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Early Enteral Feeding in Severe Acute Pancreatitis: A Randomized Clinical Trial Between Gastric vs Distal Jejunal Feeding

Stephen J.D. O'Keefe,[1] Toby Graham,[1] Gregory A. Coté,[2,3] David C. Whitcomb,[1] Anna Evans,[1] and Devavrata Soni[1], Multicenter SNAP (Study of Nutrition in Acute Pancreatitis) Consortium

[1]University of Pittsburgh, Pittsburgh, Pennsylvania; [2]Indiana University, Bloomington, Indiana; and [3]Department of Medicine, Oregon Health & Science University, Portland, Oregon

Abstract

BACKGROUND AND AIMS: Severe acute pancreatitis is one of the most catabolic illnesses. Meta-analyses have shown that enteral nutrition is safer and more effective than parenteral nutrition in suppressing these losses. However, there is intense debate about how the enteral nutrition should be delivered.

METHODS: The design was a randomized controlled trial of early nasogastric (NG) vs distal jejunal (DJ) tube feeding with a semi-elemental diet during the first 4 weeks of severe acute pancreatitis. The setting involved multiple national tertiary care centers. Two hundred and twenty-eight patients were screened, and 26 met the inclusion criteria for new onset severe acute pancreatitis based on an APACHE II score >8, computed tomography evidence of >30% necrosis or computed tomography score >8, and/or a Marshall score >2. The intervention was a randomized allocation to either feeding tube bedside placement by NG or transnasal endoscopy for DJ. The primary endpoint was "feeding failure" to tolerate a rate of >10% of the goal for a 48-hour period.

RESULTS: Twenty-six eligible patients were randomized, 12 to NG and 14 to DJ, 20 of 26 from the Pittsburgh center. Most were obese (BMI 31.5 kg/m^2). Feeding failure occurred in 0 of 14 in the DJ group and in 6 of 11 (55%) in the NG group ($P = 0.0026$). NG failures were crossed over to DJ feeding with good tolerance and eventual recovery. As a result, the quantity of feed delivered was significantly higher in the DJ group ($P < 0.05$). Serious adverse events (cardiorespiratory arrests, unrelated to endoscopy) occurred in 2 of the DJ and none of the NG group; 3 patients from the DJ group died of progressive organ failure, 2 with associated compartment syndrome.

CONCLUSION: This randomized controlled trial indicates that in patients with acute pancreatitis of this level of severity, NG feeding will be ineffective. Although this is a common indication for parenteral nutrition, a safer alternative would be endoscopic-assisted DJ feeding tube placement to bypass the usually dysfunctional or obstructed upper gastrointestinal tract.

Keywords: Tube feeding; Severe acute pancreatitis; Gastric and jejunal enteral feeding.

Introduction

Despite intense experimental and clinical research into the etiology and mechanisms responsible for the initiation and progression of severe acute pancreatitis (SAP), no specific effective treatment has yet been found, and management is primarily supportive. One of the most controversial areas is whether nutrition support can improve the outcome. Studies have shown that the rate of nitrogen loss correlates with mortality, suggesting that the inhibition of catabolism may improve survival.[1] Initially, parenteral nutrition (PN) was considered the optimal approach, as it circumvents upper gastrointestinal (GI) dysfunction or obstruction and avoids pancreatic stimulation. Unfortunately, PN is associated with severe adverse effects, such as septicemia and hyperglycemia, which might contribute to mortality, leading to efforts to use enteral nutrition (EN). Several clinical trials and their meta-analyses subsequently showed that enteral tube feeding (EN) was superior to parenteral feeding in reducing septic and metabolic complications, hospital outcome, and mortality.[2]

Abbreviations used in this paper: DJ, distal jejunal; EN, enteral nutrition; GI, gastrointestinal; NG, nasogastric; PN, parenteral nutrition; SAP, severe acute pancreatitis.

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What You Need to Know

Background

Enteral nutrition (EN) is superior to parenteral nutrition (TPN) in the management of severe acute pancreatitis. There is controversy about whether EN should be given simply into the stomach (nasogastric [NG]) or more distally down the jejunum to bypass proximal gastrointestinal compression by the inflammatory mass (distal jejunal [DJ]). Patients with obstruction are normally referred for TPN.

Findings

In a randomized controlled trial between NG and DJ feeding in acute severe pancreatitis, feeding failure occurred in 0 of 14 of the DJ group and in 6 of 11 (55%) of the NG group ($P = 0.0026$). NG failures were crossed over to DJ feeding with good tolerance and eventual recovery. As a result, the quantity of feed delivered was significantly higher in the DJ group ($P < 0.05$). As a result, TPN was avoided by the DJ approach.

Implications for Patient Care

The results of this study provide the scientific framework for the further conduct of randomized controlled trials in patients with severe acute pancreatitis referred for TPN because of gastroduodenal obstruction/compression to confirm that DJ feeding is a safer, more effective, alternative method of feeding to TPN in routine clinical practice.

What remains unclear is whether the site of EN delivery is important. From a physiological point of view, distal jejunal (DJ) feeding should be ideal, as it has minimal pancreatic stimulation, whereas feeding into the stomach or duodenum is a potent stimulant for pancreatic enzyme synthesis[3] and secretion,[4] which could be expected to exacerbate the disease process.[5,6] However, studies from Glasgow[7] and India[6] compared nasogastric (NG) to postpyloric or proximal jejunal (NJ) feeding and found no difference in the outcome, leading to the suggestion that pancreatic stimulation was not a concern. Further studies confirmed this, leading to the modification of national and international guidelines by the APA and IAP[8] and AGA and ACG[9] to suggest that either NG or NJ feeding is acceptable in the management of SAP. The controversy is, however, not over, as both these forms of feeding may not be beneficial, and we need to determine whether the avoidance of pancreatic stimulation by feeding >40 cm down the jejunum may optimize recovery. A further problem with both NG and NJ feeding is that the efficacy of both is impaired by the upper GI compression and progression to obstruction by the pancreatic inflammatory mass.

In an attempt to resolve these remaining issues and develop the ideal method for maintaining enteral feeding in SAP, the Pittsburgh group developed a transnasal endoscopic double-lumen tube-within-a-tube technique (DJ) that feeds below the obstructed bowel and avoids pancreatic stimulation.[10] To test its efficacy in clinical practice in patients with the most severe forms of SAP, we performed the following randomized controlled trial.

Methods

Study Design

The primary aim of this study was to determine the best enteral feeding approach for patients with SAP. We performed a 2-arm randomized comparative study between NG and DJ feeding (Figure 1), with superiority defined as the efficacy of nutrient delivery. As this was a study of acute disease, the feeding observation period was limited to 4 weeks. Because the inclusion and exclusion criteria (below and see Supplement 1 for details) were strict to optimize the study's internal validity, the study was conducted in 8 centers of excellence across the United States. The study was reviewed and approved by the University of Pittsburgh's Institutional Review Board. All authors had access to the study data and reviewed and approved the final manuscript.

Primary Endpoint: Feeding failure, defined as the inability to tolerate more than 10% of goal feeds for >48 hours, persistently elevated gastric residual volumes (GRVs) >400 ml/4 h, or vomiting feed containing fluid during NG feeding associated with elevated GRVs.

Secondary Endpoints: Quantity of feed delivered, total length of intensive care unit (ICU) and hospital stay, mortality.

Patient Selection

Inclusion Criteria

The inclusion criteria were strict in order to study the role of feeding in patients with early (ie, within 48-96 hours of the onset of abdominal pain), severe (for definitions, see Supplement 1) acute pancreatitis likely to need ICU management and artificial nutrition support for at least 2 weeks. Severe pancreatitis was defined (based on the Atlanta classification of severe disease[11]) as the combination of the typical history of abdominal pain for over 24 hours with raised (>3-fold) serum pancreatic enzymes on admission and the presence of 1 or more of the following:

a) Organ failure resistant to early aggressive IV fluid resuscitation as defined by a Marshall score of ≥2 in any 1 organ excluding the liver component, as the abnormality may be due to gall stones rather than the systemic inflammatory response.[12]
b) Pancreatic necrosis >30% on computed tomography (CT) scan or a modified CT severity index (CTSI) of ≥8.[13]
c) APACHE II score ≥ 8[14] (for definitions, see Supplement 2).

Exclusion Criteria (Supplement 1)

Randomization and Management: Eligible patients were randomized within 48 hours of the onset of acute pancreatitis symptoms, with stratification for the

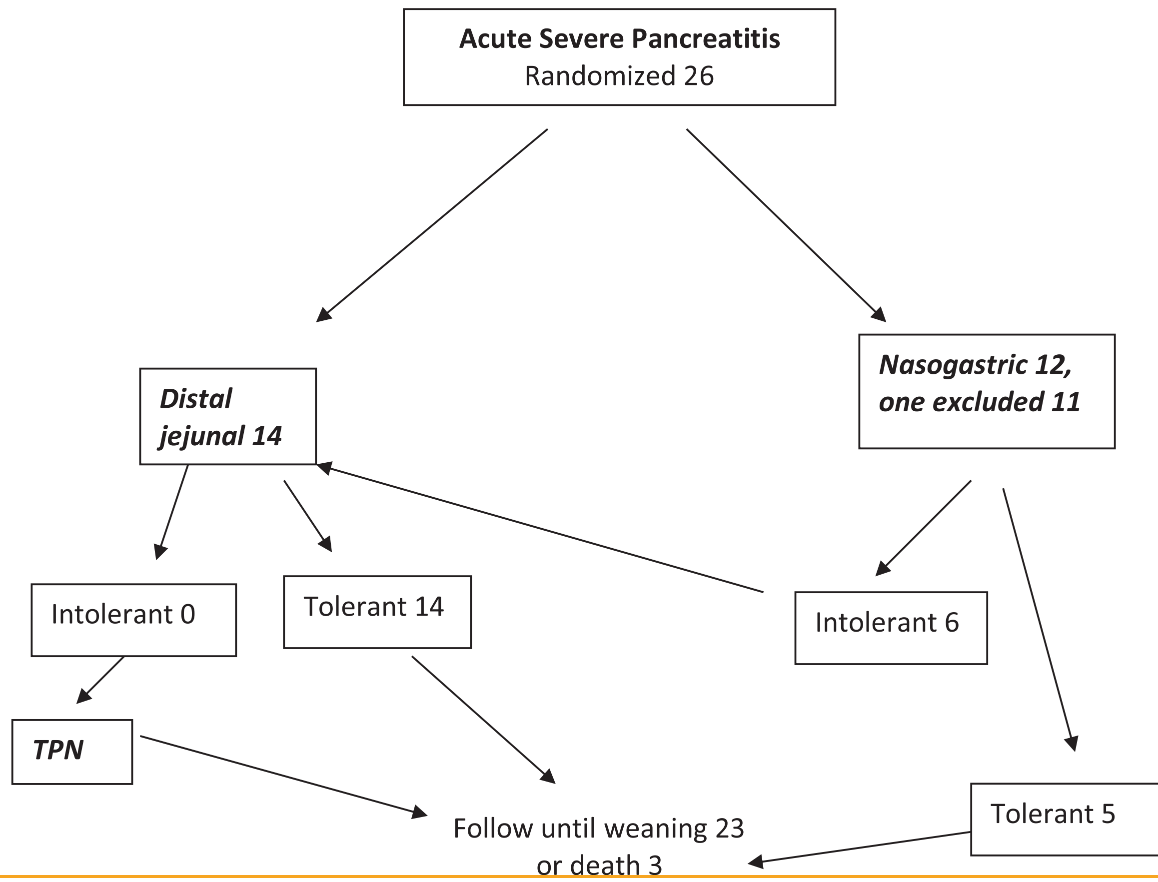

Figure 1. Study design and outcome: 2-arm randomized comparative study between NG and DJ feeding. Numbers indicate the numbers of patients entering each box.

presence of multiple organ failure with pancreatic necrosis >30%, to NG or DJ feeding. Unstable patients from a cardiovascular and metabolic point of view were first resuscitated in the ICU before commencement of feeding. Enrollment time was extended to 96 hours halfway through the study to increase recruitment, allowing for delays in transfer from peripheral hospitals. All patients were studied in the ICU.

Feeding Tube Placement (Figures 2A and 2B): DJ feeding tubes (Kendall-Dobbhoff nasojejunal feeding/gastric decompression tube system, Tyco Healthcare #752513, Mansfield, MA) were placed by the transnasal over-the-guidewire endoscopic technique as previously described.[15] All members of the consortium were invited to visit Pittsburgh for live demonstrations and practice sessions, in addition to the provision of teaching videos

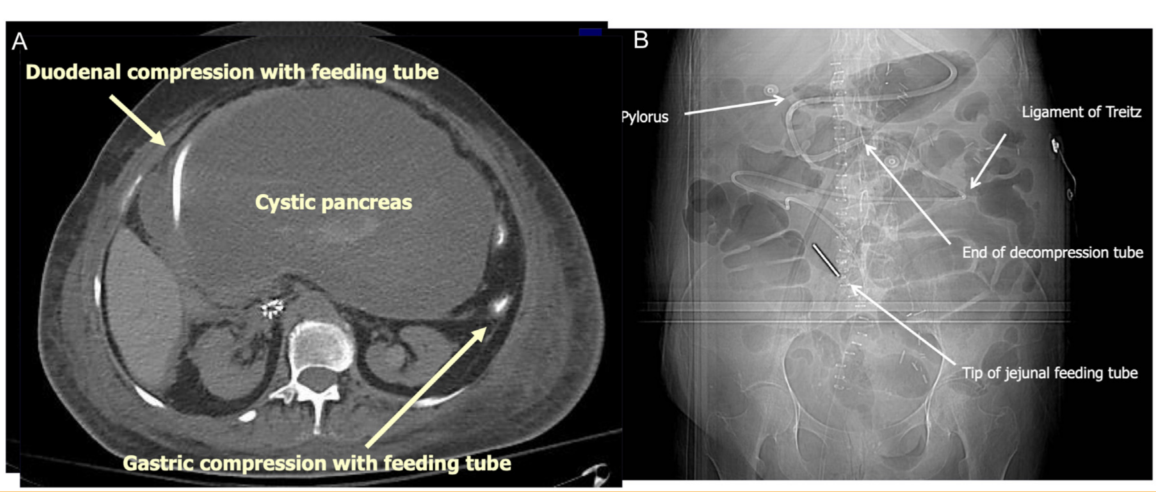

Figure 2. (A) CT scan illustrating massive cystic swelling of the pancreas secondary to pancreatic necrosis compressing the stomach and duodenum. (B) Straight X-ray showing correct placement of the DJ feeding tube well down the jejunum and the gastric decompression tube at the pylorus.

before the study commenced (https://youtu.be/YlkiY6YTnYk and https://youtu.be/UjVjDkdDLW0).

For NG feeding, we used the standard Salem 12 French gastric "sump" tube placed as per ICU routine practice at the bedside. Its final position was checked by abdominal X-ray to be lying along the greater curvature of the stomach with the tip in the antrum. Both tube systems were held in place with a nasal bridle (AMT Bridle Nasal Tube Retaining System, Chicago, IL). All tubes were inspected daily and flushed with 10 ml of tap water every 4 hours when checking gastric residuals. Only liquid medications were allowed to be injected via the DJ feeding tubes. Further details of the management of feeding progression, tolerance and weaning are provided in Supplements 3, 4, and 5.

A portable X-ray was obtained for confirmation that the tip of the DJ tube was approximately 40 cm past the ligament of Treitz and beyond the compressed upper GI tract. Gastric residuals were aspirated every 4 hours and recorded for both tube systems. Feeding was only commenced in the NG group if residuals were <400 ml,[16] whereas DJ feeding was started immediately, irrespective of GRVs, as the G-tube was kept under constant low-pressure vacuum for the first 72 hours, and then reassessed. Feeding rate was commenced at 25 ml/h and increased every 24 hours by 25 ml/h until the goal feeding rate, defined by the provision of 25 Kcal/kg ideal body weight/day of a semi-elemental formula ("*Peptinex*": Novartis Nutrition, Fremont, MI) was tolerated.

Feeding Failure: Patients with feeding failure as described above were switched to the alternative feeding method or, failing this, given PN. All other aspects of management were continued as per standard practice. Intensive metabolic monitoring was performed during the first 7 days, but feeding was continued until patients could be weaned onto oral feeding.

Statistical Methods

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as frequency and percentages. Our analytic objectives were to determine whether significant differences existed between the NG and DJ groups in 1) the number of feeding failures (Primary Endpoint), 2) the quantity of feed tolerated during the first 7 days of tube feeding (Secondary Endpoint), and 3) the total length of hospital or ICU stay (Secondary Endpoint). The Mann-Whitney test was used to compare continuous data, including median quantity of feed between groups delivered during the first 7 days of treatment. Fisher's exact test was used to compare categorical data. Statistical analysis was performed with the assistance of the University of Pittsburgh Epidemiology Data Center using SAS version 12.1 (SAS Institute, Cary, NC).

Sample Size

Determining sample size was difficult, as no previous studies had compared NG and DJ feeding in critically ill patients with SAP. The best we could base our calculations on was the Davies study from Australia that had compared NG to NJ feeding in critically ill patients *without* pancreatitis,[17] where they found a reduced incidence of intolerance with NJ feeding of 13% vs 31% for NG feeding. From this, we estimated we would need a sample size of 135 to have sufficient power to detect a significant difference in our primary endpoint, feeding failure. As explained below, recruitment proved to be very slow because of the stringent entry criteria (Figure 3), and the study had to be closed after the completion of 26 randomized patients.

Results

Screening

There were 228 patients screened for the study, of whom 26 were eligible for randomization. Figure 3 shows the outcome of the screening process, with details of reasons for exclusion and ineligibility. One possible eligible patient was removed shortly after randomization as, on review, some of his abnormal presenting laboratory values were likely due to causes other than pancreatitis: This patient's data were removed from analysis. There were therefore 25 evaluable participants for randomization to the study (Figures 1 and 3). Unfortunately, extending the recruitment time to 96 hours had no appreciable effect on recruitment rate.

Demographic Characteristics and Disease Severity

Demographic and baseline characteristics of the eligible and randomized patients were similar between the 2 treatment groups, as shown in Table 1. Twenty (80%) were from the Pittsburgh site, 4 from Indiana, and 1 from Case Western Reserve, Chicago. Sixty percent were male, and all were White, apart from 1 African American. Most patients were middle-aged and obese, with a median age of 55.6 years and a BMI of 34.1 kg/m^2.

Demographic Characteristics: Table 1 shows that the severity of disease defined by our 6 scoring systems (C-Reactive Protein (CRP), APACHE II, Marshall's, multiple organ failure, systemic inflammatory response, and CTSI) was similar in the 2 groups. Over 90% were eligible due to severity scores based on CTSI alone. Twenty-eight percent had multiple organ failure on admission, and 92% had at least 2 out of 4 positive diagnostic criteria of the systemic inflammatory response syndrome (SIRS). CTSI was performed for clinical reasons in 23 out of 25 patients during the first 7 days of admission. The mean CTSI score was 8.4 ± 2.2 in the NG group vs 6.9 ± 2.1 in the DJ group ($P = 0.08$; Table 2).

Routine Bloodwork

No significant group differences were seen in Hb, white blood cells, glucose, albumin, pancreatic enzymes, and C-reactive protein levels (Supplement 6).

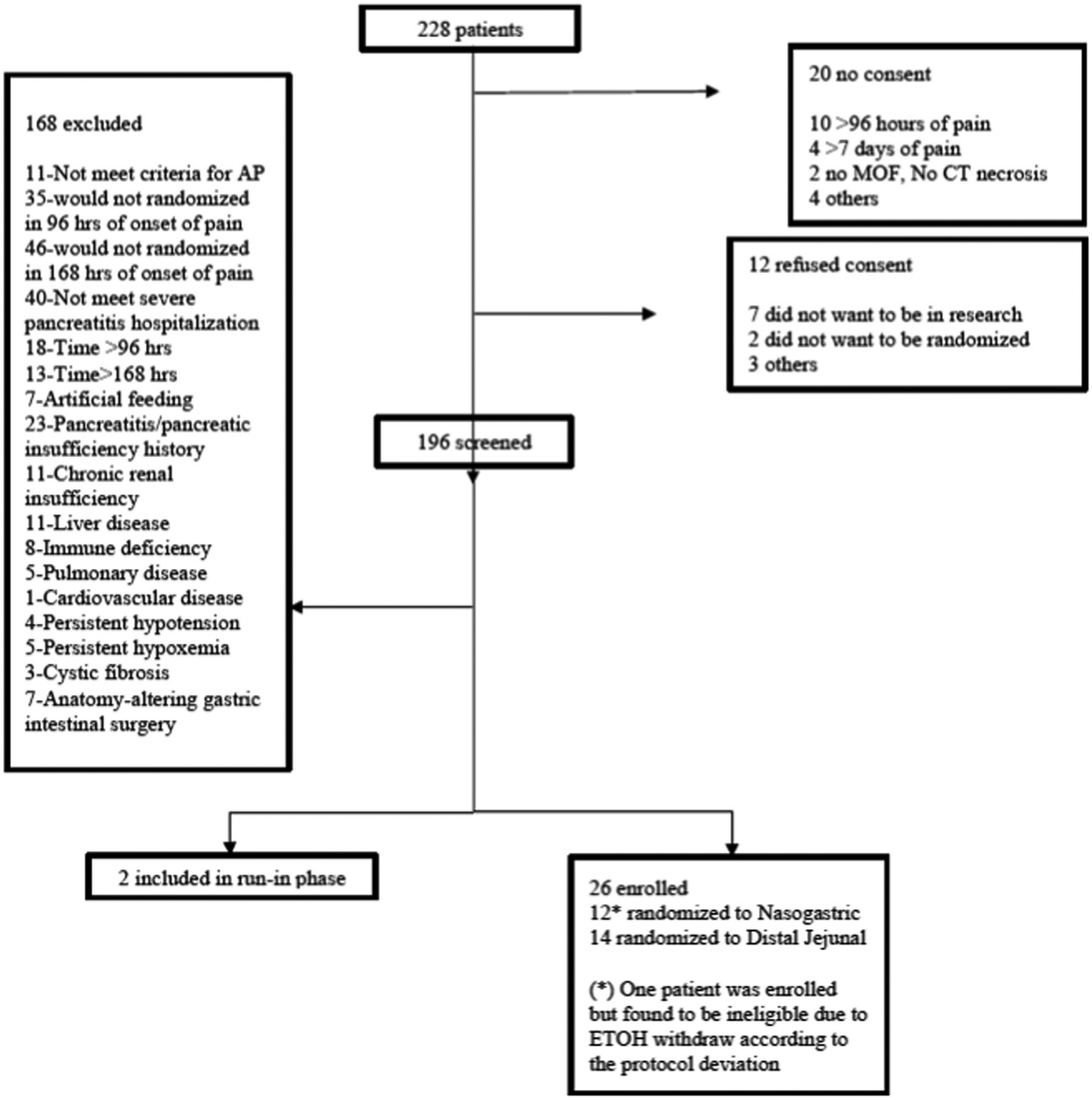

Figure 3. Details of reasons for exclusion and ineligibility. There were 228 patients screened for the study, of whom 26 were eligible for randomization. One possible eligible patient was removed shortly after randomization as, on review, some of his abnormal presenting laboratory values were likely due to causes other than pancreatitis: This patient's data were removed from analysis. There were therefore 25 evaluable participants for randomization to the study.

Outcomes (Table 2)

Feeding Tolerance and Feeding Failure

There were no significant differences between the groups in the occurrence of nausea, vomiting, or diarrhea during the first 7 days, indicating the efficacy of the protocol in maintaining gastric decompression in both groups and suggesting good absorption. The median feeding volume over the first 7 days was approximately double in the DJ vs NG group (1025 vs 527 ml/day, P = 0.048) (Figure 4 and more details in Supplement 6). Other symptoms that might be related to tolerance, such as abdominal distension, pain, and tenderness, were difficult to assess accurately due to sedation and ventilation.

Average Feeding Volumes per Person Over the First 7 Days of the Trial

The key finding in this study was the difference in feeding failures (Figure 4). Of the 11 patients randomized to NG feeding, 6 patients developed feeding failure necessitating a switch to DJ feeding between days 5 and 13. On the other hand, no feeding failures occurred in the DJ group, including those who had been switched for failing NG. This difference was highly significant (P = 0.0026) (Fisher's exact test, Table 2). Three of the 6 patients failed because they could not tolerate more than 10% of their feeding rate. The remaining 3 failed due to vomiting feed containing fluid during NG feeding in the setting of persistently high (>400 ml) GRVs. One of these patients was

Table 1. Demographics Details: The Severity of Disease Defined by Our 6 Scoring Systems (CRP, APACHE II, Marshall's, Multiple Organ Failure, Systemic Inflammatory Response, and CTSI) Was Similar in the 2 Groups

Demographics	Total	NG	DJ	*P* value
	n = 25	*n* = 11	*n* = 14	
Age, median (IQR)	55.6 (25.8)	52.9 (35.4)	57.0 (25.8)	0.87
Males, *n* (%)	14 (56)	6 (54.5)	8 (57.1)	0.90
Race, *n* (%)				
White	24 (96)	11 (100)	13 (92.9)	1
Black	1 (4)	0 (0)	1 (7.1)	
Site, *n* (%)				
Pittsburgh	20 (80)	9 (81.8)	11 (78.6)	0.65
Indiana	4 (16)	2 (18.2)	2 (14.3)	
Case W.	1 (4)	0 (0)	1 (7.1)	
Etiology, *n* (%)				
Biliary	11 (44)	5 (45.5)	6 (42.9)	
Alcohol	8 (32)	3 (27.3)	5 (35.7)	
Hyper-triglyceridemia	4 (16)	2 (18.2)	2 (14.3)	
Other	2 (8)	0	2 (14.3)	
Idiopathic	2 (8)	1 (9.1)	1 (7.1)	
Peak CRP within 72 of admission, median (IQR)	30.6 (26.3,36.4)	32.1 (26.8, 35.2)	27.0 (23.0,37.2)	0.29
Weight at presentation in pounds, median (IQR)	224.0 (53.0)	224.0 (56.0)	226.0 (57.0)	0.98
BMI, median (IQR)	34.1 (7.0)	35.4 (9.9)	33.1 (5.7)	0.81
Apache II Score, median (IQR)	12.0 (11.0)	11.0 (9.0)	12.0 (12.0)	0.41
Marshall Score, median (IQR)	2.0 (4.0)	2.0 (3.0)	0 (4.0)	0.84
Multiple organ failure, *n* (%)	7 (28)	3 (27.3)	4 (28.6)	1.00
SIRS, *n* (%)	23 (92)	10 (90.9)	13 (92.9)	1.00
CTSI, *n* (%)	8.0 (5.5)	10.0 (2.0)	8.0 (6.0)	0.20

Table 2. Summary of Key Outcome Variables Indicating Higher Feeding With DJ Feeding and the Ability of DJ Feeding to Be Successful Where NG Failed

Outcome Variables	Total	NG	DJ	*P* value[a]
	n = 25	*n* = 11	*n* = 14	
Feeding failure, *n* (%)				
No	19 (76.00)	5 (45.45)	14 (100.00)	0.0026
Yes	6 (24.00)	6 (54.55)	0 (0)	
Nausea and vomiting, *n* (%)				
None	17 (68.00)	8 (72.73)	9 (64.29)	0.4913
1	5 (20.00)	1 (9.09)	4 (28.57)	
2	3 (12.00)	2 (18.18)	1 (7.14)	
Death, *n* (%)				
No	22 (88.00)	11 (100.00)	11 (78.57)	0.2300
Yes	3 (12.00)	0 (0)	3 (21.43)	
Adverse events, *n* (%)				
No	18 (72.00)	8 (72.73)	10 (71.43)	1
Yes	7 (28.00)	3 (27.27)	4 (28.57)	
Serious adverse events, *n* (%)				
No	23 (92.00)	11 (100.00)	12 (85.71)	0.4867
Yes	2 (8.00)	0 (0)	2 (14.29)	
Treatment crossover, *n* (%)				
No	19 (76.00)	5 (45.45)	14 (100.00)	0.0026
Yes	6 (24.00)	6 (54.55)	0 (0)	

[a]Fisher's exact test.

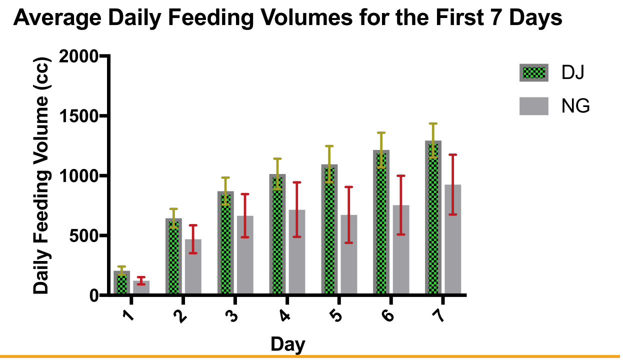

Figure 4. Comparative average feeding volumes per group over the first 7 days. The median feeding volume was approximately double in the DJ vs NG group (1025 vs 527 ml/day; $P = 0.048$) (Figure 4 and Supplement 5).

found to have feed contamination of the airways. Remarkably, 1 patient who progressed to a severe compartment syndrome continued to tolerate slow elemental diet feeding at 20 cc/h until all treatment was withdrawn.

Length of Stay in ICU and Hospital and Mortalities

The median length of ICU stay was variable and therefore not significantly different between groups: 7 days vs 18 days for the NG vs DJ group ($P = 0.230$). The median length of hospital stay was also not significantly different: 19 days for the NG group vs 30 days for the DJ group ($P = 0.366$).

Despite the fact that all the feeding failures were in the NG group, all the mortalities ($n = 3$) were in the DJ group.[18] The first deceased patient had Acute Respiratory Distress Syndrome (ARDS) and SIRS from day 1 and an ileus leading to a superior mesenteric vein thrombosis.[18] The second patient was admitted with acute tubular necrosis, SIRS, and abdominal compartment syndrome, which led to shock and ARDS, eventually causing multiple organ failure and respiratory failure.[18] The third patient also had organ failure and ARDS and was in the ICU with respiratory failure and ischemic colitis, which led to several surgeries, including a cholecystectomy and creation of an end-loop ileostomy. The patient died after the development of progressive bowel ischemia.

Systemic Inflammatory Response and APACHE II Responses

In both groups, the proportion with SIRS was at its highest point on day 2 (DJ: 71.43% vs NG: 45.45%). The general trend from day 2 was downward, with the DJ group reaching 7.14% and the NG group 9.09% by the fourth week. The proportion of SIRS in the DJ group was consistently higher than in the NG group until day 14, when they equilibrated.

The DJ group's mean APACHE II scores were consistently but not significantly higher than those of the NG group for the first 2 weeks, suggesting that the DJ group was possibly sicker.

Adverse Events

There were no significant differences in rates of adverse events between the 2 groups (27.27% vs 28.57%). There were 3 deaths in the study: All occurred in the DJ group, as discussed above.

Discussion

The results showed that the DJ method was significantly more effective in providing food during the first 2 weeks of acute illness, despite the fact that we never reached our intended sample size of 135. This could be explained by our statistical power being based on a study conducted in equally sick but non-pancreatitic general ICU patients[17] who did not have gastro-duodenal obstruction and therefore were more likely to tolerate NG feeding, reducing differences between NG and postpyloric placement. In our study, all 14 patients randomized to DJ feeding tolerated enteral feeding, whereas 6 of the 11 randomized to NG access developed feeding failure. The 6 feeding failures were crossed over to DJ feeding with good tolerance.

Very few randomized controlled enteral feeding clinical trials have been performed in patients with this level of critical illness, and even fewer with the critical illness being due to acute pancreatitis. A likely explanation is that we included patients with obstructed dysfunctional upper GI tracts, which would normally be an indication for PN. Our development of DJ feeding has opened up, for the first time, the possibility to use EN even in the sickest of patients. This was exemplified by the patient who progressed to a severe compartment syndrome who continued to tolerate slow elemental diet feeding at 20 cc/h until all treatment was withdrawn. It is true that gastric decompression and jejunal feeding can also be achieved by using 2 separate tubes, or with a percutaneous endoscopic gastrostomy with jejunal extension tube (PEG-J), but this would involve planned perforation of the stomach, which may be risky in patients with early SAP where the mucosa may be fragile and ischemic. However, a PEG-J might be a reasonable alternative in obstructive patients with established, walled-off disease or chronic obstructive pancreatitis awaiting spontaneous resolution of fluid collections or surgical decompression.[19,20] Here, it might have the benefit of avoiding nasal irritation and possible sinus infections. However, the quoted studies were observational and not randomized, and further tightly controlled trials will be needed to discern the superiority of one form of feeding over the other.

These technical issues likely contributed to the difficulty with recruitment in centers that were not familiar with the DJ technique. Despite the inclusion of leading centers in pancreatitis management in the United States, recruitment at the rate needed to enroll the calculated optimal sample size was only achieved by 1 center. Not by chance, this center was the one that developed the DJ technique and now uses it as a standard of care in patients with SAP.[15,21] This problem was anticipated, and, as mentioned previously, great effort was made to train participating centers with the construction of live demonstrations and teaching videos before the study commenced. In addition, in our wish to maximize homogeneity, our inclusion and exclusion criteria were tight, adding to restricted recruitment. One of the most limiting requirements was the need for the duration of pancreatic pain to be <48 hours at admission. However, increasing the time to <96 hours did not have an appreciable effect on recruitment, as there were many other reasons for ineligibility, as detailed in Figure 3. The chances of a type 1 statistical error are always greater in this situation, where the estimated sample size is not achieved, but in the event the difference in tolerance was so great that significant differences were achieved with a sample size of only 28.

The practice of using GRVs to assess feeding tolerance can be criticized as being too low and interfering with tube feeding delivery, but at the time this study was designed, the accepted GRV for critically ill patients was only 250 ml. Based on emerging studies from Spain,[22] we increased the limiting volume to 400 ml and included strict measures to prevent aspiration. More recent studies have led ASPEN to remove GRV as a method of monitoring tube feeding tolerance because it limits early enteral feeding.[23] It is therefore possible that our use of GRVs may have diminished the feeding capacity in the NG group, but we chose to be conservative, and further studies are needed to determine whether ignoring GRVs results in increased nutrition delivery and an improved outcome.

The downside to DJ feeding is the need for endoscopy. All our patients were too unstable to transport safely down to the GI lab for placement with sedation and fluoroscopy, and it is our standard of practice to place the tube by the bedside in critically ill ventilated patients. With practice, this is generally straightforward and well tolerated, as illustrated by our published experience.[15]

Until recently, it was believed that ramping up feeding rates to the goal within a few days of ICU admission would prevent the "energy gap" and decrease later complications thought to be a consequence of nutritional depletion.[24] Our study was insufficiently powered to determine whether the increased volume of feeding would translate into a better outcome. However, a multicenter Dutch study that included 208 patients with SAP from 19 Dutch hospitals showed that more feeding was tolerated by early tube feeding but that there were no significant subsequent reductions in complications and mortality.[25] Furthermore, 2 large, well-powered randomized clinical trials provided compelling evidence that early aggressive enteral feeding could potentially worsen outcomes in ICU patients.[26,27] Finally, Compher et al recently published the results of their analysis of differences in outcome from the ICU in patients given variable quantities and formulae of nutrition support. Their database was large, but retrospective, covering 20,578 participants. Remarkably, the outcome was not significantly different if patients were prescribed higher or lower protein or energy doses.[28]

The results of these large, well-powered clinical trials have, after the commencement of this study, tempered our enthusiasm for achieving goal feeding within the first week. The urgent need for nutritional support is also diminished by the knowledge that a large proportion of Americans today have excessive nutrient stores and are obese,[29] well exemplified by the patients included in this study who had a mean BMI of 34.1 kg/m^2. Indeed, obesity is one of the chief risk factors for SAP and is associated with a greater mortality.[30] We have argued from the basis of pathophysiological observations detailed in the "Principles and Practice of Nutritional Support"[29] that we have sufficient body stores to manage on IV fluids, micronutrients, and electrolytes alone for the first 7-14 days.[29,31] The precise timing for commencement of nutritional support remains unknown, with the exception of the severely malnourished, because no randomized controlled trial has yet compared trickle or full feeding to no feeding in the first week of a patient's ICU stay. Many consider it unethical to not feed, but it must be remembered, as so eloquently argued by Koretz in 1984, that all forms of nutritional support are interventional and have potential complications, and first we must prove that our intervention is improving the chances of patient survival.[32] Our study would suggest that NG feeding is not surprisingly ineffective early in the course of acute pancreatitis of the severity studied here. If there is evidence of depleted nutritional stores, then it would make more sense to use the DJ approach to bypass the obstructed upper gut by an endoscopically placed jejunal feeding tube to gain access to the non-obstructed jejunum to avoid the complications associated with nasogastric and parenteral feeding.

In summary, we have developed a method of nutritional support that allows virtually any critically ill patient with or without upper GI dysfunction to be fed enterally, thus obviating the need for parenteral feeding and reducing the risk of infective and metabolic complications (Supplementary Figure 1). This form of feeding will likely most benefit patients with established gastric outlet obstruction who are not surgical candidates, for example, patients becoming progressively malnourished due to the inability to eat due to post-acute pancreatitis complicated by necrosis of the pancreas and pseudocysts (Figure 2A). However, there is considerable doubt that early (ie, the first week) enteral feeding improves outcomes in the previously well-fed, where we need to prove that interventional feeding is better than no feeding. Future "early enteral" feeding trials should consider the inclusion of a no-feeding arm in non-depleted patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.tige.2023.06.002.

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Correspondence
Address correspondence to: Stephen J.D. O'Keefe, MBBS, MSc, MD, FRCP, FAGI, Division of Gastroenterology, Hepatology & Nutrition, University of Pittsburgh, Lab: 1145 Biological Sciences Tower, 200 Lothrop St, Pittsburgh, Pennsylvania 15213. e-mail: sjokeefe@pitt.edu.

Conflicts of Interest
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Author Contributions

S.J.D.O. developed the study concept and design, developed the feeding methods, performed the preliminary investigations, wrote the initial protocol, obtained NIH funding, conducted the Pittsburgh patient studies, organized and integrated the analysis, and wrote and modified the final manuscript. T.G. conducted the Pittsburgh patient studies. G.A.C. conducted the patient studies in Indiana and reviewed/revised the manuscript. D.C.W. was involved with protocol design and modifications and contributed to the patient studies in Pittsburgh. A.E. and D.S. helped evaluate the results and initial drafts of the paper. SNAP Consortium members helped with the design and interpretation of the study and critical revision of the manuscript for important intellectual content.

SNAP Consortium

University of Pittsburgh, Pittsburgh, Pennsylvania (David C. Whitcomb, Toby Graham, and Stephen J.D. O'Keefe); University of Louisville, Louisville, Kentucky (Stephen McClave); The Mayo Clinic, Rochester, Minnesota (Santhi Swaroop Vege); Harvard University Brigham Hospital, Boston, Massachusetts (Peter Banks and Darwin Conwell); University of Florida, Gainesville, Florida (Christopher Forsmark); UCLA VA Hospital, Los Angeles, California (Stephen Pandol); Indiana University, Bloomington, Indiana, and Department of Medicine, Oregon Health & Science University, Portland, Oregon (Gregory A. Coté); University Hospital, Cleveland, Ohio (Gerard Isenberg); University of Pittsburgh Department of Public Health, Epidemiology and Statistics, Pittsburgh, Pennsylvania (Steve Wisneuski).

Ethical Statement

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Reporting Guidelines

CONSORT.