Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract

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Background: **Drainage of the obstructed biliary tree is the mainstay of therapy for patients with acute cholangitis; antibiotic therapy is complementary. It is unknown whether it is necessary to continue therapy with antibiotics once biliary drainage is achieved and signs of systemic inflammation have subsided.**

Methods: **Patients who presented with acute cholangitis and were successfully treated at ERCP were studied retrospectively. Patients were followed for 6 months after ERCP.**

Results: **Eighty patients fulfilled study criteria. In 46% of patients blood cultures grew microorganisms. All patients recovered from the episode under study. Antibiotic therapy after ERCP was given for a median duration of 3 days (range: 0-42). Forty-one patients received antibiotic therapy for 3 days or less, 19 for 4 or 5 days, and 20 patients longer than 5 days. The 3 groups were well-matched. In none of the patients did the index episode of cholangitis result in a secondary complication not present at the time of ERCP. The percentage of patients with recurrent cholangitis (24%) was not statistically different for the 3 groups ($p = 0.80$).**

Conclusions: **Short-duration antibiotic therapy (3 days) appears sufficient when adequate drainage is achieved and fever is abating. (Gastrointest Endosc 2002;55:518-22.)**

Cholangitis is a well-known complication in patients with biliary tract obstruction. Bile is sterile in healthy individuals, but when the biliary tract is compromised (e.g., stone, stricture, endoprosthesis), bacteria can usually be cultured from the bile.[1] When biliary pressure rises because of obstruction, bacteria and bacterial products such as endotoxin can leak from the bile into the systemic circulation and cause septicemia and the clinical picture of cholangitis. Drainage of the obstructed biliary tree is therefore the mainstay of therapy for patients with acute cholangitis, whereas antibiotic therapy is only complementary. Antibiotic therapy is usually given for 7 to 10 days.[1,2] The aim of antibiotic therapy is to control sepsis and local inflammation and not sterilization of the bile. Whether it is necessary to continue antibiotic therapy after biliary drainage is established and signs of systemic inflammation have subsided is unknown. Studies addressing the optimal duration of antibiotic therapy are lacking. In our hospital it has become common practice to stop antibiotic therapy after a few days once the obstruction has been relieved and the patient has become afebrile. This is a retrospective study of 80 patients with acute cholangitis treated in our hospital and an analysis of whether the occurrence of infectious complications and the frequency of recurrent cholangitis were related to the duration of antibiotic therapy once adequate biliary drainage was established.

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PATIENTS AND METHODS

Eighty patients who presented with acute cholangitis and were successfully treated at ERCP were studied. The patients were identified by screening the reports of all ERCPs performed between February 1999 and September 1999 in our tertiary care medical center. Acute cholangitis was defined as an illness characterized by fever (>38°C) and bile duct obstruction, as evidenced by increased bilirubin levels or dilated bile ducts by US. If a patient was known to have one or more bile duct stent(s) in situ, obstruction was also assumed by observation of a clogged stent or pus in the bile ducts. ERCP was considered successful if after the procedure the obstruction was relieved, as evidenced by an adequate flow of bile after the procedure. After ERCP, patients were usually treated further in the referring hospital. Patients were excluded if they had primary sclerosing cholangitis, inflammatory bowel disease, bile duct atresia, or if they had undergone liver transplantation. Patients who received maintenance therapy with antibiotics were also excluded. The medical records of patients who met the inclusion criteria were reviewed. If the record was incomplete, the primary care physician was contacted to obtain missing data.

Table 1. Characteristics of 80 patients with acute cholangitis

Demographics		
Age, y (median, range)	70.0 (34-95)	
Male gender (n, %)	39 (49)	
Comorbidity (n)		
Chemotherapy or immunosuppressive medication	5	
Diabetes mellitus	12	
Cause of obstruction (n, %)		Previous stent placement
Klatskin tumor	14 (18)	13
Pancreatic carcinoma	22 (28)	20
Stones	29 (36)	6
Anatomic abnormality*	12 (15)	9
Papillary tumor	2 (3)	2
Unknown	1 (1)	0
Earlier episodes of cholangitis (median, range)	0 (0-5)	

*Stricture caused by previous surgery (7), stricture caused by other malignancy (2), papillary stenosis (2), stenosis of common bile duct caused by long-term stent therapy for choledocholithiasis (1).

Table 2. Characteristics of index episode of cholangitis

Duration of fever before procedure (n = 50)*	2.5 (1-14) d†
Temperature (n = 58)	39.0 (37.5-40.8)°C
WBC (n = 64)	11.2 (3.6-45.4) $\times 10^9$/L
Bilirubin total (n = 67)	68 (8-514) μmol/L (N <17 μmol/L)
Bilirubin direct (n = 38)	55 (12-436) μmol/L (N <7 μmol/L)
Results of blood culture (n = 46)	
No growth	25 (54)‡
E coli	14 (28)
Klebsiella species	6 (13)
Enterobacter species	4 (9)
Streptococcus species	2 (4)
Staphylococcus epidermidis	1 (2)
Other§	7 (11)

WBC, White blood cell count.
*Number of patients for which data were available.
†Median (range).
‡n (%); in some cases more than one microorganism was isolated.
§*Citrobacter* (1), *Enterococcus faecalis* (2), gram negative rods (not specified) (3), anaerobes and yeast (1).

Patient demographics, the cause of bile duct obstruction, clinical features and laboratory findings during and after the studied episode of cholangitis, results of the US examination, details of the endoscopic procedure and the antibiotic treatment, and outcome were recorded. If the relevant information could not be retrieved, the patient was excluded from analysis. Patients were followed for 6 months after the ERCP. Infectious complications and other episodes requiring antibiotic treatment, recurrent cholangitis, surgical procedures, and death were recorded as defined endpoints.

Statistical analysis

Patients were categorized according to the duration of antibiotic treatment (intravenous and/or oral administration) after the ERCP as follows: 3 days or less, 4 or 5 days, and greater than 5 days. Groups were compared by means of the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. All p values were based on two-tailed tests. Analyses were performed with SPSS for Windows (SPSS, Inc., Chicago, Ill.).

RESULTS

Study population

A total of 129 eligible patients were identified from ERCP reports. Data for 5 patients could not be retrieved. Of the remaining 124 patients, 27 met the exclusion criteria. For 17 patients, data concerning the duration of antibiotic treatment were lacking, and these patients were excluded from analysis. The remaining 80 patients were enrolled. Of these, 62 were referred from another hospital. All of these patients returned to the referring hospital after the ERCP procedure. For 12 patients data concerning follow-up were obtained from primary care physicians. Characteristics of the patients are shown in Table 1. The etiology of obstruction was equally divided between benign and malignant causes. Twenty-three patients had one or more earlier episodes of cholangitis.

Characteristics of the episode of cholangitis

Characteristics of the episode of cholangitis are shown in Table 2. Blood cultures were obtained in 58% of patients. In 46% of these patients the blood culture grew microorganisms, the majority gram-negative rods. Only 5 bile cultures were obtained. The result was no growth in 1 patient and in the other 4, *Escherichia coli* (2), *Klebsiella* species (3), *Pseudomonas aeruginosa* (1), *Streptococcus milleri* (1), *Streptococcus* group D (1), *Enterococcus faecalis* (1). Sixty-one patients (76%) received antibiotic therapy before ERCP.

Therapy

The therapy given is described in Table 3. Five patients had a complication of the endoscopic procedure: hemorrhage (successfully controlled by local epinephrine injection) (2), pancreatitis (1), hemodynamic instability with hypotension resulting in admission to the intensive care unit (ICU) (1), and congestive heart failure resulting in admission to the ICU (1). All patients recovered without further signs of cholangitis.

Antibiotic therapy after the ERCP was given for a median duration of 3 days (range: 0-42 days). Forty-one patients received antibiotic therapy for 3

Table 3. Therapy and outcome

Endoscopic procedure (n, %)				
Placement of a polyethylene stent	47 (59)			
Stone removal	16 (20)			
Stone removal and stent placement	10 (13)			
Placement of a wallstent	2 (3)			
Other	4 (5)			
Lithotripsy	1 (1)			
Duration of antibiotic therapy after ERCP	(median 3 days; range 0-42 days)			
	Patients receiving antibiotics ≤3 d (n = 41)	Patients receiving antibiotics 4 or 5 d (n = 19)	Patients receiving antibiotics >5 d (n = 20)	Total (n, %)
Antibiotics given				
Amoxicillin and aminoglycoside	15	2	2	19 (24)
Amoxicillin, aminoglycoside, and metronidazole	1	2	1	4 (5)
Piperacillin (± tazobactam)	10	3	4	17 (21)
Amoxicillin and piperacillin	4	2	1	7 (9)
Ciprofloxacin	1	2	2	5 (6)
None	5	–	–	5 (6)
Other*	5	8	10	23 (29)
Outcome				
Duration of fever after ERCP (n = 53)	(median 1 d; range 0-17 d)			
Total bilirubin (n = 61)				
Decrease to normal (n, %)	26 (43)			
Normal at next visit	6 (10)			
Decreased, but still >reference value	29 (48)			

*All other combinations were prescribed in ≤3 patients each.
†Number of patients for which data were available.

Table 4. Follow-up

Duration of antibiotic therapy	≤3 d (n = 41)	4/5 d (n = 19)	>5 d (n = 20)	Total (n = 80)	*p* Value
Length of follow-up (d) (median, range)	71 (2-214)	143 (6-184)	181 (28-184)	121 (2 - 184)	0.062*
Endpoints (n, %)					
Recurrent cholangitis	11 (27)	4 (21)	4 (20)	19 (24)	0.80†
Surgical procedures	9 (22)	4 (21)	2 (10)	15 (19)	
Death	6 (15)	2 (11)	1 (5)	9 (11)	
New course of antibiotics	4 (10)	1 (5)	2 (10)	7 (9)	
Complications related to this episode	0	0	1 (5)	1 (1)	
Total	30 (73)	11 (58)	10 (50)	51 (64)	0.17†
Time until recurrent episode of cholangitis (d) (median, range)	70 (23-173)	35 (2-60)	40.5 (8-92)	52 (2-173)	0.15*

*Kruskal-Wallis test.
†Chi-square test.

days or less, 19 patients for 4 or 5 days, and 20 patients longer than 5 days. The 3 groups were well matched for demographic and presenting clinical features (temperature, white blood cell count, bilirubin level) and the interval between onset of cholangitis and biliary drainage (data not shown).

The combination of amoxicillin and gentamicin was the most frequently used antibiotic therapy in the patients treated for 3 days or less; piperacillin was the most frequent in the 2 other groups. All patients became afebrile. All patients for whom laboratory data were available (n = 61) had a reduction in plasma bilirubin during follow-up, which was taken to indicate relief of obstruction in all cases.

Follow-up

The follow-up period was shorter in the group of patients who received antibiotic treatment for 3 days or less compared with those receiving antibiotics for more than 5 days, but this difference was not statistically significant (Table 4). Endpoints were as follows: an episode of recurrent cholangitis (24%), surgical procedure (19%), death (11%), an episode requiring use of antibiotics (9%), and infectious complications possibly caused by the index episode of cholangitis (1%). Among patients who received antibiotic therapy for 3 days or less, 73% reached an endpoint before reaching the maximum period of follow-up of 6 months.

In the group that received antibiotic therapy for 4 or 5 days and that for which therapy was continued for more than 5 days, 58% and 50%, respectively, reached a study endpoint before 6 months. In none of the patients were the endpoints of death or a surgical procedure related to an episode of recurrent cholangitis.

The indications for prescription of a new course of antibiotics were as follows: antimicrobial prophylaxis (3), ERCP-induced bacteremia after stone removal (1), pneumonia (1), urinary tract infection in a patient with bladder carcinoma (1), and an unexplained episode of fever (1). This latter patient was hospitalized and underwent short-term treatment with amoxicillin and gentamicin. His temperature decreased to normal in 1 day without further intervention. There was no evidence of associated cholestasis.

Two complications possibly related to the episode of cholangitis under study were identified. Cholecystitis occurred 4 months after ERCP in a patient treated with amoxicillin and gentamicin for 3 days after a successful clearance of bile duct stones (case 1). Considering the time span and the presence of stones in the gallbladder, the cholecystitis was not regarded as related to the index episode of cholangitis. Liver abscess was diagnosed in another patient who had been treated with piperacillin for 11 days after successful establishment of biliary drainage. Liver abscess had been suspected at the time of ERCP, but treatment with antibiotics was erroneously stopped after 11 days (case 2).

Recurrent cholangitis

An episode of recurrent cholangitis (Table 4) developed in a total of 19 patients (24%). The percentage of patients with an episode of recurrent cholangitis was not statistically different among the 3 groups ($p = 0.80$, chi-square test), nor was the length of time between ERCP and the episode of recurrent cholangitis ($p = 0.15$, Kruskal-Wallis test).

DISCUSSION

This retrospective study evaluated whether the duration of antibiotic therapy was related to the occurrence of infectious complications and the frequency of recurrent cholangitis in patients presenting with acute cholangitis in whom adequate biliary drainage was established by ERCP. The index episode of cholangitis under study resulted in a secondary complication in only 1 of 80 patients. This patient already had a liver abscess at the time of the ERCP, but this was not recognized and therefore not appropriately treated, that is, the duration of treatment was insufficient. Recurrent cholangitis during follow-up appeared to be unrelated to the duration of antibiotic therapy after adequate biliary drainage. The median duration until a recurrent episode of cholangitis was longest in the group treated for 3 days or less, which also suggests that these patients were not more prone to this complication than patients treated for longer periods.

The characteristics of our study population were similar to those in other studies of patients with biliary obstruction and cholangitis. Almost 50% of blood cultures were positive, the most frequently recovered bacteria being *E coli*, *Klebsiella* species, and *Enterobacter* species, the usual pathogens associated with cholangitis.[1] The antibiotics prescribed, amoxicillin plus an aminoglycoside, or piperacillin (with or without tazobactam), are appropriate to this situation.[2]

The present study has some limitations. First, the data were derived retrospectively. A defined follow-up period during which patients were observed was therefore used. If data were missing with respect to antibiotic therapy or the condition of the patient during follow-up, the patient was excluded. Second, whether the patients who received antibiotic therapy for a longer duration differ from those who received therapy for a short period is uncertain. However, this is unlikely because the groups were comparable with regard to clinical features and risk factors for complications caused by cholangitis, such as the interval of time between onset of cholangitis and biliary drainage.[3,4] In addition, the number of days patients received antibiotics was usually based on the policy of the hospital where the patient was treated, rather than on the condition of the patient. Third, the median time of follow-up was shorter for patients treated for 3 days or less, which is mainly explained by a slightly higher percentage of patients in this group with recurrent cholangitis, death, and surgical procedures. However, with longer follow-up, it is unlikely that the chance of reaching the main endpoints of "complications caused by studied episode of cholangitis" or "recurrent cholangitis" would have been much different. The median duration of time to a recurrent episode of cholangitis was longer in the group treated for 3 days or less compared with the other groups, which, as stated earlier, suggests that these patients were not more prone to this complication than those in the other groups.

The findings of this study provide, for the first time, data on the relationship between duration of antibiotic therapy and complications during follow-up. At present, there is no standardized duration of treatment for cholangitis.[2] Antibiotic therapy is usually given for 7 to 10 days.[1] Antibiotics are prescribed for longer periods of time because of the fear of complications. However, the results of the present

study confirm that such complications are rare if biliary drainage has been established. In studies of complications of acute cholangitis after a successful endoscopic intervention, infectious complications are usually observed immediately after the procedure.[4,5] The number of complications that occur during long-term follow-up is usually small, with the exception of recurrent cholangitis.[6,7] However, when biliary decompression is not achieved, liver abscess is an inevitable result of the high pressure in the obstructed bile ducts.[8]

In conclusion, the mainstay of therapy for acute cholangitis is endoscopic sphincterotomy with stone extraction and/or stent insertion.[5,6,9-11] Short-duration antibiotic therapy (3 days) appears sufficient when the time interval between onset of cholangitis and biliary drainage is short, adequate drainage is achieved, and fever is abating. In special clinical situations, for example patients with positive blood cultures and prosthetic joints or heart valves, or an indwelling intravenous catheter, antibiotic therapy for longer periods might be considered. A prospective study will be needed to ultimately confirm the appropriateness of short-term antibiotic therapy. The present study provides a rationale for such a study and can be used for sample size calculation. Given the low frequency of infectious complications under these circumstances, the number of patients required for such a study has to be considerable.

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