# Enteral vs. Parenteral Nutrition for Acute Pancreatitis

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## ABSTRACT

*Acute pancreatitis is a destructive inflammatory disease that can lead to the systemic inflammatory response syndrome (SIRS), multi-organ failure, and death. The mainstay of treatment has always been aggressive supportive care with bowel rest, based on the premise that ongoing stimulation of pancreatic output is dangerous. But though total parenteral nutrition (TPN) has been used to provide nutrition in severe cases, there is now a substantial body of evidence that – as in other forms of critical illness – it increases the risk of infection. This consequence seems related to the important effects of gut-associated lymphoid tissue on stimulation of a severe inflammatory response. Despite long-standing assumptions that have governed the management of acute pancreatitis, enteral nutrition (EN), given early in the course of severe pancreatitis, can actually reverse the pro-inflammatory effects of pancreatitis on neutrophils and gut-associated lymphoid tissue. Multiple studies now demonstrate improved outcomes with EN compared with TPN.*

## INTRODUCTION

Acute pancreatitis is a destructive disease process mediated by the release of numerous pro-inflammatory molecules that can lead to variable destruction of part or all of the pancreas, and to widespread organ failure. The traditional mainstay of therapy has always been supportive care while withholding nutrients to provide time for the pancreas to "rest" and to stop secreting proteolytic enzymes. In severe cases of pancreatitis, intravenous alimentation has been used to support patients either early or late in the disease process with variable results. However, concerns about its effectiveness and safety have grown, leading to a major shift in attitude toward feeding patients with even the most severe forms of acute pancreatitis. A growing number of randomized controlled trials have validated the use of early EN in severe acute pancreatitis – not only as a nutritional tool, but as a treatment that blunts the severity of the inflammatory injury.

## PATHOGENESIS OF ACUTE PANCREATITIS

Acute pancreatitis needs to be understood in the context of an inflammatory disorder. Pancreatic injury occurs when pro-inflammatory influences overwhelm normal protective mechanisms that are actually designed to prevent a widespread inflammatory cascade. When the inflammatory process gets under way, it can eventually progress from local injury of acinar cells to autodigestion of the pancreas. Other factors causing pancreatic damage include microcirculatory injury, oxidative stress, neutrophil attraction, and bacterial translocation. If these processes are not contained, the systemic inflammatory response caused by pro-inflammatory cytokines leads to multi-system organ failure and – depending upon its severity – even death. Exciting recent work has identified the gut as an immunologically active organ that can influence the nature of the response to injury, thus serving as a potential treatment target for a disease process that has traditionally been managed by supportive care only.

Regardless of the initiating condition (gallstone, alcohol, high triglycerides, medications), there is a final common pathway of injury leading to premature activation of trypsinogen in acute pancreatitis. Excessive amounts of trypsin cannot be removed in the usual fashion. Trypsin in turn activates precursors of potentially destructive enzymes including elastase, phospholipase A2, and carboxypeptidase, which leads to the process known as autodigestion of the pancreas or "autophagia." Intracellular injury leads to generation of multiple pro-inflammatory cytokines such as IL-1b, IL-17, and TNF alpha. Depending on the intensity of this response, microcirculatory changes including vasoconstriction, ischemia, and possible reperfusion injury within the body of the pancreas can lead to IL-6 release, decreased levels of anti-inflammatory cytokines (IL-4, IL-10)[1] and further generation of cytokines which – if they are released into the systemic circulation – lead to a secondary inflammatory response.

Once a plethora of cytokines are released into the systemic circulation, the so-called "second hit" inflammatory response occurs about 48 hours into the illness. This sequence leads to cellular injury in the lung and gastrointestinal tract, followed by acute respiratory distress syndrome, possible renal dysfunction, gastrointestinal

## TABLE 1. SIRS (SYSTEMIC INFLAMMATORY RESPONSE SYNDROME).

| Temp | >38 or <36 |
|---|---|
| Heart rate | >90 beats/min |
| Respiratory rate | >20/min |
| WBC | >12,000 or <4000, or >10% band forms |

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ischemia with resultant bacterial translocation, and the systemic inflammatory response syndrome (see Table 1). The severity of this cascade-like process determines the severity of acute pancreatitis, and portends higher mortality rates in association with pancreatic necrosis.

The events in the gastrointestinal tract are pertinent to the following discussion. Hypovolemia leads to microcirculatory changes implicated in the development of pancreatic necrosis, and probably causes at least focal ischemia in the GI tract. As a matter of fact, intestinal ischemia in association with acute pancreatitis has caused gangrene and perforation.[2] Bacterial translocation has a prevalence of 15% in elective surgical patients, and there is evidence linking it to septic complications.[3] This phenomenon has been proven in rodent models using electron microscopy to visualize various gram negative bacteria within intestinal epithelial cells.[4] Bacterial translocation has been indirectly established in humans by comparing nasogastric aspirates in 279 surgical patients to cultures from mesenteric lymph nodes taken at laparotomy.[5]

### THE ROLE OF GASTROINTESTINAL IMMUNITY
Until relatively recently, the role of the gastrointestinal tract as a mediator of inflammation was not really recognized. However, studies dating back to the late 1980's have shown that the gut of animals becomes more permeable after short periods of bowel rest.[3,4,5] These observations led to further studies implicating gut-associated lymphoid tissue (GALT) as a dynamic organ mediating an inflammatory process associated with critical illness, whether it be in patients with burns, trauma, or sepsis, or patients requiring intensive care for other reasons. Changes in neutrophil (PMN) function, antigen processing, and cytokine expression occur during critical illness and subsequent bowel rest. This process has been summarized by Kudsk.[6] Injury leads to increased expression of vascular adhesion molecules

Figure 1. The common mucosal immune hypothesis: naive T and B cells migrate into the Peyer's patches (PP) via modified MAdCAM-1 located on the high endothelial venules. After sensitization within the PP, they are directed into the thoracic duct via mesenteric lymph nodes (MLN) and into the blood stream for distribution for to the gut-associated lymphoid tissue (GALT) and extraintestinal sites such as the mammary glands and genitourinary tract where they produce specific IgA to bind the antigen. They also migrate through the nasal-associated lymphoid tissue (NALT) in rodent species, migrate to cervical lymph nodes (CLN) and are delivered via the blood stream as well. Peripheral lymph node addressin (PNa-D) directs these cells into effector sites within the nasal passages. Unmodified MAdCAM-1 is found throughout the body. ("Effect of route and type of nutrition on intestine-derived inflammatory responses." Kudsk KA – Am J Surg – 01-JAN-2003;185(1):16–21) Copyright permission granted by Elsevier.
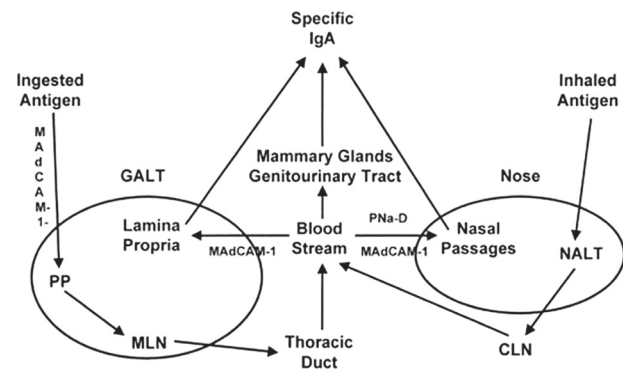


(P selectin, E selectin, I-Cam 1) which attract and "prime" PMNs. ("Priming" refers to augmentation of the inflammatory response which results in a greater degree of tissue injury. The gut is a major site for priming of PMNs.) If the patient survives the initial insult, these primed PMNs are distributed to hepatic and lung tissue where they can elicit an augmented inflammatory response to a subsequent stimulus (2nd hit).

In addition, the Peyer's Patches of the small intestine serve as the primary site for B and T cell sensitization followed by development of specific IGA antibodies for distribution to lymphoid tissue in the gut, lung, and other lymphoid areas. This process is now known as the "common mucosal hypothesis" and is summarized in Figure 1. Cytokines produced by these cells include both the Th2 IgA-stimulating types (Il-4, IL-5, IL-6, IL-10) and the Th1 IgA-inhibiting types (IFNγ, TNF β, and IL-2). These two types ordinarily counterbalance one another, but critical illness with subsequent bowel rest has pro-inflammatory effects on this process which are reversed when enteral nutrition is resumed.

### The Effect of Nutrition on Immunology of the Gut
Bowel rest in critically ill patients initiates immediate adverse effects and stimulates inflammation at the gut

level. Early studies in rats fed parenterally show a reduction in lymphocyte cell numbers in GALT and decreases in the CD4/CD8 ratios in the lamina propria after just 3 days of bowel rest. After 5 days of parenteral feeding, levels of IFNγ, IL-5, and IL-6 remain stable, but levels of IL-4 and IL-6 drop along with intestinal IgA levels.[7] Animal models have shown that the above changes functionally impair the animal's ability to fight off infection, and this ability returns when enteral feeding is restored.[6,8] In sum, the adverse effects of parenteral nutrition on function of GALT and the deleterious priming of PMNs are reversed with enteral feeding in the rodent model.

### The Benefits of Enteral Nutrition in Critically Ill Patients
It is now clear that early enteral nutrition in critically ill humans (burns, trauma, severe pancreatitis, mechanical ventilation, etc.) can change clinical outcomes. A meta-analysis by Marik and Zaloga of six studies in acute pancreatitis confirms a significantly lower risk of infection and surgical intervention, and a reduced hospital length of stay, with enteral nutrition compared with parenteral nutrition.[9] Canadian Clinical Practice guidelines published in 2003 recommend starting enteral nutrition within 24 to 48 hrs of arrival to an ICU in all mechanically ventilated patients based on a meta-analysis that included 370 critically ill patients from 12 randomized controlled trials.[10]

### TRADITIONAL MANAGEMENT OF ACUTE PANCREATITIS
In any single institution, the large majority of patients with pancreatitis have mild to moderate forms of the disease. Unfortunately severe pancreatitis is a devastating illness that often leads to multiple organ failure, sepsis, and death. Mortality rates ranging from 19% to 30% may occur for severe pancreatitis alone, and once necrosis involves more than half of the gland, mortality can approach 50%.

The mainstay of therapy has always been aggressive supportive care. To date, no pharmacologic therapy has been proven to attenuate the inflammatory cascade and lead to improved outcomes in acute necrotizing pancreatitis. Conventional management focuses on aggressive hydration to prevent ischemia and perhaps necrosis of the pancreas itself, mechanical ventilation if necessary when ARDS develops, and gut "rest" with or without TPN depending on the severity of the illness. It is now well established that nutritional therapy is not necessary for mild to moderate pancreatitis that resolves without any specific therapy. These patients can usually resume oral intake in 3 to 5 days.

Conventional wisdom suggests that rest of the gut is essential because the pancreas continues to secrete its digestive enzymes during all three phases of digestion – cephalic, gastric and intestinal – though differing concentrations of bicarbonate and enzymes are released in each phase. Secretion occurs when liquids or food are administered at any level of the gut, but the intestinal phase, mediated by cholecystokinin, has the most potent effect on pancreatic secretion. Fat has the greatest effect on pancreatic secretion and carbohydrates have the least. Less stimulation of pancreatic output occurs when nutrients are infused below the ligament of Treitz, as opposed to infusions into the stomach or duodenum, and infusions 40 to 60 cm down the jejunum do not stimulate the pancreas at all. This is due to the so-called *ileal brake* mechanism, which refers to a decrease in gastric and intestinal motility in response to nutrients in the ileum, likely due to the release of peptide YY from the ileal mucosa.

### The Problem with TPN
Severe forms of pancreatitis are associated with a variable increase in energy expenditure at rest, which mostly depends on whether sepsis supervenes.[11] Negative nitrogen balance has been linked to higher mortality rates in pancreatitis, as with other forms of critical illness. Ever since it was first introduced, TPN has been advocated as the proper form of nutrition for severe acute pancreatitis since it does not stimulate pancreatic secretion to any significant degree. However, the negative nitrogen balance seen in highly catabolic forms of critical illness including pancreatitis is not overcome even by full nutritional support. In a 1987 study by Sax, 54 patients with relatively mild pancreatitis were randomized to receive early TPN (within 24 hrs.) or no nutritional support. The decrease in amylase, improvement in nitrogen balance, and time to oral intake did not differ significantly with either regimen. This study showed that at least in mild to moderate pancreatitis, TPN provided no benefit.[12] Furthermore, studies from as early as the 1970's pointed to increases in catheter related infection rates with the use of TPN for acute pancreatitis.[13,14]

### TPN vs EN
There are now multiple studies that compare parenteral to enteral nutrition for severe acute pancreatitis. In 1997, McClave assigned 30 patients with mild pancreatitis (mean Ranson score* of 1.35) to jejunal feeding or parenteral nutrition. There were no deaths and no differences between serial pain scores, days to normalization of amylase, days to diet by mouth, or rates of nosocomial infection between

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*A set of criteria for predicting outcomes, in which a score of 5 or greater is associated with a mortality of 50%.

the 2 groups.[15] These findings established jejunal feeding as being safe and considerably less costly than TPN. Following this study, Nakad used jejunal feedings in 20 patients who had more severe pancreatitis based on Ranson's criteria (mean score 3.57) and Apache II scores (mean score 7.62). None of these patients required surgery, however, and only two were possibly septic, which suggests that these patients were not so severe by more recent clinical standards. Once again, after jejunal feedings were initiated no significant increases were seen in amylase, C-reactive protein levels, or white blood cell counts.[16] In 2002, Abou-Assi et al. more accurately stratified a group of patients with more severe pancreatitis by randomizing only those who were not improving after 48 hrs. in the hospital to receive either jejunal feeding or TPN. Those who were fed enterally needed nutritional support for 6.7 days compared with 10.8 days in the TPN group. Although the quantity of nutrients was significantly lower in the enterally fed group, there were significantly lower rates of metabolic and septic complications. Since the duration of feeding was less, there were cost savings of over $2,300 in the enterally fed group.

Attempts to assess the severity of the acute inflammatory phase have also been measured in randomized controlled trials. Windsor et al. randomized 34 consecutive patients to jejunal feedings or TPN and measured C-reactive protein levels, serum IgM endoCab antibodies (indicative of increased gut permeability), antioxidant capacity, and the incidence of SIRS, sepsis, and multiple organ failure (MOF). CRP levels fell from 156 mg/l to 84 mg/l after 7 days of jejunal nutrition but did not change in the TPN group (p < .0001). Apache II scores dropped below 8 in the EN group, but not in the TPN group. A significant rise in the IgM antibody was seen in the TPN group but there was no change in the group getting EN. Furthermore, 5 patients in the TPN group spent 10 days in intensive care compared to none in the EN group.[17]

Two separate meta-analyses of the higher quality randomized controlled trials that compared these forms of nutrition show significant reductions in infection rates, hospital length of stay, cost per patient, organ failure, and need for surgical intervention when enteral nutrition was used early during the course of pancreatitis.[18,19] Seven randomized controlled trials that compared enteral to parenteral nutrition were analyzed by McClave et al., based on a review of the Medline, Cochran, and Embase databases from 1966 to 2005. These trials included 291 patients randomized to receive EN or TPN within 48 to 96 hrs of admission. No differences in mortality were noted when combining the data from all 7 studies, but there was a 54% reduction in infectious complications when EN was used, and a trend toward decreased organ failure. As a result of these findings, enteral nutrition is now mentioned in the latest edition of the Sleisinger and Fordtran's gastrointestinal text as a treatment alternative for severe acute pancreatitis.

## Nasogastric versus Nasojejunal Feeding for Acute Pancreatitis

It was initially assumed that EN should be given below the ligament of Treitz due to the physiology of pancreatic secretion discussed previously. This requirement has caused considerable difficulty in some circumstances due to ileus, duodenal compression, and technical difficulty inherent in the placement of the feeding tubes. The literature contains descriptions of worsening pancreatitis related to migration of the tube back into the stomach, and we have seen this in our experience also. Fortunately, the rise in amylase or fever associated with this event is readily correctable when the tube is advanced back into the proper position. Other than a delay in recovery, to my knowledge no serious complications related to this occurrence have been described.

Despite all of these considerations, many patients with severe acute pancreatitis can tolerate early naso-gastric feeding without a worsening of their pancreatitis, and thus reap the benefits of post-pyloric feeding even when that is difficult to accomplish. This has been shown in a well designed study by Eatock et al. in Scotland.[20] Fifty consecutive patients with Apache II scores of 6 or higher and CRP in excess of 150 were randomized to naso-gastric (NG) or naso-jejunal (NJ) feedings. No differences in mortality or intensive care unit time were seen between the two groups. These patients were truly severe as there were 12 fatalities (5 in the NG group and 7 in the NJ group), mostly the result of multi-organ failure. Furthermore, no differences were seen in the total amount of calories given, incidence of diarrhea, or length of stay. Pain scores, CRP levels, and analgesia requirements fell similarly. It is important to note that the tube feeding formula used in this study was a low fat semi-elemental feed that is not available in the USA.

In our experience at LGH, patients with severe pancreatitis in the ICU have been fed with Peptamen® through tubes placed into the duodenum proximal to the ligament of Treitz. Our patients continued to improve all clinical parameters without experiencing a worsening of their pancreatitis.

## Methods of tube placement

Early enteral feeding is now practiced at our institution in many cases. Naso-jejunal tubes can be placed blindly,

or with endoscopic or radiologic guidance. Some institutions insert PEG-J tubes early in the course of severe pancreatitis. Another option is insertion of a naso-enteric tube over a previously placed wire. The author has done so using a thin channel nasal endoscope in critically patients (including a ventilated patient) with minimal or no sedation. (Gastroenterologists who perform upper GI endoscopy can teach themselves this technique relatively quickly, and there is literature to support this approach.[21]) However, our nutrition team has had great success in the trauma-neuro unit with a self propelled naso-jejunal tube (Tiger tube™, Cook Medical, Bloomington, In). Self-propelled tubes can reach the jejunum effectively in most instances when placed early in the course of pancreatitis. Early placement may be essential since prolonged ileus may predict failure of enteral nutrition.[22]

## CONCLUSION

As with other forms of critical illness, early enteral feeding can lead to improved outcomes and decreased risk of infection in cases of life-threatening acute pancreatitis. It is likely that enteral feeding attenuates bacterial translocation and can blunt the systemic inflammatory response even when hypocaloric amounts of formula are given. With close observation, many patients can be given the chosen nutritional supplement together with an elemental formula via a nasogastric tube. There will be some patients who will not tolerate gastric feeding, and may not be able to receive EN due to severe illness or failure to insert a small bowel tube. TPN should be avoided whenever possible, or – when enteral feeding is not possible – TPN should be given later in the course of acute pancreatitis, after the initial inflammatory injury begins to resolve.

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