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BRIEF ARTICLE

Microbial profile and antibiotic sensitivity pattern in bile cultures from endoscopic retrograde cholangiography patients

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Abstract

AIM: To identify the frequency of bacterial growth, the most commonly grown bacteria and their antibiotic susceptibility, and risk factors for bacterial colonization in bile collected from patients with different biliary diseases.

METHODS: This prospective study was conducted between April 2010 and August 2011. Patients with various biliary disorders were included. Bile was aspirated by placing a single-use, 5F, standard sphincterotome catheter into the bile duct before the injection of contrast agent during endoscopic retrograde cholangiopancreaticography (ERCP). Bile specimens were transported to the microbiology laboratory in blood culture bottles within an anaerobic transport system. Bacteria were cultured and identified according to the standard protocol used in our clinical microbiology laboratory. The susceptibilities of the organisms recovered were identified using antimicrobial disks, chosen according to the initial gram stain of the positive cultures.

RESULTS: Ninety-one patients (27% male, mean age 53.7 ± 17.5 years, range: 17-86 years) were included in the study. The main indication for ERCP was benign biliary disease in 79 patients and malignant disease in 12 patients. The bile culture was positive for bacterial growth in 46 out of 91 (50.5%) patients. The most frequently encountered organisms were Gram-negative bacteria including *Escherichia coli* (28.2%), *Pseudomonas* (17.3%) and *Stenotrophomonas maltophilia* (15.2%). There were no significant differences between patients with malignant and benign disease (58% *vs* 49%, $P = 0.474$), patients with acute cholangitis and without acute cholangitis (52.9% *vs* 50%, $P = 0.827$), patients who were empirically administered antibiotics before intervention and not administered (51.4% *vs* 60.7%, $P = 0.384$), with regard to the bacteriobilia. We observed a large covering spectrum or low resistance to meropenem, amikacin and imipenem.

CONCLUSION: We did not find a significant risk factor for bacteriobilia in patients with biliary obstruction. A bile sample for microbiological analysis may become a valuable diagnostic tool as it leads to more accurate selection of antibiotics for the treatment of cholangitis.

Key words: Cholangitis; Endoscopic retrograde cholangiopancreaticography; Bacteriobilia; Bile culture

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INTRODUCTION

Usually the bile ducts are sterile. However, the presence of gallstones within either the gallbladder or biliary tree is associated with the bacterial colonization of the bile[1]. In patients without stone disease, previous biliary intervention is associated with high rates of bacteriobilia[2,3]. Under conditions of normal bile flow, bacteria in the biliary system are of no clinical significance. Upon bile duct obstruction, bacteria proliferate within the stagnant bile while biliary pressure increases. Eventually, the bacteria presumably translocate into the circulation causing a systemic infection. Acute cholangitis spans a continuous clinical spectrum and can progress from a local biliary infection to advanced disease with sepsis and multiple organ dysfunction syndrome[4]. Even recent studies have reported mortality rates of up to 10%[5,6]. Acute cholangitis is mainly a result of microbial infection caused by bacteria and fungi[7].

Blood cultures provide an opportunity to detect the causative organism but, even in febrile patients with cholangitis, blood cultures remain negative in more than half of the cases[8]. Although definitive management of cholangitis involves the relief of bile stasis, effective empiric antibiotic therapy is an indispensable part of the treatment[4,9]. Antimicrobial therapy recommendations state that antibiotics should be administered as soon as the diagnosis of acute cholangitis is suspected or established. Empirically administered antibiotics should be selected on the basis of antimicrobial activity against the causative bacteria, the severity of the cholangitis, the presence or absence of renal and hepatic failure, a recent (one year) history of antimicrobial therapy, local susceptibility pattern (antibiogram) and the biliary penetration of the antimicrobial agent[4]. Previous studies have shown that Gram-negative bacteria, in particular *Escherichia coli*, are the most common pathogens isolated from infected bile[9,10]. Because of the rapid development of multidrug-resistant Gram-negative organisms, the choice of appropriate empiric antimicrobial therapy has become more complicated. Whenever any empirical antimicrobial agents are used, they should be switched for the best available narrower-spectrum agents to avoid superinfection or the emergence of antimicrobial resistance as a cause of treatment failure[4]. Thus, knowledge of the common etiologic agents and their local susceptibility profile is essential to ensure the appropriate choice and timely administration of empiric antimicrobial therapy.

The aim of this study was to identify the most common bacteria grown in the bile and their antibiotic susceptibility. Furthermore, we investigated risk factors for microbiological colonization of the bile in patients with different biliary diseases.

MATERIALS AND METHODS

Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Dicle University, School of Medicine. All patients provided informed written consent.

Patients

This prospective study was conducted between April 2010 and August 2011 in the Department of Gastroenterology, Dicle University Hospital. Patients with various biliary disorders were included. Written informed consent was obtained from all patients and the trial was approved by the Local Ethical Committee. Exclusion criteria were age under 16 years, incomplete clinical and laboratory data or the absence of written, informed consent before the procedure.

Methods

All duodenoscopes (Olympus-TJF-260V, 2601168) were disinfected according to the guidelines and contamination was excluded by regular smear tests. The diagnosis of cholangitis was made when a patient had a fever (higher than 38 ℃), abnormalities in liver function test results, and the exacerbation of jaundice (if any), with and without right upper quadrant pain, provided that other septic complications were ruled out. Bile was aspirated by placing a single-use, 5F, standard sphincterotome catheter (after guide-wire cannulation) into the bile duct before the injection of contrast agent for endoscopic retrograde cholangiopancreaticography procedure. Approximately 2 to 8 mL of bile (mean of 4 mL) was collected and transferred in a sterile tube.

Bile specimens were transported to the microbiology laboratory in blood culture bottles and in an anaerobic transport system (BacT/Alert 3D Culture Media bioMérieux SA; Marcy l'Etoile, France). Bacteria were cultured and identified according to the standard protocol used in our clinical microbiology laboratory. The susceptibilities of the organisms recovered were identified using antimicrobial disks, chosen according to the initial Gram stain of the positive cultures. Microorganisms in concentrations of > 10 000 per mL were considered as an infection; lower concentrations were accepted as contamination or colonization.

Statistical analysis

Data from each group (cholangitis *vs* no cholangitis, malignant *vs* benign biliary disease, antibiotic administered *vs* not administered before procedure) were compared using the χ^2 test or the Fisher's exact test. All *P*-values were based on two-tailed tests. Analysis was performed with SPSS for Windows (SPSS Inc., Chicago, IL). A P value < 0.05 was considered significant.

RESULTS

Patients and general microbiological characteristics

Initially 125 patients were included in the study. Seventeen patients were excluded because of inadequate bile aspiration and 17 patients were excluded because of missing bile culture data. Finally, a total of 91 patients (27%

male, mean age 53.7 ± 17.5 years, range: 17-86 years) were analyzed. The main indications for cholangiographic interventions (Table 1) were benign biliary disease in 79 patients and malignant disease in 12 patients. Two patients with choledocholithiasis also had plastic stents and choledochojejunostomy was performed in one patient with choledocholithiasis. Seventeen (21.5%) patients with benign biliary disease had acute cholangitis before cholangiography. Thirty-five out of 91 (38.4%) patients were administered antibiotics empirically prior to the cholangiography (at least a single dose). All patients with acute cholangitis were administered antibiotics before cholangiography.

Bile culture was positive for bacterial growth in 46 out of 91 (50.5%) patients including 39 patients with benign disease and 7 with malignant disease. There were no patients in whom the concentration of microorganisms was lower than 10 000 per mL of bile. Table 2 shows the frequency of different organisms in positive bile cultures. A total of 48 organisms were isolated, comprising 15 different species. The most frequently encountered organisms were Gram-negative bacteria including *Escherichia coli* (28.2%), *Pseudomonas* (17.3%) and *Stenotrophomonas maltophilia* (15.2%).

Of 39 patients with benign biliary disease and positive bile cultures, there were aerobic bacteria grown in bile culture of 34 patients (87%), anaerobic bacteria in 3 (8%) and both aerobic and anaerobic bacteria grown in bile culture of 2 (5%) patients. Of 7 patients with malignant disease and positive bile cultures, there were aerobic bacteria grown in 6 bile cultures (86%) and anaerobic bacteria grown in 1 bile culture (13%). Monomicrobial growth was more frequent (96%) in comparison with polymicrobial cultures (4%). There was bacterial growth in bile culture of 9 out of 17 (52.9%) patients with acute cholangitis and in bile culture of 37 out of 74 (50%) patients without acute cholangitis. There was bacterial growth in bile culture of 17 out of 35 (48.6%) patients who were administered antibiotics and in bile culture of 34 out of 56 (60.7%) patients who were not administered antibiotics.

There were no significant differences between patients with malignant and benign disease (58% *vs* 49%, $P = 0.474$), patients with acute cholangitis and without acute cholangitis (52.9% *vs* 50%, $P = 0.827$), patients who were administered antibiotics empirically before the intervention and patients who were not administered them (51.4% *vs* 60.7%, $P = 0.384$), as regards the bacterial growth in bile culture.

Antibiotic susceptibility testing and resistance profiling

Antibiotics administered were ceftriaxone in 6 patients, ceftriaxone + ciprofloxacin in 1, ceftriaxone + ornidazole in 6, ciprofloxacin + sulbactam/amoxicillin in 5, ciprofloxacin in 10, cefuroxime axetil in 1, amoxicillin/clavulanic acid in 1, cefoperazone/sulbactam in 2, meropenem in 2 and cefazolin in 1 patient. Antibiotic susceptibility was measured for at least 11 types of antimicrobial substances. Table 3 shows the antibiotic susceptibility rate of the identified bacteria in the bile culture. We observed a broad spectrum or low resistance to meropenem, amikacin and imipenem. There was high resistance for gentamicin (47%), ciprofloxacin (48%), levofloxacin (49%), ceftazidime (54%), ampicillin (79%), cefotaxime (86%) and ampicillin/sulbactam (89%). The most common bacterial organisms growing outside the covering antibiotic spectrum or with high resistance profile were *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterococcus faecium*.

Table 1 Main indications for cholangiographic intervention in the study population *n* (%)

Diagnosis	
Choledocholithiasis	75 (83)
Pancreatic cancer	6 (7)
Papilla cancer	4 (4)
Cholangiocellular cancer	2 (2)
Chronic pancreatitis	1 (1)
Bile leakage	1 (1)
Benign stricture	1 (1)
Fasciola hepatica	1 (1)

Table 2 Distribution of different organisms in positive bile cultures *n* (%)

Bacteria	
Escherichia coli	13 (28.2)
Pseudomonas	8 (17.3)
Stenotrophomonas maltophilia	7 (15.2)
Enterococcus faecium	4 (8.6)
Enterobacter cloacae	3 (6.5)
Enterobacter aerogenes	1 (2.1)
Citrobacter freundii	2 (4.2)
Staphylococcus aureus	1 (2.1)
Streptococcus acidominimus	1 (2.1)
Achromobacter species	1 (2.1)
Pentoniphilicus asaccharolyticus	1 (2.1)
Lactobacillus gasseri	1 (2.1)
Bifidobacterium	1 (2.1)
Provotella disiens	1 (2.1)
Chryseobacterium meningosepticum	1 (2.1)

Table 3 Results of antibiotic susceptibility tests

Antibiotic	Susceptibility (%)
Meropenem	86
Amikacin	86
Imipenem	79
Piperacillin/tazobactam	61
Gentamicin	53
Ciprofloxacin	52
Levofloxacin	51
Ceftazidime	46
Ampicillin	21
Cefotaxime	14
Ampicillin/sulbactam	11

DISCUSSION

The traditional presentation of cholangitis includes the

triad of jaundice, fever and right upper quadrant pain[11], though the actual presentation can be quite diverse, ranging from mild abdominal discomfort to life-threatening septic shock. Both biliary obstruction and bacteria in the bile are required for the development of cholangitis. In a healthy person, the biliary tree is normally sterile, but biliary pathologies are often associated with secondary bacterial colonization[1]. Other studies have detected bacteriobilia in 16% to 85% of patients, depending on different disease groups[8,10,12-15]. Bacterial bile culture positive rates are 58% to 76% in patients with choledocholithiasis + cholangitis, 29% to 54% in patients with acute cholecystitis, 13% to 32% in patients with cholelithiasis, and 70% to 93.9% in patients with hepatolithiasis + cholangitis[4]. There is an increased incidence of positive bile culture in patients with acute cholangitis as compared to without cholangitis (67% *vs* 33%, $P = 0.012$), which has been reported by Salvador *et al*[9]. Risk factors for bacteriobilia are orthotopic liver transplantation (OLT), steroid treatment, biliary stenting and repeated biliary intervention[10]. Although some studies have reported that malignant biliary strictures and biliary stents increase risk of fungal colonization[10], others have not reported this association[16]. In our study, bacteriobilia was found in 50.5% of all patients. There were not any patients with OLT, steroid treatment or repeated biliary intervention and only two patients had biliary stenting. We did not find significant differences between patients with malignant and benign biliary disease, with cholangitis and without cholangitis and in patients who have been administered and not administered antibiotics before the intervention, as regards bacterial growth in the bile culture. These results may suggest that bacterial colonization in bile is dependent on multiple factors. The ineffectiveness of antibiotic administration before cholangiography on the bacterial growth in the bile culture may be related to high bacterial resistance against the antibiotics used. Although we identified bacterial growth in half of all patients, there were clinical findings of acute cholangitis in only 9 out of 46 patients with positive bile culture. We also found that 8 patients had all signs of acute cholangitis, but the bile culture was negative. Therefore, we suggest that all bacteriobilia can not cause obvious clinical symptoms of acute cholangitis and some patients with acute cholangitis may have negative bile culture. However, we cannot totally exclude contamination of the endoscope when it is passed through the upper gastrointestinal tract. To avoid contamination *via* cross-transmission between different patients, the duodenoscope was vigilantly disinfected. In all our patients with positive bile cultures, the concentration of microorganisms was higher than 10 000 per mL of bile. Therefore, we conclude that all patients with positive bile culture had actual bacterial growth that originated from aspirated bile.

It has been reported that microbial organisms contained in the bile from various biliary diseases are of intestinal origin. Aerobic bacteria such as *Escherichia coli*, *Klebsiella*, *Enterococcus* and *Enterobacter* are most frequently isolated, whereas *Streptococcus spp*, *Pseudomonas* and *Proteus* are less frequently isolated[17-19]. Although anaerobic bacteria such as *Clostridium* and *Bacteroides* are often isolated, most of these patients have polymicrobial infections with aerobic bacteria[20-22]. Salvador *et al*[9] have found that Gram-negative bacilli (or *Enterobacteriacea*) are the most commonly isolated bacteria in the bile culture of both patients with (94%) and without (95%) cholangitis. In a large study involving 243 consecutive patients in Germany, polymicrobial growth in bile culture has been found more frequently (67%) in comparison with monomicrobial growth (33%). In this study, Gram-negative bacteria were found in 43% of patients, Gram-positive bacteria in 40%, *Candida* species in 10% and strict anaerobes in 7% of patients. The most frequently encountered organisms were *Enterococcus* species (31%), *Escherichia coli* (10%) and *Klebsiella* species (9%)[10]. In our study, Gram-negative bacteria were the most common bile culture isolates for patients with and without acute cholangitis and almost all patients (95%) had monomicrobial growth in bile culture. *Escherichia coli* and *Pseudomonas* were the most frequently isolated bacteria. The results of our study may suggest that most of the bacteria in bile originate from the intestinal tract.

The management of cholangitis depends primarily on interventional biliary drainage and supplementation with antibiotic treatment. The combination of ampicillin and an aminoglycoside was regarded as a standard regimen for cholangitis in the 1980s[4] and most randomized, controlled trials have concluded that recently developed antimicrobial drugs are effective and useful equivalents to that of ampicillin and aminoglycosides[23,24]. Therefore, according to the clinical trials available so far, piperacillin, ampicillin and an aminoglycoside, and several cephalosporins, are recommended for the treatment of acute cholangitis[4]. In the Tokyo Guidelines, the selection of antimicrobial agents is based on the severity of acute cholangitis. It has been recommended that antimicrobial agents administered empirically should be changed in favor of more appropriate agents, according to the identified causative microorganisms and their sensitivity to antimicrobials[4]. In our patients, the most common empirically administered antibiotics were ceftriaxone, ciprofloxacin and sulbactam/amoxicillin. We did not identify a bacterial susceptibility test for ceftriaxone, but there was high resistance to other routines using antibiotics for cholangitis in our clinic. This high resistance may be related to commonly inappropriate use of these antibiotics in our region. A bile sample collected during cholangiography for microbiological analysis and antibiotic susceptibility tests may be valuable in the selection of appropriate antibiotics for the treatment of cholangitis.

In conclusion, our results indicate that about half of patients with biliary obstruction had bacteriobilia in their bile culture and the most commonly isolated bacteria were Gram-negative bacteria including *Escherichia coli* and *Pseudomonas*. When antibiotics were administered before cholangiography, the presence of cholangitis and the etiology of biliary obstruction had no significant effect on the incidence of bacteriobilia. There was a high resistance

against routinely used antibiotics, such as ciprofloxacin, and ampicillin and ampicillin/sulbactam. A bile sample for microbiological analysis may become a valuable diagnostic tool as it leads to more accurate selection of antibiotics for the treatment of cholangitis.

COMMENTS

Background

Acute cholangitis spans a continuous clinical spectrum and can progress from a local biliary infection to advanced disease with sepsis and multiple organ dysfunction syndrome. Knowledge of the common etiologic agents of cholangitis and their local susceptibility profile is essential to ensuring the appropriate choice and timely administration of empiric antimicrobial therapy.

Research frontiers

Blood cultures provide an opportunity to detect the causative organism but, even in febrile patients with cholangitis, blood cultures remain negative in more than half of the cases. Gram-negative bacteria, in particular *Escherichia coli*, are the most common pathogens isolated from infected bile. Because of the rapid development of multi-drug-resistant gram-negative organisms, the choice of appropriate empiric antimicrobial therapy has become more complicated.

Innovations and breakthroughs

Other studies have detected bacteriobilia in 16% to 85% of patients, depending on different disease groups. In this study, bacteriobilia was found in 50.5% of all patients. There was a large covering spectrum or low resistance to meropenem, amikacin and imipenem. The authors did not find significant risk factors for bacterial growth in the bile culture. The findings show that all bacteriobilia can not cause obvious clinical symptoms of acute cholangitis and some patients with acute cholangitis may have negative bile culture.

Applications

A bile sample for microbiological analysis may become a valuable diagnostic tool as it leads to more accurate selection of antibiotics for the treatment of cholangitis.

Terminology

Acute cholangitis is bile duct microbial infection caused by bacteria and fungi. Its main clinical findings are right upper quadrant pain, fever and jaundice.

Peer review

The authors have investigated the frequency of bacterial growth in the bile, the most commonly grown bacteria, their antibiotic susceptibility and risk factors for the bacterial colonization of the bile. They show that a bile sample for microbiological analysis during cholangiography may become a valuable diagnostic tool as it leads to more accurate selection of antibiotics for the treatment of cholangitis.

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