science, engineering and health studies

Research Article

Science, Engineering and Health Studies
https://lio1.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Pathogen patterns and clinical outcomes of empirical antibiotic treatment in cholangitis: Single-center retrospective study

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***Received**: 13 September 2024*
***Revised**: 11 December 2024*
***Accepted**: 2 January 2025*
***Published**: 25 November 2025*

***Citation**:
Treethammakul, P., Boonpeng, A., & Chaipichit, N. (2025). Pathogen patterns and clinical outcomes of empirical antibiotic treatment in cholangitis: Single-center retrospective study. Science, Engineering and Health Studies, 19, 25050010.

ABSTRACT

This retrospective cohort study determines patterns of pathogens and empirical antibiotic treatment among patients with cholangitis. We examined the clinical response and in-hospital all-cause mortality between empirical antibiotic treatment among patients with acute cholangitis at a general hospital in northeast Thailand. The Nelson-Aalen estimator and the Kaplan-Meier survival curve were respectively used to calculate the hazard ratio (HR) and 95% confidence interval (95% CI). The prevalence of pathogens and patterns of empirical antibiotics used were also studied. Among 232 patients, 90 patients (38.8%) had positive blood/bile cultures with 107 pathogenic organisms. The most prevalent non-resistant bacteria were *Escherichia coli* (35.5%) and *Klebsiella pneumoniae* (11.2%), to which all were susceptible to ceftriaxone and meropenem. About 16.8% of *E. coli* isolates exhibited ceftriaxone resistance, but all were sensitive to carbapenems. No difference was noted in clinical response and mortality rates between carbapenem-based and cephalosporin-based regimens (adjusted HR (aHR), 0.88; 95% CI, 0.66–1.19; p = 0.42 and 0.36; 95% CI 0.10–1.28; p = 0.12, respectively). In empirical antibiotic treatment of acute cholangitis, a carbapenem-based regimen demonstrated the same clinical response and mortality rate as a cephalosporin-based regimen; however, carbapenems should only be used among patients at high risk of resistant infections.

Keywords: cholangitis; antibiotics; microbiology; mortality

1. INTRODUCTION

Cholangitis is a disease of which increased bacteria in the bile ducts lead to bile duct inflammation. Mild to moderate severity of the diseases were mostly observed; however, at an even lower prevalence, grade III cholangitis exhibited a significantly higher rate of 30-day all-cause mortality (2.4, 4.7, and 8.4%, respectively) (Gomi et al., 2017). About 11.2% of patients with acute cholangitis were reported as fatalities according to a study in Thailand, of which severe acute cholangitis, surgical drainage and non-stone etiology were related to mortality (Eaupanitcharoen & Saratuy, 2020). In addition, acute cholangitis also leads to complications including acute pancreatitis, liver abscess and endocarditis (Gomi et al., 2017).

In cholangitis, the main goal of antimicrobial therapy is to stop the formation of intrahepatic abscesses, limit the systemic inflammatory response and local inflammation,

and prevent surgical site infections in the superficial wound, fascia or organ space (van den Hazel et al., 1994). While treating patients with cholangitis mainly involves drainage of the obstructed biliary trees (termed source control) (van den Hazel et al., 1994), antimicrobial therapy also plays a role in encouraging patients to have elective drainage surgery rather than emergency drainage surgery (Boey & Way, 1980). Patients with septic shock should receive the appropriate empirical antimicrobial within three hours of diagnosis (Evans et al., 2021). The Tokyo Guideline 2018 (TG18) recommended antibiotic agents, based on disease severity, to treat acute cholangitis including penicillin-, cephalosporin-, carbapenem- and fluoroquinolone-based therapies. The treatment goal is to select agents that can cover common pathogens in the biliary tract. While individual patient factors and regional bacterial antibiotic susceptibility can heighten the risk of infections from drug-resistant bacteria or other pathogens, certain conditions are notably associated with acute cholangitis (AC) caused by multidrug-resistant (MDR) bacteria (Gomi et al., 2018). These conditions include male sex, hospitalization exceeding 48 h, previous biliary stenting, and antibiotic use within 14 days of bile sampling. However, prior biliary stenting emerged as the only independent predictor of both AC with MDR bacteria (OR = 3.808; 95% CI 1.323–10.960, p = 0.013) and AC with enterococci (OR = 3.694; 95% CI 1.408–9.695; p = 0.008) (Reuken et al., 2017).

One related surveillance study analyzed isolated pathogens from different regions of the world and found that *Escherichia coli* (*E. coli*), *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp. were the most common pathogens in intra-abdominal infections (IAIs). *E. coli* susceptibility to imipenem was consistently high; however, the prevalence of extended-spectrum β-lactamase (ESBLs) producing *E. coli* in Asia has steadily increased to nearly 50% in IAIs (Morrissey et al., 2013). In Thailand, the antimicrobial agent resistance rates between 2000 and 2021 were rising in *E. coli* and ESBL producing *E. coli*. Drug resistance has become a major concern, especially for first-line treatments, which has made choosing the right antibiotics challenging. In 2021, *E. coli* was significantly resistant to ampicillin (80.2%) and ciprofloxacin (54.3%). Up to 38.4 to 46.7% of ESBL producing *E. coli* were cephalosporin resistant (National Antimicrobial Resistant Surveillance Center, 2019).

Clinicians are faced with the challenge of ensuring comprehensive empirical antibiotic coverage while also avoiding overusing carbapenems in patient with biliary stent implantation or hospitalization within 180 days before admission due to the increased prevalence of cephalosporine resistance. Antibiotic-resistant bacteria can lead to higher hospital mortality rates, longer durations of fever, and extended length of hospitalization (Jeong et al., 2022). This study aimed to determine the prevalence of bacterial pathogens and review the empirical antibiotic treatment patterns among patients with AC. The clinical outcomes of empirical antibiotic treatment among patients with AC were also studied.

2. MATERIALS AND METHODS

This retrospective observational cohort study was conducted at a secondary-care hospital, located in northeastern Thailand, with 250 beds, from October 2019 to March 2022. This setting is one of the endoscopic surgery centers in the northeast region, where about 300 ERCP procedures are performed yearly. This study was conducted following the principles of the Declaration of Helsinki, reviewed ethically, and approved by the Human Research Ethics Committee of Nong Khai Provincial Public Health Office (Number 32/2565).

Patients were eligible if they were older than 18 years and had been treated with empirical antibiotics for AC. These patients were identified from the electronic hospital records using the diagnostic code for cholangitis (K80.3 or K83.0) according to the ICD-10-TM International Statistical Classification of Diseases and Related Health Problems, Version 2016. The exclusion criteria were as follows: (1) cultures showed infections other than bacteria or (2) unable to retrieve patients' data from the hospital database. Data were collected mainly by reviewing electronic medical records including demographic data, clinical and laboratory values, and history of ERCP including types of stents. Patients' vital signs were collected from paper-based medical records and cross-verified with other sources to ensure accuracy. Due to the numerous time points for vital signs throughout the day, data were collected at the time when patients exhibited their highest body temperature, as this often indicates signs of infection or worsening symptoms. The systemic inflammatory response syndrome (SIRS) score was then calculated after reviewing the electronic medical records (Bone et al., 1992).

AC was defined based on the TG18 (Kiriyama et al., 2018), and the following criteria were used: 1) the presence of symptoms or signs of fever (>38.0°C), chills, abdominal pain, jaundice and liver biochemistry suggestive of biliary obstruction; 2) laboratory evidence of inflammation and biliary obstruction; and 3) imaging evidence of biliary obstruction. Empirical antibiotic treatment was defined as antibiotics that are administered before the available reports of antibiotic susceptibility test of blood and/or bile cultures (McGregor et al., 2007).

The primary outcome was clinical response, defined as patients with cholangitis presenting improved signs and symptoms of infection assessed on the last day of empirical antibiotic treatment and hospital discharge, without changing to the broader spectrum of antibiotics or receiving additional antibiotics, and not dying within 48 h after hospital discharge. Secondary outcomes were in-hospital all-cause mortality, length of hospital stay, and re-admission with cholangitis within 30 days after discharge. In addition, direct medical costs of empirical antibiotic treatment were collected, which included costs associated with laboratory testing, medications, clinical monitoring, medication side effect management, and hospital services. The prevalence of pathogenic bacteria and patterns of empirical antibiotics used in AC were also studied.

Using sample size calculation for comparing proportions (Wang & Chow, 2007), a 10% difference in treatment success was assumed between the antibiotic groups, based on previous research on empirical antibiotic regimens in biliary tract infections (Chang et al., 2014), with a study power of 80%. To prevent the loss of patients' data, about 20% of the calculated sample size was adjusted, giving a final number of 282 patients to be included. Categorical variables between the three groups of empirical antibiotics were compared using the Chi-squared-test or Fisher's exact test (if the expected frequencies in cells were

less than 5). Continuous variables were compared using one-way ANOVA or the Kruskal–Wallis test.

To predict the clinical response and in-hospital all-cause mortality between the empirical antibiotics, the Nelson-Aalen estimator and the Kaplan-Meier survival curve were respectively used to calculate the hazard ratio (HR) and 95% CI. The input variables were age, sex, body mass index (BMI), biliary stent implantation, hospitalization within 180 days before admission, the presence of diabetes mellitus, hypertension, and cancer, renal impairment (creatinine clearance <60 mL/min), hypoalbuminemia (albumin level <3.5 g/dL), and SIRS score. To explore the differences in clinical response between antibiotic groups, subgroup analysis was performed where patients were selected whose isolates were susceptible to cephalosporin- and carbapenem-based regimens. The same variables were included in the multivariable logistic model. All analyses were performed using STATA 14SE Program (StataCorp LLC, College Station, TX, USA). All tests for significance were two-tailed, with $p < 0.05$ considered significant.

3. RESULTS AND DISCUSSION

3.1 Results

Out of the 321 patients with AC identified during the study period, 12 patients were excluded. The exclusion criteria included being younger than 18 years old (2 patients), not receiving any antibiotic treatment (6 patients), and being lost to follow-up (4 patients).

A total of 309 patients were analyzed with cholangitis receiving at least one dose of empirical antibiotics, most of which (60.1%) were cephalosporin-based regimens. Patients received the standard dosage regimen of empirical therapy for cholangitis, adjusted according to their renal function. Overall, 155 patients (50.2%) were males with a mean age of 64.18 ± 14.39 years. More than 82.8% of cephalosporin-based regimens had combination antibiotic treatment with metronidazole, whereas the higher rates of monotherapy were observed in carbapenem- and fluoroquinolone-based regimens (98.2 and 85.7%, respectively) (Table 1).

Table 1. Baseline characteristics of patients with cholangitis

Baseline characteristics	Types of empirical antibiotic treatment			Total (n = 309)	*p*
	Cephalosporin-based regimen (n = 186)	Carbapenem-based regimen (n = 109)	Fluoroquinolone-based regimen (n = 14)		
Sex, male, n (%)	86 (46.2%)	61 (56.0%)	8 (57.1%)	155 (50.2%)	0.24
Age (years)	64.23 ± 14.83	65.05 ± 13.15	56.86 ± 16.49	64.18 ± 14.39	0.23
BMI (kg/m^2)	21.4 (19.4 to 25.3)	22.8 (19.5 to 25.8)	23.2 (20.0 to 23.9)	22.1 (19.5 to 25.4)	0.49
Hypotension, n (%)	16 (8.6%)	10 (9.2%)	1 (7.1%)	27 (8.7%)	0.96
Tachycardia, n (%)	84 (45.2%)	62 (56.9%)	4 (28.6%)	150 (48.5%)	0.05
Tachypnoea, n (%)	34 (18.3%)	25 (22.9%)	0 (0.0%)	59 (19.1%)	0.11
Temperature (°C),	37.08 ± 0.98[a]	37.45 ± 1.10[a,b]	36.56 ± 0.55[b]	37.19 ± 1.03	**< 0.001**
SCr (mg/dL)	0.8 (0.7 to 1.1)	0.7 (0.6 to 1.1)	0.8 (0.7 to 1.2)	0.8 (0.6 to 1.1)	0.42
Albumin (gm/dL)	3.3 (2.8 to 3.7)	3.1 (2.6 to 3.7)	3.5 (3.1 to 4.1)	3.3 (2.8 to 3.7)	0.05
Have a history of drug allergy, n (%)	15 (8.1%)	8 (7.3%)	2 (14.3%)	25 (8.1%)	0.67
Have been hospitalized within 180 days before admission, n (%)	42 (22.6%)	39 (35.8%)	3 (21.4%)	84 (27.2%)	**0.04**
Co-morbidity, n (%)					
Diabetes mellitus	39 (21.0%)	29 (26.6%)	5 (35.7%)	73 (23.6%)	0.30
Hypertension	65 (35.0%)	34 (31.2%)	6 (42.9%)	105 (34.0%)	0.62
Cancer	61 (32.8%)	50 (45.9%)	4 (28.6%)	115 (37.2%)	0.06
SIRS score ≥2, n (%)	79 (42.3%)	66 (61.1%)	3 (21.4%)	148 (47.9%)	**0.001**
Previous ERCP					
Never	129 (69.4%)	58 (53.2%)	11 (78.6%)	198 (64.1%)	**0.02**
One ERCP	31 (16.7%)	26 (23.9%)	0 (0%)	57 (18.5%)	
More than one ERCP	26 (14.0%)	25 (22.9%)	3 (21.4%)	54 (17.5%)	
Biliary stent implantation, n (%)	36 (19.4%)	37 (33.9%)	2 (14.3%)	75 (24.3%)	0.05
Plastic stent, n (%)	21 (58.3%)	25 (67.6%)	1 (50.0%)	47 (62.7%)	
Metallic stent, n (%)	15 (41.7%)	12 (32.4%)	1 (50.0%)	28 (37.3%)	
Success stone removed, n (%)	53 (28.5%)	49 (45.0%)	3 (21.4%)	105 (34.0%)	**0.04**

Note: BMI = body mass index; SCr = serum creatinine; SIRS = systemic inflammatory response syndrome; ERCP = endoscopic retrograde cholangiopancreatography

Mean ± standard deviation was displayed for age and temperature. Median and interquartile range were displayed for serum creatinine and albumin

[a] *p*-value = 0.008; [b] *p*-value = 0.006

Of the 309 patients, specimens were collected from 232 patients (75.1%); blood cultures were tested in 229 cases and bile cultures in 22. Positive cultures were detected in 90 patients (38.8%), with samples taken from 82 blood and 13 bile sources. Among these, 12.8% were polymicrobial. The most prevalent polymicrobial isolates included *E. coli*

(29.2%), *K. pneumoniae* (16.7%) and *Enterococcus* spp. (12.5%). Altogether, 107 identified pathogenic organisms (89.72%) were mostly Gram-negative organisms (Table 2). The most prevalent isolates were *E. coli* (35.5%), ceftriaxone-resistant *E. coli* (16.8%), and *K. pneumoniae* (11.2%). Overall, 100% of the *E. coli* and *K. pneumoniae* isolates were susceptible to ceftriaxone and meropenem. In addition, 43% of *E. coli* and 10% of *K. pneumoniae* isolates were resistant to ciprofloxacin. Ceftriaxone-resistant organisms, including *E. coli* and *K. pneumoniae,* were all susceptible to carbapenems (100.00%). Gentamicin, fosfomycin and vancomycin were all 100% effective against Gram-positive *Enterococcus* spp. (Table 3).

Table 2. Microorganisms isolated from 107 blood and bile cultures among 90 patients with cholangitis

Organisms	**Number of organisms (%)**		
	Total (n = 107)	**Community-acquired infection (n = 62)**	**Healthcare-associated infection (n = 45)**
Gram-negative organisms	**96 (89.72%)**	**54 (87.10%)**	**42 (93.33%)**
Escherichia coli	38 (35.51%)	19 (30.65%)	19 (42.22%)
Escherichia coli with ceftriaxone resistance	18 (16.82%)	10 (16.13%)	8 (17.78%)
Klebsiella pneumoniae	12 (11.21%)	10 (16.13%)	2 (4.44%)
Klebsiella pneumoniae with ceftriaxone resistance	3 (2.80%)	1 (1.61%)	2 (4.44%)
Klebsiella pneumoniae [CRE]	3 (2.80%)	2 (3.23%)	1 (2.22%)
Pseudomonas aeruginosa	5 (4.67%)	5 (8.06%)	-
Pseudomonas aeruginosa [MDR]	1 (0.93%)	-	1 (2.22%)
Enterobacter spp.	3 (2.80%)	2 (3.23%)	1 (2.22%)
Acinetobacter baumannii	2 (1.87%)	2 (3.23%)	-
Stenotrophomonas maltophilia	1 (0.93%)	-	1 (2.22%)
Aeromonas spp.	3 (2.80%)	-	3 (6.67%)
Citrobacter diversus	2 (1.87%)	1 (1.61%)	1 (2.22%)
Edwardsiella tarda	3 (2.80%)	1 (1.61%)	2 (4.44%)
Burkholderia pseudomallei	1 (0.93%)	1 (1.61%)	-
Proteus mirabilis	1 (0.93%)	-	1 (2.22%)
Gram-positive organisms	**11 (10.28%)**	**8 (12.90%)**	**3 (6.67%)**
Enterococcus spp.	7 (6.54%)	5 (8.06%)	2 (4.44%)
Streptococcus spp.	4 (3.74%)	3 (4.84%)	1 (2.22%)

Note: MDR = multiple drug resistance, CRE = carbapenem-resistant *Enterobacter*

Table 3. Antibiotic susceptibilities pattern of the common isolated bacteria

Antibiotics	*Escherichia coli*	*Escherichia coli* with ceftriaxone resistance	*Klebsiella pneumoniae*	*Klebsiella pneumoniae* with ceftriaxone resistance	*Pseudomonas aeruginosa*	*Enterococcus* spp.	*Streptococcus* spp.
Amikacin	**96% (23/24)**	**100% (22/22)**	**100% (8/8)**	**100% (4/4)**	**100% (5/5)**	-	-
Augmentin	**93% (25/27)**	41% (9/22)	**100% (8/8)**	60% (3/5)	-	-	-
Ampicillin	32% (10/31)	0% (0/24)	10% (1/10)	0% (0/5)	-	**86% (6/7)**	**100% (3/3)**
Cefotaxime	**100% (31/31)**	0% (0/24)	**100% (10/10)**	0% (0/5)	**100% (1/1)**	-	75% (3/4)
Ceftazidime	**100% (27/27)**	18% (4/22)	**100% (9/9)**	25% (1/4)	67% (2/3)	-	-
Ceftriaxone	**100% (31/31)**	0% (0/24)	**100% (10/10)**	0% (0/5)	-	-	**100% (4/4)**
Ciprofloxacin	57% (17/30)	4% (1/24)	90% (9/10)	0% (0/5)	80% (4/5)	-	-
Gentamicin	**96% (24/25)**	41% (9/22)	**100% (8/8)**	**100% (5/5)**	80% (4/5)	**100% (7/7)**	-
Imipenem	**100% (29/29)**	**100% (22/22)**	**100% (9/9)**	**100% (4/4)**	**100% (4/4)**	-	-
Cotrimoxazole	68% (19/28)	36% (8/22)	**100% (10/10)**	40% (2/5)	40% (2/5)	-	0% (0/2)
Meropenem	**100% (31/31)**	**100% (24/24)**	**100% (10/10)**	**100% (5/5)**	80% (4/5)	-	-
Doripenem	**100% (5/5)**	**100% (4/4)**	**100% (3/3)**	**100% (2/2)**	75% (3/4)	-	-
Fosfomycin	**100% (30/30)**	**100% (24/24)**	**100% (1/1)**	-	-	**100% (1/1)**	-
Piperacillin/ Tazobactam	-	-	-	-	**100% (4/4)**	-	-
Penicillin	-	-	-	-	-	**86% (6/7)**	**100% (1/1)**
Vancomycin	-	-	-	-	-	**100% (7/7)**	**100% (3/3)**
Ampicillin/ Sulbactam	-	-	-	-	-	-	-
Clindamycin	-	-	-	-	-	-	**100% (4/4)**
Erythromycin	-	-	-	-	-	-	-

Because of only having a few samples of the fluoroquinolone-based regimen, the primary outcomes were compared between the two regimens among patients whose isolates were susceptible to cephalosporins or carbapenems. Although patients in the carbapenem-based regimen group had lower clinical response and mortality rates than that of the cephalosporin-based regimen group, the rates of adjusted hazard ratio did not differ [adjusted HR (aHR) 0.88; 95% CI 0.66 to 1.19; p = 0.42 and 0.36; 95% CI 0.10 to 1.28; p = 0.12, respectively] (Figures 1 and 2).

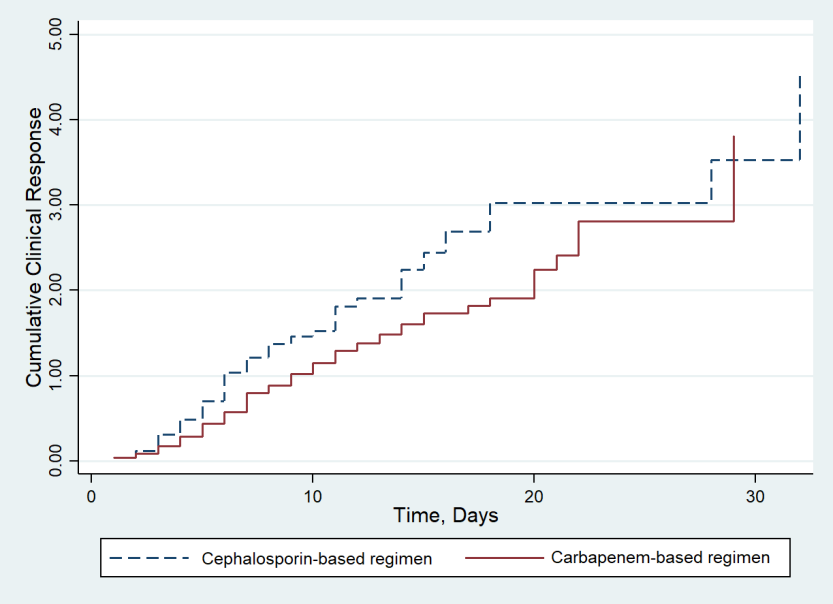

Figure 1. Nelson-Alen cumulative hazard estimates of clinical responses by empirical antibiotic regimens during hospitalization

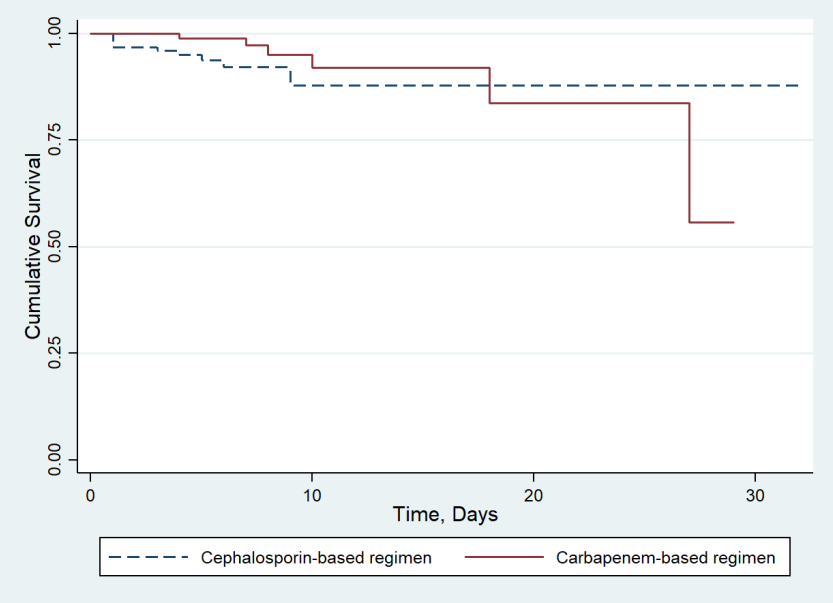

Figure 2. Kaplan-Meier survival estimates of in-hospital all-cause mortality rates by empirical antibiotic regimens

The carbapenem-based regimen showed a significantly longer duration of hospitalization (median 7.0, 6.0, and 5.5 days) and antibiotic use (median 7.0, 6.0, and 5.5 days) than the cephalosporin- and fluoroquinolone-based regimens. Re-admission with cholangitis within 30 days after discharge was generally higher in the carbapenem-based regimen group than in the cephalosporin-based and a fluoroquinolone-based regimens but did not significantly differ. No significant difference in direct medical costs was observed between the three groups (Table 4).

Table 4. Secondary outcomes of the empirical antibiotic treatment in cholangitis

Outcomes	Types of empirical antibiotic treatment			Total (n = 309)	*p*
	Cephalosporin-based regimen (n = 186)	Carbapenem-based regimen (n = 109)	Fluoroquinolone-based regimen (n = 14)		
Length of hospital stay (days), median (IQR)	6.0 (4.0 to 9.0)[a]	7.0 (5.0 to 12.0)[b]	5.5 (3.0 to 13.0)	6.0 (4.0 to 10.0)	**0.03**
Duration of antibiotic use (days), median (IQR)	6.0 (3.0 to 9.0)[b]	7.0 (5.0 to 11.0)[b]	5.5 (3.0 to 11.0)	6.0 (4.0 to 10.0)	**0.02**
Direct medical cost (Thai Baht), median (IQR)	56,440 (34,028 to 78,594)	66,991 (39,439 to 93,323)	54,645 (44,224 to 75,473)	58,674 (37,214 to 85,678)	0.15
Re-admission with cholangitis within 30 days after discharge, n (%)	7 (3.8%)	11 (10.1%)	0 (0.0%)	18 (5.8%)	0.05
Mortality, n (%)	11 (5.9%)	6 (5.5%)	0 (0.0%)	17 (5.5%)	0.65

Note: [a] *p*-value = 0.005, [b]*p*-value = 0.004

3.2 Discussion

To date, this is the first report on bacteria profiles among patients with AC in Thailand. The pathogenic bacteria and antibiotic sensitivity pattern reported here confirmed that the medication according to the current clinical guidelines was still effective (Gomi et al., 2018). The clinical response and in-hospital, all-cause mortality between the carbapenem- and cephalosporin-based regimens did not differ. Notably, about 15% of all isolates were ceftriaxone-resistant strains including ESBL-producing bacteria. Therefore, carefully screening individuals at risk for ESBL infection is important before choosing the best empirical antibiotic therapy.

In this study, the four most common bacterial species isolated from blood and bile samples were *E. coli* (35.5%), *E. coli* with ceftriaxone resistance (16.8%), *K. pneumoniae* (11.2%) and *Enterococcus* spp. (6.5%). The microbiology profiles differed slightly from those observed in a prospective study in Bangladesh, where the common pathogens isolated from blood in patients with AC included *E. coli* (36.4%), *K. pneumoniae* (23.6%), *P. aeruginosa* (7.3%) and *Enterococcus* spp. (7.3%) (Saqeb, 2020). Bile cultures collected during ERCP from patients at a tertiary center in Munich showed higher frequencies for *Enterococcus* spp., including *Enterococcus faecalis* (33.2%) and *Enterococcus faecium* (28.6%) (Reiter et al., 2021). Approximately 40% of patients in their study presented stent implantation. A surveillance report from one of the largest tertiary hospitals in China also identified post-ERCP infections as being associated with *E. faecalis* (20.7%), *E. coli* (18.9%), *K. pneumoniae* (8.6%), and *P. aeruginosa* (8.6%) (Du et al., 2017).

Since *Enterococcus* species were over 85% sensitive to ampicillin/sulbactam, this antibiotic may still be suitable for treating grade I cholangitis and cholecystitis in our setting. However, more than 23.35% of the isolates in this study were cephalosporin resistant or MDR pathogens, with the majority showing more than 70% ceftazidime resistance rates. Two thirds of patients in the resistant group had comorbidities and SIRS scores of 2 or higher. Furthermore, 38.7% of the resistant group had been hospitalized within the previous 180 days. As a result, empirical treatment with carbapenem-based regimen may be advisable. Due to the high resistance of organisms to ciprofloxacin and ampicillin, it was concluded that a fluoroquinolone-based regimen might be unsuitable for empirical therapy in this case. This conclusion is also supported by a previous study in China, which recommended limiting the use of fluoroquinolones as prophylactic treatment, particularly for post-ERCP infections (Du et al., 2017).

According to the TG18, it is advisable to conduct susceptibility testing including penicillin-based therapy to ensure the appropriateness of continuing empirical antibiotics in cases of AC. Penicillin-based therapy is primarily recommended in both community-acquired and healthcare-associated biliary infection (Gomi et al., 2018), however, susceptibility tests of piperacillin/tazobactam in our setting were not routinely performed. In 2018, The Thai National Antimicrobial Resistant Surveillance Center report over 90% of *E. coli* isolated from blood cultures were susceptible to piperacillin/tazobactam (National Antimicrobial Resistant Surveillance Center, 2019). In our study, we identified a 2.80% prevalence of CRE among patients, which underscores the need for cautious use of carbapenems. This aligns with reports from neighboring countries, such as Bangladesh, where higher rates of CRE have been observed among acute cholangitis patients (Saqeb, 2020). These similarities suggest a regional trend of increasing resistance, particularly to critical antibiotics like carbapenems. Moreover, although current guidelines indicate limited need for routine anaerobic coverage in uncomplicated cholangitis (Gomi et al., 2018), it was seen from our study that metronidazole was frequently combined with cephalosporin-based regimens (82.8%). This high usage aligns with findings from a Chinese surveillance study of post-ERCP infections, which reported 90% metronidazole use (Du et al., 2017). This practice pattern could be due to concerns about anaerobic infections, particularly in patients with biliary interventions or stent placement. However, more selective use of metronidazole based on anaerobic infection risk factors would be more appropriate than routine combination therapy. This presents an opportunity for antimicrobial stewardship to develop targeted criteria for metronidazole use.

After adjusting for risks of antibiotic resistance and SIRS score, the clinical response and survival rate between the cephalosporin- and carbapenem-based regimens did not significantly differ. Patients with healthcare-associated infection, grade 3 cholangitis severity, and previous biliary intervention were substantially more likely to have acute cholangitis with an antibiotic-resistant pathogen (Jeong et al., 2022). Prior biliary intervention was also linked to multidrug-resistant bacteria (Reuken et al., 2017). Patients

with high disease burden, including cancer, hypertension, and diabetes mellitus, were also at risk for antibiotic resistance. When choosing an antibiotic prophylaxis, patient characteristics should be considered in addition to local epidemiology and susceptibility data. The cephalosporin-based regimen appears to be a promising first-line therapy for general patients with cholangitis in the present study. For patients with multiple comorbidities, a high SIRS score, and a prior hospitalization within 180 days, it seems appropriate to maintain a carbapenem-based regimen. Related studies have shown that imipenem is the most effective antibiotic among patients with significant risk factors for antibiotic resistance, whereas piperacillin/tazobactam is somewhat effective (Jeong et al., 2022).

Median duration of antibiotic prophylaxis ranged within 5.5 to 7 days across treatment groups. According to TG18 for grades I to III community-acquired biliary infection, 4 to 7 days of treatment duration was recommended when ERCP cannot be performed. Longer treatment over two weeks was considered among patients with bacteraemia presenting Gram positive cocci or in healthcare-associated cholangitis and cholecystitis in any severity (Gomi et al., 2018). Antibiotic therapy for AC aimed to prevent progression to systemic infection and to arrange patients for elective drainage procedures. In addition, bacteria resistance was increasingly observed among patients with longer use of antibiotics. A shorter duration, two-day-antibiotic prophylaxis treatment, showed no significant severity increase among patient with mild to moderate cholangitis who had successful ERCP (Masuda et al., 2022). In bacteraemia cholangitis, the 30-day mortality rate was comparable between duration of ≤7 days and ≥8 days of antibiotic treatment (Du et al., 2017).

This study encountered limitations. Firstly, the enrolled patients were from a single center in Thailand; therefore, the study in multi-centre settings are required. Secondly, blood and bile culture tests were not performed in all cases and antibiotic sensitivity tests did not cover some drug regimens recommended in the TG18. The results showed similar patterns of pathogenic bacteria and susceptibility results as related studies, however, findings should be interpreted with caution, especially when generalizing to moderate to severe patients in different settings. Thirdly, mortality rate considered only in-hospital death because some patients who were transferred back to their original hospital could not be tracked. Future studies would benefit from incorporating longer follow-up periods to assess post-discharge outcomes. This would include monitoring for recurrent infections and evaluating the long-term effects of antibiotic resistance. Such comprehensive follow-up is crucial for understanding the full impact of treatment and improving patient care. Fourthly, as a retrospective study, the selection of empiric antibiotic regimens and the reasons for escalating antibiotic therapy were diverse, and the timing of antibiotic administration were not recorded. A study of providing a drug use form before prescribing any antibiotics is needed to investigate the rational use of antibiotics. Moreover, this study reflects real-world practice, where cultures may not be collected from patients with mild symptoms. Blood cultures are typically obtained from more severe cases, which could lead to an overestimation of nosocomial organisms. Therefore, the generalization of this study should be interpreted with caution, particularly for moderate to severe patients in other settings. Lastly, the Sequential Organ Failure Assessment (SOFA) score was not calculated in our study due to a lack of some relevant information; however, the SIRS score was then used to identify the systemic inflammatory response to both non-infectious and infectious diseases. The SOFA score or the acute physiology and chronic health evaluation II (APACHE II) scoring system, which provides better outcomes in assessing organ dysfunction among critically sick patients, should be considered for use in future studies.

4. CONCLUSION

The majority of pathogenic microorganisms isolated from patients with cholangitis in this study were highly susceptible to both cephalosporin- and carbapenem-based regimens. A carbapenem-based treatment and a cephalosporin-based regimen had no difference in clinical response or in-hospital all-cause mortality. Based on the prevalent and susceptibility data from the present study, a cephalosporin-based treatment is advised as the initial antibiotic for patients with cholangitis. In cases where individuals are at risk of antibiotic resistance, a carbapenem-based therapy is recommended.

ACKNOWLEDGMENTS

We would like to express our gratitude to Dr. Tuangpraj Srikoolwong, Dr. Chaloemphon Boonmee, Dr. Somsak Boonharn, Dr. Wanthanachai Rotchomphu, Mrs. Saiphon Naowarungsri, and Ms. Pachararin Soimeesang from the Department of Surgery at Thabo Crown Prince Hospital for their assistance with data collection. Dr. Sirayut Phattanasobhon from the Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao provided statistical assistance with data analysis.

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