Role of prophylactic antibiotics in elective laparoscopic cholecystectomy: A systematic review and meta-analysis

Sang Hoon Kim, Hee Chul Yu, Jae Do Yang, Sung Woo Ahn, and Hong Pil Hwang

Department of Surgery, Chonbuk National University Medical School and Hospital, Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk University Hospital, and Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Korea

Backgrounds/Aims: The role of prophylactic antibiotics for laparoscopic cholecystectomy in low-risk patients is still unclear. This study aimed to verify the conclusion of previous meta-analyses concerning the effectiveness of antibiotic prophylaxis for elective laparoscopic cholecystectomy in low-risk patients.

Methods: Comprehensive literature searches were performed on electronic databases and manual searches. Randomized controlled trials (RCTs), prospective studies, and retrospective studies comparing antibiotic prophylaxis to placebo or no antibiotics in low-risk elective laparoscopic cholecystectomy were included.

Results: This study included 28 RCTs, three prospective studies, and three retrospective studies. In RCTs, prophylactic antibiotics did not prevent deep surgical site infections (SSI) (RR 1.10, 95% confidence interval [CI] [0.45-2.69], \( p=0.84 \)) but reduced SSI (RR 0.70, 95% CI [0.53-0.94], \( p=0.02 \)), and superficial SSI (RR 0.58, 95% CI [0.42-0.82], \( p=0.01 \)). Prospective studies showed prophylactic antibiotics did not reduce superficial SSI (RR 0.35, 95% CI [0.01-8.40], \( p=0.52 \)) but reduced SSI (RR 0.12, 95% CI [0.04-0.35], \( p=0.0001 \)). In retrospective studies, antibiotic prophylaxis did not reduce SSI (RR 1.59, 95% CI [0.30-8.32], \( p=0.58 \)). The pooled data (12121 patients) including RCTs and prospective and retrospective studies showed that prophylactic antibiotics were not effective in preventing deep SSI (RR 1.01 95% CI [0.46-2.21], \( p=0.98 \)) but effective in reducing SSI (RR 0.67, 95% CI [0.51-0.88], \( p=0.003 \)) and superficial SSI (RR 0.61, 95% CI [0.45-0.83], \( p=0.002 \)).

Conclusions: The use of prophylactic antibiotics is effective for reducing the incidence of SSI and superficial SSI but is not effective for preventing deep SSI in low-risk patients who underwent elective laparoscopic cholecystectomy.

Key Words: Laparoscopic cholecystectomy; Antibiotic prophylaxis; Meta-analysis

INTRODUCTION

Laparoscopic cholecystectomy is the gold standard method in managing uncomplicated gallbladder stones and other benign gallbladder diseases over open cholecystectomy. Development of minimally invasive laparoscopic cholecystectomy reduced surgical site infection (SSI), length of hospital stay, healthcare costs, and postoperative pain.

Although the use of prophylactic antibiotics before elective surgery has been considered as the best way to prevent postoperative infectious complications, antibiotic prophylaxis for elective laparoscopic cholecystectomy in low-risk group is not recommended in recent guidelines on SSI from the Scottish Intercollegiate Guidelines Network and the American Society of Health-System Pharmacists. Nevertheless, low-risk patients who underwent laparoscopic cholecystectomy are still given prophylactic antibiotics in several clinical centers.

Recent meta-analyses investigating the effects of prophylactic antibiotics before elective laparoscopic cholecystectomy for the prevention of SSI have relatively small sample size and low statistical power. Moreover, controversy still exists regarding the effectiveness of anti-
Table 1. Search strategies

| Database                  | Search strategies                                                                 |
|---------------------------|-----------------------------------------------------------------------------------|
| MEDLINE                   | 1. cholecystectomy*.mp or exp cholecystectomy                                     |
| 1995 to July 2018 (N=441) | 2. laparoscop*.mp or exp cholecystectomy, laparoscopic                            |
|                           | 3. 1 OR 2                                                                          |
|                           | 4. prophyla*.mp or exp Antibiotic Prophylaxis                                      |
|                           | 5. antibiotic*.mp or exp Anti-Bacterial Agents                                     |
|                           | 6. 4 OR 5                                                                          |
|                           | 7. 3 AND 6                                                                        |
|                           | 8. limit: Publication Year 1995–Current                                           |
|                           | mp=title, original title, abstract, name of substance word, subject heading word, unique identifier |
| EMBASE                    | 1. cholecystectomy*.mp or exp cholecystectomy                                     |
| 1995 to July 2018 (N=417) | 2. laparoscop*.mp or exp cholecystectomy, laparoscopic                            |
|                           | 3. 1 OR 2                                                                          |
|                           | 4. prophyla*.mp or exp Antibiotic Prophylaxis                                      |
|                           | 5. antibiotic*.mp or exp Anti-Bacterial Agents                                     |
|                           | 6. 4 OR 5                                                                          |
|                           | 7. 3 AND 6                                                                        |
|                           | 8. limit: Publication Year 1995–Current                                           |
|                           | mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer |
| Cochrane Library          | #1 Mesh descriptor: [Cholecystectomy, Laparoscopic] explode all trees             |
| 1995 to July 2018 (N=249) | #2 Mesh descriptor: [Anti-Bacterial Agents] explode all trees                     |
|                           | #3 prophyla* or perioperative or peri-operative                                    |
|                           | #4 (#2 or #3)                                                                      |
|                           | #5 (#1 and #3)                                                                     |
| PubMed                    | #1 laparoscopic cholecystectomy*[Title/Abstract]                                  |
| 1995 to July 2018 (N=363) | #2 antibiotic*[Title/Abstract]                                                   |
|                           | #3 Prophylac*[Title/Abstract] OR Prophylaxis*[Title/Abstract]                      |
|                           | #4 (#2 OR #3)                                                                      |
|                           | #5 (#1 AND #4)                                                                     |
|                           | Filters: Publication date from 1995/01/01 to 2018/07/15                            |
| KMbase                    | 1. laparoscopic cholecystectomy antibiotic                                         |
| 1995 to 2018 (N=2)        | 2. cholecystectomy antibiotic                                                     |

Biotic prophylaxis for elective laparoscopic cholecystectomy. Therefore, we performed an up-to-date meta-analysis to assess the value of prophylactic antibiotics for low-risk elective laparoscopic cholecystectomy in terms of reducing the incidence of SSI, superficial SSI, and deep SSI with randomized controlled trials (RCTs) and prospective and retrospective studies on this topic. This study aimed to verify the conclusion of previous meta-analyses.3-13

MATERIALS AND METHODS

The study protocol for this systemic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.14

Searching and other resources

MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, PubMed, and KMbase were searched using medical subject heading terms and following keyword combinations: “laparoscopic,” “cholecystectomy,” “antibiotic,” “prophylac,” and “meta-analysis.” Table 1 shows the search strategies on electric databases in this review. Additionally, manual searches were performed with reference lists of original articles and systemic review and meta-analyses. The literature search was limited to articles published between 1995 and 2018 without restriction of languages.

Inclusion and exclusion criteria

Inclusion criteria were (i) study design: RCTs and prospective and retrospective studies evaluating the effective-
ness of antibiotic prophylaxis for elective laparoscopic cholecystectomy with placebo or untreated controlled group; (ii) population: low-risk patients undergoing elective laparoscopic surgery; (iii) all patients that were given antibiotics before operation and/or postoperative days; (iv) all studies having at least one of the following outcome parameters: SSI, superficial SSI and deep SSI.

Exclusion criteria were (i) studies that are not full-text original articles and (ii) interventions comparing different antibiotic prophylaxis groups without placebo or untreated groups.

SSIs include superficial and deep, and data were collected based on the definition of guideline. High-risk factors for SSI are defined according to the diabetes, obesity, open conversion, emergency operation, preoperative endoscopic or percutaneous biliary intervention, acute cholecystitis, intraoperative gallbladder rupture, obstructive jaundice, immunosuppression, insertion of prosthetic device, and episode of colic within 30 days in guideline.

Data collection and analysis
This systemic review and meta-analysis was performed following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

Study selection
Two reviewers (Kim and Yu) independently searched available articles to include eligible RCTs and prospective and retrospective studies. Duplicate articles were removed. The full-text articles of possibly related studies were selected to make a list of trials that fulfilled the inclusion criteria. Disagreements about study selection were resolved through discussion and consensus.

Data extraction
The following data were extracted independently by two reviewers (Kim and Yu) from each study when present: inclusion and exclusion criteria, characteristic of population, study design, type of prophylactic antibiotics and dosage, schedule of administration of antibiotics, randomization method, allocation concealment, number of randomized patients in RCTs and enrolled patients in prospective and retrospective studies, drop-outs, intention-to-treat analysis or per-protocol analysis, SSIs, and superficial and deep infections.

Quality assessment of the studies
Two investigators (Kim and Yu) independently assessed the quality of RCTs included through assessing the following risks of bias check lists provided by The Cochrane Collaboration: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Risk of bias was assessed as high, low, and unclear. Jadad et al. score was also applied to assess the quality of included randomized studies in the meta-analysis. Of the 28 RCTs, 25 studies were eligible to be included in the meta-analysis with high-quality Jadad score ≥3, and the other 3 studies were low-quality studies with Jadad score 2. Sensitivity tests were performed to assess whether including three RCTs classified as low-quality is appropriate in this meta-analysis.

Non-RCTs including 3 prospective and 3 retrospective studies were assessed based on the Newcastle-Ottawa Scale, which ranges from 0 to 9, with “high quality” defined as a Newcastle-Ottawa Scale total score ≥7. Of the 6 non-RCTs included in this meta-analysis, 2 prospective studies were classified as “high quality.” Sensitivity tests were performed to obtain pooled data rate. Disagreements about assessment were resolved through discussion and consensus.

Statistical analysis
Statistical analyses were conducted using Review Manager version 5.3 (The Cochrane Collaboration). In dichotomous variable analysis, the effect size of the intervention was represented by risk ratio (RR) with 95% confidence interval (CI) and was calculated for continuous variables. A random effect model was applied to calculate the estimated pooled event rate in the presence of significant heterogeneity, determined either when the I² value was >50% or p-value of Cochrane Q test was <0.1. The publication bias was evaluated to detect “small-study effects” by funnel plot. RCTs and prospective and retrospective studies were pooled separately to minimize the bias. Sensitivity analysis was performed to assess whether including non-randomized studies or low-quality studies is appropriate in this meta-analysis.
RESULTS

Study selection
A total of 1472 studies were screened through electronic database using our search strategies in July 2018. And 1096 articles were found by hand search. After investigation of title and abstract, 239 articles were screened. Full texts of 63 articles were reviewed and assessed for eligibility, and 34 studies including 28 RCTs and 3 prospective and 3 retrospective trials were included in this meta-analysis. Twenty-nine full-text articles$^{55-84}$ were excluded because of the following reasons: inclusion criteria not met,$^{83}$ inappropriate intervention,$^{55,57,76,77,84}$ inappropriate comparator,$^{76,79}$ insufficient data reported,$^{60,61,63-69,71-76,80-82}$ and data duplication.$^{62,64}$ The procedure for the study selection is summarized in the PRISMA flow diagram (Fig. 1).

Study characteristics
The 12121 patients who underwent laparoscopic cholecystectomy from eligible 28 RCTs with 7770 patients, 3 prospective studies with 3123 patients, and 3 retrospective studies with 1228 patients were included in this meta-analysis. Table 2 shows a summary of the characteristics of the included studies published between 1995 and 2018, including years of publication, country, language, study design, intervention, sample size, type of data collection analysis, follow-up days, and outcomes. Most of the patients included in RCTs were classified as low risk for postoperative infection. Exclusion criteria in the majority of RCTs were ASA physical status classification III or higher, antibiotics use within 7 days of the surgery, allergy, complicated gallstone with acute cholecystitis, cholecodolithiasis or pancreatitis, previous biliary tract surgery, conversion to open cholecystectomy, diabetes mellitus, immunosuppression, pregnancy, prosthetic heart valve, severe comorbidities such as Child C liver cirrhosis.

| Records identified through electronic database search (n=1,472) | Additional records identified through hand search (n=1,096) |
|---------------|--------------------------|
| MEDLINE (n=411) | Meta-analyses register (n=412) |
| EMBASE (n=417) | RCTs register (n=545) |
| Cochrane library (n=249) | Non-RCTs register (n=139) |
| Pubmed (n=363) | |
| Kmbase (n=2) | |

Fig. 1. PRISMA flow diagram for study search.
| Study          | Year | Country | Language | Center | No. of patients | Antibiotic | Injection | Dose | Control | Follow-up (days) | Data collection | SSI | Superficial SSI | Deep SSI |
|---------------|------|---------|----------|--------|----------------|------------|-----------|-----|---------|----------------|----------------|-----|----------------|----------|
| Csendes et al. | 1995 | Chile   | Portuguese | Single | 50             | Cefazolin 1 g | Pre       | 1   | Untreated | 14             | PP             |     |                |          |
| Illig et al.   | 1997 | US      | English  | Single | 128            | Cefazolin 1 g OR vancomycin | Pre & post | 3   | Untreated | 30             | ITT            |     |                |          |
| Higgins et al. | 1999 | US      | English  | Single | 137            | Cefotetan 1 g OR vancomycin | Pre       | 1   | Placebo  | 30             | PP             |     |                |          |
| Dobay et al.   | 1999 | US      | English  | Single | 29             | Cefotetan 1 g OR vancomycin | Pre       | 1   | Placebo  | 30             | ITT            |     |                |          |
| Harling et al. | 2000 | UK      | English  | Single | 39             | Cefuroxime 750 mg | Pre       | 1   | Placebo  | NA             | PP             |     |                |          |
| Tocchi et al.  | 2000 | Italy   | English  | Single | 44             | Cefotaxime 2 g | Pre & post | 2   | Placebo  | 42             | PP             |     |                |          |
| Mahatharadol   | 2001 | Thailand | English  | Single | 50             | Cefazolin 1 g | Pre       | 1   | Placebo  | 30             | PP             |     |                |          |
| Koc et al.     | 2003 | Turkey  | English  | Single | 49             | Cefotaxime 2 g | Pre & post | 2   | Placebo  | 30             | PP             |     |                |          |
| Chang et al.   | 2006 | Taiwan  | English  | Single | 141            | Cefazolin 1 g | Pre       | 1   | Placebo  | 28             | ITT            |     |                |          |
| Kuthe et al.   | 2006 | India   | English  | Single | 136            | Cefuroxime 1.5 g | Pre       | 1   | Placebo  | 28             | PP             |     |                |          |
| Souza et al.   | 2008 | Brazil  | Portuguese | Single | 82             | Cefoxitin 2 g | Pre       | 1   | Placebo  | 28             | ITT            |     |                |          |
| Uludag et al.  | 2009 | Turkey  | English  | Single | 68             | Cefazolin 1 g | Pre       | 1   | Placebo  | 30             | PP             |     |                |          |
| Yildiz et al.  | 2009 | Turkey  | English  | Single | 105            | Cefazolin 1 g | Pre       | 1   | Placebo  | 30             | ITT            |     |                |          |
| Gaur and Pujahari | 2010 | India   | English  | Multi  | 208            | Ciprofloxacin 200 mg + Metronidazole 500 mg | Pre       | 1   | Placebo  | 30             | PP             |     |                |          |
| Sharma et al.  | 2010 | India   | English  | NA     | 209            | No prophylaxis | Pre       | 1   | Placebo  | 50             | PP             |     |                |          |
|               |      |         |          |        | 50             | Ceftriaxone 1 g | No prophylaxis |     |          |                |                |     |                |          |
### Table 2. Continued

| Study                        | Year | Country | Language | Center | No. of patients | Antibiotic | Injection | Dose | Control | Follow-up (days) | Data collection | SSI | Superficial SSI | Deep SSI |
|------------------------------|------|---------|----------|--------|-----------------|------------|-----------|------|---------|------------------|----------------|-----|----------------|----------|
| Al-Qahtani35                 | 2011 | Saudi Arabia | English | Single | 112             | Cefuroxime 1.5 g | Pre | 1    | Untreated | 30               | PP             | 3   | 3             | 0        |
| Shah et al.37                | 2012 | Nepal    | English | Single | 119             | No prophylaxis | Pre | 1    | Untreated | 7               | PP             | 6   | 6             | -        |
| Hassan et al.36              | 2012 | Egypt    | English | Single | 154             | Cefazolin 1 g | Pre | 1    | Placebo  | 10              | PP             | 2   | 2             | 0        |
| Naqvi et al.38               | 2013 | Pakistan | English | Single | 150             | No prophylaxis | Pre | 1    | Placebo  | >8              | ITT            | 4   | 4             | 0        |
| Turk et al.39                | 2013 | Turkey   | English | Single | 278             | Cefazolin 1 g | Pre | 1    | Placebo  | 30              | PP             | 7   | 7             | 0        |
| Matsui et al.40              | 2014 | Japan    | English | Single | 518             | No prophylaxis | Pre & post | 3    | Untreated | >8              | ITT            | 19  | 16            | 3        |
| Mirani et al.41              | 2014 | Pakistan | English | Single | 519             | Cefazolin 1 g | Pre | 1    | Untreated | 7               | PP             | 6   | 6             | -        |
| Ruangsin et al.42            | 2014 | Thailand | English | Single | 149             | No prophylaxis | Pre | 1    | Placebo  | 30              | ITT            | 5   | 5             | 0        |
| Darizi et al.43              | 2016 | Iran     | English | Single | 182             | Cefazolin 1 g | Pre & post | 3    | Placebo  | 30              | ITT            | 5   | 5             | 0        |
| Passos and Portant-Filho44    | 2016 | Brazil   | English | Single | 50              | Cefazolin 2 g | Pre | 1    | Untreated | 30              | ITT            | 1   | -             | -        |
| Sarkut et al.46              | 2017 | Turkey   | English | Single | 186             | Cefazolin 1 g | Pre | 1    | Placebo  | 28              | PP             | 2   | 2             | 0        |
| Kim et al.45                 | 2017 | Korea    | English | Single | 193             | No prophylaxis | Pre | 1    | Placebo  | 28              | PP             | 2   | 2             | 0        |
| Nauman et al.47              | 2018 | Pakistan | English | Single | 325             | Cefuroxime 1.5 g | Pre | 1    | NA      | 21              | ITT            | 13  | 13            | -        |
| Prospective studies          |      |          |         |        |                 |             |           |      |         |                  |                |     |               |          |
| Lippert and Gastinger48      | 1998 | Germany  | English | Multi  | 739             | Ceftriaxone | Pre | 1    | NA      |                 |                | 1   | -             | -        |
|                              |      |          |         |        |                 |             |           |      |         |                  |                | 949 | -             | -        |
|                              |      |          |         |        |                 |             |           |      |         |                  |                | 1195| -             | -        |
or end-stage renal disease, body mass index > 30, and age > 70 years or < 14 years. However, in the definition of high-risk patients, the criteria of ASA score, BMI, and old age are not exactly the same in included studies.

Risk of bias and Jadad score for RCTs included in this meta-analysis are summarized in Tables 3 and 4 shows the Newcastle-Ottawa Scale for non-RCTs included in this review. In RCTs, only 12 studies\textsuperscript{21,22,28,32,36,38,40,42-45,47} showed the data from intention-to-treat analysis, and the other 16 studies\textsuperscript{20,23-27,29-31,33-35,37,39,41,46} showed data from per-protocol analysis.

### Surgical site infections

Subgroup analysis for SSI including both superficial and deep SSI was performed using 28 RCTs,\textsuperscript{20-47} 3 prospective studies,\textsuperscript{48-50} and 3 retrospective studies.\textsuperscript{22,51,52} In the 28 RCTs, 83 (2.07\%) of the 4018 patients in the prophylactic antibiotic group developed SSI compared with 119 (3.17\%) of the 3752 patients in the no prophylaxis group. The prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.70, 95\% CI [0.53-0.94], \(p=0.02\)) without significant heterogeneity (\(p=0.96\), \(I^2=0\%\)). In 3 prospective studies, 3 (0.16\%) of the 1831 patients in the prophylactic antibiotic group developed SSI compared with 22 (1.70\%) of the 1292 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.12 [0.04-0.37], \(p=0.0002\)). No significant heterogeneity was found among included prospective studies. (\(p=0.48\), \(I^2=0\%\)). In 3 retrospective studies, 15 (2.09\%) of the 717 patients in the prophylactic antibiotic group developed SSI compared with 5 (0.98\%) of the 511 patients in the no prophylaxis group. No significant difference was observed in the incidence of SSI between the prophylactic antibiotic group and the control group (RR 1.59, 95\% CI [0.30-8.32], \(p=0.58\)) without significant heterogeneity among included prospective studies. (\(p=0.58\), \(I^2=47\%\)). In the overall pooled event rate including 28 RCTs and 3 prospective studies and 3 retrospective studies, 101 (1.54\%) of the 6566 patients in the prophylactic antibiotic group developed SSI compared with 146 (2.63\%) of the 5555 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.67, 95\% CI [0.51-0.88], \(p=0.003\)). No significant heterogeneity
| Study                      | Random sequence generation | Allocation concealment | Blinding of participants & personnel | Blinding of outcome assessment | Incomplete outcome data | Selection reporting | Other bias | Jadad score |
|---------------------------|----------------------------|------------------------|--------------------------------------|-------------------------------|------------------------|---------------------|------------|-------------|
| Csendes et al. 20          | ?                         | -                      | ?                                    | ?                             | -                      | ?                   | +          | 2           |
| Illig et al. 21            | ?                         | ?                      | ?                                    | ?                             | +                      | ?                   | +          | 2           |
| Higgins et al. 23          | ?                         | +                      | -                                    | -                             | -                      | ?                   | +          | 3           |
| Dobay et al. 24            | +                         | ?                      | +                                    | +                             | +                      | ?                   | +          | 4           |
| Harling et al. 25          | ?                         | -                      | -                                    | ?                             | -                      | ?                   | +          | 4           |
| Tocchi et al. 26           | +                         | ?                      | +                                    | -                             | -                      | ?                   | +          | 3           |
| Mahatharadol 28            | +                         | ?                      | -                                    | -                             | -                      | ?                   | +          | 3           |
| Koe et al. 29              | ?                         | ?                      | +                                    | +                             | -                      | ?                   | +          | 4           |
| Chang et al. 30            | +                         | ?                      | +                                    | +                             | +                      | ?                   | -          | 5           |
| Kuthe et al. 32            | +                         | ?                      | +                                    | +                             | -                      | ?                   | +          | 5           |
| Souza et al. 33            | ?                         | ?                      | +                                    | +                             | +                      | ?                   | +          | 4           |
| Uludag et al. 34           | ?                         | +                      | +                                    | +                             | +                      | ?                   | +          | 4           |
| Yildiz et al. 35           | ?                         | ?                      | +                                    | +                             | +                      | ?                   | +          | 4           |
| Gaur and Pugahari 36       | ?                         | -                      | ?                                    | ?                             | ?                      | ?                   | +          | 4           |
| Sharma et al. 37           | ?                         | -                      | -                                    | -                             | -                      | ?                   | +          | 3           |
| Al-Qahtani 38              | +                         | +                      | ?                                    | ?                             | -                      | ?                   | +          | 3           |
| Shah et al. 39             | +                         | -                      | ?                                    | -                             | ?                      | ?                   | +          | 3           |
| Hassan et al. 40           | ?                         | +                      | +                                    | +                             | +                      | ?                   | +          | 4           |
| Nasvi et al. 41            | ?                         | ?                      | ?                                    | ?                             | ?                      | ?                   | +          | 2           |
| Turk et al. 42             | ?                         | ?                      | +                                    | +                             | -                      | ?                   | +          | 4           |
| Matsui et al. 43           | +                         | +                      | +                                    | +                             | +                      | ?                   | +          | 5           |
| Mirani et al. 44           | +                         | -                      | ?                                    | ?                             | -                      | ?                   | +          | 3           |
| Ruangsins et al. 45        | +                         | +                      | +                                    | +                             | +                      | ?                   | +          | 5           |
| Darizi et al. 46           | ?                         | +                      | +                                    | +                             | +                      | ?                   | +          | 5           |
| Passos and Portari-Filho 47| +                         | +                      | +                                    | +                             | +                      | ?                   | +          | 5           |
| Sarkut et al. 48           | +                         | +                      | ?                                    | +                             | -                      | ?                   | +          | 5           |
| Kim et al. 49              | +                         | ?                      | ?                                    | +                             | +                      | ?                   | +          | 3           |
| Nauman et al. 50           | +                         | ?                      | ?                                    | +                             | ?                      | ?                   | +          | 3           |

+, Low risk of bias; -, High risk of bias; ?, unclear risk of bias
| Study                  | Selection | Comparability | Outcome |
|------------------------|-----------|---------------|---------|
|                        | Prospective |              |         |
|                        |            |               |         |
| Lippert and Gastinger  | ★★         | ★★            | ★       |
| Han et al              | ★★         | ★★★           | -       |
| Guzman-Valdivia        | ★★         | ★★            | -       |
|                        | Retrospective |            |         |
|                        |            |               |         |
| Garcia et al           | ★          | ★★★           | -       |
| Dobay et al            | -          | ★★★           | -       |
| Chong et al            | -          | ★★★           | -       |
among included studies was presented ($p=0.47$, $I^2=0\%$) (Fig. 2).

Superficial surgical site infections

The incidence of superficial SSI was described in 22 RCTs,\textsuperscript{21-23,26,28-38,40-43,45-47} 2 prospective studies,\textsuperscript{49,50} and 1 retrospective study.\textsuperscript{52} In 22 RCTs, 59 (1.68\%) of the 3508 patients of the prophylactic antibiotic group developed superficial SSI compared with 96 (2.95\%) of the 3258 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of superficial SSI than the patients in the control group (RR 0.59, 95% CI 0.41, 0.81).

\begin{table}
\centering
\begin{tabular}{lcccccc}
\hline
Study or subgroup & Experimental & Control & Weight (%) & Risk ratio & Year & Risk ratio \\
& Events & Total & & M-H, random, 95\% CI & & M-H, random, 95\% CI \\
\hline
1.1.1 RCT & & & & & & \\
Csenges et al. & 2 & 50 & 55 & 2.0 & 1.00 [0.16, 7.52] & 1995 \\
Illig et al. & 0 & 128 & 1 & 122 & 0.7 & 0.32 [0.01, 7.73] & 1997 \\
Higgins et al. & 5 & 277 & 2 & 135 & 2.7 & 1.23 [0.24, 6.20] & 1999 \\
Dobay et al. & 0 & 29 & 0 & 24 & Not estimateable & 1999 \\
Tocchi et al. & 4 & 44 & 4 & 40 & 4.2 & 0.91 [0.24, 3.40] & 2000 \\
Harling et al. & 3 & 39 & 3 & 37 & 3.1 & 0.95 [0.20, 4.41] & 2000 \\
Mahalharadol & 0 & 50 & 1 & 50 & 0.7 & 0.33 [0.01, 7.99] & 2001 \\
Koc et al. & 1 & 49 & 1 & 43 & 1.0 & 0.88 [0.06, 13.61] & 2003 \\
Kulhe et al. & 1 & 49 & 1 & 43 & 1.0 & 0.86 [0.08, 7.05] & 2006 \\
Chang et al. & 2 & 141 & 2 & 136 & 1.9 & 0.96 [0.14, 6.75] & 2006 \\
Souza et al. & 4 & 82 & 5 & 81 & 4.4 & 0.79 [0.22, 2.84] & 2008 \\
Yildiz et al. & 4 & 105 & 3 & 103 & 3.3 & 1.31 [0.30, 5.70] & 2009 \\
Ulbang et al. & 3 & 68 & 2 & 76 & 2.3 & 1.68 [0.29, 9.73] & 2009 \\
Sharma et al. & 2 & 50 & 4 & 50 & 2.7 & 0.80 [0.10, 6.21] & 2010 \\
Gaur et al. & 5 & 208 & 8 & 209 & 6.0 & 0.83 [0.21, 3.68] & 2010 \\
Al-Qahlan et al. & 3 & 112 & 5 & 119 & 3.7 & 0.64 [0.16, 2.61] & 2011 \\
Haasen et al. & 2 & 100 & 1 & 100 & 1.3 & 2.00 [0.18, 21.71] & 2012 \\
Shah et al. & 6 & 154 & 9 & 156 & 7.1 & 0.88 [0.25, 3.08] & 2012 \\
Turk et al. & 4 & 278 & 2 & 269 & 2.5 & 1.94 [0.36, 10.48] & 2013 \\
Naqvi et al. & 8 & 177 & 7 & 173 & 7.4 & 1.12 [0.41, 3.01] & 2013 \\
Matsui et al. & 4 & 518 & 19 & 519 & 6.3 & 0.21 [0.07, 0.68] & 2014 \\
Migani et al. & 6 & 154 & 9 & 156 & 7.1 & 0.88 [0.25, 3.08] & 2014 \\
Ruangsin et al. & 2 & 150 & 5 & 149 & 2.8 & 0.40 [0.08, 2.02] & 2014 \\
Dartzi et al. & 3 & 182 & 5 & 247 & 3.6 & 0.81 [0.20, 3.36] & 2016 \\
Passos et al. & 1 & 50 & 1 & 50 & 1.0 & 1.00 [0.06, 15.55] & 2016 \\
Sarkar et al. & 4 & 377 & 3 & 193 & 3.3 & 0.68 [0.15, 3.02] & 2017 \\
Kim et al. & 0 & 81 & 0 & 82 & Not estimateable & 2017 \\
Naumen et al. & 4 & 325 & 13 & 325 & 5.9 & 0.31 [0.10, 1.03] & 2018 \\
\textbf{Subtotal (95\% CI)} & \textbf{4,018} & \textbf{7,572} & \textbf{88.3} & \textbf{0.70 [0.53, 0.94]} & \\
\hline
Total events & 83 & 119 & & & & \\
Heterogeneity: Tau^2=0.00; Ch^2=14.01, df=25 ($p=0.96$), $I^2=0\%$ \\
Test for overall effect: $Z=2.39$ ($p=0.02$) \\
\hline
1.1.2 Prospective & & & & & & \\
Lippert et al. & 3 & 1,688 & 21 & 1,195 & 5.0 & 0.10 [0.03, 0.34] & 1998 \\
Guzman - Valdivia & 0 & 65 & 1 & 69 & 0.7 & 0.35 [0.01, 8.40] & 2008 \\
Han et al. & 0 & 77 & 0 & 78 & Not estimateable & 2008 \\
\textbf{Subtotal (95\% CI)} & \textbf{1,831} & \textbf{1,292} & \textbf{5.7} & \textbf{0.12 [0.04, 0.37]} & \\
Total events & 3 & 22 & & & & \\
Heterogeneity: Tau^2=0.00; Ch^2=0.51, df=1 ($p=0.48$), $I^2=0\%$ \\
Test for overall effect: $Z=3.71$ ($p=0.0002$) \\
\hline
1.1.3 Retrospective & & & & & & \\
Garcia et al. & 0 & 110 & 1 & 81 & 0.7 & 0.25 [0.01, 5.97] & 1997 \\
Dobay et al. & 10 & 328 & 1 & 238 & 1.7 & 7.28 [0.94, 58.30] & 1999 \\
Chong et al. & 5 & 279 & 3 & 192 & 3.6 & 1.15 [0.28, 4.74] & 2015 \\
\textbf{Subtotal (95\% CI)} & \textbf{717} & \textbf{511} & \textbf{6.0} & \textbf{0.89 [0.30, 2.82]} & \\
Total events & 15 & 5 & & & & \\
Heterogeneity: Tau^2=0.11; Ch^2=3.77, df=2 ($p=0.15$), $I^2=47\%$ \\
Test for overall effect: $Z=0.56$ ($p=0.58$) \\
\hline
\textbf{Total (95\% CI)} & \textbf{6,566} & \textbf{5,555} & \textbf{100.0} & \textbf{0.67 [0.51, 0.88]} & \\
Total events & \textbf{101} & \textbf{146} & & & & \\
Heterogeneity: Tau^2=0.00; Ch^2=29.89, df=30 ($p=0.47$), $I^2=80.4\%$ \\
Test for overall effect: $Z=2.92$ ($p=0.003$) \\
Test for subgroup differences: Ch^2=10.19, df=2 ($p=0.006$), $I^2=80.4\%$ \\
\hline
\end{tabular}
\end{table}

Fig. 2. Forest plot for surgical site infections in low-risk patients undergoing elective laparoscopic cholecystectomy. A Mantel-Haenszel fixed-effect model was for used for meta-analysis. Risk ratios are shown 95\% confidence intervals.
CI [0.43–0.82], \( p=0.001 \) without significant heterogeneity among included studies (\( p=0.91, I^2=0\% \)). In 2 prospective studies, 0 (0\%) of the 143 patients in the prophylactic antibiotic group developed superficial SSI compared with 1 (1.03\%) of the 97 patients in the no prophylaxis group. No difference was observed in outcomes between the two groups (RR 0.35 95% CI [0.01–8.40], \( p=0.52 \)). In a retrospective study, 5 (1.79\%) of the 279 patients in the prophylactic antibiotic group developed SSI compared with 3 (1.56\%) of the 192 patients in the no prophylaxis group. In the overall pooled event rate including 22 RCTs, 2 prospective studies, and one retrospective study, 64 (1.63\%) of the 3930 patients in the prophylactic antibiotic group developed superficial SSI compared with 100 (2.81\%) of the 3547 patients in the no prophylaxis group. The prophylactic antibiotic group had less incidence of superficial SSI than the control group (RR 0.61, 95% CI [0.45–0.83], \( p=0.002 \)). No significant heterogeneity was found among included studies (\( p=0.94, I^2=0\% \)) (Fig. 3).

**Deep surgical site infections**

The incidence of deep SSI was described in 19

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Risk ratio M-H, fixed, 95% CI | Year |
|------------------|---------------------|---------------|------------|-------------------------------|------|
| Illig et al.     | 0 128 1 122 1.5    |    | 0.32 [0.01, 7.73] | 1997 |
| Higgins et al.   | 5 277 2 135 2.6   |    | 1.22 [0.24, 6.20] | 1999 |
| Dobay et al.     | 0 29 0 24          |    | Not estimable | 1999 |
| Mathur et al.    | 0 50 1 50 1.5      |    | 0.33 [0.01, 7.99] | 2001 |
| Kufte et al.     | 1 40 1 53 0.8      |    | 1.32 [0.09, 20.55] | 2006 |
| Chang et al.     | 1 141 2 136 2.0    |    | 0.48 [0.04, 5.28] | 2006 |
| Souza et al.     | 2 82 3 81 2.9      |    | 0.56 [0.11, 3.84] | 2008 |
| Ullung et al.    | 3 88 2 76 1.8      |    | 1.68 [0.29, 9.73] | 2009 |
| Yildiz et al.    | 3 105 3 103 2.9    |    | 0.98 [0.20, 4.75] | 2009 |
| Gaur et al.      | 0 208 4 209 4.4    |    | 0.11 [0.01, 2.06] | 2010 |
| Sharma et al.    | 2 50 4 50 3.9      |    | 0.50 [0.10, 2.61] | 2010 |
| Al-Qahthari       | 3 112 5 119 4.7    |    | 0.64 [0.16, 2.61] | 2011 |
| Haasan et al.    | 2 100 1 100 1.0    |    | 2.00 [0.18, 21.71] | 2012 |
| Shah et al.      | 6 154 9 156 8.7    |    | 0.88 [0.25, 3.05] | 2012 |
| Nacvi et al.     | 8 177 7 173 6.9    |    | 1.12 [0.41, 3.01] | 2013 |
| Ruangsin et al.  | 2 150 5 149 4.9    |    | 0.40 [0.08, 2.02] | 2014 |
| Mirani et al.    | 6 154 9 156 8.7    |    | 0.68 [0.25, 1.85] | 2014 |
| Matsui et al.    | 4 518 16 519 15.5  |    | 0.25 [0.08, 0.74] | 2014 |
| Darzi et al.     | 3 182 5 247 4.1    |    | 0.81 [0.20, 3.46] | 2016 |
| Sarkul et al.    | 4 377 3 193 3.8    |    | 0.68 [0.15, 3.02] | 2017 |
| Kim et al.       | 0 81 0 82          |    | Not estimable | 2017 |
| Nauman et al.    | 4 325 13 325 12.6  |    | 0.31 [0.10, 0.93] | 2018 |
| Subtotal (95% CI) | 3,908 3,258 95.1   |    | 0.09 [0.02, 0.42] | 2019 |

Heterogeneity: \( \chi^2=11.33, \text{df}=19 (p=0.91), I^2=0\% \)
Test for overall effect: \( Z=3.19 (p=0.001) \)

Details of the Mantel-Haenszel fixed-effect model and the meta-analysis are further discussed in the supplementary material.

**Fig. 3.** Forest plot for superficial surgical site infections in low-risk patients undergoing elective laparoscopic cholecystectomy. A Mantel-Haenszel fixed-effect model was used for meta-analysis. Risk ratios are shown 95% confidence intervals.
In a retrospective study, 0 (0.00%) of the 279 patients in the prophylactic antibiotic group developed SSI compared with 0 (0.00%) of the 192 patients in the no prophylaxis group. In the overall pooled event rate including 19 RCTs, 2 prospective studies, and one retrospective study, 10 (0.30%) of the 3312 patients in the prophylactic antibiotic group developed deep SSI compared with 10 (0.34%) of the 2926 in the no prophylaxis group. No difference was observed in outcomes between the two groups (RR 1.01, 95% CI [0.46-2.21], p=0.98) without significant heterogeneity among included studies (p=0.77, I²=0%) (Fig. 4).
Table 5. Sensitivity analyses

| Subgroup       | High-quality studies | Pooled effects      | Heterogeneity |
|----------------|----------------------|---------------------|---------------|
| SSIs           | 25 RCTs              | RR 0.60, 95% CI [0.45-0.80] | I²=0 (p=0.58) |
|                | 2 Prospective studies| (p=0.0006)         |               |
| Superficial SSI| 19 RCTs              | RR 0.54, 95% CI [0.38-0.77] | I²=0 (p=0.89) |
|                | 1 Prospective study  | (p=0.0007)         |               |
| Deep SSI       | 10 RCTs              | RR 1.10, 95% CI [0.45, 2.69] | I²=0 (p=0.57) |
|                | 1 Prospective study  | (p=0.84)           |               |

SSIs, surgical site infections; RCTs, randomized controlled trials; RR, risk ratio; CI, confidence interval.

DISCUSSION

This systematic review and meta-analysis included a total of 12121 patients from the 7770 patients in 28 RCTs, 3123 patients in 3 prospective studies, and 1228 patients in 3 retrospective studies. This study concluded that the use of prophylactic antibiotics in low-risk patients undergoing elective laparoscopic cholecystectomy prevents SSI and superficial SSI other than deep SSI. Previous meta-analyses3-13 were based only on data from RCTs and concluded that prophylactic antibiotics were not effective in preventing postoperative SSI in low-risk elective laparoscopic cholecystectomy, except for two studies.10,12

In previous several meta-analyses on this topic, only RCTs were included to determine the overall effect rate. Therefore, these meta-analyses were performed with relatively small sample sizes and were statistically under-powered. To overcome the limitation of the study including only RCTs with small sample sizes, this meta-analysis comprised a total of 12121 patients from both RCTs and non-RCTs to obtain appropriate statistical power in the subgroup analysis of SSI, superficial SSI, and deep SSI. Moreover, all available RCTs and non-RCTs that have not been published in English were used in this study to reduce language bias. Although there was a possibility of inducing significant heterogeneity by combining RCTs with non-RCTs, there were no significant differences in results between RCTs alone and RCTs and non-RCTs in all subgroup analyses.

This systematic review and meta-analysis has several limitations. First, of the 28 RCTs, 3 trials have low quality with Jadad score. In addition, of the 6 non-RCTs, 4 studies were of “low quality” assessed by the Newcastle-Ottawa Scale. Therefore, sensitivity test was performed to obtain pooled data rate. Second, there was significant
eral RCTs. Therefore, future studies need to provide a consistent set of inclusion criteria based on guidelines for defining low-risk or high-risk groups for SSI. The Scottish Intercollegiate Guidelines Network also include diabetes, emergency surgery, long duration of procedures, ASA score of 3 or higher, recent episode of colic within 30 days before surgery and age > 70 years as high-risk group for SSI. However, several studies included patients with an ASA score of 3 or the ASA score was not applied to inclusion criteria in several RCTs. Therefore, future studies need to provide a consistent set of inclusion criteria based on guidelines for defining low-risk or high-risk groups for SSI.

In conclusion, the overall pooled data of this meta-analysis is the inconsistency of the inclusion criteria for SSI. The Scottish Intercollegiate Guidelines Network and the American Society of Health-System Pharmacists guideline suggest intraoperative gallbladder rupture, open conversion, acute cholecystitis, jaundice, immunosuppression, pregnancy and implantation of prosthetic devices as high-risk factors for SSI. The Scottish Intercollegiate Guidelines Network also include diabetes, emergency surgery, long duration of procedures, ASA score of 3 or higher, recent episode of colic within 30 days before surgery and age > 70 years as high-risk group for SSI. However, several studies included patients with an ASA score of 3 or the ASA score was not applied to inclusion criteria in several RCTs.

REFERENCES

1. Network SIG. Antibiotic prophylaxis in surgery. A national clinical guideline. Elliot House: Edinburgh, 2008.
2. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14:73-156.
3. Al-Ghannami R, Benjamin IS, Patel AG. Meta-analysis suggests antibiotic prophylaxis is not warranted in low-risk patients undergoing laparoscopic cholecystectomy. Br J Surg 2003;90:365-366.
4. Catarsi M, Mancini S, Gentileschi P, Campione C, Sileri P, Grassi GB. Antibiotic prophylaxis in elective laparoscopic cholecystectomy. Lack of need or lack of evidence? Surg Endosc 2004;18:638-641.
5. Claros N, Manterola C, Vial M, Sanhueza A. Efectividad de la profilaxis antibiótica en el curso de la colecistectomía laparoscópica electiva: revisión sistemática de la literatura. Rev Chil Cir 2007;59:353-359.
6. Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK. Role of prophylactic antibiotics in laparoscopic cholecystectomy: a meta-analysis. J Gastrointest Surg 2008;12:1847-1853.
7. Zhou H, Zhang J, Wang Q, Hu Z. Meta-analysis: antibiotic prophylaxis in elective laparoscopic cholecystectomy. Aliment Pharmacol Ther 2009;29:1086-1095.
8. Sanabria A, Dominguez LC, Valdivieso E, Gomez G. Antibiotic prophylaxis for patients undergoing elective laparoscopic cholecystectomy. Cochrane Database Syst Rev 2010;(12):CD-005265.
9. Yan RC, Shen SQ, Chen ZB, Lin FS, Riley J. The role of prophylactic antibiotics in laparoscopic cholecystectomy in preventing postoperative infection: a meta-analysis. J Laparoendosc Adv Surg Tech A 2011;21:301-306.
10. Liang B, Dai M, Zou Z. Safety and efficacy of antibiotic prophylaxis in patients undergoing elective laparoscopic cholecystectomy: a systematic review and meta-analysis. J Gastroenterol Hepatol 2016;31:921-928.
11. Pasquali S, Boal M, Griffiths EA, Alderson D, Vohra RS; CholeS Study Group; West Midlands Research Collaborative. Meta-analysis of perioperative antibiotics in patients undergoing laparoscopic cholecystectomy. Br J Surg 2016;103:27-34.
12. Matsui Y, Saito S, Hirooka S, Kosaka H, Kawaura T, Kitawaki T. Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: an overview of systematic reviews. BMJ Open 2018;8:e016666.
13. Sajid MS, Ibovis J, Rehman S, Singh KK. Prophylactic antibiotics at the time of elective cholecystectomy are effective in reducing the post-operative infective complications: a systematic review and meta-analysis. Transl Gastroenterol Hepatol 2018;3:
14. T. Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: an overview of systematic reviews. BMJ Open 2018;8:e016666.
15. Sajid MS, Ibovis J, Rehman S, Singh KK. Prophylactic antibiotics at the time of elective cholecystectomy are effective in reducing the post-operative infective complications: a systematic review and meta-analysis. Transl Gastroenterol Hepatol 2018;3:
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-269.

14. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-608.

19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.

17. Higgins A, London J, Charland S, Ratzer E, Clark J, Haun W, Illig KA, Schmidt E, Cavanaugh J, Krusch D, Sax HC. Are prophylactic antibiotics required for elective laparoscopic cholecystectomy? J Am Coll Surg 1997;184:333-336.

20. Csendes A, Silva A, Burdiles P, Diaz J, Korn O, Maluenda F. The impact of prophylactic antibiotics on postoperative infectious complications in elective laparoscopic cholecystectomy: a prospective randomized study. Arch Surg 2000;135:67-70.

21. Illig KA, Schmidt E, Cavanaugh J, Krusch D, Sax HC. Are prophylactic antibiotics necessary in elective laparoscopic cholecystectomy, regardless of patient risk? Ann Surg Treat Res 2006;72:230-234.

22. Harling R, Moorjani N, Perry C, MacGowan AP, Thompson MH. A prospective, randomised trial of prophylactic antibiotics versus bag extraction in the prophylaxis of wound infection in laparoscopic cholecystectomy. Ann R Coll Surg Engl 2000;82:408-410.

23. Higgins A, London J, Charland S, Ratzer E, Clark J, Haun W, et al. Prophylactic antibiotics for elective laparoscopic cholecystectomy: are they necessary? Arch Surg 1999;134:611-614.

24. Harling R, Moorjani N, Perry C, MacGowan AP, Thompson MH. A prospective, randomised trial of prophylactic antibiotics versus bag extraction in the prophylaxis of wound infection in laparoscopic cholecystectomy. Ann R Coll Surg Engl 2000;82:408-410.

25. Tocchi A, Lepre L, Costa G, Liotta G, Mazzoni G, Maggiorini F. The need for antibiotic prophylaxis in elective laparoscopic cholecystectomy: a prospective randomized study. Arch Surg 2000;135:67-70.

26. Maharatadov L. A reappraisal of antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized controlled trial. J Med Assoc Thai 2001;84:105-108.

27. Koc M, Zulfikaroglu B, Kece C, Ozalp N. A prospective randomized study of prophylactic antibiotics in elective laparoscopic cholecystectomy. Surg Endosc 2003;17:1716-1718.

28. Chang WT, Lee KT, Chung SC, Wang SN, Kuo KK, Chen JS, et al. The impact of prophylactic antibiotics on postoperative infection complication in elective laparoscopic cholecystectomy: a prospective randomized study. Am J Surg 2006;191:721-725.

29. Kutha SA, Kaman L, Tohyama Y, Suzuki H, Kato S, Ohto T. The efficacy of cefazolin prophylaxis on postoperative infectious complications in elective laparoscopic cholecystectomy: a prospective randomized study. Tran J Med Sci 2011;6:132-138.

30. Souza HP, Breiegeron R, Cunha HM, Deves E. Antibiotic prophylaxis in elective laparoscopic cholecystectomy: a prospective, randomized and double blind study [Antibiotioprophylaxi na coloeciectomia videolaparoscopica eletiva: estudo prospectivo randomizado E duplo cego]. Rev Col Bras Cir 2008;35:168-172.

31. Uludag M, Yerkin G, Citgez B. The role of prophylactic antibiotics in elective laparoscopic cholecystectomy. JSLS 2009;13:337-341.

32. Yildiz B, Abbasoglu O, Tirnakisz B, Hamaloglu E, Ozdemir A, Sayek I. Determinants of postoperative infection after laparoscopic cholecystectomy. Hepatogastroenterology 2009;56:589-592.

33. Gaur A, Pujahari AK. Role of prophylactic antibiotics in laparoscopic cholecystectomy. Med J Armed Forces India 2010;66:228-230.

34. Sharma N, Garg PK, Hande NS, Choudhary D. Role of prophylactic antibiotics in laparoscopic cholecystectomy and risk factors for surgical site infection: a randomized controlled trial. Surg Infect (Larchmt) 2010;11:367-370.

35. Al-Qahtani HH. The impact of antibiotics prophylaxis in elective laparoscopic cholecystectomy: a prospective randomized study. J Taibah Univ Med Sci 2011;6:132-138.

36. Hassan AM, Nasr MM, Handey HE, Abbas M, Hedaya MS, Elsebae MM. Role of prophylactic antibiotic in elective laparoscopic cholecystectomy. J Egypt Soc Parasitol 2012;42:129-134.

37. Shah JN, Marajan SB, Paudyal S. Routine use of antibiotic prophylaxis in low-risk laparoscopic cholecystectomy is unnecessary: a randomized clinical trial. Asian J Surg 2012;35:136-139.

38. Naqvi MA, Mehraj A, Ejaz R, Mian A. Role of prophylactic antibiotics in low risk elective laparoscopic cholecystectomy: is there a need? J Ayub Med Coll Abbottabad 2013;25:172-174.

39. Turk E, Karagulle E, Serefhanoglu K, Turan H, Moray G. Effect of cefazolin prophylaxis on postoperative infectious complications in elective laparoscopic cholecystectomy: a prospective randomized study. Iran Red Crescent Med J 2013;15:581-586.

40. Matsui Y, Satoi S, Kainobi M, Toyokawa H, Yanagimoto H, Matsui K, et al. Antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized controlled trial. PLoS One 2014;9:e106702.

41. Mirani AJ, Suchdev SD, Jatoi AH, Haseeb A, Idrees S, Younus SM. Use of antibiotic prophylaxis in low-risk laparoscopic cholecystectomy is unnecessary: a clinical trial. Pak J Med Health Sci 2014;8:713-716.

42. Ruangsin S, Laohawiriyakamol S, Sunpaweravong S, Mahattanonbon S. The efficacy of cefazolin in reducing surgical site infection in laparoscopic cholecystectomy: a prospective randomized double-blind controlled trial. Surg Endosc 2015;29:874-881.

43. Darzi AA, Niknamesh A, Bagherian F. The effect of prophylactic antibiotics on postoperative infectious complications: a double-blind clinical trial. Electron Physician 2016;8:2308-2314.

44. Passos MA, Portari-Filho PE. Antibiotic prophylaxis in laparoscopic cholecystectomy: is it worth doing? Arq Bras Cir Dig 2016;29:170-172.

45. Kim HJ, Kang SH, Roh YH, Kim MC, Kim KW. Are prophylactic antibiotics necessary in elective laparoscopic cholecystectomy, regardless of patient risk? Ann Surg Treat Res 2017;93:76-81.

46. Sarkut P, Kiliicturgay S, Aktas H, Ozen Y, Kaya E. Routine use of prophylactic antibiotics during laparoscopic cholecystectomy does not reduce the risk of surgical site infections. Surg Infect (Larchmt) 2017;18:603-609.

47. Nauman SM, Haroon Y, Ahmad A, Saleem I. Surgical site infection; prophylactic antibiotics in laparoscopic cholecystectomy to reduce surgical site infection. Professional Med J 2018;25.

48. Lippert H, Gastinger J. Antimicrobial prophylaxis in laparoscopic and conventional cholecystectomy. Conclusions of a large prospective multicenter quality assurance study in Germany. Chemotherapy 1998;44:355-363.

49. Guzman-Valdivia G. Routine administration of antibiotics to patients suffering accidental gallbladder perforation during laparo-
scopic cholecystectomy is not necessary. Surg Laparosc Endosc Percutan Tech 2008;18:547-550.

50. Han YG, Kim IH, Mun GM, Kim JH, Hwang GS. A prospective study of prophylactic antibiotics for laparoscopic cholecystectomy. Korean J Hepatobiliary Pancreat Surg 2008;12:263-267.

51. Garcia N, Kapur S, McClane J, Davis JM. Surgical infections and prophylactic antibiotics: 341 consecutive cases of gallbladder surgery in the era of laparoscopic surgery. J Laparoendosc Adv Surg Tech A 1997;7:157-162.

52. Chong JU, Lim JH, Kim JY, Kim SH, Kim KS. The role of prophylactic antibiotics on surgical site infection in elective laparoscopic cholecystectomy. Korean J Hepatobiliary Pancreat Surg 2015;19:188-193.

53. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-605.

54. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

55. Agrawal CS, Sehgal R, Singh RK, Gupta AK. Antibiotic prophylaxis in elective cholecystectomy: a randomized, double blinded study comparing ciprofloxacin and cefuroxime. Indian J Physiol Pharmacol 1999;43:501-504.

56. Dervisoglu A, Tsiodras S, Kanellakopoulou K, Pinis S, Galanakis N, Pierakakis S, et al. The value of chemoprophylaxis against Enterococcus species in elective cholecystectomy: a randomized study of cefuroxime vs ampicillin-sulbactam. Arch Surg 2006;141:1162-1167.

57. Kumar A, Patodia M, Pandove PK, Sharda VK, Pahwa S. Role of antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized prospective study. JIMA 2013;26:209-211.

58. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on post-operative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014;312:145-154.

59. Loozen CS, Kottram K, Kornmann VN, van Ramshorst B, Vlaminckx B, Knibbe CA, et al. Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis. Br J Surg 2017;104:e151-e157.

60. Chauhan VS, Kariholu PL, Saha S, Singh H, Ray J. Can postoperative antibiotic prophylaxis following elective laparoscopic cholecystectomy be completely done away with in the Indian setting? A prospective randomised study. J Minim Access Surg 2018;14:192-196.

61. de Santibañes M, Glinka J, Pelegrini P, Alva rez FA, Elizondo V, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of nonrandomized studies in epidemiology. Eur J Epidemiol 2010;25:603-605.

62. Soza HP, Breigeiron R, da Cunha HM, Deues E. Antibiotic prophylaxis in colostectomy videoaparcápsica eletriva: estado prospectivo randomizado e duplo cego. Rev Col Bras Cir 2018;35:168-172.

63. Waterman DM, Wainwright AM, Thompson MH, Leaper DJ. Antibiotic prophylaxis in elective cholecystectomy: a 7-year clinical experience involving 3,603 patients. J Chemother 2000;12 Suppl 3:17-22.

64. de Souza HP, Breigeiron R, da Cunha HM, Deues E. Antibiotic prophylaxis in colectostomy videoaparcápsica eletriva: estado prospectivo randomizado e duplo cego. Rev Col Bras Cir 2018;35:168-172.

65. Watkin DS, Wainwright AM, Thompson MH, Leaper DJ. Infection after laparoscopic cholecystectomy: are antibiotics really necessary? Eur J Surg 1995;161:509-511.

66. Hell K. Antibiotic prophylaxis in cholecystectomy--necessary and cost saving? Zentralbl Chir 1998;123 Suppl 2:37-41.

67. Colizza S, Rossi S, Picardi B, Cearmuccio P, Pollucita S, Rodio F, et al. Surgical infections after laparoscopic cholecystectomy: ceftriaxone vs cefazidine antibiotic prophylaxis. A prospective study. Chir Ital 2004;56:397-402.

68. Immé A, Caglía P, Cardi F, Gandolfo L, Donati M. Antibiotic prophylaxis in laparotomy and laparoscopic cholecystectomy. Chir Ital 2004;56:403-407.

69. Lundenström P, Sandblom G, Osterberg J, Svennblad B, Persson G. Effectiveness of prophylactic antibiotics in a population-based cohort of patients undergoing planned cholecystectomy. J Gastrointest Surg 2010;14:329-334.

70. Dahrabi H, Videhult P, Sandblom G, Liljeholm H, Ljungdahl M, Rasmussen JC. Effectiveness of antibiotic prophylaxis in cholecystectomy: a prospective population-based study of 1171 cholecystectomies. Scand J Gastroenterol 2012;47:1242-1246.

71. Mir MA, Malik UY, Wahi H, Bali BS. Prevalence, pattern, sensitivity and resistance to antibiotics of different bacteria isolated from port site infection in low risk patients after elective laparoscopic cholecystectomy for symptomatic cholelithiasis at tertiary care hospital of Kashmir. Int Wound J 2013;10:110-113.

72. Yanni F, Mekhall P, Morris-Stiff G. A selective antibiotic prophylaxis policy for laparoscopic cholecystectomy is effective in minimising infective complications. Ann R Coll Surg Engl 2013;95:345-348.

73. Gharde P, Swarkar M, Waghmare LS, Bhagat VM, Gode DS, Wagh DD, et al. Role of antibiotics on surgical site infection in cases of open and laparoscopic cholecystectomy: a comparative observational study. J Surg Tech Case Rep 2014;6:1-4.

74. Mandal N, Nandy MM, Majhi J, Kuri S, Kumar Ghosh P, Ghosh G. Laparoscopic cholecystectomy without prophylactic antibiotics: a prospective study. Indian J Surg 2015;77(Suppl 2):419-422.

75. Vohra RS, Hodson J, Pasquali S, Griffiths EA; CholeS Study Group and West Midlands Research Collaborative. Effectiveness of antibiotic prophylaxis in non-emergency cholecystectomy using data from a population-based cohort study. World J Surg 2017;41:2231-2239.

76. McGuickin M, Shea JA, Schwartz JS. Infection and antimicrobial use in laparoscopic cholecystectomy. Infect Control Hosp Epidemiol 1999;20:624-626.

77. Farello GA, Cerofolini A. Antimicrobial prophylaxis with ceftriaxone in laparoscopic cholecystectomy: a 7-year clinical experience involving 3,603 patients. J Chemother 2000;12 Suppl 3:17-22.

78. Shindohimath VG, Seenu V, Parashad R, Chaudhry R, Kumar A. Factors influencing wound infection following laparoscopic cholecystectomy. Trop Gastroenterol 2003;24:90-92.

79. Uchiyama K, Kawai M, Onishi H, Tani M, Kinoshita H, Ueno M, et al. Preoperative antimicrobial administration for prevention of postoperative infection in patients with laparoscopic cholecystectomy. Dig Dis Sci 2003;48:1955-1959.

80. Panzotto AR, Ferreira MB. Antibiotic prophylaxis in cholecystectomies in a teaching hospital in Brazil. Ann Pharma- cother 2006;40:2003-2007.

81. Ruangsin S, Wanasuwannakul T. Variation of prophylactic antibiotic use in laparoscopic cholecystectomy. J Med Assoc Thai 2012;95:48-51.

82. Zanotto AR, Heineck I, Ferreira MB. Antibiotic prophylaxis in cholecystectomies in a teaching hospital in Brazil. Ann Pharma- cother 2006;40:2003-2007.

83. Rodríguez-Caravaca G, Gil-Yone P, Risco-Risco C, Latasa Zamalloa P, Villar del Campo MC, Fernández-Cebrián JM, et al. Antibiotic prophylaxis in elective cholecystectomy: Protocol adequacy and related outcomes in a retrospective single-centre analysis. Rev Esp Enferm Dig 2016;108:15-19.

84. Bar H, Khan MR, ShariﬀAH. Antibiotics in acute calculous cholecystitis: do Tokyo guidelines influence the surgeons’ practi-
ces? J Pak Med Assoc 2017;67:670-676.
83. Smith JP, Samra NS, Ballard DH, Moss JB, Griffen FD. Prophylactic antibiotics for elective laparoscopic cholecystectomy. Am Surg 2018;84:576-580.
84. Williams K, Baumann L, Abdullah F, St Peter SD, Oyetunji TA. Variation in prophylactic antibiotic use for laparoscopic cholecystectomy: need for better stewardship in pediatric surgery. J Pediatr Surg 2018;53:48-51.
85. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609-613.