Antibiotics for adults with acute cholecystitis or acute cholangitis or both (Protocol)

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Antibiotics for adults with acute cholecystitis or acute cholangitis or both

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ABSTRACT

Objectives
This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of antibiotics treatment versus placebo, no intervention, or another antibiotic for people with cholecystitis or cholangitis, or both.
BACKGROUND

Description of the condition

Acute cholecystitis (inflammation of the gallbladder) and acute cholangitis (inflammation of the bile duct) are conditions characterised by infection and inflammation of the biliary tract, ranging from a mild, self-limiting process to life-threatening systemic infection, especially in elderly people with comorbid diseases, or when diagnosis and treatment are delayed (Hanau 2000; Bornman 2003). The most common cause of cholangitis is stone obstruction of the normal bile flow, leading to increased biliary pressure which can induce bacteraemia (bacteria in blood), endotoxiaemia (endotoxins in the blood), and rare complications of acute cholecystitis including liver abscess and endocarditis (an infection of the endocardial surface of the heart) (Attasaranya 2008; Gomi 2017).

People with a gallstone disease (cholelithiasis; stones in the biliary tract) may be asymptomatic or may present with biliary colic or complications of the gallstone disease (Kono 1992). The term ‘complicated gallstone disease’ refers to gallstone-related complications, including acute cholecystitis, cholangitis, gallstone pancreatitis (inflammation of the pancreatic tissue), and gallstone ileus (Johnson 2001; Attasaranya 2008). Acalculous cholecystitis is an acute necroinflammatory disease of the gallbladder with multifactorial pathogenesis, mostly observed in immunosuppressed patients (Shapiro 1994; Wind 1994).

The most common bacteria found in community-acquired acute cholecystitis and cholangitis are gram-negative bacteria (Jain 2006; Kwon 2014; Gargouri 2015), which often produce extended-spectrum beta-lactamas (ESBL) and carbapenem beta-lactamase, which make them resistant to beta-lactam antibiotics such as penicillins, cephalosporins, monobactam, and carbapenems (Paterson 2005; Ishii 2008; Ishii 2011; Peirano 2012; Sung 2012). Gram-positive bacteria are rare (Jain 2006). Healthcare-associated acute cholecystitis and cholangitis are more often caused by multiresistant organisms (Zimmer 2015). The prevalence of gallstone disease is between 10% and 20% among European and Northern American adults (Cremer 2016; Wilkins 2017). Only a minority of people with symptomatic cholelithiasis (1% to 3%) will develop acute cholecystitis and cholangitis (Jensen 1991). About 5% to 15% of people who present with acute calculous cholecystitis have associated common bile duct stones (de Mestral 2013). The incidence of cholecystitis varies depending on the underlying pathology, nutritional status, age, and immune function of the person (Ecoffey 1987). The incidence of acalculous cholecystitis is not well-defined and it is typically seen in mostly elderly, critically ill men who are hospitalised (Savoca 1990; Ganpathi 2007; Barie 2010). In the US, approximately 6% of men and 9% of women have gallstones (Everhart 1999).

The severity of acute cholecystitis and acute cholangitis is graded following the Tokyo guidelines 2018/2013 (TG18/13) (Appendix 1; Appendix 2; Kiriyama 2013; Yokoe 2013; Kiriyama 2018; Yokoe 2018). TG18/13 severity grading for acute cholecystitis and the TG18/13 severity grading for acute cholangitis are adopted without any modification following the Tokyo guidelines 2013 (TG13) severity grading for acute cholecystitis and the TG13 severity grading for acute cholangitis (Kiriyama 2018; Yokoe 2018).

One multicentre retrospective observational study from Japan and Taiwan reported that the mean age of people presenting with acute cholangitis, diagnosed according to the TG13 diagnostic criteria and severity grading, was 68.7 (standard deviation (SD) 13.5) years for grade I, 76.3 (SD 12.1) years for grade II, and 74.7 (SD 12.8) years for grade III (Gomi 2017). In that study, 58.7% of people with acute cholangitis were male (Gomi 2017).

The most important steps in the management of acute cholecystitis and cholangitis seem to be early diagnosis (i.e. prompt recognition of the clinical presentation, adequate laboratory and microbiology assessments, and diagnostic imaging) (Zimmer 2015; Lan Cheong Wah 2017; Gomi 2018). People with acute cholecystitis and cholangitis may present clinically with Charcot’s classic triad (fever, right upper abdominal pain, and jaundice) and leukocytosis (Wada 2007; Wilkins 2017). More uncommon is hypotension and confusion (Reynold’s pentad), which occur in 5% to 7% of patients (Wada 2007). Elderly and immunocompromised people can present atypically (O’Connor 1982). Fever, leukocytosis, and abnormal liver function test are suggestive for acute cholecystitis and cholangitis (Attasaranya 2008). Elevations of serum alkaline phosphatases and gamma-glutamyl transpeptidase levels are detected in 90% of symptomatic people (Ancliax 1986; Caddy 2006).

Transabdominal ultrasound, biliary scintigraphy, regular or helical computed tomography, magnetic resonance cholangiopancreatography, and endoscopic ultrasound are diagnostic modalities that can support the diagnosis of acute cholecystitis and cholangitis. Computed tomography without contrast seems more sensitive than abdominal ultrasound (Indar 2002). Endoscopic retrograde cholangiopancreatography can also be a diagnostic tool when the diagnosis is strongly suspected (Palazzo 1995; Attasaranya 2008).

The mortality of a single episode of acute cholecystitis is about 3%, and the risk in a given patient depends upon the patient’s health and surgical risk (de Mestral 2013). In the 1990s, the reported worldwide mortality of severe acute cholangitis was between 11% and 27% (Lan Cheong Wah 2017). Critically ill people and people with comorbidity, such as malignancy, liver abscess, or cirrhosis, carry a poor prognosis (Gu 2014; Ahmed 2018). Emergency surgery for severe acute cholangitis results in mortality of about 20% (Lai 1990).

Acalculous cholecystitis is associated with a high mortality (Kallifas 1998). The cause of death in most people with acalculous cholecystitis is sepsis with multiorgan failure (Barie 2009).

Description of the intervention

The standard treatment of cholecystitis, especially in moderate or severe cases, is cholecystectomy (Gomi 2018). The standard treatment of cholangitis is endoscopic or percutaneous biliary drainage and decompression, especially in severe cholangitis (Lai 1990; Wilkins 2017; Gomi 2018). Intrahepatic antibiotics, fluid resuscitation, correction of coagulopathy and metabolic derangements, and analgesia are also important components of medical care for adults with acute cholecystitis and cholangitis, irrespective of stone management (Attasaranya 2008; Lan Cheong Wah 2017; Wilkins 2017). Administration of intrahepatic antibiotics in acute cholecystitis and cholangitis may limit both the local inflammation and systemic septic response, to prevent surgical site infections in the superficial wound, fascia, or organ space, and to
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of antibiotics with categories and subcategories exist. Antibiotics intervention after antibiotics therapy (van Dijk 2016). Various types had recurrence of symptoms and required an emergency surgical therapy for acute calculous cholecystitis found that 20% of patients prevent complications (Gomi 2018). The meta-analysis of antibiotic therapy for acute calculous cholecystitis found that 20% of patients had recurrence of symptoms and required an emergency surgical intervention after antibiotics therapy (van Dijk 2016). Various types

• Penicillins, the first and earliest type of antibiotics, can be administered orally or intravenously. Penicillins are generally well tolerated, but they may cause an allergic reaction: anaphylactic shock is the most frequent and serious problem, observed in 0.05% of people treated with penicillins (Wright 1983; Gladtke 1984; Katzung 2018). Extended-spectrum penicillins (ampicillin, amoxicillin, piperacillin, and ticarcillin) are available in combination with some beta-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) (Katzung 2018). Beta-lactamase inhibitors can be administered intravenously except for clavulanic acid, which should be administered orally. Gastrointestinal disorders and seizures, especially in renal failure or with high doses, have been reported as adverse effects for clavulanic acid and sulbactam (Bush 1988; Katzung 2018).

• Cephalosporins can be administered orally or intravenously. They are similar to penicillins and have a wide spectrum of activity, especially strains of Escherichia coli and Klebsiella species (Xu 2011; Katzung 2018). Cephalosporins can have a variety of hypersensitivity allergic and neurotoxic reactions, including anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, or haemolytic anaemia (Gladtke 1984; Katzung 2018). Rash is the most common adverse event, followed by anaphylactoid reaction (Katzung 2018).

• Carbapenems (e.g. ertapenem, imipenem, meropenem, doripenem) can only be administered intravenously. They are considered safe and efficacious against multiresistant bacterial infections. Carbapenem resistance itself has become of increased concern (Zahnel 2007; Galal 2010; Katzung 2018). Carbapenems are indicated for infections caused by susceptible organisms that are resistant to other available drugs (e.g. Pseudomonas species), and for treatment of mixed aerobic and anaerobic infections (Katzung 2018). Carbapenems are effective against bacteria that produce ESBLs and are resistant to penicillins, cephalosporins, and monobactams (Moczgema 2004; Katzung 2018). The most common adverse effects of carbapenems are gastrointestinal disorders, such as nausea, vomiting, and skin rash; and reactions at the infusion sites (Katzung 2018).

• Quinolones (e.g. ciprofloxacin, ofloxacin, enoxacin, perfloxacin, moxifloxacin, and levofloxacin) are all synthetic antibiotics, for oral and intravenous use. They are considered a good choice against nosocomial acute cholecystitis and cholangitis (Tanaka 2007; Salvador 2011; Sun 2016). Gastrointestinal effects are the most common adverse events for all fluoroquinolones (Rubinstein 2001). Adverse effects such as risk of tendon rupture, prolongation of the QT interval on the electrocardiogram, and arrhythmia have been reported for all quinolones (Norby 1991).

• Glycopeptides were designed only for intravenous administration, but in recent years, oral administration was approved for the treatment of clostridium difficile-associated diarrhoea (Katzung 2018). Glycopeptide use is limited to infections caused by beta-lactam resistant bacteria because of the risk of toxicity affecting kidneys and inner ears (Török 2009; Katzung 2018). Another more common reaction is the ‘red man’ syndrome which is defined as flushing, erythema, and pruritus on the face, neck, and upper torso (Katzung 2018).

• Aminoglycosides (e.g. streptomycin, gentamicin, neomycin) are used mostly in combination with a penicillin or cephalosporin or carbapenem in serious infections with gram-negative bacteria, and in combination with a penicillin or cephalosporin or carbapenem or vancomycin in infections with gram-positive bacteria and in nosocomial infections involving multiresistant organisms such as Pseudomonas species and ESBL producing gram-negative bacteria (Tanaka 2007; Salvador 2011; Sun 2016; Katzung 2018). Aminoglycosides can be administered intravenously or orally (Mingeot-Leclercq 1999). The associated adverse effects are inner ear and renal toxicity (Baykal 1986).

• Metronidazole is frequently used in the treatment of serious infections due to anaerobic bacteria (Brogden 1978). Metronidazole can be administered orally or intravenously (Stranz 1981). The drug has excellent bioavailability and good penetration in most tissues, including the cerebrospinal fluid and brain abscess contents (Falagas 1995). The most common adverse reactions are diffuse gastrointestinal symptoms, reported in 5% to 10% of people during administration of this drug (Bruce 1971). Classical adverse effects are metallic taste in the mouth and dark-coloured urine (Bruce 1971).

Table 1 shows a summary of the antibiotics used in adults with acute cholecystitis and cholangitis. Some of these antibiotics have activity against a narrow range of potential pathogens, some have additional specific anaerobic activity, and some have broad activity against potential pathogens (Katzung 2018). Empirical findings have impacted the choice of treatment for adults with acute cholecystitis and cholangitis (Paterson 2006). The usual interventions consist of antibiotics, such as penicillins, cephalosporins (with or without metronidazole), carbapenems, or fluoroquinolones (Shenoy 2014; Gomi 2018). In the case of multiresistant organisms, antibiotics such as antipseudomonal agents, carbapenems, or glycopeptides are theoretically considered to be required (Gomi 2018).

How the intervention might work

Antibiotics, in general, aim at inhibiting or killing the growth of bacteria.

Three groups of penicillins work mostly against gram-positive, gram-negative bacteria, and against Pseudomonas species. Group I penicillins (e.g. penicillin G) present with a wide spectrum of bactericidal activity; group II antistaphylococcal penicillins (e.g. nafcillin) are resistant to staphylococcal beta-lactamases and have antistaphylococci and antistreptococci actions; group III extended-spectrum penicillins are less active against gram-positive and anaerobic organisms than penicillin G, but they have much greater efficacy against gram-negative species (Katzung 2018). Penicillins prevent bacterial cell wall synthesis by binding to, and inhibiting, cell wall transpeptidases. Beta-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam, and avibactam) have very weak antibacterial activity, but they can protect some penicillins from inactivation by beta-lactamase enzymes with hydrolytic capabilities (Bush 1988; Jacoby 2005; Bush 2016; Katzung 2018).

Cephalosporins inhibit bacterial growth by interfering with the transpeptidation reaction of bacterial cell-wall synthesis and rapid bactericidal activity against susceptible bacteria (Török 2009;
Katzung 2018). There are five generations of cephalosporins: the first generation (e.g. cefalexin, cefazolin, cefalotin) is said to have moderate-spectrum activity against gram-positive bacteria, such as streptococci and staphylococci; the second generation (e.g. cefaclor, cefuroxime, and cefotetan) are less effective against gram-positive but are more effective against gram-negative bacteria than the first generation; and the third generation (e.g. cefotaxime, ceftriaxone, cefixime) have broad-spectrum activity against gram-negative bacteria (Marshall 1999). Cefazidime is the only agent with broad spectrum of Pseudomonas species activity (Shi 2013; Katzung 2018). The fourth generation of cephalosporins (e.g. ceftazime, ceftaroline, cefzolate) are considered broad spectrum antibiotics, with enhanced activity against gram-positive bacteria and beta-lactamase stability. The fifth generation is said to destroy bacteria of the genus Pseudomonas and is less susceptible to development of bacterial resistance (Tórök 2009).

Carbapenems are stable antibiotics (Galal 2010), with potent bactericidal activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Mechanism of action prevents bacterial cell-wall synthesis by binding to and inhibiting cell-wall transpeptidases (Moczygemba 2004; Katzung 2018).

Quinolones have a broad spectrum of bactericidal activity and block bacterial deoxyribonucleic acid (DNA) synthesis (Karachalios 1996; Katzung 2018).

Glycopeptides (e.g. vancomycin, teicoplanin) have a similar mechanism of action as penicillin or cephalosporin or carbapenem antibiotics and their bactericidal activity against the bacterial wall synthesis of gram-positive bacteria (Tórök 2009; Katzung 2018).

Aminoglycosides inhibit protein synthesis of gram-negative bacteria (Mingeot-Leclercq 1999), and bactericidal activity against susceptible bacteria (Katzung 2018).

Metronidazole is a synthetic nitroimidazole, with efficacy against common anaerobic bacteria (Brogden 1978; Stranz 1981).

Why it is important to do this review

If adults with acute cholecystitis or cholangitis or both are not appropriately treated in a timely fashion, the diseases can be fatal (Gomi 2018). The Tokyo 2018 international practice guidelines for treatment of people with acute cholecystitis and cholangitis recommend empirical antimicrobial therapy before the infecting bacteria are identified (Yoshida 2007; Salvador 2011; Gomi 2018). These guidelines are based on a systematic literature review of articles from PubMed, the Cochrane Database of Systematic Reviews, and Cochrane Controlled Register of Trials (CENTRAL) (Gomi 2018).

Appendix 3 and Appendix 4 show the Tokyo 2018 guidelines for antimicrobial recommendations for acute biliary infections.

One meta-analysis on antibiotics as initial treatment of acute calculus (stone-associated) cholecystitis published in 2016 included 10 randomised clinical trials, four prospective observational studies, and 10 retrospective observational studies (van Dijk 2016). Only one randomised clinical trial compared antibiotic treatment versus a conservative strategy without antibiotics (van Dijk 2016). The meta-analysis concluded that the methodological quality of the included studies was poor to moderate (van Dijk 2016). Risk of bias was high in most studies, and all but three studies had a low level of evidence (van Dijk 2016). A total of 5830 participants were included in the meta-analysis, of whom 2997 underwent early cholecystectomy, 2791 obtained initial antibiotic treatment, and 42 were treated conservatively without antibiotics (van Dijk 2016). It seems that this meta-analysis has several weaknesses among which is lack of a prepublished protocol; included studies published only after 1985; the review authors included both randomised clinical trials and observational studies, which make it difficult to assess benefits; and they excluded studies with patients in intensive care units. The meta-analysis did not take into account risks of random errors either. We could not find any further meta-analysis or systematic reviews on antibiotics for acute cholecystitis or any meta-analysis or systematic review for acute cholangitis.

Because of the vast number of antibiotics and concurrent increased resistance to them, we need to determine their benefits and harms when administered to adults with cholecystitis or cholangitis, or both. We also hope that the results of our review can provide valid information for the existing clinical guidelines when they are updated. Moreover, our systematic review will be able to inform what randomised clinical trials should be conducted in the future, in case we identify gaps.

OBJECTIVES

To assess the benefits and harms of antibiotics treatment versus placebo, no intervention, or another antibiotic for people with cholecystitis or cholangitis, or both.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials assessing the benefits and harm of antibiotics in the treatment of cholecystitis or cholangitis, or both. We will consider the trials for inclusion no matter the publication type, publication status, language, and outcomes assessed or reported.

Types of participants

Adults (at least 18 years old) of both sexes with diagnosis of cholecystitis or cholangitis, or both. The diagnosis of cholecystitis should be based on either clinical and laboratory parameters or on diagnostic imaging findings in accordance with the American College of Radiology, or both (Yarmish 2014). The diagnosis of cholangitis could be based on clinical diagnostic criteria (Charcot’s triad, Reynolds pentad, or recommendations provided in the Tokyo guidelines for the diagnosis and treatment of acute cholangitis) and positive microbiological cultures of bile cultures and gallbladder bile for cultures, or both (Lee 2009). Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis (Gomi 2018).

We will exclude randomised clinical trials including children and adolescents. The epidemiology, aetiology, pathogenesis, prognosis, and therapeutic management of paediatric acute cholecystitis or acute cholangitis significantly differ from adults (Prashanth 2012; Svensson 2012; Poddighe 2015; Poddighe 2018).
However, we will include randomised clinical trials including adults and children if adult only data are available.

### Types of interventions

**Experimental intervention**
- Any antibiotic used for treatment of cholecystitis or cholangitis, or both.

**Control intervention**
- Placebo or no intervention.
- Another antibiotic or another antibiotic regimen.

The antibiotics could have been administered at any dose, mode of administration, and duration.

We will allow cointerventions if they were administered equally to all intervention groups.

### Types of outcome measures

**Primary outcomes**
- All-cause mortality.
- Proportion of participants with one or more serious adverse events. Serious adverse events are defined as any untoward medical occurrence that led to death; was life-threatening; required hospitalisation or prolongation of hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might have jeopardised the person (ICH-GCP 1997).
- Health-related quality of life measured by any validated continuous scale.

**Secondary outcomes**
- Sepsis (as defined by trialists).
- Proportion of participants with one or more adverse events considered as non-serious. All adverse events that did not fulfil the criteria listed under serious adverse events will be considered non-serious.

**Exploratory outcomes**
- Proportion of participants with acute cholecystitis or acute cholangitis, or both without clinical response to the antibiotic treatment. Failure of antibiotic treatment will be defined as presence of infection, or recurrence, or progression of disease (e.g. need for delayed biliary drainage or endoscopic treatment or percutaneous treatment or surgery due to failure of therapy (or a combination of these); acute pancreatitis, endocarditis, liver abscess) during or after treatment.
- Length of hospital stay.
- Participant-reported outcomes (e.g. pain).
- Individual serious adverse events or complications.
- Individual adverse events considered non-serious.
- Need for biliary drainage or endoscopic treatment or percutaneous treatment or surgery (type, timing, and outcome) (or a combination of these). Such surgical interventions may both be considered important confounders for the further follow-up of the participant as well as outcomes of the antibiotics administered.

We will assess all outcomes at maximum follow-up.

### Search methods for identification of studies

#### Electronic searches

We will search The Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web), CENTRAL in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index – Science (Web of Science) (Royle 2003). We will apply no language, year, or document type restrictions. Appendix 5 shows the preliminary search strategies with the expected time spans of the searches.

#### Searching other resources

We will identify additional references by manually searching the references of articles from the computerised databases. We will also search online trial registries such as ClinicalTrials.gov (clinicaltrials.gov), the European Medicines Agency (EMA) (www.ema.europa.eu), the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/), and the Food and Drug Administration (FDA) (www.fda.gov/) for ongoing or unpublished trials. We will contact experts in the field and pharmaceutical companies to enquire about additional trials. We will search for grey literature in the System for Information on Grey Literature in Europe OpenGrey (www.opengrey.eu/).

### Data collection and analysis

We will conduct our review according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019). We will perform analyses using Review Manager Web (RevMan Web), and we will use Trial Sequential Analysis in sensitivity analysis (Thorlund 2011; TSA 2011; Wetterslev 2017). We will use a preplotted data extraction form created in Excel and present a table describing the types of serious adverse events reported in each trial. We will tabulate the types of adverse events (serious and non-serious) that are reported in the non-randomised studies retrieved only with the searches for the randomised trials. However, this will limit the information on harms in our systematic review. If benefits of certain antibiotics are found, then systematic reviews of harms, based on observational studies, should be conducted (Storebø 2019).

### Selection of studies

Two review authors (SG and FM) will independently read the electronic search output, perform additional manual searches, and list potentially eligible trials. If there are any disagreements, we will consult a third person (AF or GP). Two review authors (SG and FM) will read the potentially eligible trials and participate in the final selection of trials for inclusion. We will solve any disagreement through discussion, or, if necessary, by consulting a third person (AF or GP). For trials described in more than one publication, we will select the paper with the longest duration of follow-up as our primary reference. We will list details of all the included studies in the 'Characteristics of included studies' table, and all the excluded trials with the reasons for their exclusion in the 'Characteristics of excluded studies' table. We will describe the process of selecting studies for inclusion in the review (PRISMA 2009).
Where studies have multiple publications, we will collate the reports of the same study so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

Data extraction and management

Two review authors (SG, FM) will independently extract data. SG and FM will discuss any disagreement regarding the extracted data. If no agreement can be reached, a third author (AF or GP) will serve as arbitrator. We will contact authors of the published trials in case of missing information.

We will gather the following data from each study.

Characteristics of trials:
- date, location, and setting of trial;
- publication type, status, and trial design;
- case definitions used (clinical, serological, bacteriological);
- sponsor of trial (known or unknown; for profit or not for profit);
- trial inclusion and exclusion criteria;
- trial duration.

Characteristics of participants:
- number of participants recruited;
- number of participants excluded;
- total number of participants randomised to each intervention group;
- number of withdrawals/dropouts in each intervention group with reasons;
- protocol violation;
- missing data;
- demographic and other characteristics (e.g. age, sex, ethnicity, country, comorbidities);
- definitions, any diagnostic criteria and methods for diagnosis of cholecystitis or cholangitis or both.

Characteristics of interventions:
- number of intervention groups;
- type of antibiotic, dose, mode of administration, schedule, number of days that antibiotic treatment was provided, length of follow-up (in days) in any of the trial groups;
- description of placebo or no intervention;
- length of follow-up.

Outcome data:
- number of participants included in the analysis;
- number of participants with events for binary outcomes, mean and SD for continuous outcomes, number of events for count outcomes;
- definition of outcomes or scale used if appropriate;
- risk of bias.

Assessment of risk of bias in included studies

Two review authors (SG, FM) will independently assess the risk of bias in the included studies. If a discrepancy between the two review authors occurs and no agreement can be reached, a third review author will arbitrate. We will assess risk of bias according to the Cochrane ‘Risk of bias’ tool as described below (Higgins 2011), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: study authors performed sequence generation using computer random number generation or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the study. In general, we will classify risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (e.g. use of interactive voice response system).
- Unclear risk of bias: study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We will exclude these studies for assessment of benefit.

Allocation concealment

- Low risk of bias: participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. Investigators are unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: study authors did not describe the method used to conceal the allocation, so intervention allocations may have been foreseen before or, during, enrolment.
- High risk of bias: it is likely that investigators who assigned participants knew the allocation sequence. We will exclude these studies for assessment of benefit (i.e. known as quasi-randomised studies).

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or rarely, no blinding or incomplete blinding; but review authors judged that the outcome was not likely to be influenced by lack of blinding (Savović 2012a; Savović 2012b).
- Unclear risk of bias: either of the following: insufficient information to permit judgment of ‘low risk’ or ‘high risk’; or the trial did not address this outcome.
- High risk of bias: either of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely, no blinding of outcome assessment, but review authors judged that the outcome measurement was not likely to be influenced by lack of blinding (Savović 2012a; Savović 2012b).
• Unclear risk of bias: either of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.

• High risk of bias: either of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

**Incomplete outcome data**

• Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.

• Unclear risk of bias: information was insufficient to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.

• High risk of bias: results were likely to be biased due to missing data.

**Selective outcome reporting**

• Low risk of bias: the trial reported the following predefined primary outcomes: all-cause mortality, serious adverse events, and sepsis. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.ClinicalTrials.gov), the outcomes sought were those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.

• Unclear risk of bias: not all predefined or clinically relevant and reasonably expected outcomes were reported fully, or it was unclear whether or not data on these outcomes were recorded.

• High risk of bias: all-cause mortality or one or more predefined outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

**Overall bias risk assessment**

• Low risk of bias: all domains in a trial are classified at low risk of bias according to the definitions described above.

• High risk of bias: one or more of the bias domains in a trial are classified at unclear or high risk of bias.

**Assessing risk of bias in cluster-randomised trials**

In cluster-randomised trials, additional biases that we will consider are: recruitment bias; baseline imbalance; loss of clusters; incorrect analysis; and comparability with individually randomised trials (Higgins 2011).

We will generate a 'Risk of bias' graph and 'Risk of bias' summary to show a summary of this assessment.

**Measures of treatment effect**

**Dichotomous data**

We will calculate the risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous variables.

---

**Continuous data**

We will impute the SD from P values for continuous outcomes according to guidance given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If the data are likely to be normally distributed, we will use the median for meta-analysis when the mean is not available. If it is not possible to calculate the SD from the P value or the CIs, we will impute the SD using the largest SD in other trials for that outcome. We will calculate the mean difference (MD) (if all outcomes are measured on a similar scale, or the standardised mean difference (SMD) if the outcomes are measured on different scales) with 95% CIs. We will re-express the SMD using a general guide according to a variation of Cohen’s interpretation of effect size and interpret it with caution: less than 0.40 represents a small effect; 0.40 to 0.70 represents a moderate effect; and greater than 0.70 represents a large effect (Cohen 1988). If the SMD are dominated by one way of assessing the outcome, we will back calculate the SMD to the MD of that outcome.

**Unit of analysis issues**

Participants as randomised to the intervention groups. In the trials with two parallel groups design, we will compare the experimental antibiotic intervention group versus the control group consisting of placebo, or no intervention, or another antibiotic. In the trials with a parallel group design with more than two intervention groups, we will split the shared control group (Higgins 2019).

In case of trials with a cross-over design, we will include the data from the first trial period in order avoid residual effects from the treatment (Higgins 2019). In order to avoid repeated observations on trial participants, we will use participant trial data at the longest follow-up (Higgins 2019).

We will analyse cluster randomised trials using the procedures referenced in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019). Where results did not control for clustering, we will contact trial authors to request an estimate of the intracluster correlation coefficient (ICC). If the trial authors are unable to provide an ICC, we will calculate the ICC using design effects (Kippin 2004).

**Dealing with missing data**

We will perform an intention-to-treat analysis whenever possible. Otherwise, we will use the data that are available to us (e.g. a trial may have reported only 'per-protocol' analysis results), or if additional data are received from the trialists. As 'per-protocol' analyses may be biased, we plan to conduct best–worst case scenario analysis (good outcome in intervention group and bad outcome in control group) and worst–best case scenario analysis (bad outcome in intervention group and good outcome in control group) for our dichotomous primary outcomes only as sensitivity analyses, whenever possible (Hollis 1999). These analyses are defined as follows.

- Best–worst case scenario: none of the dropouts/participants lost from the experimental group, but all of the dropouts/participants lost from the control group experienced the outcome, including all randomised participants in the denominator.
- Worst–best case scenario: all dropouts/participants lost from the experimental group, but none from the control group.
experienced the outcome, including all randomised participants in the denominator.

For our continuous primary outcomes, we will conduct beneficial outcome (group mean plus two SD of the group mean) and harmful outcome (group mean minus two SD of the group mean) scenario analyses (Jakobsen 2014).

Assessment of heterogeneity
We will assess the presence of clinical heterogeneity by comparing effect estimates of different aetiologies for acute cholecystitis and cholangitis, severity of the disease, presence of other comorbidity, treatment applied to control infection, and based on coninterventions. We will assess methodological heterogeneity by comparing intervention effect in trials at low risk of bias to that of trials at unclear or high risk of bias (i.e. trials that lack one or more adequate domain) (Schulz 1995; Kjaergard 2001).

We will primarily inspect forest plots visually in order to assess if there are signs of statistical heterogeneity (Higgins 2019). We will also assess statistical heterogeneity using the Chi² test with significance set at a P value of less than 0.10 and measure the quantities of heterogeneity using the I² statistic (Higgins 2019).

Assessment of reporting biases
We will construct funnel plots of the primary outcomes for a visual assessment of whether treatment estimates are associated with study size, provided that the trials are sufficiently similar in terms of participants, interventions, comparators, and outcome assessment. We will use two tests to assess funnel plot asymmetry: adjusted rank correlation test and regression asymmetry test (Begg 1994; Egger 1997).

Data synthesis

Meta-analysis
We will conduct the systematic review according to recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019). We will meta-analyse data using Review Manager Web (RevMan Web).

Subgroup analysis and investigation of heterogeneity
We will assess the differences in the effect estimates between the following subgroups.

- Trials at low risk of bias compared to trials at high risk of bias (trials at high risk of bias may overestimate or underestimate the intervention effect).
- Trials at low risk of for-profit bias compared to trials at high risk of for-profit bias as these trials tend to overestimate the benefits and harms of an intervention (Lundh 2017).
- Severity of cholecystitis or cholangitis (grade I, grade II, and grade III or similar) (adults with mild cholecystitis or cholangitis may have a self-limiting process and may overestimate or underestimate the intervention effects).
- Aetiology of cholecystitis or cholangitis (stones compared to no stones) (the presence of gallstone disease may overestimate or underestimate the intervention effect).
- Type of antibiotic used for treatment because antibiotics may differ in benefits and harms in the treatment of cholecystitis or cholangitis.
- Dosage or duration of interventions. We will stratify the comparisons according to median dosage and median duration.
- Presence compared to absence of pretreatment complications (e.g. acute pancreatitis, liver abscess, endocarditis, septic shock).

Sensitivity analysis
In addition to the sensitivity analysis described in the Dealing with missing data section, we will perform sensitivity analysis on trials at low risk of bias. We also plan to assess imprecision with Trial Sequential Analysis (see below), using also the eight-step procedure for validation of meta-analytic results in systematic reviews as suggested by Jakobsen and colleagues (Jakobsen 2014).

Trial Sequential Analysis
Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). Therefore, Trial Sequential Analysis (TSA 2011) can be applied as a secondary analysis to control this risk (Thorlund 2011; Thomas 2019). We will use Trial Sequential Analysis as a sensitivity analysis to our GRADE assessments of imprecision. The former is taking meta-analytic model and diversity into consideration whereas the latter is based on a fixed-effect model and ignores diversity. The required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) can be calculated in order to control random errors (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction, and the heterogeneity of the meta-analysis (Wetterslev 2008; Wetterslev 2009; Turner 2013; Wetterslev 2017). Trial Sequential Analysis enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the required information size, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Wetterslev 2008).

If the trial sequential monitoring boundary is crossed by the cumulative Z-curve before reaching the required information size, we may conclude that sufficient evidence is collected to validly assess benefit or harm, and that inclusion of additional trial data may be redundant. In contrast, if the boundaries for benefit or harm are not crossed, we may conclude that further trials are necessary before a certain intervention effect can be evaluated. Trial Sequential Analysis also allows for assessment of the sufficiency of evidence for a postulated intervention effect. A lack of effect is evident if the cumulative Z-score crosses the trial sequential monitoring boundaries for futility.

We will make relatively conservative estimations of the anticipated intervention effect to control the risks of random error (Jakobsen 2014). Large anticipated intervention effects lead to small required information sizes, and the thresholds for significance will be less strict after the information size has been reached (Jakobsen 2014).

We will analyse all primary and secondary outcomes using Trial Sequential Analysis. These analyses will allow us to calculate the Trial Sequential Analysis-adjusted CIs based on the following assumptions.
Primary outcomes
We will estimate the diversity-adjusted required information size (Wetterslev 2009), based on the proportion of participants with an outcome in the control group. We will use an alpha of 0.025 because of our three primary outcomes, a beta of 10%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014; Castellini 2017).

As anticipated intervention effects for the primary outcomes in the Trial Sequential Analysis we will use the following.

- All-cause mortality: a relative risk reduction of 10% and the observed proportion of mortality in the control group.
- Serious adverse events: a relative risk reduction of 20% and the observed proportion of serious adverse events in the control group.
- Health-related quality of life: minimal relevant difference observed SD divided by two.

Secondary outcomes
We will estimate the diversity-adjusted required information size (Wetterslev 2009), based on the proportion of participants with an outcome in the control group when analysing dichotomous outcomes, and we will use the observed SD when analysing continuous outcomes. We will use an alpha of 0.033 because of the two secondary outcomes, a beta of 10%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014; Castellini 2017).

As anticipated intervention effects for the secondary outcomes in the Trial Sequential Analysis, we will use the following relative risk reductions or increases.

- Sepsis: a relative risk reduction of 20% and the observed incidence of failure treatment in the control group.
- Non-serious adverse events: a relative risk reduction of 20%.

Assessment of imprecision
In order to have a better judgement of imprecision in the included trials, we will compare GRADE and Trial Sequential Analysis results regarding our Primary outcomes and Secondary outcomes (Castellini 2018; Gartlehner 2018; Thomas 2019).

Assessment of significance
We will assess the intervention effects using the random-effects model meta-analysis (DerSimonian 1986). For analysis of the three primary outcomes, we will consider significant a P value less than 0.025 (Jakobsen 2014), as this will secure a family-wise error rate (FWER) below 0.05. We will apply an eight-step procedure to assess if the results from the meta-analyses have passed the thresholds for significance (Jakobsen 2014).

We may perform further sensitivity analysis if deemed necessary (Higgins 2019).

'Summary of Findings' tables
Two review authors (SG, FM) will create ‘Summary of Findings’ tables for all clinically relevant outcomes (all-cause mortality, serious adverse events, health-related quality of life, sepsis, and non-serious adverse events) reported in the review using GRADE Interactive software (GRADEpro GDT). If a discrepancy between the two review authors occurs and no agreement is reached, a third review author will arbitrate.

The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The certainty of a body of evidence considers within-study risk of bias (methodological quality), indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimates (wide CIs), and a high probability of publication bias (Balsch 2011; Mustaf 2013). We will define the levels of certainty of evidence as ‘high’, ‘moderate’, ‘low’, or ‘very low’. We will explain decisions to upgrade or downgrade the evidence in footnotes.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Acknowledgements
A new team of authors was formed in late 2018 to overtake an abandoned review protocol by Kukuruzovic and colleague, and we thank the authors of this protocol (Kukuruzovic 2002). We also thank Sanchez-Jimenez and colleagues who inspired us with their protocol entitled “Antibiotic prophylaxis versus placebo or no intervention for people with cirrhosis and variceal bleeding” (Sanchez-Jimenez 2018). The first two authors (FM and SG) thank Marija Barbateskovic for counselling on the development of protocols and assistance during our stay in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. We thank Sarah Louise Klingenberg for designing search strategies.

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Disclaimer: the views and opinions expressed in this protocol are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

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Antibiotics for adults with acute cholecystitis or acute cholangitis or both (Protocol)

Gomi 2018
Gomi 2017
Gladtke 1984
Gartlehner 2018
Gomi 2010
Falagas 1995
Galal 2010
Ganpathi 2007
Gartlehner 2015
Gladtke 1984
Gomi 2017
Gomi 2018

Ecoffey 1987
Egger 1997
Everhart 1999
Falagas 1999
Ecoffey 1987


GRADEpro GDT [Computer program]

Gu 2014

Hanau 2000

Higgins 2011

Higgins 2019

Hollis 1999

ICH-GCP 1997

Indar 2002

Ishii 2008

Ishii 2011
Mustafa 2013

Norby 1991

O’Connor 1982

Palazzo 1995

Paterson 2005

Paterson 2006

Peirano 2012

Poddighe 2015

Poddighe 2018

Prashanth 2012

PRISMA 2009

RevMan Web [Computer program]

Rubinstein 2001

Salvador 2011

Sanchez-Jimenez 2018

Savoca 1990

Savović 2012a

Savović 2012b

Savović 2018
Schulz 1995

Shapiro 1994

Shenoy 2014

Shi 2013

Storebe 2018

Stranz 1981

Sun 2016

Sung 2012

Svensson 2012

Tanaka 2007

Thomas 2019

Thorlund 2009

Thorlund 2010

Thorlund 2011

TSA 2011 [Computer program]

Turner 2013

Török 2009

van Dijk 2016

Wada 2007

Wetterslev 2008
Table 1. Antimicrobial recommendations for acute biliary infections (Tokyo guidelines 2013) (modified according to severity)

<table>
<thead>
<tr>
<th>Grade I (mild)</th>
<th>Grade II (moderate)</th>
<th>Grade III (severe)</th>
<th>Healthcare-associated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial agents</strong></td>
<td><strong>Ampicillin/sulbactam is not recommended without an aminoglycoside; cefazolin; cefotiam; cefuroxime; ceftriaxone; cefotaxime ± metronidazole.</strong></td>
<td><strong>Piperacillin/tazobactam; ceftaxime; cefotaxime; cefepime; ceftazidim; ciprofloxacin; levofloxacin ± metronidazole; moxifloxacin ± metronidazole; mepi- pine; ceftazidim; meropenem ± vancomycin; linezolid; dapto- mycin.</strong></td>
<td><strong>Piperacillin/tazobactam ± vancomycin; linezolid; daptomycin; ceftaxime; cefotaxime; ce- fepime; ceftazidim; metronidazole ± vancomycin; linezolid; daptomycin; imipenem/cilastin; meropenem ± vancomycin; linezolid; daptomycin; imipenem/cilastin; meropenem ± metronidazole.</strong></td>
</tr>
</tbody>
</table>

**References to other published versions of this review**

Kukuruzovic 2002

Antibiotics for adults with acute cholecystitis or acute cholangitis or both (Protocol)

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Table 1. Antimicrobial recommendations for acute biliary infections (Tokyo guidelines 2013) (modified according to severity) (Continued)

<table>
<thead>
<tr>
<th>Grade III (severe) acute biliary infections</th>
<th>Grade II (moderate) acute biliary infections</th>
<th>Grade I (mild) acute biliary infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin; linezolid; daptomycin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

±: with or without.

APPENDICES

Appendix 1. The Tokyo guidelines 2018/2013 severity grading of acute cholecystitis

Grade III (severe) acute cholecystitis

Grade III acute cholecystitis is associated with dysfunction of any 1 of the following organs/systems:

- cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥ 5 µg/kg per minute, or any dose of noradrenaline;
- neurological dysfunction: decreased level of consciousness;
- respiratory dysfunction: PaO₂/FiO₂ ratio < 300;
- renal dysfunction: oliguria, creatinine > 2.0 mg/dL;
- hepatic dysfunction: PT-INR > 1.5;
- haematological dysfunction: platelet count < 100,000/mm³.

Grade II (moderate) acute cholecystitis

Grade II acute cholecystitis is associated with any 1 of the following conditions:

- elevated WBC count (> 18,000/mm³);
- palpable tender mass in the right upper abdominal quadrant;
- duration of complaints > 72 hours;
- marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).

Grade I (mild) acute cholecystitis

Grade I acute cholecystitis does not meet the criteria of Grade III or Grade II acute cholecystitis. It can also be defined as acute cholecystitis in a healthy person with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

Appendix 2. The Tokyo guidelines 2018/2013 severity assessment criteria for acute cholangitis

Grade III (severe) acute cholangitis

Grade III acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction ≥ 1 of the following organs/systems:

- cardiovascular dysfunction: hypotension requiring dopamine ≥ 5 µg/kg per minute, or any dose of noradrenaline;
- neurological dysfunction: disturbance of consciousness;
- respiratory dysfunction: PaO₂/FiO₂ ratio < 300;
- renal dysfunction: oliguria, serum creatinine > 2.0 mg/dL;
- hepatic dysfunction: PT-INR > 1.5;
- haematological dysfunction: platelet count < 100,000/mm³.

Grade II (moderate) acute cholangitis

Grade II acute cholangitis is associated with any 2 of the following conditions:

- abnormal WBC count (> 12,000/mm³, < 4000/mm³);
- high fever (≥ 39 °C);
- age (≥ 75 years);
- hyperbilirubinaemia (total bilirubin ≥ 5 mg/dL);
- hypoalbuminaemia (lower limit of normal value × 0.7).

Grade I (mild) acute cholangitis

Grade I acute cholangitis does not meet the criteria of Grade III (severe) or Grade II (moderate) acute cholangitis at initial diagnosis.

FiO₂: fraction of inspired oxygen; PaO₂: partial pressure of oxygen; PT-INR: prothrombin time – international normalised ratio; WBC: white blood cell.
FiO₂: fraction of inspired oxygen; PaO₂: partial pressure of oxygen; PT-INR: prothrombin time – international normalised ratio; WBC: white blood cell.

Appendix 3. The Tokyo guidelines 2018 intravenous antimicrobial therapy recommendations for acute biliary infection

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>Community-acquired biliary infection</th>
<th>Healthcare-associated biliary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I Cholecystitis and cholangitis</td>
<td>Grade II Cholecystitis and cholangitis</td>
</tr>
<tr>
<td>Penicillin-based therapy</td>
<td>Ampicillin/sulbactam</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Cephalosporin-based therapy</td>
<td>Cefazolin, or cefuroxime, or ceftriaxone, or cefotaxime, ± metronidazole, cefmetatole, cefoxitin or flomoxef, cefoperazone/sulbactam</td>
<td>Ceftriaxone, or cefotaxime, or cefepime, or cefoperazon, ± metronidazole</td>
</tr>
</tbody>
</table>

| Carbapenem-based therapy | Ertapenem | Ertapenem | Imipenem/cilastatin, meropenem, doripenem, ertapenem | Imipenem/cilastatin, meropenem, doripenem, ertapenem |
| Monobactam-based therapy | — | — | Aztreonam ± metronidazole | Aztreonam ± metronidazole |
| Fluoroquinolone-based therapy | Ciprofloxacin, levofloxacin, pazufloxacin ± metronidazole, moxifloxacin | Ciprofloxacin, levofloxacin, pazufloxacin ± metronidazole, moxifloxacin | — | — |

±: with or without.

Appendix 4. The Tokyo guidelines 2018 oral antimicrobial therapy recommendations for acute biliary infection

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Oral antimicrobial agents for community-acquired and healthcare-associated acute cholecystitis and cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Amoxicillin/clavulanic acid</td>
</tr>
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</table>
### Appendix 5. Preliminary search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Time span</th>
<th>Search strategy</th>
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<td>(antibiotic* or ampicillin* or cefazolin* or cefepime* or cefotaxime* or cefotiam* or ceftacidim* or ceftazidim* or ceftriaxone* or cefuroxim* or cefalotin* or ciprofloxacin* or daptomycin* or imipenem* or imipenem* or imipenem* or imipenem* or levofloxacin* or linezolid* or meropenem* or metronidazole* or moxifloxacin* or piperacillin* or sulbactam* or taclobactam* or vancomycin*) AND (cholangit* or cholecystit*)</td>
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<td></td>
<td>#17 (cholangit* or cholecystit*)</td>
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</table>
Antibiotics for adults with acute cholecystitis or acute cholangitis or both (Protocol)

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(Continued)

2. exp cephalosporin derivative/
3. exp ampicillin/
4. exp ciprofloxacin/
5. exp daptomycin/
6. exp imipenem/
7. exp levofloxacin/
8. exp linezolid/
9. exp meropenem/
10. exp metronidazole/
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12. exp sulbactam/
13. exp vancomycin/
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19. 16 or 17 or 18
20. 15 and 19
21. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.
22. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23. 20 and (21 or 22)

LILACS (Bireme) 1982 to April 2020

(antibiotic$ or ampicillin$ or cefazolin$ or cefepime$ or cefotaxime$ or cefotiam$ or cef-
ta*idim$ or ceftriaxone$ or cefuroxin$ or cefalasin$ or ciprolefloxacin$ or daptomycin$ or impimonem$ or impimonem$ or impinem$ or levo-
foxin$ or metronidazole$ or linezolid$ or meropenem$ or metronidazole$ or moxi-
foxin$ or pipercillin$ or sulbactam$ or tacobactam$ or vancomycin$) [Words]
and (cholangitis$ or cholecystitis$) [Words]

Science Citation Index Expanded (Web of Science) 1900 to April 2020

#5 #4 AND #3

#4 Ti=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(cholangit* or cholecystit*)
#1 TS=(antibiotic* or Ampicillin* or cefazolin* or cefepime* or cefotaxime* or cefotiam* or ceftacidim* or ceftriaxone* or cefuroxim* or cefastin* or cilastin* or ciprofloxacin* or daptomycin* or imipenem* or imipinem* or impenem* or imipenem* or levofloxacin* or linezolid* or meropenem* or metronidazole* or moxifloxacin* or piperacillin* or sulbactam* or tacobactam* or vancomycin*)

Conference Proceedings Citation Index – Science (Web of Science) 1990 to April 2020

#5 #4 AND #3
#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(cholangit* or cholecystit*)
#1 TS=(antibiotic* or Ampicillin* or cefazolin* or cefepime* or cefotaxime* or cefotiam* or ceftacidim* or ceftriaxone* or cefuroxim* or cefastin* or cilastin* or ciprofloxacin* or daptomycin* or imipenem* or imipinem* or impenem* or imipenem* or levofloxacin* or linezolid* or meropenem* or metronidazole* or moxifloxacin* or piperacillin* or sulbactam* or tacobactam* or vancomycin*)

HISTORY
Protocol first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS
Designing the protocol: FM, SG, AF, JCJ, DN, CG, KV, GP.
Co-ordinating the protocol: DN, CG.
Writing the protocol: FM, SG.
Providing general advice on the protocol: JCJ, CG, GP.
All authors approved the current protocol version.

DECLARATIONS OF INTEREST
FM: none.
SG: none.
GP: none.
AF: none.
DN: none.
KV: none.
JCJ: none.
CG: none.

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Internal sources
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External sources
• University Hospital Centre Mostar, Bosnia and Herzegovina
• Medical School of University of Mostar, Bosnia and Herzegovina