

## Use of pre-, pro- and synbiotics in patients with acute pancreatitis: A meta-analysis

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### Abstract

**AIM:** To assess the clinical outcomes of pre-, pro- and synbiotics therapy in patients with acute pancreatitis.

**METHODS:** The databases including Medline, Embase, the Cochrane Library, Web of Science and Chinese Biomedicine Database were searched for all relevant randomized controlled trials that studied the effects of pre-, pro- or synbiotics in patients with acute pancreatitis. Main outcome measures were postoperative infections, pancreatic infections, multiple organ failure (MOF), systemic inflammatory response syndrome (SIRS), length of hospital stay, antibiotic therapy and mortality.

**RESULTS:** Seven randomized studies with 559 acute pancreatic patients were included. Pre-, pro- or synbiot-

ics treatment showed no influence on the incidence of postoperative infections [odds ratios (OR) 0.30, 95% confidence interval (CI): 0.09-1.02,  $P = 0.05$ ], pancreatic infection (OR 0.50, 95% CI: 0.12-2.17,  $P = 0.36$ ), MOF (OR 0.88, 95% CI: 0.35-2.21,  $P = 0.79$ ) and SIRS (OR 0.78, 95% CI: 0.20-2.98,  $P = 0.71$ ). There were also no significant differences in the length of antibiotic therapy (OR 0.75, 95% CI: 0.50-1.14,  $P = 0.18$ ) and the mortality (OR 0.75, 95% CI: 0.25-2.24,  $P = 0.61$ ). However, Pre-, pro- or synbiotics treatment was associated with a reduced length of hospital stay (OR -3.87, 95% CI: -6.20 to -1.54,  $P = 0.001$ ). When stratifying for the severity of acute pancreatitis, the main results were similar.

**CONCLUSION:** Pre-, pro- or synbiotics treatment shows no significant influence on patients with acute pancreatitis. There is a lack of evidence to support the use of probiotics/synbiotics in this area.

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**Key words:** Probiotics; Synbiotics; Prebiotics; Nutrition support; Acute pancreatitis

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### INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process

in mild to severe forms with a high mortality rate, frequently associated with necrosis of the gland<sup>[1]</sup>. The infected pancreatic necrosis is a principal late complication and a major cause of morbidity and mortality in patients with severe acute pancreatitis. In view of the deleterious effects of infected necrotizing pancreatitis, prophylactic antibiotics have been widely used. However, some randomized controlled trials (RCTs) and meta-analysis have not demonstrated significant benefits of prophylactic antibiotics on patients with necrotizing AP<sup>[2-4]</sup>. It is also not recommended for the routine use in sterile pancreatic necrosis<sup>[5]</sup>.

A new anti-infectious strategy is needed. The administration of probiotics/synbiotics modulating the intestinal microbiota may be a valuable treatment option. Lilly and Stillwell first defined the term “probiotics” as ingestible microorganisms that benefited the host by improving intestinal microbial balance<sup>[6]</sup>. Previous studies showed the clinical benefits of probiotics (including *Lactobacilli* and *Bifidobacteria*), such as inhibiting proliferation of harmful bacteria, protecting the intestinal barrier, preventing gut bacterial translocation to blood and distant sites, and modulating the immune function<sup>[7,8]</sup>, all of which contributed to the reduction of the incidence of nosocomial infections related to intestinal microbial imbalance. Prebiotics are also beneficial to enhancing the effects of enteral nutrition and probiotics<sup>[9-11]</sup>. For example, as one of the most important prebiotics, fibers can selectively stimulate growth or activity of certain colonic bacteria<sup>[12]</sup>. In addition, fibers are broken down by the probiotic bacteria to produce a whole series of nutrients including short-chain fatty acids which can stimulate mucosal cell growth, reduce translocation, and enhance the intestinal immune function in colon. Combined use of probiotics and prebiotics, which are called synbiotics, have been shown to enhance immunomodulating ability, balance gut microbiota, inhibit bacterial translocation and reduce the incidence of nosocomial infections in clinically surgical patients.

Evidences showed that the use of pro- or synbiotics might reduce postoperative infections after abdominal surgery<sup>[13-15]</sup>. Several RCTs have also been performed demonstrating a therapeutic and preventive effect of pre-, pro- or synbiotics treatment in patients with acute pancreatitis<sup>[16-18]</sup>. However, these studies were small in size, and have been underpowered. Recently, a multi-center RCTs reported some unexpected results contradicting the previous studies<sup>[19]</sup>. This trial was controversial for some shortcomings. Overall, the magnitude of the therapeutic effect remains unknown. We therefore performed this meta-analysis to assess the potential effects of pre-, pro- or synbiotics treatment in patients with acute pancreatitis by reviewing the current literature, and synthesizing the available data.

## MATERIALS AND METHODS

### Literature search strategy

A systematic review of the literature was performed to

identify all RCTs assessing the effects of pre-, pro- or synbiotics treatment in acute pancreatitis. Two authors independently searched the database including Medline (1966 to March 2010), Embase (1980 to March 2010), Web of Science, Chinese Biomedicine Database (1979 to March 2010) and the Cochrane Library (2010, issue 1) with no language restriction using the following terms: “(prebiotic\* OR probiotic\* OR synbiotic\* OR lactobacillus OR Bifidobacterium OR Lactobacilli) AND (acute pancreatitis)”. We identified relevant studies initially by title, abstract, and finally by full text. The reference lists of all selected RCTs and previous systematic reviews were also searched by hand. If duplicate article was published by the same author using the same case series, the data from the most recent manuscript publications was included.

### Inclusion and exclusion criteria

Only RCTs evaluating the use of pre-, pro- or synbiotics in patients with acute pancreatitis were included in this review. The trials should have at least one of the followings as a primary outcome variable: number of infections and pancreatic infectious complications, number of multiple organ failure (MOF) and systemic inflammatory response syndrome (SIRS), surgical interventions, length of hospital stay, and mortality. Major reasons for exclusion of studies were (1) animal studies; (2) duplicate publication; and (3) no usable data reported.

### Data extraction

Data was abstracted independently by two reviewers according to the following selection criteria: study design and period, population, intervention, and outcome variables listed above. Disagreement was resolved by discussion.

### Methodological quality

We assessed the quality of the studies based on the random method, allocation concealment, blinding and follow-up. The methodological quality of the studies included in the meta-analysis was also scored with the Jadad scale<sup>[20]</sup>, which was a 5-point quality scale defining low quality studies as having a score of < 3 and high-quality studies as having a score of ≥ 3.

### Statistical analysis

The statistical analysis was performed using the free software Review Manager (Version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008). Dichotomous data was presented as odds ratio (OR) with 95% confidence intervals (CI). Statistical heterogeneity was measured using the Chi-square test and the inconsistency index ( $I^2$ ). A  $\chi^2$   $P$  value < 0.05 was considered to indicate statistically significant heterogeneity. Fixed effects model was used when there was no heterogeneity of the results. Otherwise, the random effects model was used. Subgroup analyses stratified by the severity of acute pancreatitis were performed. Sensitivity analyses were performed only in high quality trials to avoid errors caused by poor quality studies. Visual

Table 1 Methodological characteristics of the clinical trials included in this meta-analysis

Trial	Patients (synbiotics/control)	Characteristics of patients (synbiotics/control)	Intervention	Control group	Length of treatment (d)
Oláh <i>et al</i> <sup>[16]</sup> (UK, 2002)	45 (22/23)	Mean Glasgow score (2.5/2.8), mean CRP (206.5/188.7) mg/L	10 <sup>9</sup> <i>L. plantarum</i> 299 + EN + 10 g oat fiber	EN + heat-killed <i>L. plantarum</i> 299 + oat fiber	7
Oláh <i>et al</i> <sup>[17]</sup> (UK, 2007)	62 (33/29)	Mean Imrie score (2.9/3.1), mean CRP (216.7/191.2) mg/L	Four LAB: 10 <sup>10</sup> <i>P. pentosaceus</i> , <i>Leuconostoc mesenteroides</i> , <i>L. paracasei</i> and <i>L. plantarum</i> + four bioactive fiber (Synbiotics 2000) + EN	EN + four bioactive fiber	7
Karakan <i>et al</i> <sup>[25]</sup> (Turkey, 2007)	30 (15/15)	Mean APACHE II score (9.4/9.6), mean CRP (232/244) mg/L	24 g multi-fibers including soluble fibers and insoluble fibers + EN	EN	6-13
Qin <i>et al</i> <sup>[18]</sup> (China, 2008)	74 (36/38)	Mean APACHE II score (8.8/8.9), mean CRP (125/136) mg/L	10 <sup>8</sup> <i>L. plantarum</i> + EN + PN	PN	7
Besselink <i>et al</i> <sup>[19]</sup> (Netherlands, 2008)	296 (152/144)	Mean APACHE II score (8.6/8.4), mean Imrie score (3.3/3.4), mean CRP (268/270) mg/L	Six LAB: 10 <sup>10</sup> <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. salivarius</i> , <i>L. lactis</i> , <i>B. bifidum</i> , and <i>B. lactis</i> (Ecologic 641) + cornstarch + maltodextrins + fiber-riched EN	Cornstarch + maltodextrins + fiber-riched EN	28
Li <i>et al</i> <sup>[26]</sup> (China, 2007)	25 (14/11)	APACHE II score 8-20	Three LAB: 7.2 × 10 <sup>7</sup> <i>B. longum</i> , <i>L. bulgaricus</i> and <i>S. thermophilus</i> (Golden Bifid)	Water	7
Wu <i>et al</i> <sup>[27]</sup> (China, 2009)	27 (14/13)	APACHE II score 8-20	Three strains: > 6 × 10 <sup>4</sup> <i>L. lactis</i> + <i>L. acidophilus</i> and <i>S. lactis</i>	N/A	7

N/A: Not applicable; APACHE II: Score of the second acute physiology and chronic health evaluation; CRP: C-reactive protein; LAB: Lactic acid bacteria; *L.*: *Lactobacillus*; *B.*: *Bifidobacterium*; *E.*: *Enterococcus*; *P.*: *Pediococcus*; *S.*: *Streptococcus*; EN: Enteral nutrition; PN: Parenteral nutrition.

inspection of asymmetry in funnel plots was conducted to assess the potential for publication bias.

## RESULTS

### Main characteristics of the studies

A total of 48 papers relevant to the searching words were identified through the bibliographic search. After initial eligibility screening, 41 of these papers were excluded, of which 24 were not randomized controlled studies, 10 were not conducted in humans, 3 did not report usable data, and 4 were duplicate publications<sup>[21-24]</sup>. Only 7 RCTs involving 559 patients met the inclusion criteria and were included in the meta-analysis<sup>[16-19,25-27]</sup>. The flow chart of study selection is summarized in Figure 1.

The main characteristics of the included patients between two groups were well matched in all RCTs (including age and gender). Five studies compared the score of the second acute physiology and chronic health evaluation (APACHE II)<sup>[18,19,25-27]</sup>, and five studies compared C-reactive protein<sup>[16-19,25]</sup>. Two of the studies tested a probiotics<sup>[16,18]</sup>, one of the studies tested a prebiotics<sup>[25]</sup>, while the remaining four studies tested a synbiotics (probiotics plus prebiotics)<sup>[17,19,26,27]</sup>. Five studies recruited patients with severe acute pancreatitis<sup>[17,19,25-27]</sup>, and two studies recruited patients with mild, moderate and severe degrees of pancreatitis<sup>[16,18]</sup>. Patients with biliary tract diseases were excluded in one of the studies<sup>[16]</sup>. Only three studies reported adverse effects associated with administration of pre-, pro- or synbiotics, which included bowel ischemia, catheter-related sepsis, tube intolerance and re-intube. The study details are summarized in Table 1. The surgical outcomes from the RCTs included in this meta-analysis are presented in Table 2.

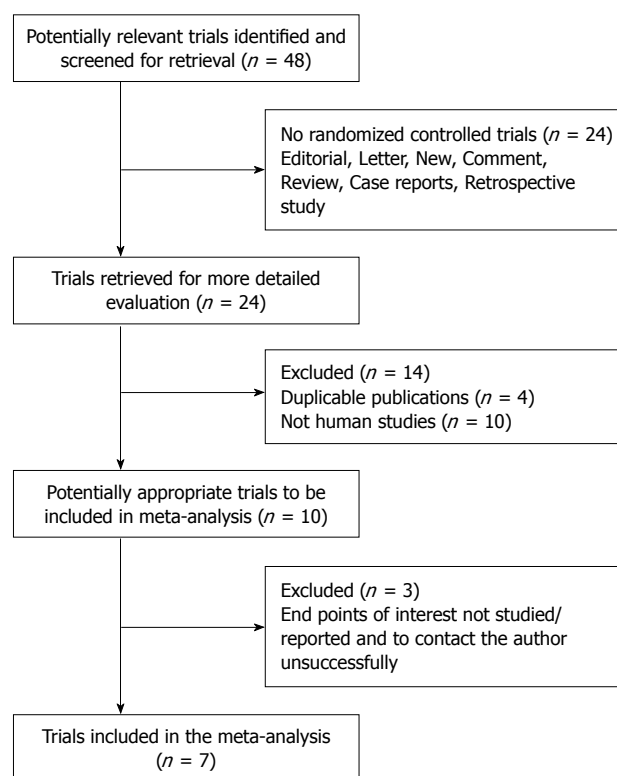


Figure 1 Flow chart showing the study selection procedure.

### Quality assessment

Four of these studies were double blind<sup>[16,17,19,25]</sup>. Allocation concealment was adequate in 3 studies<sup>[17,19,25]</sup>, and unclear in 4 studies<sup>[16,18,26,27]</sup>. The Jadad score of the studies was evaluated and ranged from 1 to 5 (mean 2.9). Most of the studies were small in size (85.7% had 100 or less

Table 2 Surgical outcomes from randomized studies included in this meta-analysis

Trial	No. of patients	Septic morbidity (%)	MOF (%)	SIRS (%)	Pancreatic infections (%)	Surgical interventions (%)	Hospital stay (d)	Mortality (%)
Oláh <i>et al</i> <sup>[16]</sup>	22/23	5 (22.7)/ 20 (87)	2 (9.1)/ 2 (8.7)	11 (50)/ 6 (26.1)	1 (4.5)/ 7 (30.4)	1 (4.5)/ 7 (30.4)	13.7/21.4 (median)	1 (4.5)/2 (8.7)
Oláh <i>et al</i> <sup>[17]</sup>	33/29	9 (27.3)/ 15 (51.7)	5 (15.1)/ 9 (31)	3 (9)/ 5 (17.2)	4 (12.1)/ 8 (27.6)	4 (12.1)/ 7 (24.1)	14.9/19.7 (median)	2 (6.1)/6 (20.7)
Karakan <i>et al</i> <sup>[25]</sup>	15/15	2 (13.3)/ 2 (13.3)	1 (6.7)/ 2 (13.3)	N/A	N/A	N/A	10 ± 4/15 ± 6	2 (13.3)/4 (26.7)
Qin <i>et al</i> <sup>[18]</sup>	36/38	11 (30.6)/ 29 (76.3)	4 (11.1)/ 7 (18.4)	6 (16.7)/ 14 (36.8)	N/A	N/A	20.9/24.2 (median)	0 (0)/0 (0)
Besselink <i>et al</i> <sup>[19]</sup>	152/144	46 (30.3)/ 41 (28.47)	33 (22)/ 15 (10)	N/A	21 (14)/ 14 (10)	28 (18)/ 14 (10)	28.9 ± 41.5/23.5 ± 25.9	24 (16)/9 (6)
Li <i>et al</i> <sup>[26]</sup>	14/11	N/A	N/A	N/A	N/A	N/A	42 ± 5/49 ± 6.8	N/A
Wu <i>et al</i> <sup>[27]</sup>	14/13	N/A	N/A	N/A	N/A	N/A	34 ± 6/40 ± 6	5 (35.7)/6 (46.2)

N/A: Not applicable; MOF: Multi-organ failure; SIRS: Systemic inflammatory response syndrome.

Table 3 Quality assessment of the included randomized trials

Trial	Generation of random	Allocation concealment	Blinding	Follow-up	Baseline similarity	Jadad score
Oláh <i>et al</i> <sup>[16]</sup>	Unclear	Unclear	Double blinded	No	Similar	4
Oláh <i>et al</i> <sup>[17]</sup>	Unclear	Adequate	Double blinded	No	Similar	4
Karakan <i>et al</i> <sup>[25]</sup>	Clear	Adequate	Double blinded	No	Similar	3
Qin <i>et al</i> <sup>[18]</sup>	Clear	Unclear	No blinding	Yes	Similar	3
Besselink <i>et al</i> <sup>[19]</sup>	Clear	Adequate	Double blinded	Yes	Similar	5
Li <i>et al</i> <sup>[26]</sup>	Unclear	Unclear	No blinding	No	Similar	1
Wu <i>et al</i> <sup>[27]</sup>	Unclear	Unclear	No blinding	No	Similar	1

participants). Follow-up was only reported in two studies<sup>[18,19]</sup>. The quality assessment of the studies is presented in Table 3.

### Infectious complications and pancreatic infection

The incidence of infectious complications was reported in all 7 RCTs in the meta-analysis. The type of infections included pancreatic abscess, infected pancreatic necrosis, pneumonia, catheter-related septic complication, urinary tract infections, wound infections, and sepsis or bacteraemia. Overall, there were no significant differences of incidence of total infections in pancreatic patients between the probiotics/synbiotics group and the control group (OR = 0.3, 95% CI: 0.09-1.02,  $P = 0.05$ ) (Figure 2A). There was significant heterogeneity between studies ( $I^2 = 84%$ ,  $P < 0.0001$ ).

Only three studies reported pancreatic infections<sup>[16,17,19]</sup>. Pancreatic infections included pancreatic abscess and infected pancreatic necrosis. There was no significant difference in the pancreatic infections between the probiotics/synbiotics group and the control group (OR 0.50, 95% CI: 0.12-2.17,  $P = 0.36$ ) (Figure 2B). The test result for heterogeneity was also significant ( $I^2 = 73%$ ,  $P = 0.03$ ).

### MOF and SIRS

There were no significant differences in the incidence of MOF and SIRS between the probiotics/synbiotics group and the control group. The odds ratio and 95% CI: were 0.88 (0.35-2.21,  $P = 0.79$ ) in MOF based on five studies<sup>[16-19,25]</sup>, and 0.78 (0.20-2.98,  $P = 0.71$ ) in SIRS based

on three studies<sup>[16-18]</sup>. Combination analysis of MOF and SIRS also showed no significant differences between the two groups (OR 0.75, 95% CI: 0.23-2.50,  $P = 0.64$ ) (Figure 2C). The significant heterogeneity was present among the studies ( $I^2 = 83%$ ,  $P < 0.0001$ ).

### Length of antibiotic therapy, and hospital stay

Four studies involved in the meta-analysis provided applicable data on length of hospital stay<sup>[19,25,27]</sup>. The length of hospital stay was significantly shorter in the probiotics/synbiotics group (OR -3.87, 95% CI: -6.20 to -1.54,  $P = 0.001$ ) (Figure 2D). However, there was no significant difference in the length of antibiotic therapy (three RCTs, OR 0.75, 95% CI: 0.50-1.14,  $P = 0.18$ ) between the probiotics/synbiotics group and the control group<sup>[16,18,19]</sup>. The test result for heterogeneity was not significant ( $P = 0.08$  in hospital stay,  $P = 0.33$  in antibiotic therapy).

### Surgical intervention and mortality

Three studies reported significant difference in surgical intervention (OR 0.59, 95% CI: 0.11-3.07). Mortality was reported in six of seven RCTs<sup>[16-19,25,27]</sup>. There was no significant difference in the mortality between the probiotics/synbiotics group and the control group (OR 0.75, 95% CI: 0.25-2.24,  $P = 0.61$ ) (Figure 2E). The significant heterogeneity was present between studies ( $P = 0.009$  in surgical intervention;  $P = 0.04$  in mortality).

### Stratification, sensitivity analysis and publication bias

We analyzed the surgical outcomes stratified by the se-

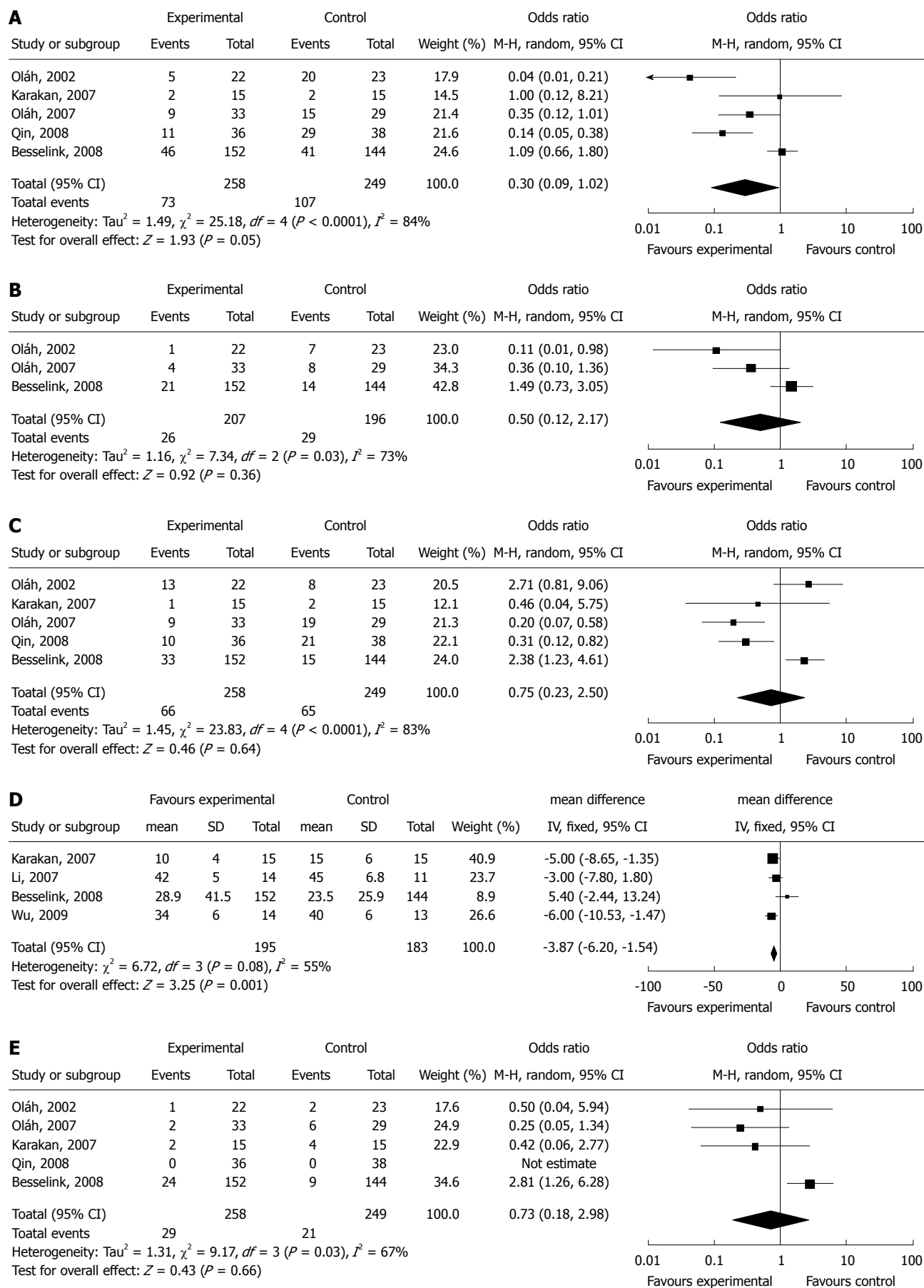


Figure 2 Forest plot for the effects of probiotics/synbiotics in patients with acute pancreatitis. A: Infectious morbidity; B: Pancreatic infections; C: Multiple organ failure (MOF) and systemic inflammatory response syndrome (SIRS); D: Length of hospital stay; E: Mortality.

Table 4 Surgical outcomes stratified by severity of pancreatitis in this meta-analysis

	No. of studies	Synbiotic	Control	OR (95% CI)	P for effect size	P for heterogeneity
Septic morbidity	3	57/200	58/188	0.89 (0.57, 1.37)	0.58	0.16
Pancreatic infections	2	25/185	22/173	1.06 (0.58, 1.96)	0.84	0.07
Surgical intervention	2	32/185	21/173	1.07 (0.23, 4.92)	0.94	0.04
MOF and SIRS	3	43/200	36/188	0.65 (0.09, 4.44)	0.66	0.0005
Mortality	4	33/214	25/201	0.77 (0.22, 2.72)	0.69	0.02

OR: Odds ratio; CI: Confidence interval; MOF: Multi-organ failure; SIRS: Systemic inflammatory response syndrome.

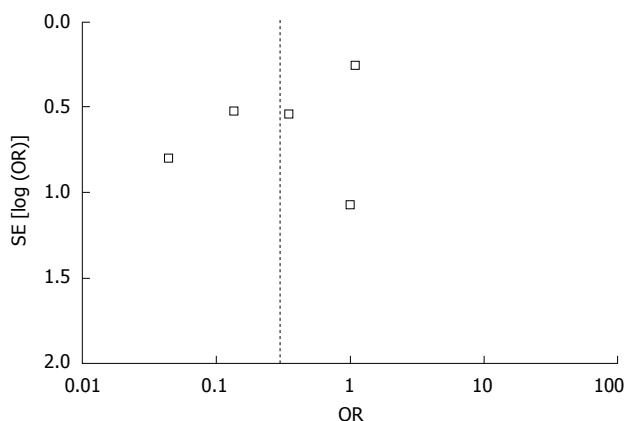


Figure 3 Funnel plot of publication bias.

severity of acute pancreatitis. The use of pre-, pro- or synbiotics had no significant influence on the main surgical outcomes including septic morbidity, pancreatic infections, surgical intervention, mortality, MOF and SIRS in severe acute pancreatitis (Table 4).

Allocation concealment and blinding were unclear in three of included studies<sup>[18,26,27]</sup>. The results of the sensitivity analysis based on the remaining four studies, after excluding trials of low quality, are similar to the previous results, indicating that the results of meta-analysis are relatively credible. Review of funnel plots is present in Figure 3, which can not rule out the potential for publication bias in all analyses.

## DISCUSSION

The microbiota colonizing the gastrointestinal tract has been considered as the main causes of the pathogenesis of the nosocomial infections<sup>[28,29]</sup>. Surgical trauma, especially surgical trauma of the digestive tract, may result in physical injury and atrophy of the gastrointestinal mucosa, increased intestinal permeability, microbial imbalance, and intraluminal bacterial or bacterial products translocation cross the intestinal barrier to local lymph nodes and distant organs, and ultimately induce an increased morbidity of infectious complications and sepsis<sup>[30,31]</sup>. At present, probiotics and prebiotics have been administrated in surgical trauma<sup>[28,32-34]</sup>, cancer<sup>[30,35,36]</sup>, active ulcerative colitis<sup>[37]</sup>, and critically ill patients<sup>[31,38,39]</sup>.

Up to now, nine RCTs including 733 patients have been published reporting the effects of pre-, pro- or syn-

biotics treatment in patients undergoing abdominal surgery. Six studies showed a significantly positive effect of probiotics with or without prebiotics in postoperative septic complications, and the remaining three studies showed no effects. A meta-analysis based on these studies demonstrated that the use of pre-, pro- or synbiotics might reduce the incidence of postoperative infections, duration of hospital stay and length of antibiotic therapy after abdominal surgery<sup>[40]</sup>. Another meta-analysis based on eight randomized studies reported that the use of pre-, pro- or synbiotics in critically ill adult patients showed no statistically significant benefit in the length of ICU stay, hospital mortality and the incidence of nosocomial infections<sup>[41]</sup>. However, this meta-analysis did not include postoperative patients and trauma patients admitted to ICU, most of them benefited from probiotics treatment<sup>[29-31]</sup>. From our meta-analysis, we found that the use of pre-, pro- or synbiotics had no influence on the main outcomes including postoperative infections, pancreatic infections, MOF, SIRS and mortality in patients with acute pancreatitis. In the subgroup analysis and sensitivity analysis, a similar result was observed, after the stratification was conducted by the severity of acute pancreatitis and the trials of low quality were excluded.

There were controversies on the use of pre-, pro- or synbiotics in patients with acute pancreatitis among the recent studies. Three studies suggested that probiotics administration was effective in preventing complications of the experimental acute pancreatitis by decreasing bacterial translocation<sup>[42-44]</sup>. The first clinical trial was performed by Oláh *et al*<sup>[16]</sup> to evaluate the use of probiotics and fiber in clinical patients with acute pancreatitis. The study demonstrated that a dose of  $10^9$  of *L. plantarum* 299 together with oat fiber significantly reduced infected pancreatic necrosis and the number of surgical interventions. Subsequently, several studies reported similarly positive effects of probiotics with or without prebiotics<sup>[17,18,25-27]</sup>. However, the sample size in these studies was small and the conclusion from them was inconclusive. A large multi-center, randomized double-blinded controlled trial by Besselink *et al*<sup>[19]</sup> was designed to see whether probiotics could reduce the incidence of infectious complications in patients with severe acute pancreatitis. The trial involved 296 patients in 15 hospitals, and compared the use of a multi-species probiotics preparation with a placebo. The results showed that infectious complications occurred in 30% of the pa-

tients in the probiotics group and in 28% of the placebo group. Nine patients developed bowel ischaemia (8 died) in the probiotics group, whereas none developed this complication in the placebo group. Multiple organ failure occurred in 22% of the patients in the probiotics group and in 10% in the placebo group. In all, 16% patients in the probiotics group and 6% in the placebo group died. The results were opposite to previous evidences, and raised safety question on the use of pre-, pro- or synbiotics. Although Dutch's study was criticized for its design, approval, and conduct, this trial should still be carefully considered for its large sample size<sup>[45]</sup>. The previous studies have demonstrated that probiotics are safe for use in healthy persons, but should be used with caution in patients with underlying immune compromise, chronic disease, or debilitation because of the risk of sepsis<sup>[46]</sup>. However, bowel ischemia has never been reported in the previous studies including acute pancreatitis, trauma, critical illness and elective abdominal surgery, and the high incidence of MOF and mortality associated with probiotics treatment were only reported in Besselink's study. Besselink *et al*<sup>[19]</sup> explained that it was probably not the combination of probiotics but the administration of the combined probiotics together with the severity of the disease that was largely responsible for the effects obtained. This explanation may be one of potential reasons, but not the only one.

There are three major differences between Besselink's study and the other studies in the meta-analysis: the patients in the former received a higher number and more strains of probiotic organisms (six strains of probiotics *vs* 1-4 strains of probiotics in other studies); patients received probiotics administration for a longer period in Besselink's study (28 d *vs* 7 d in the other studies), and the pressor agents were administrated during probiotics feeding in some patients. Little work has been performed and no accepted recommendation was reported on the therapeutic strategy (including the optimal dose and time) of probiotics. The dose of probiotics administered was usually based on the previous studies showing clinical benefit from probiotics. Furthermore, the dose of probiotics varies considerably among different studies. In this meta-analysis, three of the studies tested a probiotics or prebiotics<sup>[16,18,25]</sup> and showed preventive effects. The remaining four studies tested different doses of synbiotics (probiotics plus prebiotics)<sup>[17,19,26,27]</sup>, 3 of which showed positive results<sup>[17,26,27]</sup>. Combination of several strains of probiotics was regarded as more powerful in previous opinion. This study indicates that the inappropriate combination of probiotic strains may be harmful, while a single use of probiotics or prebiotics may be safer. Evidences suggest that intestinal blood flow at the mucosal level is generally reduced in acute pancreatitis and critically ill patients<sup>[47]</sup>. The reduced blood flow and oxygen supply in intestinal mucosa might be further compromised by the administration of enteral nutrition and probiotic bacteria<sup>[48,49]</sup>. On the other hand, feeding probiotics might cause local mucosal damage with an inflammatory response of the small bowel wall.

Multispecies probiotics mixture may strongly increase the concentration of IL-10, and reduce the concentration of IL-6<sup>[50]</sup>. Experimental studies demonstrated that the increasing IL-10 is able to induce intestinal damage during intestinal ischemia/reperfusion<sup>[51]</sup>, whereas IL-6 is able to protect enterocytes<sup>[52]</sup>. One may speculate that a long duration of probiotics treatment and a high number of bacterial organisms may lead to probiotics overload in the small bowel, which aggravate the disorder of inflammatory response and reduction of intestinal blood flow and oxygen supply at the phase of acute stage of severe acute pancreatitis, and ultimately lead to bowel ischemia.

The unexpected deleterious effects may refer to more biologic actions of probiotics. It is clear that different strains of probiotics can have different effects. Moreover, their effects may vary in healthy people and patients, in different disease states, and among different age groups. Thus, clinical effects of one probiotics strain in one population cannot be automatically generalized to other strains or to other populations<sup>[46]</sup>. Although the individual strains used in this study are credible on the basis of their capacity to inhibit growth of pathogenic bacteria and to modulate immune responses, the benefits, disadvantages and interaction of different probiotics strains and their mechanisms of action in special illness is still unclear, and the combination of several strains should be thoroughly evaluated for safety and clinical benefits.

### Limitations of study

This meta-analysis has several limitations. The included studies were significantly heterogeneous, so the results should be interpreted with caution. Since these studies include diverse patient groups with diverse severity of disease, the effects of pre- pro- or synbiotics may differ among them. The type and the concentration of the probiotics vary considerably in these reviewed studies, which may explain some of the differences in results between studies. In addition, some strains are effective and some may be harmful, and the interaction of several stains of probiotics as a mixture may lead to the deleterious effects in some special illness. Most of these studies are small in scale and two of them are of low quality, which may influence the analysis. There were also differences in the study design, the population and study team among these studies. Finally, meta-analysis remains retrospective that is subject to the methodological deficiencies of the studies, it is therefore possible that studies with different results may be unpublished, which leads to publication bias.

In conclusion, there are a few recommendations can be offered and further studies are required. In view of the questions raised in safety and efficacy, use of pre- pro- or synbiotics should be cautious in critically ill patients, especially in patients with severe acute pancreatitis. Unless new and strong evidence is presented, probiotics use can no longer be considered risk-free. However, we can not draw a conclusion that the use of pre- pro- or synbiotics is dangerous, and it is too early and inappropriate to deny the beneficial effects of all of pre- pro- or synbiotics in critically ill patients and severe acute pancreatitis. After

all, a single large trial is not sufficient to draw a definitive conclusion. Well-designed randomized controlled trials are needed to further explore the mechanistic issues and probiotic interactions, and assess the effect and safety of pre-, pro- or synbiotics.

## COMMENTS

### Background

The administration of pre-, pro- or synbiotics has been shown to enhance immunomodulating ability, modulate the intestinal microbiota, inhibit bacterial translocation and reduce the incidence of nosocomial infections in clinically surgical patients, and may be a new anti-infectious strategy for patients with acute pancreatitis.

### Research frontiers

Some randomized controlled studies (RCTs) demonstrated a therapeutic and preventive effect of pre-, pro- or synbiotics in patients with acute pancreatitis. However, a multicenter RCTs reported some unexpected results. These studies were controversial for their shortcomings. Overall, the magnitude of the therapeutic effect remains unknown. This meta-analysis was performed to assess the potential effect and safety of pre-, pro- or synbiotics in patients with acute pancreatitis.

### Innovations and breakthroughs

Currently, there is still a lack of evidence to support the use of pre-, pro- or synbiotics in patients with acute pancreatitis.

### Applications

Pre-, pro- or synbiotics treatment shows no statistically significant benefit in the main outcome of patients with acute pancreatitis. In view of the questions in safety and efficacy, use of pre- pro- or synbiotics should be cautious in critically ill patients, especially in patients with severe acute pancreatitis. Further studies are needed to explore mechanistic issues and probiotic interactions in critical illnesses.

### Terminology

Probiotics, is defined as ingestible microorganisms that benefit the host by improving intestinal microbial balance.

### Peer review

In this meta-analysis, the use of pre- pro- and synbiotics was compared to placebo in patients with acute pancreatitis. In general, I find the study interesting and clinically relevant. However, the manuscript needs to undergo major revision.

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