Systematic Review/Meta-analysis

A meta-analysis of early oral refeeding and quickly increased diet for patients with mild acute pancreatitis

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Abstract

Background/Aim: The objective of the study is to clarify whether early oral refeeding (EORF) and quickly increasing diet (QID) are of benefit to patients with mild acute pancreatitis compared with a traditional oral refeeding strategy.

Materials and Methods: Studies were searched in PubMed, Cochrane library, ScienceDirect, SpringerLink, China Biology Medicine disc and Embase. A meta-analysis was then performed, using relapse of abdominal pain, nausea/vomiting, and length of hospital stay (LOHS) as the evaluation indices.

Results: Eight trials met the inclusion criteria. For the oral refeeding time group, EORF could significantly decrease the LOHS (mean deviation [MD] −1.97; 95% confidence interval (CI) −3.32 to −0.62; $P = 0.004$), and there was no significant difference for relapse of abdominal pain (relative risk [RR] 1.17; 95% CI 0.69–2.00; $P = 0.56$) or nausea/vomiting (RR 1.30; 95% CI 0.19–8.82; $P = 0.79$) when compared with conventional oral refeeding. For the oral refeeding material group, there was no significant difference for relapse of abdominal pain (RR 0.86; 95% CI 0.53–1.40; $P = 0.54$), nausea/vomiting (risk difference −0.01; 95% CI −0.19–0.18; $P = 0.94$), or LOHS (MD −0.88; 95% CI −2.24–0.48; $P = 0.20$) between the QID and stepwise increasing diet groups.

Conclusion: Pure EORF or QID caused no damage to patients with mild acute pancreatitis, and EORF could significantly decrease the LOHS.

Keywords: Abdominal pain, acute pancreatitis, oral refeeding, length of hospital stay

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INTRODUCTION

Acute pancreatitis is one of the most common acute abdominal pains that causes hospitalization worldwide; the annual incidence ranges from 13 to 45 per 100,000 persons.[1] Acute pancreatitis results in nearly 250,000 hospitalizations in the United States each year, incurring costs of approximately 2.2 billion dollars.[2,3] In the United Kingdom, the incidence of pancreatitis increased from 14.8 in 100,000 (1990–1994) to 31.2 in 100,000 (2010–2013) in males, and from 14.5 to 28.3 in 100,000 in females (2010–2013).[4] It seriously threatens people's health and places a huge economic burden on society.

The majority of cases are classified as mild, and oral refeeding is an important step in the course of recovery in patients with mild acute pancreatitis, and its tolerance is

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the basic condition for discharge. Traditionally, the timing and method of restart of oral feeding after mild acute pancreatitis is based on experience rather than scientific research.

Some scholars have investigated oral refeeding time and materials for patients with acute pancreatitis. For the oral refeeding time, the traditional view considers that oral refeeding should not be performed before the abdominal pain is controlled, gastrointestinal function is recovered, and pancreatic enzymes are normalized.[5] By contrast, some researchers believe that normalization of serum lipase is not obligatory[6] and early oral refeeding (EORF), based on returning bowel sounds,[7] feeling of hunger,[8] or immediate oral feeding, is feasible and safe and might accelerate recovery in mild acute pancreatitis.[9,10] Most of the trials of EORF were performed in patients with mild acute pancreatitis. For patients with moderate and severe acute pancreatitis, a prospective randomized controlled clinical trial[11] confirmed the effectiveness and feasibility of EORF based on hunger, which could shorten the length of hospitalization.

In terms of oral refeeding material, the conventional stepwise refeeding protocol starts with a clear liquid diet, and if it is well tolerated, a light diet and full diet are introduced consecutively until the patient can tolerate a full oral diet. Some trials have shown that a full solid diet or a soft diet as the initial meal is well tolerated and may lead to a shorter total length of hospitalization compared with that achieved using a stepwise increasing diet (SID) in mild acute pancreatitis.[7,12-15]

Although differences exist between the traditional and the latest opinions, there has been no large multicenter randomized controlled trial to determine the optimal solution. Therefore, we performed this meta-analysis to compare previous studies to identify the best schedule, which will allow clinicians to select a more effective and safe refeeding strategy for patients with mild acute pancreatitis.

METHODS

Searching for studies

Two independent reviewers searched the following databases: PubMed, Cochrane library, ScienceDirect, SpringerLink, China Biology Medicine disc and Embase.

They combined the following search terms with different forms as much as possible to avoid publication bias: "pancreatitis," "pancreatic inflammation," "refeeding," "oral refeeding," and "oral nutrition."

Eligibility criteria

All published control trials in the last 10 years, written in English, comparing "oral refeeding time" or "oral refeeding material" between the traditional and the latest opinions were included. The criteria for traditional opinion for starting oral refeeding were as follows: abdominal pain was controlled, gastrointestinal function was recovered, and pancreatic enzymes became normalized (conventional oral refeeding [CORF]), a clear liquid diet should be first performed for the stepwise refeeding protocol (SID). For refeeding according to the latest opinion, oral refeeding was performed earlier (EORF) and started with a full solid diet or a soft diet (quickly increasing diet [QID]).

The selected studies were all nonrandomized comparative studies; therefore, they were evaluated using the Methodological Index for Nonrandomized Studies (MINORS),[16] which includes 12 items: a clearly stated aim, inclusion of consecutive patients, prospective collection of data, end points appropriate to the aim of the study, unbiased assessment of the study end point, follow-up period appropriate to the aim of the study, loss to follow-up less than 5%, prospective calculation of the study size, an adequate control group, contemporary groups, baseline equivalence of groups, and adequate statistical analyses. These items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). Publications scoring ≥18 (the maximum possible score was 24) were included.

Screening studies and extracting data

Clinical controlled trials that met the inclusion criteria were screened. All these steps mentioned above were performed independently by two reviewers and then cross-checked to rule out discrepancies; different opinions were resolved by discussion or with the aid of a senior investigator.

Statistical analysis

Relative risk (RR), risk difference (RD), mean deviation (MD), and 95% confidence interval (CI) were used as statistical indices and statistical significance was represented as $P < 0.05$. RevMan 5.1 provided by the Cochrane Collaboration was used to perform this meta-analysis and according to the degree of heterogeneity, a fixed or random-effect model was used. The χ^2 test was used to assess heterogeneity and significance set at $P < 0.10$. The quantity I^2, which describes the percentage of total variation that is caused by heterogeneity rather than chance, was also used to evaluate heterogeneity. An I^2 value of 0–25% indicates no significant heterogeneity, 26–50% indicates low heterogeneity, 51–75% indicates moderate heterogeneity, and 76–100% indicates high heterogeneity.[17]

When I^2 >50%, the random-effect model was performed. Otherwise, the fixed-effect model was used.

RESULTS

Quantity of the included studies

A search of databases identified a total of 530 references (PubMed 56, Cochrane library 24, ScienceDirect 267, SpringerLink 159, China Biology Medicine disc 16, Embase 8).

After scanning the titles and abstracts, and removing duplications, 18 references remained for intensive reading and assessment using MINORS. Finally, eight trials remained to perform this meta-analysis [Figure 1]: four trials to analyze oral refeeding time[6-9] [Table 1], and five trials to analyze oral refeeding material[7,12-15] [Table 2].

Oral refeeding time

The four analyzed trials included 388 patients in this analysis and we assessed the difference between EORF and CORF in terms of abdominal pain, nausea/vomiting, and length of hospital stay (LOHS).

For abdominal pain, the χ^2 and I^2 were 0.82 ($P = 0.67 > 0.1$) and 0%, respectively, suggesting homogeneity among the studies. The fixed-effect model was used and the results showed no significant difference (RR 1.17; 95% CI 0.69–2.00; $P = 0.56$) [Figure 2a]. The included studies were heterogeneous for the comparison of nausea/vomiting ($\chi^2 = 3.56$, $P = 0.06 < 0.1$; $I^2 = 72\%$). Thus, the random-effect model was used and the results revealed no significant differences (RR 1.30; 95% CI 0.19–8.82; $P = 0.79$) [Figure 2b]. For LOHS, the results showed that the included studies were heterogeneous ($\chi^2 = 11.57$, $P = 0.009 < 0.1$; $I^2 = 7$ 4%) and the use of EORF could significantly decrease the LOHS (MD −1.97; 95% CI −3.32 to −0.62; $P = 0.004$) [Figure 2c].

Oral refeeding material

Five trials including 457 patients participated in this analysis and we assessed the difference between QID and SID in terms of abdominal pain, nausea/vomiting, and LOHS.

For abdominal pain, the χ^2 and I^2 were 1.47 ($P = 0.69 > 0.1$) and 0%, respectively, suggesting homogeneity among the

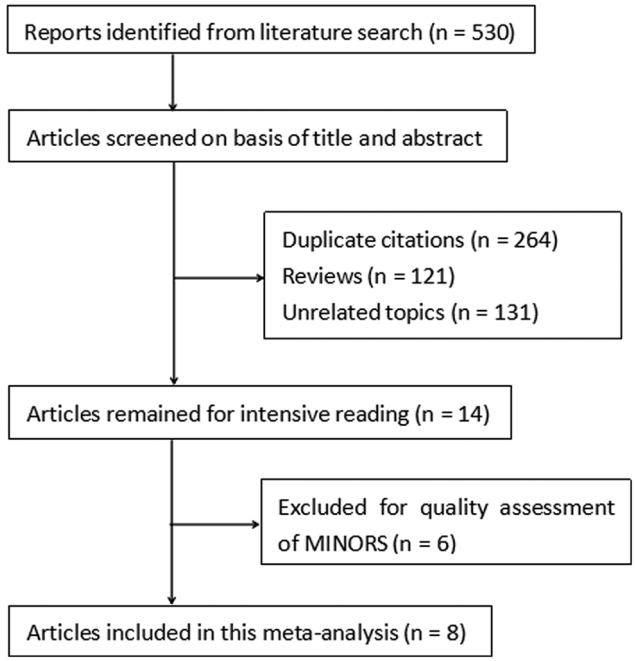

Figure 1: Flow chart of included studies

Table 1: Information from the selected studies for oral refeeding time

Trials	MINORS score	Severity	Group	Oral refeeding time	Oral refeeding material	Patients number	Abdominal pain	Nausea/Vomiting	LOHS
Larino-Noia 2014	20	Mild	EORF	Bowel sounds are present	SID[a]	20	7	5	6 (4-15)
			CORF	Standard time[b]	SID	17	6	1	7 (4-16)
Li 2013	22	Mild	EORF	Subjectively felt hungry	Gradually progressed from clear liquid diet to low-fat diet	75	6		6.8±2.1
			CORF	Symptoms, signs and test results relieve	Gradually progressed from clear liquid diet to low-fat diet	74	3		10.4±4.1
Teich 2010	21	Mild	EORF	Abdominal pain relief	A low-fat diet and tea	69			7 (5-10.5)
			CORF	Lipase below twofold upper limit	A low-fat diet and tea	74			8 (5.75-12)
Eckerwall 2007	20	Mild	EORF	Immediately if tolerated	Liquid	29	9	13	4 (2-10)
			CORF	Standard time[c]	Liquid	30	9	21	6 (2-14)

[a]Stepwise increase from 1207 to 1470, and then to 1767 kcal over 3 days, [b]bowel sounds are present, no abdominal pain, no fever, decreasing pancreas-specific amylase and decreasing blood leukocyte levels to below 15,000/mm^3, [c]abdominal pain has resolved and levels of pancreatic and inflammatory markers have decreased. LOHS: Length of hospital stay; EORF: Early oral refeeding; CORF: Conventional oral refeeding; MINORS: Methodological Index for Nonrandomized Studies; SID: Stepwise increasing diet

Table 2: Information from the selected studies for oral refeeding material

Trials	MINORS score	Severity	Group	Oral refeeding time	Oral refeeding material	Patients number	Abdominal pain	Nausea/Vomiting	LOHS
Larino-Noia 2014	20	Mild	QID	Standard time[a]	Immediately full caloric	18	3	3	7.5 (4-18)
			SID	Standard time	SID[b]	17	6	1	7 (4-16)
Rajkumar 2013	20	Mild	QID	Absence of pain	Soft diet	30	6		4.23±2.08
			SID	Absence of pain	Clear liquid diet	30	6		6.91±2.43
Moraes 2010	23	Mild	QID	Symptoms and signs relieve	A hypocaloric soft diet	70	12		8.2±2.4
			SID	Symptoms and signs relieve	A hypocaloric clear liquid diet	70	14		8.2±2.6
Sathiaraj 2008	19	Mild	QID	Symptoms and signs relieve	Soft diet	49	4	0	5.92±2.978
			SID	Symptoms and signs relieve	A clear liquid diet	52	3	4	8.71±4.995
Jacobson 2007	20	Mild	QID	Symptoms and signs relieve	Low-fat solid diet	55			4 (3-6)
			SID	Symptoms and signs relieve	Clear liquid diet	66			4 (3-5)

[a]Bowel sounds are present, no abdominal pain, no fever, decreasing pancreas-specific amylase and decreasing blood leukocyte levels to below 15,000/mm^3, [b]stepwise increase from 1207 to 1470, and then to 1767 kcal over 3 days. LOHS: Length of hospital stay; MINORS: Methodological Index for Nonrandomized Studies; SID: Stepwise increasing diet; QID: Quickly increasing diet

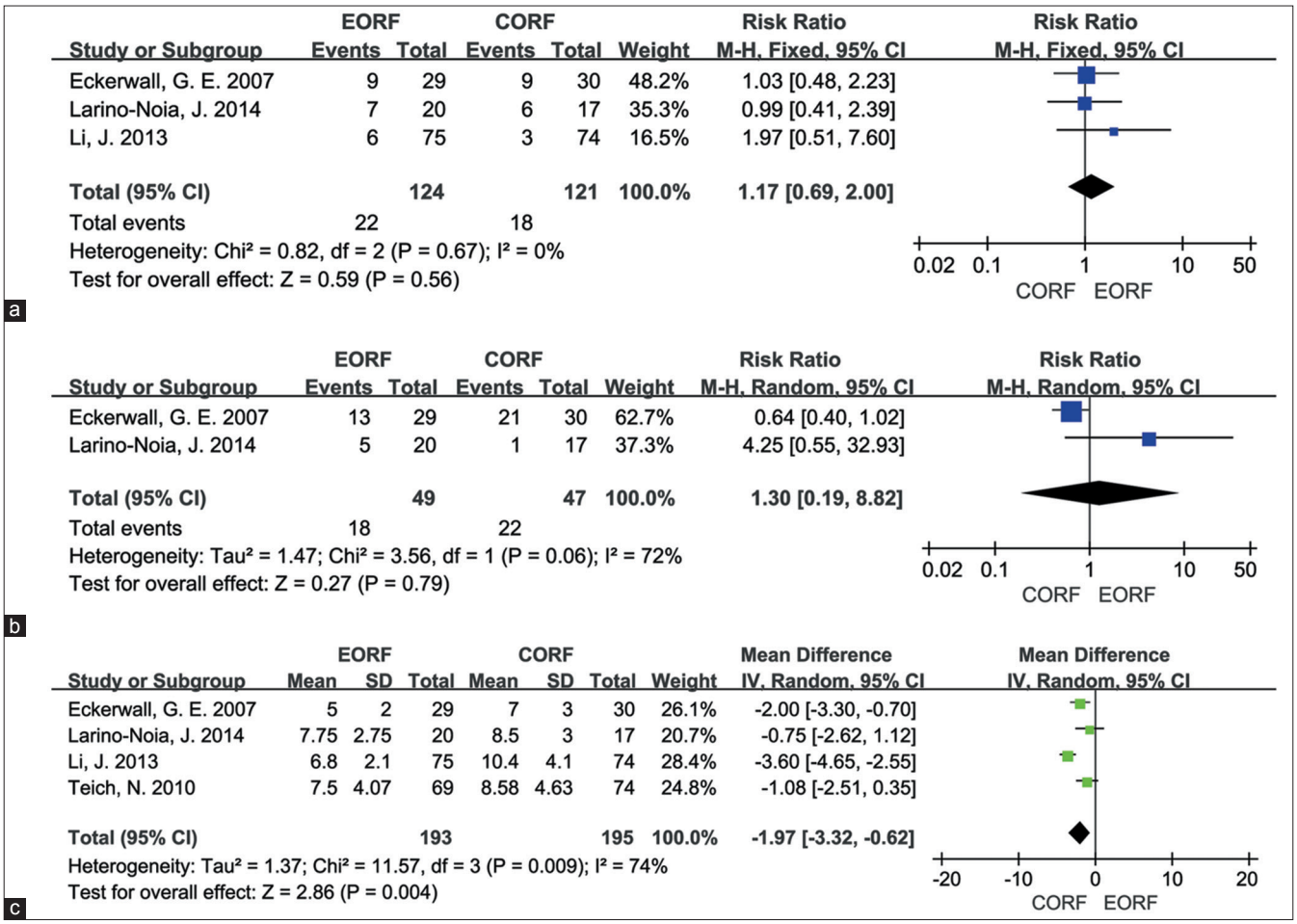

Figure 2: Results of meta-analysis for oral refeeding time: (a) results for abdominal pain ($P = 0.56$); (b) results for nausea/vomiting ($P = 0.79$); (c) results for length of hospital stay ($P = 0.004$)

studies. The fixed-effect model was used and the results showed no significant difference (RR 0.86; 95% CI 0.53–1.40; $P = 0.54$) [Figure 3a]. The included studies were heterogeneous for nausea/vomiting ($\chi^2 = 3.07$, $P = 0.08 < 0.1$; $I^2 = 67\%$). Thus, the random-effect model was used and the results revealed no significant

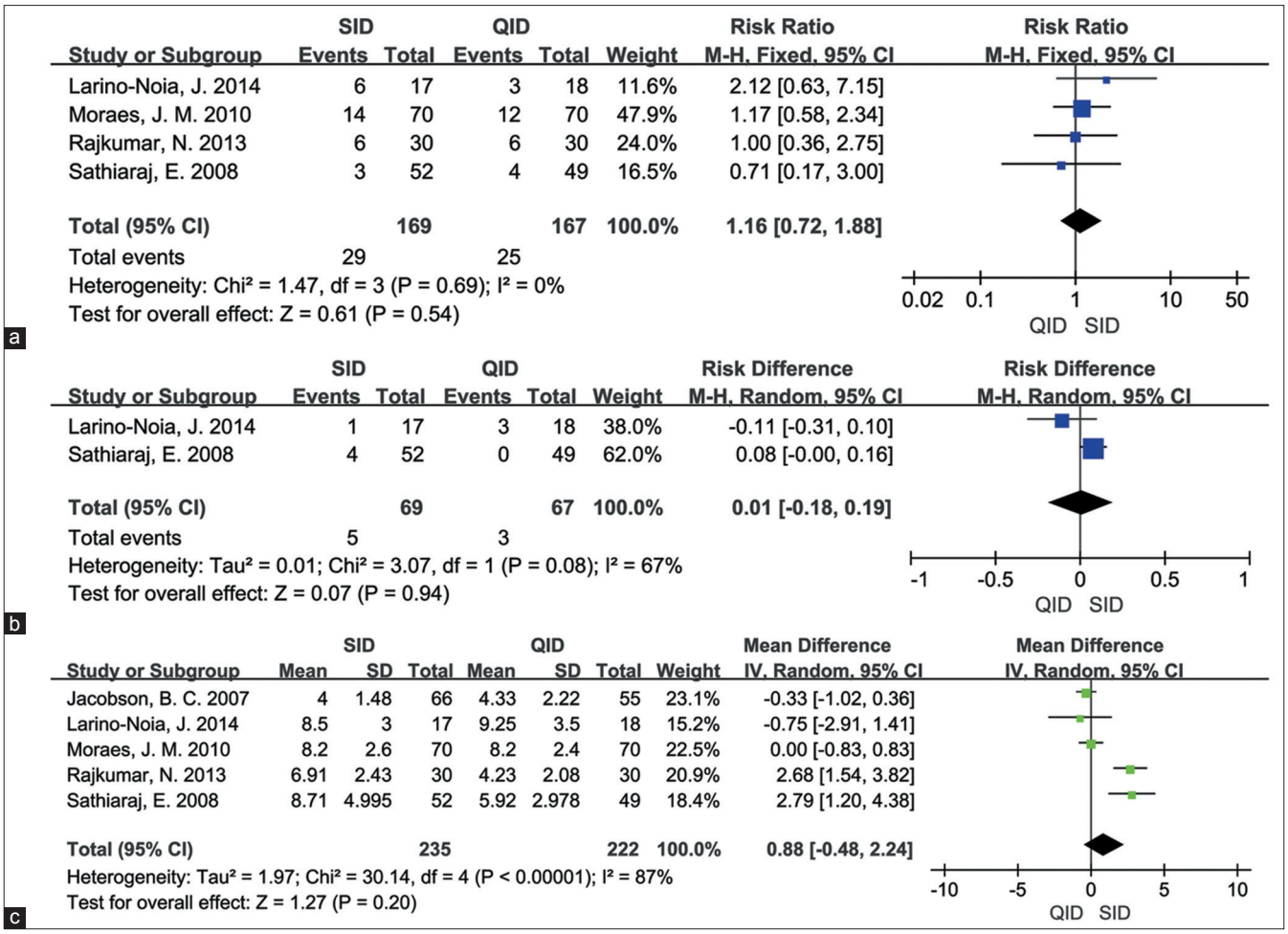

Figure 3: Results of meta-analysis for oral refeeding material: (a) results for abdominal pain ($P = 0.54$); (b) results for nausea/vomiting ($P = 0.94$); (c) results for length of hospital stay ($P = 0.20$)

difference (RD −0.01; 95% CI −0.19–0.18; $P = 0.94$) [Figure 3b]. For LOHS, the results showed that the included studies were heterogeneous ($\chi^2 = 30.14$, $P \leq 0.00001$; $I^2 = 87\%$); however, there was no significant difference between QID and SID (MD −0.88; 95% CI −2.24–0.48; $P = 0.20$) [Figure 3c].

DISCUSSION

Acute pancreatitis seriously harms human health, with high morbidity and mortality rates. Indeed, the overall mortality rate could reach 5% and in the most severe cases may be as high as 30%.[18] Thus, the present meta-analysis was performed to determine a better schedule in terms of oral refeeding time and material for patients with acute pancreatitis.

For the oral refeeding time, the results showed that EORF, based on bowel sounds being present, subjective feelings of hunger, or abdominal pain relief, could significantly decrease the LOHS and did not increase the incidence of abdominal pain or nausea/vomiting. For the oral refeeding material, the differences of abdominal pain, nausea/vomiting, and LOHS between QID and SID were not significant.

From the included articles, we observed that in the oral refeeding time group, most of the patients received SID. While in the oral refeeding material group, most of the patients started oral refeeding when the signs and symptoms of acute pancreatitis resolved, i.e., they received CORF. We assumed that EORF-combined QID could be more beneficial to patients. One article[7] compared Group I (standard time + stepwise increasing caloric intake), Group II (early refeeding + stepwise increasing caloric intake), Group III (standard time + immediate full caloric intake), and Group IV (early refeeding, immediate full caloric intake), and the results showed EORF-combined QID was safe and well tolerated. However, the sample size was small; thus, a large multicenter study should be performed to confirm these conclusions.

In this meta-analysis, the included patients had mild acute pancreatitis, and only one article[11] compared patients with moderate and severe acute pancreatitis for EORF; the results showed that EORF could shorten the LOHS in patients with moderate or severe acute pancreatitis and did not increase incidence of adverse events or complications. However, its small sample size limited its wider clinical application, and a large multicenter clinical trial is required.

For other studied oral refeeding materials, like pancreatic enzymes, glutamine, or placebo supplementation,[19,20] large-scale studies are required to obtain more reliable results for clinical application.

CONCLUSION

Pure EORF or QID causes no harm to patients with mild acute pancreatitis, and EORF could significantly decrease the LOHS. Combined EORF and QID for patients with mild disease, and EORF for patients with moderate and severe disease, appear to be safe and well tolerated and could shorten LOHS; however, a larger sample size is needed to obtain more accurate results.

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Conflicts of interest
There are no conflicts of interest.

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