RESEARCH STUDY PROTOCOL

1. **Project Summary**

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure used to diagnose and treat problems in the bile and pancreatic ducts. One common issue it addresses is stones in the common bile duct. However, ERCP can be risky and may lead to complications like pancreatitis, bleeding, perforation, and infections. Infections can occur in 5% to 18% of cases and are responsible for about 7.8% of deaths related to ERCP complications. To reduce infection risks, some methods have been suggested, such as using fewer contrast injections, lowering bile duct pressure, ensuring complete drainage, and using preventive antibiotics. However, the use of preventive antibiotics is debated because it can lead to antibiotic resistance, which is a growing global problem. Major medical societies recommend antibiotics only in specific cases, but the evidence supporting this is not strong. This study aims to find out if using preventive antibiotics can lower infection rates after ERCP in patients with bile duct stones.

Study aims: we designed this study to evaluate whether prophylactic antibiotic use can reduce infectious complications after ERCP in patients with common bile duct stones.

Methods: This study is expected to be conducted from December 2022 to December 2025 at 108 Military Central Hospital, Hanoi, Vietnam. Participants will be patients with bile duct stones who need ERCP but do not have cholangitis. They will be randomly assigned to one of three groups: Prophylactic Antibiotic Group: Will receive Amikacin (an antibiotic) before the ERCP procedure. Full-dose Antibiotic Group: Will receive Amikacin and a third-generation cephalosporin antibiotic from before the ERCP until hospital discharge. Control Group: Will not receive antibiotics, only normal saline. After ERCP, patients will be monitored for signs of infection through symptoms and lab tests.

Outcomes: Primary Outcome: Infectious Complications post-ERCP. Secondary Outcomes: Cholangitis, Cholecystitis, Bacteremia and Inflamatory markers.

2. **General information**

Study Title

Does Prophylactic Antibiotics Reduce Infectious complications Post Endoscopic Retrograde Cholangio Pancreatography in Common Bile Duct Stones Patients: A Clinical Trial?

Principal Investigator

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Study Site: 108 Military Central Hospital

3. **Rationale and Background Information**

Endoscopic Retrograde Cholangiopancreatography (ERCP) is an important method for diagnosing and treating biliary and pancreatic diseases, among which common bile duct stones are one of the most frequently encountered causes. However, ERCP is an invasive procedure with a high risk of complications, including acute pancreatitis, bleeding, hollow organ perforation, and infection. Among these, infectious complications occur in approximately 5% to 18% of cases and account for around 10% of ERCP-related mortality[1-3].

To minimize the risk of infection, several strategies have been proposed, such as limiting the injection of contrast into the bile duct, aspirating bile to reduce biliary pressure, ensuring complete biliary drainage, and using prophylactic antibiotics[4]. However, the clinical effectiveness of prophylactic antibiotic use remains controversial. A meta-analysis by Cochrane et al. (2010) showed that prophylactic antibiotics can reduce the risk of bacteremia and cholangitis[5]. In contrast, a more recent meta-analysis by Maria Fernanda Shinin Merchan (2022), along with several other studies, suggested that prophylactic antibiotics may reduce the rate of bacteremia but do not significantly decrease the incidence of cholangitis, sepsis, post-ERCP pancreatitis, or mortality[6-8].

Rational antibiotic use remains a significant challenge for clinicians, as broad-spectrum antibiotic treatment can lead to unnecessary costs and contribute to the growing problem of antibiotic resistance—a serious global health concern causing approximately 700,000 deaths annually and an estimated economic burden ranging from 1 to 3.4 trillion USD. This figure continues to rise[9-11].

According to guidelines from major organizations such as the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE), routine prophylactic antibiotic use is not recommended, except in cases of incomplete biliary drainage or in immunocompromised patients. However, these recommendations are based on low-quality evidence and remain weak in strength.

Therefore, we designed this study to evaluate whether prophylactic antibiotic use can reduce infectious complications after ERCP in patients with common bile duct stones.

4. Objectives

To evaluate whether prophylactic antibiotic use can reduce infectious complications after ERCP in patients with common bile duct stones.

5. Study Design

Interventional Study, open-label, randomized controlled trial.

6. Methodology

- Eligibility

Participant inclusion criteria:

• Patients ≥ 18 years with common bile duct stones are diagnosed by abdominal ultrasound, endoscopic ultrasound, CT scan, or abdominal MRI.

• No signs of cholangitis at the time of admission, defined by the following criteria:

+ Non fever (temperature < 37°C)

+ White blood cell count between 4 G/L and 10 G/L

• Good general condition, classified as ASA Physical Status I or II

Participant exclusion criteria:

• Patients with severe coagulopathy (INR > 1.5 or platelet count < 50 G/L)

Patients with severe systemic illnesses, such as unstable myocardial infarction, respiratory failure, or circulatory failure

• Patients with duodenal perforation or failed ERCP due to inability to access the papilla

• Patients with active infections in other organ systems requiring antibiotic therapy

• Patients have received any systemic antibiotics within 48 hours prior to the ERCP procedure

• Patients are allergic to antibiotics used in the study.

- **Interventions**

Patients with common bile duct stones without signs of cholangitis at the time of hospital admission. Patients have an indication for ERCP stone extraction and randomly assigned to one of three study groups by using a simple randomization method in which the remainder of their record number divided by 3 determined the group allocation.

•*Control Group: No Antibiotics Group (Group 1)*

+ Medication: normal saline

+ Administration: No antibiotics administered. Patients will receive an intravenous infusion of normal saline on the day of the procedure.

•*Prophylactic Antibiotic Group (Group 2)*

+ Medication: Amikacin

+ Administration: Amikacin at a dose of 15 mg/kg, diluted in 0.9% NaCl to a total volume of 100mL, administered via intravenous infusion over 60 minutes

+ Timing: Administered 60 minutes before ERCP procedure. For patients with renal impairment,

the Amikacin dose will be adjusted based on glomerular filtration rate (GFR).

+ Other Names: Antibiotic prophylaxis

•*Full-dose Antibiotic Group (Group 3)*

+ Medication: Amikacin + Third-generation Cephalosporine

+ Administration: Amikacin at 15 mg/kg/day in combination with Cefoperazone 2 g twice daily, administered by slow intravenous injection every 12 hours

+ Timing: From before the ERCP procedure until hospital discharge, typically lasting 4–7 days.

After undergoing ERCP, patients will be monitored for signs of infectious complications through clinical symptoms and laboratory tests within 24 to 48 hours post-procedure.

Clinical symptoms include: pulse, blood pressure, consciousness, abdominal pain, fever, jaundice, and melena.

Laboratory tests include: complete blood count and blood biochemistry (urea, creatinine, GOT, GPT, GGT, ALP, total bilirubin, direct bilirubin, CRP, procalcitonin, amylase, lipase).

Patients with high fever > 38°C will undergo blood culture and abdominal CT scan if necessary.

Patients with complications will be monitored clinically, undergo laboratory tests, and receive treatment according to guidelines until they are stable and discharged from the hospital.

- **Outcomes**

- Primary Outcome:

Infectious Complications post-ERCP: Fever > 38°C occurring within 24 to 48 hours following ERCP. [12]

- Secondary Outcomes:

+ Cholangitis: worsening right upper quadrant abdominal pain; fever (ear temperature >38.0 °C); evidence of systemic inflammation: either elevated white blood cell count (>10 G/L) or increased C-reactive protein levels (>10 mg/L), or a further rise if already above the upper normal limit (UNL) prior to ERCP; and indicators of hepatobiliary dysfunction—such as jaundice (total bilirubin >2.0 mg/dL, or worsened if pre-existing), or elevated liver enzymes (GGT, ALP, AST, ALT >1.5×UNL, or further increased if already above UNL before the procedure)[13].

+ Cholecystitis: Diagnosis was made according to the criteria of the Tokyo Guidelines 2018(TG18)[13].

+ Inflamatory markers: WBC, CRP, Procalcitonin

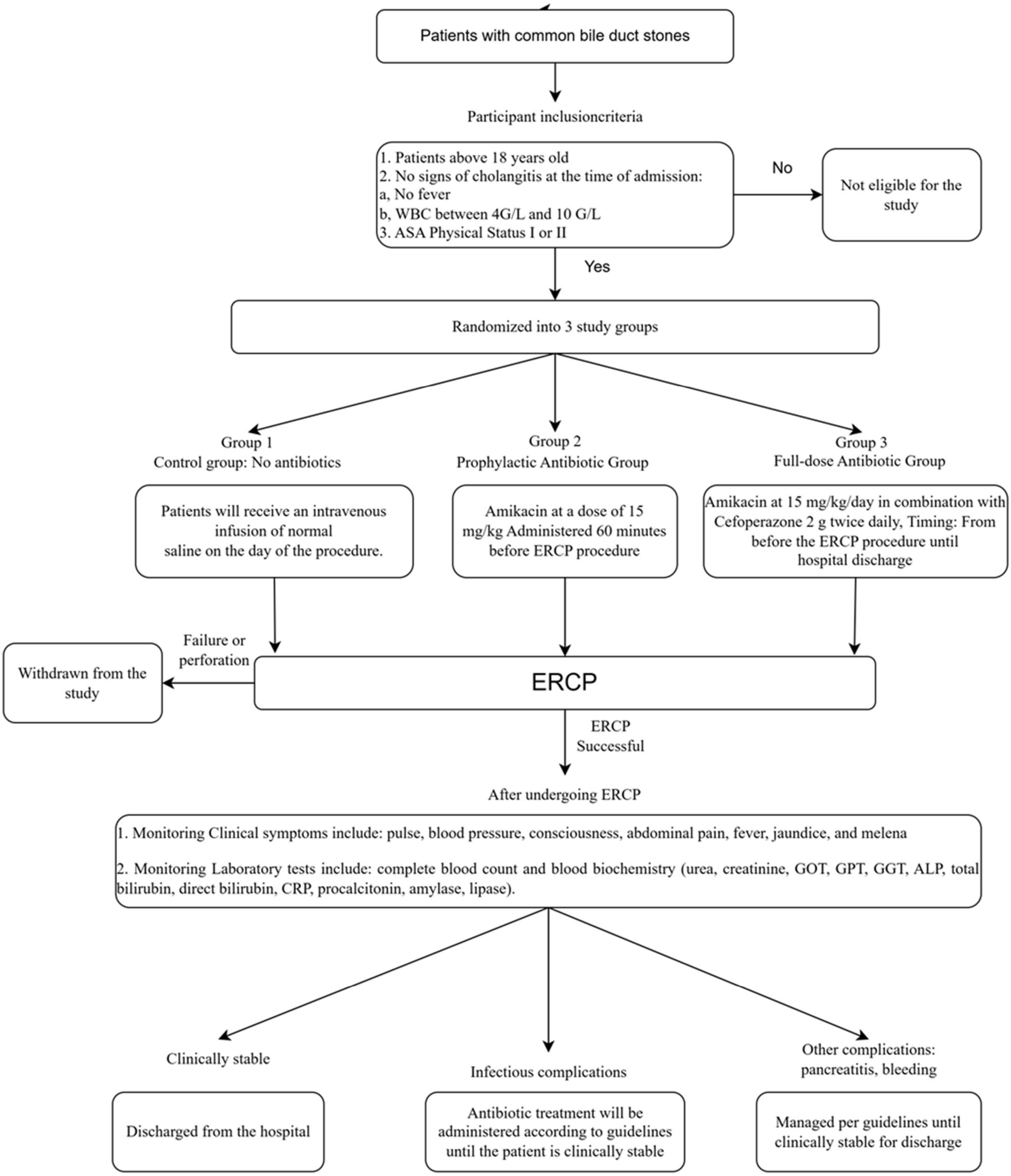
+ Bacteremia: Positive blood culture for bacteria[14]

- Other Outcomes:

+ Bleeding: Bleeding observed during the procedure or clinical signs such as melena, anemia, and a decrease in hemoglobin level exceeding 2 g/dL[15].

+ Pancreatitis: Diagnosis based on the Revised Atlanta Classification (2012)[16]

- Study flowchart



3. Safety considerations

Patients who show signs of infection after undergoing ERCP will be treated with antibiotics according to the Tokyo Guidelines 2018 and the recommendations of the Vietnamese Ministry of Health until they are stable and discharged from the hospital.

Patients who develop other complications such as acute pancreatitis or gastrointestinal bleeding will be treated according to the respective protocols for acute pancreatitis and gastrointestinal bleeding until they are stable and discharged.

Patients who experience duodenal perforation during ERCP will be withdrawn from the study and treated with endoscopic clip placement or surgery.

Patients who are admitted while awaiting ERCP and develop signs of infection with a fever >37°C will be withdrawn from the study and treated with antibiotics according to the Tokyo Guidelines 2018 and the recommendations of the Vietnamese Ministry of Health

4. Follow-up

Participants will be followed for 7 days after the ERCP procedure to monitor for adverse events, including post-ERCP pancreatitis, cholangitis, bleeding, or gastrointestinal perforation. Monitoring will be performed through daily clinical assessments during hospitalization, supported by laboratory tests (Ure, Creatinin, GOT, GPT, GGT, ALP, total bilirubin, direct bilirubin, CRP, procalcitonin, amylase, lipase and CT scan as needed) and vital signs.

For participants discharged before day 7, follow-up will continue via telephone to assess health status and identify any signs or symptoms suggestive of post-procedural complications. If concerning symptoms are reported, participants will be advised to return for medical evaluation.

All adverse events (AEs) and serious adverse events (SAEs) will be documented, managed appropriately, and reported in accordance with the study's safety protocol. Follow-up will conclude at day 7 post-ERCP unless complications arise, in which case follow-up will continue until resolution.

5. Data management and statistical analysis

- Data Management:

Study data will be collected using paper-based Case Report Forms (CRFs) and subsequently entered manually into a Microsoft Excel spreadsheet designed by the research team. Each participant will be assigned a unique study identification number (ID) to maintain confidentiality. The dataset will be encrypted and stored on a password-protected computer with access restricted to authorized study personnel.

- Statistical analysis

Data analysis will be performed using SPSS version 22.

- **Descriptive analysis**

Quantitative variables will be presented as mean and standard deviation if normally distributed, or as median and interquartile range if not normally distributed.

Qualitative variables (e.g., gender, rate of cholangitis, etc.) will be presented as frequency and percentage.

- **Comparison between groups**

Categorical variables (e.g., rate of cholangitis, mortality rate, etc.) will be compared among the three groups using the Chi-square test. If expected cell counts are small, Fisher's exact test will be used.

Continuous variables (e.g., length of hospital stay, biochemical indices, etc.) will be compared using one-way ANOVA if the data are normally distributed, or the Kruskal-Wallis test if not.

If statistically significant differences are found among the three groups, post-hoc analyses will be conducted to determine which group pairs differ. Differences between groups will be assessed using Relative Risk (RR) along with a 95% Confidence Interval (95% CI). A p-value of less than 0.05 will be considered statistically significant.

- **Sample Size Calculation**

The sample size was calculated using G*Power software (version 3.1), applying a Chi-square test (goodness-of-fit test) with the following parameters: significance level (α) = 0.05, power ($1 - \beta$) = 0.80, and a medium effect size (w = 0.3) as recommended by Cohen[17]. This yields a total sample size of 108 participants (36 per group) for a chi-square goodness-of-fit test with 2 degrees of freedom.

6. Quality assurance

The study will be conducted in accordance with ethical regulations for biomedical research involving human participants and has been approved by the Institutional Ethics Committee.

To ensure quality and consistency throughout the implementation process, the research team has developed standard procedures for all steps, including patient selection, intervention, data collection, and data processing.

Monitoring of adverse events, as well as ensuring the integrity and safety of participants, will be jointly conducted by the research team members, the principal investigator, and the hospital's Ethics Committee.

7. Expected outcomes of the study

The study is expected to provide scientific evidence on the effectiveness of prophylactic antibiotic use in preventing post-ERCP infections in patients with common bile duct stones. This may contribute to improving clinical practice guidelines, optimizing antibiotic use, and reducing the risk of antibiotic overuse and resistance

8. Dissemination of results and publication policy

Results will be submitted to peer-reviewed journals and presented at scientific meetings. Participants will be informed of the study outcomes upon request

9. Duration of the Project

The study is expected to be conducted from December 2022 to December 2025

10. Project management

The principal investigator will be responsible for the overall management and coordination of the project, including protocol adherence, data collection, data analysis, and reporting.

11. Ethical Considerations

This study has been reviewed and approved by the Institutional Ethics Committee. All participants will provide written informed consent prior to any study procedures.

12. Monitoring and Adverse Events Reporting

Adverse events and serious adverse events will be recorded and reported to the Ethics Committee according to institutional guidelines.

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