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Assessment of prophylactic antibiotics administration for acute pancreatitis: a meta-analysis of randomized controlled trials

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Abstract

Background: Recent evidence has shown that prophylactic antibiotic treatment in patients with acute pancreatitis is not associated with a significant decrease in mortality or morbidity. The use and efficacy of prophylactic antibiotic treatment in acute pancreatitis remain controversial. This meta-analysis was conducted to assess whether antibiotic prophylaxis is beneficial in patients with acute pancreatitis.

Methods: We searched randomized controlled trials (RCTs) of prophylactic use of antibiotics using Medline (PubMed), Embase, the Cochrane Library, and Web of Science. The data were analyzed using Review Manager 5.3 software. We performed pooled analyses for infected pancreatic necrosis, mortality, surgical intervention, and non-pancreatic infection. Odds ratios (ORs) from each trial were pooled using a random or fixed effects model, depending on the heterogeneity of the included studies. Sub-group analysis or sensitivity analysis was conducted to explore potential sources of heterogeneity, when necessary.

Results: Totally, 11 RCTs involving 747 participants were included, with an intervention group (prophylactic use of antibiotics, $n = 376$) and control group ($n = 371$). No significant differences were found regarding antibiotic prophylaxis with respect to incidence of infected pancreatic necrosis (OR, 0.74; 95% confidence interval [CI], 0.50–1.09; $P = 0.13$), surgical intervention (OR, 0.92; 95% CI, 0.62–1.38; $P = 0.70$), and morality (OR, 0.71; 95% CI, 0.44–1.15; $P = 0.16$). However, antibiotic prophylaxis was associated with a statistically significant reduction in the incidence of non-pancreatic infection (OR, 0.59; 95% CI, 0.42–0.84; $P = 0.004$).

Conclusions: Prophylactic antibiotics can reduce the incidence of non-pancreatic infection in patients with AP.
Keywords: Acute pancreatitis; Prophylactic administration; Antibiotics; Meta-analysis

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases. AP is an inflammatory condition of the pancreas, mostly caused by gallstones or excessive alcohol consumption.[1] AP is classified as mild, moderate, or severe based on the 2012 revised Atlanta classification definition.[2] Mild AP (MAP) is a self-limiting disease, with recovery usually occurring in the first week. The primary treatment for MAP is supportive care, including fluid resuscitation and pain control. The mortality rate of AP is roughly 5%; this rate is higher for severe AP (SAP). SAP is usually associated with a systemic inflammatory response, infection of the pancreas and peripancreatic necrosis, single or multiple organ failure, and even death.[3-5]

About 20% to 40% of patients with SAP develop infection of the pancreas and peripancreatic necrosis, with infected necrosis representing the primary cause of death. It is unclear whether prophylactic antibiotics are beneficial in AP to prevent infected necrosis and reduce the incidence of death. Several studies have demonstrated that prophylactic antibiotic treatment may reduce the incidence rate of infected pancreatic necrosis.[6,7] However, other studies have shown that the use of antibiotic prophylaxis is not associated with the incidence of pancreatic infection and death.[8,9] In addition, several clinical guidelines suggest that prophylactic antibiotics are not recommended.[10-12] Although several clinical trials and guidelines point out that prophylactic antibiotics are not beneficial in preventing infected necrosis and reducing the incidence of complications and death, some physicians still choose to administer prophylactic antibiotics to patients with AP.

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Clearly, the use and efficacy of prophylactic antibiotic treatment in AP remain a point of controversy. Moreover, there is no conclusive evidence available in this regard among published meta-analyses and reviews.[13-15] Thus, we conducted the present meta-analysis to assess whether antibiotic prophylaxis is beneficial in AP. In this meta-analysis, we focused not only on mortality and morbidity but also on specific infections such as pneumonia, urinary tract infection (UTI), positive blood culture, and fungal infection.

Methods

Systematic literature search

A systematic literature search was conducted independently by two authors using methods of the Cochrane Collaboration. We systematically searched MEDLINE (PubMed), Embase, the Cochrane Library, and Web of Science. We performed a literature search for randomized controlled trials (RCTs) published from inception to June 2019 evaluating the prophylactic use of antibiotics in patients with AP or SAP. Databases were queried for eligible studies using combinations of the following keywords: "acute pancreatitis," "severe acute pancreatitis," "prophylactic use of antibiotics," "antibiotic prophylaxis," "antibiotics," and "prophylaxis." We reviewed the titles and abstracts of possibly relevant studies. Full-text articles were obtained for comprehensive evaluation, and eligible studies were included in our meta-analysis.

Eligibility criteria

Peer-reviewed reports of studies that met the following criteria were eligible for inclusion: (1) the aims of the trial were to assess prophylactic use of antibiotics; (2) written in any language; (3) study population comprised patients with AP or SAP or acute necrotizing pancreatitis; (4) the name and dose of antibiotics were described; and (5) RCTs.

Outcome measures

The following parameters were extracted using standardized forms: (1) primary outcome parameters: the incidence of infected pancreatic necrosis and mortality; (2) secondary outcome parameters: the incidence of surgical intervention, non-pancreatic infection, pneumonia, UTI, positive blood culture, and fungal infection.

Quality assessment

The quality of 11 RCTs was assessed using Cochrane Collaboration Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). The risk of bias among RCTs was evaluated with the Cochrane Collaboration's Risk of Bias Tool. Items were judged as "low risk," "unclear risk," or "high risk"; red indicates "high risk," green "low risk," and yellow "unclear risk." Seven parameters were used to estimate the quality of each included study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other risks.

Data extraction

Data were extracted independently by two authors. The extracted data included first author, year of publication, the number of patients allocated to each group, name, and dose of antibiotics, time of antibiotics administration, duration of antibiotics prophylaxis, and the outcome variables listed above. Disagreement between investigators was discussed and resolved by consensus.

Statistical analysis

This meta-analysis was carried out using Cochrane Collaboration Review Manager 5.3 software; outcomes are presented as forest plots. The vertical line represents the line of equivalence between the groups being compared. The squares for each trial represent the point estimate, with the area of the square being proportional to the sample size; the line represents the 95% confidence interval (CI). Summary measures are depicted using diamonds, where the width of the diamond represents the 95% CI. Statistical analysis was conducted using the Mantel-Haenszel method, and summary statistics are presented as odds ratios (ORs). An OR of less than 1 favors the intervention group, and the point estimate of the OR was considered statistically significant at the $P < 0.05$ level if the 95% CI did not include value 1. A fixed effects model was adapted for all outcome measures. We calculated the I^2 value to estimate homogeneity. When the I^2 value was greater than 50%, a random effects model was adopted.

Results

Description of eligible studies

In this comprehensive literature review, we initially searched 817 potential titles and abstracts, after selection, 11 RCTs finally met the inclusion criteria.[6-9,16-22] A detailed search flow diagram is shown in Figure 1. After reading the full text of the remaining articles, 11 articles were selected. The characteristics of RCTs included in the meta-analysis are shown in Table 1. Summarized results of the risk of bias assessment are shown in Figure 2.

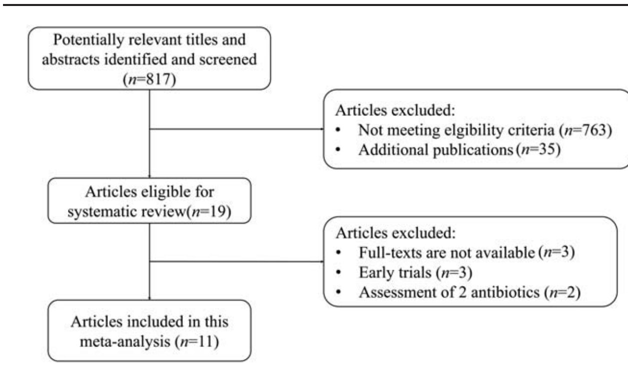

Figure 1: Flow diagram for the selection of randomized controlled trials included in the meta-analysis.

Table 1: Characteristics of randomized controlled trials included in the meta-analysis.

First authors	Year	Study design	Clinical features	Number of patients (intervention/control), *n*	Gender (male/female)	Antibiotics and dosage	Time of administration (h)	Antibiotic duration (days)	Outcome measures*
Dellinger *et al*[8]	2007	RCT (multicenter)	Pancreatic necrosis on CT scan	100 (50/50)	70/30	Meropenem (1 g, q8h)	<120	7–21	1, 2, 3, 4
García-Barrasa *et al*[9]	2009	RCT (single-center)	Pancreatic necrosis on CT scan	41 (22/19)	29/12	Ciprofloxacin (300 mg, q12h)	48–72	10	1, 2, 3, 4
Isenmann *et al*[19]	2004	RCT (multicenter)	Pancreatic necrosis on CT scan; CRP > 150 mg/L	114 (58/56)	87/27	Ciprofloxacin (400 mg, q12h), metronidazole (500 mg, q12h)	<72	14–21	1, 2, 3, 4
Nordback *et al*[18]	2001	RCT (single-center)	Pancreatic necrosis on CT scan	58 (25/33)	51/7	Imipenem (1 g, q8h)	<48	Not stated	1, 2, 3, 4
Pederzoli *et al*[6]	1993	RCT (multicenter)	Pancreatic necrosis on CT scan	74 (41/33)	Not stated	Imipenem (0.5 g, q8h)	<72	14	1, 2, 3, 4
Poropat *et al*[17]	2016	RCT (single-center)	Acute pancreatitis APACHE II score >8	47 (23/24)	Not stated	Imipenem (0.5 g, q8h)	Not stated	10	1, 2, 4
Poropat *et al*[20]	2017	RCT (single-center)	Acute pancreatitis APACHE II score ≤8	98 (49/49)	Not stated	Imipenem (0.5 g, q8h)	Not stated	10	1, 4
Røkke *et al*[22]	2007	RCT (multicenter)	Pancreatic necrosis on CT scan; CRP >120 mg/L (24 h); CRP >240 mg/L (48 h)	73 (36/37)	49/24	Imipenem (0.5 g, q8h)	<72	5–7	1, 2, 3, 4
Sainio *et al*[7]	1995	RCT (single-center)	Low enhancement on CT; CRP >120 mg/L	60 (30/30)	53/7	Cefuroxime (1.5 g, q8h)	<48	14	1, 2, 3
Schwarz *et al*[16]	1997	RCT (single-center)	Pancreatic necrosis on CT scan	26 (13/13)	Not stated	Ofloxacin (200 mg, q12h), metronidazole (500 mg, q12h)	Not stated	10	1, 2
Xue *et al*[21]	2009	RCT (single-center)	>30% pancreatic necrosis on CT scan	56 (29/27)	28/28	Imipenem (0.5 g, q8h)	<72	7–10	1, 2, 3, 4

*Meaning of numbers for outcome measures: 1: Death; 2: Infected pancreatic necrosis; 3: Surgical intervention; 4: Non-pancreatic infection; RCT: Randomized controlled trial; CT: Chemotherapy; CRP: C-reaction protein; APACHE II: Acute Physiology and Chronic Health Evaluation I.

Meta-analysis of infected pancreatic necrosis

A total of 747 patients were included in the 11 articles with results regarding infected pancreatic necrosis [Figure 3]. Totally, 63 of 376 patients (16.8%) in the antibiotic prophylaxis group developed infected necrosis whereas 76 of 371 (20.5%) in the control group developed infected necrosis. The overall OR was 0.74 (95% CI, 0.50–1.09; $P = 0.13$; $I^2 = 0$), demonstrating no statistical significance.

Meta-analysis of mortality

Totally, 32 of 327 (9.8%) patients in the intervention group and 43 of 322 (13.4%) patients in the control group died [Figure 4]. The overall OR was 0.71 (95% CI, 0.44–1.15; $P = 0.16$; $I^2 = 0$), indicating that antibiotics were not associated with significantly reduced mortality.

Meta-analysis of surgical intervention

A total of 576 patients were included in eight studies comparing the use of prophylactic antibiotics with controls, with regard to surgical intervention [Figure 5]. Totally, 66 of 291 (22.7%) patients in the antibiotic prophylaxis group and 66 of 285 (23.2%) in the control group underwent surgery. The overall OR was 0.92 (95% CI, 0.62–1.38; $P = 0.70$; $I^2 = 0$). Antibiotics use was not associated with significantly reduced surgical intervention.

Meta-analysis of non-pancreatic infection

Among the included studies, non-pancreatic infections included pneumonia, UTI, positive blood culture, fungal infection, and others. Totally, 80 of 333 (24.0%) patients in the intervention group and 109 of 328 (33.2%) in the control group developed non-pancreatic infections [Figure 6]. The overall OR was 0.59 (95% CI, 0.42–0.84; $P = 0.004$), indicating that the use of antibiotics was associated with a significant reduction in the incidence of non-pancreatic infections. There was moderate heterogeneity among the trials ($P = 0.06$; $I^2 = 47\%$). The Egger's test for heterogeneity showed no publication bias ($t = -0.04$, $P = 0.972$) [Figure 7]. In the sensitivity analysis, after gradually eliminating each study, the outcome was found to be stable [Figure 8]. Sub-group analysis showed that there was no significant difference with respect to different study years [Figure 9A], sample size [Figure 9B], and antibiotics [Figure 9D]. However, a significant difference was found in single-center *vs*. multicenter sub-groups (single-center sub-group, five RCTs, 300 patients, OR: 0.86, 95% CI: 0.45–1.67; multicenter sub-group, OR: 0.40, 95% CI: 0.18–0.86) [Figure 9C].

Meta-analysis of pneumonia

Five included studies provided data on endocrine pneumonia [Figure 10], including 188 patients in the antibiotics group and 181 in the control group. Twenty-three of 188 (12.2%) patients in the antibiotics prophylaxis group developed pneumonia whereas 32 of 181 (17.7%) in the control group developed pneumonia (OR, 0.61; 95% CI, 0.32–1.14; $P = 0.12$; $I^2 = 0$).

Meta-analysis of positive blood culture

Fourteen of 130 (10.8%) patients in the antibiotics group had positive blood cultures whereas 20 of 125 (16.0%) in the control group had positive blood culture results (OR, 0.61; 95% CI, 0.29–1.30; $P = 0.20$; $I^2 = 0$) [Figure 11].

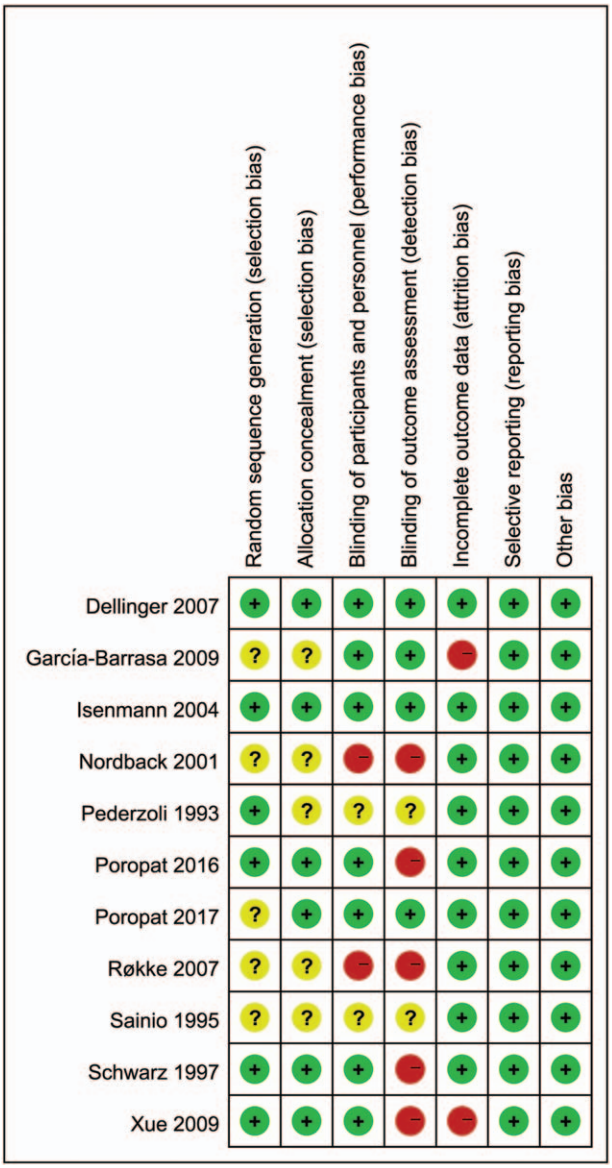

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Red indicates "high risk," green "low risk," and yellow "unclear risk."

Meta-analysis of fungal infection

Five of 177 (12.2%) patients in the antibiotics prophylaxis group developed fungal infection [Figure 12] compared with 5 of 168 (17.7%) patients in the control group (OR, 0.95; 95% CI, 0.30–3.03; $P=0.12$; $I^2=0$).

Meta-analysis of urinary tract infection

A total of 369 patients were included in five studies comparing prophylactic antibiotics use with controls with respect to UTI [Figure 13]; the incidence was 15 of 188 (25.0%) and 28 of 181 (33.9%) patients, respectively. Because the I^2 value was greater than 50%, the random effects model was adopted; the overall OR was 0.44 (95% CI: 0.22–0.89). Antibiotics use was associated with a statistically significant reduction in the incidence of UTI.

Discussion

Early clinical trials[6,7] have shown that the use of antibiotic prophylaxis can obviously reduce the incidence rate of infected pancreatic necrosis. However, the 2015 Japanese guidelines for the management of AP suggest that prophylactic use of antibiotics in SAP and necrotizing pancreatitis could improve the prognosis if carried out in the early phase of pancreatitis (within 72 h of onset).[23] Moreover, the results of subsequent clinical studies differ with respect to a reduction in the mortality rate, surgical intervention, infected pancreatic necrosis, and non-pancreatic infection.[24,25] García-Barrasa *et al*[9] conducted an RCT to compare 22 patients who received intravenous ciprofloxacin with 19 who received placebo. Their findings suggested that the prophylactic use of ciprofloxacin did not significantly reduce the risk of developing pancreatic infection and did not decrease mortality. A recent study in Japan suggested that routine early prophylactic antibiotic use has no significant clinical benefit in patients with SAP but may increase the risk of hospital-acquired infections.[26] Xue *et al*[21] suggested that prophylactic use of antibiotics may increase the prevalence of multi-drug resistant bacteria and the incidence of fungal infection.

Study or Subgroup	Antibiotics Events	Antibiotics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dellinger 2007	9	50	6	50	8.3%	1.61 [0.53, 4.92]
García-Barrasa 2009	8	22	8	19	9.3%	0.79 [0.22, 2.77]
Isenmann 2004	7	58	5	56	7.6%	1.40 [0.42, 4.70]
Nordback 2001	1	25	6	33	8.4%	0.19 [0.02, 1.67]
Pederzoli 1993	5	41	10	33	16.5%	0.32 [0.10, 1.05]
Poropat 2016	2	23	3	24	4.5%	0.67 [0.10, 4.41]
Poropat 2017	3	49	2	49	3.2%	1.53 [0.24, 9.60]
Røkke 2007	3	36	7	37	10.7%	0.39 [0.09, 1.64]
Sainio 1995	9	30	12	30	14.2%	0.64 [0.22, 1.87]
Schwarz 1997	8	13	7	13	4.6%	1.37 [0.29, 6.53]
Xue 2009	8	29	10	27	12.7%	0.65 [0.21, 2.00]
Total (95% CI)		**376**		**371**	**100.0%**	**0.74 [0.50, 1.09]**
Total events	63		76			

Heterogeneity: Chi² = 8.45, df = 10 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)

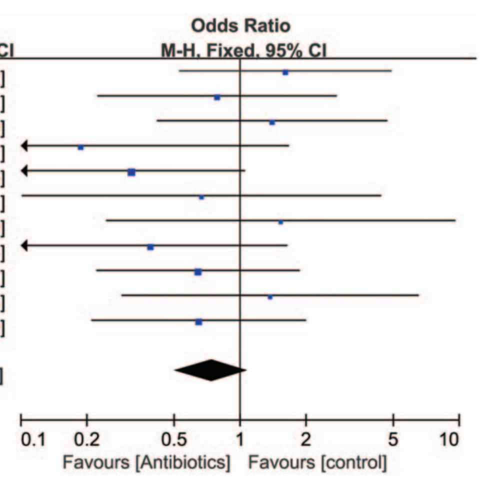

Figure 3: Forest plot of comparison: antibiotic prophylactic effect on infected pancreatic necrosis. CI: Confidence interval; M-H: Mantel-Haenszel.

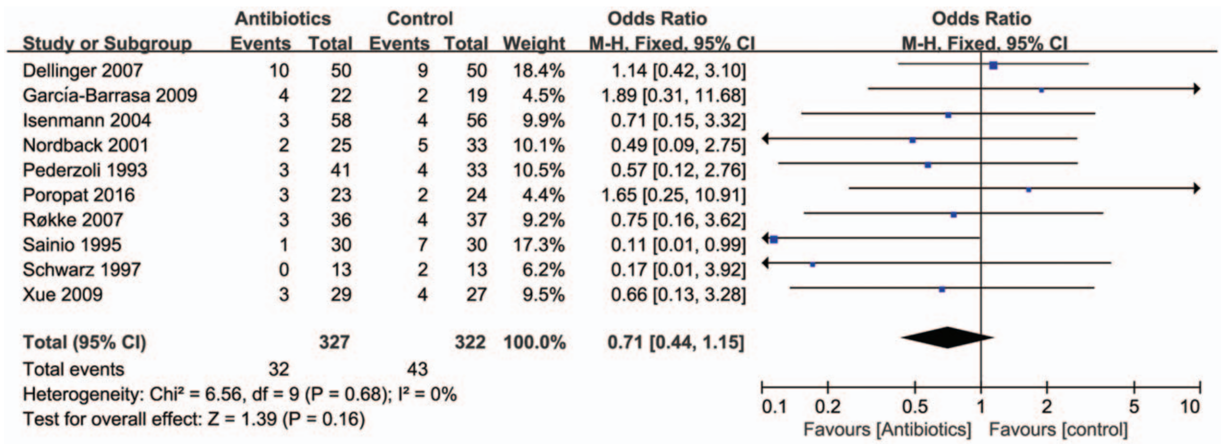

Figure 4: Forest plot of comparison: antibiotic prophylactic effect on mortality. CI: Confidence interval; M-H: Mantel-Haenszel.

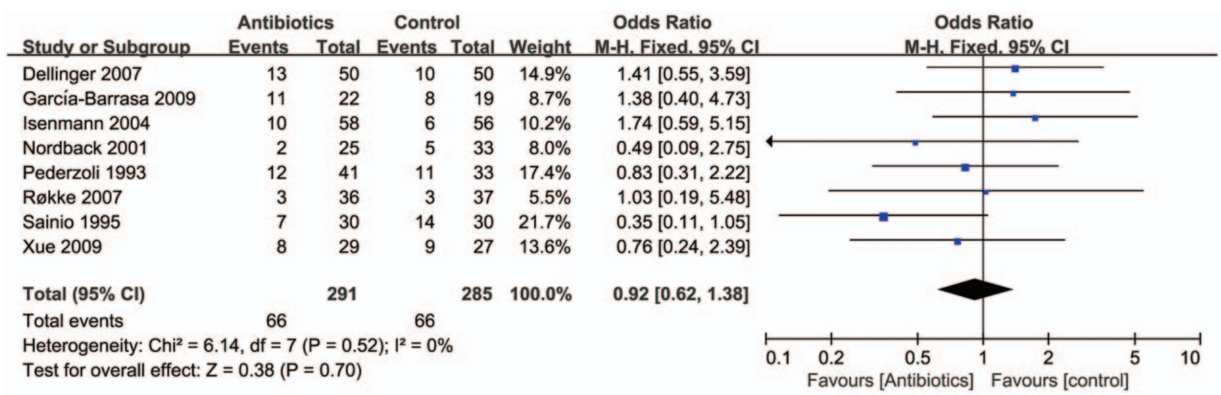

Figure 5: Forest plot of comparison: antibiotic prophylactic effect on surgical intervention. CI: Confidence interval; M-H: Mantel-Haenszel.

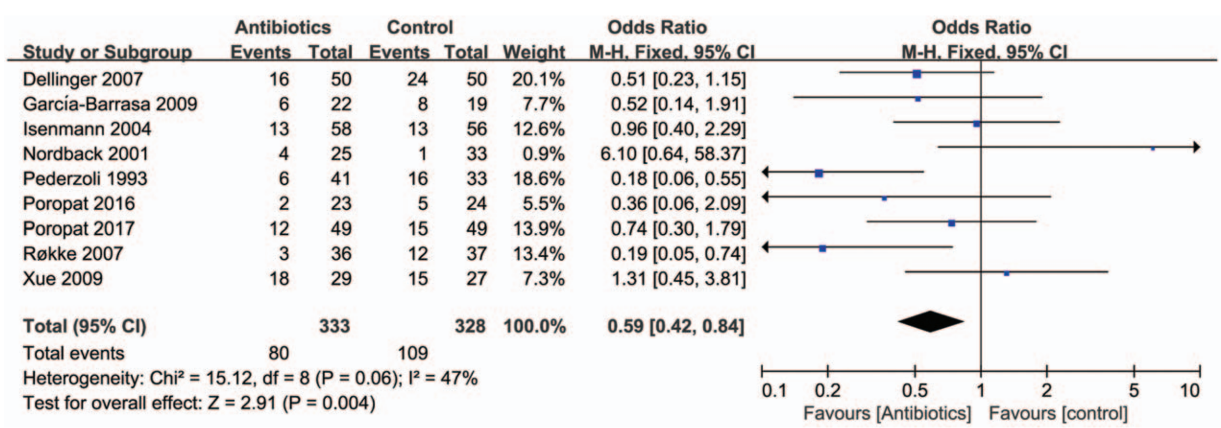

Figure 6: Forest plot of comparison: antibiotic prophylactic effect on non-pancreatic infection. CI: Confidence interval; M-H: Mantel-Haenszel.

Owing to the different study designs, these studies showed conflicting and contradictory outcomes.

The results of several previously published meta-analyses have also differed.[13-15,27] Most published meta-analyses have not focused on specific non-pancreatic infections such as pneumonia and UTI. Therefore, we conducted this meta-analysis to address this issue and included two newly published RCTs in the analysis. Our meta-analysis not only assessed the effects of the prophylactic use of antibiotics on mortality and infected pancreatic necrosis but also on pneumonia, UTI, and fungal infection, among others. In the present meta-analysis, we found that prophylactic use of antibiotics did not reduce the rate of mortality (OR = 0.71; 95% CI, 0.44–1.15; $P = 0.16$) [Figure 4], surgical intervention (OR = 0.92; 95% CI, 0.62–1.38; $P = 0.70$) [Figure 5], or infected pancreatic necrosis (OR = 0.74; 95% CI, 0.50–1.09; $P = 0.13$) [Figure 3]. However, the use of antibiotics was associated with a statistically significant reduction in the incidence of non-pancreatic infections (OR = 0.59; 95% CI, 0.42–0.84; $P = 0.004$) [Figure 6]. Non-pancreatic infections included pneumonia, UTI, positive blood culture, fungal infection, and others. Therefore, we further analyzed the effect of prophylactic use of antibiotics on pneumonia, UTI, positive blood culture, fungal infection. In this meta-analysis, we found that prophylactic use of antibiotics did not reduce the incidence of pneumonia (OR = 0.61; 95% CI, 0.32–1.14; $P = 0.12$) [Figure 10], positive blood culture (OR = 0.61; 95% CI, 0.29–1.30; $P = 0.20$) [Figure 11], or fungal infection (OR = 0.95; 95% CI, 0.30–3.03; $P = 0.94$) [Figure 12]. These results are mostly consistent with previous studies. However, antibiotic prophylaxis could reduce the incidence of UTI (OR = 0.44; 95% CI, 0.22–0.89; $P = 0.02$) [Figure 13].

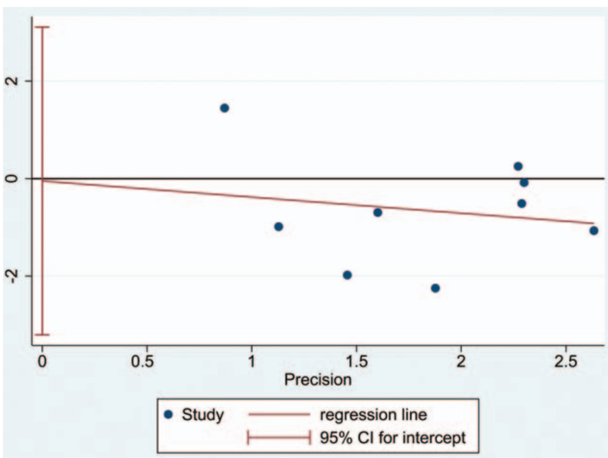

Figure 7: Egger's test illustrating the publication bias. CI: Confidence interval.

Infected pancreatic necrosis is a leading cause of death in patients with AP.[5] However, we found that antibiotic prophylaxis did not reduce the incidence rate of infected pancreatic necrosis and mortality. The prophylactic use of antibiotics may reduce the incidence of non-pancreatic infection according to our meta-analysis. We found that antibiotic prophylaxis only reduced the incidence of UTI. Sub-group and sensitivity analyses were implemented to investigate non-pancreatic infection owing to moderate heterogeneity. The Egger's test indicated no publication bias and a stable outcome of sensitivity analysis. In the sub-group analysis, the results regarding non-pancreatic infection suggested that there were no differences in the before year of 2009 sub-group *vs*. year 2009 and later sub-group, <50 sub-group *vs*. 50 to 99 sub-group *vs*. ≥100 sub-group, and imipenem sub-group *vs*. other antibiotics sub-group. According to results for single-center *vs*. multicenter studies, patients treated with antibiotic prophylaxis had significantly less infection in the multicenter sub-group. A possible explanation may be that this finding is limited by the single-center's medical level and regional differences.

According to the results of our meta-analysis, antibiotic prophylaxis did not reduce the incidence of infected pancreatic necrosis and surgical intervention. Mowery *et al*[28] suggested that demarcation of necrosis results in less injury to vital tissues with delayed surgery; there is less bleeding, and necrosectomy is more effective. The 2019

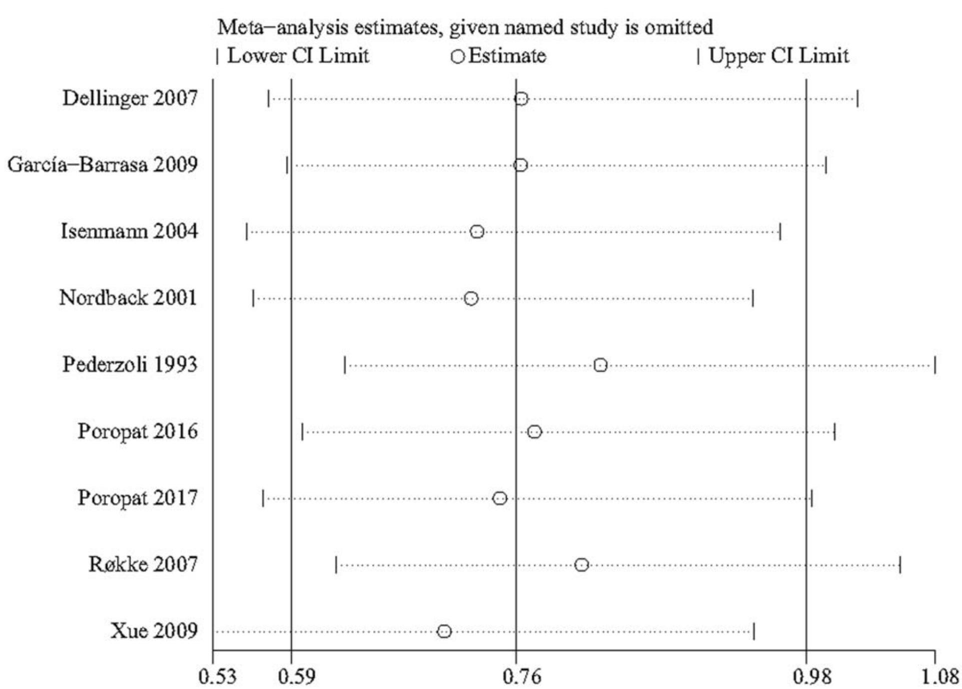

Figure 8: The sensitivity analysis for the incidence of non-pancreatic infections. CI: Confidence interval.

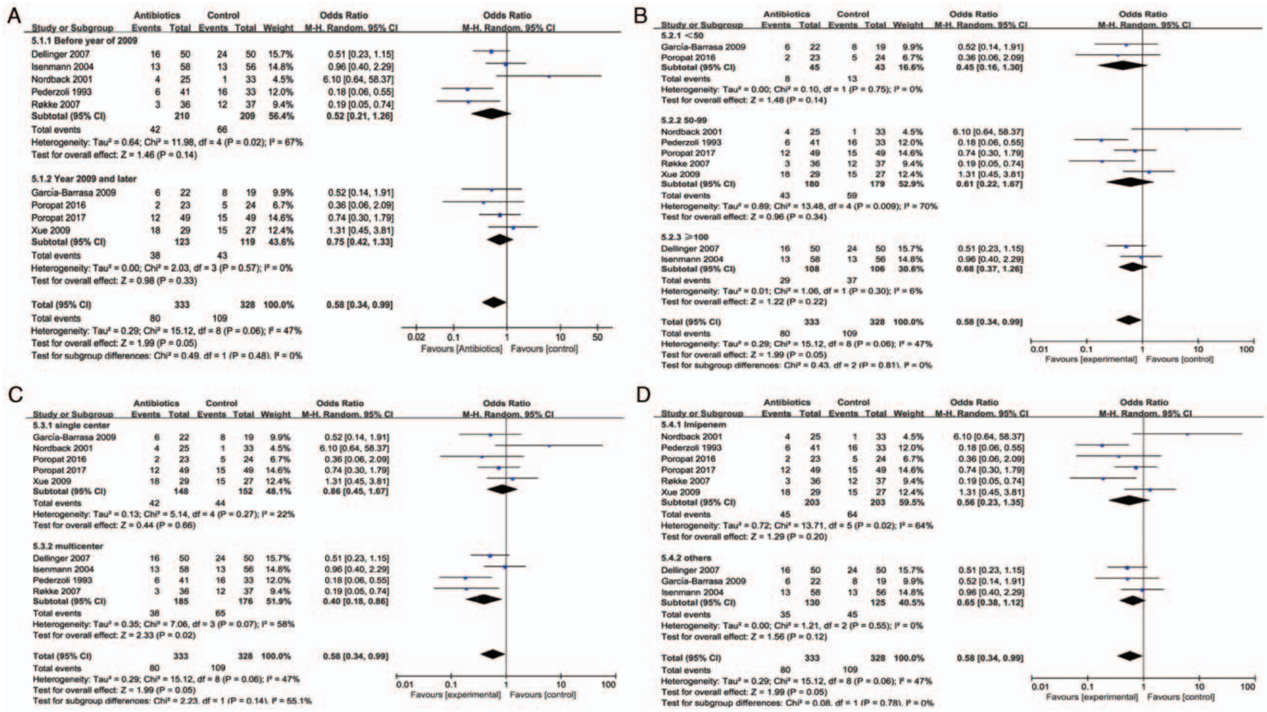

Figure 9: The sub-group analysis for the incidence of non-pancreatic infections. (A) Forest plot showing OR for non-pancreatic infections based on publication date of included RCTs. (B) Forest plot showing unadjusted OR for non-pancreatic infections based on sample size. (C) Forest plot showing OR for non-pancreatic infections based on single-center or multiple centers. (D) Forest plot showing OR for non-pancreatic infections based on kinds of antibiotics. CI: Confidence interval; M-H: Mantel-Haenszel; OR: Odds ratio; RCT: Randomized controlled trial.

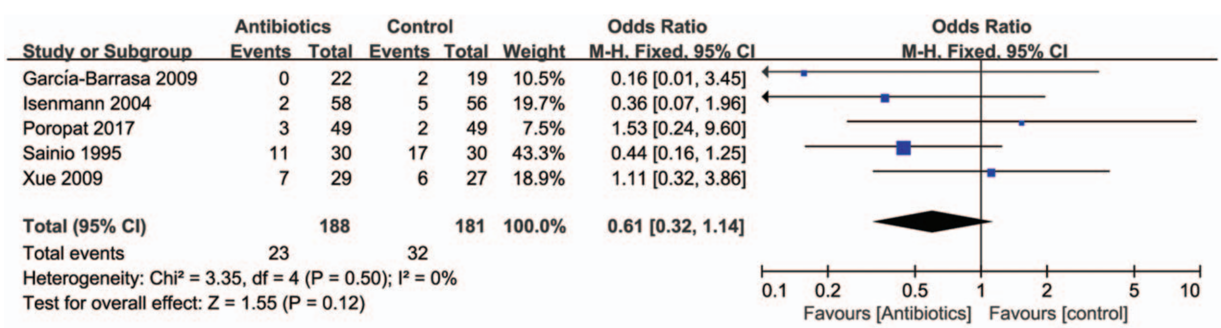

Figure 10: Forest plot of comparison: antibiotic prophylactic effect on pneumonia. CI: Confidence interval; M-H: Mantel-Haenszel.

World Society of Emergency Surgery guidelines for the management of SAP suggests that postponing surgical interventions for more than 4 weeks after the onset of disease results in less mortality.[10] Additional trials are needed to clarify whether antibiotic prophylaxis can delay surgical intervention in AP. In addition, a focus is required beyond only whether antibiotic prophylaxis is beneficial in AP. Greater attention is needed regarding the adverse effects of antibiotic prophylaxis in future studies, including increased prevalence of multi-drug resistant bacteria and incidence of fungal infection, among other effects. Fungal infection is a severe complication of AP related to an increase in morbidity and mortality.[29] Thus, additional RCTs investigating the efficacy of antifungal prophylaxis in AP should be designed. Moreover, whether the results of antibiotic prophylaxis differ according to the etiology of pancreatitis is worth further exploration. The mechanism of infected pancreatic necrosis remains unclear. Some studies consider that transmission of organisms from the gastrointestinal tract to the pancreas is one cause. Thus, future trials should explore the cause of infected pancreatic necrosis.

There are several limitations in this meta-analysis. First, there is possible heterogeneity of the included articles. For instance, the different antibiotics, dosage, medical levels, timing of administration, antibiotic duration, and regional differences in each trial may have contributed to the heterogeneity. Second, the sample in some included articles was small. Third, there were differences with regard to pancreatitis etiology and severity of disease, among other factors. In the future, more high-quality RCTs are needed to yield a more persuasive meta-analysis.

In conclusion, the findings of our meta-analysis suggest that antibiotic prophylaxis may reduce the incidence of

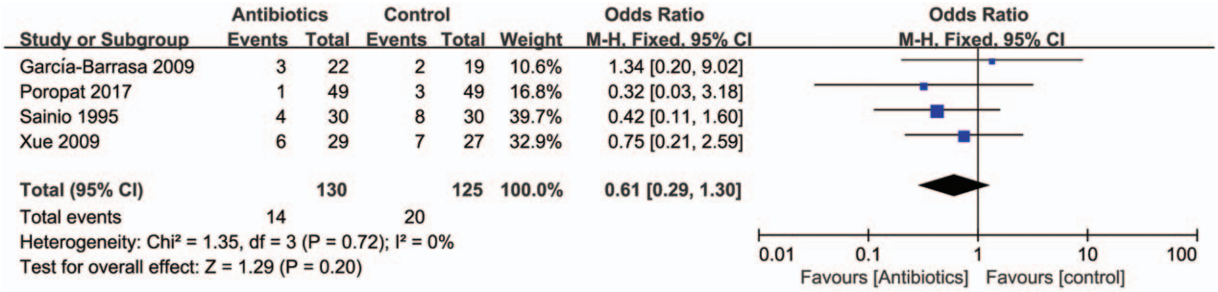

Figure 11: Forest plot of comparison: antibiotic prophylactic effect on positive blood culture. CI: Confidence interval; M-H: Mantel-Haenszel.

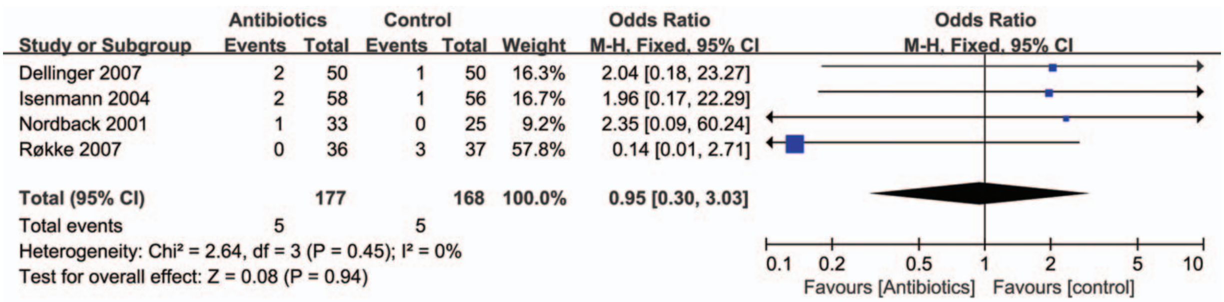

Figure 12: Forest plot of comparison: antibiotic prophylactic effect on fungal infection. CI: Confidence interval; M-H: Mantel-Haenszel.

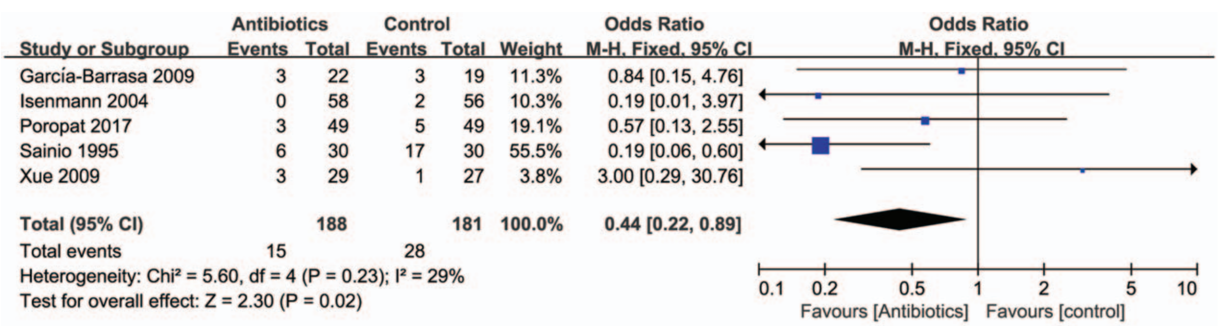

Figure 13: Forest plot of comparison: antibiotic prophylactic effect on urinary tract infection. CI: Confidence interval; M-H: Mantel-Haenszel.

non-pancreatic infection and UTI in patients with AP. However, our results showed no differences in terms of infected pancreatic necrosis, mortality, surgical intervention, pneumonia, positive blood culture, and fungal infection. Therefore, the present study findings showed no statistically significant benefit of prophylactic antibiotic use in AP. Additional higher quality RCTs with larger sample sizes are needed to comprehensively assess the efficacy of antibiotic prophylaxis in patients with AP.

Conflicts of interest

None.

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