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Resistant pathogens in biliary obstruction: Importance of cultures to guide antibiotic therapy

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Abstract

Background. Cholangitis, infection of the bile ducts, is a serious condition that necessitates prompt and efficacious treatment for a good clinical outcome. A single center retrospective study of cholangitis was conducted to better define the spectrum of responsible pathogens and their antibiotic sensitivities.

Methods. We studied all patients at our hospital who had cholangitis from January 1998 to June 2004. Patients were identified by ICD-9 codes and the cause of the cholangitis, the treatment and culture data were noted by review of the medical record.

Results. Thirty patients presented with cholangitis as noted by the clinical symptoms of jaundice, fever and abdominal pain. The cause of the biliary obstruction was gallstones in 18 patients, benign biliary strictures in 5 and malignant obstruction in 7. All the patients with malignant obstruction with cholangitis had stents; there were no cases of cholangitis in malignant obstruction unless prior instrumentation had been performed. The most common isolates were Enterococcus > E. coli > Enterobacter > Klebsiella. Sixty-four percent of blood cultures and all but one of the bile cultures grew organisms. Seventy-two percent of patients had positive blood cultures with at least one resistant organism present and 36% had organisms resistant to multiple antibiotics. Fifty percent of patients with benign biliary disease and positive blood cultures had multiple organisms growing in their blood. Three-quarters of the isolates were resistant to one or more antibiotics and one-quarter of isolates were resistant to three or more antibiotics. Resistant organisms were found regardless of the cause of the biliary obstruction.

Discussion. For all causes of cholangitis, there is a high incidence of positive blood cultures and a high rate of antibiotic resistance. For optimal treatment, blood and/or bile cultures should be routinely performed to optimize antibiotic therapy.

Key Words: *Antibiotic resistance, biliary infection, cholangitis*

Introduction

Increasingly medical centers guide antibiotic therapy through the use of hospital antibiotic formularies or clinical pathways. Review of culture and sensitivity data in various clinical settings is needed to help guide these antibiotic choices. While biliary tract infections are common, cholangitis, infection of the bile ducts, is less frequently encountered. Cholangitis is associated with a high mortality making appropriate and prompt treatment important to improve outcome.

Cholangitis involves both obstruction and infection of the bile ducts. Usually the bile ducts are sterile. However, the presence of gallstones within either the gallbladder or biliary tree is associated with bacterial colonization of the bile [1]. In patients without stone disease, previous biliary intervention is associated with high rates of bacterobilia [2,3]. Under conditions of normal bile flow, bacteria in the biliary system are of no clinical significance. Upon bile duct obstruction, bacteria proliferate within the stagnant bile while biliary pressures increase. Eventually, the bacteria presumably translocate into the circulation causing a systemic infection.

This associated inflammatory response can be quite severe leading to profound sepsis. The impressive presentation of these toxic patients underscores the importance of appropriate antibiotic therapy at the time of presentation. Much of the data on bacterial causes of cholangitis is dated and there has been a wide range of proposed antibiotics for the treatment of biliary infections. We wished to review our experience with cholangitis, focusing on characterization of the bacterial pathogens and antibiotic sensitivities. A single center retrospective review of cholangitis was conducted to better define the clinical presentation and spectrum of pathogens responsible for bile duct infections to better guide future antibiotic therapies.

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Methods

Patients with cholangitis were identified through search of ICD-9 codes 576.1 (Cholangitis) and 576.9 (Bile duct, infection). We examined the charts of all 30 patients with cholangitis who were admitted to Ann Arbor VAMC between 1 January 1 1998 to 1 June 2004. Cholangitis was confirmed with the presence of jaundice, fever, abdominal pain, and biochemical and radiographic evidence of biliary obstruction. Data obtained included: demographic information (age, sex), clinical presentation (complaints and lab values), radiographic evaluation (diagnosis and treatment), clinical history (comorbidities and history of previous biliary disease, etc.), bile and blood culture results, surgical course, and long-term follow-up data. This study was reviewed and approved by our Institutional Human Subjects Review Board.

Clinical characteristics were compared using Fisher's exact test for dichotomous variables and the Wilcoxon rank-sum test for continuous variables. Statistical analysis was performed using SAS v.8.0 (SAS Institute, Cary, NC). Data is expressed as value $\pm$ standard deviation.

Results

The median patient age was 70 years with a range of 49–87 years old. The mean follow-up was 18 months. All but one of the patients were male. The cause of the biliary obstruction was gallstones in 18 patients, benign biliary strictures in 5 and malignant obstruction in 7. All three groups of patients had elevated white blood cell count and bilirubin (Table I). Data in Table I are expressed as mean $\pm$ standard error of the mean (SEM). The serum bilirubin, alkaline phosphatase and white blood cell counts were similar regardless of the type of obstruction. The serum glutamic-oxaloacetic transaminase or [SGOT] levels were significantly lower with benign biliary strictures and cholangitis.

Table I. Clinical presentation of cholangitis

	CBD stones	Benign stricture	Malignant stricture	All cholangitis
Age (years $\pm$ SEM)	69 $\pm$ 3	65 $\pm$ 3	71 $\pm$ 4	69 $\pm$ 2
Fever (>101.6°F)	67%	80%	71%	77%
Abdominal Pain	78%	50%	71%	70%
Jaundice (Bili >4)	72%	60%	67%	69%
Vomiting	33%	0%	57%	37%
Hypotension	33%	25%	29%	30%
WBC ($\times$1000 $\pm$ SEM)	17.8 $\pm$ 3.1	16.1 $\pm$ 1.8	16.6 $\pm$ 1.4	17.2 $\pm$ 1.9
Bili (mg/dl)	6.1 $\pm$ 0.9	4.6 $\pm$ 1	5.7 $\pm$ 1.6	5.8 $\pm$ 0.7
Alk Phos (U/l)	370 $\pm$ 51	472 $\pm$ 149	533 $\pm$ 87	421 $\pm$ 45
SGOT (U/l)	190 $\pm$ 35	54 $\pm$ 3*	184 $\pm$ 61	165 $\pm$ 26

* $p < 0.05$ compared to CBD stone, malignant stricture, and all cholangitis groups.

The significance of this is unclear and may be related to the fact that this group had the smallest number of patients. The possibility exists that this group may have had less hepatocellular damage with the biliary obstruction than the other two, yet more patients would need to be studied for any conclusions to be drawn. The poor overall medical condition of the majority of patients with cholangitis in this series is exemplified by the fact that only 13% had no significant medical comorbidity (Table II).

There was a 13% 30-day mortality for all patients with cholangitis. The 30-day mortality was high regardless of the cause of the biliary obstruction (11% for stone disease, 20% for benign strictures and 29% for malignant obstruction). One patient presented with a liver abscess at the time of initial presentation with cholangitis. Forty-three percent (13) of the patients died during the period of follow-up. Of those who died, there was a mean survival from time of diagnosis of cholangitis to death of 4 months. All of the patients with malignant biliary obstruction died. Of the six patients with malignancies, three had Stage IV pancreatic cancer, three had unresectable hilar cholangiocarcinoma (Klatskin tumors with two being Stage III and one Stage IV), and one patient had gallbladder cancer with liver metastasis (Stage IV). Six patients died who did not have a malignant biliary obstruction, and three of these deaths were directly related to cholangitis.

Ninety percent (27) of patients underwent ERCP. Many patients had multiple ERCPs and a total of 52 were done on this group of 30 patients. Forty-four percent (8/18) of the patients with gallstone disease had a stent placed at the initial ERCP and later had stone extraction and sphincterotomy. Six patients went on to have a percutaneous transhepatic cholangiocatheter (PTC) placed (several due to unsuccessful attempts at ERCP and several due to the location of biliary obstruction).

Thirty percent (9) of patients had significant hemodynamic instability and a prolonged ICU course related to the biliary obstruction. Five patients with choledocholithiasis had a cholecystectomy in the distant past. Twelve patients who had choledocholithiasis were referred for surgery. One refused, three had a laparoscopic cholecystectomy, two had a

Table II. Medical comorbidities in patients with cholangitis

Medical comorbidities	Percent of patients
Hypertension	57%
Cardiac disease	40%
Diabetes	37%
Malignancy (non-biliary)	33%
Pulmonary disease	17%
Renal failure	17%
Liver disease	13%
Vascular disease	10%

Table III. Bacterial isolates in cholangitis

Organism	Number of Isolates	
	Blood	Bile
Enterococcus faecalis	8	5
E. coli	6	2
Enterobacter cloaca	3	4
Klebsiella pneumoniae	2	3
Streptococcus	3	1
Staphylococcus	2	1
Hemophilus influenza	1	0
Pseudomonas aeriginosa	0	1
Proteus mirabilis	0	1
Citrobacter freundii	0	1

laparoscopic converted to open cholecystectomy, and two had an open cholecystectomy. Three patients had an open common bile duct exploration (failed ERCP removal of stones).

All the patients with malignant obstruction that presented with cholangitis had stents; there were no cases of cholangitis in malignant obstruction unless prior instrumentation had been performed. Seventy-seven percent (23) of patients had blood cultures at the time of presentation and 65% (15) of those blood cultures were positive. Thirty-three percent (10) had bile cultures and all but one were positive. Multiple organisms were isolated from the bile and the blood (Table III). Bile cultures tended to correlate with the organisms isolated from blood. There was a significant degree of antibiotic resistance. Seventy-two percent of patients who had positive blood cultures (8 of 11 patients) had at least one resistant organism present when sensitivity data was available and 36% of patients had positive blood cultures with several resistant organisms present (Table IV). Many isolates were not sensitive to commonly used antibiotics (Table V).

Statistical analysis revealed no clinically significant statistical differences between the three groups of patients.

Table IV. Blood culture microbial resistance

	Choledocho-lithiasis	Benign duct obstruction	Malignant obstruction
% of patients with blood cultures	78	75	71
% of patients with positive culture	64	38	80
% isolates resistant to 1+ antibiotics	75	100	75
% isolates resistant to $\geqslant 3$ antibiotics	25	0	33
% patients with resistant organisms to 1+ antibiotics	72	100	75
% patients with resistant organisms to $\geqslant 3$ antibiotics	36	0	25

Table V. Antibiotic sensitivities of blood culture isolates

Selected antibiotics	Gram positive organisms	Gram negative organisms	All organisms
Ampicillin	85% (11/13)	42% (5/12)	64% (16/25)
Amikacin	100% (1/1)	100% (11/11)	100% (12/12)
Aztreonam	100% (1/1)	92% (11/12)	92% (12/13)
Cefazolin	100% (2/2)	64% (7/11)	69% (9/13)
Cefotaxime	100% (5/5)	100% (8/8)	100% (13/13)
Cefotetan	Not done	91% (10/11)	91% (10/11)
Ciprofloxacin	67% (6/9)	100% (12/12)	86% (18/21)
Gentamicin	80% (4/5)	100% (12/12)	94% (16/17)
Imipenum	75% (3/4)	100% (11/11)	93% (14/15)
Levofloxacin	83% (5/7)	100% (9/9)	88% (14/16)
Piperacillin	Not done	75% (3/4)	75% (3/4)
Pip/Tazo	100% (3/3)	86% (8/9)	92% (11/12)
Ticar/clav	Not done	100% (7/7)	100% (7/7)
Tobramycin	Not done	100% (9/9)	100% (9/9)
TMP/SMX	50% (1/2)	75% (9/12)	71% (10/14)
Vancomycin	91% (10/11)	Not done	91% (10/11)

Discussion

Cholangitis was first described in 1877 by Charcot. The traditional presentation includes the triad of jaundice, fever and right upper quadrant pain [4], though the actual presentation can be quite diverse, ranging from mild abdominal discomfort to life-threatening septic shock. In our series, in addition to fever, abdominal pain and jaundice, the two most common symptoms included vomiting (33%) and hypotension (33%). Both biliary obstruction and bacteria in the bile are required for the development of cholangitis. In a healthy person, the biliary tree is normally sterile, but biliary pathology is often associated with secondary bacterial colonization [1]. Effective management of cholangitis involves three steps: appropriate resuscitation, initiation of broad-spectrum antibiotics to address the systemic infection, and biliary decompression.

A 5% rate of toxic cholangitis with patients requiring immediate resuscitation and ICU admission upon presentation is frequently quoted in the literature [5]. In our series, 30% of patients presented severely toxic requiring ICU admission. This significant proportion is likely related to the medical comorbidities (Table II) in the population of veterans in this series. The medical comorbidities and mean patient age (69 ± 3 years) also likely influenced the significant mortality in our series. The high proportion of males in this series may also be important. A higher mortality from biliary disease [6] and a higher conversion rate to open operation in males [7,8] suggest that biliary disease in the male may be more virulent, or tends to present later in the course of the disease. These critically ill patients required aggressive resuscitation with concurrent management of their multiple medical comorbidities.

No cancer patients presented with cholangitis without previous stent placement. This reflects the palliative nature of stents and their well-described high rate

of occlusion [9]. Stenting for malignant biliary obstruction is predominantly for advanced surgically unresectable disease. This was the case for all of the patients in this series.

Election of the appropriate empiric antibiotic is critical. Unfortunately, the data most frequently quoted reflects bacterial data that is old and may not be applicable to current practice [1,10,11]. Many of the patients in our series had pathogens in either their bile or blood that have been well described in cholangitis (Enterococcus, E. coli, Enterobacter, and Klebsiella) [12]. Our series showed that even these more common biliary isolates were often resistant to multiple antibiotics. Interestingly, 23% of the bile bacterial isolates were organisms rarely described in cholangitis (Table III). Pathogens such as staph aureus, pseudomonas, and citrobacter may not be covered by routine broad-spectrum coverage. Antibiotic coverage broad enough to cover a broad range of organisms should be considered, especially in patients with biliary stents. Enterococci and polymicrobial infections are found more commonly in patients with a biliary stent than in those without a stent [13]. Polymicrobial infections were also common in patients with gallstone disease in this series. Half of the patients with cholangitis from choledocholithiasis had multiple organisms cultured from their blood. The polymicrobial nature of cholangitis along with the high rate of antibiotic resistance for all causes of cholangitis emphasizes the importance of local antibiotic sensitivity data to guide clinical pathways involving antibiotic therapy. Blood cultures are important to guide therapy, especially if bile cultures are not sent early in the treatment. As in our study, bile cultures have been shown to correlate with positive blood cultures in patients with cholangitis [13,14]. Either blood or bile cultures data can effectively guide antibiotic choices. Often patients are initially treated with antibiotics, and definitive treatment to relieve biliary obstruction done days later. Unless a stent is in place, bile cultures may not be available. In our study only 37% of patients had bile cultures done and the majority of patients had indwelling biliary stents. At the time of presentation, blood cultures are important as one of the initial steps in the care and treatment of cholangitis.

Antibiotic regimens may vary for different institutions and may be guided by local sensitivity data. For our institution, a fluoroquinilone or ureidopenicillin (such as piperacillin with tazobactam) for patients presenting with cholangitis is a good choice. Fluoroquinilones have good biliary excretion even with the presence of biliary obstruction [15]. There is also a high percentage of biliary isolates that are sensitive to this antibiotic. In more complex patients, such as those who have been extensively exposed to broad-spectrum antibiotics or those with an endoprostheses, imipenem or meropenem may be a good choice until culture data is available. Ampicillin, which has been recommended as the antibiotic of choice for prophylaxis in biliary obstruction [13], may not be a good choice for the treatment of cholangitis given that only about half of the biliary isolates were sensitive to ampicillin in our series. Others have seen similar resistance. Likewise, although cephazolin is often given for prophylaxis in biliary surgery [16], one third of the bacterial isolates in our series of cholangitis were resistant to this drug.

Similar to other reports we found a wide variation in the length of treatment with antibiotics in cholangitis. Van Lent *et al.* found that short-duration antibiotic therapy (3 days) appears sufficient when adequate biliary drainage is achieved and the patient is clinically improving [17]. Adequate antibiotic therapy is needed to avoid sepsis and a need for urgent biliary decompression. Tachycardia, low albumin, high bilirubin and elevated protime were associated with a higher risk of a need for emergent ERCP in a prospective study done by Hui *et al.* [18]. The choice of antibiotics in reducing the need for emergent ERCP has not been investigated, yet given the culture data found by this series and others, a broader spectrum choice of initial antibiotics is likely to be more successful in improving outcome.

More important than the length of antibiotic treatment is the early relief of biliary obstruction [19,20]. The etiologies of the bile duct obstruction include: choledocholithiasis, malignant strictures (cholangiocarcinoma, pancreatic cancer, ampullary carcinoma), and benign strictures (pancreatitis, post-operative/iatrogenic, congenital, or bilio-pancreatic ascariasis). Common bile duct stones have been the most common cause in the past (80% in one series and 56% in our series), but recently the proportion of malignant and benign strictures has increased [5].

The timing of biliary decompression depends on the patient's response to the resuscitation and antibiotics. In our experience, the sepsis syndrome usually resolves allowing time for a detailed evaluation of the cause of the biliary obstruction. If the patient already has an endoprosthesis, then stent malfunction is very likely. In patients with choledocholithiasis, ERCP is the diagnostic and therapeutic modality of choice [21]. A delay in biliary decompression in patients who are refractory to conservative measures has been associated with increased mortality [19,20]. Various endoscopic options are available for managing choledocholithiasis, including endoscopic papillotomy with stone extraction or placement of a biliary drainage system. In patients who respond to initial conservative therapy, papillotomy with stone extraction is preferred, while in those with ongoing sepsis and multiple large stones, the placement of a stent is the safest option [22]. If the patient has no signs of ongoing sepsis and upon ERCP a lesion is noted that will potentially be managed operatively, then placement of a stent can complicate the surgical procedure and should not be placed without surgical consultation. Percutaneous transhepatic biliary catheter placement (PTC) is reserved for failure of endoscopic drainage and for patients with suspected hilar cholangiocarcinoma or intrahepatic

stones. Emergent surgical management of cholangitis is rarely necessary and should be avoided unless less invasive modalities (ERCP and PTC) have failed.

Following biliary decompression and patient recovery, surgical management is often necessary to prevent recurrence of cholangitis, though not always effective. Four patients presented years following cholecystectomy with primary choledocholithiasis. Treatment of cholangitis with ERCP and spincterotomy alone, without cholecystectomy, may be appropriate in individuals who are a high surgical risk. The risk of recurrent biliary infection is high after ERCP with sphincterotomy alone. All but four patients with choledocholithiasis in our series were referred for surgery. The patients not referred for surgery had other malignancies and/or severe medical comorbidities. The majority of the patients with gallstones subsequently had a cholecystectomy. One patient refused cholecystectomy and had recurrent biliary symptoms months later. Unless there is a prohibitive surgical risk, an elective cholecystectomy is recommended once the clinical condition stabilizes in patients with cholangitis. Most studies have shown recurrent symptoms in one-quarter to one-third of patients if the gallbladder is left in situ for stone related cholangitis [21,23]. Exceptions to this may be patients who no longer have any evidence of residual gallstones or in populations where primary bile duct stones are prevalent [24]. Due to the high morbidity and mortality associated with cholangitis, we feel in patients with cholangitis due to stone disease, cholecystectomy should be performed unless other medical conditions predict a short survival or there is a prohibitive surgical risk.

In conclusion, cholangitis is an infectious disease of the biliary system with associated biliary obstruction. The cornerstones of therapy include resuscitation, broad-spectrum antibiotics, and biliary decompression. Polymicrobial infections are common. Atypical biliary pathogens should be considered in complex and critically ill patients with cholangitis, especially when a biliary stent is present. Initial antibiotic therapy should include a more intensive regimen than those suggested for biliary tract infection prophylaxis. Given the prevalence of antibiotic resistance, blood and/or bile cultures are important to ensure effective antibiotic therapy for patients with cholangitis.

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