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Original article

Timing of enteral nutrition in acute pancreatitis: Meta-analysis of individuals using a single-arm of randomised trials

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ABSTRACT

Introduction: In acute pancreatitis, enteral nutrition (EN) reduces the rate of complications, such as infected pancreatic necrosis, organ failure, and mortality, as compared to parenteral nutrition (PN). Starting EN within 24 h of admission might further reduce complications.
Methods: A literature search for trials of EN in acute pancreatitis was performed. Authors of eligible trials were requested to provide the data of all patients in the EN-arm of their trials. A meta-analysis of individual patient data was performed. The cohort of patients with EN was divided into patients receiving EN within 24 h or after 24 h of admission. Multivariable logistic regression, adjusting for predicted disease severity and trial, was used to study the effect of timing of EN on a composite endpoint of infected pancreatic necrosis, organ failure, or mortality.
Results: Observational data from 165 individuals from 8 randomised trials were obtained; 100 patients with EN within 24 h and 65 patients with EN after 24 h of admission. In the multivariable model, EN started within 24 h of admission compared to EN started after 24 h of admission, reduced the composite endpoint from 45% to 19% (adjusted odds ratio [OR] of 0.44; 95% confidence interval [CI] 0.20–0.96). Within the composite endpoint, organ failure was reduced from 42% to 16% (adjusted OR 0.42; 95% CI 0.19–0.94).
Conclusions: In this meta-analysis of observational data from individuals with acute pancreatitis, starting EN within 24 h after hospital admission, compared with after 24 h, was associated with a reduction in complications.

Introduction

Acute pancreatitis is the most common gastro-intestinal reason for hospitalization in the United States with over 274.000 admissions annually [1]. Inpatient costs are estimated to exceed 2.5 billion dollar per year. The mortality of patients with acute pancreatitis is determined by the presence of organ failure or

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition; OR, odds ratio; CI, confidence interval; RD, risk differences; APACHE-II score, acute physiology and chronic health evaluation-II score; CRP, C-reactive protein.

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infection of pancreatic necrosis [2,3]. Organ failure and infected pancreatic necrosis are associated with a mortality of up to 30%. To improve outcome, early intervention strategies in patients with acute pancreatitis aim at reducing the duration of organ failure and the development of infected pancreatic necrosis. So far, several randomised trials, using pharmacotherapeutics, antibiotics, or probiotics, have failed to reduced the rate of either organ failure or infected pancreatic necrosis [4–6]. However, enteral nutrition (EN) has shown that, when compared to parenteral nutrition (PN), it reduces the rate of infected pancreatic necrosis, organ failure and mortality [7].

In acute pancreatitis, in the first hours after onset of symptoms, injury to the pancreatic gland initiates a local inflammatory response which causes the release of cytokines, chemokines, neutrophils and other inflammatory mediators [8,9]. This evolving inflammatory response can cause a series of pathophysiological events in distant organs and especially the gut, including disturbed gastrointestinal motility, bacterial overgrowth, reduction of arterial blood flow, increased permeability of the gastrointestinal mucosal barrier and bacterial translocation [10–13]. Increased bacterial translocation exacerbates the systemic inflammatory response and may cause distant infections such as infected pancreatic necrosis [14]. So, the gut plays a pivotal role in the development of organ failure and infected necrosis in acute pancreatitis. As a potent stimulator of intestinal blood flow and gut motility, early intraluminal EN is hypothesized to preserve intestinal mucosa, prevent bacterial translocation, reduce the inflammatory response and potentially reduce the rate of organ failure and infected necrosis [15]. In a meta-analysis of 15 randomised trials in critically ill patients, but without patients with acute pancreatitis, EN started within 24 h of admission reduced the rate of infections [16].

To investigate whether the hypothesized benefit of starting EN very early in acute pancreatitis is supported by evidence from clinical trials, we performed a meta-analysis of individual patient data from the EN-arm of randomised trials.

Methods

Search strategy and selection of trials

A systematic literature search was performed for randomised trials investigating a very early start of EN. However, the results of this literature search showed that no randomised trials have been performed that specifically investigated a very early start of EN compared to a delayed start of EN. Therefore, a second literature search was performed that was directed at randomised trials with early EN in one arm of the study in adults with acute pancreatitis. To investigate the effect of timing of EN based on data from randomised trials with an EN-arm, we aimed to aggregate the individual data of all patients who were included in the EN-arm of the trials. The following inclusion criteria were used: consecutive patients with acute pancreatitis, use of a validated classification system or generally accepted parameter to predict severity on admission, and initiation of EN according to a prespecified protocol.

We searched in Pubmed, Embase, Cochrane, CINAHL and Web of knowledge with the Highly Sensitive Search Strategy [17] and the search term 'acute pancreatitis' (date of literature search 31st of January 2011). In addition, Haynes' clinical query (broad, sensitive search) in combination with 'acute pancreatitis' was used to check if all trials were retrieved with the first strategy [18]. Titles and abstracts were screened for eligibility and reference lists of reviews, meta-analyses and all included studies were cross-checked manually to search for additional eligible papers.

Trial eligibility and quality assessment

The quality of included studies was assessed for the presence of allocation concealment, reporting of incomplete data, selective outcome reporting and intention-to-treat analysis [19]. Two authors (OJB and SvB) independently assessed the eligibility of the selected full text publications. The primary investigators of all selected trials were asked for the raw data of their trials. In case primary investigators did not reply they were contacted at regular intervals or attempts were made to reach them by telephone. The data obtained were checked for consistency, integrity of randomisation and follow-up. All trials obtained informed consent and ethics approval.

Outcome variables

The primary outcome was a composite of mortality, infected pancreatic necrosis, or organ failure. This composite endpoint was chosen as infected pancreatic necrosis and organ failure are the major causes of mortality in acute pancreatitis [2,3]. Secondary outcomes were the individual components of the primary outcome.

Prespecified subgroups

Prespecified subgroup analyses were performed for patients with predicted severe pancreatitis (regardless of the predictive score used) and for patients with necrotizing pancreatitis. These subgroups were prespecified as most complications occur in patients with predicted severe pancreatitis and in patients with necrotizing pancreatitis [20].

Statistical analysis

To assess whether timing of EN is associated with the incidence of the different endpoints, we performed a one stage meta-analysis using logistic regression analysis. In this model, the independent variables were: EN within or after 24 h after admission and the potential confounders (age, gender, etiology, presence of necrosis, and predicted severity based on Acute Physiology And Chronic Health Evaluation-II [APACHE-II], Imrie or modified Glasgow score, Ranson score, or CRP). A dummy variable was added to adjust for in between variance and to identify each study within the regression analysis [19]. To increase statistical efficiency and to reduce bias, we developed the covariate 'predicted severe pancreatitis'. Patients were classified as having 'predicted severe pancreatitis' if these patients either had an APACHE-II $\geq$8, an Imrie score $\geq$3, a Ranson score $\geq$3, or a CRP $\geq$150 mg/L. This covariate was available for all patients and was used in the model instead of the separate severity predictors. Risk differences (RD) and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and the number-needed-to-treat (NNT) were calculated for the composite primary endpoint and for the secondary endpoints. Sensitivity analyses were planned to assess whether results would differ if data from unavailable trials would have been included in the meta-analysis [19].

Results

Out of 20.320 abstracts retrieved from 5 different databases, we identified 13 trials that met the eligibility criteria (Fig. 1) [21–33]. Data from 6 trials [23,24,30,32,33] could not be retrieved because data were no longer available ($n = 3$) or no contact was established with the principal investigators despite repeated attempts ($n = 3$). After personal communication with one of the authors, data from 29 consecutive patients with acute pancreatitis and EN, who were

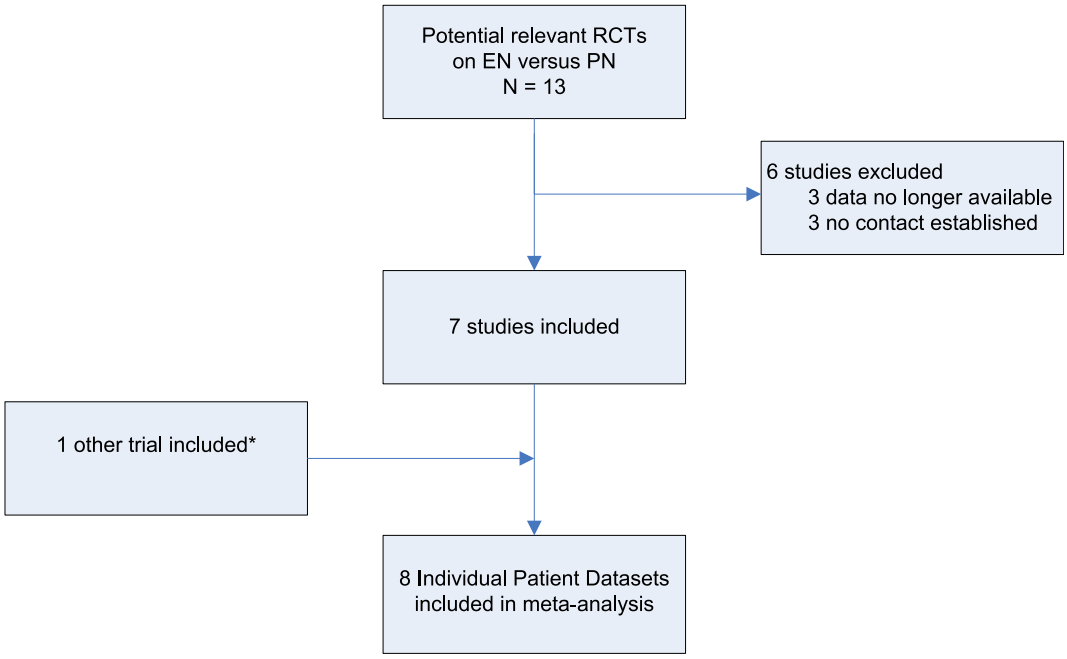

Fig. 1. Selection of studies for individual patient data meta-analysis on timing of enteral nutrition. NOTE *After personal communication with the author, data from one other trial were included. This trial was published after the literature search for this study.

considered for inclusion in another randomised trial that was pending publication at the time of our literature search, was added to the dataset [34]. Out of 13 potentially eligible trials, including 325 patients treated with EN, we obtained the data from 165 patients (51%).

From one trial, which included additional patients during a second phase of recruitment to reach the estimated sample size, only data from the first phase of recruitment were available [21]. One trial compared EN with conventional therapy instead of comparing EN to PN [31]. Conventional therapy consisted of a nil-by-mouth regimen until patients were able to tolerate oral nutrition. Although, no patients within the conventional therapy group received EN within 24 h, they were included in the study. These patients were included for two reasons. First, duration of fasting prior to start of EN or oral diet was carefully recorded. Second, they did not receive PN and hence were not prone to its potential complications. Therefore, these patients were included in the cohort of patients with start of EN after 24 h.

Table 1 shows the main characteristics of the 8 included studies. Five of 8 trials included patients with predicted severe pancreatitis based on APACHE-II, Imrie score, or CRP [22,25–27,29,31]; one trial included patients who did not clinically improve after 48 h after admission and recorded Ranson score as a predicted severity parameter [21]; one trial included patients with predicted severe pancreatitis and inability to tolerate oral fluids [27], and one trial included consecutive patients with acute pancreatitis without signs of severe or critical disease on admission [34]. All trials used a protocol for the timing of start of EN which varied from within 6 h

Table 1
Characteristics of the 8 included trials in the meta-analysis.

Study	Country	Year	Patients with EN	Participants	EN protocol			Outcomes
					Timing	Route	Type	
Kalfarentzos [26]	Greece	1997	18	APACHE ≥ 8, Imrie ≥ 3, CRP ≥ 120, Balthazar D or E	<48 h of admission	Nasojejunal	Semielemental	Complications
Powell [31]	UK	2000	28[a]	APACHE ≥ 7, Imrie ≥ 3	<24 h vs after clinical improvement	Nasojejunal	Polymeric	Modulation of markers of the inflammatory response, complications
Abou-Assi [21]	USA	2002	20[b]	No clinical improvement after 48 h	>48 h of admission	Nasojejunal	Elemental	Duration of hospitalization, complications
Olah [29]	Hungary	2002	41	APACHE ≥ 6, Imrie ≥ 3, CRP ≥ 150	<24 h of admission	Nasojejunal	Elemental	Complications
Gupta [25]	UK	2003	8	APACHE ≥ 6	<6 h of diagnosis	Nasojejunal	Polymeric	Measurements of systemic inflammation, complications
Louie [27]	Canada	2005	10	Ranson ≥ 3, intolerance for oral fluids after a maximum of 96 h	<24 h of enrolment	Nasojejunal	Semielemental	Measures of nutrition and inflammation, complications
Casas [22]	Spain	2006	11	APACHE ≥ 8, CRP ≥ 150, Balthazar D or E	<48 h of admission	Nasojejunal	Semielemental	Acute inflammatory response, complications
Petrov [34]	New Zealand	2012	29	Consecutive patients with acute pancreatitis	<24 h of admission	Nasogastric	Semielemental	Complications

NOTE. EN denotes enteral nutrition.
[a] In the original study, one patient was excluded after randomisation [31]. According to the intention-to-treat principle this patient has been included in the present study.
[b] Original study recruited patients in 2 phases [21]. For this meta-analysis only data from the first phase of the study were available.

of diagnosis to after 48 h of admission. The methodological quality of included trials was generally high, although none of the studies were blinded for intervention (as this was not possible due to the nature of interventions) and none of the trials used a blinded endpoint assessment. Allocation concealment was adequate. All patients randomised completed the study and data for the composite endpoint were complete. Individual patient data showed that despite protocol, timing of EN differed between patients within trials and ranged from start on day of admission to start on the 10th day after admission. One hundred patients (61%) were given EN within 24 h of admission and 65 patients (39%) received EN more than 24 h after admission.

Baseline characteristics are given in Table 2. As definitions and parameters used for predicted severe pancreatitis differed between trials, no particular score or parameter was available for all patients (see Table 2). The overall parameter 'predicted severe pancreatitis' based on APACHE-II score ≥8, Imrie score ≥3, Ranson score ≥3, or CRP >150 mg/L was available for all patients. Although, 5 out of 8 trials aimed to include patients with predicted severe pancreatitis, individual data showed that only 95 of 165 patients (58%) were deemed to have predicted severe pancreatitis (as defined in the methods section). In the cohort of patients who received EN after 24 h, a significantly greater proportion was defined as having predicted severe pancreatitis (74% compared to 47%; $P < 0.001$). The proportion of patients with necrotizing pancreatitis did not differ between groups. The modified Glasgow score differed significantly between both groups (median 2 versus 4; $P = 0.01$) but was only available for 47% of patients.

Our one-stage meta-analysis, using multivariable logistic regression analysis and adjusting for predicted severity and trial, showed that EN within 24 h after admission was associated with a lower incidence of the primary composite endpoint (Table 3). Nineteen percent of patients with EN within 24 h suffered from infected pancreatic necrosis, organ failure, or mortality compared to 45% of patients with EN after 24 h. This resulted in an adjusted OR of 0.44 (95% CI 0.20–0.96) and an NNT of 4 patients. Within the composite endpoint, a significant reduction was seen in the rate of organ failure following EN within 24 h (16% compared to 42%; adjusted OR 0.42; 95% CI 0.19–0.94, NNT 4).

Table 2
Baseline characteristics of patients in the 8 trials.

	EN within 24 h ($n = 100$)	EN after 24 h ($n = 65$)	*P* value	Missing Data ($n = 165$)
Age	53 (42–66)	55 (45–70)	0.20	1 (1%)
Women	37 (37%)	22 (34%)	0.74	0 (0%)
Etiology			0.06	0 (0%)
Alcohol	44 (44%)	23 (35%)		
Biliary	35 (35%)	25 (39%)		
Hypertriglyceridemia	0 (0%)	3 (5%)		
Medication	1 (1%)	4 (6%)		
Other	4 (4%)	4 (6%)		
Idiopathic	16 (16%)	6 (9%)		
Predicted severe pancreatitis[a]	47 (47%)	48 (74%)	<0.001	0 (0%)
APACHE-II Score	8 (6–12)	9 (7–13)	0.17	72 (44%)
CRP on admission	53 (18–129)	110 (34–229)	0.05	47 (28%)
CRP within 48 h of admission	186 (77–285)	149 (58–286)	0.66	118 (72%)
Imrie or modified glasgow score	2 (1–4)	4 (2–5)	0.01	78 (47%)
Necrotizing pancreatitis	40 (40%)	29 (45%)	0.40	17 (10%)

Continuous variables are median (interquartile range). EN denotes enteral nutrition. APACHE-II = Acute Physiology and Chronic Health Evaluation II; CRP = C-reactive protein.
[a] Predicted severe pancreatitis defined as APACHE-II score ≥8, Imrie score ≥3, Ranson score ≥3, or CRP >150 mg/L (on admission or within 48 h of admission).

Table 3
Outcome of patients with enteral nutrition within and after 24 h of admission.

	EN within 24 h	EN after 24 h	Adjusted OR (95% CI)	NNT
All patients	**(n = 100)**	**(n = 65)**		
Infected pancreatic necrosis, organ failure, or mortality	19 (19%)	29 (45%)	0.44 (0.20–0.96)	4
Infected pancreatic necrosis	7 (7%)	9 (14%)	0.65 (0.21–1.99)	15
Organ failure	16 (16%)	27 (42%)	0.42 (0.19–0.94)	4
Mortality	3 (3%)	8 (12%)	0.38 (0.09–1.56)	11
Predicted severe pancreatitis[a]	**(n = 47)**	**(n = 48)**		
Infected pancreatic necrosis, organ failure, or mortality	18 (38%)	26 (54%)	0.55 (0.24–1.26)	6
Infected pancreatic necrosis	7 (15%)	9 (19%)	0.66 (0.21–1.99)	26
Organ failure	15 (32%)	24 (50%)	0.51 (0.22–1.20)	6
Mortality	3 (6%)	7 (15%)	0.46 (0.11–1.93)	12
Necrotizing pancreatitis	**(n = 40)**	**(n = 29)**		
Infected pancreatic necrosis, organ failure, or mortality	14 (35%)	17 (59%)	0.50 (0.18–1.43)	4
Infected pancreatic necrosis	7 (18%)	9 (31%)	0.56 (0.17–1.81)	7
Organ failure	11 (28%)	15 (52%)	0.48 (0.16–1.42)	4
Mortality	3 (8%)	5 (17%)	0.67 (0.13–3.53)	10

EN denotes enteral nutrition.
CI = Confidence Interval; NNT = Number Needed to Treat; OR = Odds Ratio.
[a] Predicted severe pancreatitis defined as APACHE-II score ≥8, Imrie score ≥3, Ranson score ≥3, or CRP >150 mg/L.

Results for the prespecified subgroups are given in Table 3. In the subgroups of patients with predicted severe pancreatitis and in patients with pancreatic necrosis results were consistently better if EN was started within 24 h. However, none of these differences reached statistical significance. In the subgroup of patients with predicted severe pancreatitis, the composite endpoint was reduced from 54% to 38% (adjusted OR 0.55, 95% CI 0.24–1.26). We were unable to perform the planned sensitivity analyses as from the publications of the unavailable trials the essential data on start of EN could not be extracted.

Discussion

This meta-analysis of individual patient data from a single-arm of randomised trials showed that start of EN within 24 h of admission was associated with a reduction in the composite endpoint of mortality, infected pancreatic necrosis, and organ failure. In a multivariable logistic regression analysis adjusting for a significant difference in predicted severity at baseline, the NNT was 4, i.e. 4 patients should be treated with EN to prevent one endpoint. Within the composite endpoint, it also reduced the onset of organ failure compared to EN after 24 h of admission.

This study is the first individual patient data meta-analysis of randomised trials in acute pancreatitis. A collaboration between physicians from 7 countries resulted in a dataset of patients from 8 trials. Individual patient data meta-analyses have certain advantages over meta-analyses of the literature such as the ability to perform additional analyses, adequate subgroup analyses and multivariable regression analyses [19]. From the previous published data of the trials included in this meta-analysis, the timing of EN in individual patients cannot be extracted. The individual data on the exact start of EN in each patient enabled us to perform a comparison between a start of EN within and after 24 h of hospital admission. Second, the individual data enabled the construction of a multivariable logistic regression model. In this model, we were able to adjust for the potential confounding effect of the baseline characteristic 'predicted severe pancreatitis'. In addition, by adding a dummy variable for each trial, we adjusted for potential hidden confounders and heterogeneity between trials. Third, no large scale randomised trials on timing of EN in acute pancreatitis have been performed. So, for a meaningful comparison, it is necessary to

combine data from several studies. At this moment, this observational meta-analysis of single-arm data from randomised trials provides the most accurate conclusions based on the available literature and provides a basis for development of future guidelines. Fourth, the individual data enabled us to perform subgroup analyses. In the subgroup analyses of patients with predicted severe pancreatitis and in patients with necrotizing pancreatitis, the effect of EN within 24 h seemed consistently in favour of EN within 24 h of admission although statistical significance was not reached. This lack of statistical significance may be due to a type II error or a false negative result. A larger sample of patients with predicted severe pancreatitis might show a significant reduction. Unfortunately in acute pancreatitis such large studies are performed infrequently. Last, the NNT for the primary endpoint was 4. If this beneficial effect of EN turns out to be only half as strong as was found in this study, it will still be an important clinical improvement that can be achieved with a relatively simple, safe and inexpensive treatment strategy.

This meta-analysis also has several weaknesses. The aim of the included randomised trials was mainly to compare EN to PN instead of investigating timing of EN. This study is a secondary analysis of single-arm data from randomised trials and should therefore be considered as a meta-analysis of prospective observational studies (instead of a pooled comparison of two randomized interventions). Second, the composite primary outcome of this study was not the primary outcome in the included trials. One could argue that data collection on secondary endpoints might be less accurate. The endpoints used in this study are, however, well-known and established complications of acute pancreatitis [2,3]. Even more, mortality, infected pancreatic necrosis, and organ failure, are major clinical events that do not require extensive additional investigations to be detected during standard care. Hence, we believe that the risk of missing endpoints is low. Third, it is known that combined outcomes can make a treatment seem more, or less, effective than it really is [35]. We therefore performed sensitivity analyses using different composite outcomes, which all showed similar results. By using such a composite endpoint we were able to aggregate our data and generalise results. This was critical to accomplish our aim of establishing whether early EN is effective in patients with pancreatitis. Fourth, inclusion criteria differed between the trials. Different cut-offs were used to define predicted severe pancreatitis. A combination of available APACHE-II score, Imrie score, Ranson score, and CRP resulted in an overall binary 'predicted severe pancreatitis' variable, which was available for all patients. Previous studies have also used a combination of scores or parameters to define predicted severe pancreatitis [4,26,29]. One trial included patients after a period of fasting of at least 48 h after admission [21]. As a result, patients from that trial could only be included in the cohort of EN after 24 h. Exclusion of patients from that trial did not change results (data not shown). Fifth, of 13 potentially eligible trials, data from only 7 trials were collected (see Fig. 1). Would the results differ if other trials would have been included? We believe the results would not be different as the unavailable trials used similar inclusion criteria and EN regimens. Most importantly, the outcomes from the unavailable trials were comparable to the ones from the trials included in this study [23,24,28,30,32,33]. Unfortunately, the planned sensitivity analyses to statistically confirm the lack of selection bias could not be performed as the start of EN was not available in the published articles.

The results found in this study confirm findings from earlier experimental and clinical studies on the role of EN and its influence on the gut barrier in acute pancreatitis [36]. Intestinal mucosal integrity is compromised in acute pancreatitis. A clinical study in 58 patients with acute pancreatitis showed an early increase in intestinal permeability [11]. Experimental studies have shown that, compared with TPN, EN has the ability to maintain gut barrier function [37,38]. In a small retrospective study of 17 selected patients with acute pancreatitis in the intensive care unit, early initiation of EN was associated with a low mortality rate [39]. A larger retrospective study of 197 patients with predicted severe pancreatitis showed that EN started within the first 48 h after admission might lead to a reduction in mortality, infected pancreatic necrosis, respiratory failure and intensive care admission [40]. A meta-analysis of randomised controlled trials of EN versus PN investigated the effect of timing of EN on clinical outcomes in patients with acute pancreatitis [41]. This was based on the start of nutrition that was described in the manuscripts as opposed to the individual patient data as was used in this study. The outcomes in trials that planned to start EN within 24 h and within 48 h after admission were compared to the outcome in trials that planned to start EN after 24 h and after 48 h, correspondingly. Results suggested that EN administered between 24 and 48 h leads to best clinical outcomes. A recent randomised trial compared EN within 48 h after admission to EN after 8 days of fasting in 60 patients with acute pancreatitis [42]. The primary aim was to investigate immune function. The authors concluded that early EN moderates the excessive immune response. Despite the relative small sample size differences in clinical outcomes were found. Multiple organ dysfunction syndrome, systemic inflammatory response syndrome, pancreatic infection and duration of intensive care stay were significantly reduced in the early EN group.

This study also confirms results found in studies on early EN in critically ill patients in general. In these patients, early EN is recommended as standard treatment [43,44]. This is the result of substantial evidence confirming the benefits of very early initiation of EN in critically ill patients [45]. For example, in a meta-analysis of 15 randomised trials including critically ill patients but no pancreatitis patients, very early EN was associated with a lower incidence of infections (relative risk reduction, 0.45 95% CI 0.30–0.66) [16]. A recent large cohort study in intensive care patients found that EN within 48 h of the start of mechanical ventilation was associated with reduced mortality [46]. This finding is remarkable as all included patients were on vasopressors and required ventilatory support for more than 2 days.

Patients with mild pancreatitis in general do not need tube feeding [47,48]. Oral feeding is feasible in these patients though it may lead to pain relapse in a considerable proportion of patients [49,50]. Patients with severe pancreatitis need nutritional support. To predict on admission whether patients will develop severe pancreatitis, predicted severity scoring systems are usually used. Five out of 8 trials in this study included patients with predicted severe pancreatitis. However, the subgroup of patients with predicted severe pancreatitis in this study consisted of only 95 of 165 (56%) patients. This is explained by the fact that the definition we used for predicted severe pancreatitis is more stringent than the definition used in some of the trials. Specifically, in this study predicted severe pancreatitis was based on an APACHE-II score $\geq$8, while in 2 trials an APACHE-II $\geq$6 [25,26] was used and in one trial an APACHE-II $\geq$7 [31] was used. In addition, one trial did not use a predictive scoring system but included patients that showed no clinical improvement after 48 h [21] and one trial used Ranson $\geq$3 or intolerance for oral fluids [27]. Also, most trials used 48–96 h after admission to stratify patients into predicted mild or predicted severe pancreatitis. In this study, patients were stratified within 24 h into predicted mild or predicted severe based on the individual data on admission. For these reasons, the subgroup of patients with predicted severe pancreatitis in this study is relatively small. On the other hand, when we consider the non-negligible percentage of complications such as organ failure and infected necrosis that occurred in the group of patients that we stratified as having

predicted mild pancreatitis, we can conclude that our stratification has been conservative.

In conclusion, this study found that initiation of EN within 24 h after hospital admission in patients with acute pancreatitis was associated with a large reduction of complications, especially organ failure. Early EN in only 4 patients is needed to prevent complications in one. However, as this was a secondary analysis of single-arm data from a selection of randomised trials and only a subgroup of patients were defined as having predicted severe pancreatitis. Further studies are warranted to investigate the optimal timing of EN administration in patients with acute pancreatitis.

Author contributions

OJB and MMR and several other members of the group designed the study. OJB requested and received the data from the different trials. SvB performed on-site additional data collection. OJB and MMB designed the analysis plan and performed the statistical analysis. OJB drafted the first and subsequent versions of the manuscript. OJB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read, corrected and approved the final manuscript.

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