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Original Article

The microbiology of acute cholangitis and associated in-hospital mortality

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Abstract

Aim: Acute cholangitis is an infection that may become life-threatening. In this study, we investigated the most prevalent organisms identified in cultures, antibiotic resistance patterns and associated in-hospital mortality.

Materials and Methods: Patients diagnosed as having acute cholangitis were included in the study retrospectively. The study patients were classified in two groups by culture results as culture-negative or culture-positive patients. The aim of the study was to identify offending organisms, antibiotic resistance and in-hospital mortality based on culture results.

Results: Overall, 108 patients with acute cholangitis were evaluated in two groups. Sixty six patients (61.2%) had positive cultures and 43 (40%) of these patients had polymicrobial culture results. There was a predominance of gram-negative bacteria (63%) and particularly, Klebsiella spp. and E.coli were the most commonly isolated organisms. The patients who died had 90.9% positive cultures, whereas those who survived had 53.6% culture positivity (p=0.02)

Conclusions: Biliary stent implantaiton was found to be the most common etiological factor for acute cholangitis. In terms of culture results, *K. pneumoniae* and *E. coli* were the most commonly isolated causative agents. ESBL resistance was found with a rate of 48.5% and carbapenem resistance was found with a rate of 22% for gram negative bacilli. Culture positivity was a risk factor in terms of in-hospital death.

Keywords: Acute cholangitis; antibiotic resistance; microorganism; mortality

INTRODUCTION

Acute cholangitis is an infection that may become life-threatening if early diagnosis and treatment cannot be accomplished (1). The first international practice guidelines were developed in 2007 for acute cholangitis. They were later revised in 2013 and 2018 (Tokyo Guidelines) (2-4). During cholangitis, bacteremia occurs in about 20-80% of cases (5, 6). In fact, biliary tract infections are an important cause for community acquired and hospital-acquired bacteremia (7).

Endoscopic or percutaneous biliary drainage is the main pillar of acute cholangitis treatment along with antimicrobial therapy (8,9). In the past decade, there has been substantial advancements in medical technology for treatment of acute cholangitis. Particularly, techniques of endoscopic biliary drainage have improved rapidly. Despite the new biliary drainage techniques, increasing incidences of antimicrobial resistance along with increasing numbers of older patients who have multiple comorbidities, have caused some changes in the epidemiological and clinical features observed in acute cholangitis.

Identification of causative microorganisms takes time and treatment with empirical antibiotics is initiated for possible causative agents. However, the prevalence of antibiotic resistant microorganisms is increasing (10). Antimicrobial resistance has shifted towards gram-negative organisms owing to the empirical antibiotic administration. Therefore, antimicrobial agents should be used very carefully and wisely (11).

On the other hand, current and comprehensive data on this subject in the world and in our country are insufficient. In our study, we aimed to investigate the demographics, clinical features, spectrum of microbiological agents and the antibiotic resistance patterns in patients who were hospitalized because of acute cholangitis. We also aimed to examine the association of in-hospital mortality with respect to culture results

MATERIALS and METHODS

Study Population

Hospital records of patients who were hospitalized in the gastroenterology department because of acute

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cholangitis between January 2018 and December 2019, were retrospectively analyzed, and those with acute cholangitis over the age 18 were enrolled in the study. Collected data included gender, age, clinical symptoms, acute cholangitis etiologies, previous biliary tract diseases, biliary tract procedures (any process to the biliary system, cholecystectomy, biliary stent and biliary enteroanostomosis), results of microbiological blood and bile culture and resistance patterns and laboratory findings.

Acute cholangitis was defined according to the revised 2018 Tokyo criteria. The diagnosis of cholangitis required at least two of the following findings: (a) upper quadrant pain and fever (b) biliary tract stenosis either confirmed by radiological (computed tomographic or sonographic) or endoscopic findings (c) high serum alkaline phosphatase and bilirubin levels. Local ethics committee approval was provided from Bezmialem Vakif University (Approval date and number: 19/02/2020-2909).

The study patients were classified in two groups by culture results; (1) patients with acute cholangitis and negative culture results; (2) patients with acute cholangitis with positive culture results. An infectious diseases physician who was blinded to the in-hospital outcomes, reviewed and categorized the microbiological analyses of all culture results.

Definition of Infections

Infections that occurred 72 hours after hospitalization were classified as nosocomial infections, and those that occured in the first 72 hours of hospitalization were classified as community-acquired infections. In addition, infections that occurred in patients with a history of hospitalization over the past 3 months were also considered as nosocomial infections. The following antibiotic resistant pathogens were specified: (a) third-generation cephalosporin-resistant escherichia coli, klebsiella, enterobacter, (b) carbapenem-resistant klebsiella, pseudomonas; (c) ampicillin-resistant enterococcus; (d) pseudomonas resistant ceftazidime; and (e) methicillin resistant staphylococcus.

The outcomes of the study included specification of the agents isolated from the cultures, antibiotic resistance patterns and associated in hospital mortality.

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean and standard deviation or median (interquartile range) where appropriate. Comparison of two continuous variables was performed using either T test or Mann Whitney U test, whereas statistical analysis of ordinal variables was performed using Chi square or Fisher's exact test. A p value (two-tailed) of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinical properties of the study population are summarized in Table 1. Overall, 108 patients were included in the final analysis (median age 63.7 (±15.8), males: 71 (65.7%)). Patients with

Table 1. Baseline clinical characteristics and laboratory values of the study patients

	All patients (n=108) Median (min-max) or %	Negative culture cholangitis (n=42, 38.8%) Median (min-max) or %	Positive culture cholangitis (n=66, 61.2%) Median (min-max) or %	P value
Age (years) Mean (±std)	63.7 (±15.8)	65 (±14.3)	62.9 (±16.7)	0.521
Gender (Male)	71 (65.7%)	27 (64.3%)	44 (66.7%)	0.799
Etiology of cholangitis				
Bile duct stones	45 (41.7%)	23 (54.8%)	22 (33.3%)	0.029
Endoscopic procedure	5 (4.6%)	1 (2.4%)	4 (6.1%)	
Biliary stent	52 (48.1%)	14 (33.3%)	38 (57.6%)	
Tumor	6 (5.6%)	4 (9.5%)	2 (3%)	
Sampling				
Blood	85 (78.7%)	36 (85.7%)	49 (74.2%)	
PTC	4 (3.7%)	0 (0.0%)	4 (6%)	<0.01
Endoscopic sample	13 (12%)	0 (0.0%)	13 (19.7%)	
History of biliary tract disease				
Cholecystitis /bile duct stones	75 (69.4%)	29 (69%)	46 (69.7%)	
Acute pancreatitis	2 (1.9%)	0 (0.0%)	2 (3%)	0.029
Biliary malignancy	13 (12%)	2 (4.8%)	11 (16.7%)	
Cholecystectomy	3 (2.8%)	3 (7.1%)	0 (0.0%)	
Laboratory findings				
ALT	43 (14-506)	42.5 (15-340)	49 (16-506)	0.917
AST	49 (9-417)	44 (11-417)	57 (9-385)	0.757
ALP	219 (50-1941)	149 (50-1493)	269 (83-1941)	0.002
GGT	233 (14-1474)	144 (14-1096)	333.5 (16-1474)	0.004
WBC	9.600 (1.720-14.000)	9.000 (3.900-14.000)	10.000 (1.720-11.000)	0.360
CRP	16.3 (0.06-189)	12.7 (0.06-189)	24.6 (0.44-187)	0.089
Complications				
Pericholangitic abcess	6 (5.5%)	2 (4.8%)	4 (6%)	0.794
Multiorgan failure	2 (1.9%)	0 (0.0%)	2 (3.1%)	

ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; CRP: C reactive protein; PTC: Percutaneous transhepatic cholangiography GGT: Gamma-glutamyl transferase; WBC: white blood cell acute cholangitis were evaluated in two groups; culture positive (n=66, 61.2%) and culture negative (n=42, 38.8%). Blood cultures were obtained from 85 patients (78.7%) and endoscopic samples were obtained from 13 (12%) patients. In culture positive cholangitis (n=66), 74.2% of the microorganisms were isolated from blood culture, 19.7% from endoscopic samples and 6% from percutaneous trasnhepatic cholangiography samples. The most common diagnosis of acute cholangitis was biliary stenting (n=52, 48.1%) which was followed by bile duct stones with a rate of 41.7% (n= 45), cancer with a rate of 5.6% (n=6) and endoscopic procedure with a rate of 4.6% (n=5). According to culture results, a significant difference was found in terms of etiologies (p=0.029). A significant difference was found in serum ALP and GGT values between the two groups (p= 0.002 and 0.004).

Fourty three (40%) patients had polymicrobial culture results. Ninety seven microorganisms were isolated in the culture positive cholangitis patients (n=66). The distribution and antibiotic resistances of the isolated microorganisms are shown in Table 2. Among the microorganisms isolated, 70.1% were gram negative bacilli, 24.8% were gram positive cocci and 5.1% were *Candida spp*. The percentages of the most commonly isolated microorganisms were as follows: *E.coli* 24.7% (n=24), *Klebsiella spp*. 24.7% (n=24), *Pseudomonas spp*. 16.5% (n=16), *Enterococcus spp*. 13.4% (n=13), *Staphylococcus spp*. 7.2% (n=7). Among gram negative bacilli, ESBL resistance was 48% and carbapenem resistance was 22%. *Candida spp*. were the only fungi detected with a rate of 5% (n = 5). *Enterococcus spp*. were the most prevalent gram-positive bacteria detected with a rate of 12% (n=13).

Culture results of the patients who were lost during the hospitalization period, are shown in Table 3. In the univariate analysis, the patients who were lost during the hospitalization period, had a higher rate of culture positivity compared to surviving patients, and this difference was statistically significant (90.0% vs 53.6%, p=0.023). Also, the rate of gram negative bacilli was higher in the patients who were lost (36.4%) compared to the patients who survived (25.8%), but the difference was statistically insignificant (p = 0.09). The rate of Candida spp. was higher in the patients who were lost (18.2%) compared to the patients who survived (3.1%), but this difference was not statistically significant (p = 0.08).

Table 2. Isolated microorganisms and antibiotic resistance in patients with cholangitis

Microorganisms	Total N=97 N(%)	Polymicrobial N=71 N(%)
Gram-negative bacilli	68 (70.1)	48 (67.6)
E. coli	24 (24.7)	19 (26.7)
ESBL resistant *E.coli*	17 (70.8)	15 (78.9)
Klebsiella spp.	24 (24.7)	15 (21.1)
ESBL resistant *Klebsiella*	14 (58.3)	10 (66.6)
Carbapenem resistant *Klebsiella*	4 (16.6)	3 (20)
Pseudomonas spp.	16 (16.5)	11 (15.5)
Carbapenem resistant Pseudomonas	10 (62.5)	8 (72.7)
Enterobacter spp.	2 (2)	2 (2.8)
ESBL resistant *Enterobacter*	2 (100)	2 (100)
Citrobacter spp.	1 (1)	1 (1.4)
Carbapenem resistant *Citrobacter*	1 (100)	1 (100)
Acinetobacter spp	1 (1)	0 (0.0)
ESBL resistance in gram negative bacilli	33 (48.5)	27 (56.2)
Carbapenem resistance in gram negative bacilli	15 (22)	12 (25)
Gram-positive cocci		
Staphylococcus spp.	24 (24.8)	18 (25.3)
Coagulase negative *staphylococcus*	7 (7.2)	5 (7)
Meticiline-resistance	7 (7.2)	5 (7)
Enterococcus spp.	0 (0.0)	0 (0.0)
Penicillin resistance	13 (13.4)	11 (15.5)
Streptococcus spp.	2 (15.4)	2 (2.8)
Fungi	4 (4.1)	2 (2.8)
Candida spp.	5 (5.1)	5 (7)

Table 3. In-hospital mortality risk factors in patients with cholangitis			
	In-hospital death (n=11) n(%)	**Living patients (n=97) n(%)**	**P values**
Gender			
Male	9 (81.8)	62 (63.9)	0.325
Female	2 (18.2)	35 (36.1)	
Culture positive cholangitis	10 (90.9)	52 (53.6)	**0.023**
Gram negative-bacilli	7 (63.6)	34 (35.1)	0.099
ESBL in gram-negative bacilli	4 (36.4)	25 (25.8)	0.256
Carbapenem resistance in gram-negative bacilli	3 (27.3)	11 (11.3)	0.256
Gram positive cocci	4 (36.4)	17 (18.3)	0.226
Candida spp.	2 (18.2)	3 (3.1)	0.080
Polymicrobial etiology	8 (80)	35 (63.6)	0.474

ESBL: Extended spectrum beta lactamase

DISCUSSION

In this study, culture results indicated gram-negative bacterial predominance, *Klebsiella* and *E. coli* being the most prevalent. Also, culture positivity was a significant risk factor for in-hospital mortality. The most common encountered antibiotic resistance was ESWL and karbepenem resistance among gram negative bacteria; penicillin resistance in gram positive bacteria.

Acute cholangitis is a significant disease that may lead to morbidity and mortality, however, relatively few studies have been conducted on this issue. Gomi et al (12) presented a large-scale study that included comprehensive updated epidemiological and microbiological data and outcomes in patients diagnosed as having acute cholangitis. In their study, the patients with acute cholangitis had a mortality rate of 8.4%. Similar to our study, E. coli and K. pneumoniae were the most prevalent causative agents grown in blood and bile cultures. Reuken et al. (13) found a high proportion of acute cholangitis due to *Enterococcus spp*. and *E. coli*.

In our study, biliary stent implantation was found to be the most frequent underlying etiological factor. In a study conducted by Tohda G et al., bile duct stones were found to be the most common etiology of acute cholangitis in accordance with the latest reported studies (14). In the study reported by Gomi et al. (12), the most commonly encountered etiologies included bile duct stones, biliary stent occlusion and tumors.

In our study, ESBL resistance was 48.5% and carbapenem resistance was 22% for gram negative microorganisms. In a study evaluating biliary system infections conducted by Sung et al. (15) ESBL resistance was found with a rate of 27.6% for gram negative microorganisms. An increase in antibiotic resistance rates has been detected over the years.

In that study it was also shown that nosocomial infection, hospitalization or antibiotic administration over the past 3 months, and the presence of a biliary drainage catheter were all risk factors in terms of antibiotic resistance in acute cholangitis. (15).

In our study, high rates of endoscopic procedures and biliary stent placement were thought to be effective in high rates of resistant microorganisms. On the other hand, the increase in antibiotic resistance rates particularly in gram-negative microorganisms should be considered especially in the empirical antibiotic treatment for severe acute cholangitis.

When risk factors affecting in-hospital mortality were analyzed, culture positivity was found to be related to mortality. In a previous study, regarding 30-day mortality, malignancy was the most important risk factor. In addition to that, underlying liver disease, severe bacteremia, inappropriate antibiotic use, and hospital admission before bacteremia were also found as contributing factors (15). In their study, antibiotic resistance rates were not associated with mortality, similar to our study. However, many researchers have studied the clinical importance of infections caused by antibiotic-resistant pathogens, and some have drawn a conclusion that antibiotic resistance was an important independent predictor of mortality in patients with bacteremia (16,17). On the other hand, some researchers have not found a relationship between antibiotic resistance and mortality (18,19). It is likely that timely intervention such as biliary decompression and other supportive treatments might have played a role in those studies.

LIMITATIONS

Our study was a single-center study with a retrospective design and a small number of patients.

CONCLUSION

Biliary stent implantation that was found to be the most common etiological factor for acute cholangitis. *E. coli* and *K. pneumoniae* were the most common causative agents. ESBL resistance was found with a rate of 48.5%

and carbapenem resistance was found with a rate of 22% for gram negative bacilli. Culture positivity was a risk factor in terms of in-hospital death.

Competing Interests: The authors declare that they have no competing interest.

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