Clinical & bacteriological profiles of patients with acute cholangitis

A dissertation submitted in part fulfillment of

DM (Gastroenterology) examination of the

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to be held in August 2009

CERTIFICATE

This is to certify that this dissertation entitled **"Clinical & bacteriological profiles of patients with acute cholangitis"** is a bonafide work done by Dr Manoj Kumar Sahu in partial fulfillment of the rules and regulations for DM (Gastroenterology) examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in August 2009.

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I N D E X

INTRODUCTION

Acute cholangitis, is an infection of the biliary system with a wide spectrum of clinical presentations. In its most severe form, it is life threatening and associated with significant morbidity and mortality (1).

Stone in the CBD is the most common cause of acute cholangitis. Other causes of cholangitis are neoplasm, benign strictures, parasitic infections, post operative conditions like sump syndrome and post choledochoduodenostomy and congenital anomalies of the bile ducts(1).

In patients with bacterial cholangitis, bacteremia is seen in 1/3rd of blood cultures (2) . Over two-thirds of the bile cultures show mixed infection of two or more organisms (3). Empiric broad- spectrum antibiotics and prompt biliary decompression, the mainstay of therapy (4) significantly improves outcomes (5).

There is no study from India which compares etiology, microbiological profile, interventions and outcomes in patients with acute cholangitis from different regions of the country. There is also no Indian data evaluating anaerobic cultures (blood / bile) in patients with acute cholangitis.

Aims and Objectives of the study

1) To study the etiological profile, clinical features, interventions and outcomes in patients with acute cholangitis from different regions of the country

2) To study the bacteriological profile (aerobic and anaerobic) and antibiotic sensitivity in a subset of prospectively enrolled patients with acute cholangitis.

REVIEW OF LITERATURE

DEFINITION:

Acute cholangitis is a clinical syndrome with a wide spectrum of presentation ranging in severity from a mild form with fever and jaundice, to a severe form with septic shock, that develops as a result of stasis and infection in the biliary tract (1).

ETIOLOGY & PREDISPOSING FACTORS:

In approximately 85% of cases, cholangitis is caused by an impacted stone in the CBD, with resulting bile stasis (8). Other causes of cholangitis are neoplasm, benign strictures, parasitic infections, post operative status like sump syndrome, post choledochoduodenostomy and congenital anomalies of the bile ducts (1). Foreign bodies, such as blocked biliary endoprosthesis and surgical sutures, may also lead to acute cholangitis (4). Acute cholangitis may also be a complication from direct cholangiography due to failed drainage procedures in patients with malignant obstructive jaundice (4).

A series from GB Panth Hospital, New Delhi, reported 175 patients of cholangitis, of whom 138 had benign causes (122 had CBD stone) and 37 had malignant causes of biliary obstruction (9). Another series on cholangitis reported that two third of their patients had obstruction caused by stones or benign strictures (10).

PATHOGENESIS :

Mechanism of bacterial entry into the biliary tract :

Acute cholangitis is caused primarily by bacterial infection. The organisms typically ascend from the duodenum; hematogenous spread from the portal vein is a rare source of infection (11).

The sphincter of Oddi normally forms an effective mechanical barrier to duodenal reflux and ascending bacterial infection. The continuous flushing action of bile plus the bacteriostatic activity of bile salts also help to maintain bile sterility. Secretory IgA and biliary mucous function as antiadherent factors, preventing bacterial colonization (4).

When the barrier mechanism is disrupted, as occurs after endoscopic sphincterotomy, choledochal surgery, or biliary stent insertion, pathogenic bacteria enter the biliary system at high concentrations. Thus, cholangitis frequently develops after endoscopic or percutaneous manipulation with incomplete biliary drainage or as a late complication of stent blockage.

Bacteria can also pass spontaneously through the sphincter of Oddi in small numbers. The presence of a foreign body, such as a stone or stent, can then act as a

nidus for bacterial colonization. The nutrient rich bile serves as a good culture medium for bacteria to multiply (13).

Bile duct obstruction is necessary, but not sufficient to cause cholangitis. Chronic biliary obstruction raises the intrabiliary pressure, a central pathogenetic event in the development of acute cholangitis. High pressure promotes the migration of bacteria from the portal circulation into the biliary tract and subsequent colonization. It also favors migration of bacteria from bile into the systemic circulation, resulting in a higher incidence of septicemia (11).

Bacteriology:

In normal patients, the gallbladder and biliary tree are sterile (15). In patients with bacterial cholangitis, culture of bile is positive in over 90 percent of cases, yielding a mixed growth of gram negative and gram positive bacteria. The most common bacteria isolated are of enteric origin (14).

- Escherichia coli is the major gram negative bacterium isolated (25 to 50 percent), followed by Klebsiella (15 to 20 percent) and Enterobacter species (5 to 10 percent) (55).

- The most common gram positive bacteria are Enterococcus species (10 to 20 percent) (16).

- Anaerobes, such as Bacteroides and Clostridia, are usually present as a mixed infection. They are rarely the sole infecting organisms and it is not clear if they play a role in acute cholangitis. Recovery of anaerobes appears to be more common after repeated infections or surgery on the biliary tree (16).

A study from Hong Kong analysed the bile and the blood cultures of 579 patients with cholangitis who presented over a 7 year period (3). The blood cultures were positive in 21% of patients and almost always yielded a single organism,predominantly E coli.In contrast, over two-thirds of the bile cultures showed mixed infection of two or more organisms. Two- third of the patients with bacteremia had similar organisms isolated from blood and bile. E.coli, Klebsiella, Enterococcus, and streptococcus were the most commonly isolated bacteria.

Anaerobic organisms, most commonly Bacteroides were found in 2% of positive bile cultures in elderly patients and in patients who had iatrogenic cholangitis (3). Anaerobic bacteria are usually isolated in conjuction with aerobic bacteria, rather than as sole isolates from bile (52). Anaerobes tend to be associated with a more severe infection (29). Candida albicans is the most common fungal cause of cholangitis, usually seen in immunocompromised patients (3). Case reports of cholangitis due to

Aspergillus and Blastomyces suggests that fungal infection of biliary tree (17) need to be considered in the differential diagnosis of biliary tract disease in elderly and immunocompromised patients (18).

A retrospective study of 1394 patients with biliary tract diseases from Korea showed that gram negative bacteria were the most common organisms cultured in 74% of patients. E coli (36%) and klebsiella (15%) were most commonly isolated followed by gram positive bacteria (15%) such as Enterococcus (6%), staphylococcus (3%) and streptococcus (2%). Bacteroids were isolated in 5% of patients (19).

Another retrospective study from USA, evaluated patients with cholangitis with (Group 1) or without (Group 2) plastic biliary endoprosthesis. Bile culture were positive in 55% of Group 1 and 98% of Group 2 patients. E coli (17%) was the most common organism in Group 1 and Enterococcus (31%) most common in Group 2. Bacteremia was more common in Group 2 (46% vs 21%). Ciprofloxacillin and Ceftriaxone were the most effective antibiotics against gram negative bacilli, and Vancomycin against Enterococcus (20).

A study from Seth GS Medical College and KEM Hospital, Mumbai evaluated the bacterial profile from duodenum and biliary tree in patients with cholangitis. Bactobilia was found in 83.3%, E coli being the most frequently isolated organism. 63.2% of the

bacterial strains from the common bile duct and gall bladder were similar to those from duodenum (21).

A study from Amrita Institute of medical Sciences, Kerala studied the aerobic bacterial isolates from choledochal bile in patients with biliary tract disease. Predominant aerobic bacterial isolates obtained were E coli (30%), Klebsiella (23.98%) and Enterococcus (12.21%). Multidrug resistance was noted in 57%. High resistance rates to antibiotics were observed for Gram negative bacilli to ampicillin (92.4%), ciprofloxacin (68.42%), piperacillin (64.33%). Sensitivity to meropenam was 90.64% and amikacin was 76.61%. Gram positive bacteria were sensitive to ampicillin (86.5%) and penicillin (81.4%). Vancomycin and teicoplanin showed 100% sensitivity (22).

Malini et al from V M Medical college & Safdarjung Hospital, New Delhi studied the microflora of bile aspirates in patients with acute cholecysitis with or without cholelithiasis. The most common organisms isolated were E.coli (29.7%), Klebsiella (27%), Salmonella (8.1%), Cytrobacter (3.8%). The majority of Enterobacteriaceae isolates were susceptible to piperacillin-tazobactum and meropenam.

A study from Tata Memorial Hospital, Mumbai, evaluated bile cultures and sensitivity patterns in malignant obstructive jaundice. 26% had positive bile culture. The most common organisms were E.coli (36.6%), Klebsiella (18.3%), pseudomonas

(8.3%), Proteus vulgaris (8.3%), and coagulase negative staphylococci (8.3%). Amikacin, Gentamycin, cefotaxime, ceftazidime, and Cefoperazone/salbactum combination showed good activity against E coli and Klebsiella infections (24).

Bac et al from Korea retrospectively studied 212 patients with cholangitis and evaluated bile cultures and anti microbial susceptibility. The overall positive rate of bile culture was 71.7%. The organisms cultured were E coli (25%), Klebsiella (11.1%), Pseudomonas (11.1%), and coagulase negative Staphylococcus (9.7%) and Enterococcus (3.4%). Effective antibiotics for gram negative organisms were amoxicillin/clavulanic acid, amikacin, imepenam and pipercillin / tazobactum. Blood culture was positive in 31.2% of patients (25).

CLINICAL MANIFESTATIONS :

The clinical presentation of patients of with acute cholangitis can be extremely varied. The hallmark of cholangitis is Charcots classical triad, consisting of RUQ pain, jaundice, and fever. The full triad is present in only 70% of patients (12). Confusion and hypotension can occur in patients with suppurative cholangitis, producing Reynold's pentad, which is associated with significant morbidity and mortality (57). Hypotension, confusion or lethergy may be the only presenting symptom in elderly patients or those

on corticosteroids. Septic shock in severe cases can lead to multiorgan failure (16).

Chills resulting from intermittent bacteremia are prominent in about two third of patients, and this can be a clue in an atypical presentation (16).

On physical examination fever is almost universal, occurring in 95% of patients. RUQ tenderness is elicited in approximately 90% of patients, but jaundice is clinically detectable in only 80% (7). Profound jaundice suggests a malignant etiology (4).

Chronic biliary obstruction may give rise to multiple liver abscesses, liver atrophy, and eventually secondary biliary cirrhosis (26). The spread of infection into portal circulation may lead to pyelephlebites and portal vein thrombosis (4).

Severity assessment of acute cholangitis - Tokyo Guidelines (7):

The severity of acute cholangitis can be classified into three grades, mild (grade I), moderate (grade II), and severe (grade III), on the basis of two clinical factors, the onset of organ dysfunction and the response to the initial medical treatment. “Severe (grade III)” acute cholangitis is defined as acute cholangitis accompanied by at least one new-onset organ dysfunction. “Moderate (grade II)” acute cholangitis is defined as acute cholangitis that is unaccompanied by organ dysfunction, but that does not respond to the initial medical treatment, with no improvement in clinical manifestations and/or laboratory data. “Mild (grade I)” acute cholangitis is defined as acute cholangitis with no

organ dysfunction and response to the initial medical treatment, with clinical improvement.

Risk factors that predict mortality. A study from France has identified seven risk factors that predict mortality in acute cholangitis:

1) age over 50 years, 2) female gender, 3) associated liver abscess, 4)associated cirrhosis, 5) cholangitis due to a high grade malignant obstruction, 6) cholangitis after percutaneous transhepatic cholangiography, and 7) acute renal failure (27)

Laboratory tests:

Routine laboratory tests typically reveal an elevated white blood cell count with neutrophil predominance, and a cholestatic pattern of liver dysfunction with elevations in the serum alkaline phosphatase, gammaglutamyl transpeptidase (GGT), and bilirubin (predominantly conjugated) (16).

The WBC count is elevated in 80% of patients. In many patients who have a normal WBC count, examination of the peripheral blood smear reveals a dramatic shift to immature neutrophil forms. The serum bilirubin level exceeds 2 mg/dl in 80 % of patients (28). Serum Alkaline phosphatase levels are elevated in more than 90% of patients of acute cholangitis (29).

Depending on the degree and duration of biliary obstruction,elevations in serum aminotransferases may present in either a cholestatic or a hepatitis fashion. With acute gallstone obstruction of the CBD and sudden biliary pressure increase, the level of serum aminotransferases may reach thousands within 24 to 48 hours, then rapidly decline to lower values. Mild hyperamylasemia can be found in 40% of cholangitis patients without concomitant pancreatitis (30).

Diagnosis :

Ultrasonography is recommended as the first imaging study in patients suspected of having cholangitis to look for CBD dilatation and stones. Ultrasonography may be negative when small stones are present in the bile ducts, or in acute obstruction when the bile duct has not had time to dilate (16).

Stones in the CBD are seen on ultrasound in only 50 % of cases, but can be inferred by detection of a dilated CBD in about 75% of cases (31).

An abdominal CT is an excellent test for excluding complications of gallstone disease, but not a good test for excluding CBD stones.

EUS is highly accurate for excluding or confirming stones in the CBD. Concordance of EUS with ERCP in diagnosing choledocholithiasis is 95% (28).

ERCP is the recommended test for the diagnosis and therapy in cholangitis. The

ability of ERCP to establish drainage of infected bile under pressure is often life saving. Occlusive cholangiography should not be performed in patients with acute suppurative cholangitis as it can lead to septicaemia (16).

Magnetic resonance cholangiopancreatography (MRCP) for the evaluation of etiology of cholangitis is advised when ERCP is unsuccessful or fails to completely delineate ductal abnormalities. In the presence of a dilated CBD, this test has a 90 to 95 percent concordance with ERCP in diagnosing CBD stones (10). MRCP has an overall sensitivity of 95% and specificity of 94% in all biliary diseases (29).

TREATMENT

Untreated acute cholangitis is fatal. Management begins with early recognition of the condition. Empiric broad- spectrum antibiotics and prompt biliary decompression are the mainstay of therapy (4).

Other general measures include fluids to maintain urine output, correction of coagulopathy, and frequent monitoring of vital signs for evidence of sepsis (16).

Antibiotics:

In suspected cases of acute cholangitis,blood culture specimens are obtained immediately and therapy started with antibiotics effective against the likely causative organism (32).

Data on antibiotic sensitivity to common organism seen in bile is conflicting and there is no consensus opinion regarding the best initial antibiotic regimen for cholangitis. Broad spectrum antibiotics effective against E.coli, Klebsiella and Enterococcus should be started. In critically ill patients, antibiotics effective against Pseudomonas Bacteriodes and Yeast should be considered (33). A frequently used combination includes a third generation cephalosporin to cover gram-negative bacilli, ampicillin to cover gram-positive cocci and metronidazole to cover anaerobes (4).

Gram negative aerobes are well covered by the ureidopenicillins, carbapenams, fluoroquinolones, aminoglycosides and the third generation cephalosporins (1). Beta lactam-based therapy appears to be as effective as treatment with ampicillin and gentamicin with less toxicity (50). Fluoroquinolones appear to have relatively high rates of biliary excretion, and one study found that ciprofloxacin may be as effective as triple therapy with ceftazidime, ampicillin and metronidazole (34).

Invitro activity of moxifloxacin and pipercillin/salbactum was prospectively evaluated in 65 consecutive patients with acute cholangitis. Antibiotic resistances were observed in 34.9% of patients for pipercillin/salbactum and in 36.5% for moxifloxacin (35).

Empiric antibiotic therapy for ascending cholangitis should include broad-spectrum parenteral antibiotic until culture results are available. Suggested empiric antibiotic regimens are (16).

- Monotherapy with a beta-lactam/beta-lactamase inhibitor, such as ampicillin-sulbactam (3 g every six hours) OR piperacillin/ tazobactam (4.5 g every six hours) OR ticarcillin-clavulanate (3.1 g every four hours)
- Monotherapy with a carbapenem, such as imipenem (500 mg every six hours) OR meropenem (1 g every 8 hours) OR ertapenem (1 g daily
- Metronidazole (500 mg IV every eight hours) PLUS a third generation cephalosporin, such as ceftriaxone (1 g IV every 24 hours)
- Metronidazole (500 mg IV every eight hours) PLUS a fluoroquinolone (ciprofloxacin 400 mg IV every 12 hours or levofloxacin 500 mg IV daily)

Antimicrobial therapy for acute cholangitis - Tokyo Guidelines (2007) – (38)

1. Bile/Blood culture should be performed at all available opportunities(recommendation B)
2. In Moderate (Grade II) or Severe (Grade III) acute cholangitis, antimicrobial agents should be administered for a minimum duration of 5-7 days (recommendation A)
3. In Mild (Grade I) acute cholangitis,the duration of antimicrobial therapy could be shorter (2-3 days) (recommendation A)
4. Biliary penetration should be considered in the selection of antimicrobial agents in acute cholangitis (recommendation A)
5. Antimicrobial drugs should be selected according to the severity assessment (recommendation A)
6. The presence of biliary obstruction may significantly influence the biliary penetration of the antimicrobial.Therefore patients with acute cholangitis, especially those with severe (Grade III) disease, should have immediate biliary drainage along with appropriate antimicrobial therapy (recommendation A)
7. Antibacterials for Grade I cholangitis: First–generation cephalosporins/ second generation cephalosprin/ penicillin /B-lactamase inhibitor
8. Antibacterials for Grade II and Grade III cholangitis:

First option - Wide spectrum penicillin/ beta - lactamase inhibitor (as single agent)

Third or Fourth generation cephalosporins / Monobactums + Metronidazole

Second option - Fluroquinolones+ metronidazole

- carbapenams

Regardless of initial drug regimen, therapy should be modified to reflect effectiveness against organism(s) recovered in cultures. In general, antibiotics should be continued for seven to ten days, although the duration should be tailored according to clinical improvement (6). There is some evidence that once good drainage is established, 3 days of antibiotic treatment may be sufficient (36).

The patients condition should improve within 6-12 hours, and in most cases the infection comes under control within 2-3 days, with defervescence, relief of discomfort and a decline in the WBC count (28).

What if the organism is carbapenam resistant? A recent study from China showed that Thymosin alpha 1 - and ulinastatin – based immunomodulatory therapy for sepsis

arising from intra-abdominal infection due to carbapenam-resistant bacteria was effective in improving organ failure score end survival rate (37).

Establishment of biliary drainage:

Biliary drainage can be achieved by ERCP, a direct percutaneous approach, or open surgical decompression.

Endoscopic sphincterotomy with stone extraction and/or stent insertion is now the treatment of choice for establishing biliary drainage in acute cholangitis (16). The prime objective of an urgent endoscopy is to reduce the biliary pressure effectively by a safe and expeditious method, rather than to eliminate the underlying lesion (4). Endoscopic drainage is associated with a significantly lower overall rate of mortality and morbidity compared to surgical decompression (4.7 to 10 percent versus 10 to 50 percent, respectively) (39).

In patients with underlying coagulopathy, those in whom drainage is inadequate due to the presence of large stones, or those who are too ill to leave the intensive care unit and undergo the procedure with fluoroscopy, drainage can be achieved by insertion of a nasobiliary catheter. This procedure permits active decompression of the CBD by

aspiration and provides a route for irrigation of the biliary system (40).

An internal stent may be another option. Its relative disadvantages include 1) a tendency to be blocked by viscous pus in the absence of access for irrigation and 2) the need for a follow-up endoscopy session to remove the stent (11). A controlled trial suggested that an internal stent permitted adequate drainage even when performed without a sphincterotomy (41). Nasobiliary drain and biliary stenting are equally effective in managing patients of severe cholangitis (42).

Hui and colleagues randomised 74 patients who had acute cholangitis into one group that was treated with ES and stenting and another group that was treated with stenting alone.There was no significant difference in the two groups with respect to success rate for stent insertion, complications, length of hospital stay, or resolution of jaundice (44).

Chopra and colleagues from UK, studied 43 high risk patients- elderly or with debilitating disease. They were randomised to duct clearance or stent insertion . At 72 hours, the group that had stent insertion had a complication rate of 7% and the group that underwent ductal clearance had a complication rate of 16% (45).

In a study of 105 patients with acute cholangitis, who underwent emergency endoscopy, biliary drainage was successful in 102 patients and clinical improvement was achieved in 99 patients,even though 40% of these patients were in septic shock prior to the endoscopic procedure(46).

A study from G B Pant Hospital, New Delhi, studied effectiveness of endoscopic biliary drainage for severe acute cholangitis due to malignant and benign diseases. 27of 43 patients studied had benign disease. Patients received either a nasobiliary catheter(n-38) or an indwelling stent (n-5) with or without sphincterotomy for biliary drainage.Clinical and biochemical response were similar in both groups (24).

Another study from the same centre described endoscopic management of acute cholangitis in elderly patients. There was a higher incidence of severe cholangitis, renal failure, hypotension and higher mortality (10%) even after successful biliary drainage (9).

Percutaneous drainage can be considered when ERCP is unavailable, unsuccessful or contraindicated.Success rate of PTBD ranges from 80- 100 %(24).In most serises

urgent percutaneous decompression had morbidity less than 10% and a mortality rate of 5% (47).

In a non-randomised study comparing percutaneous transhepatic biliary drainage with ERCP in elderly patients with cholangitis patients,endoscopic drainage yielded significantly lower morbidity and mortality (48).

The result of successful endoscopic biliary drainage is dramatic and gratifying.The patient may feel an almost immediate amelioration of pain when the intrabiliary pressure is reduced.Over the next 24-48 hours,defervescence occurs with appropriate antibiotic therapy, along with resolution of delirium (5).

Role of surgery:

Emergency surgery for acute cholangitis has largely been replaced by nonoperative biliary drainage. Once the acute cholangitis is controlled, patients with difficult ductal stones may undergo surgical exploration of the CBD for stone removal. Elective surgery carries a very low morbidity and mortality compared with emergency surgery. If emergent surgery is needed due to failure of a nonsurgical drainage procedure, choledochotomy with placement of a large-bore T tube carries a lower

mortality compared to cholecystectomy with CBD exploration (27)

Prognosis :

With effective antibiotics and biliary drainage, the prognosis for mild to moderate cholangitis is much improved. However, the mortality rate remains very high (approximately 50 percent) for patients with severe cholangitis (13).

METHODOLOGY

A) RETROSPECTIVE ANALYSIS OF PATINTS WITH ACUTE CHOLANGITIS

Retrospective descriptive study:

Retrospective analysis of patients diagnosed to have Acute Cholangitis attending Christian Medical College Hospital, Vellore during the period from January 2004 to December 2008 (5 Years).

Subjects:

185 patients with Acute Cholangitis were included in the analysis.

Details of demographic data, etiology of biliary obstruction, clinical features, biochemical parameters, microbiological spectrum, interventions and outcomes were recorded.

Diagnosis of Acute Cholangitis:

The diagnosis of Acute Cholangitis was based on presence of clinical evidence of infection (fever, leucocytosis and abdominal pain) in patients with biliary obstruction (1,29,42). Biliary obstruction was detected by LFT abnormalities and common bile

duct/intrahepatic bile duct dilatation on imaging.

Patients were labelled as having severe acute cholangitis if they had features like hypotension, impaired level of consciousness or any organ failure (6, 7).

B) PROSPECTIVE ANALYSIS OF PATIENTS WITH ACUTE CHOLANGIITS

Prospective observational study:

31 patients with Acute Cholangitis were prospectively analysed for Bacteriological profile and Antibiotic Sensitivity during the period from April 2007 to December 2008.

Inclusion Criteria :

1. All patients suspected to have cholangitis.
2. Patients more than 18 years of age

Exclusion Criteria:

1. Patient in shock.
2. Antibiotics prior to ERCP
3. ERCP/PTBD not possible.

Protocol:

All patients with suspected cholangitis had the following:

- Blood sent for Hb, Platelets, TC/DC, LFT, Creatinine, PT, PTT
- Blood for aerobic and anaerobic cultures
- Emergency Ultrasound abdomen
- Emergency ERCP was performed and bile collected for both aerobic and anaerobic cultures. Bile duct decompression was performed in all patients.
- After collection of bile of culture (5-10ml) empiric antibiotic was started immediately.
- Microbiologists were requested to perform routine and special sensitivity study for all cultures.

ANALYSIS:

Details of demographic data, etiology of biliary obstruction, clinical features, biochemical parameters, microbiological spectrum and sensitivity, interventions and outcomes were recorded and analysed.

CONSENT:

Informed written consent (Annexure I) was taken for all patients included in the study. Written consent was also taken prior to ERCP/PTBD as per department protocol.

STATISTICAL ANALYSIS:

Data was analysed by statistical software SPSS (Statistical Package for Social Sciences, release 11.0, standard version; SPSS Inc.).

This was a retrospective and prospective study. Data was reported as means with standard deviation for normally distributed continuous data or median with ranges for non normally distributed continuous data and as frequencies and percentages for catageorical variables.

Student-test was used for normally distributed continuous variables and Mann Whitney test for non normally distributed continuous variables. For comparing categorical variables chi-square test was used. A P value of less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 185 patients were analysed in the combined group and 31 patients were prospectively studied for bacteriological profile and antibiotic sensitivity.

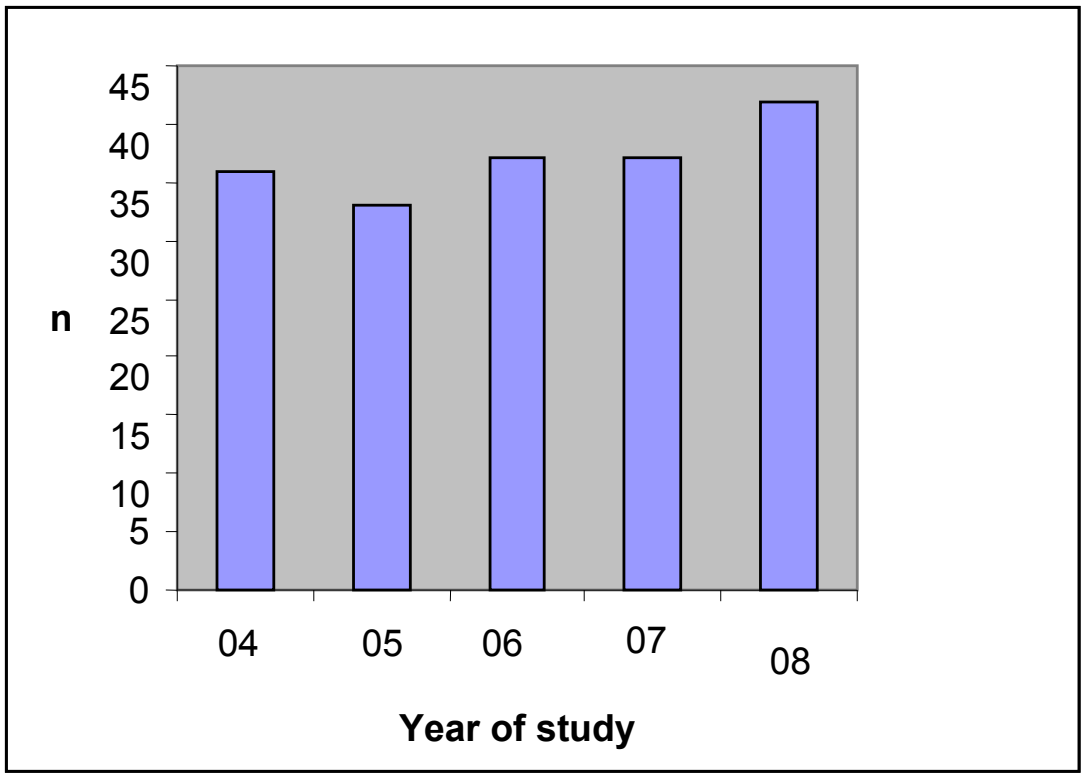
Demographic characteristics and clinical profile of patients is shown in Table 1.

The mean age of patients was 51.3 ± 13.4 Years. 102 (55.1%) patients were males and rest 83(44.9%) females, the male: female ratio being 1.3:1. 84(45.4%) patients were from south and 101(54.6%) patients from the eastern parts of India, reflecting patient profile visiting CMC.

The frequency of patients with cholangitis over past 5 years is shown in Fig. 1. The number of patient / year (2004: 36; 2005: 33: 2006: 37; 2007: 37; 2008: 42) is similar over 5 years.

Figure 1 : Frequency of patients / year with cholangitis

n = number of patients



The most common symptom at presentation was fever(96.8%). Pain abdomen and jaundice were present in 75.7% and 75.1% of patients respectively. Anorexia and weight loss were present in 70.3 % and 57.3% of patients. Seven (3.8%) patients had history of melena at presentation.

Past history of biliary colic and jaundice were present in 38.9% and 15.1% of patients respectively. Forty six (24.9%) patients had ERCP for biliary diseases in the past. Twenty two (11.9%) patients had history of cholecystectomy. History of diabetes and hypertension were present in 13.5% and 6.5% of patients respectively. Very few patients had history of alcoholism and smoking (5.9% and 3.2% respectively).

On examination icterus was present in 80.5% of patients. Seven (3.8%) patients had altered sensorium at presentation. Signs of liver failure was detected in 7% of patients.

Table – 1 : Demographic and clinical profile of patients with cholangitis

Variables	**All patients (N-185)**
Age (Mean + SD) yrs.	51.3±13.4
Sex (Male),number	102(55.1%)
Region(South/East)	84(45.4%)/101(54.6%)
Fever	179(96.8%)
Pain	140(75.7%)
Jaundice	139(75.1%)
Anorexia	130(70.3%)
Weight loss	106(57.3%)
Cholestatic symptoms	74(40.2%)
GI Bleed	7(3.8%)
Past H/O biliary colic	72(38.9%)
Past H/O ERCP	46(24.9%)
Past H/O Jaundice	28(15.1%)
DM	25(13.5%)
Hypertension	12(6.5%)
Alcohol	11(5.9%)
Smoking	6(3.2%)
Icterus	149(80.5%)
Altered sensorium	7(3.8%)
Signs of Liver Failure	13(7%)
Abdominal tenderness	54(29.2%)

Past H/O Cholecystectomy	22(11.9%)

Imaging findings: (Table 2)

Of the 185 patients analysed, 170 had US and 33 had MRI abdomen. IHBRD was detected in 88.2% of patients by US and 97.2% by MRI abdomen.

The mean CBD diameter on US was 13.3 ± 4.9mms. US detected CBD stone in 55.3% of patients. On ERCP 63.9%, 25.7% and 2.8% of patients were detected to have choledocholothiasis, stricture in CBD and choledochal cyst respectively.

Table - 2 : Imaging findings in patients with cholangitis

Variables	**All patients (n = 185)**	
	U/S(N-170)	**MRI(N-33)**
IHBRD , numbers	150(88.2%)	35(97.2%)
Dilated CBD (%)	84.9	88.8
CBD Diameter (mms) Mean+SD)	13.3±4.9	-
Gall stone/sludge , n-169	67(39.6%)	-
Stone in CBD (%)	55.3	42.1
Stricture (%)	8.2	22.1
Malignancy (%)	20	36.8

Laboratory profile (Table 3):

The mean Haemoglobin and serum albumin were 11.1 ± 2.3 gm% and 3.2 ± 0.7 gm% respectively. The median serum bilirubin, SGOT, SGPT, serum alkaline phosphatage were 7.1 mg% (0.4-40),87.50 U/L(18-500),80.50 U/L (6-463) and 371.50 U/L (59-2511) respectively.

The median serum cretinine was 0.9 mg% (0.4-7)

Table – 3 : Laboratory profile

Laboratory profile	**All patients (n-185)**
Haemoglobin (gm%) (Mean+SD)	11.1±2.4
Total count (cu mm) (Median&Range)	13800 (2200-80000)
Ser Bilirubin(mg%) (Median&Range)	7.1 (0.4-40)
Ser Albumin(gm%) (Mean+SD)	3.2±0.7
SGOT(U/L) (Median&Range)	87.50 (18-500)

SGPT(U/L) (Median&Range)	80.50 (6-463)
Alkaline phosphatase(U/L) (Median&Range)	371.50 (59-2511)
Ser Creatinine(mg%) (Median&Range)	0.90 (0.4-7)

Microbiological profile (Table 4):

Combined Group (retrospective and prospective group) : One hundred and seventy eight patients had aerobic blood culture prior to empiric antibiotic therapy. Bacteremia was seen in 26.4% of cultures. Most of the cultures grew single organism (91.5 %). E. coli was the predominant organism (70.2%), followed by Klebsiella(14.9%), Pseudomonas (4.3%) and Enterococcus (2.1%) .

Bile culture was done in 88 patients. Most (92.6%) of the cultures showed growth. In contrast to blood cultures, most (75%) of the bile cultures grew multiple organisms. E. Coli and Enterococci were the predominant organisms (64.8 and 43.2% respectively), followed by Klebsiella (30.7%), Pseudomonas (13.6%) and Citrobacter (10.2%).

Prospective study group :

All 31 patients had blood culture done. 32.3% had bacteremia and most cultures (80%) grew a single organism. E coli was the most common (90%) organism grown, followed by klebsiella and Enterococcus (10% each).

All 31 patients had aerobic bile cultures and 93.5% of the cultures showed growth. Most of the cultures grew multiple organisms (82.8%). E.coli and Enterococci were the most common organisms grown (65.5 % each), followed by Klebsiella (34.5%), Citrobacter (13.8%) and Pseudomonas (6.8%).

None of the anaerobic cultures (Blood- 29, Bile – 31) showed any growth.

Table – 4 : Microbiological profile of patients with cholangitis

Culture/Organisms	Combined group(N-185)				Prospectively study group(N-31)			
	Blood culture (Aerobic n-178)	Blood culture (Anaerobic n-30)	Bile culture (Aerobic n-95)	Bile culture (Anaerobic n-31)	Blood culture (Aerobic n-31)	Blood culture (anerobic n-29)	Bile culture (Aerobic n-31)	Bile culture(Anaerobic n-31)
Growth	47 (26.4%)	0	88 (92.6%)	0	10 (32.3%)	0	29 (93.5%)	0
Multiple Organisms (%)	8.5	-	75%	-	20%	-	8 (2.8%)	-
E.Coli	34 (72.3%)	-	57 (64.8%)	-	9 (90%)	-	19 (65.5%)	-
Klebs Sp	7 (14.9%)	-	27 (30.7%)	-	1(10%)	-	10 (34.5%)	-
Pseudo monas	2(4.3%)	-	12 (13.6%)	-	0	-	2 (6.8%)	-
Citrobacter	0	-	9 (10.2%)	-	0	-	4 (13.8%)	-

Enterococcus	**1(2.1%)**	**-**	**38 (43.2%)**	**-**	**1(10%)**	**-**	**19 (65.5%)**	**-**
α- Hemostep	**0**	**-**	**2 (2.3%)**	**-**	**0**	**-**	**1 (3.4%)**	**-**

Comparision of microbiological profile in retrospective and prospective groups (Table 5):

147 blood cultures and 64 bile cultures were analysed in the retrospective group(Group- 1) and 31 blood and bile cultures were analysed in the prospective group(Group – 2). Microbial profile in prospective study group was similar to the retrospectively studied group of patients.

Table – 5 Comparison of the microbial profile between retrospective and prospective study groups

Bacteriological profile and sensitivity	**Blood cultures**			**Bile cultures**		
	Group-1 (n-147)	**Group-2 (n-31)**	**p-value**	**Group-1 (n-64)**	**Group-2 (n-31)**	**P-value**
Growth	**37 (25.2%)**	**10 (32.3%)**	**0.5**	**59 (92.2%),**	**29 (93.5%)**	**1**
Multiple organisms	**1 (2.7%)**	**2 (20%)**	**0.08**	**47 (73.4%)**	**24 (82.8%)**	**0.8**
E. coli	**23 (62.2%)**	**9 (90%)**	**0.1**	**37 (62.7%)**	**19 (65.5%)**	**0.83**
Klebsiella sp	**5 (13.5%)**	**1 (10%)**	**1**	**14 (23.7%)**	**10 (34.5%)**	**0.3**
Pseudomonas sp	**2 (6.4%)**	**0**	**1**	**8 (13.6%)**	**2 (6.8%)**	**0.5**

Antibiotic sensitivity:

Bile cultures (Table 6)

All 31 patients had bile culture. The sensitivity of E coli to Imipenam and Meropenam was 100% followed by Netilmicin (88.2%), Amikacin (78.9%), Piperacillin / Tazobactum (56.4%), Gentamycin (45%), Cefoperazone/salbactum (39.6%), Ticarcillin / clavulinic acid (38.8%), Ceftazidime (21.1%), Cefotaxime (16.7%), Ampicillin (16.7%) and Ciprofloxacin (14.3%).

The sensitivity of Klebsiella to Imipenam and Meropenam was 100%, followed by Amikacin (72.7%), Netilmicin (66.7%), Piperacillin / Tazobactum (52.4%), Gentamycin (36.3%), Cefoperazone / salbactum (41.2%), Ticarcillin / clavulinic acid (36.8%), Ceftazidime (18.2%), Ciprofloxacin (18.2%), Ampicillin (16.7%), Cefotaxime (10.5%).

The sensitivity of Pseudomonas to Imipenam and Meropenam was 100%, followed by Piperacillin / tazobactum (68.7%), Cefoperazone / salbactum (68.7%), Amikacin (66.7%), Netilmicin (66.7%), Ticarcillin / clavulinic acid (66.7%), Ceftazidime (66.7%), Ciprofloxacin (66.7%), Gentamycin (50%).

The sensitivity of Enterococci was 94.7% to Teicoplanin and Vancomycin, followed by Ampicillin (84.2%), high dose gentamycin (78.9%) and Ciprofloxacin (26.3%).

Table – 6 Bile culture and sensitivity of prospective study enrolled patients with cholangitis

Antibiotics	E.Coli (%)	Klebsiella sp (%)	Pseudomonas sp (%)	Enterococcus (%)
Amikacin	**78.9**	**72.7**	**66.7**	**-**
Cefotaxime	**16.7**	**10.5**	**-**	**-**

Ticar/Clavul	**38.8**	**36.8**	**66.7**	**-**
Cefoper/Salbact	**39.6**	**41.2**	**68.7**	**-**
Ceftzidime	**21.1**	**18.2**	**66.7**	**-**
Gentamycin	**45**	**36.3**	**50**	**-**
Netilmicin	**88.2**	**66.7**	**66.7**	**-**
Piper/ Tazobac	**56.4**	**52.4**	**68.7**	**-**
Ciprofloxacin	**14.3**	**18.2**	**66.7**	**26.3**
Ampicillin	**16.7**	**16.7**	**ND**	**84.2**
Imipenam	**100**	**100**	**100**	**-**
High dose gent-amycin	**-**	**-**	**-**	**78.9**
Teicoplanin	**-**	**-**	**-**	**94.7**
Vancomycin	**-**	**-**	**-**	**94.7**

Blood culture and sensitivity (Table 7):

All 31 patients had blood culture. The sensitivity of E coli to Imipenam and Meropenam was 100%, followed by Netilmicin (85.7%), Amikacin (62.5%), Piperacillin / tazobactum (57.1%), Gentamycin (37.5%), ciprofloxacin (37.5%), Ticarcillin / clavulinic acid (33.4%), Cefoperazone / salbactum (28.6%), Ceftazidime (25%), Ampicillin (25.7%), Cefotaxime (25%).

The sensitivity of Enterococcus was 100% to Teicoplanin and Vancomycin, Ampicillin and high dose gentamycin. The organism was resistant to ciprofloxacin.

Table - 7 : Blood culture and sensitivity of prospective study patients with cholangitis

Antibiotics	E.Coli (%)	Enterococcus (%)
Amikacin	62.5	-
Cefotaxime	25	-
Ticar/Clavul	33.4	-
Cefoper/Salbac	28.6	-
Ceftazidime	25	-
Gentamycin	37.5	-
Netilmicin	85.7	-
Piper/Tazobac	57.1	-
Ciprofloxacin	37.5	0
Ampicillin	25.7	100
Imipenam	100	-
High dose gentamycin	-	100
Teicoplanin	-	100
Vancomycin	-	100

Etiological profile and Intervention (Table 8):

Stone disease (Choledocholithiasis) was the most common (61.6%) etiology in patients of cholangitis, followed by malignancy(29.7%) and benign stricture (9.2%).

Nasobiliary drainage (NBD) was performed in 53 (28.7%) patients and biliary stenting in 55(29.7%) patients. Stone clearance of CBD was performed in 26(14.1%) patients. In 15(8.1%) patients percutaneous trans-hepatic biliary drainage (PTBD) was done as ERCP was not feasible or unsuccessful. Thirty- four (18.4%) patients were treated with antibiotics alone.

Table - 8 : Etiological profile and Intervention

Etiology & Intervention	All patients (n-185)
Stone disease	114(61.6%)
Benign stricture	17(9.2%)
Malignancy	54(29.2%)
NBD	53(28.6%)
Biliary stenting	55(29.7%)
Stone clearance	26(14.1%)
PTBD	15(8.1%)
Antibiotics alone	34(18.4%)

Comparison of microbiological profile and outcome between benign and malignant obstruction (Table 9):

Benign and malignant etiologies were found in 129 and 56 patients respectively.

Benign group: The mean age was 51.5 $\pm$ 13.8 years.67 (51.9%) patients were male. Out of 67 bile cultures, 63(94.1%) showed bacterobilia. Most of the cultures (68.3%) grew multiple organisms. E. coli was the most common organism (66.7%) grown, followed by Enterococcus (44.4%), Klebsiella (26.9%) and Pseudomonas (11.1%).

NBD was performed in 38 (30.2%) patients and biliary stenting in 35(27.1%) patients. Six (4.7%) patients had PTBD. Twenty one (16.3%) patients did not have any intervention and were treated with antibiotics alone. One hundred and twenty three

(91.9%) patients were stable at discharge. Eight (6.5%) patients died during treatment.

Malignancy Group: The mean age was 51± 12.7 years. 35(62.5%) patients were male. Out of 28 bile cultures, 25(89.3%) were positive and mostly with multiple organisms (64%). E coli was the most common organism(56%) grown, followed by Enterococcus (40%), Klebsiella (12%) and Pseudomonas (12%).

NBD was done in 12 (21.4%) patients and biliary stenting in 20(35.7%) patients. Nine (16.1%) patients had PTBD. Thirty-five (74.5%) of patients were stable at discharge. Two (4.2%) patients died during treatment. Except PTBD which was done more often in Malignant group, other variables were similar between the two groups.

Table – 9 : Microbiological profile, intervention and outcome between benign and malignant groups

Microbiological profile,sensitivity, Intervention and outcome	Benign Gr (n-129)	Malignant Gr (n-56)	P-value
Age(Mean+SD)	51.45+13.808	51+12.676	0.8
Sex(Male)	67(51.9%)	35(62.5%)	0.2
Growth in bile culture*	63(94.1%)	25(89.3%)	0.42
Multiple organisms	43(68.3%)	16(64%)	0.6
E. coli	42 (66.7%)	14 (56%)	0.3
Klebsiella	17 (26.9%)	3 (12%)	0.17
Pseudomonas	7 (11.1%)	3 (12%)	1
Enterococcus	28 (44.4%)	10 (40%)	0.65
NBD	38(30.2%)	12(21.4%)	0.3
CBD stenting	35(27.1%)	20(35.7%)	0.3
PTBD	6(4.7%)	9(16.1%)	0.02
Antibiotics alone	21(16.3%)	15(26.8%)	0.1
Death	8(6.5%)	2(4.2%)	0.73

*** Bile culture: Benign group: 67, Malignant group: 28**

Comparison of etiological and microbiological profile and outcomes in patients from different regions of the country (Table 10):

CMC being a tertiary care referral hospital, patients come from different parts of India for treatment. 84 patients were from southern region (SR) and 101 from eastern region (ER).

Southern region: The mean age was 53.3± 14.5 years. 52(61.9%) patients were male. Stone disease (choledocholithiasis) was the most common etiology (76.2%), followed by malignancy(19.1%) and benign stricture (4.7%). Out of 37 bile cultures performed, 34 (91.9%) were positive with multiple organisms in 67.7% of cultures. E coli was the most common organism grown (55.8%), followed by Enterococcus (52.9%), Klebsiella (35.3%) and Pseudomonas (2.9%). NBD was done in 25 (29.8%) of patients and biliary stenting in 28 (33.3%) patients. Six (7.1%) patients had PTBD. Seventy-four (90.5%) of patients were stable at discharge. Four (5.4%) patients died during treatment.

Eastern region: The mean age was 49.7 ± 12.3 years. 50 (49.5%) patients were male. Stone disease (choledocholithiasis) was the most common (48.5%) etiology, followed by malignancy (37.6%) and benign stricture(13.8%). Out of 58 bile cultures performed, 54 (93.1%) were positive, with 42 (72.4%) of cultures showing multiple organisms. E coli was the most common organism grown (66.7%), followed by Enterococci (38.9%),

Klebsiella (18.5%) and Pseudomonas (12.9%).

NBD was done in 26(25.7%) of patients and biliary stenting in 27(26.7%) of patients.Nine (8.9%) patients had PTBD. Eighty-one (84.4%) of patients were stable at discharge.Six (6.2%) patients died during treatment. Stone disease was found to be significantly more common in patients from southern region and malignancy in Eastern region. There was no difference in the microbiological profile and outcome between patients from Southern and Eastern region of India.

Table – 10 Etiology,microbiological profile, interventions and outcomes in two region groups

Etiology,microbiological profile,intervention and outcomes	Group 1 (south) (n-84)	Group 2 (East) (n- 101)	P- value
Age(Mean+SD)	53.3±14.5	49.7±12.3	0.08
Sex(Male)	52(61.9%)	50(49.5%)	0.1
Stone disease	64(76.2%)	49(48.5%)	<0.001
Malignancy	16(19.1%)	38(37.6%)	0.05
Growth in bile culture*	34(91.9%)	54(93.1%)	1
Multiple organisms	26(67.6%)	42(72.4%)	0.8
E. coli	19(55.8%)	36(66.7%)	0.4
Klebsiella sp	12(35.3%)	10(18.5%)	0.13
Pseudomonas	1(2.9%)	7(12.9%)	0.14
Enterococcus	18(52.9%)	21(38.9%)	0.29
NBD	25(29.8%)	26(25.7%)	0.6
CBD stenting	28(33.3%)	27(26.7%)	0.34
PTBD	6(7.1%)	9(8.9%)	0.8
Death	4(5.4%)	6(6.2%)	1

*** Bile culture performed: Group 1: 37; Group 2: 58**

Comparison of etiology and outcome in NBD(NBDG) and stenting (SG) groups (Table 11):

NBD was done in 51 patients and biliary stenting in 55 patients.

NBD Group: The most common etiology was stone disease (72.5%), followed by malignancy (23.6%) and benign stricture (3.9%). None of the patients had any post procedure complication. None of them required repeat procedure. Forty-four (95.6%) patients were stable at discharge.One (2.2%) patient died during treatment. The mean

duration of hospital stay was 8.6 days.

Stent Group: The most common etiology was stone disease (56.9%), followed by malignancy (32.7%) and benign stricture (3.6%).

One patient had mild pancreatitis after biliary stenting, which was managed conservatively. Another patient did not improve with biliary stenting and required NBD. Fifty-four (81.5%) patients were stable at discharge. One (1.8%) patient died during treatment. The mean duration of hospital stay was 6.6 days.

There was no difference between the NBD and stenting groups with regard to technical success and outcome. Both procedures were found to be equally effective.

Table -11 : Etiology and outcome between NBD and Stenting groups

Etiology and outcome	**NBD Group (n-51)**	**Stenting Group (n-55)**	**P- value**
Stone disease	**37(72.5%)**	**31(56.9%)**	**0.1**
Benign stricture	**6(3.9%)**	**2(3.6%)**	**0.15**
Malignancy	**12(23.6%)**	**18(32.7%)**	**0.4**
Complication	**0**	**1(1.8%)***	**1**
Rpt procedure	**0**	**1(1.8%)****	**1**
Stable at discharge	**n-46 44(95.6%)**	**n-54 44(81.5%)**	**1**
Duration of	**8.57**	**6.6**	**0.064**

hospital stay (mean)			

*** Mild pancreatitis**

**** 1 patient had NBD after stenting**

Factors predicting mortality (Table – 12):

147 patients were stable at discharge and 10 patients died during treatment**.**

Multiple factors were analysed between patients who were stable at discharge and those who died during treatment to predict mortality. In Univariate analysis, sensorium at admission, ICU care, serum bilirubin, systolic blood pressure and pulse rate were found to be significant factors in predicting mortality. After multivariate analysis only ICU care was found to have significant association with mortality.

Table - 12 : Factors that predicts mortality

Variables	**Univariate analysis**			**Multivariate analysis**
	Alive	**Dead**	**P- value**	**P- value**
Sensorium	**1/147**	**3/10**	**0.001**	**0.17**
ICU care	**0/147**	**3/10**	**<0.001**	**0.001**
Bilirubin	**6.5(1-37)**	**11.6(5-19)**	**0.012**	**0.401**
BP systolic	**114.7(10.3)**	**97(10.6)**	**<0.001**	**0.06**
Pulse	**89.5(12.1)**	**108.4(15)**	**0.003**	**0.83**

DISCUSSION

The current study is a retrospective analysis of etiological factors, microbiological profile, interventions and outcomes in 185 patients diagnosed to have acute cholangitis over a 5 year period. As the microbial profile and antibiotic sensitivity changes over time, we prospectively analysed the bacteriological profile (aerobic and anaerobic) and antibiotic sensitivity in 31 patients with acute cholangitis.

DEMOGRAPHY:

The mean age of patients was 51 years and the male: female ratio was 1.3:1. Similar findings were observed in earlier studies (23). Majority of patients (54.6%) were from eastern region, reflecting the profile of patients seeking health care at Christian Medical College. Clinical presentation of patients in the present study (fever: 97%; Abdominal pain: 76%, Jaundice: 75%) were similar to previous studies (4,28). Pamela et al (1) showed that around 5% of patients present with severe acute cholangitis. In our study 3.8% presented with altered sensorium suggestive of severe cholangitis.

Imaging studies:

Previous studies have shown that, the sensitivity of US in detecting stones in CBD is only about 50 %. However, biliary obstruction can be inferred by detection of a dilated biliary system in about 75% of cases (31). In the present study, US detected CBD stone in 55.3% of patients, IHBRD in 85% and MRI in 89% of patients.

Laboratory profile:

Laboratory tests typically reveal leucocytosis with shift to left and cholestatic pattern of liver function (16). Elevated WBC count and serum bilirubin more than 2 mg/dl is seen in 80 % of patients (28) . Serum Alkaline phosphatase levels are elevated in more than 90% of patients with acute cholangitis (29). In this study, the median total peripheral count was 13800 /cmm (range 2200-80000**)**, the median serum Bilirubin and alkaline- phosphatase were 7.1 mg% (0.4-40) and 372 U/L (59- 2511) respectively. Laboratory findings in the present study were similar to the previous studies.

Etiological profile :

A series from Delhi, reported stone disease to be the most common cause of biliary obstruction, followed by malignancy in patients of acute cholangitis (9). Boey JH et al in a series from the West also reported stone disease as the predominant cause

of biliary obstruction (10). Results from the present study is similar to other studies. Choledocholithiasis is the most common cause (62%) followed by malignant obstruction (30%) and benign bile duct stricture (9%).

Microbiological profile:

Numerous studies from India and West showed positive blood culture in 20-30% and positive bile cultures in 70- 90% of patients. A single organism was commonly grown in blood cultures and multiple organisms in bile cultures. The most common gram negative bacteria grown was E coli and gram positive bacteria was Enterococcus (16, 3, 2, 19, 21, 22, 23, 24, 25). Microbial profile of blood and bile cultures in the present study is similar to previous studies. In the present study bacteremia was seen in 26.4% of blood cultures. Most blood cultures grew single organism (91.5 %). E. coli was the predominant organism (70.2%), followed by Klebsiella (14.9%), Pseudomonas (4.3%) and Enterococcus (2.1%). Bacterobilia was seen in 92.6% of bile cultures. Most (75%) of the bile cultures grew multiple organisms. E.coli was the predominant organism (64.8%), followed by Enterococcus (43.2%) Klebsiella (30.7%) and Pseudomonas (13.6%).

Leung JW et al reported anaerobic growth, predominantly Bacteroides in 2% of bile cultures in elderly patients and patients with iatrogenic cholangitis (3). Chang WT et al, in a retrospective study of 1394 patients with biliary treact diseases, found anaerobic

infection in 5% of the patients (19). There is no Indian data regarding anaerobic infection in patients with acute cholangitis. None of the blood (n =29) or bile cultures (n=31) done in patients with acute cholangitis in the present study showed anaerobic infection. Larger number of patients need to be studied to opine about frequency of anaerobic infections in patients with acute cholangitis.

Comparison of the microbiological profile in blood and bile between retrospective(154 patients) and prospective groups (31 patients) showed no major change suggesting that the microbial profile is constant over a period of 5 years.

Antibiotic sensitivity profile in prospective study group:

Studies in the past (both Indian and Western) showed gram negative organisms were sensitive to Cefotaxime, Ceftazidime, Ciprofloxacin, Cefoperazone / salbactum and gram positive organisms to Ampicillin and ciprofloxacin (20, 24). In the present study, the gram negative bacteria in a majority of patients were resistant to Cefotaxime, Ceftazidime, Ciprofloxacin, Ampicillin, Cefoperazone-salbactum, Ticarcillin-clavulinic acid, the common antibiotics recommended as empiric therapy for patients with acute cholangitis. These organisms in the majority of patients were however sensitive to Carbapenams, Netilmicin, Amikacin and Piperacillin/tazobactum in decreasing order of sensitivity. Gram positive organisms were resistant to ciprofloxacin and sensitive to ampicillin, vancomycin, Teicoplanin and high dose gentamycin. Antibiotic sensitivity

profile in the present study is similar to two recent Indian studies, from Kerala, and New Delhi (22, 23). These results suggest that there is a need for fresh recommendation on empiric antibiotic therapy for cholangitis.

Interventions:

Nasobiliary drainage (NBD) was performed on 51 patients and bile duct stenting on 55 patients. The technical success rate and outcome were compared between NBD and stenting groups. No significant difference was found between the two groups. This is similar to a study from New- Delhi which showed, Nasobiliary drain and biliary stenting were equally effective in managing patients of severe cholangitis (42).

Microbiological profile, intervention and outcome between benign and malignant groups:

The microbiological profile and outcomes were similar in both groups of patients. As expected PTBD was performed more often in patients with malignant obstruction. This result is similar to a study from New Delhi, where the outcome was similar between malignant and benign groups (24). Another study from Mumbai, showed similar microbiological profile in patients with benign and malignant biliary obstruction (23).

Etiology, microbiological profile, interventions and outcomes in patients from different regions:

There is no study in Indian patients with acute cholangitis which compared patients from different regions of the country. In our study, stone disease was more common in patients from southern regions and malignant biliary obstruction in patients from eastern regions. The reason for the difference in etiology of obstruction between two regions, may be because sick patients with malignancy travel south to a tertiary centre while those with benign stone disease are treated at local hospitals close to home. The microbiological profile interventions and outcomes were not different between two groups.

Factors that predicts mortality :

In a multivariate analysis from France (27), seven risk factors were identified to predict the mortality in acute cholangitis: 1) age over 50 years, 2) female gender, 3) associated liver abscess, 4) associated cirrhosis, 5) cholangitis due to a high grade malignant obstruction, 6) cholangitis after percutaneous transhepatic choledochography, and 7) acute renal failure.

In the present study, multiple factors were analysed between patients who were stable at discharge and those who died during treatment to predict mortality. In

Univariate analysis, sensorium at admission, ICU care, serum bilirubin, systolic blood pressure and pulse rate were found to be significant in predicting mortality. After multivariate analysis only ICU care was found to have significant association with mortality.

CONCLUSIONS

1. The most common cause of biliary obstruction in patients with acute cholangitis is stone disease (Choledocholithiasis). Malignant disease is responsible for obstruction in 1/3 of patients.

2. Ultrasound examination of abdomen is an effective, inexpensive and non-invasive test for diagnosis of biliary obstruction. It should be the initial imaging test performed in patients with acute cholangitis.

3. Bacteremia with single organisms (Gram negative) is seen in 1/3rd of patients with acute cholangitis, Gram positive organisms are rare in blood cultures.

4. More than 90% of bile cultures show positive growth with multiple organisms in 2/3rd of the cultures. Most common organisms are E.coli and Enterococcus, followed by Klebsiella and Pseudomonas.

5. The bacteriological profile has not changed over time. It is the same in our patients over the past 5 years.

6. Anaerobic bacteria were not grown in bile or blood in the present study. Large

numbers of patients need to be studied to opine about frequency of anaerobic infection in Indian patients.

7. Gram negative bacteria are resistant in a majority of patients to the commonly recommended antibiotics like cefotaxime, Ceftazidime, Ciprofloxacin, Ampicillin, Cefoperazone-salbactum and Ticarcillin-clavulanic acid. They are sensitive to Imipenam, Meropenam, Netilmicin, Amikacin, and Piperacillin / Tazobactum in decreasing order of sensitivity. Gram positive bacteria are sensitive to Vancomycin, Teicoplanin, high dose Gentamycin and Ampicillin in the decreasing order of sensitivity.

8. There is a need for change in strategy for empiric antibiotic therapy in patients with cholangitis. Amikacin, Netilmycin or Piperacillin / Tazobactum is recommended as initial empiric therapy to cover gram negative organisms and Ampicillin or high dose Gentamycin for gram positive organisms. Carbapenams for gram negative organisms, and Teicoplanin or Vancomycin for gram positive organisms should be reserved for patients resistant to first line therapy to prevent development of resistance.

9. Naso-biliary drainage and stenting for biliary decompression in patients of acute cholangitis are equally effective

10. Stone disease is more common in patients from southern region and malignant cause of biliary obstruction is more common in eastern region reflecting referral patterns from East India.

11. The microbiological profile and treatment outcomes are similar in patients with cholangitis due to benign and malignant obstruction.

12. Several risk factors were identified in previous studies to predict mortality in patients with acute cholangitis. The present study showed only ICU care to be significantly associated with mortality. Further studies with large sample size need to be performed to evaluate risk factors that predict mortality.

BIBLIOGRAPHY

1) Pamela A. Lipsett , Henry A. Pitt . Acute Cholangitis.Frontiers in biosciences . 2003 (8),1229-1239.

2) Saharia PC.Clinical management of acute cholangitis.Surg Gynecol Obstet 1996(6), 369-72.

3) Leung JW,Ling TK.Antibiotics,biliary sepsis and bile duct stones.Gastrointest Endoscopy, 1994;40,716-21.

4) Andy s. Yu, Joseph W.Leung.Acute cholangitis .Diseases of bile duct, 2006, 205-15.

5) Leung EC,Mok FP.Endoscopic management of intrahepatic stones.Gastrointest Endosc 1991;35,226-31

6) Rector WGJr.Fever shock and chills in gram negative bacillemia.Johns Hopkins Med J 1981;149(5),175-78

7) Wada,Keita,Takada. Diagnostic criteria and severity assessment of acute cholangitis. Tokyo Guidelines, Journal of Hepato-Biliary-Pancreatic Surgery, 2007(14), 52-58(7).

8) Lillemoe KD. Surgical treatment of biliary tract infections. Am surg . 2000, 66(2),138-44.

9) Naresh A,B C Sharma, S K Sarin. Endoscopic management of acute cholangitis in elderly patients.World J of gastroent, 2006 ;12(40),6551-55.

10) Boey JH,Way LW. Acute cholangitis.Ann Surgery, 1980; 191,264-70.

11) Sung, JY, Costeron, JW, Shaffer, EA. Defense system in the biliary tract against bacterial infection. Dig Dis Sci. 1992, 37(5):689-96.

12) Pitt HA, Cameron JL. Acute Cholangitis. WB Saunders,1987, 295-99.

13) Csendes A, Becerra M, Burdiles P et al. Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstone disease. Eur J Surg 1994 , 160:363

14) Van den Hazel SJ, Speelman P, Tygat GN et al. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. Clin Infect Dis 1994, 279-86.

15) Csendes A.Bacteriology of the gallbladder bile in normal subjects.Am J Surg , 1975(129),629-31

16) Nezam H Afdhal, Sanjiv Chopra, Stephen B Calderwood.Acute cholangitis.Uptodate,2008,16.3

17) Steven H. Aspergillus cholangitis, A late complication after Kasai portoenterostomy.J of Ped Surg, 2002(37),923-25 .

18) Chou ST,Recurrent pyogenic cholangitis, A necropsy study. Pathology 1980;12:415-28

19) Gigot JF,Leese T. Acute cholangitis,multivariate analysis of risk factors.Ann of surgery, 1998;209,435 -38

20) Michael E.Cholangitis due to blastomyces dermatitidis.Gastroent 1989;96,1346-49.

21) Chang WT,Lee KT.Bacteriology and antimicrobiological susceptibility in biliary tract disease:an audit of 10 years experience.Kaohsinung J Med Sci,2002 ; 18(5):221-8.

22) Rerknimitr R.Microbiology of bile in patients with cholangitis with or without plastic

biliary endoprosthesis.Gastrointest Endosc. 2002;56(6),885-89.

23) RD Bapat,A N Supe . Biliary sepsis : An ascending infection. Indian J of Gastroent 1996; 15(4)126-28.

24) Shivaprakasha S,Harish R .Aerobic bacterial isolates from choledochal bile at a tertiary hospital.Indian J of pathol Microb.2006 ;49(3),464-67.

25) Malini R,Deepthi N,Microflora of bile aspirates in patients with acute cholecystitis with or without cholelithiasis.Brazilian j of Inf Dis,2008;12(3)222-25

26) Rakesh K, Barjesh C Sharma, Shiv K Sarin.Endoscopic biliary drainage for severe acute cholangitis in biliary obstruction as a result of malignant and benig diseases.J of Gastroent Hepatology,2004, 19,994-97.

27) Bae WK,Moon YS. Microbiological study of the bile culture and antimicrobiological susceptibility in patients with biliary tract infection.Korean J gastroent, 2008;51(4),248-54.

28) Jeffrey D,Browining, Jayaprakash S. Gall stone disease.Sleisenger & Fordtrans, Gastrointestinal and Liver disease,2007, 1412-13.

29) Waqar A.Qureshi.Approach to a patient who has suspected acute bacterial cholangitis.Gastoint clin N Am,2006(35),409 -23.

30) Abbruzzese A . Marked elevations of serum SGOT and LDH in chronic extrahepatic biliary disease. Am J Dis 1969;14,332-38.

31) Einstein DM. The intensity of sonography in the detection of choledocholithiasis.AJR Am j Roentgenol . 1994;142,725-29.

32) Hanau LH,Steigbigel NH.Acute (Ascending) Cholangitis .Inf Dis Clin North Am,2000;14,521-28.

33) Lipsett PA, Pitt HA. Acute cholangitis.Front Biosci, 2003 ; 8, 1229-39.

34) Sung, JY, Lyon, DJ, Seun, R, et al. Intravenous ciprofloxacin as treatment for patients with acute suppurative cholangitis: A randomised, controlled clinical trial. J Antimicrob Chemother 1995; 35,855- 64.

35) Weber A,Huber W.Invitro activity of moxifloxacin and pip/salb against pathogens of acute cholangitis.Worlld J of Gastroent ,2008,14(20),317-18.

36) Van Lent AU,Tytgat GN.Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract.Gastroint Endosc, 2002;55(4),518-22.

37) Zhang Y,Chen H. Thymosin alpha1- and ulinastatin- based immunomodulatory strategy for sepsis arising from intraabdominal infection due to carbapenam resistant bacteria.J Inf Dis,2008;198(5)723-30.

38) Antimicrobial therapy for acute cholangitis: Tokyo guidelines.J Hepatology Panceat Surg,2007; 14, 59-67.

39) Lai EC, Tam PC, Paterson IA. Emergency surgery for acute cholangitis. Ann Surg, 1990; 211, 55-59.

40) Lee DW, Chan AC, Lam YH et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc, 2002; 56,361-65.

41) Hui CK, Lai KC, Yuen MF et al. Does the addition of endoscopic sphincterotomy to stent insertion improve drainage of the bile duct in acute suppurative cholangitis?. Gastrointest Endosc 2003; 58:500.

42) Sharma BC,Kumar R, Agarwal N.Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis.Endoscopy 2005; 37, 439-43.

43) Mishra SP,Dwivedi M,Biliary endoprosthesis as an alternative to endoscopic nasobiliary drainage in patients with acute cholangitis.Endoscopy 1996; 28:746-9.

44) Hui CK,Lai KC.Does the addition of ES to stent insertion improve drainage of bile duct in acute suppurative cholangitis.Endosc 2003; 58(4),500-4.

45) Chopra KB, Peters RS, William SG.Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bile duct stones in high risk patients.Lancet, 1996;348(9030),791-93.

46) Leung JW,Chung SC.Urgent endoscopic drainage for acute suppurative cholangitis.Lancet, 1989;1:1037-39.

47) Kadir S. Percutaneous biliary drainage in the management of biliary sepsis. AJR AmJ Roentgenol,198(138),25-29.

48) Sugiyama M,Atomi Y.Treatment of acute cholangitis in elderly and younger patients.Arch Surg, 1997;132,1129-33.

49) Chan Y, Chan AC, Lam WW et al. Choledocholithiasis: Comparison of MR cholangiography and endoscopic retrograde cholangiography. Radiology,1996; 200(1),85-89.

50) Gerecht WB, Henry NK, Hoffman WW et al. Prospective randomized comparison of mezlocillin therapy alone with combined ampicillin and gentamicin therapy for patients with cholangitis. Arch Intern Med 1989; 149:1279

51) Chen MF,Jan YY, Percutaneous transhepatic biliary drainage for acute cholangitis.Int Surg 1987;72:131-3

52) Keaveny AP, Infections of the bile duct.Gall bladder and biliary tract disease.2000,773-821

53) Chetan V,Santam S,Prevalence of salmonella enterica in bile and stool of patients with biliary diseases.Jpn J Infect Dis, 58,363-65,2005

54) Nave R,Biswas S,Bile cultures and sensitivity patterns in malignant obstructive jaundice. Indian J of Gastroent. 2003 Jan-Feb ; 22(1):16-9.

55) Ian F. Yusoff, Diagnosis and management of cholecystitis and cholangitis.Gastroenterol Clin N Am 32(2003)1145-1168

56) Lai EC, Tam PC, Paterson IA. Emergency surgery for acute cholangitis. Ann Surg 1990; 211:55.

57) DenBesten L, Doty JE. Pathogenesis and management of choleolithiasis. Surg Clin North Am 1981; 61, 893-98.

PROFORMA

Sl No: DOA: DOD:

Name: Age:

Sex: 1) Male 2) Female Hos No:

State of origin:1) TN , 2) AP , 3) KL , 4) KT , 5) WB ,6) BIHAR , 7) Others(mention names)

Occupation:

Phone No:

Final Diagnosis:

History

1) Pain : Yes(1- mild, 2-moderate,3- severe) , 4-No Duration:

2) Fever: Yes (1- low grade, 2-moderate, 3-highgrade) , 4-No Duration

3) Chills : 1- yes , 2- No

4) Jaundice: 1- Yes , 2- No Duration

5) Cholestatic symptoms: 1) yes (pale stools, pruritus), 2) No

6) Wt loss: yes (1- mild, 2- moderate, 3- severe) , 4-No

7) Anorexia:1-Yes, 2- No

8) Altered bowel habits: (Diarrohea , Constipation) 1- yes, 2-No

9) GI bleed: 1-Hematemesis, 2- Melena, 3- haematochazia, 4-No

10) Others:

Past history

Surgery: 1-yes (nature of sx) ,2-No

Biliary colic: 1- yes, 2-No

Jaundice: 1-yes,2-No

H/O ERCP: 1- yes, (Indication),2-No

DM: 1- yes, 2-No
TB: 1-yes, 2-No
HTN: 1- yes, 2-No
IHD: 1-yes, 2-No

Personal History

Alcohol: 1- yes (Duration , Amount), 2-No

Smoking: 1- yes (Duration, No of cig/bidis per day, pack per year),2-No

High risk behaviour:1- yes, 2- no

Family History:

On Examination

Pallor: y/n Icterus:y/n Lymphnode:pos/neg Clubbing:pres/abs
Edema:pres/abs sensorium: norm/alttered
Nails:nor/abnorm scratch marks: pres/abs
Oral cavity: norm/abnor Eye: norm/abnorm
Signs of livercell failure:pres/abs

BP: Pulse; Wt: Height: BMI:

P/A: 1-tendernes, 2- hepatomegaly, 3- palpable GB/mass, 4- ascites

P/R:

LAB

Tests	**Date**	**Date**	**Date**

Hb			
TC			
DC			
Toxic changes			
LFT			
Crt			
Na			
K			
BBVS			
Stool parasites			
Urine R/M			
Blood C/S(aerobic)			
Blood C/S(anerobic)			
BileC/S(aerobic)			
Bile C/S(anerobic)			

CXR:

USG:

IHBRD : yes, (1- mild,2- moderate,3- severe), 4-No
Dilated CBD:1-Yes(cm), 2-No
GB stone: 1-yes, 2-No
Lesion: 1-stone, 2-stricture,3-malignancy, 4-others, 5-none

MRI :

IHBRD : yes, (1- mild,2- moderate,3- severe), 4-No
Dilated CBD:1-Yes(cm), 2-No
GB stone: 1-yes, 2-No

Lesion: 1-stone, 2-stricture,3-malignancy, 4-others, 5-none

EUS:

IHBRD : yes, (1- mild,2- moderate,3- severe), 4-No
Dilated CBD:1-Yes(cm), 2-No
GB stone: 1-yes, 2-No
Lesion: 1-stone, 2-stricture,3-malignancy, 4-others, 5-none

CT:

IHBRD : yes, (1- mild,2- moderate,3- severe), 4-No
Dilated CBD:1-Yes(cm), 2-No
GB stone: 1-yes, 2-No
Lesion: 1-stone, 2-stricture,3-malignancy, 4-others, 5-none

ERCP(Cholangiogram): 1-stone,2- stricture,3-malignancy, 4-choledochal cyst, 5-normal

Treatment

ICU care**: 1-**yes(duration), 2-No

Duration of hospitalisation:
Interval between onset of symptom and intervention(ERCP/PTBD/ Surgery):

Intervention:1-ERCP/2-PTBD/3-Surgery/4-Antibiotics

Antibiotic received:Details(Dose/ Duration)

Status at discharge:1-sick,2- healthy, 3-death

PATIENT CONSENT FORM

Patient Hospital Number: ----------

Name of Researcher: ----------

It has been explained clearly to me in a language that I understand.

1. That a research study on bacteriological profile and antibiotic sensitivity in acute cholangitis is being conducted in the Department of GI Sciences, CMCH, Vellore.

2. I understand that taking part in this study is voluntary and that I am free to withdraw at any time, without any reason and doing so will not affect my medical and legal rights.

3. I understand that some of my medical notes will need to be looked at by responsible indivisuals from Christian Medical College, Vellore where the treatment is to be carriedout.I give permission for these indivisuals to have access to my records.

4. I hereby give my full consent to take part in the study.

Name of the Patient: _____
Tel.No.: _____

Address: _____

_____

Signature:_____ Date:_____

Name of Witness: _____ Date:_____

Two copies of this are needed. One to be kept with the patients study file and the another to be given to the patient