

Hypocaloric Jejunal Feeding Is Better Than Total Parenteral Nutrition in Acute Pancreatitis: Results of a Randomized Comparative Study

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OBJECTIVES: The aims of this study were to define the indications for, and to evaluate the cost-effectiveness of, nutritional support in patients with acute pancreatitis.

METHODS: All admissions during the 12-month period from January through December 2000, were entered into a common management protocol consisting of an initial 48-h fast with *i.v.* fluids and analgesics. After 48 h, those patients who were improving were restarted on oral feeding (group O). The remaining patients were randomized to receive nasogastric (group EN) or parenteral feeding (group TPN). The randomization study was continued until 50 patients had been accrued. Outcomes in the three groups were compared with respect to length of hospital stay, duration of feeding, complications, and hospital costs.

RESULTS: A total of 156 admissions were evaluated in the first 12 months. Of these, 87% patients had mild disease, 10% moderate, and 3% severe; 62% were related to alcohol abuse, 18% gallstones, and 8% idiosyncratic drug reactions. Of the patients, 75% improved on 48 h bowel rest and *i.v.* fluids, and were discharged within 4 days. The remainder were randomized to jejunal elemental ($n = 26$) or parenteral ($n = 27$) feeding. Duration of feeding was shorter with EN (6.7 vs 10.8 days, $p < 0.05$) and nutrition costs were lower, representing an average cost saving of \$2362.00 per patient fed. EN was less effective in meeting estimated nutritional requirements (54 vs 88%, $p < 0.0001$), but metabolic ($p < 0.003$) and septic complications ($p = 0.01$) were lower. Subgroup analysis of patients with severe disease showed similar findings.

CONCLUSION: Despite concerns that metabolic expenditure is increased and that food-stimulated pancreatic secretion might exacerbate the disease process, hypocaloric enteral feeding seems to be safer and less expensive than parenteral feeding and bowel rest in patients with acute pancreatitis. (Am J Gastroenterol 2002;97:2255–2262. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Acute pancreatitis results from the premature activation of proteolytic digestive enzymes within the pancreatic acinar cells, resulting in autodigestion and a severe local and systemic cytokine-generated inflammatory response (1, 2). Measurement of metabolic expenditure by indirect calorimetry (3) and protein catabolism by urinary nitrogen excretion (4) has shown that nutritional requirements are considerably elevated. As nutritional depletion can be expected to impair recovery and to increase the risk of complications, nutritional support is an essential part of management. However, oral feeding stimulates the production of new pancreatic enzymes and may, therefore, exacerbate autodigestion and the disease process. Because of these concerns, conventional management has been to place patients on strict bowel rest and use intravenous feeding, or total parenteral nutrition (TPN) to bypass the stimulatory effects of oral feeding until the serum enzymes normalize.

Unfortunately, TPN has its problems. Although it is very effective in maintaining nutrition in almost any critically ill patient, it can cause serious complications: in particular, catheter sepsis and hyperglycemia. This is a major concern, as patients with acute pancreatitis are prone to sepsis, and sepsis adds substantially to the risk of death (5). Second, hyperglycemia is common because of the concomitant pancreatic endocrine damage (6). A further concern is that bowel rest may potentiate the cytokine response and thereby the systemic inflammatory response (7).

These concerns have led to the search for a safer alternative method of feeding. Results of canine studies indicate that elemental dietary formulae, *i.e.*, ones that are predigested, consisting of simple sugars and amino acids, have little stimulatory effect on the pancreas (8). Furthermore, studies in animals (9) and, more recently, in humans (10) have demonstrated that the stimulatory effect of nutrients is minimized if the diet is infused distally in the jejunum. Encouraged by these observations, a number of groups have recently performed comparative studies between TPN and jejunal feeding (11–14). Although the study designs varied,

a common finding was that enteral feeding did not seem to exacerbate the disease. Furthermore enteral feeding was one fifth the cost, and septic and metabolic complications were, as anticipated, less common. In an analysis of the nutritional costs associated with the management of acute pancreatitis, we found that for the year 1998, \$291,110.00 was spent on TPN in comparison to only \$2,981.00 on enteral feeding (15). The difference was explained not only by the lower cost of enteral feeds, but also by the fact that TPN was the favored technique for interventional feeding of pancreatitis patients at our hospital.

One factor that has been overlooked is the fact that most cases of acute pancreatitis are mild and self-limiting, with serum enzyme levels returning toward normal within 2–4 days. Because pre-existing severe malnutrition is uncommon in these patients, nutrient stores should be sufficient to cover the acute period without the need for nutritional support. Consequently, it is possible that interventional nutrition is being overused in practice.

With these considerations in mind, we performed the following prospective evaluation of outcomes for all patients admitted to our institution during a 12-month period. To standardize management, we developed a protocol whereby nutritional support was only used if patients had not improved by 48 h and were unable to tolerate resumption of normal feeding.

MATERIALS AND METHODS

Nutritional Management Protocol

The protocol was first submitted to the Institution Review Board for approval. For the first 12 months, the study was applied to all patients admitted to our institution with the diagnosis of acute pancreatitis. Then for the 3 months afterward, the data collection was limited to only those patients with acute pancreatitis who were in need of nutritional support. All patients admitted with acute abdominal pain and 3-fold elevation of serum pancreatic enzymes, amylase, and lipase, with a primary diagnosis of acute pancreatitis, were entered into the study. For 48 h, these patients were kept nil per os and given intravenous fluids and electrolytes in addition to analgesics. Patients with an alcoholic etiology were also given a “goody-bag” containing 5% glucose, a multivitamin preparation, folic acid, and thiamin. At the end of this period, their condition was reassessed, with particular attention to signs, symptoms, and serum enzyme levels. Those patients who showed improvement were restarted on a trial of a soft oral diet (group O). If tolerance was good, they were advanced to a normal diet, and if this was also tolerated they were discharged home. Patients who failed to show improvement were graded by Ranson’s criteria (16) to gauge disease severity and prognosis, and then were commenced on nutritional support in the form of either TPN and bowel rest (group PN) or jejunal elemental feeding (group EN). Informed, signed consent was obtained from randomized participants, or next-of-kin for ICU patients. TPN was

delivered via central vein catheters in patients in the ICUs and by peripheral catheter in floor patients. Jejunal tubes (“Silk,” Corpak, Wheeling, IL; “Stay-Put,” Novartis, St. Louis Park, MN; or “Dobhoff,” Kendall HealthCare, Mansfield, MA) were placed by fluoroscopy or endoscopy. Goal feeding rates were the provision of 1.5 g protein/kg/day and 25–30 kcal energy/kg/day. With TPN, electrolytes were first corrected before full nutritional infusions were given, whereas tube feeding was commenced at 20 ml/h and increased progressively to goal rates over 48 h.

Patients were monitored and reassessed each day by clinical examination and blood tests. Patients receiving tube feeding were assessed for tube tolerance, high residual volumes, exacerbation of abdominal pain, and diarrhea. Fevers were investigated by culture of blood and appropriate bodily fluids. Fluctuations in blood sugar were monitored by capillary blood testing every 6 h and controlled with *s.c.* injections of insulin (on a sliding scale). After initial assessment of insulin requirements, insulin was added directly to the TPN solution. In patients with severe disease, spiral CT examinations were performed to detect necrosis and possible abscess formation.

Weaning from nutritional support was attempted when abdominal pain and distention had settled and enzyme elevations had consistently decreased toward normal levels over 3 days. Oral liquids were first reintroduced and, if tolerated, were advanced to soft and then to solid oral feeding, with suspension of nutritional support.

Main Outcome Measures

The efficacy of management was determined by measurement of duration of hospitalization, duration of interventional (enteral or parenteral) feeding. This also provided a measure of the rate of resolution of disease, the incidence of nutrition-associated complications (*i.e.*, hyperglycemia needing insulin for control and catheter-related sepsis and septicemia), and tolerance to recommencement of oral feeding. Tolerance was measured by the absence of nausea, vomiting, and recurrent abdominal pain. Finally, a cost-effectiveness analysis was performed that related nutritional costs to total hospitalization costs and duration of feeding, and to the incidence of nutrition associated complications.

Statistical Analysis

Based on the results of similar previous studies (11–13), we calculated that we would have more than 80% power to reveal significant differences in nutritional outcome, complications, and costs if 50 patients were randomized. Results are given, unless otherwise stated, in group mean (SE) values. The two nutritional groups were compared on an intention-to-treat basis. Significance of differences in group means for continuous variables were determined using the Student’s *t* test if the data were normally distributed, or the Mann-Whitney nonparametric test if they were not. Differences between group nominal variables were assessed by the χ^2 analysis and Fisher’s exact test.

Table 1. Demographic Details of the Study Population: 1 Yr of Hospital Admissions

Number of patients	156
Age (yr)	46 (1.0)
Sex (female/male)	56/100
Body mass index (kg/m ²)	25.5 (0.6)
Etiology	
Alcohol	96 (61.6%)
Gallstones	28 (18%)
Drug-related	12 (7.7%)
Idiopathic	10 (6.4%)
Hypertriglycerides	3 (2%)
Severity	
Mild (Ranson's <3)	136 (87.3%)
Moderate (Ranson's 3-5)	15 (9.6%)
Severe (Ranson's >5)	5 (3.2%)
Nutrition support	
None	117 (75%)
Enteral	20 (12.8%)
Parenteral	19 (12.2%)

RESULTS

In the 12-month period of observation, 156 admissions for acute pancreatitis were studied (Table 1). The average age of the patients was 46 (range 21–91) years; most were black (71%) and male (64%). Average body mass index was 25.5 kg/m² with 15% being malnourished (*i.e.*, BMI <20) and 18% obese (BMI >30). Mean albumin concentration was 2.9 (0.06) g/L, with 57% of patients presenting with low levels. Identified etiological factors were ethanol toxicity in 62%, gallstones in 18%, drugs in 8%, and hypertriglyceridemia in 2%. The etiology was complicated by HIV infection in 9%. Of the patients, 55% were admitted for their first attack of acute pancreatitis, 24% for a recurrent attack, and 21% with acute or chronic pancreatitis. Sixteen patients were readmitted for disease recurrence during the study period; one patient had two recurrences. Most had mild disease (87% with Ranson's criteria <3), with 6% either presenting or progressing to severe disease (RC >5). A total of 85% were managed on medical and 12% on surgical services; 15% needed ICU management.

Average serum amylase levels were 376 (28) IU/L and lipase 2746 (331) IU/L on admission. CT scans were performed on 68 patients, with 41% showing pancreatic edema, 28% gallstones, 4% biliary sludge, 4% pseudocysts, and 3% necrosis within the parenchyma.

Outcome

Overall average length of stay in hospital was 8 days. In all, 117 patients (75%) settled on 48-h bowel rest (Fig. 1) and therefore did not require nutritional support (*i.e.*, group O), being discharged home by day 4. Of those who did not improve, 19 (12.2%) were randomized to TPN (group TPN) and 20 (12.8%) to jejunal feeding (group EN) during the first 12 months of the study. Subsequently, 14 more patients were randomized in the next 3 months, to reach our goal number of 27 patients on TPN (group TPN) and 26 on jejunal feeding (group EN). Two of the TPN patients de-

Percentages of Admissions in Each of the Three Groups

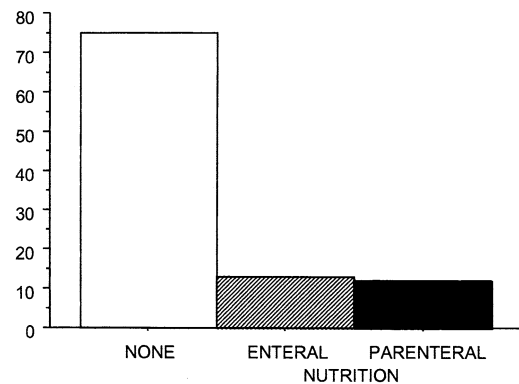


Figure 1. Breakdown of admissions into the following three groups: group O ("none") needed no nutrition support, group EN ("enteral") received jejunal tube feeding, and group PN ("parenteral") received *i.v.* nutrition.

veloped severe sepsis syndrome necessitating conversion to jejunal tube feeding, whereas two enterally fed patients needed emergency abdominal surgery and were subsequently given TPN. Another enterally fed patient had to be converted to TPN because of intolerance to the nasoenteric tube and persistence of abdominal pain.

The average length of stay in hospital was shorter in the EN group (14 vs 18 days) than in the TPN group, but not significantly different ($p = 0.1$).

Readmission analysis demonstrated that early recurrence of the disease within 1 month was unusual, occurring in two patients only. One-year recurrence was 11%. Of the recurrences, 70% could be accounted for by continuing alcohol abuse, and 18% by HIV disease and related therapy.

Influence of Feeding

Table 2 shows the results of the nutritional randomization study. As there were no significant differences in the de-

Table 2. Randomization Trial Between Jejunal (EN) and Parenteral (TPN) Nutrition: Intention-to-Treat Analysis

	EN Group (n = 26)	TPN Group (n = 27)
Age (yr)	48 (3)	50 (3)
Sex (female/male)	10/16	14/13
Ethnicity (black/white/Hispanic)	14/11/1	14/12/1
Body mass index (kg/m ²)	26.6 (1.3)	25.7 (1.6)
Amylase pre (n < 150 U/L)	612 (247)	494 (98)
Amylase post	225 (112)	117 (14)
Lipase pre (n < 300 U/L)	3456 (677)	3057 (811)
Lipase post	810 (155)	829 (135)
Ranson's criteria	3.1 (0.5)	2.5 (0.4)
Duration of nutrition (days)	6.7 (1.1)*	10.8 (1.7)
Hospital stay (days)	14.2 (1.9)	18.4(1.9)

There were no significant differences in age, sex, body mass indices (BMI), hospital stay, and serum pancreatic enzymes on admission (pre) and on restarting normal feeding (post). Group EN had shorter feeding days than TPN group.

* $p = 0.03$.

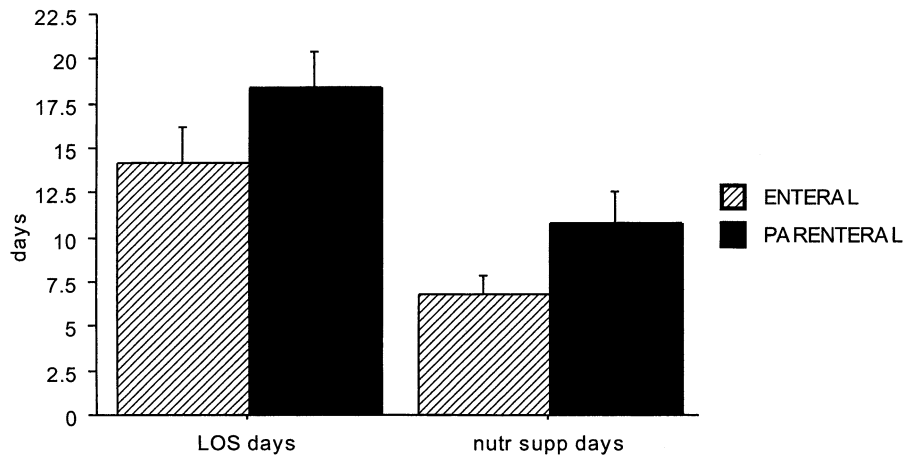


Figure 2. Differences in length of hospitalization and duration of nutritional support in the three study groups. Enterally fed patients spent less time on nutrition support than those fed parenterally ($p < 0.05$, Mann-Whitney test).

mographics or initial serum enzyme levels, these features could not be used to predict the rate of disease resolution

Patients who were fed enterally needed nutritional support for a significantly shorter time than patients fed parenterally (average 6.7 days, range 2–21 days, vs 10.8 days, range 2–43 days; $p = 0.03$) (Fig. 2). Furthermore, the daily quantity of nutrients given to enterally fed patients was also significantly ($p < 0.005$) lower (average 49% of estimated caloric and 42% of protein requirements) than parenterally fed patients, who received 85% of their protein and energy requirements (Fig. 3). After disease resolution, reintroduction of oral feeding was better tolerated in those patients who were randomized to enteral feeding, with 80% advancing to an oral diet without problem, in comparison to 63% in the TPN group. In the patients developing symptoms, oral feeding was held for a further 24 h and then tried again. This time, 90% of both groups tolerated the change without difficulty.

Disease severity was comparable between patients given

enteral or parenteral feeding, with approximately 50% having moderate or severe disease ($RC > 3$). There were no significant differences in the admission or final blood levels of amylase and lipase between the groups given enteral or parenteral nutrition.

Nutrition-associated complications were significantly more common in the TPN-fed patients. Although prefeeding blood glucose levels were similar, median blood glucose concentrations were significantly higher, at 180 (26) versus 138 (22) mg/dl, $p = 0.03$, in patients receiving TPN, as were maximal glucose concentrations, at 325 (26) versus 200 (22) mg/dl. Additionally, hyperglycemia requiring insulin in patients who were not previously diabetics was more common in the TPN group (14 vs four patients, $p = 0.03$). Septic complications were also more common in the TPN group: catheter-related infections necessitating intravenous line removal and antibiotic treatment were detected in nine TPN and only one enteral patient ($p = 0.01$). On the other hand, the incidence of adult respiratory distress syndrome, multi-

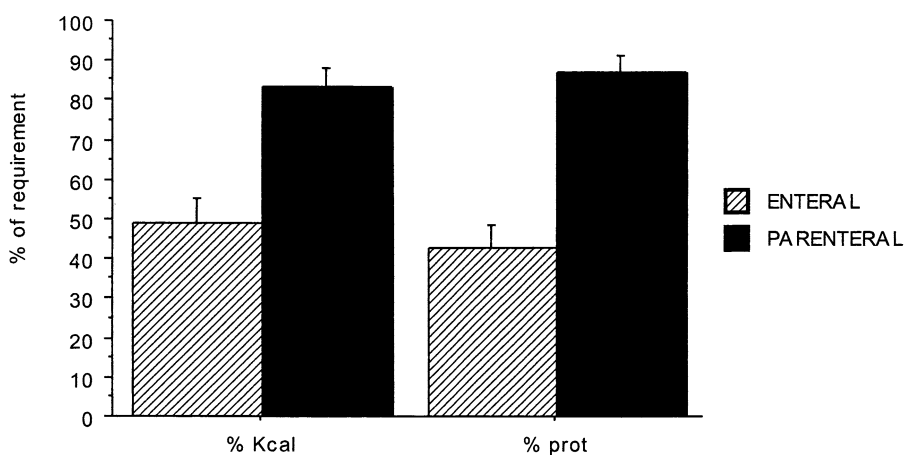


Figure 3. Comparison of the mean (SE) intakes of energy and protein, expressed as percentage of requirements, in patients managed with enteral or parenteral feeding. Intakes of energy and protein ($p < 0.05$) were significantly lower with enteral (jejunal) infusions.

Table 3. Complications in the Nutritional Support Groups

	TPN Group (n = 27)	EN Group (n = 26)
Hyperglycemia	14*	4
Line infection	9†	1
Death	6	8
MOF	8	7
Pancreatic necrosis	3	3
ARDS	5	3
Pseudocyst	1	0

TPN group had significantly more line infections, and hyperglycemia requiring insulin therapy. No differences were seen in regard to adult respiratory distress syndrome, (ARDS), multiple organ failure (MOF), deaths, pancreatic necrosis, and pseudocyst.

* $p = 0.03$.

† $p = 0.01$.

ple organ failure, pancreatic necrosis, pseudocysts, and death was similar in the two groups (Table 3).

Fifteen patients died in hospital, eight of complications associated with acute pancreatitis. Four patients in each nutritional group died of sepsis and multiple organ failure resulting from uncontrollable disease. After resolution of acute pancreatitis, two other patients from the TPN group and four from the EN group died of unrelated causes (cardiac surgery, intracerebral hemorrhage, squamous cell carcinoma of the pharynx, and cancer of the liver). Finally, one 37-yr-old man with end-stage AIDS was admitted with severe acute pancreatitis (five Ranson's criteria). Because his condition was complicated by sepsis, pneumonia and liver failure and because of his extremely poor prognosis, he was given palliative care and was not given interventional feeding. He died 8 days later.

Because of the concern that patients with severe pancreatitis may behave differently, a *post hoc* analysis was made on patients with more than three Ranson's criteria. It can be seen that the pattern of response was similar, with significant faster resolution of the disease process in the EN group (Table 4).

Hospital Costs

The average cost for hospitalization was \$11,183 per patient with acute pancreatitis. There was a strong positive association between severity of disease (as defined by Ranson's

Table 4. Subgroup Analysis of Patients With Ranson's Criteria >3

	EN Group	TPN Group
Number of patients	13	13
Age (yr)	53 (4.3)	55 (4.2)
Body mass index (kg/m ²)	27.5 (1.7)	24.7 (1.9)
Amylase pre (n < 150 U/L)	943.4 (180)	764.6 (169)
Amylase post	355.4 (105)	136.7 (22.8)
Lipase pre (n < 300 U/L)	4282.5 (1223)	4117.6 (1552)
Lipase post	958.1 (262)	863 (220.8)
Ranson's criteria	5.4 (0.5)	4.5 (0.4)
Duration of nutrition (days)	6.8 (1.6)*	12.8 (2.8)
Hospital stay (days)	12.8 (1.6)	20.1 (3.2)

There were no significant differences in age, body mass indices (BMI), Ranson's criteria, hospital stay, and serum pancreatic enzymes on admission (pre) and on restarting normal feeding (post). EN group had shorter feeding days than TPN group.

* $p = 0.03$.

criteria), hospital length of stay, and total hospital costs. For example, the average cost of hospitalization for patients with no Ranson's criteria was \$6,794 with a length of stay 5.7 days, in contrast to \$39,597 and 21.5 days respectively, for patients with four criteria.

In addition, costs were considerably lower for those who improved sufficiently not to need nutritional support, in which case the average cost per stay was only \$4,597. The nutritional costs were minimal (\$18.70) and related to vitamin and mineral supplementation. For the sicker patients needing nutritional support, those given enteral feeding had lower total average hospitalization costs of \$26,464 *versus* \$34,530 per patient, based on intention-to-treat analysis. The significantly lower average nutritional costs in the enteral group of \$394 per patient in comparison to \$2,756 per patient in the parenteral group ($p = 0.0004$; see Fig. 4) could be explained by the combination of the lower daily costs of enteral feeding (\$23.30/day *vs* \$222/day), and the shorter duration of feeding (6.7 *vs* 10.8 days). Consequently, the proportion of hospital costs resulting from enteral feeding was significantly lower than for parenteral feeding (1.8% *vs* 8.4%, $p < 0.0001$).

DISCUSSION

An important practical observation in our analysis was that most patients (75%) who were admitted with acute pancreatitis settled within 48 h if treated with bowel rest, *i.v.* fluids, and analgesics, without the need for specialized feeding. Furthermore, 87% were able to recommence oral feeding within the next 2 days and to be discharged home, despite the fact that although serum enzyme levels had decreased significantly, these levels had rarely returned to normal. Readmission analysis demonstrated that remission was sustained and that early recurrence of the disease was rare.

In addition, our results confirm those of others that jejunal feeding given after 48 h, does not seem to exacerbate the disease, and is safer and cheaper than TPN. Despite the fact that most patients complained of nausea, and some even vomiting, tube feeding in this manner was well tolerated. In comparison to those patients treated with TPN and bowel rest, enterally fed patients had less nutritional support-related complications (*i.e.*, hyperglycemia, catheter sepsis) and required feeding for a shorter time (6.7 *vs* 10.8 days), suggesting faster recovery. Although a number of earlier studies have highlighted the lower complication rates with enteral feeding (11–14, 17), the faster reinstatement of normal feeding is a novel observation and may be explained by the ability of enteral feeding to maintain gut function. A further benefit was a cost saving of \$2362 per patient enterally fed.

The reason for the apparent failure of enteral feeding to exacerbate the disease is unclear. Until recently, standard medical practice has been not only to forbid any form of oral alimentation, but to also apply nasogastric suction to prevent gastric contents from entering the duodenum (18). This

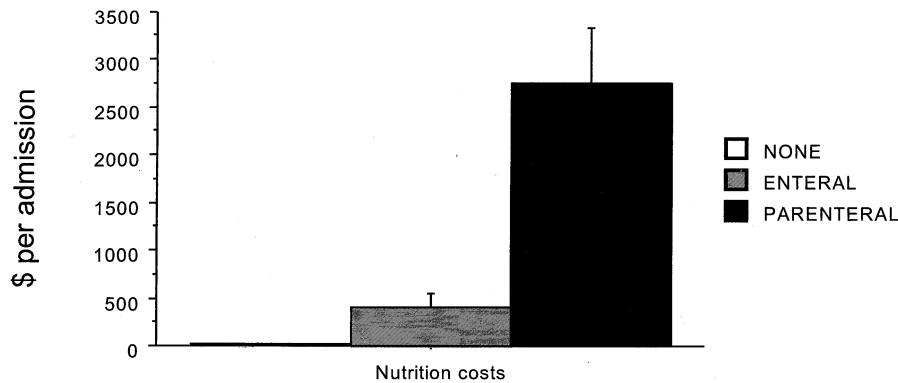


Figure 4. Relative costs for nutritional support in the three groups of patients treated by 48-h fast (group O), enteral tube feeding (group EN), or parenteral feeding (group PN). Parenteral nutrition was significantly more expensive than enteral ($p < 0.0001$).

recommendation was based on substantial experimental evidence that acute disease was a result of preactivation of proteolytic proenzymes within the pancreatic acinar cells (19, 20), which was supported by anecdotal reports of disease relapse after restarting oral feeding. However, the natural history of the disease involves fluctuation in both symptoms and serum enzyme levels, necessitating controlled studies to substantiate cause-and-effect relationships. It is now clear, not only from our study but also from the recent publication of three controlled clinical trials (11–14), that jejunal feeding, in comparison with TPN and bowel rest, neither exacerbates the disease nor prolong its course. McClave *et al.* reported the first well controlled study in 1997 (11). Like us, they noted that jejunal feeding was associated with a lower incidence of metabolic complications and lower costs. Their cost estimates of \$761 for enteral and \$3,294 for parenteral were remarkably similar to ours, despite the fact that they were based on charges to the patient and included tube and line placement. However, these investigators noted no difference in septic complications, number of days of feeding, and length of hospitalization. Part of the explanation may involve the degree of sickness: their mean Ranson's score was only 1.3 (*vs* our score of 3.0), and their average length of feeding was only 5–7 days (*vs* our 7–12 days). Perhaps the best example of the safety of enteral feeding was provided by Kalfarentzos *et al.*, who managed to randomize 40 patients with necrotizing pancreatitis over a 4-yr period to a jejunal peptide formula or TPN (13). Not surprisingly, their patients spent considerably more time in the hospital and on nutrition support, averaging 40 days and 34 days, respectively. Unfortunately, these investigators did not explain how and when they weaned their patients back onto oral feeding. This is important, as some studies have waited for normalization of serum enzyme levels, whereas we often started oral feeding again when levels were still high but symptoms were better. These investigators commented that “no patient developed clinical symptoms or laboratory abnormalities as a result of an adverse effect on the course of the disease.” Based on their finding of less infectious and total complications, they con-

cluded that enteral nutrition should be the preferred method of feeding patients with severe disease.

How can the failure of enteral feeding to exacerbate the disease be explained? One suggestion has been that jejunal feeding with a predigested “elemental” diet avoids pancreatic stimulation by bypassing the cephalic and gastric phases of stimulation. To investigate this possibility, we have recently measured the relative secretory responses in normal healthy volunteers to oral complex diets, duodenal complex and elemental diets, and *i.v.* nutrient infusions. The results have shown that although duodenal elemental diets produced less stimulation than either oral or duodenal complex diets, the secretory response was still 3- to 4-fold higher than the response to *i.v.* feeding (21). A more likely alternative explanation is that the pancreas becomes unresponsive to enteral feeding stimulation during an acute attack of pancreatitis. Results of animal studies have supported this suggestion (22). In addition, we have performed preliminary studies in patients with varying severity of disease that have shown that the secretory response to enteral feeding is suppressed to basal rates (23). This would suggest that any form of oral feeding might be used. However, most patients with severe disease are critically ill with anorexia, gastroparesis, and nausea and vomiting, and the only effective way of maintaining nutrient intake is to use slow, constant jejunal infusions of liquid diets. Although a polymeric formula could be used in patients with milder disease, it seems more rational to use an elemental diet in view of the observed reduction in pancreatic enzyme secretion and therefore digestive capacity.

Enteral feeding has been shown to be more effective than TPN in supporting the rate of resolution in most forms of critical illness (17, 24). There is substantial experimental and clinical evidence that maintenance of enteral nutrition helps to ameliorate the cytokine-generated stress response that characterizes critical illness (7, 13). In the third comparative trial between enteral and parenteral feeding in acute pancreatitis, Windsor *et al.* demonstrated that acute phase response and high serum endotoxin antibody levels noted in TPN-managed patients were suppressed in those enterally

fed (12). It seems likely, therefore, that the benefits of enteral feeding are best explained by its ability to maintain gut function, to prevent bacterial overgrowth as well as endotoxin production and absorption, and, at the same time, to reduce TPN-associated complications.

The results of our investigations provide strong evidence that the implementation of protocolized management, as outlined in the algorithm, will both improve quality of care and reduce hospital costs. Audit of the pattern of hospital costs at our hospital over the past 2 yr has shown that patients with mild disease are now discharged sooner than they were previously. The average length of stay is now only 3.5 days, in comparison to 5.5 days previously, with a consequent reduction in average costs from \$7300 to \$4000, and with no significant change in early readmissions (data provided by MCV Hospital Information Systems). For patients with more severe disease, our greater use of enteral feeding has reduced nutrition costs from 12% to only 1.5% of total hospital costs. Expressed differently, this change has culminated in estimated cost savings of \$2,362.00 per patient referred for nutritional support, because of the combined effects of the lower unit costs of enteral feeds and shorter duration of feeding.

A question that arises from our analysis is whether it is important to precisely match protein and energy expenditure rates with nutrient infusions. Numerous investigators have advocated early intensive nutritional support in patients with severe disease, as patients are hypermetabolic and the rate of nitrogen loss has been related to mortality (25). Measurements of energy expenditure by indirect calorimetry and protein catabolism by urea kinetic measurements have indicated that the rates are increased by 20% (3) and 80% (4), respectively. Although our goal was to provide 25 kcal/kg/day of energy and 1.5 g/kg/day of protein in both enterally and parenterally fed patients, our analysis clearly demonstrates that we rarely achieved these goals, particularly in enterally fed patients, who, on average, received only 54% of estimated requirements. This was also noted in two of the other pancreatitis studies discussed above (11, 12). It is a common observation in hospital practice (26, 27) and results from a number of logistical factors, including stoppages for tests and bag changes. Because the enterally fed patients did better, it could be argued that hypocaloric feeding is, in fact, better, and that conventional nutritional goals (particularly for glucose) are too high. For example, the increased complication rates in the TPN group could be accounted for by the fact that most of the energy was supplied as glucose, thus increasing the risk of hyperglycemia. Patients with acute pancreatitis are at increased risk for hyperglycemia because of the combined effects of pancreatic endocrine damage and acute stress (6, 28). Objective studies have reported that 90% of such patients are glucose intolerant (29). There is increasing concern that hyperglycemia adversely influences outcome in critically ill patients (30), increasing the risk of fluid and electrolyte imbalance, infections (31), and suppressed GI motility (32). Consequently, the observed dif-

ferences in metabolic and septic complications, as well as duration of bowel dysfunction and hospital stay between our patients given enteral or parenteral feeding may, ironically, be explained by the fact that nutritional goals were more commonly achieved in patients given TPN. Clearly, further studies are needed to determine 1) whether enteral feeding at normocaloric infusion rates is as effective as feeding at the hypocaloric rates used in usual daily practice, and 2) whether better control of blood sugar with concurrent insulin infusions improves outcome in parenterally fed patients. For the present, we would advocate a practice based on this study, whereby patients are observed on bowel rest and *i.v.* fluids for 48 h. Those patients who do not improve should be given a trial of jejunal feeding and, only if this fails, should TPN then be considered.

In conclusion, based on the results of this study, most patients (75%) with acute pancreatitis do not need any nutritional support, and are able to resume oral feeding in 2 days and discharged home in 4 days. For patients with more severe disease, jejunal feeding with an elemental diet was shown to be safer and less expensive, and resolved the disease faster than did TPN, thus enabling earlier resumption of oral feeding.

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REFERENCES

1. Fernandez-Del Castillo C, Rattner DW, Warshaw AL. Acute pancreatitis. *Lancet* 1993;342:474-9.
2. Abou-Assi S, O'Keefe SJD. Nutrition in acute pancreatitis. *Am J Clin Gastroenterol* 2001;32:203-9.
3. Dickerson R, Vehe K, Mullen J, Feurer I. Resting energy expenditure in patients with pancreatitis. *Crit Care Med* 1991; 19:484-90.
4. Shaw JHF, Wolfe RR. Glucose, fatty acid, and urea. Kinetics in patients with severe pancreatitis. *Ann Surg* 1986;204:665-72.
5. Grant J, James S, Grabowski V, Trexler K. Total parenteral nutrition in pancreatic disease. *Ann Surg* 1984;200:627-31.
6. Di Carlo V, Nespoli A, Chiesa R, et al. Hemodynamic and metabolic impairment in acute pancreatitis. *World J Surg* 1981;5:329-39.
7. Fong Y, Marano M, Barber A, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. *Ann Surg* 1989;210:449-567.
8. Ragins H, Levenson S, Signer R, et al. Intrajejunal adminis-

- tration of an elemental diet at neutral PH avoids pancreatic stimulation. *Am J Surg* 1973;126:606-14.
9. Cassim MM, Allardyce DB. Pancreatic secretion in response to jejunal feeding of elemental diet. *Ann Surg* 1974;180:228.
 10. Vu M K, Van Der Veek P, et al. Does jejunal feeding activate exocrine pancreatic secretion? *Eur J Clin Invest* 1999;29:1053-9.
 11. McClave S, Greene L, Snider H, et al. Comparison of the safety of early enteral vs. parenteral nutrition in mild acute pancreatitis. *J Parenter Enter Nutr* 1997;21:14-20.
 12. Windsor ACJ, Kanwar S, Li AGK, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998;42:431-5.
 13. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of a randomized prospective trial. *Br J Surg* 1997;84:1665-9.
 14. Hernandez-Aranda JC, Gallo-Chico B, Ramirez-Barba EJ. Nutrition support in severe acute pancreatitis. Controlled clinical trial. *Nutr Hosp* 1996;11:160-6.
 15. O'Keefe SJD, Day, Wassef W. The costs of nutritional care in acute pancreatitis. *Gastroenterology* 1999;116:G-5000.
 16. Ranson JHC, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974;139:69-81.
 17. 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.
 18. Toskes PP, Greenberger NJ. Approach to the patient with pancreatic disease. Section 3: Disorders of the pancreas. In: Harrison TR, ed. *Harrison's Principles of internal medicine*, 14th ed. New York: McGraw-Hill, 1998:1745-6.
 19. Steer ML, Meldolesi J. The cell biology of experimental pancreatitis. *N Engl J Med* 1987;316:144-50.
 20. Leach SD, Modlin IM, Scheele GA, Gorelick FS. Intracellular activation of digestive zymogens in rat pancreatic acini. *J Clin Invest* 1991;87:362-6.
 21. O'Keefe SJD, Abou-Assi SA, Lee RB, et al. Elemental diets infused into the duodenum are more potent stimulants of pancreatic trypsin and lipase secretion than oral polymeric diets. *Gastroenterology* 2000;118:A-4149.
 22. Niederau C, Niederau M, Luthen R, et al. Pancreatic exocrine secretion in acute experimental pancreatitis. *Gastroenterology* 1990;99:1120-7.
 23. O'Keefe SJD, Abou-Assi SA, Lee RB, Seibel NM. Impairment of nutrient-stimulated pancreatic trypsin and lipase secretion in patients with acute pancreatitis. *Gastroenterology* 2000 (abstract).
 24. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding compared with parenteral reduces postoperative septic complications: The results of a meta-analysis. *Ann Surg* 1992;216:874-81.
 25. Sitzmann J, Steinborn P, Zinner M, Cameron J. Total parenteral nutrition and alternate energy substrates in treatment of severe acute pancreatitis. *Surg Gynecol Obstet* 1989;168:311-6.
 26. Keohane PP, Attrill H, Love M, et al. Relation between osmolarity of diet and gastrointestinal side effects in enteral nutrition. *Br Med J* 1984;288:678-80.
 27. Spain DA, McClave SA, Sexton LK, et al. Infusion protocol improves delivery of enteral tube feeding in the critical care unit. *J Parenter Enter Nutr* 1999;23:288-92.
 28. Havala T, Shronts E, Cerra F. Nutritional support in acute pancreatitis. *Gastroenterol Clin North Am* 1989;18:525-40.
 29. Pisters P, Ranson J. Nutritional support for acute pancreatitis. *Surg Gynecol Obstet* 1992;175:275-84.
 30. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837-53.
 31. Wallace LK, Starr NJ, Leventhal MJ, et al. Hyperglycemia on ICU admission after CABG is associated with increased risk of mediastinitis or wound infections. *Anesthesiology* 1996;85:A286.
 32. Masclee AAM, Gielkens WF, Lam WF, et al. Effects of parenteral nutrients on gastrointestinal motility and secretion. *Scand J Gastroenterol* 1996;31(suppl 218):50-5.