral formulas do not deliver nucleic acids, whereas some enteral formulas contain these substrates. What quantities of vitamins and minerals should parenteral formulas contain? Many nutritionists believe that parenteral formulas are low in antioxidant compounds. Parenteral formulations containing larger quantities of arginine, glutamine, omega-3 polyunsaturated fatty acids, and medium-chain triglycerides, many of which are available in Europe, are expected to soon be available worldwide.

There are clearly major differences in the nutrient contents between enteral and parenteral formulations. Furthermore, there are substantial variations in nutrient contents within parenteral and enteral formulations. Clearly, both types of formulations can maintain people during both health and disease. Although certain formulations are probably better than others, the optimum formula contents for various diseases remain unknown.

## Effects of parenteral and enteral nutrition on organ function

The biochemical and physiological effects of parenteral and enteral formulas on organ function have been assessed in many studies over the past two decades. A complete description of all these studies is beyond the scope of this Review. Panels 1 and 2 list the effects of both parenteral and enteral formulas on gastrointestinal and immune functions. The results are derived from studies in both animals and man, and clearly show that parenteral formulas, compared with enteral formulas, are less supportive to the immune and gastrointestinal systems. Interestingly, parenteral formulas cause dysfunction of B and T lymphocytes, macrophages, and neutrophils. The net result is an increase in infections. Parenteral formulas also result in greater proinflammatory cytokine production (ie, tumour necrosis factor-alpha, interleukin-1, interleukin-6) in response to several stimuli (ie, sepsis, endotoxin, burns, trauma). Most of these studies were done in acute models of illness. Long-term starvation also causes immune depression, gastrointestinal dysfunction, and impaired functions of other organs. At some point in time, the detrimental effects of long-term starvation (if the



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**Panel 1: Effects of parenteral compared with enteral nutrition on gastrointestinal functions**

**Parenteral nutrition is associated with:**
Gut atrophy*
Loss of gut hormone secretion
Reduced gut absorption
Decreased gut blood flow that is worse with vasopressor administration
Loss of the gut barrier (mucus secretion, IgA, gut associated lymphoid tissue, motility)
Altered gut microflora
Increased bacterial adherence
Increased microbe translocation
Increased gut permeability after inflammatory insults*
Decreased gastric, intestinal, and pancreatic secretions*
Slower healing of anastomotic sites
Increased apoptosis
Hepatic dysfunction*
Decreased drug clearance by liver*
Hepatic injury*
Rare hepatic failure*
Cholestasis, gallstones*

Most data are derived from animal studies. Only a few of the changes have been confirmed in man (designated with *).

**Panel 2: Effects of parenteral compared with enteral nutrition on immune system function**

**Parenteral nutrition is associated with:**
B and T cell dysfunction
Macrophage and neutrophil dysfunction
Impaired chemotaxis
Impaired phagocytosis
Impaired bacterial/fungal killing
Loss of gut associated lymphoid tissue
Decreased IgA secretion
Reticuloendothelial dysfunction
Increased infections
Increased proinflammatory cytokines

patient is not fed) are likely to exceed the short-term effects of parenteral feeding; at that time, these patients are likely to benefit from parenteral nutrition.

## Outcome in animals

Several investigators[10–19] have assessed parenteral versus enteral nutrition in animal models of acute illnesses. These models include peritonitis, methotrexate-induced enterocolitis, haemorrhagic shock, pneumonia, hepatectomy, and pancreatitis. Survival was diminished by parenteral nutrition in all[10–18] but the pancreatitis study.[19] For example, Petersen and colleagues[12] assessed the effect of enteral feeding versus parenteral nutrition with and without lipids on survival using a model of Escherichia coli-haemoglobin peritonitis. Survival was significantly decreased in the animals receiving parenteral nutrition (ie, <5% *vs* about 60% in the enteral group). Lin et al[17] studied nutritional route and survival after intraperitoneal administration of *E coli*. Survival was significantly higher in animals receiving nutrition via the enteral route (60% enteral *vs* 20% parenteral). Another group[13] assessed different enteral diets versus parenteral nutrition in an animal model of haemorrhage. Survival was significantly better in the enterally fed animals (76–100% enteral *vs* 37% parenteral). These workers[14] also reported significantly better survival in animals receiving enteral versus parenteral nutrition after high-dose methotrexate administration (50% *vs* 0%). Others[13] reported improved survival in animals after 70% hepatectomy with enteral versus parenteral feeding (91% *vs* 32%). There was no difference in survival between nutrient routes in the pancreatitis study,[19] despite greater bacterial translocation in the parenteral group. As a whole, animal work indicates that survival is improved with enteral compared with parenteral nutrition after various acute insults. However, investigators should be careful not to over-extrapolate from work in animals to man since results in animals might not indicate changes in people. Differences in outcomes between animals and man can result from species differences, differences in cell metabolism, and the nature of the models, which do not always indicate the true disease process in people.

## Outcome in human beings

Parenteral nutrition was developed to support patients who did not have functioning gastrointestinal tracts, since without nutritional support many of them would die. However, as a result of the ease of administration, a failure to properly understand gut function and enteral feeding techniques, and an absence of simple enteral feeding devices, parenteral nutrition developed as a major technique for feeding patients with functioning gastrointestinal tracts. In my experience, up to 70% of patients receiving parenteral nutrition have impaired gastric emptying and diminished colonic motility. However, many have adequate small-bowel function and can be fed by the enteral route.

Notably, the popularisation of parenteral nutrition in patients with functioning small intestines took place in the absence of supporting evidence from prospective randomised trials. In this section, randomised studies of parenteral nutrition in acutely injured patients are reviewed.

Randomised clinical studies have assessed outcomes after trauma.[20–25] Most of these studies showed more infections and longer lengths of stay in intensive care units in patients receiving parenteral nutrition than those receiving enteral nutrition.[21–25] Cost of parenteral nutrition was higher than for enteral nutrition in these studies. Moore and colleagues[21] reported a 17% frequency of infectious complications in enterally fed patients



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compared with 37% in those fed parenterally; major infections were significantly higher in parenterally fed patients (20% *vs* 3%). Kudsk and colleagues[24] reported pneumonia, abscesses, or line infection or all three in 40% of parenterally fed patients versus 16% of enterally fed patients.[24] The difference in infection rate between the two groups rose as the severity of illness worsened. In patients with an injury severity score greater than 20 and an abdominal trauma index score greater than 24, the rate of infections was 67% in parenterally fed patients versus 15% in those fed enterally.[24] Feliciano and colleagues[25] reported higher infection rates (three of 11 *vs* one of 11), longer hospital stay (27 *vs* 14 days), and higher cost of nutrition in parenterally versus enterally fed patients. A meta-analysis[23] of data from eight medical centres showed a 35% rate of infection in parenterally fed patients compared with 16% in those fed enterally. Length of stay in hospital was longer in parenterally fed patients after penetrating trauma (22 days *vs* 17 days), but mortality was similar in patients on parenteral nutrition compared with those fed enterally (10% *vs* 7%). On the other hand, others[20] reported no differences in outcomes between nutrition groups. In an assessment of complications and costs of postoperative parenteral versus enteral nutrition in trauma patients using data from published trials, Trice and colleagues[26] showed that parenteral nutrition was associated with greater infections and higher costs than was enteral nutrition.

Increased infections with parenteral nutrition in trauma patients were not thought to be due to raised blood glucose concentrations in Kudsk and colleagues' analysis.[27] However, most studies of enteral versus parenteral nutrition fail to assess the effect of hyperglycaemia on outcomes. Although blood glucose concentrations are known to be higher when glucose is given via the parenteral versus enteral route, whether control of glucose to similar concentrations would improve the effects of parenteral feeding on outcomes is unclear.

Many cite Van den Berghe and colleagues'[28] findings as proof that tight glucose control improves outcomes from parenteral nutrition. However, that trial did not randomise patients receiving enteral versus parenteral nutrition to tight versus conventional glucose control and cannot directly address the issue. Patients in the trial received large quantities of intravenous dextrose (200–300 g per day) in addition to parenteral and enteral feeding, but the amount of parenteral versus enteral feeding and the compositions of feeding were not reported in the study groups. Moreover, the benefits for mortality were seen only in patients who remained in intensive care for 5 or more days (long-term patients). There was no benefit on mortality in the subgroup of trauma patients.

In a consecutive case study (before and after tight glucose control), Krinsley[29] also noted no benefits on mortality in the trauma subgroup despite benefits in other patient groups. Thus, although we advocate tight control of blood glucose in critically ill patients and believe that some outcomes in parenterally fed patients such as infection should be improved with tight glucose control, definitive data to support these statements are not yet available.

In five studies, investigators assessed route of feeding in patients with head injuries. Three studies showed similar outcomes[30–32] and two showed enhanced cognitive recovery with enteral feeding,[33,34] despite similar blood glucose concentrations in one study.[33] The American Gastroenterological Association (AGA) reviewed three randomised clinical trials of parenteral feeding in patients after burn injury.[6] Two trials compared parenteral with enteral nutrition and one compared parenteral nutrition with lipid/dextrose solutions. In one study,[35] of 28 patients with burns greater than 50% total body surface area, mortality was similar in those on oral feeding with parenteral supplementation (eight of 13) and those on oral alimentation (eight of 15). In a subsequent study[36] of 39 such patients mortality was significantly higher (63% *vs* 26%) in the parenterally supplemented group than with enteral feeding alone.

Many workers have assessed parenteral and enteral nutrition in the perioperative period. Studies done before 1986 are summarised in a meta-analysis.[37,38] Eighteen clinical trials were included in the analysis. In most studies, the control groups did not receive enteral tube feeding but instead standard hospital care (intravenous fluids until the patient could eat). One study showed statistically significant reductions in complications and mortality with parenteral nutrition,[39] whereas another study recorded significantly increased mortality with parenteral nutrition.[40] Overall, there were no differences between parenteral nutrition and control groups in reasonably well-nourished patients undergoing surgery.

Since the previous analyses,[37,38] several additional prospective randomised trials have been done. Most of these studies compared parenteral nutrition with enteral tube feeding. A multicentre trial[41] assessed patients undergoing surgery for gastrointestinal cancers. By comparison with patients fed parenterally (n=158), fewer patients in the enteral group (n=158) had postoperative complications (34% *vs* 49% ) and the mean length of stay was shorter in the enteral group (13·4 *vs* 15·0 days). However, gastrointestinal intolerance (ie, distention, cramps, diarrhoea) was higher in the enteral group than in the parenteral group. Reynolds and colleagues[42] randomly assigned 67 patients after major upper gastrointestinal surgery to parenteral or enteral nutrition. Although the investigators concluded that there were no differences in outcomes between groups, the total parenteral nutrition group had more infections than did the enteral nutrition group (59% *vs* 39%). In another study,[43] 20 patients undergoing major upper gastrointestinal surgery were randomly assigned to parenteral or enteral feeding. Both groups had similar outcomes. Cost of nutritional support was lower in the enteral group than in



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the parenterally fed patients. However, gastrointestinal intolerance was more common in the enteral group.

In a small trial[44] of enteral versus parenteral feeding in 29 patients undergoing total gastrectomy, complications (38% *vs* 50%), concentrations of C-reactive protein (32 *vs* 61 g/L), and cost were lower in the enteral group than in the parenteral group. An intention-to-treat analysis[45] of 300 patients after major surgery (gastrointestinal, vascular, bladder) showed no difference in mortality (8% *vs* 6·6%) or length of hospital stay between groups randomly assigned to total parenteral nutrition or intravenous glucose and electrolytes. However, the number of complications was higher in the parenteral nutrition group than in the glucose and electrolytes group (227 in 150 patients *vs* 171 in 150 patients).

Other randomised trials have compared parenteral and enteral nutrition in patients undergoing major hepatic resection for liver cancer,[46] in those undergoing total laryngectomy,[47] and postoperatively in patients having gastrointestinal surgery.[48] In hepatic resection patients, the parenteral group had a greater number of infections than the enteral group (8/13 *vs* 1/13). In 48 patients undergoing total laryngectomy, those in the enteral group had shorter lengths of stay than the parenteral group (26 *vs* 34 days). After gastrointestinal surgery, complications, infections, length of stay, and mortality were much the same between groups given either total parenteral nutrion or enteral nutrition. However, costs were four-fold lower in the enteral group.

Brennan and colleagues[49] randomly assigned patients undergoing pancreatic resection for malignant disease to postoperative adjuvant parenteral nutrition (30–35 Kcal/kg daily) versus intravenous dextrose containing fluids alone until adequate oral intake could be achieved. No benefit could be seen from the use of parenteral nutrition in these patients. Complications (especially infection) were significantly greater in the patients receiving parenteral nutrition. Mortality was not substantially different in patients receiving parenteral feeding compared with those fed enterally; fistula, abscess, anastomotic leak, and re-operation were more common in parenterally fed patients. Another randomised study[50] compared parenteral nutrition with one of two enteral formulas in patients undergoing pancreaticoduodenectomy or gastrectomy for cancer. Parenterally fed patients had more infections ($p=0·06$), higher sepsis scores ($p\leq0·01$), and longer length of hospital stay ($p\leq0·01$) than enterally fed patients. There was no difference in mortality between groups. By contrast, Fan and colleagues[51] studied 124 patients undergoing hepatic resection for hepatocellular carcinoma. Patients assigned to parenteral nutrition had fewer infections (17% *vs* 37%), decreased perioperative morbidity (34% *vs* 55%), and lower mortality (8% *vs* 15%) than did those in the enteral group.

The absence of differences in outcomes between enteral and parenteral nutrition in studies of predominantly well nourished postoperative patients prompted the Veterans Affairs Cooperative Study[52] of malnourished patients undergoing elective surgical procedures. Most patients in this study underwent surgery for gastrointestinal and lung cancers. Patients were randomly assigned to preoperative and postoperative parenteral nutrition or to diet. Overall, total complications and 90-day mortality were similar between groups. However, major infections were significantly greater in the group receiving parenteral nutrition (14% *vs* 6%). There were more catheter-related complications (ie, pneumothorax, air embolus) in the parenteral group than in the enteral group. In the subgroup of severely malnourished patients, infection rates were similar in enteral and parenteral groups, but non-infectious complications were lower in the parenteral group. Moreover, the parenterally fed patients received an excess of calories compared with the oral-diet group. Some experts speculate that the detrimental effects of parenteral nutrition in this study resulted from overfeeding. In an economic analysis of the Veterans Affairs Cooperative Study Eisenberg and colleagues[53] reported that the cost of caring for patients with parenteral nutrition was US$3169 (in 1993 dollars) more per patient than the cost of caring for similar patients without parenteral nutrition (ie, diet group).

In a study by Cerra and and colleagues,[54] no differences in mortality or development of organ failures were shown between intensive care patients with sepsis after surgery who were given either enteral or parenteral nutrition.[54] Nutrition costs were higher in the parenteral group. The investigators concluded that enteral nutrition was as good as parenteral nutrition in these patients and could be used safely and at a lower cost.

The results of a recent meta-analysis[6] of perioperative nutritional support from the AGA showed no clinically significant differences in mortality, post-operative complications, or duration of treatment in hospital with parenteral nutrition. However, there was a small (6%) non-significant decrease in complications compared with enteral nutrition. Notably, this analysis showed that perioperative patients who received lipids had better outcomes (compared with no lipids), and well-nourished patients were more likely to demonstrate benefits from parenteral nutrition than were malnourished surgical patients. On the basis of these studies, routine use of parenteral nutrition in patients undergoing elective surgery is not recommended. Parenteral nutrition should be used in those patients who cannot tolerate enteral feeding.

Patients receiving chemotherapy and radiation treatment for cancer frequently develop anorexia, nausea, vomiting, diarrhoea, and mucositis. They are at high risk for nutritional depletion. Several analyses[6,55–58] have assessed use of parenteral nutrition in patients receiving cancer therapy. The results of these analyses accord with each other. McGeer and colleagues[57] concluded that parenteral nutrition was associated with higher infection



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rates (odds ratio 4·1, 95% CI 2·4–6·9), decreased survival (0·81, 0·62–1·00), and poorer tumour responses (0·68, 0·4–1·1) in patients receiving chemotherapy. On the basis of these data, the American College of Physicians[56] stated "that parenteral nutritional support was associated with net harm, and no conditions could be defined in which such treatment appeared to be of benefit. Thus, the routine use of parenteral nutrition for patients undergoing chemotherapy should be strongly discouraged." The AGA[6] concluded that there was no effect of parenteral nutrition on survival in patients receiving chemotherapy or radiation therapy. However, parenteral nutrition was associated with increased complications (+40%, 95% CI 14–66), infections (+16%, 8–23), and decreased tumour response (–7%, –12 to –1). Parenteral nutrition had no effect on bone marrow or gastrointestinal toxicity. Importantly, the patients in these studies[6,55–58] were able to tolerate oral diets or tube feeds. Individuals unable to tolerate enteral diets for long periods (greater than 5 days) might benefit from parenteral nutrition.

There has been considerable debate on the use of parenteral versus enteral nutrition in patients with acute pancreatitis. A common belief that is still held by many clinicians is that parenteral nutrition rests the pancreas and improves recovery in patients with acute pancreatitis, whereas enteral nutrition worsens pancreatic injury. Thus, to assess the effect of parenteral and enteral nutrition on outcomes in patients with acute pancreatitis, we[59] did a meta-analysis of six prospective randomised clinical trials of patients (n=263) with acute pancreatitis. The results indicate substantial improvement in outcomes with enteral feeding. Compared with parenteral nutrition, enteral nutrition was associated with reduced infection (relative risk [RR] 0·45, 95% CI 0·26–0·78), a fall in the need for surgery (0·48, 0·22–1·0), shortened length of stay (2·9 days, 1·6–4·3), fewer complications (0·61, 0·31–1·22), and lower mortality (0·66, 0·32–1·37). Although all indices were not significant all were consistent and favoured the enteral groups. McClave[60] concluded that "enteral nutrition has emerged as the gold standard of therapy for nutrition support in the patient with severe acute pancreatitis" and that "enteral nutrition in severe acute pancreatitis is primary therapy and is a therapeutic management tool capable of favorably altering the patient's hospital course". Kaushik and O'Keefe[61] noted in patients with acute pancreatitis that total parenteral nutrition is associated with catheter-related sepsis and uncontrolled hyperglycemia that increases the risk of adverse outcomes and death. Thus enteral nutrition is the preferred route of nutrition support in patients with pancreatitis and should be initiated before starting parenteral nutrition.[62]

Many patients with inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis) have serious protein-energy malnutrition. In the past, total parenteral nutrition and bowel rest were thought to cure or improve disease activity in patients with inflammatory bowel disease. The results of some studies report an improvement in symptoms in patients with inflammatory bowel disease on total parenteral nutrition. However, overall, parenteral nutrition results in much the same remission rates as those for control diets. Crohn's patients treated with parenteral nutrition and elemental enteral diets showed similar short-term and long-term remission rates.[63] However, the benefits of enteral versus parenteral nutrition are best addressed in randomised studies.

Greenberg and colleagues[64] undertook a multicentre controlled trial in which 51 patients with active Crohn's disease were randomly assigned to total parenteral nutrition, defined-formula diets (tube feeds), or partial parenteral nutrition plus a low residue diet. There was no difference in response rates or remissions at 1 year. Similar results were reported by other investigators in both prospective[65,66] and retrospective[67] studies. Remission rates and need for surgery were similar between parenteral and enteral nutrition groups in patients with severe acute ulcerative colitis receiving glucocorticoids.[68] Additional studies in patients with ulcerative colitis have documented similar outcomes in parenteral compared with enteral nutrition.[69,70] In a mixed group of patients with ulcerative colitis and Crohn's disease given enteral or parenteral nutrition, clinical improvement was similar in both nutritional categories.[71] On the basis of the evidence, parenteral nutrition provides little benefit over oral diet or enteral nutrition in the treatment of inflammatory bowel disease in patients with functional gastrointestinal tracts. Parenteral nutrition should be reserved for inflammatory bowel disease patients who cannot tolerate enteral diets.

In a meta-analysis of 26 prospective randomised trials Heyland and colleagues[72] compared total parenteral nutrition with standard care in critically ill patients. They did not include studies using tube feeds. Standard care (intravenous fluids until the patient could eat), and parenteral feeding showed similar effects on complication rates and survival. In studies of malnourished patients, parenteral feeding was associated with lower complication rates but no difference in mortality. The mortality rates in the subgroup of non-surgical critically ill patients were higher with parenteral feeding than with standard care. Parenteral nutrition was associated with lower complication rates than standard care but had no effect on mortality in surgical patients. Complication rates were lowest in parenterally fed patients, but mortality was unaffected, in studies of parenteral nutrition that did not use lipids.

The Canadian clinical practice guidelines[73] were based on studies of parenteral versus enteral nutrition in critically ill patients receiving mechanical ventilation. In these studies, although there was no difference in mortality between nutrition groups, enteral feeding was associated with a significant decrease in infections (RR 0·61, 95% CI 0·44–0·84, p=0·003). Braunschweig



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and colleagues[74] assessed randomised clinical trials of parenteral nutrition versus standard care and parenteral versus enteral nutrition in severely ill patients. Both standard care and enteral nutrition were associated with significant decreases in infection rates (25% and 35%, respectively) compared with parenteral nutrition. Complications were also decreased (although not significantly) with standard care and enteral feeding. There were no differences in mortality rates. In studies of predominantly malnourished patients, the same researchers showed that enteral feeding was better than parenteral feeding in having a decreased rate of infections.[74] However, the mortality and infection rates associated with parenteral nutrition were lower than those for standard care in this subgroup.

Gramlich and colleagues[75] assessed enteral versus parenteral nutrition from 13 studies in critically ill patients (excluding surgical patients). Enteral nutrition was associated with reduced infections (RR 0·64) but no difference in mortality (1·08). There was no difference in length of hospital stay. However, parenteral nutrition was associated with a higher incidence of hyperglycaemia and higher costs than enteral nutrition.

A meta-analysis[76] of 30 randomised clinical trials compared early enteral with early parenteral feeding. Ten trials were in medical patients, 11 in surgical patients, and nine in trauma patients. There was no difference between nutrition groups for mortality. However, enteral feeding was associated with shortened length of stay in hospital (mean reduction 1·2 days). By contrast, parenteral nutrition was associated with significantly more infections (7·9%) and non-infectious complications (4·9%, p=0·04); the enteral groups had more diarrhoea (8·7%, p=0·001).

Simpson and colleagues[77] investigated standard enteral nutrition compared with standard parenteral nutrition on outcomes in critically ill patients using meta-analysis of studies applying the intention-to-treat principle. 11 studies of trauma, cancer, and pancreatitis patients were included in the analysis. Overall, there was a mortality benefit in favour of parenteral nutrition. However, the mortality benefit was recorded only in studies of late enteral feeding (an a-priori subgroup analysis). Patients receiving early enteral feeding (before 24 h) had similar survivals compared with patients receiving parenteral feeding. Overall, infections were increased in patients receiving parenteral feeding. The investigators concluded that the overall findings of this meta-analysis would not lead them to recommend the use of parenteral nutrition in patients in whom enteral nutrition could be initiated within 24 h of injury or admission to intensive care. An evidence-based recommendation of grade B+ could be generated for the use of parenteral nutrition in patients in whom enteral nutrition could not be initiated within 24 h of injury or admission to intensive care. Overall, the results of these analyses in critically ill patients indicate that enteral feeding is the preferred route of nutritional support in critically ill patients who can tolerate early enteral feeding, and parenteral nutrition should be reserved for those who cannot tolerate early enteral nutrition.

Severe gastrointestinal side-effects and dietary depletion are common in bone marrow transplant patients, and predispose these patients to infections. Weisdorf and colleagues[78] randomly assigned 137 well-nourished bone marrow transplant patients to total parenteral nutrition or intravenous fluids, starting 1 week before transplantation. All patients were encouraged to maintain oral intake. However, oral intake and total calorie/protein intake was very low in the control group. Thus, the controls received very little nutrition whereas those given parenteral nutrition received adequate nutrition for the stress state. 40 of the controls eventually received parenteral feeding because of caloric depletion. Minimum follow-up was 1 year (median 2 years). There was no difference in engraftment, incidence of bacteraemia, and duration of treatment in hospital. However, survival, time to relapse, and disease-free survival were significantly better in the parenteral nutrition group.

Other researchers[79] examined bone marrow transplant patients given either total parenteral nutrition or enteral feeding (included tube feeding if necessary). Compared with enteral feeding, parenteral nutrition was associated with more frequent hyperglycaemia, more catheter-related complications, and higher nutrition-related costs. There was no difference in rate of haemopoietic recovery, length of stay in hospital, or survival. The investigators concluded that "TPN [total parenteral nutrition] be reserved for BMT [bone marrow transplant] patients who demonstrate intolerance to enteral feeding".[79]

A prospective non-randomised study[80] assessed parenteral nutrition designed to meet metabolic demands versus partial parenteral nutrition (hypocaloric, no lipids, low protein), in 61 patients undergoing autologous haemopoietic stem-cell transplantation. Both groups were allowed ad lib food intake. Unfortunately, the amount in each group was not recorded. The formulas also differed in nutrient composition: the full parenteral nutrition formula contained lipids, trace elements, and vitamin K. Compared with the group receiving partial parenteral nutrition, the group receiving full parenteral nutrition had higher serum urea and glucose concentrations, a higher incidence of infections, and delayed platelet engraftment requiring more platelet transfusions. However, this study really compares two levels of intake and formulas differing in nutrient composition. The results suggest that underfeeding of calories and lipid-free nutrition was associated with improved outcome.

Four randomised clinical trials[6] assessed parenteral nutrition in patients undergoing bone marrow transplantation for cancer. One of these trials assessed the role of home parenteral nutrition. When data from the remaining three trials were combined, there was a trend toward lower mortality with parenteral nutrition than with enteral nutrition.[6] Another study[81] assessed



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24 patients undergoing orthotopic liver transplantation, who were randomly assigned to enteral or parenteral nutrition. There were no differences between groups for number of days on ventilators, length of hospital stay, infections, or mortality.

Parenteral nutrition has been assessed in seven studies of alcoholic hepatitis.[6] Five of these trials compared protein-sparing therapy with standard care. Parenteral nutrition failed to improve survival or reduce total complications. However, there was a trend toward less encephalopathy. Hepatic encephalopathy improved more often or more rapidly in patients receiving branched-chain aminoacid solutions.[6] A previous meta-analysis also suggested that branched-chain aminoacid-based parenteral nutrition was of benefit in treating hepatic encephalopathy.[82] None of the trials compared parenteral with enteral branched-chain aminoacid formulas.

Five randomised clinical trials assessed parenteral nutrition with essential aminoacids in patients with acute renal failure.[6,83] Control groups received isocaloric dextrose without aminoacids in three trials, whereas two trials used parenteral nutrition with standard aminoacids. A meta-analysis concluded that there was no effect of the parenteral nutrition based on essential aminoacids on survival.[6,83] However, recovery from organ dysfunction was improved with the essential aminoacid-based parenteral nutrition. I identified no trials that assessed enteral versus parenteral nutrition on outcomes in patients with acute renal failure.

### Supplemental parenteral nutrition

Herndon and colleagues[35] randomly assigned 28 patients with burns greater than 50% of total body surface area to parenteral nutrition supplementation of oral alimentation or oral alimentation alone. Mortality was similar in each group. In an additional study of burn patients, these workers[36] randomly assigned 39 patients with burns greater than 50% total surface area to intravenous parenteral supplementation of enteral diets or enteral diets alone. In this small study, mortality was significantly higher (63% *vs* 26%) in the parenteral supplemented group compared with enteral feeding alone. Another study[84] assessed supplemental parenteral nutrition in patients after blunt trauma. Mortality was similar between groups. No difference in mortality was recorded in two additional studies of critically ill patients.[85,86] In a meta-analysis[87] of the five studies cited above overall mortality was 1·27 (95% CI 0·82–1·94, p=0·3). Two studies[85,86] reported infectious complications and length of stay; there were no differences between groups. Overall, there are no data to indicate benefit from supplementing parenteral nutrition to enteral nutrition in hospital inpatients. However, the absence of benefit from supplemental parenteral nutrition might have resulted from administration of excess calories.

Most parenteral nutrition formulas do not contain glutamine, a conditionally essential aminoacid that is an important fuel and modulator of gut and immune function. The addition of glutamine to parenteral formulas has been associated with fewer complications and lowered mortality rates.[88–93] Although intravenous glutamine is not available in the USA, intravenous glutamine formulations are available in Europe. Furthermore, the most common lipid sources used during parenteral feeding are high in omega-6 long-chain polyunsaturated fatty acids. These lipids show proinflammatory and immunosuppressive actions. Some studies of parenteral nutrition suggest that administration of the formula without lipids is associated with fewer infections.[72,94,95] Only high omega-6 polyunsaturated intravenous lipid sources are available in the USA. However, intravenous lipids supplemented with omega-3 polyunsaturated fatty acids, olive oil, and medium-chain triglycerides are available for use in parenteral nutrition in Europe. Improvements in parenteral formulas might improve their performance.

### Benefits of enteral nutrition

Although there remains little controversy about the superiority of enteral over parenteral nutrition in most patient groups, the mechanisms of the beneficial effects of enteral over parenteral nutrition remain unclear, and full discussion is beyond the constraints of this Review. Available data indicate many potential mechanisms. The exact mechanisms are likely to be patient-, disease-, and time-specific. Beneficial effects of enteral formulas might relate to the substrates used (ie, proteins and peptides, omega-6 and omega-3 lipids, complex carbohydrates), which are more supportive of cell and organ functions than nutrients present in parenteral feedings. Most parenteral formulas do not contain (or are low in) some conditionally essential aminoacids (such as glutamine) and can be too low in antioxidants and other micronutrients. Enteral nutrition is associated with lower blood glucose concentrations than is parenteral feeding. Recent data from many sources suggest that hyperglycaemia suppresses immune functions, increases infections rates, and reduces survival in critically ill patients. Thus, improved control of circulating glucose concentrations could account for lower infections in patients receiving enteral nutrition. Enteral nutrition is frequently administered at lower rates than parenteral nutrition, resulting in less overfeeding. Enteral feeding better supports gut mass and barrier function, and diminishes microbe translocation across the intestinal mucosa. Enteral feeding is also more supportive than parenteral feeding of immune functions. Further study into these mechanisms is needed so as to allow for improvement in nutrient administration.

## Indications for parenteral feeding

There are specific advantages to parenteral nutrition. Nutrient bioavailability is more dependable after parenteral compared with enteral administration, and



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many nutrient effects can be obtained in shorter times. Parenteral nutritional support does not require a functioning gastrointestinal tract and gut access. Nutrients can be easily administered, and the quantity given is not affected by satiety, abdominal distention, nausea/vomiting, diarrhoea, fistula drainage, or bowel ischaemia. Parenteral nutrition can be easily given to patients in whom enteral feeding is contraindicated (eg, gastrointestinal bleeding, gut ischaemia). Enteral nutrition could be associated with aspiration, diarrhoea, and gut ischaemia. In patients with these complications, parenteral nutrition offers an alterative to enteral feeding.

Previously well-nourished patients rarely benefit from the acute administration of parenteral nutrition. The benefits of parenteral nutrition are seen largely in patients who are malnourished and unable to receive adequate enteral nutrients as a result of gastrointestinal insufficiency. Such patients include those with short gut syndromes, severe gut dysfunction (eg, dysmotility, malabsorption), mesenteric vascular insufficiency, gut ischaemia or infarction, bowel obstruction, gastrointestinal bleeding, severe abdominal distention, severe diarrhoea, large volume fistula output, and inability to access the gastrointestinal tract. In many of these patient groups, parenteral nutrition is life saving.

## Future research

Parenteral nutrition remains an important patient support modality in people without functional gastrointestinal tracts; future research should be aimed at improving the technique. Vital to this research is the identification of subgroups of patients who are likely to benefit from parenteral nutrition and establishment of the optimum timing of the intervention. Research should also be oriented towards the identification of the mechanisms that underly the adverse effects of parenteral nutrition, and of methods to overcome these effects. Finally, future research should continue to explore the use of new substrates and improved compositions to better support patients with many different diseases. These aims are not unique to parenteral nutrition but also apply to enteral feeding.

## Conclusions

Almost all outcome studies from clinical trials comparing parenteral with enteral nutrition or intravenous fluids in acutely ill adults with functioning gastrointestinal tracts fail to document improved outcomes from parenteral nutrition. In many patient groups, enteral nutrition resulted in significantly reduced rates of infection, sepsis, length of stay in hospital, and costs. The exact reasons for the effectiveness of enteral over parenteral nutrition in patients with functional gastrointestinal tracts are not wholly clear. Potential reasons include the nature of the substrates, support of the gastrointestinal tract, adverse effects from the technique of nutrient administration (ie, overfeeding, hyperglycaemia), use in subgroups that do not benefit, methodological constraints of the clinical trials (ie, patient selection, size of the studies, heterogeneity of the study populations), and pre-injury nutritional and organ status of the patients.

In my experience, many patients with functioning gastrointestinal tracts continue to be fed with parenteral nutrition. Hospitals need to develop evidence-based guidelines for the appropriate use of enteral and parenteral nutrition; nutritional support offers unique opportunities to improve patient care, reduce complications, and decrease costs.

**Conflict of interest statement**

I receive speaker's fees and have received past research funding from Nestlé Nutrition, Novartis Nutrition, and Abbott Nutrition.

**References**

1 Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg* 1980; **139:** 160–67.

2 Detsky AS, Baker JP, O'Rourke K, et al. Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. *JPEN J Parenter Enteral Nutr* 1987; **11:** 440–46.

3 Middleton MH, Nazarenko G, Nivison-Smith I, Smerdely P. Prevalence of malnutrition and 12-month incidence of mortality in two Sydney teaching hospitals. *Intern Med J* 2001; **31:** 455–61.

4 Robinson G, Goldstein M, Levine GM. Impact of nutritional status on DRG length of stay. *JPEN J Parenter Enteral Nutr* 1987; **11:** 49–52.

5 Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients—a systematic review. *Crit Care Med* 2001; **29:** 2264–70.

6 American Gastroenterological Association clinical practice and practice economics committee. AGA technical review on parenteral nutrition. *Gastroenterology* 2001; **121:** 970–1001.

7 Zaloga GP, Siddiqui RA. Biologically active dietary peptides. *Mini Rev Med Chem* 2004; **4:** 815–21.

8 Roberts PR, Zaloga GP. Dietary bioactive peptides. *New Horiz* 1994; **2:** 237–43.

9 Furst P, Stehle P. Are intravenous amino acid solutions unbalanced? *New Horiz* 1994; **2:** 215–33.

10 Kudsk KA, Carpenter G, Petersen S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with *E coli*-hemoglobin adjuvant peritonitis. *J Surg Res* 1981; **31:** 105–10.

11 Kudsk KA, Stone JM, Carpenter G, Sheldon GF. Enteral and parenteral feeding influences mortality after hemoglobin-*E coli* peritonitis in normal rats. *J Trauma* 1983; **23:** 605–09.

12 Petersen SR, Kudsk KA, Carpenter G, Sheldon GF. Malnutrition and immunocompetence: increased mortality following infectious challenge during hyperalimentation. *J Trauma* 1981; **21:** 528–33.

13 Zaloga GP, Knowles R, Black KW, Prielipp R. Total parenteral nutrition increases mortality after hemorrhage. *Crit Care Med* 1991; **19:** 54–59.

14 Zaloga GP, Roberts P, Black KW, Prielipp R. Gut bacterial translocation/dissemination explains the increased mortality produced by parenteral nutrition following methotrexate. *Circ Shock* 1993; **39:** 263–68.

15 Alverdy JC, Aoys F, Moss BS. Parenteral nutrition results in bacterial translocation from the gut and death following chemotherapy. *JPEN J Parenter Enteral Nutr* 1990; **14:** 8S (abstr).

16 Shou J, Lappin J, Daly JM. Impairment of pulmonary macrophage function with total parenteral nutrition. *Ann Surg* 1994; **219:** 291–97.

17 Lin MT, Saito H, Fukushima R, et al. Route of nutritional supply influences local, systemic, and remote organ responses to intraperitoneal bacterial challenge. *Ann Surg* 1996; **223:** 84–93.

18 Delany HM, John J, Teh EL, et al. Contrasting effects of identical nutrients given parenterally or enterally after 70% hepatectomy. *Am J Surg* 1994; **167:** 135–43.

19 Kotani J, Usami M, Nomura H, et al. Enteral nutrition prevents bacterial translocation but does not improve survival during acute pancreatitis. *Arch Surg* 1999; **134:** 287–92.



www.manaraa.com

20 Adams S, Dellinger EP, Wertz MJ, Oreskovich MR, Simonowitz D, Johansen K. Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. *J Trauma* 1986; **26:** 882–92.

21 Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN *vs* TPN following major abdominal trauma-reduced septic morbidity. *J Trauma* 1989; **29:** 916–23.

22 Peterson VM, Moore EE, Jones TN, et al. Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic reprioritization. *Surgery* 1988; **104:** 199–207.

23 Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared to parenteral, reduces postoperative complications. The results of a meta-analysis. *Ann Surg* 1992; **216:** 172–83.

24 Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg* 1992; **215:** 503–13.

25 Feliciano DV, Spjut-Patrinely V, Burch JM. Enteral versus parenteral nutrition in patients with severe penetrating abdominal trauma. *Contemp Surg* 1991; **39:** 30–36.

26 Trice S, Melnik G, Page CP. Complications and costs of early postoperative parenteral versus enteral nutrition in trauma patients. *Nutr Clin Pract* 1997; **12:** 114–19.

27 Kudsk KA, Lauledeerkind A, Hanna MK. Most infectious complications in parenterally fed trauma patients are not due to elevated blood glucose levels. *JPEN J Parenter Enteral Nutr* 2001; **25:** 174–79.

28 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345:** 1359–67.

29 Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; **79:** 992–1000.

30 Young B, Ott L, Twyman D, et al. The effect of nutritional support on outcome from severe head injury. *J Neurosurg* 1987; **67:** 668–76.

31 McDermott MK, Posillico DB. Nutritional support and neurotrauma: a critical review of early nutrition in forty-five acute head injury patients. *Neurosurgery* 1986; **19:** 367–73.

32 Borzotta AP, Pennings J, Papasadero B, et al. Enteral versus parenteral nutrition after closed head injury. *J Trauma* 1994; **37:** 459–68.

33 Suchner U, Senftleben U, Eckart T, et al. Enteral versus parenteral nutrition: Effects on gastrointestinal function and metabolism. *Nutrition* 1996; **12:** 13–22.

34 Borzotta AP, Osborne A, Bledsoe F, et al. Enteral nutritional support enhances cognitive recovery after severe closed head injury. *Surg Forum* 1993; **44:** 29–31.

35 Herndon DN, Stein MD, Rutan TC, Abston S, Linares H. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma* 1987; **27:** 195–204.

36 Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemented feeding in severely burned patients. *J Burn Care Rehabil* 1989; **10:** 309–13.

37 Detsky AS, Baker JP, O'Rourke K, Goel V. Perioperative parenteral nutrition: a meta-analysis. *Ann Intern Med* 1987; **107:** 195–203.

38 American College of Physicians. Perioperative nutritional support. *Ann Intern Med* 1987; **107:** 252–53.

39 Muller JM, Brenner U, Dienst C, Pichlmaier H. Preoperative parenteral feeding in patients with gastrointestinal carcinoma. *Lancet* 1982; **1:** 68–71.

40 Sako K, Lore JM, Kaufman S, Razack MS, Bakamjian V, Reese P. Parenteral hyperalimentation in surgical patients with head and neck cancer: a randomized study. *J Surg Oncol* 1981; **16:** 391–402.

41 Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicenter trial. *Lancet* 2001; **358:** 1487–92.

42 Reynolds JV, Kanwar S, Welsh FKS, et al. Does the route of feeding modify gut barrier function and clinical outcome in patients after major upper gastrointestinal surgery. *JPEN J Parenter Enteral Nutr* 1997; **21:** 196–201.

43 Bower RH, Talamini MA, Sax HC, Hamilton F, Fischer JEF. Postoperative enteral *vs* parenteral nutrition. *Arch Surg* 1986; **121:** 1040–45.

44 Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomized pilot study. *Eur J Surg* 1997; **163:** 761–66.

45 Sandstrom R, Drott C, Hyltander A, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993; **217:** 185–95.

46 Shirabe K, Matsumata T, Shimada M, et al. A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection: the results of a randomized prospective study. *Hepatogastroenterology* 1997; **44:** 205–09.

47 Iovinelli G, Marsili I, Varrassi G. Nutrition support after total laryngectomy. *JPEN J Parenter Enteral Nutr* 1993; **17:** 445–48.

48 Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, DiCarlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med* 2001; **29:** 242–48.

49 Brennan MF, Pisters PWT, Posner M, Quessada O, Shike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for maliganancy. *Ann Surg* 1994; **220:** 436–44.

50 Gianotti L, Braga M, Vignali A, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* 1997; **132:** 1222–29.

51 Fan ST, Lo CM, Lai ECS, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med* 1994; **331:** 1547–52.

52 Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; **325:** 525–32.

53 Eisenberg JM, Glick HA, Buzby GP, Kinosian B, Williford WO. Does perioperative total parenteral nutrition reduce medical costs? *JPEN J Parenter Enteral Nutr* 1993; **17:** 201–09.

54 Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM. Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. *Surgery* 1988; **104:** 727–33.

55 Klein S, Simes J, Blackburn GL. Total parenteral nutrition and cancer clinical trials. *Cancer* 1986; **58:** 1378–86.

56 American College of Physicians. Parenteral nutrition in patients receiving cancer chemotherapy. *Ann Intern Med* 1989; **110:** 734–36.

57 McGeer AJ, Detsky AS, O'Rourke KD. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. *Nutrition* 1990; **6:** 233–40.

58 Koretz RL. Parenteral nutrition: is it oncologically logical? *J Clin Oncol* 1984; **2:** 534–538.

59 Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ* 2004; **328:** 1407–13.

60 McClave SA. Defining the new gold standard for nutrition support in acute pancreatitis. *Nutr Clin Pract* 2004; **19:** 1–4.

61 Kaushik N, O'Keefe SJD. Severe acute pancreatitis: Nutritional management in the ICU. *Nutr Clin Pract* 2004; **19:** 25–30.

62 ASPEN board of directors and the clinical guidelines task force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr* 2002; **26** (suppl 1): 68SA–70SA.

63 Zaloga GP. Timing and route of nutritional support. In: Zaloga GP, ed. Nutrition in critical care. St Louis, MO, USA: Mosby, 1994: 313–15.

64 Greenberg GR, Fleming CR, Jeejeebhoy KN, Rosenberg IH, Sales D, Tremaine WJ. Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. *Gut* 1988; **29:** 1309–15.

65 Wright RA, Adler EC. Peripheral parenteral nutrition is no better than enteral nutrition in acute exacerbation of Crohn's disease: a prospective study. *J Clin Gastroenterol* 1990; **12:** 396–99.

66 Jones VA. Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. *Dig Dis Sci* 1987; **32** (suppl 12): 100S–07S.

67 Cravo M, Camilo ME, Correia JP. Nutritional support in Crohn's disease: which route? *Am J Gastroenterol* 1991; **86:** 317–21.

68 Gonzalez-Huix F, Fernandez-Banares F, Esteve-Comas M, et al. Enteral *vs* parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993; **88:** 227–32.

69 Dickinson RJ, Ashton MG, Axon ATR, Smith RC, Yeung CK, Hill GL. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjuvant to the routine therapy of acute colitis. *Gastroenterology* 1980; **79:** 1199–204.




www.manaraa.com

70 McIntyre PB, Powell-Tuck J, Wood SR, et al. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986; **27:** 481–85.

71 Abad-Lacruz A, Gonzalez-Huix F, Esteve M, et al. Liver function tests abnormalities in patients with inflammatory bowel disease receiving artificial nutrition: a prospective randomized study of total enteral nutrition *vs* total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1990; **14:** 618–21.

72 Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient. *JAMA* 1998; **280:** 2013–19.

73 Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, and the Canadian critical care clinical practice guidelines committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003; **27:** 355–73.

74 Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr* 2001; **74:** 534–42.

75 Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004; **20:** 843–48.

76 Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Crit Care Med* 2005; **33:** 213–20.

77 Simpson F, Doig GS. Parenteral *vs* enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med* 2005; **31:** 12–23.

78 Weisdorf SA, Lysne J, Wind D, et al. Positive effect of prophylactic total parenteral nutrition on long-term outcome of bone marrow transplantation. *Transplantation* 1987; **43:** 833–38.

79 Szeluga DJ, Stuart RK, Brookmeyer R, Utermohlen V, Santos GW. Nutritional support of bone marrow transplant recipients: a prospective randomized clinical trial comparing total parenteral nutrition to an enteral feeding program. *Cancer Res* 1987; **47:** 3309–16.

80 Cetin T, Arpaci F, Dere Y, et al. Total parenteral nutrition delays platelet engraftment in patients who undergo autologous hematopoietic stem cell transplantation. *Nutrition* 2002; **18:** 599–603.

81 Wicks C, Somasundaram S, Bjarnason I, et al. Comparison of enteral feeding and total parenteral nutrition after liver transplantation. *Lancet* 1994; **344:** 837–40.

82 Naylor CD, O'Rourke K, Detsky A, Baker JP. Parenteral nutrition with branched chain amino acids in hepatic encephalopathy. *Gastroenterology* 1989; **97:** 1033–42.

83 Naylor CD, Detsky AS, O'Rourke K, Fonberg E. Does treatment with essential amino acids and hypertonic glucose improve survival in acute renal failure? A meta-analysis. *Ren Fail* 1987; **10:** 141–52.

84 Dunham CM, Frankenfield D, Belzberg H, Wiles C, Cushing B, Grant Z. Gut failure: predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994; **37:** 30–34.

85 Chiarelli AG, Ferrarello S, Piccioli A, et al. Total enteral nutrition versus mixed enteral and parenteral nutrition in patients in an intensive care unit. *Minerva Anestesiol* 1996; **62:** 1–7.

86 Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in critically ill. *Intensive Care Med* 2000; **26:** 893–900.

87 Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. *Intensive Care Med* 2004; **30:** 1666–71.

88 Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; **13:** 295–302.

89 Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone-marrow transplantation: a randomized double blind controlled study. *Ann Intern Med* 1992; **116:** 821–28.

90 Wischmeyer P, Lynch J, Leidel J, et al. Glutamine administration reduces gram-negative bacteremia in severely burned patients: a prospective randomized double blind trial versus isonitrogenous control. *Crit Care Med* 2001; **29:** 2075–80.

91 Powell-Tuck J, Jamieson CP, Bettany GEA, et al. A double blind randomized controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999; **45:** 82–88.

92 Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves six month outcome in critically ill patients. *Crit Care Med* 2002; **30:** 2032–37.

93 Novak F, Heyland D, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* 2002; **30:** 2022–29.

94 McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications. A randomized clinical trial. *Crit Care Med* 2000; **28:** 3606–11.

95 Basttistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* 1997; **43:** 52–60.




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