Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371:1983-93. DOI: 10.1056/NEJMoa1404393

Supplementary Appendix to manuscript:

- Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis –

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for the *Dutch Pancreatitis Study Group.*

The protocol and statistical analysis plan are published in *Trials* 2011;12:73.

Additional information:

Additional information: exclusion criteria

Excluded were patients with recurrent acute or chronic pancreatitis, pancreatitis due to endoscopic retrograde cholangiopancreaticography or malignancy, patients with enteral or parenteral nutrition at home, pregnant patients, patients assessed (or transferred from other hospitals) more than 24 hours after presentation to the emergency department, or patients presenting to the emergency department more than 96 hours after symptom onset.

Additional information: feeding regimen

Early Nasoenteric Feeding

If assigned to early nasoenteric feeding, patients received a nasojejunal feeding tube as soon as possible but not later than 24 hours following randomization. Feeding tubes were placed endoscopically or radiologically according to local practice. After tube placement nasoenteric feeding was started at 20 ml per hour during the first 24 hours after initiation of feeding. After 24 hours, the volume of nutrition was increased to 45 ml per hour, after 48 hours to 65 ml per hour and after 72 hours to full nutrition depending on patient's actual body weight. Nasoenteric feeding was administered as Nutrison Protein Plus (Nutricia, Zoetermeer, The Netherlands). Per 100 ml this provided 125 kcal, 6.3 g protein, 4.9 g fat and 14.2 g carbohydrate (http://www.nutriciamedischevoeding.nl/patienten-en-verzorgers/onze-producten/nutrison-protein-plus/voedingswaarden-ingredienten).
Standard amounts of minerals, vitamins and trace elements were included. The solutions osmolarity was 275 mOsmol/l and the osmolality was 355 mOsmol/kg H_20. For both study groups, full nutrition was defined as an energy target of 25 kcal/kg/day for patients in the intensive care unit and 30 kcal/kg/day for patients in the ward. At 3 and 7 days after admission a dietician assessed nutritional status and nutritional requirements and made adjustments accordingly.

The position of the feeding tube was not checked routinely but only in case of suspected dislodging. A plain abdominal radiograph was performed in case of nausea or vomiting, lowered consciousness in non-intubated patients, or gastric residual volumes exceeding 250 ml per 6 hours in patients with a nasogastric decompression tube. In patients with symptoms of delayed intestinal passage, the nutritional dose was decreased by 50% and gradually increased again the

next day or stopped completely if symptoms progressed to a distended abdomen with an abdominal X-ray that showed dilated small and large bowel. When a patient was judged to be able to tolerate an oral diet, tube feeding was gradually decreased and replaced by an oral diet. If pain relapsed during start of an oral diet, tube feeding was restarted.

Additional information: general supportive treatment

Fluid resuscitation was commenced at the emergency department and continued throughout the first days. The amount of fluid administered was titrated using vital signs and serum markers. Antibiotics were administered based on culture results and were not given as prophylaxis in patients with necrotizing pancreatitis.

A contrast enhanced abdominal CT was performed 5 to 7 days after admission in all patients to evaluate the presence of local complications. In patients with infected pancreatic necrosis, interventions were generally postponed until the acute necrotic collections had progressed to walled-off necrosis.

Patients were discharged from the hospital if this was deemed feasible by the treating physician. In general, patients were discharged after resolution of major abdominal pain, normalization of inflammatory parameters such as serum C-reactive protein and when oral intake reached energy targets.

Additional information: end points

Predefined secondary end points included the development of necrotizing pancreatitis as diagnosed on CT, new onset organ failure, APACHE II scores, C-reactive protein levels and the presence of the Systemic Inflammatory Response Syndrome (SIRS) measured daily from admission up to day 7, and healthcare utilization. Secondary end points also included gastrointestinal symptoms and tolerance of early nasoenteric or oral feeding, such as the number of patients requiring requiring a nasoenteric feeding tube in the on-demand tube feeding group. Full tolerance of an oral diet was defined as consuming an oral diet that reaches energy targets without clinically relevant gastrointestinal symptoms as judged by the treating physician.

Additional information: data collection and end-point assessment

A case-record form was filled in by local dieticians who registered the caloric intake and calculated caloric energy targets during the first week after admission based on actual body weight. For patients with nasoenteric tube feeding, the caloric intake in kcal was deducted from the amount of tube feeding administered. Possible reasons for discontinuation of nasoenteric tube or oral feeding such as vomiting were noted and accounted for when calculating the caloric intake. For patients with an oral diet, the dieticians registered the type and quantity of hospital food tolerated and calculated the amount of kcal provided per patient. Routine follow-up visits took place 3 and 6 months after discharge. Data collection was performed by local physicians using a paper case-record form. The trial nurse, who was not involved in patient care, repeatedly motivated physicians to fill in all forms and collected the forms .

Additional information: patient safety

To optimize patient safety an independent data and safety monitoring committee (DSMC) evaluated the progress of the trial and examined safety end points after the completion of follow-up in each consecutive group of 25 patients. All involved physicians were repetitively asked to report any potential adverse events. These adverse events were listed and presented to the DSMC in an unblinded fashion. The DSMC discussed the implications of the data presented. In addition, all deceased patients were extensively evaluated by the DSMC for cause of death and possible intervention related serious adverse events. The outcome of the meeting of the DSMC was discussed with the trial steering committee and was reported to the responsible investigational review board. All adverse events were reported to the Dutch Central Committee on Research involving Human Subjects and the investigational review board.

Additional information: statistical analysis

Variables are summarized as frequencies and percentages, means with standard deviations or 95% confidence intervals, or medians and interquartile ranges, as appropriate. Results are presented as risk ratios with corresponding 95% confidence intervals. Dichotomous data were compared with the use of Fisher's exact test, continuous data with the Mann-Whitney U test, and categorical data with the linear-by-linear association test. The variables used as stratification factors were not included in the analyses.

Additional information: interim analysis

Planned interim analysis was performed after all 104 patients had completed 6 months follow-up. At that time, 142 patients were randomized. Although P values for stopping were not reached, interim results showed a trend towards increased mortality in the early feeding group. The DSMC unanimously recommended the steering committee to pause recruitment to allow for additional safety analyses. These analyses showed a higher rate of baseline organ failure in the early eeding group. After a joint meeting the steering committee and DSMC decided to resume recruitment anticipating the difference in baseline organ failure to disappear.

Box S1: Definitions of infections used for primary end point.	
Infection	**Definition**
Infected pancreatic necrosis	Positive culture of pancreatic or extrapancreatic necrotic tissue obtained with fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT.
Bacteremia	Positive blood culture. For non-pathogens (e.g. coagulase negative staphylococci) at least 2 samples had to be positive.
Pneumonia	Coughing or dyspnoea, radiography with infiltrative abnormalities, raised inflammatory variables and positive sputum culture. For intubated patients a positive endotracheal culture was mandatory.

Figure S1: Trial Enrollment, Randomization and Follow-up.

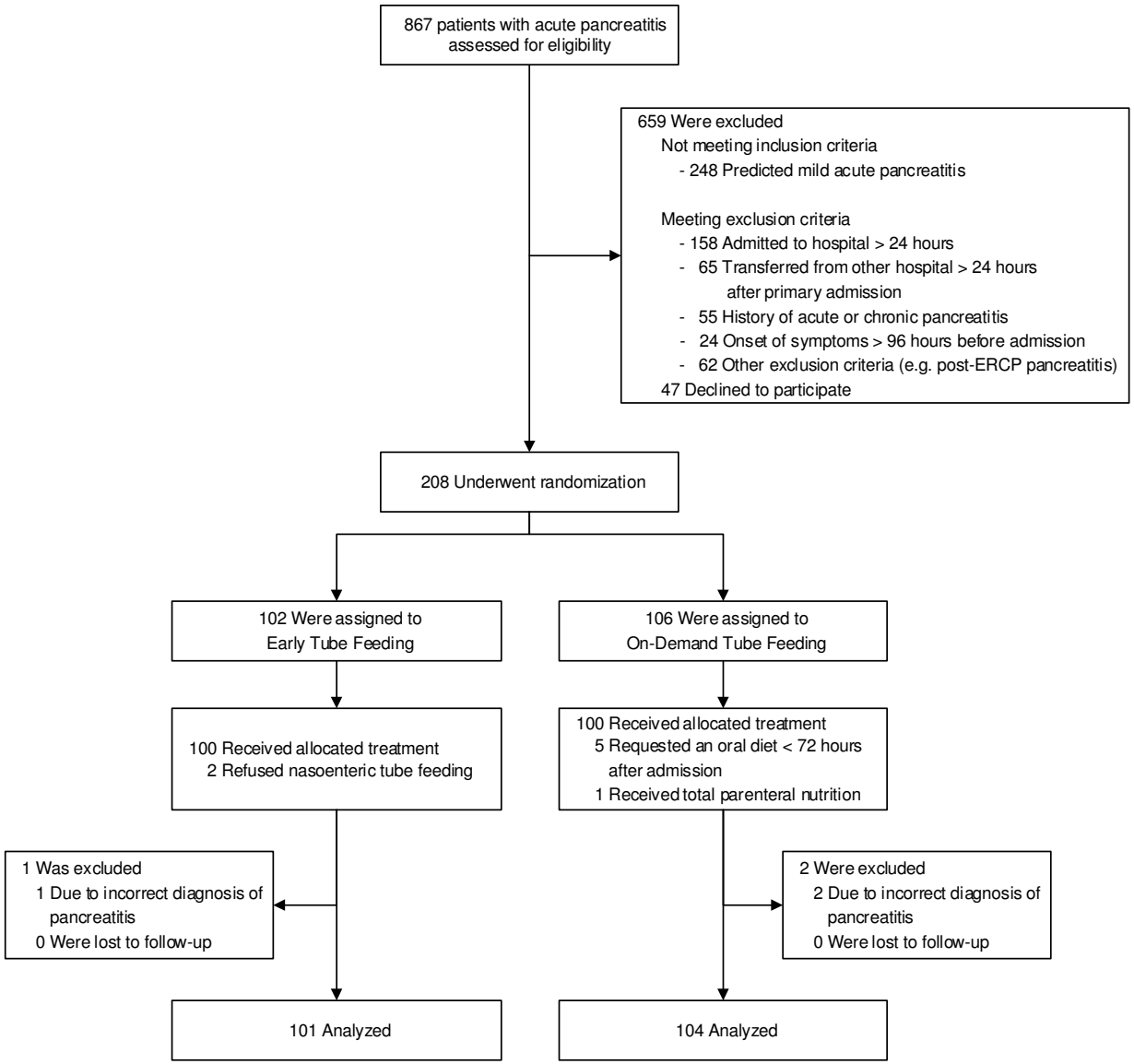


Figure S2: Amount of calories delivered (% of energy target)

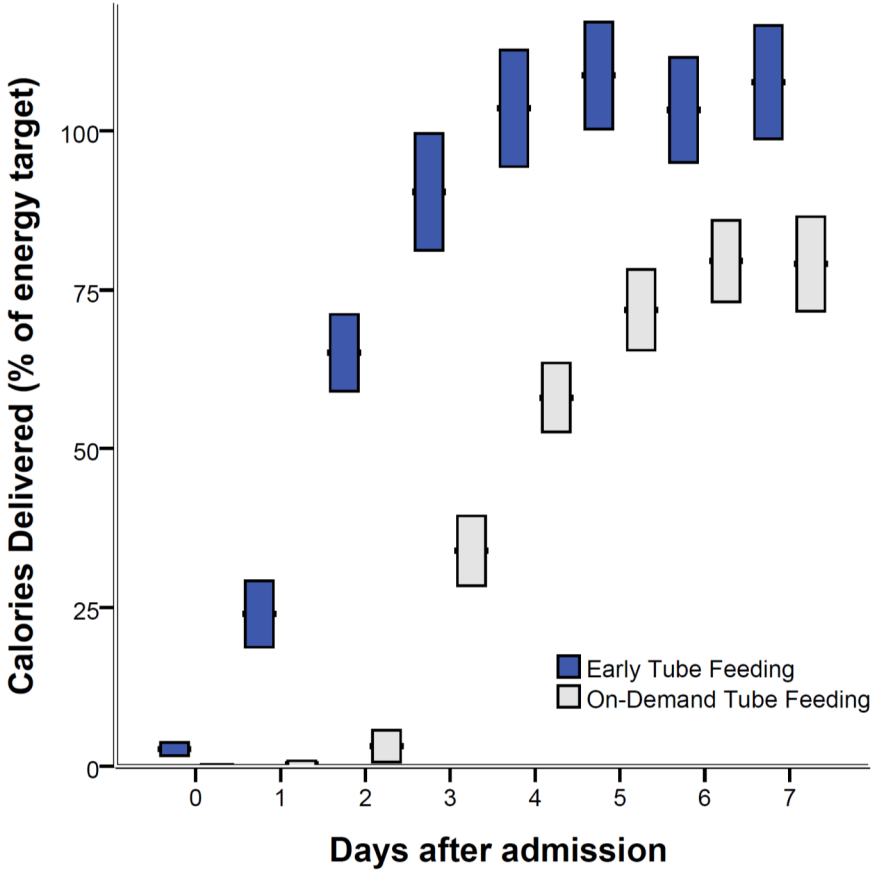


Table S1. Time to start of Early or On-Demand Nasoenteric Tube Feeding			
Time to start – hrs*	**Early Tube Feeding (N = 101)**	**On-Demand Tube Feeding (N = 104)**	**P value**
From randomization	8 (2-20)	64 (50-69)	<0.001
From presentation to the emergency ward	23 (18-27)	72 (69-79)	<0.001
From onset of symptoms	41 (27-54)	91 (77-117)	<0.001

* Values are medians and interquartile ranges.

Table S2. Baseline Characteristics of the Patients – additional information^		
Characteristic	**Early Tube Feeding (N = 101)**	**On-Demand Tube Feeding (N = 104)**
Coexisting condition – no. (%)		
Cardiovascular disease	62 (61)	51 (49)
Pulmonary disease	14 (14)	16 (15)
Chronic renal insufficiency	3 (3)	0 (0)
Diabetes	17 (17)	20 (19)
Other systemic disease	26 (26)	25 (24)
ASA class on admission – no. (%)‡		
I: healthy status	24 (24)	26 (25)
II: mild systemic disease	59 (58)	55 (53)
III: severe systemic disease	16 (16)	22 (21)
IV: severe systemic disease constant threat to life	2 (2)	1 (1)
Disease severity		
Blood Urea Nitrogen – mg/dL	22±12	21±12
Renal failure – no. (%)	8 (8)	9 (9)
Cardiovascular failure – no. (%)	2 (2)	1 (1)
Single-organ failure – no. (%)††	34 (34)	31 (30)

^ Plus-minus values represent means±SD.

‡ ASA denotes American Society of Anesthesiologists.

†† Organ failure was defined as a modified Marshall score of 2 or more (on a scale of 0 to 12 with higher score indicating more severe disease) as proposed in the revised Atlanta classification of acute pancreatitis.

Table S3. Results of subgroup analyses for primary end point*				
Subgroup – No. (%)	**Early Tube Feeding**	**On-Demand Tube Feeding**	**Risk Ratio (95% CI)**	**P value**
Predefined				
APACHE II ≥13	14/32 (44)	14/29 (48)	0.92 (0.57 – 1.49)	0.80
Post hoc				
SIRS at randomization	23/63 (37)	25/70 (36)	1.02 (0.70 – 1.48)	1.00
BMI <25 or ≥35	10/32 (31)	6/36 (17)	1.48 (0.90 – 2.42)	0.25

*Data are number and percentages. Tests for interaction were not significant (P>0.05).

Figure S3. Inflammatory response during the first week after admission as depicted by daily APACHE II scores (A), serum C-reactive protein levels (B) and presence of SIRS (C). For Figures A and B, the boxes represent 95% confidence intervals and the horizontal lines within the boxes represent the means. For Figure C the height of the boxes represents the number of patients.

Figure S3A.

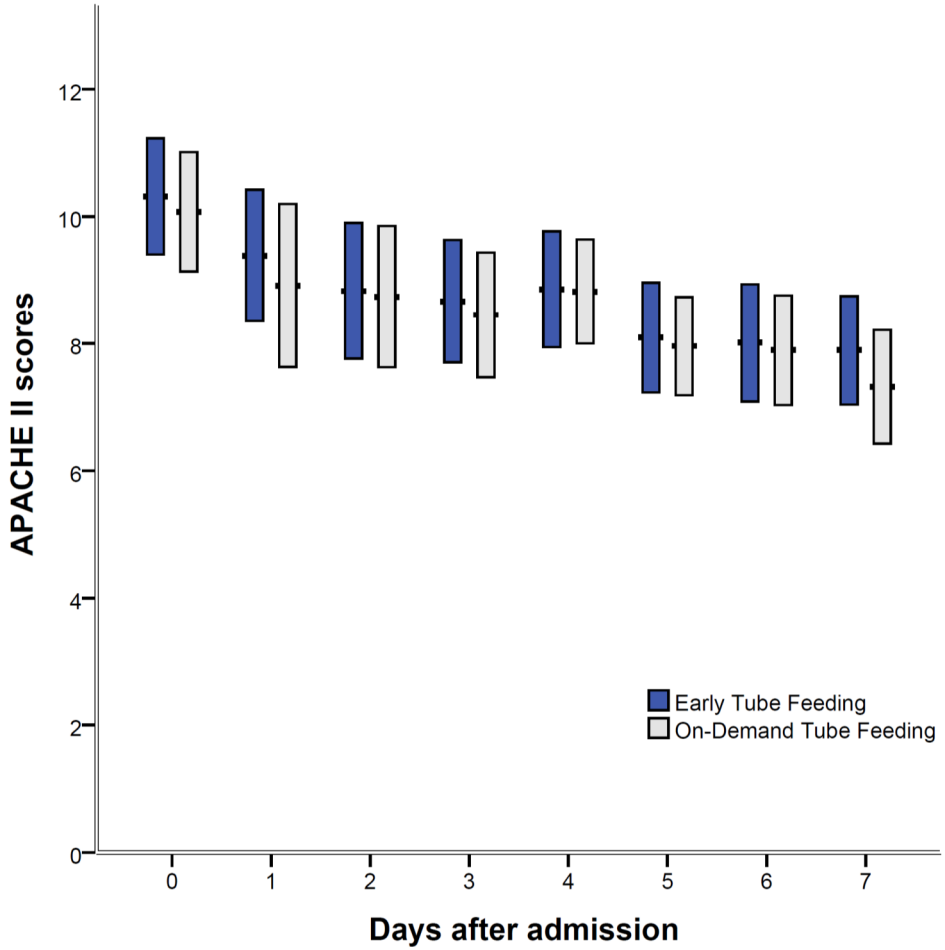


Figure S3B.

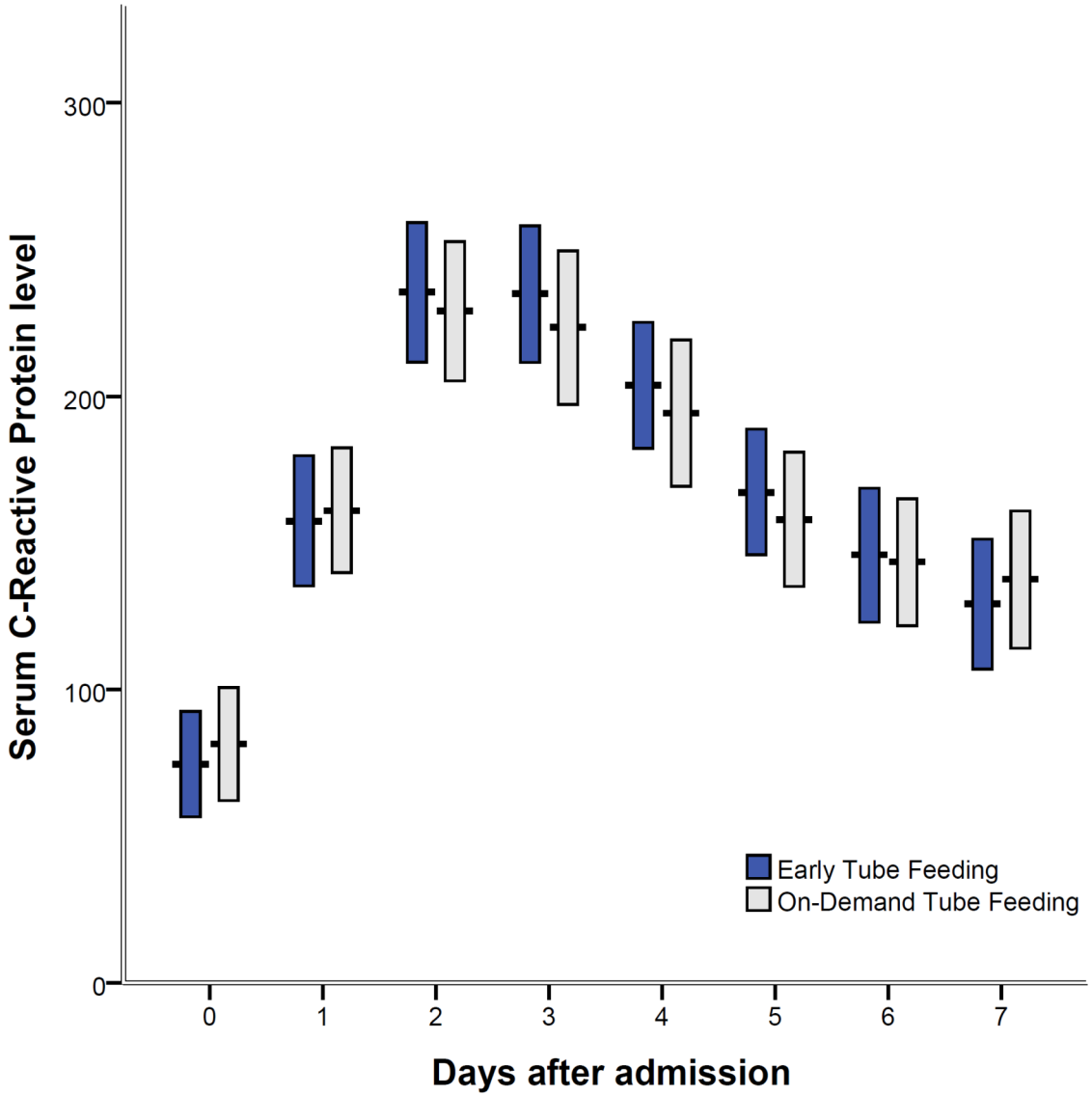

Serum C-Reactive Protein level
300
200
100
0
0
1
2
3
4
5
6
7
Days after admission
Early Tube Feeding
On-Demand Tube Feeding

Figure S3C.

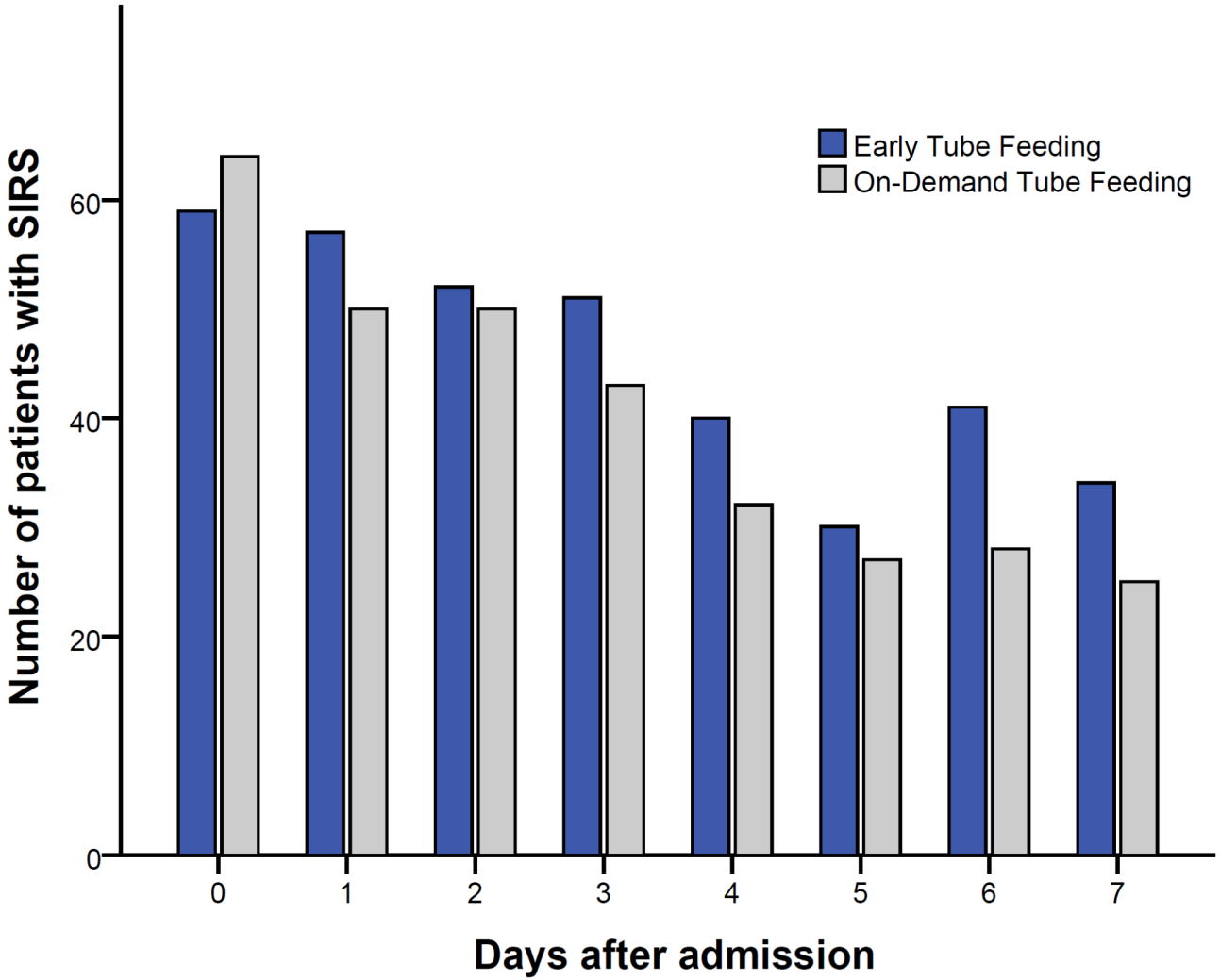

Early Tube Feeding
On-Demand Tube Feeding
Number of patients with SIRS
60
40
20
0
0
1
2
3
4
5
6
7
Days after admission

Table S4. Healthcare utilization			
Outcome	**Early Tube Feeding (N = 101)**	**On-Demand Feeding (N = 104)**	**P value^**
Days in hospital#	15 (10 – 22)	14 (9 – 25)	0.98
Days in ICU##	5 (3 – 14)	6 (3 – 23)	0.70
Interventions - Total no. (range per patient)			
Nasojejunal tube placements‡	145 (0 – 6)	57 (0 – 11)	<0.001
ERCP	37 (0 – 3)	50 (0 – 6)	0.76
Percutaneous catheter drainage**	24 (0 – 13)	46 (0 – 15)	0.13
Endoscopic transgastric drainage or necrosectomy**	8 (0 – 7)	6 (0 – 2)	0.43
Surgical necrosectomy**	3 (0 – 1)	7 (0 – 2)	0.49
Other interventions†	39 (0 – 3)	49 (0 – 3)	0.58
Radiology - Total no. (range per patient)			
X-ray (chest or plain abdominal)	449 (0 – 39)	592 (0 – 69)	0.84
CT	232 (0 – 16)	283 (0 – 19)	0.38
MRCP or MRI	17 (0 – 2)	16 (0 – 2)	0.65
Microbiology cultures	2 (0 – 6)	3 (0 – 7)	0.49
Visits to outpatient clinic	2 (1 – 6)	2 (1 – 4)	0.39
Visits to general practitioner	2 (1 – 4)	2 (1 – 4)	0.30
Visits to physiotherapist – Total no. (range per patient)	226 (0 – 40)	299 (0 – 93)	0.85

Continuous data are median and interquartile ranges (IQR) or total number per study group and range per patient when indicated.

ICU denotes intensive care unit. ERCP denotes Endoscopic Retrograde Cholangiopancreaticography. CT denotes Computed Tomography. MRCP denotes Magnetic Resonance Cholangiopancreaticography. MRI denotes Magnetic Resonance Imaging.

[#] Including readmissions.

[##] For patients admitted in the ICU for at least 24 hours.

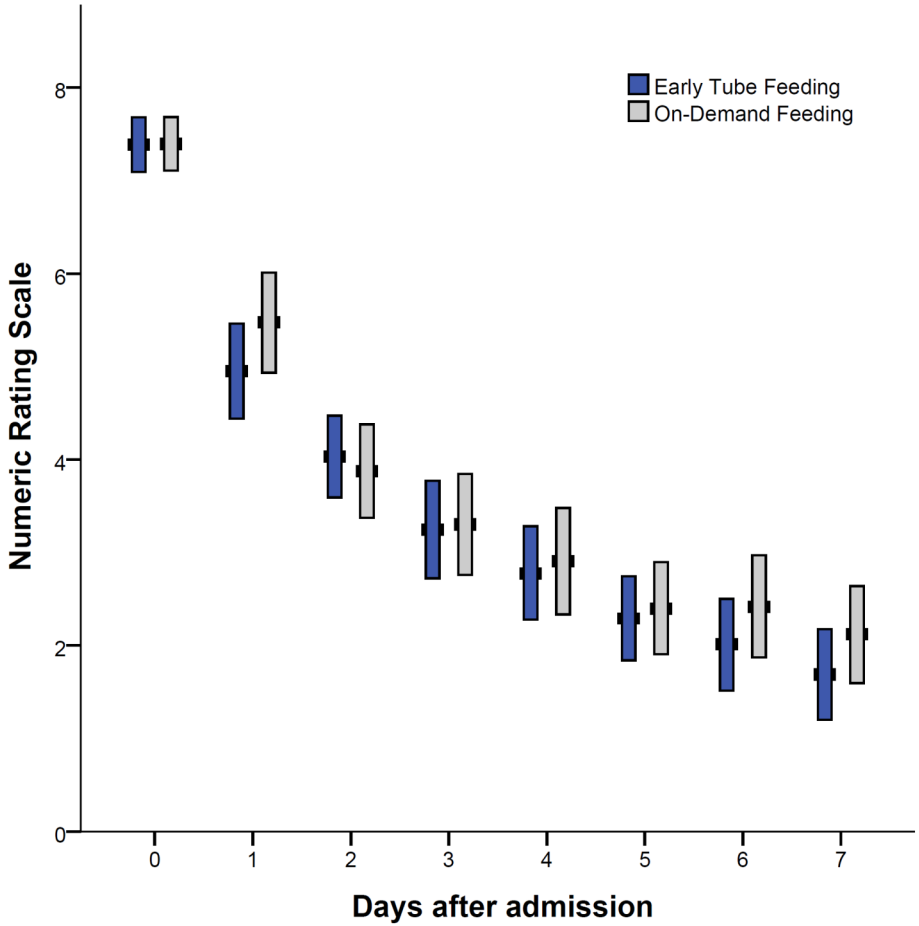
[‡] Endoscopically or radiologically and including replacements after dislodging or obstruction.

** For necrotizing pancreatitis.

[†] For example cholecystectomy for biliary pancreatitis.

^ P value calculated with Mann-Whitney U test.

Figure S4. Abdominal pain during the first week after admission.



Abdominal pain measured daily during the first week on a scale from 0 to 10, with 10 meaning the most severe pain imaginable, i.e. the Numeric Rating Scale.

Table S5. Adverse Events other than primary and secondary endpoints*		
Adverse Events	**Early Nasoenteric Feeding (N = 101)**	**On Demand Feeding (N = 104)**
Gastro-intestinal		
Bowel ischemia	2	1
Abdominal compartment syndrome	0	1
Peritonitis	0	1
Perforation of a hollow viscus	1	2
Entero-cutaneous fistula	1	0
Volvulus	1	0
Acute cholecystitis or cholangitis	8	7
Bile duct injury	1	0
Bleeding after ERCP[#]	1	0
Dislocated percutaneous transhepatic biliary catheter	0	1
Dislocated percutaneous gallbladder catheter	0	1
Suspected gastrointestinal blood loss	1	7
Colitis	1	0
Ascites	2	0
Clostridium infection	0	2
Cardiovascular		
Acute Coronary Syndrome	0	2
Atrial Fibrillation	3	11
Myocardial Infarction	2	3
Congestive heart failure	10	5
Pericarditis	2	0
Portal thrombosis	0	2
Malignant hypertension	2	2
Postoperative bleeding	0	1
Pulmonary		
Pulmonary embolus	2	0
Exacerbation of chronic obstructive pulmonary disease	1	0
Pleural fluid requiring percutaneous catheter drainage	1	1
Neurologic		
Brain herniation	0	1
Delerium	3	5
Headache	1	0

Peroneal nerve palsy	0	1
Critical illness polyneuropathy	1	3
Urinary tract		
Urinary Tract Infection	10	9
Pyelonephritis	1	0
Hematuria	0	1
Other		
Gout	1	0
Infection of epidural catheter	1	1
Surgical site infection	1	0
Hyperkalemia	2	0
Hypokalemia	3	3
Hyponatremia	2	0
Hyperglycemia	1	4
Exocrine pancreatic insufficiency	0	2

* Adverse events as noted in case record forms by attending physicians and reported to the Data and Safety Monitoring Board. These adverse events were not predefined in the study protocol.

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Authors' contributions

OJB, HCvS, MGB, MAB, CHD, HvG, BvR, BJW, UAA, HGG and several other members of the study group participated in the design of the study.

OJB, SvB and TLB collected the data.

OJB performed the statistical analyses apart from the primary end point which was performed by the independent statisticians.

OJB drafted the first and subsequent versions of the manuscript.

All authors read and approved the final manuscript.

HGG supervised the current study.

The authors vouch for the accuracy and completeness of the data and analyses.