



# Preoperative antibiotic prophylaxis in acute cholecystectomy: a systematic review and meta-analysis of randomised controlled trials

Anurag Singh, Mandeep Kaur, Christie Swaminathan, Atreya Subramanian, Krishna K. Singh, Muhammad S. Sajid

Department of Gastrointestinal Surgery, Royal Sussex County Hospital Brighton, Brighton, UK

**Contributions:** (I) Conception and design: A Singh, MS Sajid; (II) Administrative support: M Kaur, KK Singh, A Singh; (III) Provision of study materials or patients: C Swaminathan, M Kaur, A Subramanian; (IV) Collection and assembly of data: A Singh, A Subramanian, C Swaminathan, M Kaur; (V) Data analysis and interpretation: A Singh, MS Sajid, C Swaminathan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Mr. Anurag Singh, MBBS (AFMC, Pune), MRCS (RCS Edinburgh). Junior Clinical Fellow, Department of Gastrointestinal Surgery, Royal Sussex County Hospital Brighton, Eastern Road, Brighton BN2 5BE, UK. Email: anuragsingh3139@gmail.com.

**Background:** Laparoscopic cholecystectomy (LC) in patients admitted with acute cholecystitis is considered the preferred, feasible and safe mode of managing gallstone disease. The objective of this study is to evaluate the role of single-dose pre-operative prophylactic antibiotics in patients undergoing emergency LC for mild to moderate acute cholecystitis.

**Methods:** All randomized control trials (RCTs) reporting the use of single-dose pre-operative prophylactic antibiotics in patients undergoing acute cholecystectomy were retrieved from the search of standard medical electronic databases and analysis was conducted by using the principles of meta-analysis on the statistical software RevMan version 5.

**Results:** Standard medical databases search produced only 3 RCTs on 781 patients undergoing acute cholecystectomy. There were 384 patients in single dose pre-operative antibiotics group whereas 397 patients were recruited in the no-antibiotics group. In the random effects model analysis, the use of single-dose preoperative prophylactic antibiotics in patients undergoing acute cholecystectomy for mild to moderate cholecystitis failed to demonstrate any extra advantage of reducing the risk of [risk ratio (RR) =0.69; 95% confidence interval (CI): 0.46–1.03; Z=1.80; P=0.07] infective complications. There was no heterogeneity [ $Tau^2 = 0$ ;  $Chi^2 = 1.74$ ,  $df = 2$  ( $P = 0.42$ ;  $I^2 = 0\%$ )] among included studies.

**Conclusions:** A preoperative single dose of prophylactic antibiotics in patients undergoing acute LC for mild to moderate acute cholecystitis does not offer extra benefits to reduce infective complications.

**Keywords:** Antibiotic prophylaxis; acute cholecystectomy; post-operative infective complications; surgical site infection

Received: 16 July 2023; Accepted: 07 October 2023; Published online: 24 October 2023.

doi: 10.21037/tgh-23-48

View this article at: <https://dx.doi.org/10.21037/tgh-23-48>

## Introduction

Acute cholecystitis is one of the most common presentations for emergency admission and surgery in any hospital. It is defined as acute inflammation of the gall bladder with or without underlying gallstones usually

associated with a critical illness (1). It is diagnosed in about 200,000 individuals in the USA (1) every year. In the world, prevalence of gallstones is around 10–15% and 10–15% of these patients initially present with acute cholecystitis (2). There is also a significant cumulative mortality (0.9%) and

morbidity (17.8%) associated with cholecystectomy (3). It is globally acceptable that acute cholecystitis should be managed with emergency cholecystectomy (4).

The use of preoperative antibiotics in cholecystitis has been a topic of debate for a long. There are existing guidelines advocating the use of pre-operative antibiotic prophylaxis for patients undergoing laparoscopic cholecystectomy (LC) in acute cholecystitis (5,6), but the evidence used in these guidelines seems to be inadequate because recently published randomized control trials (RCTs) are contradictory (7-9). Colling *et al.* have also recommended the use of perioperative antibiotic prophylaxis for patients undergoing LC for acute cholecystitis (10). The risk of developing post-operative infective complications after grades 1 and 2 acute cholecystitis is around 17% (11). The major pathogenesis thought to be behind this is thought to be due to contamination with the infected bile intra-operatively. In a normal individual biliary tree is supposed to be sterile (12). The outflow obstruction of the biliary tree leads to an inflammatory process which eventually is the cause hypothesized for bacterial colonisation. In acute cholecystitis, bile becomes colonized in about 35–60% of the patients (13). The most common microbes leading to this colonization are gram-negative bacteria and enterococci species (6,14).

Therefore, it is imperative to analyze the recently published data about the use of pre-operative antibiotic prophylaxis in patients undergoing acute cholecystectomy and evaluate the effectiveness of prophylactic antibiotics

in reducing perioperative infective complications. The objective of this study is to evaluate the role of single-dose pre-operative prophylactic antibiotics in acute cholecystectomy for mild to moderate acute cholecystitis. We present this article in accordance with the PRISMA reporting checklist (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-48/rc>).

## Methods

### *Data sources and literature search technique*

Literature exploration was systematically carried out from electronic databases like MEDLINE, EMBASE, PubMed and Cochrane Library using the MeSH search terms. Boolean operators (AND, OR, NOT) were used for protracted search results. The titles were carefully examined for study selection. Moreover, references from selected articles were analyzed to find any further relevant trials.

### *Trial selection*

The inclusion criteria were the combined analysis of RCTs, reporting the effectiveness of preoperative antibiotic prophylaxis versus placebo for patients undergoing acute cholecystectomy.

### *Data collection and management*

Reported data were collected from the included trials by independent researchers on a standard data extraction sheet. The collected dataset was matched and found to be in satisfactory inter-researcher agreement. The extracted data consisted of a list of the authors, title of the published study, journal of publication, country and year of the publication, testing sample size, the number of patients in each group of antibiotics and placebo and development of any postoperative infective complications. Researchers discussed the results following the data extraction and if a disagreement was reached, then mutual consensus was used for resolution.

### *Quality of analysis*

The methodological quality of the included trials was initially assessed using the published guidelines of Jadad *et al.*, Chalmers *et al.* and Rangel *et al.* (15-17). A comprehensive table for the assessment of quality among

## Highlight box

### Key findings

- Preoperative prophylactic antibiotics for mild to moderate acute cholecystitis does not offer extra benefit to reduce infective complications during acute cholecystectomy.

### What is known and what is new?

- Existing guidelines advocate the use of pre-operative antibiotic prophylaxis for acute cholecystitis.
- In random effect model, use of single does preoperative prophylactic antibiotics in patients undergoing acute cholecystectomy for mild to moderate cholecystitis fails to demonstrate any advantage of reducing the risk of infective complications.

### What is the implication, and what should change now?

- This systematic review has shown that there is no benefit of using preoperative antibiotics in emergency laparoscopic cholecystectomy for grades 1 and 2 of acute cholecystitis.

**Table 1** Quality variables of included studies

Study	Randomization technique	Concealment	Blinding	Intention to treat analysis	Ethical approval	Registration number	Power calculation
Jaafar 2020 (7)	Manually	Sealed envelope	Double	Reported	Reported	NCT02619149	Reported, power not achieved
Park 2023 (8)	Computer generated	Serial opaque sealed envelope	Double	Reported	Not reported	NCT04661371	Reported, power achieved
van Braak 2022 (9)	Computer generated	Independent programmer	Not reported	Reported	Reported	NTR5802	Reported, power achieved

the included trials is given in *Table 1*.

### Statistical analysis

RevMan 5.4 (18) statistical analysis tool was used in this analysis (Review Manager 5.4, The Nordic Cochrane Centre, Copenhagen, Denmark). The random-effects model analysis was used for both the continuous and dichotomous variables and risk ratio (RR) with a confidence interval (CI) of 95% was used for the binary data analysis (19,20). A forest plot was used for calculating the heterogeneity and computing  $\text{Chi}^2$ , significance was set at  $P < 0.05$  and the  $I^2$  test was used for identifying the heterogeneity, with a maximum value of 30% (21). Under the random effect model, RR was used for calculation as per the Mantel-Haenszel method (22). For the sensitivity analysis, in each cell frequency, 0.5 was added in the studies where no event occurred in either the treatment or control group, as per the guidelines recommended by Deeks *et al.* (23). In the event of unavailability of the standard deviation, Cochrane collaborations guidelines were used for the risk of bias calculation (19). In this event, it was assumed that variance was the same in both groups, which is not true in every case. In this case, variance was estimated either from the P value or range. Both techniques were used for pooling the estimate of difference, depending upon the effect weights in results determined by each trial estimate variance. Results were graphically displayed as a forest plot. The horizontal line represented the 95% CI and the square around the estimate stood for the accuracy of the estimation (sample size).

### Endpoint

Post-operative occurrence or absence of infective complication was considered as the primary endpoint in this

meta-analysis.

## Results

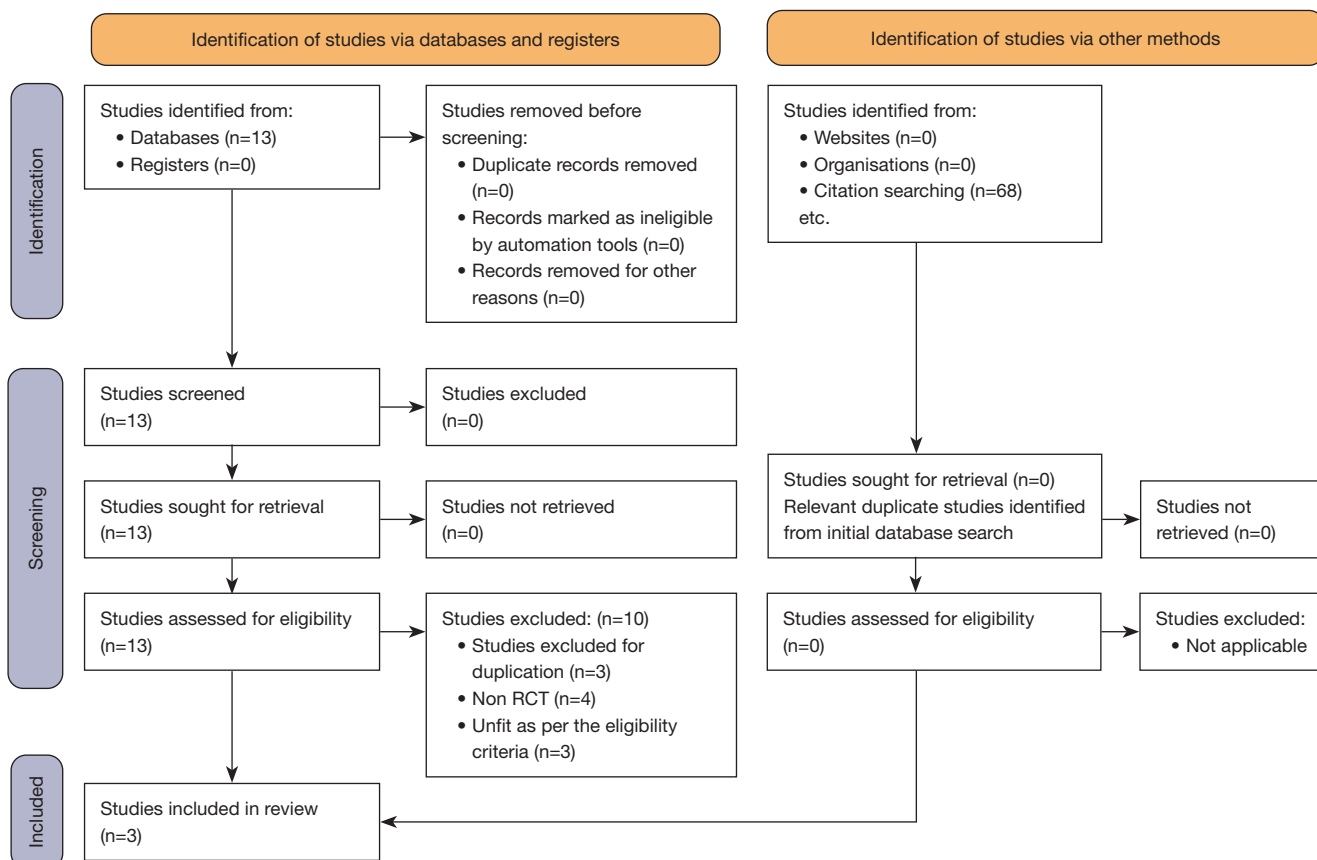
The initial database search generated 13 studies. After assessment of the studies for duplication, study type and inclusion criteria, 10 were excluded. Three RCTs were included in the final meta-analysis (*Figure 1*).

### Characteristics and demographics of included studies

This meta-analysis is done in accordance with the guidelines provided by the Cochrane Collaboration, it includes three RCTs on 781 patients. A flow chart in accordance with the PRISMA guidelines is given in *Figure 1*. The included trials were conducted in Sweden (7), Korea (8) and The Netherlands (9). The demographic characteristics from the studies included are given in *Table 2*. A detailed review of the treatment protocol among the included studies is given in *Table 3*. The quality of the included trials is included in *Table 1*.

### Outcome of the primary variable

There were 384 patients in single dose pre-operative antibiotics group whereas 397 patients were recruited in the no-antibiotics group. In the random effects model analysis, the use of single-dose preoperative prophylactic antibiotics in patients undergoing acute cholecystectomy for mild to moderate cholecystitis failed to demonstrate any advantage of reducing the risk of [RR =0.69; 95% CI: 0.46–1.03;  $Z=1.80$ ;  $P=0.07$ ] infective complications. There was no heterogeneity [ $\text{Tau}^2 =0$ ;  $\text{Chi}^2 =1.74$ ,  $df =2$  ( $P=0.42$ ;  $I^2=0\%$ )] (*Figure 2*) among included studies. Also, the similarity of the included studies is presented as a funnel plot (*Figure 3*).



**Figure 1** PRISMA flowchart showing the literature review in the meta-analysis. RCT, randomized control trial.

**Table 2** Characteristics of included studies

Study	Country	Antibiotic group			No antibiotic group			Follow-up (days)
		N value	Men (%)	Age (years)	N value	Men (%)	Age (years)	
Jaafar 2020 (7)	Sweden	42	18.0	48.5 (median)	48	23.0	49 (median)	30
Park 2023 (8)	Korea	116	47.4	50.9±15.28 (mean ± standard deviation)	118	36.4	52.2±13.64 (mean ± standard deviation)	30
van Braak 2022 (9)	The Netherlands	226	47.3	58 (median)	231	50.6	57.5 (median)	30

## Discussion

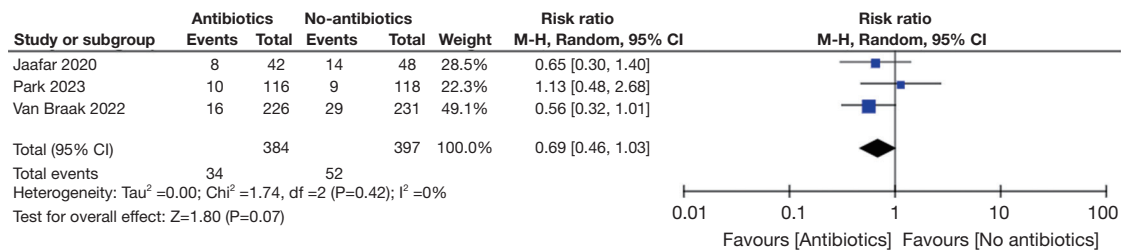
### Key findings

The debate on using preoperative antibiotic prophylaxis for acute cholecystitis has been a topic of discussion for a very long time. Different antibiotics have been used by surgeons to minimize the risk of post-operative infective

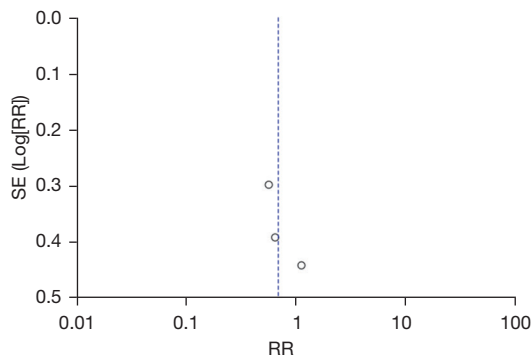
complications. In this systematic review 781 patients were studied from 3 RCTs, 384 patients in single dose preoperative antibiotics group and 397 patients were recruited in the no antibiotic or placebo group. A preoperative single dose of prophylactic antibiotics in patients undergoing emergency LC for mild to moderate acute cholecystitis does not offer the benefit of reducing post-operative infective

**Table 3** Treatment protocol adopted on included studies

Study	Cholecystitis grade (Tokyo guidelines)	Antibiotics/dose	N value (antibiotic group)	No antibiotic	N value (no antibiotic group)	Time between surgery and antibiotic dose	Single dose	Type of cholecystectomy
Jaafar 2020 (7)	Grades 1 & 2	Piperacillin-tazobactam/4,000 mg	42	Nil	48	1–72 h	79%	Laparoscopic/converted/open
Park 2023 (8)	Grades 1 & 2	First generation cephalosporin/1,000 mg	116	10 mL saline	118	Within 24 h	All	3 or 4 port laparoscopic
van Braak 2022 (9)	Grades 1 & 2	First generation cephalosporin/2,000 mg	226	Nil	231	15–30 min	All	4 port laparoscopic



**Figure 2** Forest plot showing the risk of postoperative infective complications in preoperative antibiotics versus no antibiotics group. M-H, Mantel-Haenszel; CI, confidence interval.



**Figure 3** Funnel plot for the included RCTs in the systematic review. RR, risk ratio; SE, standard error; RCTs, randomized control trials.

complications.

**Comparison with existing literature**

In the literature review, there have not been any published systematic reviews on this topic for comparison. There have been multiple systematic reviews comparing the efficacy of preoperative antibiotic prophylaxis for elective LC. There have been studies favouring the use of preoperative

antibiotic prophylaxis for elective LC (24,25) while there have been systematic reviews showing no added benefits of preoperative antibiotic prophylaxis (26). Two RCTs used in the review showed no significant benefit of antibiotic use in the prevention of post-operative infective complications in grades 1 and 2 of acute cholecystitis (7,8). One RCT concluded that it is not possible to select a subset of patients based on pre- and post-operative characteristics that will benefit from antibiotic prophylaxis (9).

**Strength and limitations**

Two of the RCTs used computer-generated randomization (8,9) and all three and the intention to treat analysis were given. There was double blinding in two RCTs (7,8) and concealment with sealed envelopes was also used in them. Therefore, the three RCTs which were used in this meta-analysis were of solid strength. Also, there was no heterogeneity among the trials used in this systematic review.

The primary limitation of this systematic review was the lack of evidence for the use of pre-operative antibiotics in moderate and severe acute cholecystitis (as per Tokyo guidelines) (6). Also, the lack of the presence of manual

randomization (7) and the presence of independent programmer-generated concealment (9) also limits the RCTs used in this meta-analysis. Another limitation of this systematic review is paucity of the RCTs and the number of patients. This can be overcome in the future by conducting a major multicentre RCT with adequate power calculation.

### Implications

This systematic review has shown that there is no benefit of using preoperative antibiotics in grades 1 and 2 of acute cholecystitis. Nonetheless, the use of pre-operative antibiotics can be limited to exceptional cases as per the surgeon's judgment, especially in the case of grades 1 and 2 of acute cholecystitis.

### Conclusions

A preoperative single dose of prophylactic antibiotics in patients undergoing acute cholecystectomy for mild to moderate acute cholecystitis does not offer extra benefits to reduce infective complications. A further major multicentric RCT is needed to confirm the findings of this systematic review.

### Acknowledgments

The provisional abstract of this systematic review has been presented at the annual conference of "The Association of Surgeons of Great Britain and Ireland" on 17<sup>th</sup>–19<sup>th</sup> May 2023 at Harrogate, United Kingdom.

*Funding:* None.

### Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-48/rc>

*Peer Review File:* Available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-48/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-48/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tgh-23-48

**Cite this article as:** Singh A, Kaur M, Swaminathan C, Subramanian A, Singh KK, Sajid MS. Preoperative antibiotic prophylaxis in acute cholecystectomy: a systematic review and meta-analysis of randomised controlled trials. *Transl Gastroenterol Hepatol* 2023;8:37.