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REVIEW ARTICLE

Reduction of risk of infection during elective laparoscopic cholecystectomy using prophylactic antibiotics: a systematic review and meta-analysis

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Abstract

Background Whether perioperative administration is required in elective laparoscopic cholecystectomy (LC) in patients with low risk of infection remains controversial.

Objective To investigate whether perioperative use of prophylactic antibiotics during elective LC can reduce the incidence of postoperative infection using a meta-analysis.

Methods Pubmed, Cochrane Library, Embase, and reference lists were searched up to October 26, 2020, for randomized controlled trials (RCTs) of the perioperative use of antibiotics during LC. A systematic review with meta-analysis, meta-regression, and GRADE (Grading of Recommendations Assessment, Development and Evaluation) of the evidence was conducted. The Cochrane (RoB 2.0) tool was used to assess the risk of bias.

Result A total of 14 RCTs were ultimately included in the meta-analysis, involving a total of 4360 patients. The incidence of surgical site infections, distant infections, and overall infections was investigated and the relationship with the perioperative use of prophylactic antibiotics during LC analyzed. The results indicated that in low-risk patients undergoing elective LC, prophylactic antibiotics reduce the incidence of surgical site infections (RR 0.66; 95% CI 0.45–0.98), with a moderate GRADE of evidence, distant infections (RR 0.34; 95% CI 0.16–0.73), with a low GRADE of evidence and overall infections (RR 0.57; 95% CI 0.40–0.80), with a moderate GRADE of evidence.

Conclusions The present meta-analysis demonstrates that the perioperative use of antibiotics in LC is effective in low-risk patients, possibly reducing the incidence of surgical site infections, distant infections, and overall infections. However, in view of the limitations of the study, it is recommended that studies with a more rigorous design (for downgraded factors) and larger sample size should be conducted in the future so that the conclusions above can be further verified through key result indicators.

Keywords Elective laparoscopic cholecystectomy · Prophylactic antibiotics · Perioperative · Meta-analysis

Laparoscopic cholecystectomy (LC) is the gold standard surgical technique for the treatment of symptomatic gallbladder stones and particular benign gallbladder diseases [1, 2]. LC has the advantages of a small wound, light postoperative pain of incision, quick recovery of gastrointestinal function, early return to activity and eating, a short hospital stay with a low incidence of surgical site infection [3, 4]. Studies have shown that the incidence of infection at the surgical site of

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LC is approximately 0.4–1.13%, which is significantly lower than that of open cholecystectomy (OC) by 3–47% [5–7]. The possible reason is that the LC incision is smaller, and the chance of wound exposure and contamination using a trocar is lower, significantly reducing the incidence of surgical site infections [8, 9].

Due to the low incidence of LC surgical site infections and unnecessary high medical costs, current guidelines do not support the routine preventive use of antibiotics in elective LC [10]. In addition, multiple clinical RCTs have been conducted both nationally and internationally, in order to clarify the role of the preventive use of antibiotics in elective LC [11–15]. The ultimate goal is to reduce unnecessary antibiotic use, thereby addressing antibiotic resistance, medical costs, and other issues such as toxic epidermal necrolysis (TENS), and increasing rates of antibiotic-associated (pseudomembranous) colitis caused by Clostridium difficile [16, 17]. However, despite the suggestions and guidelines above, in many clinical practices, the majority of surgeons still use intravenous antibiotics (single dose of cephalosporin) during LC perioperatively to reduce the possibility of postoperative infections [18–20]. According to a survey by McGuckin et al. [6], 79% of patients received prophylactic antibiotics during the perioperative period in LC, while 63% were administered postoperative antibiotics. Therefore, are perioperative antibiotics really required in LC to prevent postoperative infection? This question is worth considering.

High-quality meta-analyses are increasingly considered a key tool for obtaining the required level of evidence and have been widely used in multiple fields [21–23]. Many published meta-analyses have evaluated the role of LC perioperative preventive use of antibiotics, indicating that their use in the perioperative period in LC is unnecessary [11, 12, 14, 15, 24–28]. Conversely, different conclusions have been drawn in prospective studies, indicating that they can reduce the incidence of postoperative infections [1, 29, 30]. Whether prophylactic use of antibiotics in elective LC can reduce the incidence of postoperative infections remains inconclusive, and authors' opinions are not consistent. In addition, previous meta-analyses have not provided any judgment of the quality of the pooled evidence using a GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach or with any other methodology, nor did it use the RoB 2.0 risk of bias evaluation tool provided by the Cochrane Collaboration to assess the overall risk of bias in the study [31, 32]. In addition, subgroup regression is not used according to the characteristics of the subgroup to confirm whether the outcome indicators were influenced by some covariates. Therefore, a systematic review and meta-analysis of randomized controlled trials (RCTs) of related studies was conducted. The purpose of the analysis was to evaluate the effectiveness of the perioperative administration of antibiotics in elective LC.

Methods

Search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for interventional studies [33]. A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used to assess methodological quality [34]. Two researchers (J. Y. and Sy. G.) independently searched the Pubmed, Embase, Cochrane Library, and reference lists, for RCTs of antibiotics used during the perioperative period in LC. Only articles written in English from the date of establishment of the database to October 26, 2020 were searched. Search terms included cholecystectomy, laparoscopic cholecystectomy, antibiotics, prophylactic antibiotics, and perioperative antibiotics. In addition, we also searched the reference lists of related studies. The search strategy is detailed in Online Appendix 1. Because the present study was a systematic review and meta-analysis, Institutional Review Board (IRB) approval was not required.

Inclusion and exclusion criteria

Inclusion criteria

Only studies that satisfied the following inclusion criteria were included: (1) Patients with low-risk benign gallbladder diseases who had undergone LC surgery and were over 18 years of age, (not including patients with high-risk factors prior to surgery, patients > 60 years of age, those with acute cholecystitis, bile duct stones, obstructive jaundice, immunosuppression, history of antibiotic allergy, pregnancy, conversion to laparotomy, cholangitis, insertion of prosthetic devices, or intraoperative bile spillage [10]). including multicenter and single-center trials; (2) Whether the use of antibiotics during the perioperative period was described (Definition of perioperative antibiotics: use of antibiotics before and/or after LC surgery); (3) All studies had to provide at least one of the following endpoint indicator: reporting of surgical site infections (superficial or deep incisional infections or organ/space infections), distant infections (infections occurring outside the surgical site, such as respiratory or urinary tract infections), and overall infections (surgical site infections and distant infections), within 30 days of the infection occurring. If the time is not clearly stated in the original study, it is considered to be within 30 days; (4) the duration of preoperative and postoperative antibiotic use and the number of days of postoperative follow-up, were recorded; and (5) RCTs.

Exclusion criteria

Studies were excluded if: (1) the methodology did not clearly state the method of random allocation; (2) the report duplicated data already included, or research where data were unavailable; (3) the investigation was of high-risk patients prior to surgery; and (4) no control group was included.

Data extraction

All data were independently extracted by two researchers (J. Y. and Sy. G.) using standardized extraction forms. For research that lacked the required information, the author was contacted via email to request the original data. The extracted information includes the following information:

(1) General information of the research: author, year of publication, location, study design.
(2) Basic data included in the study: mean age of participants, sample size, inclusion criteria intervention measures, dose of antibiotics, days of follow-up, type of antibiotics, and clinical outcome indicators

Primary outcome indicators: surgical site infections, distant infections, and overall infections. Secondary outcome indicators: medical costs (including hospitalization and outpatient costs) and adverse reactions (allergic reactions, TENS, and antibiotic-associated (pseudomembranous) colitis caused by Clostridium difficile).

For data extraction, two rigorously trained researchers processed articles independently. Prior to the formal data extraction process, the researchers processed sample articles to ensure consistency and accuracy of the results of the evaluation. Inconsistency in particular information between researchers was resolved by discussion or negotiation with a third researcher (Tt. L).

Risk of bias and assessment of quality of evidence

The Cochrane Collaboration risk of bias assessment tool RoB 2.0 represents a unique literature quality assessment process for randomized controlled studies [31]. Methodological quality evaluation can be divided into high risk of bias, low risk of bias, and some concerns, encompassing 5 domains: randomization, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported result. The GRADE method was used to determine the level of evidence for major outcome indicators [32]. Quality was appraised as ''very low,'' ''low,'' ''moderate,'' or ''high'' based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. In addition, widely accepted "funnel chart" visualization was used to assess publication bias.

Statistical analysis

RevMan 5.3 software (Nordic Cochrane Centre; Oxford, UK) provided by the Cochrane Collaboration network was used to perform statistical analysis of the data. The occurrence of surgical site, distant, and overall infections was calculated as a relative risk (RR) and 95% confidence interval (CI). Mantel–Haenszel (M–H) methodology was used for the meta-analysis of included studies. Meta-regression analysis was conducted to determine whether the associations between surgical site infections, distant infections, and overall infections were influenced by a covariate (such as: type of antibiotics, geographical areas, doses of antibiotics, time of antibiotic use before LC), influencing factors identified as having a positive meta-regression coefficient ($P < 0.05$). I^2 and χ^2 statistics were used to evaluate the heterogeneity between studies. Values of $I^2 > 50\%$ represent clear heterogeneity, in which case a random effects model was used. A fixed effects model was used where $I^2 < 50\%$. P-values < 0.05 were considered statistically significant.

Subgroup analyses

Subgroup analyses based on 4 aspects were conducted: (1) Type of antibiotics (First-generation cephalosporin, Second-generation cephalosporin, Third-generation cephalosporin); (2) Geographical region (Asia, Europe, or America); (3) Antibiotic administration (only before LC, or before and after LC); (4) Time antibiotics were administered prior to LC (30 min, 60 min, during induction of anesthesia).

Results

Literature screening

A total of 2467 studies were retrieved from a search of databases, as shown in Fig. 1. A total of 1585 records were excluded after reading the title and abstract of each article. Of the remaining 33 studies, one had no control group [35], 5 investigated acute cholecystitis [36–40], and 13 studies had a high risk of bias and so were excluded [8, 41–52]. Finally, 14 studies met the inclusion and exclusion criteria and so were included in the meta-analysis (4360 cases in total, including 2128 in the antibiotic group and 2,232 in the non-antibiotic group) [53–66].

Characteristics of included studies

The 14 studies included in the review were single-center studies in which the mean age of patients was between 40 and 54 years, publication year was 1999 to 2016, the surgical method was elective LC (low-risk benign gallbladder

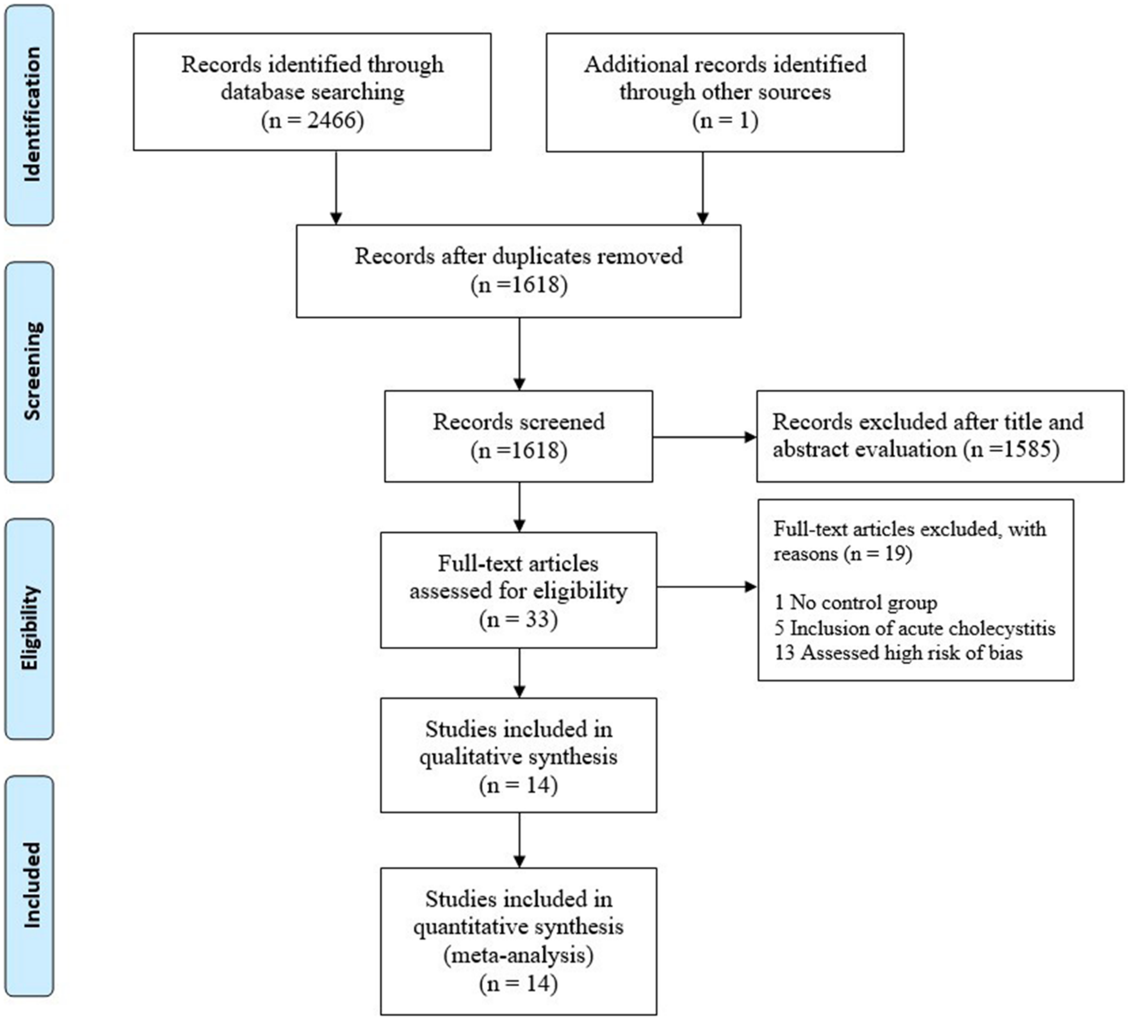


Fig. 1 Study flow diagram

diseases), with antibiotics administered intravenously. The characteristics of the articles included in the review can be summarized as follows: (1) The number of patients in each study varied: cohorts ranged from 84 to 1037. Twelve studies had fewer than 500 patients [53–57, 59, 62–66], while one had between 500 and 1000 [58]. One study had more than 1000 cases [60]; (2) Year of publication varied: 6 studies were published prior to 2010 [55, 57, 59, 62, 63, 66] and 8 were published on or after 2010 [53, 55, 57, 58, 60, 61, 64, 65]; (3) Patients were from different geographical regions: patients in Asia were investigated in 6 studies [53, 57, 60, 62, 64, 65], 5 studies researched patients in Europe [57–59, 63, 66], 2 in America [55, 61], and 1 studied patients in Africa [54]; (4) Different types of antibiotics were used: second-generation cefuroxime was used in 1 study [53], 3 studies used the third-generation antibiotics ceftazidime or cefotaxime [54, 57, 63], while 10 studies used the first-generation cefotetan or cefazolin [55, 56, 58–62, 64–66]; (5) The control group, antibiotic dose, and the number of days of follow-up after surgery varied: patients were untreated in 4 studies [53, 60, 61, 64], 11 studies used a placebo [54–59, 62, 63, 65, 66], 1 dose of antibiotics was used prior to surgery in 10 studies used [53–56, 58, 59, 61, 62, 64, 66], while 2–3 doses of antibiotics were administered before and after surgery in 4 studies [57, 60, 63, 65]. Postoperative follow-up was performed after 7 to 42 days across all studies (Table 1).

Risk of bias and assessment of quality of evidence

A total of 14 studies were evaluated for risk of bias in accordance with the Cochrane RoB 2.0 tool and provide detailed justifications in a supplement [53–66], as shown in Table 2 (Supplementary Material 1, 2, 3). The methodological quality of all studies was relatively high (fair or good methodological quality). In 7 studies [53, 55, 56, 58, 59, 61, 62], the overall risk of bias in the evaluation of the results

Table 1 Characteristics of the 14 included studies

Source	Location	Study design	Inclusion criteria	Participants	Intervention		Dose	Follow-up (day)	Types of antibiotics
					Antibiotics	Control			
Al-Qahtani et al. [53] 2011	Saudi Arabia Asia	Single-center (RCTs)	Elective laparoscopic cholecystectomy	Patients ($n=221$) Mean age 40 years;	IV Cefuroxime 1.5 g (Only before LC, 30 min before LC)	U	1	30	②
Hassan et al. [54] 2012	Egypt Africa	Single-center (RCTs)	Patients included in the study were those with chronic calculate gall bladder disease with an overall good health (ASA I/II)	Patients ($n=200$) Mean age 41 years;	IV Ceftazidime / (Only before LC, 60 min before LC)	P	1	30	③
Higgins et al. [55] 1999	London America	Single-center (RCTs)	Elective laparoscopic cholecystectomy aged between 18 and 80 years with biliary colic	Patients ($n=412$) Mean age 48 years;	IV Cefotetan 1 g OR Cefazolin 1 g (Only before LC, 60 min before LC)	P	1	30	①
Ruangsin et al. [56] 2015	Thailand Asia	Single-center (RCTs)	Symptomatic gallstones without underlying disease	Patients ($n=299$) Mean age 54 years;	IV Cefazolin 1 g (Only before LC, 30–60 min before LC)	P	1	30	①
Tocchi et al. [57] 2000	Italy Europe	Single-center (RCTs)	Elective laparoscopic cholecystectomy	Patients ($n=84$) Mean age 52 years;	IV Cefotaxime 2 g (Before and after LC, 30 min before and 24 h after LC)	P	2	42	③
Turk et al. [58] 2013	Turkey Europe	Single-center (RCTs)	Being in ASA I and II categories upon anesthesiologic examination; Having symptomatic cholelithiasis	Patients ($n=547$) Mean age 50 years;	IV Cefazolin 1 g (Only before LC, At the time of anesthesia induction)	P	1	30	①
Uludag et al. [59] 2009	Turkey Europe	Single-center (RCTs)	Elective laparoscopic cholecystectomy	Patients ($n=144$) Mean age 44 years;	IV Cefazolin 1 g (Only before LC, during induction of anesthesia)	P	1	30	①
Matsui et al. [60] 2014	Japan Asia	Single-center (RCTs)	Patients with gallbladder stones or polyps scheduled to undergo elective laparoscopic cholecystectomy	Patients ($n=1037$) Mean age/years	IV Cefazolin 1 g (Before and after LC, the first, just before skin incision, and the second and the third at 12 h and 24 h)	U	3	30	①
Passos et al. [61] 2016	Brazil America	Single-center (RCTs)	Uncomplicated lithiasic cholecystitis undergoing elective laparoscopic cholecystectomy	Patients ($n=100$) Mean age 48 years;	IV Cefazolin 2 g (Only before LC, during induction of anesthesia)	U	1	30	①
Chang et al. [62] 2006	Taiwan Asia	Single-center (RCTs)	Symptomatic gallbladder stones or polyps disease with or without acute cholecystitis	Patients ($n=277$) Mean age 52 years	IV Cefazolin 1 g (Only before LC, during induction of anesthesia)	P	1	30	①
Koc et al. [63] 2003	Turkey Europe	Single-center (RCTs)	Elective laparoscopic cholecystectomy	Patients ($n=92$) Mean age 49 years;	IV Cefotaxime 2 g (Before and after LC, first before the operation and then again 24 h afterward)	P	2	30	③
Mirani et al. [64] 2014	Pakistan Asia	Single-center (RCTs)	Symptomatic patients scheduled for LC of ASA 1 and 2 (without diabetes)	Patients ($n=310$) Mean age 41 years;	IV Cefazolin 1 g (Only before LC, Not started)	U	1	7	①
Yildzi et al. [66] 2009	Turkey Europe	Single-center (RCTs)	Elective laparoscopic cholecystectomy	Patients ($n=208$) Mean age 51 years;	IV Cefazolin 1 g (Only before LC, during induction of anesthesia)	P	1	30	①

Table 1 (continued)

Source	Location	Study design	Inclusion criteria	Participants	Intervention		Dose	Follow-up (day)	Types of antibiotics
					Antibiotics	Control			
Asghar et al. [65] 2016	Iran Asia	Single-center (RCTs)	Symptomatic gallbladder stones or polyps	Patients ($n=429$) Mean age 42 years;	IV Cefazolin 1 g (Before and after LC, 30 min before anesthesia and then, six and 12 h after anesthesia)	P	3	30	①

RCTs randomized controlled trials, *LC* laparoscopic cholecystectomy, *ASA* American society of anesthesiologists, *IV* intravenous administration, *U* untreated, *P* placebo (isotonic sodium chloride solution); ①, first-generation cephalosporin; ②, second-generation cephalosporin; ③, third-generation cephalosporin

of surgical site infections was low. In 10 studies [54, 56, 57, 59–61, 63–66], the overall risk of bias in the evaluation of the results of distant infections was with some concern. Similarly, 10 studies that assessed the overall risk of bias in the overall infection results was with some concern [53–55, 57, 60, 62–66]. The overall quality of evidence among the three primary outcomes ranged from low to moderate for the RCTs in accordance with the GRADE criteria (full score is 4) (Table 3). Risk of bias, inconsistency, and imprecision were downgraded.

A funnel chart of the incidence rate of surgical site infections, distant infections, and overall infections is displayed in Fig. 2. As shown in the funnel diagrams in Fig. 2a and c, there was only a slight asymmetry in publication bias, while Fig. 2b has no asymmetry.

Meta-analyses

Surgical site infections

Fourteen studies evaluated the incidence of surgical site infections [53–66]. The results indicate that there was a difference between the prophylactic antibiotic group (42/2228) and the non-antibiotic group (61/2132) (RR 0.66; 95% CI 0.45–0.98; $P=0.04$) (Fig. 3), while heterogeneity was statistically significant ($\chi^2=9.87$, $I^2=0\%$), so a fixed effects model was used.

Distant infections

Fourteen studies evaluated the incidence of distant infections [53–66]. A difference was found between the prophylactic antibiotic group (9/2228) and the non-antibiotic group (25/2132) (RR 0.34; 95% CI 0.16–0.73; $P=0.005$) (Fig. 4). Heterogeneity was statistically significant ($\chi^2=4.78$, $I^2=37\%$), so a fixed effects model was used.

Overall infections

Fourteen studies evaluated the incidence of overall infections [53–66], the results of which demonstrated that there was a difference between the prophylactic antibiotic group (51/2228) and the non-antibiotic group (86/2132) (RR 0.57; 95% CI 0.40–0.80; $P=0.001$) (Fig. 5), with heterogeneity that was statistically significant ($\chi^2=15.47$, $I^2=16\%$) and so a fixed effects model was used.

Medical costs

Only one study described the problem of medical costs for the use of antibiotics related to LC perioperatively, which has demonstrated that the postoperative medical costs of

Table 2 Risk of bias of Included Randomized Controlled Trials (RoB-2.0)

Study ID	Outcomes	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported result	Overall risk of bias
Al-Qahtani et al. [53] 2011	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	+	+	+
	Overall infections	+	+	+	?	+	?
Hassan et al. [54] 2012	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Higgins et al. [55] 1999	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	+	+	+
	Overall infections	+	+	+	?	+	?
Ruangsin et al. [56] 2015	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	+	+	+
Tocchi et al. [57] 2000	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Turk et al. [58] 2013	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	+	+	+
	Overall infections	+	+	+	+	+	+
Uludag et al. [59] 2009	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	+	+	+
Matsui et al. [60] 2014	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Passos et al. [61] 2016	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	+	+	+
Chang et al. [62] 2006	Surgical site infections	+	+	+	+	+	+
	Distant infections	+	+	+	+	+	+
	Overall infections	+	+	+	?	+	?
Koc et al. [63] 2003	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Mirani et al. [64] 2014	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Yildzi et al. [66] 2009	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?
Asghar et al. [65] 2016	Surgical site infections	+	+	+	?	+	?
	Distant infections	+	+	+	?	+	?
	Overall infections	+	+	+	?	+	?

+ low risk; ? some concerns;—high risk

Table 3 Assessment of quality of evidence

Outcomes (No. of Studies)	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Risk ratio (95% CI)	Quality of certainty Evidence (GRADE)
Surgical site infections (14)	− 0.5	0	0	− 0.5	None	RR = 0.66, (0.45–0.98)	⊕ ⊕ ⊕ ◯[ad]
Distant infections (14)	− 1	− 0.5	0	− 0.5	None	RR = 0.34, (0.16–0.73)	⊕ ⊕ ◯◯[bcd]
Overall infections (14)	− 1	0	0	0	None	RR = 0.57, (0.40–0.80)	⊕ ⊕ ⊕ ◯[b]

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; *CI*, Confidence interval; *RR*, Risk ratio

[a]Downgraded by half level for mild risk of bias (− 0.5 score). Because the surgical site infections were not properly described

[b]Downgraded by one level for risk of bias (− 1 score). Because the distant infections and overall infections are not properly described

[c]Downgraded by half levels for mild statistical heterogeneity (− 0.5 score). Because $I^2 = 37\%$ is between 30 and 60%

[d]Downgraded by half level for mild statistical imprecision (− 0.5 score). Due to wide confidence intervals, possibly lowering statistical power to select the true effect; 0, Not serious. Evidence quality, ⊕ ◯◯◯: very low; ⊕ ⊕ ◯◯: low; ⊕ ⊕ ⊕ ◯: moderate; ⊕ ⊕ ⊕ ⊕: high

the prophylactic use of antibiotics during the perioperative period in LC are reduced ($P = 0.047$) [60].

Adverse reactions

Only one study reported an allergic reaction to antibiotics (2 out of 504, 0.39%) [60]. None of the 14 included studies reported the incidence of antibiotic-related infections.

Subgroups analysis and meta-regression

The effectiveness of different types of antibiotics was investigated. The results of subgroup analysis indicated that first (RR 0.64; 95% CI 0.41–0.99; $P = 0.05$), second (RR 0.58; 95% CI 0.14–2.38; $P = 0.45$), and third-generation antibiotics (RR 0.93; 95% CI 0.31–2.27; $P = 0.89$) were similar in reducing the incidence of surgical site infections. However, first-generation antibiotics significantly reduced the incidence of distant (RR 0.34; 95% CI 0.15–0.77; $P = 0.01$) and overall infections (RR 0.55; 95% CI 0.37–0.80; $P = 0.002$) compared with second and third-generation antibiotics. The perioperative use of antibiotics resulted in a lower incidence of surgical site infections (RR 0.47; 95% CI 0.27–0.80; $P = 0.006$), distant infections (RR 0.13; 95% CI 0.03–0.54; $P = 0.005$) and overall infections (RR 0.41; 95% CI 0.23–0.74; $P = 0.003$) in Asian patients, while European and American patients experienced similar levels of infections in all three. The results indicate that 2–3 doses of antibiotics before and after LC significantly reduced the incidence of surgical site infections (RR 0.44; 95% CI 0.21–0.93; $P = 0.03$), distant infections (RR 0.16; 95% CI 0.05–0.56; $P = 0.004$) and overall infections (RR 0.39; 95% CI 0.17–0.92; $P = 0.03$), but there was no difference where only one dose of antibiotics was administered prior to LC.

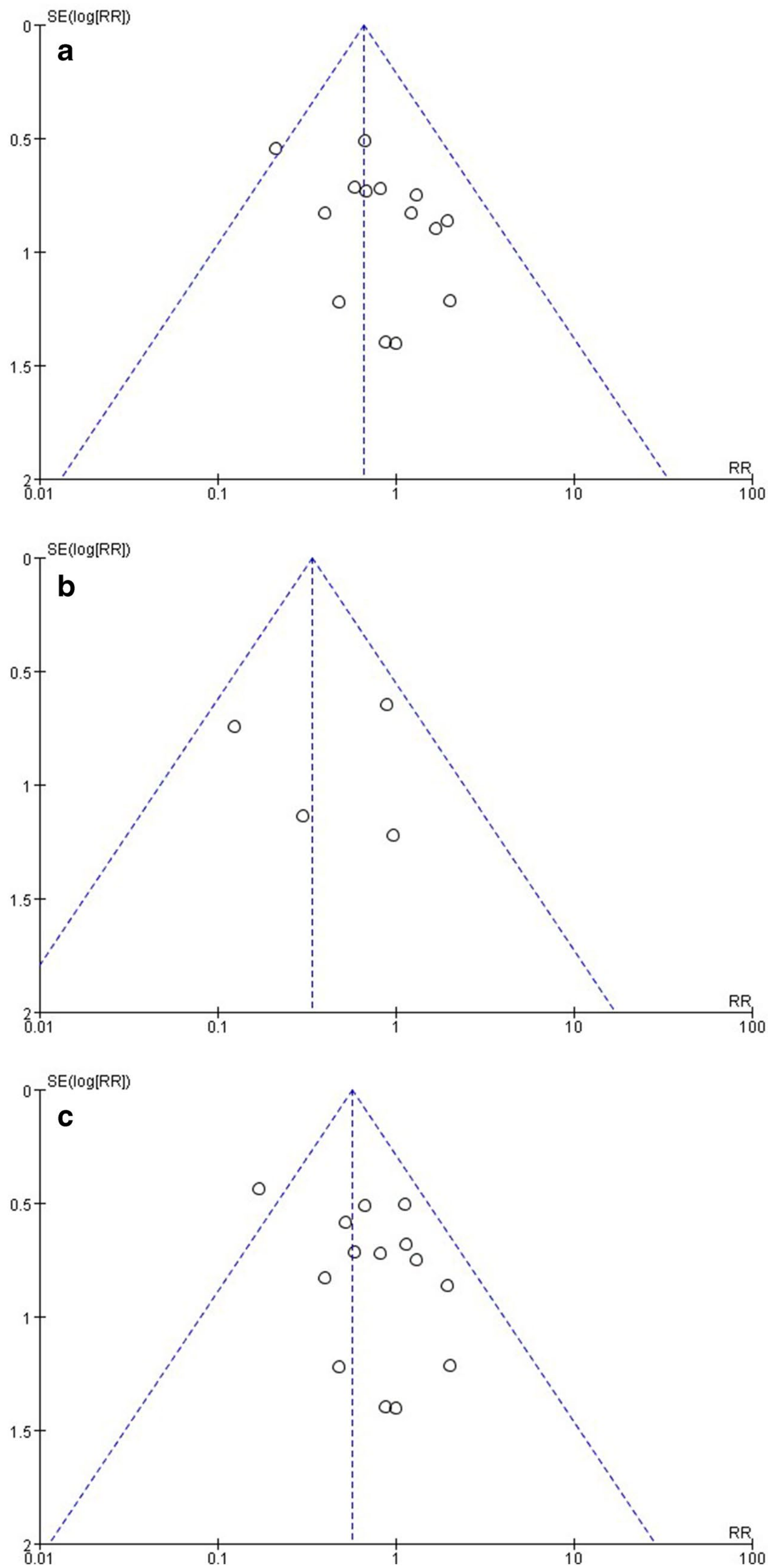
In addition, by subgroup analysis, it was found that the timing of antibiotics administration (30 min, 60 min, or during induction of anesthesia) prior to skin incision was not correlated with surgical site infections, distant infections, or overall infections (Table 4).

A meta-regression was performed to identify the possible influencing factors. We found that type of antibiotics (first-generation cephalosporin, second-generation cephalosporin, third-generation cephalosporin), geographic area (Asia, Europe, America), doses of antibiotics (1 dose, 2–3 doses), and time of antibiotics use before LC (30 min before LC, 60 min before LC, during induction of anesthesia) were not factors that influence surgical site infections or overall infections (type of antibiotics: $P = 0.642/0.920$; geographic area: $P = 0.055/0.074$; doses of antibiotics: $P = 0.154/0.217$; time of antibiotics use before LC: $P = 0.335/0.390$). Distant infections occurred in only 4 studies. At this time, the number of studies was less than 10 (insufficient observations), so meta-regression analysis could not be conducted (Table 5).

Discussion

The present meta-analysis demonstrates that the prophylactic administration of antibiotics perioperatively in LC can reduce the incidence of surgical site infections (moderate-quality evidence), distant infections (low-quality evidence), and overall infections (moderate-quality evidence), and represents an updated meta-analysis that includes recent data. The results contradict previously published meta-analyses [11, 12, 14, 15, 24–28]. There are three possible reasons: Firstly, previous analyses were affected by the methodological quality of a proportion of the original included studies, and so were not statistically convincing. In addition, we have strictly abided by the scope of the definition of surgical site infection, and only included RCTs of relevant studies of sufficient size. We excluded all small studies with poor methodological quality, fully ensuring that the standard of evidence and authenticity were robust. An appropriate level of statistical power was obtained in subgroup analysis of

Fig. 2 Funnel plots. **a** Surgical site infections; **b** Distant infections; **c** Overall infections



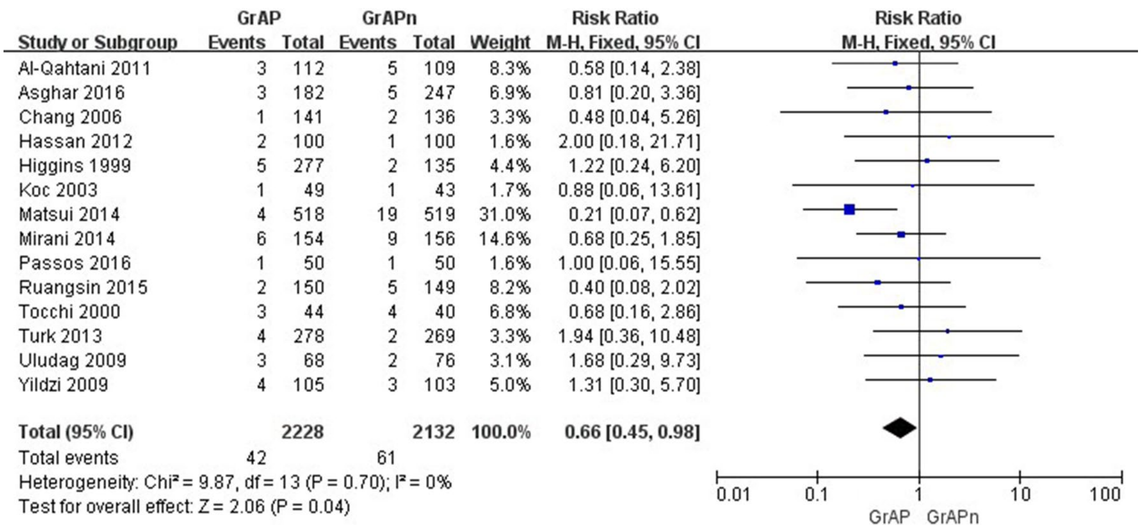


Fig. 3 Forest plot of Surgical site infections

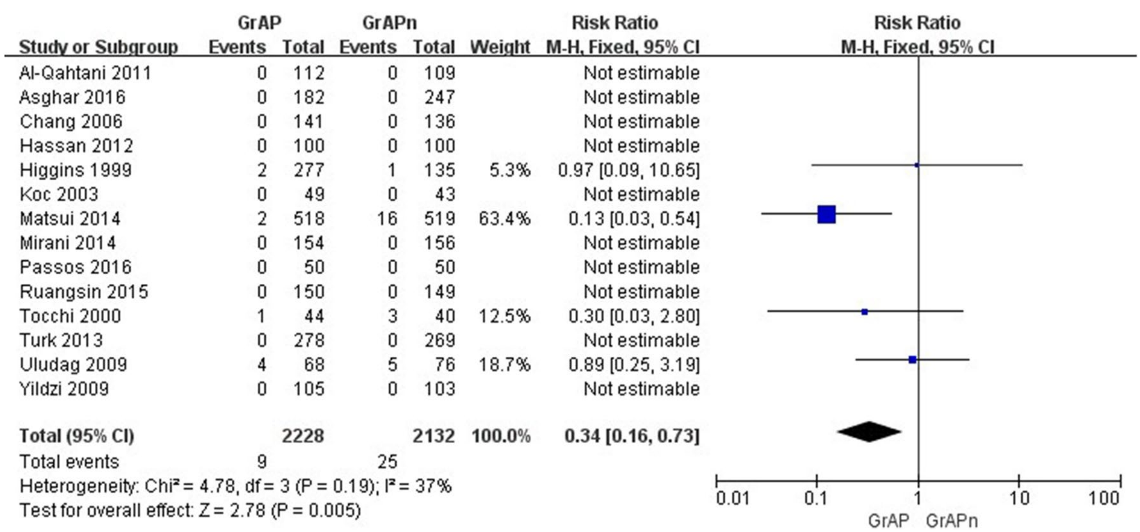


Fig. 4 Forest plot of Distant infections

surgical site infections, distant infections, and overall infections. Secondly, because the majority of trials used only one dose of antibiotics prior to surgery [53–56, 58, 59, 61, 62, 64, 66], it had no apparent effect on the prevention of postoperative infections. Therefore, using subgroup analysis, we found that the use of 2–3 doses of antibiotics before and after surgery was more effective than just 1 dose prior to surgery [57, 60, 63, 65]. In addition, the use of antibiotics perioperatively in Asian patients was more beneficial than for European or American patients. The reason for this may be that the physique, biology, intensity of patient management, local epidemiology, medical treatment, and the living environments of Asian patients are different from those of patients in Europe and America. In particular, the majority of published studies are limited to the results obtained in Asian countries. Therefore, the specific reasons for antibiotics only preventing infections in Asian patients needs to be further explored. Under normal circumstances, for cholecystectomy performed in day surgery (but excluding those performed in clinics or outpatient clinics), in addition to intravenous administration at the time of skin incision, an additional dose of antibiotics (1 tablet) should be given orally after surgery to prevent postoperative infections. This observation should suggest to clinicians that they reconsider the key use of antibiotics in the perioperative period for LC. Thirdly, generally speaking, the development of postoperative complications

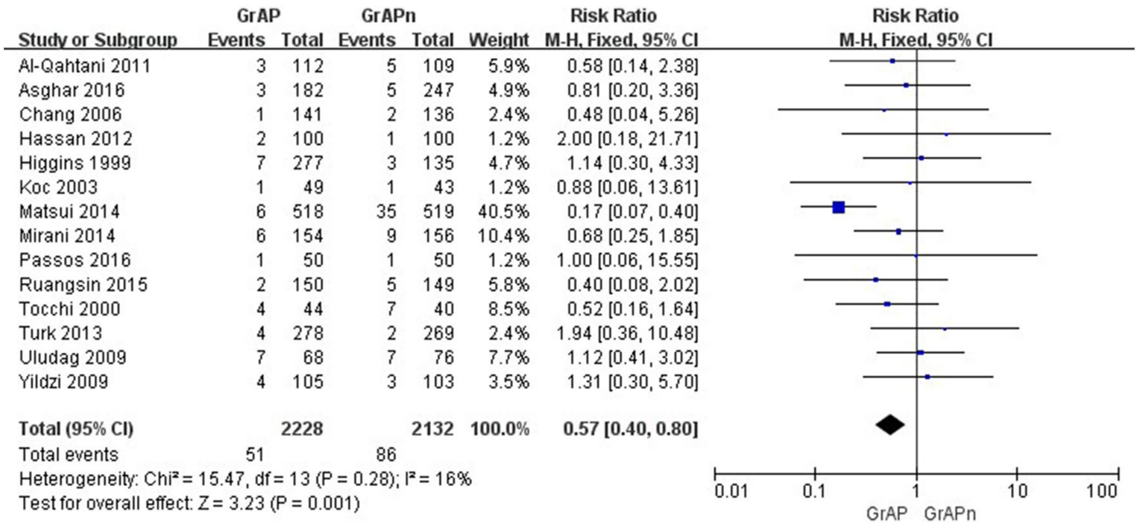


Fig. 5 Forest plot of Overall infections

(respiratory or urinary tract infections) is found in outpatient clinics in follow-up, and represents the best mode of tracking patient prognosis and recovery. However, none of the studies included in the analysis explained the rate of problems observed during follow-up, which suggests a relatively higher rate of postoperative complications of infection in patients not using antibiotics.

The three questions above (study quality, dose of antibiotics, and follow-up rate) may explain why the results of the present meta-analysis are contrary to those of previous meta-analyses. In addition, the majority of studies that lacked the use of antibiotics resulted in a higher trend in postoperative infection rate, which seems to be consistent with our findings.

The study of Chang et al. [62]. in clean or contaminated surgery recommended the use of a single dose of cephalosporin before skin incision or during induction of anesthesia. However, it is generally unknown whether the timing of antibiotics administration has an impact on postoperative infection. To exclude the influence of this variable, subgroup analysis was conducted from which we found that there was no correlation between the timing of preoperative antibiotics and postoperative infection.

The present study reviewed a total of 14 randomized controlled trials in a meta-analysis involving a total of 4360 patients. We found that prophylactic antibiotics lowered the surgical site infection rate from 2.86% (61/2132) to 1.89% (42/2228), distant infection rate from 1.17% (25/2132) to 0.4% (9/2228), and the overall rate of infections from 4.03% (86/2132) to 2.29% (51/2228), all of which were statistically significant findings. Due to the large numbers in the underlying study population, the costs of administering prophylactic antibiotics to thousands of patients could potentially be significantly more than the costs of the treatments of the relatively few infections that occur. However, there is very little evidence that not using prophylactic antibiotics during the perioperative period can reduce medical costs, even though clinicians generally believe this to be the case. Only one study reported on the issue of medical costs in relation to the use of preventive antibiotics [60]. Surprisingly, the study of Matsui et al. [60]. demonstrated that preventive use of antibiotics reduced postoperative medical costs, rather than the converse.

Widespread use of preventive antibiotics may increase antibiotic resistance, but this view is open to discussion. From clinical experience, antibiotic resistance has been shown not to be caused by short-term use of a small quantity of prophylactic antibiotics, but by the long-term administration of therapeutic antibiotics [67]. When infections occur after surgery, the use of therapeutic antibiotics may increase antibiotic resistance. If antibiotics can be used to prevent postoperative infections, reducing antibiotic resistance can be achieved by reducing the use of therapeutic antibiotics. Because long-term use of antibiotic treatment is positively correlated with the prevalence of resistance. Therefore, optimal preventive antibiotics are required to prevent antibiotic resistance [30]. We found from subgroup analysis of antibiotics type, that the use of first-generation antibiotics in the LC perioperative was superior to second and third-generation antibiotics in reducing the incidence of distant and overall infections. Additionally, narrow-spectrum antibiotics are low-cost and display low toxicity. There is no need to use second or third-generation antibiotics that have broad-spectrum antibiotic effects [68, 69].

All antibiotics have some side effects (including allergic reactions and infection with Clostridium difficile), although

Table 4 Subgroup analyses of the 14 included studies

Variables	S/P	Surgical site infections			S/P	Distant infections			S/P	Overall infections		
		Statistical method	Effect estimate	*P* value		Statistical method	Effect estimate	*P* value		Statistical method	Effect estimate	*P* value
Types of antibiotics												
First-generation cephalosporin	10/3763	RR (M–H, Fixed, 95% CI)	0.64 (0.41, 0.99)	0.05	10/3763	RR (M–H, Fixed, 95% CI)	0.34 (0.15, 0.77)	0.01	10/3763	RR (M–H, Fixed, 95% CI)	0.55 (0.37, 0.80)	0.002
Second-generation cephalosporin	1/221	RR (M–H, Fixed, 95% CI)	0.58 (0.14, 2.38)	0.45	1/221	RR (M–H, Fixed, 95% CI)	Not estimable	/	1/221	RR (M–H, Fixed, 95% CI)	0.58 (0.14, 2.38)	0.45
Third-generation cephalosporin	3/376	RR (M–H, Fixed, 95% CI)	0.93 (0.31, 2.77)	0.89	3/376	RR (M–H, Fixed, 95% CI)	0.30 (0.03, 2.80)	0.29	3/376	RR (M–H, Fixed, 95% CI)	0.72 (0.28, 1.84)	0.49
Geographical areas												
Asia	6/2573	RR (M–H, Fixed, 95% CI)	0.47 (0.27, 0.80)	0.006	6/2573	RR (M–H, Fixed, 95% CI)	0.13 (0.03, 0.54)	0.005	6/2573	RR (M–H, Fixed, 95% CI)	0.41 (0.23, 0.74)	0.003
Europe	5/1075	RR (M–H, Fixed, 95% CI)	1.07 (0.54, 2.09)	0.85	5/1075	RR (M–H, Fixed, 95% CI)	0.66 (0.22, 1.93)	0.45	5/1075	RR (M–H, Fixed, 95% CI)	0.98 (0. 54, 1.81)	0.96
America	2/512	RR (M–H, Fixed, 95% CI)	1.20 (0.56, 2.55)	0.64	2/512	RR (M–H, Fixed, 95% CI)	0.97 (0.09, 10.65)	0.98	2/512	RR (M–H, Fixed, 95% CI)	1.11 (0. 33, 3.69)	0.87
Doses of antibiotic												
Only before LC (1)	10/2718	RR (M–H, Fixed, 95% CI)	0.90 (0.54, 1.49)	0.68	10/2718	RR (M–H, Fixed, 95% CI)	0.91 (0.30, 2.80)	0.87	10/2718	RR (M–H, Fixed, 95% CI)	0.90 (0.57, 1.43)	0.67
Before and after LC (2–3)	4/1642	RR (M–H, Fixed, 95% CI)	0.44 (0.21, 0.93)	0.03	4/1642	RR (M–H, Fixed, 95% CI)	0.16 (0.05, 0.56)	0.004	4/1642	RR (M–H, Fixed, 95% CI)	0.39 (0.17, 0.92)	0.03
Time of antibiotic use before LC												
30 min before LC	1/221	RR (M–H, Fixed, 95% CI)	0.58 (0.14, 2.38)	0.45	1/221	RR (M–H, Fixed, 95% CI)	Not estimable	/	1/221	RR (M–H, Fixed, 95% CI)	0.58 (0.14, 2.38)	0.45
60 min before LC	3/911	RR (M–H, Fixed, 95% CI)	0.84 (0.31, 2.23)	0.72	3/911	RR (M–H, Fixed, 95% CI)	0.97 (0.09, 10.65)	0.98	3/911	RR (M–H, Fixed, 95% CI)	0.85 (0.34, 2.11)	0.73
During induction of anesthesia	5/1276	RR (M–H, Fixed, 95% CI)	1.31 (0.58, 2.95)	0.74	5/1276	RR (M–H, Fixed, 95% CI)	0.89 (0.25, 3.19)	0.86	5/1276	RR (M–H, Fixed, 95% CI)	1.17 (0.60, 2.31)	0.64

S study, *P* patients, *LC* laparoscopic cholecystectomy, *RR* risk ratio, *M–H* Mantel–Haenszel, Fixed-effect model, *MN* mean difference, *IV* inverse variance, Random-effect model, *CI* confidence interval

Table 5 Meta-regression analyses with subgroup characteristics as moderators

Surgical site infections					Overall infections			
Covariate	Types of antibiotics	Geographical areas	Doses of antibiotic	Time of antibiotic use before LC	Types of antibiotics	Geographical areas	Doses of antibiotic	Time of antibiotic use before LC
Coefficient	0.146	0.502	−0.673	0.412	0.033	0.449	−0.989	0.336
Standard error	0.305	0.234	0.442	0.398	0.322	0.227	0.392	0.367
95% lower	−0.519	−0.013	−1.637	−0.530	−0.699	−0.051	−1.843	−0.532
95% upper	0.810	1.017	0.290	1.353	0.735	0.948	0.216	1.205
t value	0.48	2.15	−1.52	1.03	0.10	1.98	−1.63	0.92
p value	0.642	0.055	0.154	0.335	0.920	0.074	0.217	0.390

LC laparoscopic cholecystectomy

$p<0.05$

usually trivial. But those, too, could be amplified as a result of widespread antibiotic use, including rare antibiotic-associated phenomena such as TENS, and antibiotic-associated (pseudomembranous) colitis caused by Clostridium difficile. However, only one study reported that two patients had allergic reactions due to antibiotics [60]. It is unbelievable that, in the remaining studies, such as allergic reactions, TENS, and antibiotic-associated (pseudomembranous) colitis caused by infection with Clostridium difficile were not reported, due possibly to not having been specifically recorded in the original study.

Intravenous administration of a single dose of cephalosporin antibiotics to prevent infection may not affect costs or the emergence of resistance, but cumulatively (such as postoperative intravenous administration of 2 and 3 doses of antibiotics), compared with postoperative oral antibiotics, requiring the patient to stay in hospital to receive intravenous antibiotics will increase the financial burden for low-risk patients, and an unnecessary waste of time and workload for medical staff [70]. However, the original research lacks data related to medical costs, and the side effects of antibiotics and antibiotic resistance are also unclear (insufficient information). Therefore, it is necessary to carefully design, larger sample size RCTs to answer these questions.

Strengths and limitations

An advantage of the present meta-analysis is that it reassessed the classification of infections using guidelines for the prevention of surgical site infections formulated in 1999 [71], and from this classification, a key question about whether surgeons should use antibiotics perioperatively in LC. Secondly, we provided a judgment about the quality of the pooled evidence using the GRADE approach and used the RoB 2.0 tool provided by the Cochrane Collaboration to assess the overall risk of bias in the studies reviewed here [31, 32]. Thirdly, we only included studies of fair or good methodological quality and largely avoided the main influencing factors by meta-regression analysis. In addition, even if the included RCTs provided the highest level of evidence, due to the large sample size included in Matsui's study and the small sample size of the remaining studies [60], the results of the meta-analysis may be affected. However, to further confirm our research conclusions, it is necessary to conduct rigorous studies in the future, using RCTs with a large sample size.

Some of the literature in this meta-analysis included patients with a history of diabetes, biliary colic, and liver cirrhosis. These are considered high-risk factors for infection and may affect patients with comorbidities associated with benign gallbladder disease. However, due to the lack of such data in the original articles and the low proportion of the population with high-risk factors, subgroup or sensitivity analyses were not performed on these factors. Secondly, due to the inadequacy of articles and strategies for their retrieval from electronic databases, relevant literature may have been overlooked, leading to publication bias. In addition, a number of studies did not specify the method used for randomization, which may represent a potential source of bias. Thirdly, medical costs and adverse reactions were reported in only one of the 14 studies included here. No study reported on TENS, or antibiotic-associated (pseudomembranous) colitis caused by Clostridium difficile. Therefore, we cannot rule out whether the associated potential risk of bias affects the results of the present study. Fourthly, even if articles reporting related conditions were to be included, to enhance the evidence for perioperative antibiotics use in LC, the number of cases in the two groups is in any case relatively small, and would not prevent type II errors. A larger sample is still required, with multi-center RCTs with sufficient statistical power to further demonstrate the difference in postoperative infection rates in high-risk patients.

Implications for practice

The results of the present meta-analysis are not applicable to all patients undergoing elective LC. The strategies to prevent postoperative infections are multifaceted. Clinicians should attempt to eliminate or limit confounding factors that may affect the results (types of antibiotics, timing, and dose). In addition, more detailed clinical evaluation and larger clinical trials are required to confirm the safety and feasibility of perioperative antibiotics in low-risk populations.

Conclusions

The present meta-analysis demonstrated that there were differences in surgical site infections, distant infections, and overall infections, depending on antibiotic use. The use of antibiotics during the perioperative period in LC is effective and may reduce the incidence of postoperative infection. Based on GRADE rating from low to moderate, the downgraded factors resulted in a risk of bias, inconsistency, and imprecision. However, in view of the limitations of this study, it is recommended that RCTs with a larger sample size and more rigorous design (for downgraded factors) should be conducted in the future so that the conclusions above can be further verified through key result indicators.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-021-08658-w.

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Declarations

Disclosures Jia Yang, Shiyi Gong, Tingting Lu, Hongwei Tian, Wutang Jing, Yang Liu, Moubo Si, Caiwen Han, Kehu Yang and Tiankang Guo have declared that no conflict of interest or financialties to disclose.

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