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META-ANALYSIS

# Extended antimicrobial prophylaxis after gastric cancer surgery: A systematic review and meta-analysis

Chun-Dong Zhang, Yong-Ji Zeng, Zhen Li, Jing Chen, Hong-Wu Li, Jia-Kui Zhang, Dong-Qiu Dai

Chun-Dong Zhang, Yong-Ji Zeng, Zhen Li, Jing Chen, Hong-Wu Li, Jia-Kui Zhang, Dong-Qiu Dai, Department of Gastrointestinal Surgery, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, Liaoning Province, China
Author contributions: Zhang CD and Dai DQ conceived the study; Zhang CD and Zeng YJ collected data and performed data analysis; all authors designed the study and wrote the paper, read and approved the final manuscript for submission.
Correspondence to: Dong-Qiu Dai, Professor, Chief Physician, Department of Gastrointestinal Surgery and Cancer Center, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, Liaoning Province,
China. daidq63@163.com
Telephone: +86-24-62043110 Fax: +86-24-62043110
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## Abstract

**AIM:** To investigate the efficacy of extended antimicrobial prophylaxis (EAP) after gastrectomy by systematic review of literature and meta-analysis.

**METHODS:** Electronic databases of PubMed, Embase, CINAHL, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register and the China National Knowledge Infrastructure were searched systematically from January 1980 to October 2012. Strict literature retrieval and data extraction were carried out independently by two reviewers and meta-analyses were conducted using RevMan 5.0.2 with statistics tools risk ratios (RRs) and intention-to-treat analyses to evaluate the items of total complications, surgical site infection, incision infection, organ (or space) infection, remote site infection, anastomotic leakage (or dehiscence) and mortality. Fixed model or random model was selected accordingly and forest plot was conducted to display RR. Likewise, Cochrane Risk of Bias Tool was applied to evaluate the quality of randomized controlled trials (RCTs) included in this meta-analysis.

**RESULTS:** A total of 1095 patients with gastric cancer were enrolled in four RCTs. No statistically significant differences were detected between EAP and intraoperative antimicrobial prophylaxis (IAP) in total complications (RR of 0.86, 95%CI: 0.63-1.16, $P$ = 0.32), surgical site infection (RR of 1.97, 95%CI: 0.86-4.48, $P$ = 0.11), incision infection (RR of 4.92, 95%CI: 0.58-41.66, $P$ = 0.14), organ or space infection (RR of 1.55, 95%CI: 0.61-3.89, $P$ = 0.36), anastomotic leakage or dehiscence (RR of 3.85, 95%CI: 0.64-23.17, $P$ = 0.14) and mortality (RR of 1.14, 95%CI: 0.10-13.12; $P$ = 0.92). Likewise, multiple-dose antimicrobial prophylaxis showed no difference compared with single-dose antimicrobial prophylaxis in surgical site infection (RR of 1.10, 95%CI: 0.62-1.93, $P$ = 0.75). Nevertheless, EAP showed a decreased remote site infection rate compared with IAP alone (RR of 0.54, 95%CI: 0.34-0.86, $P$ = 0.01), which is the only significant finding. Unfortunately, EAP did not decrease the incidence of surgical site infections after gastrectomy; likewise, multiple-dose antimicrobial prophylaxis failed to decrease the incidence of surgical site infection compared with single-dose antimicrobial prophylaxis.

**CONCLUSION:** We recommend that EAP should not be used routinely after gastrectomy until more high-quality RCTs are available.



**Key words:** Gastric cancer; Gastrectomy; Extended antimicrobial prophylaxis; Intraoperative antimicrobial prophylaxis; Meta-analysis

**Core tip:** We investigated the efficacy of extended antimicrobial prophylaxis (EAP) after gastrectomy through systematic review of literature and meta-analysis. We recommend that EAP should not be used routinely after

gastrectomy until more high-quality randomized controlled trials are available.

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## INTRODUCTION

Although the incidence of gastric cancer is sharply declining, it still remains the second cause of cancer-related death worldwide[1,2]. Administration of a first-generation cephalosporin as intraoperative antimicrobial prophylaxis (IAP) to prevent surgery-associated infection has been recommended[3]. Nevertheless, most patients after gastrectomy still receive further extended antimicrobial prophylaxis (EAP) routinely to reduce surgical site infection even until 3-4 postoperative days[4-6]. Few randomized controlled trials (RCTs) have investigated the efficacy of EAP[7-10]. Moreover, EAP administration is controversial and there is no worldwide accepted validation as a result of its scarce efficacy.

However, the administration of antimicrobial prophylaxis may result in antibiotics-associated diarrhea (AAD), which can occur as early as few hours after the first dose of antibiotics[11]. The incidence of AAD varies from 10% to 30%, and AAD has been identified as the leading cause of diarrhea in hospitalized patients, especially in patients with surgery of gastrointestinal tract[12]. Abuse of antibiotics also aggravates the burden of patient hospital costs.

A total of 21 320 new gastric cancer cases and 10 540 deaths from gastric cancer were projected to occur in the United States in 2012[2]. Generally, complete surgical resection of gastric cancer with negative margin (R0 resection) and D2 lymphadenectomy is considered as the most effective treatment strategy for gastric cancer in East Asia[13-15]. Surgical site infections have suggested the essential administration of IAP. However, only few RCTs have investigated the efficacy of EAP[7-10], and almost no meta-analysis has been conducted to assess the efficacy of EAP. Meta-analysis is considered a more powerful evidence for clinical decision marking compared with RCTs. In light of these considerations, we performed this meta-analysis to assess the efficacy of EAP in patients after gastrectomy.

## MATERIALS AND METHODS

### Literature search

To identify additional studies and published abstracts, electronic databases of PubMed, Embase, CINAHL, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register and the China National Knowledge Infrastructure were searched systematically from January 1980 to October 2012. MeSH terms of "stomach neoplasm", "gastrectomy", "antibiotic prophylaxis" and "randomized controlled trial" were used. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant trials.

### Data collection process

Two reviewers (Zhang CD and Zeng YJ) in our group independently extracted relevant data, including: study and population features, outcomes, titles, abstracts, and even full articles when it was necessary. They compared the results and synthesized the same opinions, and disagreements were solved by discussion with a third reviewer in our group.

### Inclusion and exclusion criteria

The inclusion criteria and exclusion criteria were established based on the Cochrane Handbook for Systematic Review of Interventions (Version 5.0.2). The inclusion criteria were: (1) all originally published and unpublished high-quality RCTs; (2) trials concerning antimicrobial prophylaxis after gastrectomy; (3) if studies were from the same author or institution, the most informative and latest ones were selected; and (4) no restriction on publishing language. Exclusion criteria were as follows: (1) studies with little information about the items to be investigated; (2) loss to follow-up exceeding 10%; and (3) non-RCTs.

The following data were acquired: study and year, country, sample size, sex ratio, median age, body-mass index, operation time, blood loss, median follow-up time, participants, interventions, total complications, surgical site infection, incision infection, organ/space infection, anastomotic leakage/dehiscence, and mortality (Tables 1-3).

### Quality evaluation

Methodological quality of RCTs was evaluated according to the Cochrane Risk of Bias Tool with regard to randomization, allocation concealment, blind, withdrawal and dropout, and selective reporting bias (Table 4).

### Statistical analysis

Data analysis was conducted using Review Manager 5.0.2 (RevMan 5.0.2) with statistics tools risk ratios (RRs). Intention-to-treat analyses were performed. Dichotomous variables were analyzed with RRs. $P < 0.05$ was defined as statistically significant and 95%CI was applied. Fixed model was used if $I^2 < 50\%$ and $P > 0.1$, while random model was selected if $I^2 \geqslant 50\%$ or $P \leqslant 0.1$. Likewise, forest plot was conducted to display RR.

## RESULTS

Among a total of 52 studies retrieved, 48 studies were found unrelated to our selection criteria after further assessment. Thus, only four RCTs[7-10] were eligible for the meta-analysis: three RCTs[7-9] comparing EAP with IAP and one RCT[10] comparing multiple-dose with single-

**Table 1 Primary characteristics of the randomized controlled trails included in the meta-analysis**

| Ref. | Country | Sample size | Male | Median age (yr) | Body mass index (kg/m$^2$) | Operation time (min) | Blood loss (mL) | Median follow-up time (d) |
|---|---|---|---|---|---|---|---|---|
| Schardey *et al*[7] | Germany | 102 | 60 | 63.7 ± 11.4 | NM | 301.6 ± 87.7 | NM | 42 |
| | | 103 | 59 | 62.6 ± 11.9 | NM | 314.8 ± 107 | NM | |
| | | | *P* > 0.05 | *P* > 0.05 | NM | *P* > 0.05 | NM | |
| Farran *et al*[8] | Spain | 22 | 33 | 57(31-87) | NM | NM | NM | > 22 |
| | | 27 | | | NM | NM | NM | |
| Imamura *et al*[9] | Japan | 179 | 125 | 65 | 22.5 (12.4-32.9) | 200 (64-415) | 210 (1-1700) | 30 |
| | | 176 | 115 | 66 | 22.3 (16.3-33.0) | 209 (58-428) | 200 (1-880) | |
| | | | *P* = 0.536 | *P* = 0.429 | *P* = 0.190 | *P* = 0.499 | *P* = 0.903 | |
| Mohri *et al*[10] | Japan | 243 | 174 | 68 (22-91) | 21.6 (13.4-31.6) | 232 (43-70) | 338.0 (10-2811) | 30 |
| | | 243 | 164 | 68 (23-90) | 21.4 (13.6-34.0) | 234 (70-492) | 405.7 (10-2917) | |
| | | | *P* = 0.375 | *P* = 0.642 | *P* = 0.446 | *P* = 0.798 | *P* = 0.028 | |

NM: Not mentioned.

**Table 2 Secondary characteristics of the randomized controlled trails included in the meta-analysis**

| Ref. | Participants | *n* | Interventions | Complications |
|---|---|---|---|---|
| Schardey *et al*[7] | 205 patients August 1991-March 1994 Germany, multi-centre, ≥ 18 yr, total gastrectomy | 102 *vs* 103 | Polymyxin B 0.1 g, tobramycin 0.08 g, vancomycin 0.125 g and amphotericin B 0.5 g four times per day orally from the day before operation until 7th postoperative day plus perioperative intravenous prophylaxis: cefotaxime 2 × 2 g *vs* placebo plus perioperative intravenous prophylaxis: cefotaxime 2 × 2 g | Infections: Pulmonary, urinary tract; abscess; Insufficiency: Pancreatic, esophagointestinal; miscellaneous; pancreatic fistula |
| Farran *et al*[8] | 49 patients January 2000-March 2005, single centre, ≥ 18 yr, total gastrectomy | 22 *vs* 27 | 20 mL oral suspension of erythromycin 0.5 g + gentamicine 0.08 g + nystatin sulfate 0.1 g *vs* 20 mL placebo solution. Both groups started treatment 12 h before surgery and continued until the 5th postoperative day | Dehiscence; sepsis; abscess; pulmonary infection; pulmonary distress syndrome |
| Imamura *et al*[9] | 355 patients June 2005-December 2007, Japan, multi-centre, ≥ 35 yr, distal gastrectomy | 179 *vs* 176 | Intraoperative administration plus cefazolin 1 g once after closure and twice daily for 2 postoperative days *vs* intraoperative administration: cefazolin 1 g before surgical incision and every 3 h as intraoperative supplements | Anastomotic leakage; remote infections; surgical site infections |
| Mohri *et al*[10] | 486 patients May 2001-December 2004 Japan, single-centre, ≥ 20 yr, elective gastrectomy | 243 *vs* 243 | Intraoperative schedule: cefazolin 1 g or ampicillin-sulbactam 1.5 g by intravenous infusion > 15 min and an additional dose was administrated if operation > 3 h *vs* intraoperative schedule plus further treatment at 12-h intervals, a total of 7 doses | Surgical site infection: incision or organ or space; abscess |

**Table 3 Basic data of the comparisons included in the randomized controlled trails**

| Ref. | Total complication | Surgical site infection | Incision infection | Organ/ space infection | Remote site infection | Anastomotic leakage/ dehiscence | Mortality |
|---|---|---|---|---|---|---|---|
| Schardey *et al*[7] | 31/102 | NM | NM | NM | 16/102 | NM | 5/102 |
| | 46/103 | NM | NM | NM | 31/103 | NM | 11/103 |
| Farran *et al*[8] | 2/22 | NM | NM | NM | 1/22 | 1/22 | 2/22 |
| | 3/27 | NM | NM | NM | 3/27 | 0/27 | 0/27 |
| Imamura *et al*[9] | 22/179 | 16/179 | 5/179 | 11/179 | 6/179 | 4/179 | NM |
| | 17/176 | 8/176 | 1/176 | 7/176 | 9/176 | 1/176 | NM |
| Mohri *et al*[10] | NM | 23/243 | 14/243 | 12/243 | NM | NM | NM |
| | NM | 21/243 | 11/243 | 10/243 | NM | NM | NM |

NM: Not mentioned.

dose antimicrobial prophylaxis after gastrectomy, including 1095 patients (Tables 1-5).

### *Primary outcomes: Intraoperative vs EAP*

**Total complications:** Three RCTs[7-9] were included (303 EAP and 306 IAP) and fixed model was applied ($I^2$ = 42%, *P* = 0.18). No statistically significant difference was detected (RR of 0.86, 95%CI: 0.63-1.16, *P* = 0.32).

**Surgical site infection, incision infection and organ/space infection:** Only one RCT[9] comparing EAP and IAP reported surgical site infection, which showed no statistical difference (RR of 1.97, 95%CI: 0.86-4.48, *P* = 0.11). There were also no significant differences in the analysis of incision infection (RR of 4.92, 95%CI: 0.58-41.66, *P* = 0.14) and organ or space infection (RR of 1.55, 95%CI: 0.61-3.89, *P* = 0.36).

**Table 4 Quality assessment of the randomized controlled trails included based on the Cochrane Risk of Bias Tool**

| Ref. | Randomization | Allocation concealment | Blind | Withdrawal and dropout | Presence of selective reporting bias |
|---|---|---|---|---|---|
| Schardey *et al*[7] | Without details | Envelope | Double-blind | Well reported | Unclear |
| Farran *et al*[8] | Well reported | Envelope | Double-blind | Well reported | No |
| Imamura *et al*[9] | Well reported | Envelope | No | Well reported | No |
| Mohri *et al*[10] | Well reported | Without details | No | Well reported | Unclear |

**Table 5 Summary of comparisons between extended antimicrobial prophylaxis and intraoperative antimicrobial prophylaxis**

| Items | Heterogeneity | | Analysis model | Overall effect | | RR (95%CI) | Ref. |
|---|---|---|---|---|---|---|---|
| | $I^2$ | $P$ | | $Z$ | $P$ | | |
| Total complications | 42% | 0.18 | Fixed | 0.99 | 0.32 | 0.86 (0.63-1.16) | [7-9] |
| Surgical site infections | NP | NP | Fixed | 1.61 | 0.11 | 1.97 (0.86-4.48) | [9] |
| Incision infections | NP | NP | Fixed | 1.46 | 0.14 | 4.92 (0.58-41.66) | [9] |
| Organ/space infections | NP | NP | Fixed | 0.92 | 0.36 | 1.55 (0.61-3.89) | [9] |
| Remote site infections | 0% | 0.90 | Fixed | 2.58 | 0.01 | 0.54 (0.34-0.86) | [7-9] |
| Anastomotic leakage/dehiscence | 0% | 0.97 | Fixed | 1.47 | 0.14 | 3.85 (0.64-23.17) | [8,9] |
| Mortality | 62% | 0.10 | Random | 0.10 | 0.92 | 1.14 (0.1-13.12) | [8,9] |

NP: Not applicable; RR: Risk ratio.

**Remote site infection:** Three RCTs (303 EAP and 306 IAP)[7-9] evaluated remote site infection and fixed model was conducted ($I^2$ = 0%, $P$ = 0.90), however, there was a significantly decreased remote site infection rate in EAP compared with IAP (RR of 0.54, 95%CI: 0.34-0.86, $P$ = 0.01).

**Anastomotic leakage or dehiscence:** Two RCTs (201 EAP and 203 IAP)[8,9] were evaluated, showing no statistical difference in anastomotic leakage or dehiscence (RR of 3.85, 95%CI: 0.64-23.17, $P$ = 0.14).

**Mortality:** Two RCTs (124 EAP and 130 IAP)[7,8] were included, which suggested no survival benefit of EAP compared with IAP (RR of 1.14, 95%CI: 0.10-13.12, $P$ = 0.92).

### *Secondary outcomes: Multiple-dose antimicrobial prophylaxis vs single-dose antimicrobial prophylaxis*

Only one RCT[10] compared the efficacy of multiple-dose antimicrobial prophylaxis with single-dose antimicrobial prophylaxis, however, no significant differences were detected in surgical site infection (RR of 1.10, 95%CI: 0.62-1.93, $P$ = 0.75), incision infection (RR of 1.27, 95%CI: 0.59-2.75, $P$ = 0.54) and organ/space infection (RR of 1.20, 95%CI: 0.53-2.73, $P$ = 0.66). The incidence of surgical site infection after gastrectomy was similar by the two antimicrobial prophylaxis regimens.

## DISCUSSION

Meta-analysis is considered an ideal statistical tool increasing the statistical power, in other words, meta-analysis is a more powerful evidence for clinical decision marking compared with RCTs. In light of these considerations, this meta-analysis was conducted to assess the efficacy of EAP after gastrectomy.

Although it has been widely accepted that patients with gastrectomy will benefit from preoperative antimicrobial prophylaxis and IAP[16,17], there is still no worldwide accepted validation for EAP. In this meta-analysis, we found that postoperative EAP did not decrease the incidence of total complications in patients with gastrectomy. Additionally, EAP failed to improve surgical site infection rate, including incision infection and organ/space infection; likewise, no significant difference was detected in anastomotic leakage/dehiscence and mortality between EAP and IAP. The same striking finding was that patients did not benefit from multiple-dose antimicrobial prophylaxis compared with single-dose antimicrobial prophylaxis; yet, only one RCT[10] was included in this meta-analysis. Based on the present evidence, we do not recommend the administration of EAP after gastrectomy; however, our results need to be validated and re-evaluated by more high-level RCTs.

Surgical site infections remain a substantial cause of postoperative mortality[18]. We therefore conjecture that if EAP can decrease the surgical site infection rate, it may subsequently decrease the postoperative mortality. Unfortunately, EAP failed to decrease the surgical site infection rate. We assessed the mortality of EAP and IAP groups, and found no significant differences between the two groups. In light of these considerations, our findings suggested that EAP fails to decrease mortality in patients after gastrectomy; in other words, no survival benefit can be observed from EAP after gastrectomy based on the present evidence.

Many factors, such as male ratio, median age, obesity, operation time and intraoperative blood loss, may affect the postoperative infection risk[18-23]. For example, the effect of antibiotics will be diminished as a result of intraoperative blood loss; likewise, longer operation time will increase blood loss; meanwhile, obesity may increase the difficulty of operation and the operation time. Taking all these factors into consideration, we evaluated the statistical difference systematically; fortunately, we did not detect any significant difference among these items. Therefore, these factors have not affected the outcomes in these RCTs (Table 1).

The only significant difference between EAP and IAP is the remote site infection rate. However, we recommend that EAP should not be applied routinely unless the individuals experience a remote site infection. Therefore, we suggest delivering an "individualized treatment" rather than a routine treatment. The drugs used for EAP in these trials varied from cefazolin 1-1.5 g[9,10], erythromycin 0.5 g + gentamicine 0.08 g + nystatin sulfate 0.1 g[8], polymyxin B 0.1 g, tobramycin 0.08 g, vancomycin 0.125 g to amphotericin B 0.5g[7]. The incidence of surgical site infection in these RCTs ranged from 4.5% to 9.5%, which is in keeping with published rates of 5%-14%[24,25]. Despite these differences, the infection rates were similar, and no difference was detected (Table 2). However, our results still need to be validated for patients who require surgery on other sites of the body because the micro-flora in these operation sites differs from that in gastrointestinal tract[26].

There was no country or language restriction in the data search process for this meta-analysis. It is the first meta-analysis concerning the efficacy of EAP after gastrectomy. There are some limitations of these studies, such as various antimicrobial prophylaxis regimens used and disappointing statistical power, thus, more high-level RCTs are needed to validate our results.

Based on the present evidence, EAP fails to decrease the incidence of surgical site infections after gastrectomy; multiple-dose antimicrobial prophylaxis fails to decrease the incidence of surgical site infection compared with single-dose antimicrobial prophylaxis. Therefore, we believe that our findings are significant to all patients with gastrectomy, and suggest that EAP should not be used routinely after gastrectomy until more high-level RCTs are available.

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## COMMENTS

### Background

Administration of intraoperative antimicrobial prophylaxis (IAP) to prevent surgery-associated infection has been recommended. Although extended antimicrobial prophylaxis (EAP) has been recommended to be discontinued within 24 h of surgery, most patients after gastrectomy still receive further EAP routinely, as a result of insufficient evidence. This meta-analysis was conducted to investigate the effectiveness of EAP aimed at guiding clinical practice.

### Research frontiers

Meta-analysis was conducted to evaluate the effectiveness of EAP *vs* IAP for patients undergoing gastric cancer surgery.

### Innovations and breakthroughs

The evidence obtained from this meta-analysis proved that EAP failed to demonstrate the advantages over IAP for patients with gastric cancer surgery with regard to total complications, surgical site infection, incision infection, organ or space infection, anastomotic leakage or dehiscence and mortality. These findings suggested that EAP should not be used routinely after gastrectomy.

### Applications

The results of this meta-analysis suggest that EAP should not be administrated routinely after gastric cancer surgery and IAP is a standard treatment strategy for gastric cancer surgery.

### Terminology

Surgical site infection: Infection occurs within one month after operation and involves superficial incision, deep incision, organ or space, which may generate some symptoms of infection, such as pain or tenderness, local swelling, redness, heat and so on.

### Peer review

The period of the investigation extended over 32 years, during which different types and combinations of antibiotics have been used, but does not permit any evaluation of any particular antibiotics which might have been valuable. It is a valuable finding that intra-operative antibiotic prophylaxis is as efficient as an extended post-operative course in preventing post-operative infections.

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