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Original Research Article

Bacteriological profile of patients with biliary obstruction in tertiary care center

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ABSTRACT

Background: Bile ducts are usually kept sterile by bacteriostatic and flushing effects of bile. Patients presenting with biliary obstruction especially due to benign etiology have either single or multiple bacterial organisms. Acute cholangitis carries significant morbidity with variable mortality rate. The serious presentation of such toxic patients signifies the requirement of appropriate antibiotic treatment. Choledocholithiasis followed by neoplasm and benign biliary strictures are the common predisposing factors for obstruction. Widespread use of antibiotics over years lead to change in sensitivity pattern of organisms which necessitates change in empiric antibiotic usage.
Methods: This retrospective study was conducted in department of medical gastroenterology. We studied 50 patients with biliary obstruction (clinical and demographic data were recorded). The diagnosis of cholangitis was made according to TG2018. While undergoing therapeutic ERCP, bile aspirate was collected by biliary cannulation and sent for microbiological analysis. The antibiotic susceptibility pattern and rest of the data were analyzed by appropriate statistical tests.
Results: Mean age of the study group was 49 years. Majority were female in study (60%). Overall, 74% had benign etiology, 32% had cholangitis. Bile cultures were positive in 64% patients 75% of them had benign etiology (gallstone being most common; 56%) and 25% had malignant etiology. Bacterobilia in cholangitis patients was statistically significant in comparison to patients without cholangitis (p-0.01). Organisms grown are mainly aerobic gram negative, most common being *E. coli*, *Klebsiella* and *Pseudomonas* species. Patients having bacterobilia had mortality of 6.25% during hospital stay.
Conclusions: In this study we found higher sensitivity to colistin (90.6%), tigecycline (81.25%), amikacin (75%) and least sensitivity was noted for ampicillin (6.25%) followed by cefixime (12.5%). Sensitivity to previously commonly used ciprofloxacin antibiotic was 31.25%. Study confirms the significance of obtaining routine bile sample during ERCP in obstructed biliary system to prevent dreaded complications of cholangitis.

Keywords: Bacterobilia, Biliary obstruction, Cholangitis, ERCP, Sensitivity

INTRODUCTION

Normally Bile ducts are sterile by continuous flushing action of bile and the bacteriostatic effects of bile salts. Presence of bacteria in the biliary tree don't have clinical significance as long as bile flow is maintained. The common causes of biliary obstruction are choledocholithiasis, biliary stricture, parasitic infection, malignancy etc. Once there is a bile duct obstruction proliferation of bacteria takes place within the stagnant bile and leads to rise in biliary pressure. Ultimately, regurgitation of bacteria from bile into hepatic venous blood takes place leading to a systemic infection and this is proportional to the degree of biliary obstruction.[1] As obstruction advances it complicates (cholangitis) with associated inflammatory response, which can be quite

severe leading to profound sepsis and multi organ dysfunction and with mortality rate as high as 10%.[2]

The serious presentation of such toxic patients signifies the need of appropriate antibiotic treatment. Blood cultures helps to detect the causative organism but it is found that even in febrile patients with cholangitis, blood cultures were sterile in more than 50% of the cases.[3] Hence it is necessary to collect bile for culture and sensitivity for institution of effective antibiotics. Most commonly cultured bacterial organisms from the bile are *E. coli*, *Klebsiella*, *Pseudomonas* and *Enterococci*, anaerobes like *Bacteroides fragilis* and *Clostridium perfringens* were found in 15% of appropriately cultured cases.[4]

It has become complicated to choose appropriate empirical antibiotic because of the rapid development of multi-drug-resistant Gram-negative organisms. If any antimicrobial agents are being used, one should prefer the best available narrower-spectrum agents to avoid the emergence of antimicrobial resistance or super infection as a cause of treatment failure.[5]

We conducted a single center retrospective study focusing the better depiction of clinical presentation and spectrum of pathogens responsible for bile duct infections and antibiotic sensitivities for the better guidance of future antibiotic therapies.

METHODS

We conducted a retrospective study in 50 patients from January 2023 to June 2023 in Gandhi Medical College, Secunderabad. The institutional ethics committee approval was taken for the protocol prior to initiation of the study.

Inclusion and exclusion criteria

We included patients presenting with extra-hepatic biliary obstruction undergoing ERCP in our department. The informed written consent was taken from all the patients. Those not willing to participate for the study and patients less than 18 years were excluded from the study.

All patients with biliary obstruction with cholangitis are started on empirical antibiotic Piperacillin-tazobactam in a dose of 4.5 grams 8 hourly. Based on culture reports and clinical condition antibiotics were escalated. Acute cholangitis diagnosis and grading was made according to Tokyo guidelines 2018 (TG18).[6] The biliary obstruction was detected by dilated intra/extra-hepatic biliary system on imaging (ultrasound abdomen/ computed tomography of the abdomen). The diagnosis of malignant causes of biliary obstruction was made by biliary cytology, ampullary biopsy or ultrasound guided/endoscopic ultrasound guided fine needle aspiration cytology/biopsy.

ERCP was performed using a side viewing endoscope. The scope and all accessories used for ERCP were routinely disinfected according to the institutional guidelines. Bile was aspirated after guide-wire cannulation was established, by placing a single-use, standard sphincterotome catheter (Ultratome XL, Boston scientific) into the bile duct before the injection of contrast agent. First 2 ml of bile was discarded and after that approximately 2-5 ml of bile was collected and transferred in a sterile tube and was transported to the microbiology laboratory under all aseptic precautions. Within 15-30 minutes of collection the bile sample was inoculated on blood agar/Mac Conkey agar. At 24 hours after inoculation the culture was reported. Using Kirby Bauer disc diffusion method antibiotic sensitivity testing was done if any bacteria was isolated from culture.

The history of prior antibiotic usage or attempted biliary drainage in the preceding 7 days, demographic data, clinical symptoms, blood investigations including liver and renal biochemistry, radiological tests were recorded. Statistical analysis was done using SPSS (Statistical Package for Social Sciences, release 20.0, standard version) software. Categorical data were presented as proportions. For qualitative data, frequency and percent distribution were calculated. All p values were based on two-tailed tests. A p value <0.05 was considered significant.

RESULTS

Mean age of study group was 49.5±14.10 years (range: 20 to 80 years). In our study 60% were females. Among 50 patients, 16 (32%) had cholangitis. Cholangitis due to benign etiology noted in 11 cases (68.75%) and rest 5 cases were by malignancy. Choledocholithiasis was responsible for half of all cholangitis cases. Jaundice was present in 45 (90%), abdominal pain in 38 (76%), fever in 40 (80%), shock in 10 (20%), acute kidney injury in 9 (18%), altered sensorium in 3 (6%) patients respectively. ICU care was required for 10 cases due to AKI, Altered sensorium and shock because of grade 2 and 3 cholangitis. Mortality during hospital stay noted in 2 (4%) patients. Due to failure of endoscopic therapy, six patients were referred for percutaneous transhepatic biliary drainage (PTBD). Benign etiology was present in 37 (74%) cases of extrahepatic biliary obstruction and malignant etiology in rest. Around half of the cases were due to choledocholithiasis. Laboratory parameters were; mean value of total leukocyte count 12895/mm^3 and 9025/mm^3, mean values of aspartate transaminase 120 U/l and 41.5 U/l, alanine transaminase 122 U/l and 43.5 U/l, alkaline phosphatase 304 U/l and 625.5U/l, total serum bilirubin 12.7 mg/dl and 11.2 mg/dl in patients with and without cholangitis respectively. Patients with cholangitis (16) received empirical antibiotics prior to ERCP.

Table 1: Clinical and demographic profile.

Characteristics			N (%)
Median age	49 years		
Range	20-80		
Gender	Female		30 (60)
	Male		20 (40)
Etiology	Choledocholithiasis		26 (52)
	Distal CBD stricture		9 (18)
	Portal cavernoma chalangiopathy		1 (2)
	Pseudocyst compression		1 (2)
	carcinoma gallbladder		2 (4)
	Carcinoma of pancreas		3 (6)
	Perihilar cholangiocarcinoma		6 (12)
	Distal cholangiocarcinoma		1 (2)
	Periampullary carcinoma		1 (2)
Fever	Present		40 (80)
	Absent		10 (20)
Pain abdomen	Present		38 (76)
	Absent		12 (24)
Jaundice	Present		45 (90)
	Absent		5 (10)
Cholangitis	Present		16 (32)
	Absent		34 (68)
	Benign		11 (68.75)
	Choledocholithiasis		8
	Malignant		5 (31.25)
Shock			10 (20)
Acute kidney injury			9 (18)
Altered sensorium			3 (6)
Mortality during hospital stay			2 (4)
Laboratory parameters	**Complete study group**	**Cholangitis (mean)**	**No cholangitis (mean)**
TLC/ml^3 (median, range)	8000 (4350-19050)	12895	9025
Serum bilirubin mg/dl (median, range)	12.6 (1.2-28.5)	12.7	11.2
AST U/l (median, range)	79.5 (28-238)	120	41.5
ALT U/l (median, range)	84 (27-241)	122	43.5
ALP U/l (median, range)	435 (116-1250)	304	625.5

TLC- Total leukocyte count, AST- aspartate transaminase, ALT- alanine transaminase, ALP- alkaline phosphatase.

Table 2: Bacteriological profile.

		N (%)
Bile culture	**Positive**	32/50 (64)
	Choledocholithiasis	18 (56.25)
	Distal CBD stricture	5 (15.62)
	Carcinoma gallbladder	2 (6.25)
	Carcinoma of pancreas	2 (6.25)
	Perihilar cholangiocarcinoma	2 (6.25)
	Portal cavernoma chalangiopathy	1 (3.12)
	Distal cholangiocarcinoma	1 (3.12)
	Periampullary carcinoma	1 (3.12)
	Negative	18/50 (36)
	Positive culture in cholangitis	14/16 (87.5)
	Positive culture in without cholangitis	18/34 (52.94)
	Positive culture in benign cause	24/37 (64.86)
	Positive culture in malignant cause	8/13 (61.53)

Continued.

		N (%)
Organisms	Monomicrobial	27 (84.37)
	E. coli	12 (37.5)
	Klebsiella species	7 (21.87)
	P. aeruginosa	6 (18.75)
	Citrobacter	1 (3.12)
	Proteus species	1 (3.12)
	Polymicrobial	5 (15.63)
	E. coli + *P. aeruginosa*	3 (9.36)
	E. coli + *Klebsiella* species	1 (3.12)
	Klebsiella + *Proteus* species	1 (3.12)

of the 50 patients, 32 (64%) patients had positive bile culture, among them 27 (54%) had monomicrobial and 5 had polymicrobial growth. Most of the growths were of *Escherichia coli* (50%) followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (each 28.12%) (Table 2). The bacterobilia in patients with cholangitis (14 among 16 cases) was statistically significant (p=0.01) in comparison with patients of without cholangitis (18 among 34 cases). Bacterobilia in patients with benign causes of biliary obstruction 24/37 (64.86%) when compared to malignant cause 8/13 (61.53%) was not statistically significant (p=0.83). Patients having bacterobilia had a mortality of 6.25% (2/32) during the hospital stay and none of those who did not have bacterobilia. The difference between two groups was statistically significant (p=0.01)

Table 3: Antibiotic sensitivity pattern.

Antibiotic	Percentage of sensitivity
Colistin	90.65
Tigecycline	81.25
Amikacin	75
Tobramycin	68.75
Meropenem	65.62
Gentamycin	46.87
Cefoperazone+ Sulbactam	46.87
Imipenem	40.62
Levofloxacin	40.62
Piperacillin+ Tazobactam	34.37
Ciprofloxacin	31.25
Moxifloxacin	31.25
Cefotaxime	25
Amoxicillin+ Clavulanate	21.85
Ceftriaxone	18.75
Trimethoprim+ Sulfamethoxazole	18.75
Piperacillin	15.65
Ceftazidime	15.65
Cefixime	12.5
Ampicillin	6.25

In this study, out of 50 bile culture 32 were positive for bacterobilia, all together had 37 microbial growth (including monomicrobial and polymicrobial) and all were gram negative. As shown in Table 3, highest sensitivity found for colistin (90.65%) followed by tigecycline (81.25%), amikacin (75%), tobramycin (68.75%) and meropenem (65.62%). Ampicillin was least sensitive 6.25%.

DISCUSSION

Continuous flushing and bacteriostatic effect of bile keeps biliary tree sterile. Biliary obstruction by various causes lead to bacterial colonization (from ascending infection) and proliferation. Once the significant pressure builds up, bacterial regurgitation in to hepatic veins leads to systemic spread, which presents as acute cholangitis that carries significant morbidity and mortality. Hence it is necessary to consider empirical antibiotics depending on local resistance pattern and initiate endoscopic or percutaneous interventional radiological treatments based on severity of cholangitis. Many studies are conducted with various sample size prospectively and retrospectively for the knowledge of local pattern of bacterobilia and their antibiotic sensitivity to make an institutional/regional standard operating protocol.

We recorded the clinical and microbial profiles of 50 patients underwent ERCP for biliary obstruction. In this study, mean age was 49.5 years, 60% were females and 40% were males. Mean age of our study group was comparable to study conducted in south India by Sahu et al (mean age 51.5 years).[7] Biliary obstruction in our study due to benign etiology was 74% and 26% were due to malignant etiology. Of all cases, choledocholithiasis noted in half of cases (52%), malignant stricture 26% cases and benign stricture in 18% cases. In study of Sahu et al benign etiology found in 72% cases and malignant etiology in 28% cases.[7] Raghhupatruni et al study also had choledocholithiasis as the most common cause (54.3%) of biliary obstruction and cholangitis.[8] Another study conducted by Noor et al in central India had benign etiology in 65% cases and malignant etiology in 35% cases, among all cases 56% were due to choledocholithiasis.[9] Similar to this, study by Goo et al, 54% cases were due to choledocholithiasis and 42% were due to malignant etiology.[10]

Cholangitis is a dreaded complication in biliary obstruction, more common in benign cases compare to malignancy. Various studies found the incidence cholangitis at different frequencies between benign and malignant causes. Bile duct obstruction in stones and strictures is partial that permits ascending infection and is unusual due to malignant obstruction as it is more often complete obstruction, up to 10-15% malignant cases may present with cholangitis.[4] In this study, cholangitis noted in 32% cases, of them 69% were by benign etiology and was statistically significant in comparison with malignancy related cholangitis. 50% of all cases were due to choledocholithiasis. In a study by Lee et al, 54.6% of cholangitis were due to choledocholithiasis followed by malignancy (25%), which were similar to our study.[11]

The laboratory parameter in patients with biliary obstruction reveals cholestatic pattern and leukocytosis if patient has cholangitis. In this study the mean value of total leukocyte count (TLC) in patients with and without cholangitis were 12895/mm^3 and 9025/mm^3 respectively. In study of Sahu et al it was 13800/mm^3, in Raghhupatruni et al it was 11060/mm^3 in patients of moderate to severe cholangitis.[7,8] The aspartate and alanine transaminases were elevated significantly in patients with cholangitis compare to patients without cholangitis and is statistically significant. The same was not seen in study of Raghhupatruni et al.[8] The alkaline phosphatase was higher in patient without cholangitis in our study compare to cholangitis cases. This may be due to partial obstruction in benign etiology.

In this study out of 50 bile samples, culture was positive in 32(64%) cases, of them 75% cases were benign and 25% were malignant. Among all benign causes 56.25% cases were due to choledocholithiasis and 15.6% cases were biliary stricture. Bacterobilia in cholangitis (87%) patients was statistically significant from bacterobila in patient without cholangitis (53%). Noor et al reported 66% bacterobilia in their study which was similar to our study and among them 70% were due to benign causes and rest had malignant etiology, 61% of cholangitis patients had positive bile culture.[9] Study conducted by Ruan among 956 patients in China, bile culture was positive in 38% cases, among them 88.7% cases were benign and 96.7% were monomicrobial infection.[12] The above differences could be due to different study designs and sample size and patient selection.

In this study among 32 positive bile cultures, 27 (84%) were monomicrobial and 5 (16%) were polymicrobial. All were gram negative, aerobic *Enterobacteriaceae.* Most common organism isolated was *E. coli* (50%) followed by *Klebsiella* species and *Pseudomonas aeruginosa* (28% each). Similarly, Salvador et al have reported *Enterobacteriaceae* as the most commonly isolated bacteria in the bile culture of both patients with (94%) and without (95%) cholangitis.[13] Another retrospective study by Shenoy et al found *E. coli* and *Klebsiella* spp. as the most common organisms grown on bile cultures.[13,14] Noor et al study, 70.76% cases of benign etiology had bacterobilia as compared to 57.14% in those malignant causes, in that study *Escherichia coli* and *Pseudomonas aeruginosa* were both equally common, followed by *Klebsiella pneumonia*.[9]

The management of patients presenting with biliary obstruction depends primarily on interventional biliary drainage along with antibiotic supplementation especially when patients having cholangitis. For cholangitis, during 1980s ampicillin and an aminoglycoside was considered as a standard regimen[15] but later trials have shown newer drugs are more effective. Tokyo Guidelines suggests antimicrobial agents selection is according to the severity of cholangitis.[15] Antimicrobial agents should be started empirically and later changed according to improvement in clinical condition of patients and as per bile culture sensitivity reports.

In this study we found higher sensitivity to colistin (90.6%), tigecycline (81.25%), amikacin (75%) and meropenem (65%). In Noor et al study, the highest sensitivity was to the polymyxins group (colistin- 96.97% and polymyxin B- 85.71%) followed by aminoglycoside group (amikacin- 82.09%, gentamicin- 80.95%) and imipenem (71.64%).[9] In contrast to the study of Sahu et al highest sensitivity to the commonly isolated biliary organisms were to the imipenem (100%) followed by netilmicin (50-89.5%) and amikacin (50-78.9%).[7] Such differences may be due to infection by resistant bacteria and prevalence of local sensitivity/resistance pattern. In our study least sensitivity noted for ampicillin (6.25%) followed by cefixime (12.5%) and ceftazidime (15.65%). A study by Shivaprakasha et al in 128 biliary bacterial isolates least sensitivity noted for ampicillin (7.6%) followed by cephalexin (11.54%).[16] In our study sensitivity to previously commonly used ciprofloxacin antibiotic is 31.25% which was similar to Shivaprakasha et al study (31.58%).[16] In Sahu et al study also the least sensitivity was noted for ciprofloxacin (14.3%) and ampicillin (15.7%).[7]

Limitations of the study are: sample size was small, anaerobic organisms were not studied. Bacterobilia was not compared with simultaneous blood culture in cholangitis.

CONCLUSION

From above study we concluded, choledocholithiasis was the most common indication for ERCP, most common cause of bacteriobilia and acute cholangitis. Cholangitis is also on the rise in patients with malignant strictures. The antimicrobial susceptibility pattern of causative organisms has changed over time requiring a change in empiric antibiotic policy and there is rise in multidrug resistance bacterobilia necessitating the use of higher antibiotics for appropriate management.

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