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Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial

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ABSTRACT

Background/objectives: There is substantial evidence of superiority of enteral nutrition (EN) to parenteral nutrition in acute pancreatitis (AP) treatment, but few studies evaluated its effectiveness compared to no intervention. The objective of our trial was to compare the effects of EN to a nil-by-mouth (NBM) regimen in patients with AP.

Methods: Patients with AP were randomized to receive either EN via a nasojejunal tube initiated within 24 h of admission or no nutritional support. Systemic inflammatory response syndrome (SIRS) was assessed as the primary outcome. Secondary outcomes included mortality, organ failure, local complications, infected pancreatic necrosis, surgical interventions, length of hospital stay, adverse events and inflammatory response intensity. Outcomes were compared using Student's t-test and Mann–Whitney U test as appropriate.

Results: 214 patients were randomized in total, 107 to each group. SIRS occurrence was similar between groups, with 48 (45%) versus 51 (48%), respectively (RR 0.94; 95% CI 0.71–1.26). No significant reduction of persistent organ failure (RR 0.81; 95% CI 0.52–1.27) and mortality (RR 0.59; 95% CI 0.28–1.23) was present in the EN group. There were no significant differences in other outcomes between the groups. When analyzing the occurrence of SIRS and mortality in subgroup of patients with severe disease no significant differences were noted.

Conclusion: Our results showed no significant reduction of persistent organ failure and mortality in patients with AP receiving early EN compared to patients treated with no nutritional support (NCT01965873).

Introduction

Over decades traditional approaches to treating acute pancreatitis (AP) patients included fasting with or without concomitant use of total parenteral nutrition (TPN). According to the rationale the avoidance of stimulation of the exocrine pancreas should have reduced the inflammation and slowed down the progression of the disease, while, at the same time, the use of TPN should have improved the patients' nutritional status. However, this concept was not supported by clinical trials, and consequently nutritional management of AP changed over time. Today there is substantial experimental evidence proving that administration of enteral nutrition helps preserve gut barrier integrity and function, reduces colonic bacterial overgrowth, and diminishes endotoxin and bacterial translocation [1–3]. Studies on the management of trauma and burn patients showed that EN decreases the systemic inflammatory response and reduces septic complications. Furthermore, EN is associated with far less complications than TPN, and is less expensive [4,5]. AP-related clinical trials showed certain advantages of the use of EN regarding the attenuation of inflammation, the length of hospital stay and the occurrence of infectious complications. While two trials reported a significant decrease in mortality rate [6,7], other randomized trials did not confirm a significant reduction in mortality and organ failure [8–10], and one trial showed an even higher overall early complication rate in patients receiving EN [11]. In view of a rather small sample size and other methodological issues, whether nutritional support is

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beneficial for the outcome of AP remains an open question, and more adequately powered randomized trials are needed.

According to the recently published guidelines, EN is recommended as the preferable nutritional approach for the prevention of infectious complications in severe acute pancreatitis (SAP). TPN should be avoided, unless nutritional requirements cannot be met by enteral route, EN is not tolerated or available. Mild AP is not typically a cause of nutritional status deterioration and therefore specific nutritional intervention is not needed. Oral intake can be started as soon as the patient is able to tolerate it [12].

The aim of our study was to compare the beneficial and harmful effects of enteral nutrition administered via nasojejunal route versus the nil-by-mouth regimen treatment in patients with acute pancreatitis and an APACHE II $\geq$ 6.

Patients and methods

Study design

We conducted a prospective, randomized clinical trial on the use of enteral nutrition in patients with acute pancreatitis. Our local ethics committee approved the study protocol. As our national laws and regulations did not require protocol registration at the time the study was designed, we registered the protocol several years after study commencement at www.ClinicalTrials.gov (NCT01965873). All authors had access to study data and have approved the final manuscript.

Participants

Patients suffering from first AP attack, irrespective of etiology, were enrolled in the study. Inclusion criteria were: the onset of symptoms consistent with AP within 72 h before admission to the hospital; a 3-fold increase in serum amylase (normal value less than 90 U/L) or lipase (normal value less than 160 U/L) concentrations; a predicted disease severity defined as an Acute Physiology and Chronic Health Evaluation (APACHE) II score $\geq$ 6, calculated within the first 24 h from admission. Patients younger than 18 years of age, as well as pregnant and breastfeeding women were excluded from the trial. A signed informed consent was obtained from all participants.

Interventions

Patients were randomly assigned in a 1:1 ratio to one of the two groups, according to a computer generated sequence. Randomization was performed by the hospital pharmacist who was unaware of the participants' characteristics and was not otherwise involved in the study. Patients in the intervention group received EN delivered via a nasojejunal feeding tube (Freka® Trelumina, Fresenius Kabi AG, Germany). The tube was placed endoscopically, and its placement confirmed radiographically. Nutritional support, supplying daily 105 kJ (25 kcal)/kg and 1.5 g/kg of protein based on ideal body weight, was provided within 24 h of admission. Patients received a semi-elemental, high protein formula enriched with glutamine and arginine (Alitraq®, Abbott Nutrition, Ireland). The nutritional support started at 25 ml/h and increased every 6 h by 10 ml/h, until the target rate of 100 ml/h was reached within 48 h. EN administration was continued for a minimum of seven days. Failure to provide adequate nutrition was defined as the inability to maintain adequate nasojejunal tube placement, and the inability to achieve 50% of maintenance energy needs after five days of EN administration. Patients in the NBM group did not receive nutritional support. An oral diet was gradually instituted to both groups, starting with clear liquids on the third day of the protocol, and progressing to a low-fat diet on the fifth day, if tolerated by the patients. When the patients were able to receive 50% of their maintenance energy requirements through fluid diet, the rate of EN was halved. Upon achieving this goal and starting the low-fat diet with no occurrence of pain, EN was stopped. Both study groups received intravenous fluid replacement via peripheral veins, consisting of crystalloid (0.9% saline and 5% glucose) and colloid (10% hydroxyethyl starch and 3.5% plasma expander) solutions in a 3:1 ratio. Fluid replacement was based on the volume of the lost fluid, calculated from the difference of measured fluid intake and output. Upon patient's hospital admission fluid replacement was started and continued individually according to the clinical status. Standard symptomatic treatment was the same for both groups. Antibiotic prophylaxis with imipenem 500 mg i.v. three times a day was administered to all patients during the first ten days. A contrast-enhanced abdominal CT scan was performed in all patients between the third and seventh day of hospitalization in order to confirm diagnosis. Additional CT examinations were performed if required by clinical indications.

Outcomes

Systemic inflammatory response syndrome (SIRS) was assessed as the primary outcome measure. SIRS was defined as presence of at least two following parameters for a continuous period of $\geq$48 h: body temperature > 38 °C or <36 °C; heart rate > 90 beats per minute; hyperventilation with a respiratory rate > 20 breath per minute or a $PaCO_2$ < 32 mmHg; and white blood cell count > 12,000/mm^3 or <4000/mm^3 [13]. Mortality was initially set as the primary outcome, but due to a lower observed mortality rate than expected, this was changed to SIRS, while the estimated sample size was calculated as appropriate (see discussion). Marshall organ dysfunction scoring system (MODS) was used to define organ failure in the case of cardiovascular, renal and respiratory system function [14]. Secondary outcome measures comprised: mortality, organ failure, local complications as defined by the Atlanta criteria (pancreatic necrosis, peripancreatic fluid collection, pseudocyst, and pancreatic abscess) [15]; infected pancreatic necrosis; surgical interventions; length of hospital stay; adverse events; and inflammatory response intensity assessed by C-reactive protein (CRP) measured on day 1 and 3 of admission. We performed subgroup analyses for mortality and SIRS according to disease severity. After the publication of the Revised Atlanta criteria in 2012 [16], a radiologist unaware of patients allocation reassessed all the performed abdominal CT scans and reclassified local complications according to the newly published criteria. Patient severity stratification was also performed post hoc, according to the new guidelines.

Sample size

Sample size calculation was performed for a two-sample comparison of proportions with a presumed alpha error of 0.05 and power of 0.8. The proportion of patients suffering from SIRS in the EN and NBM group were 0.4 and 0.6, respectively [17]. Estimated required sample size for each group was 107 patients.

Statistical analysis

Statistical analysis was performed on an intention-to-treat (ITT) principle. Results for dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Normally distributed data were statistically compared using Student's t-test, while for non-normally distributed data the Mann–Whitney U test was implemented. A two-tailed P < 0.05 was considered statistically

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significant. Missing data were managed on a last observation carried forward principle.

Results

Five hundred and thirty-eight patients admitted to a tertiary care setting in Rijeka, Croatia, between May 2007 and February 2012 were screened for potential enrollment, of which three hundred and twenty-four patients were excluded (reasons given in Fig. 1). Of the 214 patients eligible for consent, 107 were randomized to each group. Baseline demographic and clinical characteristics (Table 1) of both groups were similar. Enteral nutrition was started at a median of 4 h after admission (range 30 min to 14 h), and at a median of 11 h after symptom onset (range 6–36 h). Ingestion of small amounts of clear liquids was started in both groups on the third day, and a low-fat initial meal was tolerated on the fifth day by approximately 39% (42/107) and 47% (50/107) of patients in the EN and NBM groups, respectively.

Primary outcome measures

At baseline SIRS was present in 62 (58%) patients receiving nutrition and in 66 (62%) patients receiving no nutritional support (RR 0.94; 95% CI 0.75–1.17, P = 0.577). At 48 h SIRS resolved in 18 and 17 patients in the EN and NBM groups, respectively, while developing in 4 and 2 patients, respectively, bringing the final number of 48 (45%) and 51 (48%) patients with SIRS, respectively (RR 0.94; 95% CI 0.71–1.26, P = 0.681).

Secondary outcome measures

An overall 12.6% mortality rate was found in the study. Ten patients (9.4%) died in the EN group, and 17 (15.9%) in the NBM group, showing an RR of 0.59 (95% CI 0.28–1.23, P = 0.156). The most common cause of death was multiple organ failure. Persistent organ failure (>48 h) developed in 26 (24.3%) EN group patients and 32 (29.9%) NBM group patients, while multiple organ failure was present in 10 (9.3%) and 16 (15%) patients, respectively. The RRs for both outcomes were 0.81 (95% CI 0.52–1.27, P = 0.358) and 0.63 (95% CI 0.3–1.31, P = 0.215), respectively. Shock was present in 5 (4.7%) and 12 (11.2%) patients in the EN and NBM groups (RR 0.42; 95% CI 0.15–1.14), respectively. Fourteen patients (13.1%) developed renal failure in the EN group compared to 21 patients (19.6%) in NBM group (RR 0.67; 95% CI 0.36–1.24). No significant difference occurred with development of respiratory failure either, with 20 (18.7%) versus 22 (20.6%) cases in the EN and NBM groups, respectively (RR 0.91; 95% CI 0.53–1.56). There was no statistically significant difference in the occurrence of transient organ failure as well, with 12 (11%) cases in the EN group and 11 (10%) cases in the NBM group (RR 1.09; 95% CI 0.50–2.36; P = 0.825).

The occurrence of local complications was similar in both groups. Fifty-four (50.5%) patients in the EN group developed any type of local pancreatic complication detectible on CT, versus 46 (43%) patients in the NBM group, RR 1.17 (95% CI 0.88–1.57, P = 0.275). Results for specific local complications according to the revised Atlanta criteria are given in Table 2. Infection of necrotic pancreatic tissue was suspected, based on clinical and laboratory data, in 7 (6.5%) EN group patients and confirmed by fine needle aspiration (FNA) in two. Percutaneous drainage was performed in both patients and surgical necrotic debridement in one of the latter. Infected necrosis was ruled out by FNA in the remaining patients. Four of the seven patients died, including one with confirmed infected necrosis. Nine NBM patients were suspected to have infected necrosis. This was discarded by FNA in seven patients and not performed due to

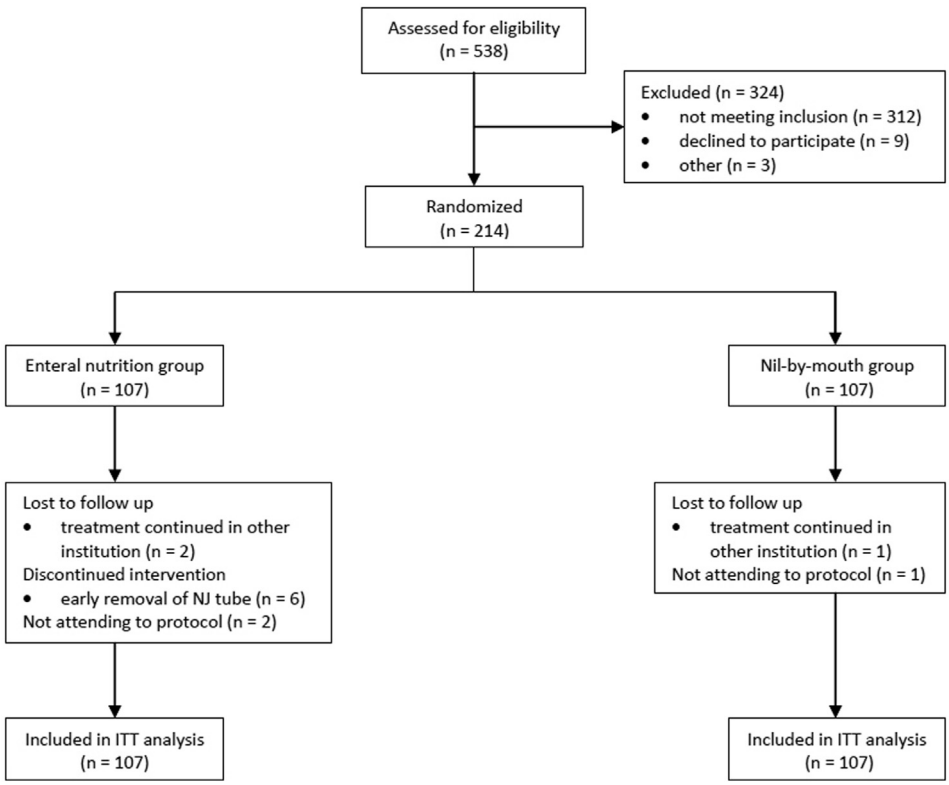

Fig. 1. Patients recruitment and follow-up.

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Table 1
Baseline demographic and clinical characteristics of patients.

Group	Enteral nutrition group (n = 107)	Nil-by-mouth group (n = 107)	P-value
Age, median (IQR)	69 (28–88)	72 (26–90)	NS
Gender, M:F	63:44	57:50	NS
Etiology, n (%)			
Biliary	68 (63)	64 (60)	NS
Alcohol	17 (16)	23 (21)	
Hypertriglyceridemia	5 (5)	1 (1)	
Post-ERCP	4 (4)	2 (2)	
Drug-induced	0 (0)	1 (1)	
Unknown	13 (12)	16 (15)	
APACHE II score, mean (SD)	9.84 (3.26)	9.74 (4.06)	NS
Ranson's score, mean (SD)	2.98 (1.69)	2.83 (1.81)	NS
CTSI, mean (SD)	2.64 (2.73)	2.84 (2.78)	NS
BMI, mean (SD)	28.63 (4.83)	27.48 (4.32)	NS
Creatinine, μmol/L			
Baseline, mean (SD)	95.91 (39.04)	96.83 (34.58)	NS
At 48 h, mean (SD)	80.4 (45.27)	79.15 (40.56)	
Mean difference (95% CI)	−15.51 (−27.33 to −3.69)	−17.68 (−28.95 to −6.41)	
BUN, mmol/L			
Baseline, mean (SD)	10.79 (2.62)	11.24 (2.98)	NS
At 48 h, mean (SD)	5.79 (4.28)	6.01 (3.03)	
Mean difference (95% CI)	−5 (−5.99 to −4.01)	−5.22 (−6.06 to −4.38)	
Hematocrit			
Baseline, mean (SD)	0.412 (0.06)	0.438 (0.047)	NS
At 48 h, mean (SD)	0.377 (0.047)	0.391 (0.041)	
Mean difference (95% CI)	−0.035 (−0.05 to 0.019)	−0.047 (−0.059 to −0.035)	
Intravenous fluids, ml			
Day 1, mean (SD)	4487.5 (1222.01)	5185 (1261.37)	0.0001
Day 3, mean (SD)	3222.5 (861.79)	4015 (708.03)	<0.0001
Day 5, mean (SD)	3177.5 (957.09)	3332.5 (821.31)	0.21

IQR = interquartile range; APACHE II = Acute Physiology and Chronic Health Evaluation II; CTSI = Computed Tomography Severity Index; BMI = body mass index; SD = standard deviation; BUN = blood urea nitrogen.

Table 2
Occurrence of specific local complications according to the Revised Atlanta criteria.

Group	Enteral nutrition group (n = 107)	Nil-by-mouth group (n = 107)	RR (95% CI)	P-value
Pts with local complications, n (%)	54 (50.5)	46 (43)	1.17 (0.88–1.57)	NS
Necrosis, n (%)	37 (34.6)	33 (30.8)	1.12 (0.76–1.65)	NS
Peripancreatic fluid collection, n (%)	17 (15.9)	13 (12.2)	1.31 (0.67–2.56)	NS
Pseudocyst, n (%)	3 (2.8)	1 (0.9)	3.0 (0.32–28.39)	NS
Acute necrotic collection, n (%)	35 (32.7)	32 (29.9)	1.1 (0.74–1.63)	NS
Walled-off necrosis, n (%)	7 (6.5)	5 (4.7)	1.4 (0.46–7.27)	NS

technical reasons in two patients. Four patients in the NBM group died. We observed no significant difference in length of hospital stay, with a mean of 16.67 ± 8.67 days in EN group, and a mean of 15.53 ± 8.13 days in the NBM group (P = 0.536). Four patients in the EN group had recurrence of pain, which was not associated with worsening of pancreatitis. No other adverse events were registered in both groups. CRP levels in both groups showed a statistically significant rise between day 1 and day 3. The mean CRP levels increased from 75.91 ± 91.12 to 167.88 ± 106.42 (P < 0.0001) in the EN group. In the NBM group the mean CRP level rose from 73.81 ± 75.05 to 157.72 ± 75.72 (P < 0.0001). However, there were no statistically significant differences in CRP values between the groups on day 1 (P = 0.854) and day 3 (P = 0.423).

We analyzed SIRS and mortality in subgroups of patients stratified according to disease severity, defined by the Revised Atlanta criteria [16]. Our data suggest that patients treated with EN are less prone to develop the severe form of the disease characterized by persistent organ failure. No fatalities were found in patients with moderate AP, and one patient with mild pancreatitis died in the NBM group due to complications related to gastric cancer. There were no differences in the occurrence of SIRS in all patient subgroups. Detailed data are shown in Table 3.

Discussion

This prospective randomized study compared the effects of enteral nutrition administered in the early course of acute pancreatitis beyond the ligament of Treitz via an endoscopically placed nasojejunal feeding tube to a nil-by-mouth treatment regimen. At the time we started our research use of EN in severe AP patients was not strictly implemented in treatment guidelines, and according to the 2006 UK guidelines EN was an optional, not mandatory treatment in severe AP cases [18]. Performing a single center randomized trial requires time, and although several trials have been published demonstrating advantage of EN over TPN, our trial ended before the official publication of the latest American guidelines advocating strict use of EN in severe AP [12].

According to the results of several experimental and clinical trials, enteral nutrition is emerging as a relevant and integral part of severe acute pancreatitis management. Several studies have shown beneficial effects of EN on the reduction of organ failure and mortality [6,7,19]. According to data from meta-analyses EN is preferred over TPN in acute pancreatitis treatment as it significantly reduces mortality, organ failure, and infectious complications [20,21]. However, these conclusions have been made solely on studies comparing EN to TPN, where TPN has never been acknowledged as

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Table 3
Occurrence of mortality and SIRS according to specific grade of disease severity as defined by the Revised Atlanta criteria.

Group	Enteral nutrition group	Nil-by-mouth group	RR (95% CI)	P-value
Severe AP, n (%)	26 (24.3)	32 (29.9)	0.81 (0.52–1.27)	NS
Mortality, n (%)	10 (38.5)	16 (50)	0.77 (0.42–1.40)	NS
SIRS, n (%)	21 (80.8)	25 (78.1)	1.03 (0.80–1.34)	NS
Moderate AP, n (%)	35 (32.7)	27 (25.2)	1.30 (0.85–1.98)	NS
Mortality, n (%)	0 (0)	0 (0)		NS
SIRS, n (%)	19 (54.3)	16 (59.3)	0.95 (0.56–1.61)	NS

the standard of treatment in AP, and is potentially, by itself, associated with higher occurrence of infectious complications. The effectiveness of TPN has been reported questionable in other non-surgical, non-pediatric and non-oncologic patients as well [22]. The association between malnutrition and adverse clinical outcomes is well established, however existence of a clear causal link has not been confirmed. Malnutrition in AP may be precipitated by an intense cytokine response and the development of severe SIRS, which is directly associated with severe disease and a higher complication rate [22]. Therefore, only by comparing an intervention to a similar control group, which in this case is comparing EN to no nutritional support, is it possible to estimate the effectiveness of EN on outcomes of patients with AP. To our knowledge only one trial by Lu et al. showed a significant reduction of mortality and organ failure when using EN comprised of ebselen and ethyl-hydroxyethyl starch compared to no intervention [23]. Petrov et al. in their study of EN versus nil-by-mouth regimen in patients with mild to moderate AP did not assess mortality or organ failure as outcomes [24], while a recent study by Bakker et al. showed no superiority of early enteral feeding compared to on-demand enteral feeding on mortality and rate of infections [25]. At present, our study is the largest trial that compares the use of EN to no nutritional support in AP.

Our trial failed to show a beneficial effect of EN in the early course of acute pancreatitis. There are several factors possibly influencing results that should be addressed. Patients treated with no nutritional support received a significantly higher amount of parenteral fluids than enterally fed patients given the analyzed data on day 1 and day 3 (Table 1). However, patients in the enteral nutrition group received additional fluids via the nasojejunal route. The difference in early amount of intravenous fluid resuscitation volume and the higher overall volume received by the nil-by-mouth group could be a potential factor that affects the ultimate lack of significant differences in study outcomes, as the importance of adequate early fluid resuscitation has been widely emphasized in literature before [26].

Furthermore, mortality was initially defined as the primary outcome. However, since the observed mortality rate and disease severity were lower than expected, this was changed to SIRS, and the required sample size was calculated accordingly. This of course is a potential source of bias in the trial that needs to be stated. The most common cause of death in the early phase (within the first week) of AP is the development of persistent organ failure as a consequence of SIRS. Around two thirds of patients in both groups had SIRS at presentation which is in accordance with other published data [17,25]. This is often not associated with infection, but mostly a result of host immune response to acinar cell injury. Experimental studies have shown that the traditionally accepted theory of premature trypsinogen activation is not sufficient to cause and maintain SIRS, while gene susceptibility as well as intra-acinar activation of the nuclear factor kappa B signaling pathway have an important role in the pathogenesis of SAP [27]. Whether early administration of EN can modulate the immune response and ameliorate SIRS is still debatable. In order to evaluate the potential effects of EN on the early course of disease and its complications, as well as early causes of death, authors determined SIRS as the primary outcome. All deaths in our study occurred in patients having persistent single or multiple organ failure, except for the one in the NBM group who died of gastric cancer-related complications. It is therefore of utmost importance to timely identify these patients and start aggressive treatment to resolve organ failure. According to the Revised Atlanta classification SAP is defined only by the presence of persistent organ failure [16]. Consequently, a number of patients previously defined as suffering from SAP (i.e. having local and/or systemic complication(s) according to the original Atlanta criteria) have been excluded from this subgroup and allocated into a new category of patients suffering from intermediate (or moderate) type of AP. These patients are often diagnosed with various levels of pancreatic necrosis based on CT scan and/or APACHE II score $\geq$ 8 due to underlying chronic illnesses (e.g. chronic obstructive pulmonary disease). As previous studies do not differentiate between the two subgroups, it is possible that the observed beneficial effects of EN could have been a consequence of misclassification rather than an effect of EN on SAP *per se*. Our results show that mortality in this subgroup is low, regardless of the use of EN, and that these patients should be clearly differentiated from severe cases in order to assess the potential effects of EN on SAP. Although not conventionally chosen as a threshold of severity, at time of trial design we defined an APACHE II $\geq$ 6 as an inclusion criteria based on several previously published trials [28–30] in order to include also patients with so called intermediate disease. By performing subgroup analysis based on disease severity we intended to determine a difference in effect of EN depending on disease severity and to establish a direct effect on organ failure and mortality.

In most clinical studies SIRS has not been assessed as an outcome of AP. The intensity of inflammatory reaction is often assessed by measuring CRP levels or specific cytokines. Doley et al. found no difference in initial levels as well as in the decrease of CRP between the enterally and parenterally fed patients [9]. A recent study of Sun et al. compared the effects of early start of EN (within 48 h after admission) to delayed start of EN (8 days after admission) on immune function. Patients who were given early EN had significantly lower CRP levels, CD4+ T-lymphocyte percentage, and CD4+/CD8+ ratio from the 7th day of hospitalization onward. This was followed by a significantly lower incidence of SIRS and MOF, but with no difference in mortality [31]. Comparatively, in our study there were no differences in the CRP levels between the two groups on days 1 and 3. A definite drawback is the lack of analysis of further CRP levels' flow. Observations of the available CRP values show a clear decrease in the majority of our patients between days 5 and 7. These findings also support the lack of beneficial influence of EN administered in the early phase of acute pancreatitis on early complications in our results.

The late phase of SAP can be characterized by the development of infected pancreatic necrosis and other systemic septic complications, which significantly increase mortality. Experimental and clinical studies suggest that infectious complications are a

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consequence of disruption of gut mucosal integrity due to bowel rest, metabolic abnormalities of enterocytes and ischemia induced by hemodynamic impairment. All above mentioned mechanisms are supposed to facilitate bacterial overgrowth and promote bacterial and endotoxin translocation into the lymphatic system and circulation, potentially causing septic complications. Therefore, early administration of EN should help preserve the structural and functional integrity of the intestinal barrier [32–35]. Our study failed to find a significant difference in the rate of infected necrosis, although these outcomes were confirmed in a very limited number of patients. A potential explanation for this phenomenon could be found in the routine use of antibiotic prophylaxis in our patients. Due to a very low number of clinical events, and the fact the study was not primarily designed to assess these outcomes, there is not enough available evidence to evaluate and conclude on the potential effects of EN on the late phase of the course of AP and the development of complications, such as infected necrosis.

In summary, EN is feasible and generally well-tolerated, and has been shown to be more effective than TPN in treating AP. The most probable mechanisms by which EN achieves positive effects in the management of AP consist of the preservation of bowel mucosal integrity, the reduction of bacterial overgrowth and translocation, as well as the avoidance of TPN-related complications. However, when compared to no intervention, EN in various diseases, including AP has not been unequivocally found to be beneficial [29,36,37]. Based on our results, there is no evidence that EN administered in the early course of acute pancreatitis has beneficial effects on systemic inflammatory processes which can lead to more severe disease cases and detrimental clinical outcomes.

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