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ORIGINAL ARTICLE

Microbial profile and antibiotic sensitivity pattern in acute bacterial cholangitis

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Abstract
Introduction The changing antimicrobial sensitivity pattern of causative organisms poses a therapeutic challenge in treating patients with acute cholangitis. We therefore evaluated the microbial profile and sensitivity pattern to antibiotics in patients with acute bacterial cholangitis.
Methods Data of patients above 18 years of age with acute bacterial cholangitis seen between January 2004 and March 2007 were retrospectively analyzed. The study was continued prospectively from April 2007 to December 2008. Data on clinical features, etiological and microbial profile and therapy, and patient outcomes were analyzed. In the prospective group, the antibiotic susceptibility patterns of organisms grown on bile and blood culture were also obtained.
Results One hundred and eighty-five patients with acute cholangitis were studied. Choledocholithiasis (62.7%) and malignancy (29.2%) were the main predisposing factors. Bile culture was positive in 88 of 95 patients, and blood culture was positive in 47 of 178 (26.4%) patients. Bile cultures were predominantly polymicrobial (69.5%) in contrast to blood cultures (2.2%). *E. coli* was the predominant isolate in blood and bile. No growth was seen on anaerobic bile or blood cultures. The prospective group showed high resistance of *E. coli* to third generation cephalosporins and ciprofloxacin.
Conclusions Changing antimicrobial sensitivity patterns requires a revision of empiric antibiotic therapy policy in cholangitis.

Keywords Acute cholangitis · Etiology · Microbial resistance

Introduction

Acute cholangitis results from bacterial infection in an obstructed biliary system [1]. Stones in the common bile duct (CBD), neoplasms and benign biliary strictures are the common predisposing factors [2, 3]. Initial therapy includes empiric broad-spectrum antibiotics and prompt decompression of the biliary system [2]. Change of antibiotics if necessary is tailored according to blood/bile culture reports. Widespread and indiscriminate use of antibiotics over the years has altered the sensitivity pattern of micro-organisms which necessitates a change in empiric antibiotic policy [4–6].

In this study we report the clinical, etiological and microbial profile of patients with acute bacterial cholangitis seen at our center during the past 5 years. We have also prospectively evaluated the microbiological profile and antibiotic sensitivity pattern of microorganisms isolated from blood and bile in a group of 31 patients with

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cholangitis to decide whether there is a need for change in empiric antibiotic policy.

Methods

The medical records of all patients above 18 years of age with acute cholangitis seen at Christian Medical College, Vellore from January 2004 to March 2007 were reviewed retrospectively. The demographic, clinical, laboratory and etiological profile as well as details of therapy and patient outcome were recorded on structured data forms. The study was continued prospectively from April 2007 to December 2008, where, in addition to above parameters, the antibiotic susceptibility pattern of organisms grown on bile and blood culture (aerobic and anaerobic) were obtained. For the prospective group, only patients who had not received antibiotics prior to endoscopic retrograde cholangiopancreatography (ERCP) and had given written informed consent were included.

The diagnosis of acute cholangitis was based on the presence of clinical evidence of infection (fever and leucocytosis) in patients with biliary obstruction [7, 8]. Biliary obstruction was detected by elevated serum alkaline phosphatase and/or dilated intra/extra-hepatic biliary system on imaging [7]. Ten milliliters of bile was collected during ERCP in a sterile tube using a sterile biliary cannula and sent immediately to microbiology laboratory for inoculation for culture. Organ failure was defined as presence of any of the following features—hypotension (systolic blood pressure <90 mmHg), hypoxia (blood oxygen saturation <90%), renal failure (serum creatinine >1.5 mg%) and altered sensorium (Glasgow coma scale score <12) [8]. Approval was obtained from the institute review board and ethics committee prior to the study.

Statistical analysis

Categorical data are presented as proportions. Normally distributed continuous data are presented as mean with standard deviation. Non-normally distributed continuous data are presented as median with range. Data was analyzed using SPSS (Statistical Package for Social Sciences, release 11.0, standard version; SPSS Inc.)

Results

One hundred and eighty-five patients with cholangitis were studied. The retrospective group consisted of 154 patients and prospective group of 31 patients. Flow chart of prospectively recruited patients is shown in Fig. 1. Table 1 shows the demographic, clinical, laboratory and etiological profile of all patients. The mean age was 51.3 (13.4) years and 55.1% were males. All the patients were either from eastern or southern India. Fever, abdominal pain and jaundice were the common presenting symptoms. Anorexia and weight loss were present in 70.3% and 57.3% of patients, respectively. About a quarter of the patients had organ failure; the most common being renal failure. Fifteen patients had failure of more than one organ. Twenty-five (13.5%) patients had diabetes mellitus.

The most common imaging modality used for diagnosis was ultrasonography of abdomen (n=170). Dilated intrahepatic biliary radicles (IHBR) were seen in 150 patients and common bile duct (CBD) was dilated in 144. CBD stones were seen in 94 patients, gallstones in 67, neoplasm in 34 and stricture in 9. Magnetic resonance imaging abdomen was done in 33 patients which included 15 patients in whom ultrasonogram of abdomen was not done. CBD stone was detected in 14, malignancy in 12 and biliary stricture in 6 patients. Malignancy was diagnosed in an additional 4 patients on computed tomography of abdomen. After non-invasive imaging, etiology was not clear in 15 patients. In this group of patients, therapeutic ERCP helped in identifying the etiology (choledocholithiasis in 10, biliary stricture in 3 and malignancy in 2). Overall, stone in bile duct (62.7%) was the most common predisposing factor followed by malignancy (28.1%).

Aerobic blood culture was done in 178 patients (Table 2). Bacteremia was seen in 47 (26.4%) patients and was predominantly monomicrobial (n=43). *E. coli* was the predominant organism (n=34), followed by *Klebsiella* (n=7) and *Pseudomonas* (n=2). Bile culture was done in 95 patients before starting antibiotics (Table 2). Bacterobilia was seen in 88 (92.6%) of 95 patients. In contrast to blood cultures, most of the bile cultures (n=66) grew multiple organisms. *E. coli* (n=57) and *Enterococci* (n=38) were the predominant organisms. Aerobic blood and bile culture isolates from the prospective group were subjected to susceptibility testing against a uniform and predetermined group of antimicrobials. The results are shown in Table 3. *E. coli* and *Klebsiella* were resistant to third generation cephalosporins and ciprofloxacin with intermediate sensitivity to amikacin and netilmycin. *Pseudomonas* had intermediate sensitivity to all the above agents. All these organisms were uniformly susceptible to imipenem. *Enterococcus,* which was isolated from 19 bile and 1 blood specimen, had high sensitivity to vancomycin and teicoplanin and intermediate sensitivity to ampicillin. Anaerobic blood and bile cultures done on all prospectively studied patients (n=31) showed no growth.

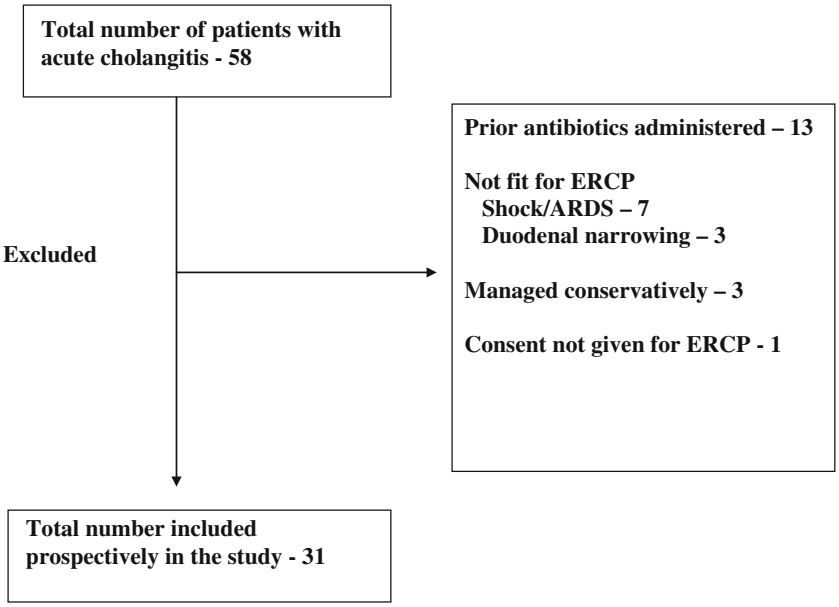

Fig. 1 Flow chart of prospectively recruited patients with acute cholangitis

Percutaneous or endoscopic biliary drainage were performed in 148 patients. Interventions done during ERCP were stenting of biliary system in 55 patients, placement of nasobiliary drain in 53 and biliary sphincterotomy with CBD stone clearance in 26 patients. In 15 patients percutaneous trans-hepatic biliary drainage (PTBD) was done as ERCP was not feasible (n=14) or unsuccessful (n=1). Thirty-seven (20%) patients were treated with antibiotics alone. None of the patients underwent surgery. Eighteen patients with acute cholangitis died.

Table 1 Demographic, clinical, laboratory and etiological profile of patients with acute cholangitis (n=185)

Age	51.3 (13.4) years
Sex (males)	102 (55.1%)
Fever	163 (96.8%)
Abdominal pain	140 (75.7%)
Jaundice	139 (75.1%)
Organ failure	43 (23.2%)
Shock	9
Renal failure	38
Altered sensorium	7
Hypoxia	7
Total leukocyte count (median, range)	13800 (2200–80000)/mm^3
Serum albumin (mean, SD)	3.2 (0.7) g/dL
Total bilirubin (median, range)	7.1 mg/dL (0.4–40)
SGOT (median, range)	87 U/L (18–500)
SGPT (median, range)	80 U/L (6–463)
Serum alkaline phosphatase (median, range)	371 U/L (59–2511)
Etiology	
Choledocholithiasis	116 (62.7%)
Malignancy	52 (28.1%)
Benign biliary stricture	17 (9.2%)

Discussion

Acute cholangitis is a life-threatening complication of bile duct obstruction requiring emergency care. Fever, jaundice and abdominal pain (Charcot's triad), the common symptoms seen in our patients are similar to other studies [1, 2]. In the current study, as in most other series, the commonest etiological factor was choledocholithiasis [2, 7]. In a study from India, Agarwal et al. reported that 70% of their 175 patients with acute cholangitis had CBD stones and 21% had malignancy [2]. Another study from Taiwan on 112 patients with cholangitis showed CBD stones were responsible in 54.6% of cases and malignancy in 25% [7]. The incidence of cholangitis in malignant obstruction is on the rise because of the frequent use of endoscopic/radiological biliary drainage procedures [3, 9]. One-third of our patients with malignant biliary obstruction had a prior history of ERCP.

Bile in individuals with normal biliary tract is sterile [10]. Presence of biliary obstruction leads to bacterial colonisation of bile [11, 12]. Ascending infection from duodenum and/or bacterial translocation from portal vein are the likely sources of infection [1, 13]. Increase in CBD pressure, due to obstruction, in the presence of infected bile promotes bacterial reflux into lymphatics and hepatic sinusoids resulting in acute cholangitis [1]. Aerobic blood cultures are reported positive in about 20% to 30% of patients [14, 15]. The results of aerobic bile cultures are

Table 2 Blood and bile aerobic bacterial culture isolates in the study patients

	Blood culture (n=178)	Bile culture (n=95)
Positive culture	47 (26.4)	88 (92.6)
Polymicrobial infection	4 (2.2)	66 (69.5)
Escherichia coli	34 (19.1)	57 (60)
Klebsiella pneumoniae	7 (3.9)	27 (28.4)
Pseudomonas aeruginosa	2 (1.1)	12 (12.6)
Enterococcus spp.	1 (0.56)	38 (40)
Citrobacter spp.	–	9 (9.5)
Viridans *streptococcus*	–	2 (2.1)

Data are as n (%)

more impressive with positive yield of around 70% in most studies [14, 16]. Bae et al. reported positive bile culture in 71.7% cases and positive blood culture in 31.3% cases [14]. Similar to these studies, we found bile culture to be positive in 92.6% patients and blood culture positive in only 26.4% of patients. Consistent with previous observations, a single organism was isolated from most blood cultures, while bile cultures were predominantly polymicrobial [17, 18]. The predominant organisms isolated from both blood and bile were gram negative with *E. coli* being the most frequent isolate [6, 14–16, 18, 19]. The gram positive organism *Enterococcus* was almost exclusively isolated from bile. Anaerobic bacterial isolates from bile and blood are uncommon being less than 15% in most reports [7, 12, 15]. None of the anaerobic cultures from blood or bile in the current study were positive.

The bacteriological profile of acute cholangitis has remained stable over the last three decades but their antibiotic susceptibility pattern has changed [6, 18, 20, 21]. Ampicillin with gentamicin was the agent of choice in the past. With increasing resistance to ampicillin and significant nephrotoxicity caused by aminoglycosides, this combination fell out of favour [22–24]. Several randomised trials in the past two decades showed quinolones to be very effective [5, 21, 25]. A recent report from India by Shivaprakasha and colleagues on biliary bacterial isolates from 128 samples showed high resistance of gram-negative bacilli (GNB) to ampicillin (92.4%), cephalexin (82.46%), ciprofloxacin (68.42%) and piperacillin (64.33%) [6]. Comparative antibiotic sensitivity patterns of *E. coli* from bile at our center in 2004 and 2008 showed a change in antibiotic susceptibility pattern—cefotaxime: 71.4% vs. 15.7%; ceftazidine 80% vs. 21.1%; gentamicin 66.7% vs. 42%, ciprofloxacin 33.5% vs. 14.3%. The prospective arm of our study showed that GNB had high resistance to ampicillin, ciprofloxacin and third generation cephalosporins. A high sensitivity of GNB to imipenem was observed in our study as documented in other studies [6, 9, 15, 17]. *Enterococcus*, the predominant gram positive isolate, had high resistance to ciprofloxacin but good sensitivity to vancomycin and teicoplanin. The high resistance of microorganisms to susceptible antibiotics of the past may be due

Table 3 Bacterial antibiotic sensitivity pattern in prospectively enrolled patients (n=31)

Antibiotic	Bile culture (% sensitive)				Blood culture (% sensitive)
	E. coli n= 19	*Klebsiella n= 10*	*Pseudomonas n= 2*	*Enterococcus n= 19*	*E. coli n= 9*
Amikacin	78.9	70	50	–	66.7
Cefotaxime	15.7	10	–	–	22.2
Ticarcillin/Clavulanic acid	38.8	40	50	–	33.3
Cefoperazone/Sulbactam	36.6	40	50	–	33.3
Ceftazidime	21.1	20	50	–	22.2
Gentamicin	42	40	50	–	33.3
Netilmicin	89.5	70	50	–	88.8
Piperacillin/Tazobactum	57.7	50	50	–	55.5
Ciprofloxacin	14.3	20	50	26.3	33.3
Ampicillin	15.7	20	–	84.2	22.2
Imipenem	100	100	100	–	100
Teicoplanin	–	–	–	94.7	–
Vancomycin	–	–	–	94.7	–

to widespread and indiscriminate use of antibiotics. These observations suggest that a fresh empiric antibiotic policy for cholangitis be made depending on the changed antibiotic susceptibility pattern.

In conclusion, choledocholithiasis continues to be the most common etiology of acute cholangitis. The antimicrobial susceptibility pattern of causative organisms has changed over time requiring a change in empiric antibiotic policy.

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