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Pre-operative antibiotics in patients with acute mild cholecystitis undergoing laparoscopic cholecystectomy: is it really useful? A systematic review

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Abstract

Background Empirical antibiotic therapy is often initiated during the hospital stay while awaiting laparoscopic cholecystectomy. This approach is generally justified in patients with moderate (Tokyo II) and severe (Tokyo III) acute cholecystitis, where organ dysfunction occurs as a result of the inflammatory or infectious process. However, there is no clear consensus regarding the use of antibiotics in patients with mild (Tokyo I) cholecystitis. This study aimed to evaluate the impact of preoperative antibiotic use on outcomes in patients with acute cholecystitis.

Methods A systematic review of PubMed, Embase and Cochrane was conducted following the PRISMA methodology. Studies were eligible for inclusion if they were randomized controlled trials or non-randomized comparative studies evaluating the use or non-use of preoperative antibiotics in patients with acute cholecystitis. Eligible studies were required to provide at least one of the following datasets: postoperative complication rate, postoperative infectious complication rate, or positive culture rate. The synthesis reports were prepared using the Synthesis Without Meta-analysis (SWiM) framework.

Results A total of 622 articles were initially identified, of which 2 met the inclusion criteria. These two articles included 331 patients. They reported higher rates of postoperative complications and bacterobilia in the group that received preoperative antibiotics; however, the differences were not statistically significant ($p > 0.05$).

Conclusion Based on current evidence, no recommendation can be made regarding the therapeutic use of antibiotics in mild acute cholecystitis while awaiting laparoscopic cholecystectomy.

Keywords Acute cholecystitis, Antibacterial agents, Antibiotics, Cholecystectomy, Complications

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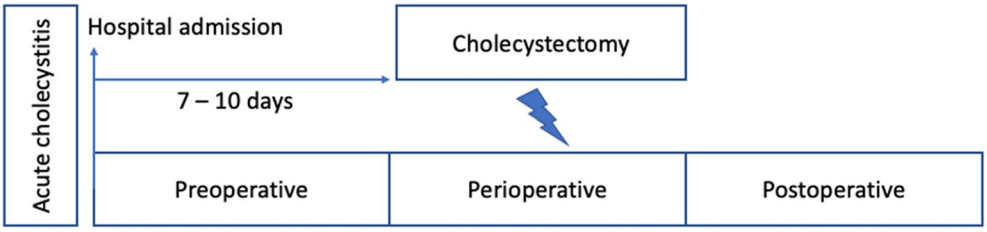

Fig. 1 Timing of antibiotic administration in the natural course of acute cholecystitis after hospital admission

Table 1 Recommendations for preoperative antibiotic management according to the available clinical practice guidelines

Guidelines	Recomendations
Tokyo Guidelines 2018	Antimicrobial therapy for patients with Grade I and II acute cholecystitis is recommended only before and at the time of surgery [5]. Particularly, preoperative antibiotics are indicated for patients with CCI 6 or greater and/or ASA class III or greater (not low risk).
Surgical Infection Society	As current practice and 2018 Tokyo Guidelines recommend treatment with antibiotic agents upon admission, we recommend use of peri-operative antibiotic agents for patients undergoing laparoscopic cholecystectomy for acute cholecystitis [6].
World Society of Emergency Surgery	No recommendation [2, 7].
Panamerican Journal of Trauma, Critical Care & Emergency Surgery	It is recommended that all patients diagnosed with acute cholecystitis receive antibiotics to prevent progressive gallbladder inflammation, development of secondary infection, or sepsis [8].

Introduction

Laparoscopic cholecystectomy is the treatment of choice for patients with acute cholecystitis [1]. Current guidelines from the World Society of Emergency Surgery (WSES) and the Tokyo Guidelines 2018 (TG18) recommend performing early cholecystectomy for patients with mild (grade I) and moderate (grade II) acute cholecystitis who do not respond to the initial conservative treatment. The WSES guidelines suggest performing surgery within 7 days of hospital admission and within 10 days of symptoms onset, while the TG18 recommends surgery within 24–72 h of symptom onset. Both guidelines advocate for early surgery, regardless of the precise duration since symptom onset, as it reduces wound infections, hospital stay, and operation time, while also improving quality of life [2–4]. However, the timing of surgery from symptom onset or hospital admission may vary depending on resource availability and the final diagnosis.

During hospital stay while awaiting laparoscopic cholecystectomy, empirical antibiotic therapy is often initiated. This practice is generally justified in patients with moderate (Tokyo II) and severe (Tokyo III) acute cholecystitis, in which organ dysfunction results from inflammatory or infectious processes. However, there is no clear consensus regarding the use of antibiotics in patients with mild (Tokyo I) cholecystitis.

Antibiotics may be administered during three main phases in patients with acute cholecystitis: preoperatively, perioperatively (as prophylaxis, typically within 120 min before incision, in accordance with hospital policies), and postoperatively (see Fig. 1).

For perioperative and postoperative antibiotics, established recommendations and supporting evidence guide the use; however, the role of preoperative antibiotics remains uncertain (Table 1).

In the pathophysiology of acute cholecystitis, the primary cause is mechanical (obstruction of the cystic duct) rather than infectious, with infection occurring as a secondary process. During the first phase of acute cholecystitis (the congestive and edema phase), obstruction and circulatory disturbance of the gallbladder typically occur between days 2 and 4. The second phase (the hemorrhagic and necrotic phase) occurs between days 3 and 5 and is characterized by necrosis of the gallbladder wall. Finally, the third phase (the suppurative phase), marked by purulence within the gallbladder lumen, occurs between days 7 and 10. If left untreated, the condition may progress to the subacute phase or chronic cholecystitis [9, 10].

It is also important to note that bactibilia (the presence of bacteria in bile) varies across studies and is not observed in all cases of cholecystitis [11]. This finding aligns with the pathophysiological understanding that infection is neither a necessary nor a sufficient cause of this condition [12]. Given this, patients admitted with mild (uncomplicated) acute cholecystitis who undergo early laparoscopic cholecystectomy may not derive significant benefit from antibiotic management.

This study aimed to evaluate the impact of preoperative antibiotic use on outcomes in patients with acute cholecystitis. To achieve this, we conducted a systematic review of all published studies.

Methodology

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [13] and

was registered in PROSPERO (registration number: CRD42024594069).

Search strategy and screening

Two authors (CR and AP) independently searched for published studies indexed in PubMed/MEDLINE, EMBASE and Cochrane CENTRAL, from inception to September 2024, without language, country of origin or age restrictions. Databases were searched using the following search string (which was created with the help of ChatGPT4.0 [14]): "("cholecystitis"[MeSH Terms] OR cholecystit*[Title/Abstract] OR "acute cholecystitis"[Title/Abstract] OR gallbladder inflammation[Title/Abstract])AND ("antibiotic prophylaxis"[MeSH Terms] OR "antibiotic agents"[MeSH Terms] OR preoperative antibiotic*[Title/Abstract] OR prophylactic antibiotic*[Title/Abstract] OR antibiotic administration[Title/Abstract] OR antimicrobial agent*[Title/Abstract] OR "anti-bacterial agents"[MeSH Terms]) AND ("morbidity"[MeSH Terms] OR "mortality"[MeSH Terms] OR complication*[Title/Abstract] OR outcome*[Title/Abstract] OR postoperative complication*[MeSH Terms] OR length of stay[Title/Abstract] OR surgical site infection*[Title/Abstract] OR SSI[Title/Abstract]) AND (randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR cohort stud*[Title/Abstract] OR observational stud*[Title/Abstract] OR clinical trial*[Title/Abstract] OR prospective stud*[Title/Abstract] OR retrospective stud*[Title/Abstract])". References of selected retrieved articles were also manually reviewed to identify any studies missed during the search strategy.

After identifying and removing duplicate studies, electronically identified published papers were screened based on their titles and/or abstracts. Full-text papers that were considered relevant for inclusion were reviewed. Two investigators (CR and IV) independently evaluated the full texts of the selected records and resolved any discrepancies through consensus. All studies identified during the search process were organized using Rayyan®, a validated web and mobile application for systematic reviews [15].

Studies were eligible for inclusion in systematic review of the literature and randomized controlled trials or non-randomized comparative studies evaluating the use versus non-use of preoperative antibiotics in patients with acute cholecystitis. To qualify, studies had to report atleastone of the following outcomes: postoperative complication rate, postoperative infection complication rate, and positive culture rate. In cases where studies did not overlap cohorts, the study with the largest cohort was selected for analysis. Case reports, comments, editorials, and reviews were also excluded.

Quality Assessment was performed using the Joanna Briggs Institute (JBI) Critical Appraisal tools for use in Systematic Reviews Checklist, tailored to the study design [16] (see Supplement 1). Data synthesis was conducted without meta-analysis, following the qualitative analysis framework outlined in the "Synthesis Without Meta-analysis" (SWiM) guidelines [17].

Results

A total of 622 articles were identified in the search. After removing duplicates and screening titles and abstracts, 2 articles met the inclusion criteria (Fig. 2). The key characteristics of the included studies are summarized in Tables 2 and 3.

Postoperative complication rate

In the study by Mazeh et al., the complication rate was higher in the group without antibiotic treatment than in the group with antibiotics; however, the difference was not statistically significant. Among the reported complications, one case involved bleeding that required reintervention, and the other was due to choledocholithiasis, necessitating endoscopic retrograde cholangiopancreatography . No rescue procedures were required for either group. Drain placement was more frequent in the antibiotic-treated group (30%) than in the non-antibiotic treated group (19%), but this difference was also not statistically significant [18].

In a study by Park et al., the rates of postoperative complications and infectious complications were higher in the antibiotic-treated group (25.6% and 8.8%, respectively); however, these differences were not statistically significant compared to the group that did not receive antibiotics [19].

Positive bile cultures

In the studies included in this review, the incidence of bactibilia was higher in the group receiving antibiotic treatment; however, the difference was not statistically significant. The most commonly isolated organisms in the study by Mazeh et al. were *Escherichia coli* and *Klebsiella pneumoniae*. Similarly, in a study by Park et al., the predominant organisms were *Escherichia coli*, *Klebsiella pneumoniae*, and bacteria from the *Enterococcaceae* family [18, 19].

Discussion

Evidence of preoperative antibiotic management is limited, with studies focusing on antibiotic prophylaxis (administered before surgical incision) and postoperative antibiotics.

The study by Mazeh et al. is the most representative work on preoperative antibiotics. No statistically significant differences were found in postoperative

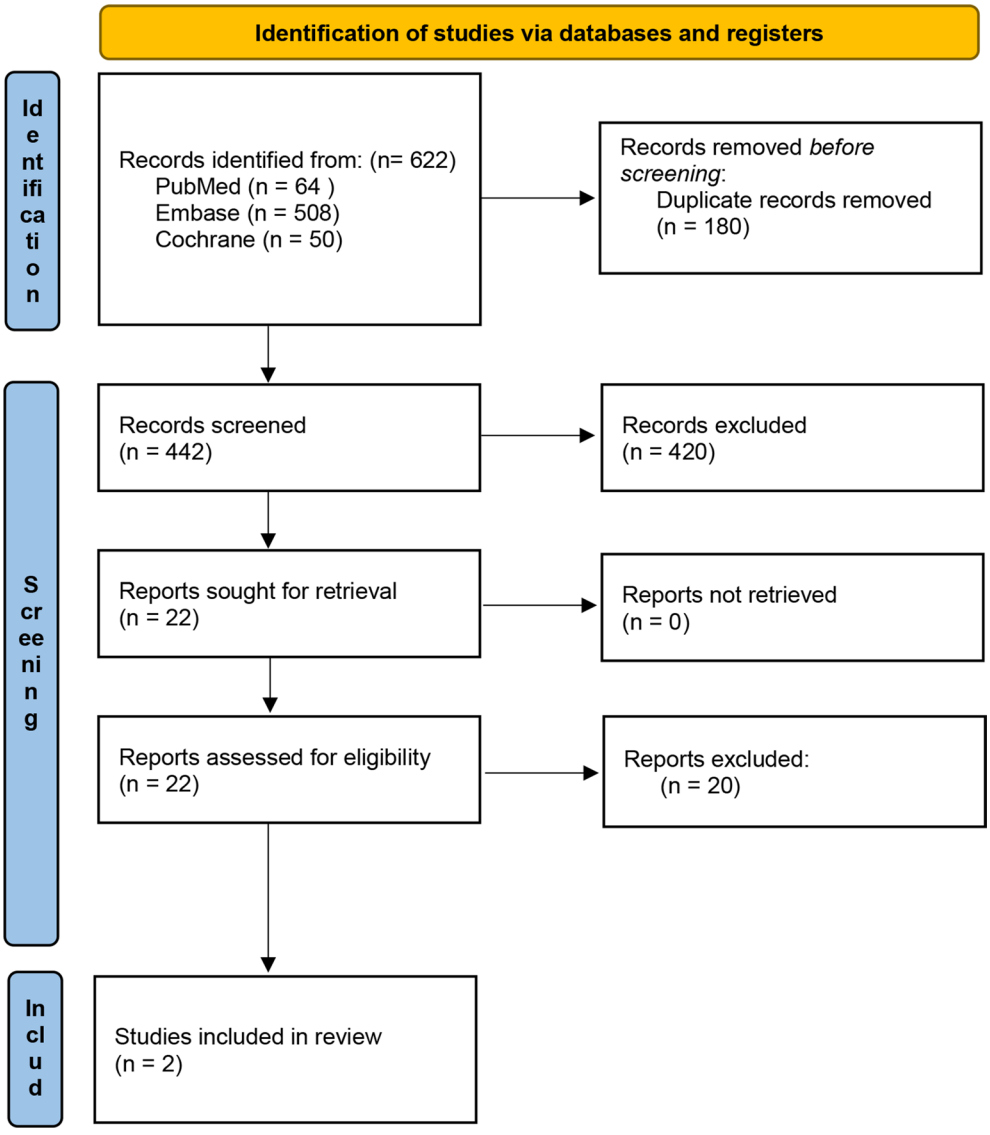

Fig. 2 Flowchart of the studies included using the PRISMA methodology

Table 2 Characteristics of the included studies

Study	Location	Type of study	Total of patients	Time to cholecystectomy	Inclusion criteria	Intervention
Mazeh, et al. 2012 [18]	Jerusalem, Israel	RCT	84 patients Group A: 42 patients Group B: 42 patients	Group A: 58 (17–156) days Group B: 55 (17–240) days	Mild acute cholecystitis Patients were 18 to 70 years old	Group A: amoxicillin clavulanate (Augmentin) (1 g IV every 8 h) until discharge. Patients allergic to penicillin ($n=12$) were treated with a combination of ciprofloxacin (400 mg IV every 12 h) and metronidazole (500 mg IV every 8 h). Group B: nonantibiotic treatment. Supportive care.
Park, et al. 2022 [19]	Seoul, Korea	RCT	247 patients Group A: 125 patients Group B: 122 patients	First 24 h	Mild and moderate acute cholecystitis (without empyema, gangrenous, perforation, or peritonitis)	Group A: 1.0 g of first-generation cephalosporin (cefazolin). Group B: 10 mL of intravenous normal saline.

Table 3 Outcomes of the included studies

Study	Follow-up	Outcomes	Comments
Mazeh, et al. 2012 [18]	17.1 months (range 4–28 months) **Group A**: 16.4 ± 5.0 months **Group B**: 17.7 ± 6.0 months	**Postoperative complication rate** Group A: 0% Group B: 7.7% **Positive bile cultures** Group A: 22% Group B: 12%	The course of the disease with the use of antibiotics did not change significantly compared to the group without antibiotics. The use of antibiotics may result in bacterial overgrowth. Late cholecystectomy is performed, but the standard of care nowadays is early cholecystectomy.
Park, et al. 2022 [19]	Not reported	**Postoperative complication rate** Group A: 25.6% Group B: 23.8% **Postoperative infection rate** Group A: 8.8% Group B: 7.4% **Positive bile cultures** Group A: 16.8% Group B: 12.3%	The absence of preoperative antibiotics does not increase the rate of infectious and non-infectious complications. There was a higher proportion of positive cultures in patients who received antibiotics. Cholecystectomy was performed within the first 24 h, which is ideal. However, in the clinical setting, it is not always possible to perform the surgical procedure within the first 24 h.

complications or bactibility between patients who received antibiotics and those who did not. However, this study has several limitations. First, cholecystectomy was delayed, which does not align with the current recommendations for the management of cholecystitis, limiting the applicability of these findings. Second, the sample size was calculated to detect statistically significant differences in hospital stay (the primary endpoint) but not in infection rates or postoperative complications. Finally, the study was not blinded and did not includ a placebo group [18].

The study by Park et al. is a more recent investigation on preoperative antibiotics; however, it also has some limitations. In our opinion, the main limitation is that cholecystectomy was performed within the first 24 h, which may not be feasible in many clinical settings. For example, at one of the authors' institutions, the median time from admission to cholecystectomy is 3.0 days (IQR: 5.0) [20]. This delay is due to various factors, such as the need for additional diagnostic studies including magnetic resonance cholangiography, stabilization of comorbidities, bridging therapy for chronic anticoagulation, pacemaker reprogramming, and operating room availability, making cholecystectomy within 24 h unlikely [19].

The use of antibiotics is generally undisputed in patients with moderate or severe cholecystitis who exhibit a systemic inflammatory response and/or clear evidence of local infection. Debate centers in patients with mild cholecystitis who do not show signs of local or systemic infection. These patients, who should undergo early cholecystectomy, as recommended by current clinical guidelines, may not require antibiotic treatment. As seen in disease pathophysiology, inflammation initially occurs without infection, with infection being a consequence rather than a cause.

The potential benefits of with holding antibiotics in these patients include prevention of antibiotic resistance, an issue linked to overuse [21], and reduced healthcare costs. In the two studies reviewed, we observed that patients who did not receive antibiotics had a lower proportion of bactibilia [18, 19]. Antibiotic resistance evolves over time, and inappropriate use of antibiotics in acute cholecystitis contributes to the selection and proliferation of resistant bacterial strains. The increasing prevalence of multidrug-resistant Enterobacterales, such as extended-spectrum beta-lactamase producing E. coli and Klebsiella, represents a growing concern. Risk factors for resistant pathogens include previous antibiotic use, particularly broad-spectrum agents, recent hospitalization or surgery, advanced age or immunosuppression, and healthcare-associated infections. Such misuse, including unnecessary or incorrect antibiotic choices, accelerates the emergence of resistance, complicates treatment options, and increases the risk of persistent infections and more severe clinical outcomes. This underscores the importance of appropriate antibiotic stewardship, particularly in managing infections such as cholecystitis, where the emergence of resistant pathogens significantly affects patient outcomes and healthcare costs [22, 23].

Additionally, adverse drug events, including allergic reactions, end-organ toxic effects, subsequent infections with antibiotic-resistant organisms, and Clostridium difficile infections, can be avoided by reducing the use of unnecessary antibiotics [24, 25]. In a cohort of hospitalized patients in whom antibiotics were used, up to 20% of the patients experienced adverse drug events. Therefore, using them only in necessary cases would decrease the number of adverse drug events [25].

Rather than offering a definitive recommendation of preoperative antibiotic management, where evidence is limited, high-quality studies are needed to support

evidence-based guidance for this common surgical condition. Van Dick et al. conducted a systematic review and meta-analysis in 2016, identifying only one study that compared antibiotic administration with non-administration in patients undergoing cholecystectomy—the study by Mazeh et al. Other studies in the review compared delayed cholecystectomy or operative versus non-operative management [26]. Despite the time that has passed since this publication and the significance of the issue, only one additional study addressing this research question has emerged.

A similar situation occurred with mild diverticulitis, where antibiotic treatment was once standard. However, studies comparing antibiotic therapy with conservative management have reported no differences in outcomes [9, 27]. As a result, mild diverticulitis came to be understood as inflammation rather than infection, challenging previous paradigms.

Moreover, it is important to assess the role of bactibilia in acute cholecystitis and its risk factors to better predict which patients would benefit from antibiotic therapy [28].

The main limitation of this study is the limited existing literature on preoperative antibiotic use. Another limitation was the inherent constraints of the individual studies included.

Given the current evidence, no definitive recommendations can be made regarding the therapeutic use of antibiotics for mild acute cholecystitis. A high-quality clinical trial is needed to compare antibiotic administration with placebo during hospitalization in patients undergoing early laparoscopic cholecystectomy prior to the surgical procedure (preoperatively).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13017-025-00574-x.

Supplementary Material 1

Author contributions

Camilo Ramírez-Giraldo: Study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript. Antonio Pesce: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript. Isabella Van-Londoño: Acquisition of data, analysis and interpretation of data, critical revision of manuscript. All authors and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Ethical compliance with the Helsinki Declaration and current legislation on research 008430 – 1993 and Res. 2378 – 2008 (Colombia) and the International Committee of Medical Journal Editors (ICMJE) were ensured.

Registration of research studies

Available on PROSPERO (ID: CRD42024594069).

Competing interests

The authors declare no competing interests.

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