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Microbiology of Acute Cholangitis and Cholecystitis and Antimicrobial Susceptibility

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ABSTRACT

Background: Acute cholecystitis and cholangitis are life-threatening if not treated promptly. Empiric antibiotic therapy is crucial, relying on local studies of bile culture for guidance.

Objective: To identify the microbiological and antibiotic susceptibilities of organisms in bile cultures of patients with acute cholangitis and cholecystitis.

Materials and Methods: Adults diagnosed with acute cholangitis and/or cholecystitis at the Hospital Regional ISSSTE Puebla (2022-2023) underwent bile aspiration via laparoscopy or open surgery. Microorganisms were isolated from bile cultures and antibiograms were obtained. Patients were classified according to severity according to the Tokyo Guidelines 2018.

Results: A total of 88 patients with bile cultures for cholangitis/cholecystitis were included. Fourteen percent of cultures showed no bacterial growth, and E. coli was the most common pathogen with significant antibiotic resistance. Multivariate analysis identified recent antimicrobial therapy ($p < 0.03$), concomitant malignancy ($p < 0.001$), and age >65 years ($p < 0.0001$) as factors associated with resistant bacteria. Thirty-day mortality was 2.3%.

Conclusions: Empirical antimicrobial therapy based on TG 2018 was effective across all severity grades.

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KEYWORDS: Acute Cholangitis, Acute Cholecystitis, Antimicrobial drug resistance, cholangitis.

INTRODUCTION

Acute cholangitis and cholecystitis are fatal if not appropriately treated in a timely manner. The Tokyo Guidelines 2018 [1] reported the first large-scale study of patients with acute cholangitis. The mortality rates were 2.4%, 4.7%, and 8.4% by severity grades I, II, and III, respectively, and the incidence of complications was 2.0% and 0.26%, respectively). Bile is normally sterile, but in the presence of obstruction, the risk of cholangitis increases. The most common organisms isolated from bile are Escherichia coli, Klebsiella spp., Enterococcus spp., Streptococcus spp., Enterobacter spp., and Pseudomonas spp. The microbiological characteristics of cholangitis have not changed significantly; however, the emergence of drug resistance among these organisms is a matter of concern [2–8]. The primary goal of antimicrobial therapy is to limit both systemic septic response and local inflammation. Drainage of obstructed biliary trees (source control) has been recognized as the mainstay of therapy for patients with acute cholangitis. The role of antimicrobial therapy in acute cholangitis is to allow patients to undergo elective drainage procedures in addition to emergencies. In the TG 18 guidelines, empiric

therapy is defined as antimicrobial therapy until cultures and susceptibility testing results are available. Once the causative microorganisms and susceptibility testing results are available, antimicrobial therapy should be adjusted to specific antimicrobial agents targeting these organisms. This process is defined as the de-escalation of antimicrobial therapy in the TG 18 guidelines [1,9,10]. The role of antimicrobial therapy varies depending on the severity and pathology of the acute cholecystitis. In early and non-severe cases (or patients with acute cholecystitis of TG 18 Severity Grade I), it is not clear whether bacteria play a significant role in the pathology. In these patients, antimicrobial therapy is the best prophylactic treatment to prevent progression to infection. In more progressed, moderately severe, or severe cases with clinical findings of a systemic inflammatory response, antimicrobial therapy is therapeutic, and antimicrobial therapy may be required until the gallbladder is removed [4,9,11]. Antimicrobial therapy largely depends on local antimicrobial susceptibility data. The emergence of antimicrobial resistance in clinical isolates of Enterobacteriaceae from patients with community-acquired intra-abdominal infections has been widely reported [4,10,12]. In particular, extended-spectrum beta-lactamase (ESBL)-and carbapenemase (i.e., metallo-beta-lactamase and non-metallo-beta-lactamase)-producing bacilli have been reported to significantly affect the selection of empirical therapy for patients with intra-abdominal infections, including acute cholangitis and cholecystitis [13]. A prospective cohort study in patients with acute cholecystitis involving 116 institutions worldwide showed that among 96 isolated E. coli strains, 16 (16.7%) were producing ESBL [6]. However, the proportion of ESBL-producing E. coli varies regionally from 31.2 % to 70.0 % [3,14,15]. There are few reports on the prevalence of carbapenem-resistant bacteria, specifically in patients with acute cholangitis and cholecystitis. One study from Korea reported that 13 of 376 (3.5%) bile isolates were carbapenemase-producing [12].

Bacteria isolated from blood are similar to those isolated from bile; therefore, isolation from bile cultures can provide solid evidence for the selection of a susceptible antimicrobial agent [15]. Cholangitis is often caused by polymicrobial infection. Blood culture has low sensitivity and may not detect the causative organism, whereas bile culture collected through ERCP has low specificity and may detect enteric bacteria that are not the cause of inflammation, resulting in difficulties in the accurate identification of causative organisms [16]. The bile samples obtained by ERCP may have been contaminated with autologous oral and duodenal microflora. Routine bile sampling during ERCP is not generally recommended by the current guidelines [14,17]. This approach is justified by the argument that the highest bacterial burden during Acute Cholangitis is suspected to be in the biliary system, that blood cultures show a lower sensitivity than bile cultures, and that even if duodenal contamination plays a role, the presence of MDR gut bacteria may be a risk factor for ascending acute cholangitis due to MDR [3,14].

Monitoring and updating local antibiograms are critical for providing effective therapy in a timely fashion in the clinical setting. Tian et al [18] recommended empiric therapy for resistant isolates if they occur in more than 20% of patients, and ampicillin/sulbactam can be used as the initial therapy if susceptibility remains over 80% in the local area. However, its susceptibility has been reported to decrease in many places worldwide. Ampicillin/sulbactam can be used once its susceptibility is known as definitive or targeted therapy. The 2013 and 2018 Tokyo guidelines state that if a patient develops severe cholangitis, the choice of empiric antibiotics should be anti-gram-negative bacteria, while covering gram-positive bacteria. Guidelines emphasize that severe cholangitis could be due to a mixed infection of Gram-negative and Gram-positive bacteria, but there is no evidence to support this [12].

MATERIALS AND METHOD.

Adults diagnosed with acute cholangitis and/or acute cholecystitis at Hospital Regional ISSSTE Puebla between 2022-2023 will undergo bile aspiration by laparoscopy or open surgery, microorganisms will be isolated from bile cultures, and antibiograms will be performed. The patients will be divided according to the severity of the Tokyo 2018 guidelines.

All values are presented as raw numbers or percentages. Qualitative variables were analyzed using Fisher's exact test. Quantitative variables are expressed as mean ± standard deviation (SD) and analyzed using ANOVA. The analysis was performed using Microsoft Excel (SPSS 28. Differences were considered statistically significant at $P < 0.05$.

RESULTS

In our study, patients were managed according to TG 2018 guidelines with biliary drainage and appropriate empirical antibiotic therapy.

A total of 88 patients with cholangitis/cholecystitis with bile culture were included in this study (fig. 1). All patients were referred from the second level of care and antibiotics were administered before referral. Surgical management was performed in all patients (Tables 1 and 2). The proportion of cultures without bacterial growth was (14%) and there were no significant differences in the bacteriology of either group. Patients with acute cholangitis underwent laparoscopic biliary drainage because of a lack of endoscopic equipment or the presence of common bile duct stones that were too large. Patients with acute cholecystitis underwent laparoscopic cholecystectomy. Biliary samples were collected by direct puncture of the bile duct or the gallbladder. The culture results of 13 bile samples (14.7 %) were negative. E coli was the most common bacterium in both groups (Table 3), and it was also the bacterium with the highest resistance to antibiotics.

Multivariate analysis demonstrated significant factors associated with resistant bacteria, including recent

antimicrobial therapy (p <0.03), presence of concomitant malignancy (p <0.001), and age >65 years (p <0.0001).

Appropriate empirical antimicrobial therapy was associated with better survival, whereas delayed biliary decompression (> 48 hours) worsened patient outcomes.

Univariate analysis revealed significant factors associated with mortality in the presence of generalized peritonitis (p= 0.05) and inadequate empirical antimicrobial therapy (p= 0.01).

DISCUSSION

The average age of our patients was slightly higher than that in most recently published studies [14][15][11]. Like other studies, the prevalence of Acute Cholangitis in our study was higher than that of Acute Cholecystitis [13][18][7]. The most frequent etiology of acute cholangitis is bile duct stones, which is consistent with the latest epidemiological data [1][9][19][15], however, these authors included patients with different strategies for biliary drainage, as in their study, percutaneous biliary drainage/ERCP was used as the first-line technique for sepsis source control, whereas in our study, we failed to perform ERCP/percutaneous biliary drainage were our study population.

The proportion of cultures without bacterial growth was slightly lower (14%) than that reported in the recent literature [5][10][16][3][20]

Regarding antibiotic resistance, the bacterium with the highest resistance to antibiotics was E. coli (5.6%), although this percentage was lower than that reported in other studies [20][6][21][12]. The remaining antibiotic resistance was lower than that reported in other studies [3][6][12].

CONCLUSION

The most frequent etiology of acute cholangitis is bile duct stone. E. coli and K. pneumoniae were the most frequently isolated organisms from blood and bile across the severity grades.

Our study had several limitations. First, this was a retrospective observational study, and the data collection and accuracy were limited. Second, this study did not analyze biliary drainage procedures, and these therapeutic procedures should be analyzed to determine their impact on patient outcomes. Third, this study did not determine which patients had multidrug-resistant organisms and what kind of risk factors, such as a history of enterobiliary anastomosis, should be prospectively investigated in future studies. In our study, the empirical antimicrobial therapy of TG 2018 was valid.

Further prospective multicenter studies are needed to evaluate the effect of biliary decompression timing on mortality.

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CONFLICT OF INTEREST:

No conflicts of interest exist.

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ETHICAL APPROVAL:

The study protocol was reviewed and approved by the Research and Ethics Committee of the hospital (registration no. 1812022).

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Table 1. Characteristics of patients with acute cholangitis/cholecystitis.

Variable	n=88. Freq. (%)
Gender	
Women	47 (53.4)
Man	41 (46.6)
Diagnosis	
Acute cholangitis	62 (70.5)
Acute cholecystitis	26 (29.5)
Cause of cholangitis	
Bile duct stone	77 (88.5)
Benign bile duct stricture	6 (6.9)
Malignant stricture	4 (4.6)
ASA score	
I	10 (11.4)
II	69 (78.4)
III	9 (10.2)
Tokyo severity grade	
Mild	29 (33)
Moderate	29 (33)
Severe	8 (9.1)
Septic shock	6 (4.5)
30 day mortality	2 (2.3)

Table 2. Descriptive characteristics of patients with acute cholangitis/cholecystitis.	
Variable	n=88 ± SD
Age (years)	61.8 ± 13.8
At admission	
Temperature (degrees Farenheit)	98.7 ± 32.6
SOFA score	4.58 ± 1.54
Onset of symptoms (hours)	93.2 ± 25.1
Leukocytes (per microliter)	15230 ± 4591
Neutrophils (per microliter)	9842 ± 3960
INR	1.2 ± 0.32
Alanine aminotransferase	125.7 ± 129.3
Aspartate aminotransferase	141.4 ± 133.6
Gamma-glutamyl transferase	220.8 ± 256.7
Alkaline phosphatase	244.6 ± 231.4
Total bilirrubin	3.5 ± 4.1
Conjugated bilirrubin	2.3 ± 2.7

Table 3. Bacteriological data in bile cultures of patients with acute cholangitis/cholecystitis.			
Bacteria	Acute cholangitis	Acute cholecystitis	*p
Negative culture	7 (8%)	6 (6.8)	0.13
E. coli	42 (47.7)	19 (21.6)	0.41
K. pneumoniae	5 (5.7)	2 (2.3)	0.66
Enterobacter spp	1 (1.1)	1 (1.1)	0.50
Enterococcus	1 (1.1)	1 (1.1)	0.50
Streptococcus spp	1 (1.1)	1 (1.1)	0.50
P. aeruginosa	0 (0)	1 (1.1)	0.29

Table 4. Resistant against of bacteria isolated in bile cultures of patients with acute cholangitis/cholecystitis.							
Bacteria	Piperacillin / tazobactam	Meropenem	Ceftriaxone	Cefepime	Ciprofloxacin	Levofloxacin	*p
E. coli	3 (3.4)	0 (0)	0 (0)	2 (2.2)	0 (0)	0 (0)	0.3
K. pneumoniae	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0.2
Enterobacter spp	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	1 (1.1)	0.4
Enterococcus	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	0.1
Streptococcus spp	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.1
P. aeruginosa	0 (0)	0 (0)	2 (2.2)	0 (0)	0 (0)	0 (0)	0.2

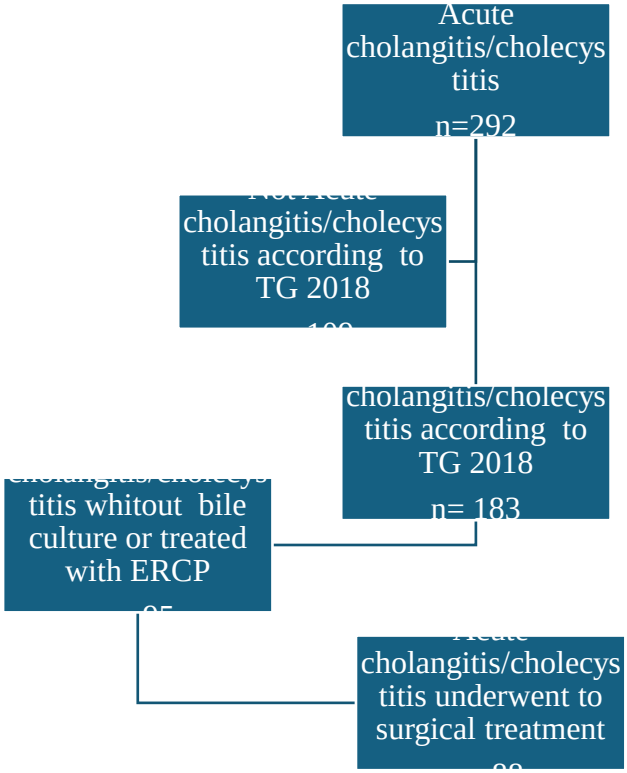

Fig. 1. Study population

The hospital records of patients treated from March 2021 to March 2022 were searched to identify those with acute cholangitis/cholecystitis who had bile cultures and underwent surgical treatment. ERCP, endoscopic retrograde cholangiopancreatography; TG2018, Tokyo Guidelines 2018.