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Contents

Monthly Volume 14 Number 12 December 27, 2022

MINIREVIEWS

- 1320 Timing of individualized surgical intervention in Crohn's disease
Xia K, Gao RY, Wu XC, Yin L, Chen CQ

ORIGINAL ARTICLE

Basic Study

- 1329 Hydrogen gas and preservation of intestinal stem cells in mesenteric ischemia and reperfusion
Yamamoto R, Suzuki S, Homma K, Yamaguchi S, Sujino T, Sasaki J

Retrospective Study

- 1340 Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study
Huang XM, Zhang ZJ, Zhang NR, Yu JD, Qian XJ, Zhuo XH, Huang JY, Pan WD, Wan YL
- 1350 Low preoperative skeletal muscle index increases the risk of mortality among resectable pancreatic cancer patients: A retrospective study
Cai ZW, Li JL, Liu M, Wang HW, Jiang CY

Observational Study

- 1363 Development of a prediction model for enteral feeding intolerance in intensive care unit patients: A prospective cohort study
Lu XM, Jia DS, Wang R, Yang Q, Jin SS, Chen L

Prospective Study

- 1375 Real-time *in vivo* distal margin selection using confocal laser endomicroscopy in transanal total mesorectal excision for rectal cancer
Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Jiang W, Yan J

META-ANALYSIS

- 1387 Short- and long-term outcomes of laparoscopic *vs* open surgery for T2 gallbladder cancer: A systematic review and meta-analysis
Zhang W, Ouyang DL, Che X
- 1397 Meta-analysis of transanal *vs* laparoscopic total mesorectal excision of low rectal cancer: Importance of appropriate patient selection
Bhattacharya P, Patel I, Fazili N, Hajibandeh S, Hajibandeh S

CASE REPORT

- 1411 Secondary sclerosing cholangitis in a young COVID-19 patient resulting in death: A case report
Steiner J, Kaufmann-Bühler AK, Fuchsjäger M, Schemmer P, Talakić E

- 1418** Rectal tubular adenoma with submucosal pseudoinvasion misdiagnosed as adenocarcinoma: A case report
Chen D, Zhong DF, Zhang HY, Nie Y, Liu D
- 1425** Malignant transformation of perianal tailgut cyst: A case report
Fang Y, Zhu Y, Liu WZ, Zhang XQ, Zhang Y, Wang K
- 1432** Acute appendicitis in the short term following radical total gastrectomy misdiagnosed as duodenal stump leakage: A case report
Ma J, Zha ZP, Zhou CP, Miao X, Duan SQ, Zhang YM

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Retrospective Study

Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study

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Abstract

BACKGROUND

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment. There is no consensus on bile microbial culture profiles in previous studies, and identified microbial spectrum and drug resistance is helpful for targeted preventive and therapeutic drugs in the perioperative period.

AIM

To analyze the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

METHODS

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

RESULTS

This study included 185 patients, of whom 163 (88.1%) were diagnosed with gallstones and 22 (11.9%) were diagnosed with gallstones and common bile duct stones (CBDs). Bile culture in 38 cases (20.5%) was positive. The presence of CBDs (OR = 5.4, 95%CI: 1.3-21.9, $P = 0.03$) and longer operation time (> 80 min) (OR = 4.3, 95%CI: 1.4-13.1, $P = 0.01$) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. The resistance rate to cephalosporin in *E. coli* was above 42% and varied across generations. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

CONCLUSION

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β -lactam antibiotics and β -lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended. Additionally, regular monitoring of emerging resistance patterns is required in the future.

Key Words: Bacterial infection; Drug resistance; Cholelithiasis; Gallbladder bile culture

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Core Tip: In this work, we analyzed the microbial spectrum of the bile of cholelithiasis patients, and their drug susceptibility pattern. We found that the presence of common bile duct stones and longer operative duration were independent risk factors for positive bile culture for patients complicated with cholelithiasis. The most commonly detected bacterium was *Escherichia coli*. In addition, the combination of β -lactam antibiotics and β -lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens secondary to carbapenems or glycopeptides and is recommended, but its resistance should also be noted.

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INTRODUCTION

Bacteria can easily enter the biliary system from the duodenum; however, continuous bile secretion in the biliary system prevents their growth and colonization. Despite this, the presence of bacteria in bile has been reported in 9.5%-54.0% of patients with cholelithiasis or gallstones[1-3], and up to 70.2%-78.0% of patients with common bile duct stones (CBDs)[4,5]. As the presence of bacteria in the biliary tract may increase the risk of postoperative septic complications[6-8], it is essential to identify the risk factors for positive bile culture during cholecystectomy and, accordingly, design a suitable antibiotic prophylaxis regimen[6,8].

The indiscriminate use of antibiotics in the last few decades has led to the emergence of multidrug-resistant (MDR) pathogenic bacteria[9], which have also been isolated from bile specimens[10]. Such

MDR microbes reduce the efficacy of empirical drugs[11,12]. Therefore, it is essential to identify the species of pathogenic bacteria found in the bile of cholelithiasis patients, as well as their drug susceptibility profile, in order to develop effective antibiotic regimens for biliary tract infections. To this end, we analyzed the distribution and drug resistance patterns of pathogens isolated from bile samples obtained from patients with cholelithiasis on the basis of bile culture and drug susceptibility test results.

MATERIALS AND METHODS

Study population

This study included patients with bile culture results who underwent cholecystectomy with or without common bile duct exploration, stone extraction, and T tube drainage between May 2013 and December 2018 at the Department of Hepatobiliary Surgery at The Sixth Affiliated Hospital of Sun Yat-sen University. The indications for surgical treatment were cholelithiasis and its complications. Most patients had presented with right upper abdominal pain or other discomfort at the time of admission. In all the included patients, a gallstone with acute or chronic cholecystitis was preoperatively diagnosed based on abdominal ultrasound and computed tomography (CT) imaging and confirmed after cholecystectomy. Each surgical procedure was performed by a professional hepatobiliary surgical team. Access to clinical data was approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (2022ZSLYEC-352).

Inclusion and exclusion criteria

Inclusion criteria were patients aged ≥ 18 years, who underwent cholecystectomy indicated by cholelithiasis and its complications. All included patients had complete clinicopathological and bile culture results. Exclusion criteria were cholecystectomy indicated by other reasons ($n = 12$), lack of bacterial culture results ($n = 64$), and contaminated bile culture sample ($n = 2$). Demographic characteristics, microbial spectrum and drug resistance of pathogens in patients were assessed. A total of 185 patients were included, and the clinicopathological and microbiological data were retrospectively collected from the medical record system. The research flow chart is outlined in Figure 1.

Bile culture, identification of bacteria, and drug sensitivity tests

Bile samples (5 μ L) were extracted during cholecystectomy and promptly transported in sterile containers to a microbiology laboratory for bacterial culture as per standard protocols. Bacterial identification and drug susceptibility tests were performed using the French Bio-Merieux ATB-Expression Automatic Bacterial Identification and Drug Susceptibility Test instrument. The results were evaluated according to the 2010 recommendations of the American Society for Clinical Laboratory Standardization.

Statistical analysis

Data analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, United States). Continuous variables that followed Gaussian distribution were expressed as mean \pm SD, and those with non-normal distribution were expressed as the median with interquartile range. Categorical variables were described using frequencies. Data were compared using the two-tailed student *t*-test, chi-square test, Fisher's exact test, or Mann-Whitney *U*-test, as appropriate. Significant covariates identified by univariate analysis were further analyzed by multivariate logistic regression analysis to determine the independent risk factors for positive bile culture. A *P* value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

Out of a total of 285 patients who underwent cholecystectomy between May 2013 and December 2018, 185 fulfilled the inclusion criteria and were included in this study. The cohort comprised 80 (43.2%) male and 105 (56.8%) female patients, and their mean age was 54.3 years (SD = 15). Twenty-two patients were diagnosed with gallstones accompanied by CBDs, and bile cultures were positive for 17 (77.3%) of these patients. In contrast, only 12.9% (21/163) of the patients who did not have CBDs had bacterial colonization in their bile samples. In addition, 155 (83.8%) patients had right upper abdominal discomfort. Laparoscopic cholecystectomy is the most common procedure used for removing gallstones, but four patients with calculous cholecystitis underwent open surgery due to severe adhesions. In addition, one patient with CBDs underwent complete laparoscopic surgery. The median operative time was 80 (59-120) min, and cefotaxime/sulbactam sodium and cefamandole were the main preventive or therapeutic antibiotics used preoperatively. The overall rate of septic complications was 5.4% (10/185), and the incidence of septic complications was similar in the culture-positive and culture-negative

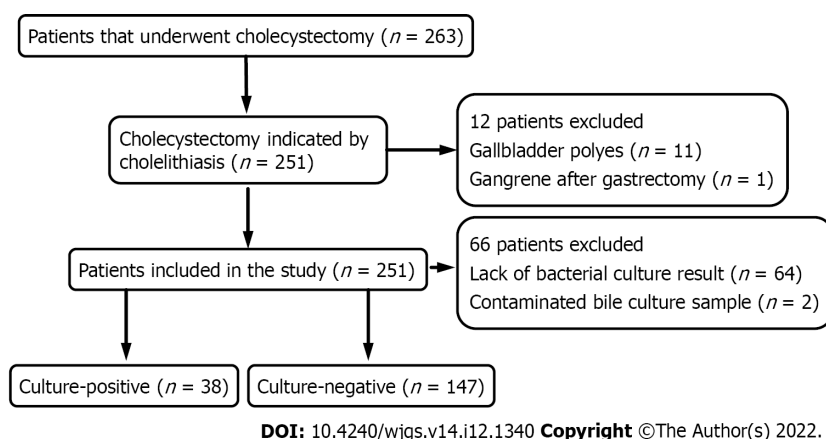


Figure 1 Flowchart of the patient selection process.

patients [4.1% (6/147) *vs* 10.5% (4/38)]. The detailed demographic characteristics of both groups are summarized in Table 1, and they show significant differences in age, BMI, presence of CBDs, previous endoscopic retrograde cholangiopancreatography (ERCP), previous use of antibiotics, presence of multiple stones, open surgery, operation time, and preoperative therapeutic antibiotics. Multivariate logistic regression analysis of these significant variables indicated that the presence of CBDs (OR = 5.4, 95%CI: 1.8-21.9, $P = 0.029$) and longer operation time (OR = 4.3, 95%CI: 1.4-13.1, $P = 0.01$) were independent risk factors for bacterial colonization of bile samples (Table 2).

Microbial spectrum of bile specimens

Of the 38 (20.5%) patients with positive bile culture results, 28 (73.7%) harbored gram-negative bacteria that were predominantly from the family *Enterobacteriaceae*, including *Escherichia coli* (19 cases), *Klebsiella pneumoniae* (5 cases), *Enterobacter cloacae* (2 cases), *Enterobacter aerogenes* (1 case), and *Enterobacter mirabilis* (1 case). Gram-positive bacteria were detected in 10 (26.3%) patient samples and included *Enterococcus faecalis* (6 cases), *Enterococcus faecium* (3 cases), and *Staphylococcus aureus* (1 case) as the predominant species. No fungal species were detected, as shown in Table 3.

Antibiotics susceptibility test results

Based on the antibiotics susceptibility test results, the pathogens were divided into sensitive, intermediate resistant, and resistant groups, and pathogens assigned to the latter two groups were included in the resistance rate analysis. Due to differences in test strips, the results of the susceptibility tests differed across the patients. The resistance rate of *E. coli* against cephalosporins decreased with more advanced generations, and the rates were 68.4%, 57.9%, 52.6%, and 47.3% for cefuroxime, cefotaxime, ceftazidime, and cefepime, respectively. The resistance rate against ciprofloxacin was similar to that against cefoxitin (42.1%). *E. coli* also displayed a high level of resistance against broad-spectrum penicillins, that is, 78.9% and 63.2% against ticarcillin and piperacillin, respectively. Furthermore, *E. coli* exhibited a resistance rate of 83.3% against amoxicillin in 12 of the specimens tested. The combination of piperacillin and the β -lactamase inhibitor tazobactam was effective against *E. coli*, as it was associated with a low resistance rate of 15.8%. In addition, almost all the isolated bacteria were sensitive to carbapenems, with the exception of one that was resistant to imipenem. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*, except that it had lower resistance against amikacin and ciprofloxacin. *Enterococcus* spp. exhibited a high resistance rate of 88.9% against aminoglycosides (gentamicin and streptomycin), while *E. faecalis* exhibited 100% sensitivity to glycopeptide. In contrast, several strains of *E. faecium* were resistant to glycopeptides (1/3) and penicillins (2/3). The results are summarized in Tables 4 and 5. Finally, 24 of the 38 patients harbored MDR strains, with 10 (52.6%) *E. coli* strains and 1 (20%) *K. pneumoniae* strain producing extended spectrum β -lactamases (ESBLs).

DISCUSSION

The gallbladder is a sterile organ, but pathological conditions, such as gallstones, polyps, and tumors, create favorable conditions for bacterial colonization by blocking bile circulation, which results in cholestasis[5,13]. Bacterial colonization can lead to inflammation of the biliary tract and even sepsis in severe cases. The main sources of biliary tract infection are the blood and duodenum[10]. In our study, bacteria were detected in the bile specimens of 20.5% cholelithiasis patients, and *Enterobacteriaceae* (73.7%; mainly *E. coli* and *K. pneumoniae*) and *Enterococcus* spp. (23.7%; *E. faecium* and *E. faecalis*) were the dominant species. Consistent with previous studies, most of the bacteria detected here were

Table 1 Baseline characteristics of the bile culture-positive group and culture-negative group

Parameter	Total	Culture-negative	Culture-positive	P value
Number	185	147	38	-
Age (yr; mean \pm SD)	54.3 \pm 15.0	52.4 \pm 14.7	61.3 \pm 14.2	0.001
BMI (kg/m ² ; mean \pm SD)	23.1 \pm 3.4	23.4 \pm 3.2	22.1 \pm 3.8	0.040
Male (%)	80 (43.2)	61 (33.0)	19 (10.3)	0.346
Combined with CBDS (%)	22 (11.9)	5 (2.7)	17 (9.2)	< 0.001
Right upper abdominal pain (%)	155 (83.8)	120 (64.9)	35 (18.9)	0.118
Positive Murphy sign (%)	27 (14.6)	24 (13.0)	3 (1.6)	0.189
Diabetes mellitus (%)	11 (5.9)	8 (4.3)	3 (1.6)	0.699
Hypertension (%)	41 (22.2)	32 (17.3)	9 (4.9)	0.800
History of ERCP (%)	7 (3.7)	1 (0.5)	6 (3.2)	< 0.001
Previous intake of antibiotics (%)	44 (23.8)	29 (15.7)	15 (8.1)	0.011
WBC count ($> 10 \times 10^9/L$)	16 (8.6)	11 (5.9)	5 (2.7)	0.267
Multiple stones (%)	132 (71.3)	99 (53.5)	33 (17.8)	0.018
Max diameter of stone (cm; mean \pm SD)	1.2 \pm 0.8	1.1 \pm 0.8	1.3 \pm 0.7	0.177
Non-laparoscopic surgery (%)	41 (22.2)	19 (10.3)	22 (11.9)	< 0.001
Operative time (min), median (IQR)	80 (59-120)	70 (56.5-93.8)	124 (95.0-188.8)	< 0.001
Septic complications (%)	10 (5.4)	6 (3.2)	4 (2.2)	0.125

CBDS: Common bile duct stone; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; WBC: White blood cell.

Table 2 Multivariate analysis results of risk factors for positive bile culture

Variables	OR (95%CI)	P
Operation time > 80 min	4.3 (1.4-13.1)	0.01
Combined with CBDS	5.4 (1.3-21.9)	0.02

95%CI: 95% confidence interval; OR: Odds ratio; CBDS: Common bile duct stone.

endogenous and of intestinal origin[12,14,15]. Unlike other studies, however, we did not detect *Pseudomonas aeruginosa* or any fungal species[15,16]; this could probably be explained by our limited sample size.

The risk of bacterial invasion of the bile is associated with biliary obstruction, older age (> 70 years), acute cholecystitis, CBDSs, cholangitis, ERCP before cholecystectomy, and dysfunctional gallbladder[8, 15,17]. In our study, the presence of CBDSs and longer operation time were identified as independent risk factors for positive bile culture. In the case of positive bile culture, postoperative antibiotic use needs to be adjusted in order to minimize the risk of infection after surgery. Studies have shown a higher incidence of postoperative septic complications in patients with positive bile culture than in those without bile infection[6,8,18], with the overall rates varying from 0.9% to 20.0%[6,8,19]. In contrast to these studies, in the present study, the rate of septic complications was 3.2% in the negative culture group and 2.2% in the positive culture group. This indicates that there was no significant correlation between the presence of bacteria and biliary sepsis. The differences in the findings may be associated with the empirical use of cefotaxime/sulbactam sodium and the smaller sample size in our cohort.

According to the definition of MDR proposed by the European Centre for Disease Prevention and Control Advisory Forum in 2010, it is described as resistance to one agent of at least three or more classes of antibiotics, but it does not cover intrinsic resistance or resistance against a key antimicrobial agent[9]. In the present study, although the antibiotic sensitivity tests did not include all the relevant antibiotics, the lowest incidence of MDR was 63.2%, which indicates that the rate of MDR is high in pathogens that infect bile. Cephalosporins and quinolones are commonly used to treat biliary tract infections, and the concentration of these drugs increases in bile after their absorption and metabolism [20,21]. However, as a result of the emergence of drug-resistant bacteria, the efficacy of conventional

Table 3 Composition of bile isolated bacteria

Isolated microbes	Total strains	Frequency
Gram-negative	28	73.7%
<i>Escherichia coli</i>	19	50.0%
<i>Klebsiella pneumoniae</i>	5	13.2%
<i>Enterobacter cloacae</i>	2	5.3%
<i>Enterobacter aerogenes</i>	1	2.6%
<i>Enterobacter mirabilis</i>	1	2.6%
Gram-positive	10	26.3%
<i>Enterococcus faecalis</i>	6	15.8%
<i>Enterococcus faecium</i>	3	7.9%
<i>Staphylococcus aureus</i>	1	2.6%
Fungus	0	0

Table 4 Antibiotics susceptibility test results for *Enterococcus* spp

Antimicrobial agents	<i>Enterococcus faecalis</i> (6)		<i>Enterococcus faecium</i> (3)	
	AST	Resistance (%)	AST	Resistance (%)
Gentamicin	1S + 5I	5 (83.3)	3I	3 (100)
Streptomycin	1S + 4I + 1R	5 (83.3)	2I + 1R	3 (100)
Ciprofloxacin	3S + 3I	3 (50)	2S + 1R	1 (33.3)
Levofloxacin	5S + 1I	1 (16.7)	2S + 1R	1 (33.3)
Vancomycin	6S	0	2S + 1I	1 (33.3)
Teicoplanin	6S	0	3S	0
Ampicillin	6S	0	1S + 1I + 1R	2 (66.7)
Penicillin	6S	0	1S + 2R	2 (66.7)
Quinupristin-dalfopristin	1S + 5R	5 (83.3)	2S + 1I	1 (33.3)
Tetracycline	3S + 3R	3 (50)	2S + 1R	1 (33.3)
Rifampin	1S + 1I + 4R	5 (83.3)	2S + 1R	1 (33.3)
Erythromycin	4I + 2R	6 (100)	1S + 2R	2 (66.7)

AST: Aspartate aminotransferase.

antibacterial drugs has begun to decline[9,10]. In this study, the gram-negative bacteria showed nearly 100% sensitivity to meropenem and imipenem, while 40% of the strains were resistant to cephalosporins and quinolones and over 50% were resistant to second- or third-generation cephalosporins. This high rate of resistance is mainly attributed to the emergence of ESBL-producing bacteria, which accounted for 52.6% of the *E. coli* strains isolated from our cohort. Therefore, the empirical treatment of biliary infections should take into account ESBL-producing bacteria. Treatment with multiple drug combinations, including β -lactamase inhibitors, has been highly effective against gram-negative bacilli[21-23]. This was confirmed by the high sensitivity of *E. coli* to piperacillin and tazobactam in the present study; however, *E. coli* exhibits a fairly high resistance rate against ticarcillin/clavulanic acid or amoxicillin/clavulanic acid. Aminoglycosides are also used to treat biliary infections[20], and the resistance rates of *E. coli* against gentamicin and amikacin were found to be 36.8% and 15.8%, respectively.

MDR *Enterococcus* spp. has been increasingly detected in recent years, and these species exhibit intrinsic resistance to most cephalosporins and carbapenems[9,24]. The overall prevalence of vancomycin-resistant *Enterococcus*, one of the major nosocomial pathogens worldwide[25], is 5%-20% [25,26]. In this study, *Enterococcus* spp., especially *E. faecalis*, were highly sensitive to ampicillin and penicillin. Interestingly, while only 14.7% of *E. faecalis* strains isolated in Japan are resistant to β -lactam

Table 5 Antibiotics susceptibility test results for *Enterobacteriaceae*

Antimicrobial agents	<i>Escherichia coli</i> (n = 19)		<i>Klebsiella pneumoniae</i> (5)		<i>Enterobacter cloacae</i> (2)	<i>Enterobacter aerogenes</i> (1)	<i>Enterobacter mirabilis</i> (1)
	AST	Resistance (%)	AST	Resistance (%)	AST	AST	AST
Amikacin	16S + 3R	3 (15.8)	5S	0	2S	1S	1S
Gentamicin	12S + 7R	7 (36.8)	4S + 1R	1 (20)	2S	1S	1S
Amoxicillin	2S + 10R	-	5R	5 (100)	1R	1R	-
Amoxicillin/clavulanic acid	11S + 3I + 5R	8 (42.1)	3S + 1I + 1R	2 (40)	1R	1I	1S
Ticarcillin	4S + 15R	15 (78.9)	5R	5 (100)	2S	1S	1S
Ticarcillin/clavulanic acid	4S + 8R	-	3S + 1R	-	1S + 1R	1S	1S
Piperacillin	7S + 12R	12 (63.2)	1S + 3I + 1R	4 (80)	2S	1S	1S
Piperacillin/tazobactam	16S + 3R	3 (15.8)	5S	0	2S	1S	1S
Cefazolin-1 st	1S + 5R	-	1R	-	-	-	1R
Cefoxitin	11S + 8R	8 (42.1)	3S + 2R	2 (40)	1R	1R	1R
Cefuroxime-2 nd	6S + 13R	13 (68.4)	2S + 3R	3 (60)	2S	1R	1S
Cefotaxime-3 rd	8S + 1I + 10R	11 (57.9)	4S + 1I	1 (25)	2S	1S	1S
Ceftazidime-3 rd	9S + 10R	10 (52.6)	4S + 1R	1 (25)	2S	1S	1R
Cefepime-4 th	10S + 1I + 8R	9 (47.3)	4S + 1R	1 (25)	2S	1S	1S
ESBLs (+)	10	10 (52.6)	1	-	-	-	-
Ciprofloxacin	11S + 8R	8 (42.1)	4S + 1R	1 (20)	2S	1R	1I
Imipenem	18S + 1R	1 (5.3)	5S	0	2S	1S	1R
Meropenem	19S	0	5S	0	2S	1S	1S

AST: Aspartate aminotransferase; ESBLs: Extended spectrum β -lactamases.

antibiotics, 85.7% of the *E. faecium* strains are resistant to ampicillin and all strains of both species are resistant to penicillin[26]. In addition, *Enterococcus* spp. were found to be highly resistant to aminoglycosides and sensitive to teicoplanin, and only one vancomycin-resistant *Enterococcus* strain was detected in our study. All these results indicate that the antibiotic regimen against biliary infections should be based on both the antibacterial spectrum of the drugs and the resistance patterns. Therefore, clinicians should routinely test bile samples collected during cholecystectomy in order to monitor the pathogenic species and drug susceptibility. This will not only provide a definite guide for postoperative treatment, but also provide data for future empirical use of antimicrobial agents.

This single-center retrospective study is based on data from hospital medical records, and several limitations should be noted. This study is limited by its retrospective design, that is, a heterogeneous population and the possibility of a type II error. In particular, owing to the small number of patients included, further studies are required to validate our findings.

CONCLUSION

The risk of biliary infection increases in patients with cholelithiasis, and the risk is higher in patients with CBDs and longer operation time. The dominant pathogens detected in this study were *E. coli*, *K. pneumoniae*, *E. faecium*, and *E. faecalis*. In addition, the combination of β -lactam antibiotics and β -lactamase inhibitors was found to be an effective first-line treatment against bile pathogens. However, we must also be aware of the emergence of resistance to certain types of drugs.

ARTICLE HIGHLIGHTS

Research background

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment.

Research motivation

Identified microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens is helpful for targeted preventive and therapeutic drugs in the perioperative period.

Research objectives

Investigate the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

Research methods

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

Research results

The presence of common bile duct stones (OR = 5.4, 95% CI: 1.3-21.9, $P = 0.03$) and longer operation time (> 80 min) (OR = 4.3, 95% CI: 1.4-13.1, $P = 0.01$) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

Research conclusions

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β -lactam antibiotics and β -lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended.

Research perspectives

To explore the characteristics of patients infected with drug-resistant bacteria and the prevention and treatment of drug-resistant bacteria.

FOOTNOTES

Author contributions: Huang XM, Zhang ZJ, and Zhang NR contributed equally to this study; Huang XM, Zhang ZJ, and Zhang NR contributed to study design, patient inclusion and exclusion, data collection, data analysis and interpretation, and manuscript writing; Yu JD, Qian XJ, Zhuo XH, and Huang JY contributed to data collection; Pan WD and Wan YL contributed equally to the work; Pan WD and Wan YL contributed to critical revision of the manuscript for important intellectual content and study supervision; all authors read and approved the final manuscript.

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