

Antibiotic Prophylaxis Prior to Elective ERCP Does Not Alter Cholangitis Rates or Shorten Hospital Stay: Results of an Observational Prospective Study of 138 Consecutive ERCPS

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ABSTRACT

Objectives: The role of prophylactic antibiotherapy prior to elective endoscopic retrograde cholangiopancreatography (ERCP) is unclear. We aimed to determine whether patients receiving systemic antibiotics prior to ERCP had lower morbidity and mortality rates as well as shorter hospitalization compared to patients who did not receive antibiotic prophylaxis.

Materials and methods: We conducted a prospective study of all patients undergoing ERCP in our unit. Antibiotic use, postERCP cholangitis rates, 30-day mortality and hospital stay were studied. Also, bacteriological examination of bile aspirates from these patients was conducted and antibiotic susceptibility was determined for the isolated pathogens.

Outcomes: One hundred-thirty eight consecutive ERCPS conducted in our unit in a 9 month period were included. Cholangitis developed in 3 (4.6%) cases in the antibiotics groups and 3 (4%) cases in the control group ($p=0.8$). Hospital stay did not differ significantly between the two study groups ($p=0.58$). There was only one procedure-related death which was the result of postERCP pancreatitis in a patient with severe associated illnesses. Bile aspirates showed bacterial growth in 75% of the cases where bile was obtained, with *E. coli* being the most frequently isolated microorganism. No differences in bacteriological profiles were noted between the two study groups.

Conclusion: There seems to be no influence on patient-related outcome of antibiotic prophylaxis prior to elective ERCP.

Keywords: antibiotic prophylaxis, ERCP, acute cholangitis, hospital stay

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INTRODUCTION

The role of prophylactic antibiotherapy preceding endoscopic retrograde cholangiopancreatography (ERCP) is unclear. Initial randomized controlled trials of preprocedural antibiotics showed conflicting results regarding post-procedural cholangitis (1,2) and this uncertainty has carried over into subsequent meta-analyses. A Cochrane systematic review and meta-analysis (3) suggests that administration of antibiotics prior to the procedure reduces the risk of bacteremia and cholangitis, while other meta-analyses failed to show any benefit for antibiotherapy (4,5). This is also reflected by consensus guidelines where antibiotics are recommended only for those procedures where incomplete biliary drainage is anticipated, but the strength of the recommendation is weak (grade 3) (6).

Recent studies have shown that bacteriobilia, even in the absence of overt cholangitis, can be proven in a majority of patients undergoing ERCP (7-11). While the clinical impact of routine biliculture at ERCP is still unclear, some experts recommend that each unit assess its own pattern of infection for better targeted antibiotic therapy (10).

We aimed to compare procedure-related outcome in patients receiving systemic antibiotics to the outcome of patients who did not receive antibiotic prophylaxis prior to ERCP. We also analyzed bile aspirates from patients undergoing ERCP in order to test for bacterial growth and, subsequently, antibiotic-susceptibility patterns in our unit. □

MATERIALS AND METHODS

We conducted a prospective observational study at a tertiary referral centre for endoscopy (Colentina Hospital, Bucharest). The study was conducted in accordance with the principles of the Declaration of Helsinki and approval of the local Ethics Committee was obtained. Informed consent forms were obtained from all patients prior to the endoscopic procedure.

All attempted elective ERCPs in the Endoscopy Unit of the Gastroenterology Department were included. The practice in our unit is that antibiotic treatment before elective ERCP is administered at the discretion of the attending physician. Patients receive a regimen of Ceftri-

axone, Ciprofloxacin or Amoxicilin, chosen on an individual basis.

Outcome assessment: Our main end-points were the advent of postERCP cholangitis, procedure-related mortality (up to 30 days postERCP) and length of hospital stay in patients receiving antibiotics prior to ERCP compared to patients who did not receive prophylactic antibiotics. Cholangitis was defined according to the Tokyo Guidelines (12). Antibiotic prophylaxis was defined as administration of at least one dose of any systemic antibiotic in a 12-hour interval prior to ERCP.

Our secondary end point was to assess the pattern of bacterial growth and antibiotic sensitivity in the bile aspirate of patients undergoing ERCP.

Relevant clinical and laboratory data (patient gender, age, indication for ERCP, antibiotic treatment prior to the procedure, C – reactive protein values, leucocyte levels, bilirubinemia) as well as data regarding the length of hospital stay and the occurrence of procedure related complications (cholangitis) was acquired from the patients' charts. Thirty day mortality was assessed by examining patient charts or by telephone.

Bile sample collection and examination:

ERCP was performed using Olympus Exera II 145 TJF standard duodenoscopes. At our center cannulation is always first attempted using a triple-lumen sphincterotome with a 0.0035 inch guidewire. All endoscopists were instructed to adapt cannulation technique as needed, but bile was only aspirated for analysis if cannulation was successful using the guidewire technique, without prior contrast injection inside the biliary ducts. Precut technique was accepted, provided no contrast injection was undertaken. Two to four milliliters of bile were aspirated from the bile duct of all patients undergoing ERCP and transferred to a sterile transportation tube. Bile specimens were then transferred to the bacteriology laboratory where they were cultured according to the standard procedures. Briefly, bile samples were inoculated on McConkey and blood agar and they were incubated 18 hours at 37°C. Cultures obtained were identified using Gram stained smears and were sub-cultured. For staphylococci differentiation, Manitol Salt Agar (Chapman) medium was used and in addition, slide coagulase tests were used to identify coagulase positive staphylococci strains. For stre-

ptococci differentiation, blood agar with optochin-bacitracin disks with bile-esculin and 6.5% NaCl medium were used. Gram negative bacteria were differentiated with biochemical tests. Antibiotic susceptibility to the five main antibiotics used in the prophylaxis of biliary infections in our service (Ciprofloxacin, Amoxicillin, Ceftriaxone, Gentamicin, Imipenem) was identified using disk diffusion tests on Mueller Hinton agar according to current EUCAST guidelines (13).

Data recording and analysis: Data was recorded and analyzed using SPSS 16.0 (Illinois, USA). Results are reported as means and standard deviations for variables with a normal distribution, and median, minimum and maximum respectively for variables with a non-normal distribution. Univariate analysis was conducted using nonparametric tests for variables with nonnormal distribution (Mann Whitney U), student *t*-test for variables with a normal distribution and chi square for dichotomic variables, with a $p < 0.05$ considered statistically significant. □

OUTCOMES

One hundred seventy-eight consecutive ERCPs performed in our centre between December 2012 – September 2013 were included in this study. Forty patients (22.6%) fulfilled the Tokyo criteria for acute cholangitis and were excluded and 138 patients (50.6% male) were included in the final analysis (Figure 1). Patient characteristics are further described in Table 1.

	Antibiotics	No antibiotics	P
Gender (male/total)	37/63	31/75	0.08
Mean age, years (SD)	62 (16)	62 (16)	0.93
Benign disease	53	67	.95
Malignant obstruction	10	8	
Prior sphincterotomy (/total)	5/63	14/75	0.06
Mean CRP levels mg/L (range)	24 (1-155)	16.6 (0-119)	0.003
Mean bilirubin levels mg/dL (range)	7.1 (0.3-45)	3.1 (0.1-19.6)	0.001
Leucocytosis* (/total)	6/63	10/75	0.6

TABLE 1. Characteristics of patients receiving systemic antibiotics prior to ERCP compared to patients not receiving antibiotic prophylaxis. Antibiotic prophylaxis was used more often for patients with higher bilirubin and CRP levels.

* leucocytosis was assessed according to our laboratory cut-off values, $>10,000$ leucocytes / mm^3

Procedure and patient-related outcomes

Three patients in the antibiotic group (4.7%) and 3 patients in the control group developed postprocedural cholangitis (4%) ($p=1$, Chi Square). In all cases incomplete biliary drainage was documented as the direct cause of cholangitis onset. One patient with severe co-existing illness in the control group died 7 days after the procedure, but his death was the result of multiple system and organ failure brought on by post ERCP pancreatitis. Also, there was no significant difference in postERCP cholangitis rates in patients with preexisting sphincterotomy compared to those with a native papilla ($p=0.8$ Mann Whitney U).

Length of hospital stay did not differ significantly between the 2 groups, with patients on antibiotics having a mean stay of 6.1 days (range 2-15) as compared to a mean stay of 6.3 days (range 2-49) in the control group ($p=0.58$ Mann Whitney U).

Microbiology cultures

Bile was obtained from 111 procedures (80.4%), in the rest of the cases there was breach of cannulation protocol (i.e. injection into the ducts before bile aspiration) and no bacteriological study was available. Twenty-eight bile aspirates did not grow any microorganisms and were deemed sterile (25.2%). Overall, the most frequently isolated bacteria were *E. coli* (39 cases, 35.1%), *Enterococcus* sp (19 cases, 17.1%) and *Klebsiella pneumoniae* (10 cases, 9%), with a complete list of pathogens in the two study groups provided in Table 2. Seventy one percent of patients receiving antibiotic prophylaxis showed some bacterial growth compared with 78% of patients who did not receive prophylaxis ($p=0.56$ Chi Square).

Antibiotic susceptibility testing showed low resistance to imipenem, gentamicin and amoxicillin, but higher resistance rates for ceftriaxone and ciprofloxacin, especially in the antibiotic prophylaxis groups (Table 3). Bile aspirates from twenty-six patients (23.4%) showed bacteria which was resistant to at least 2 different antibiotics, with no significant difference between study groups ($p=0.11$ Chi Square). □

CONCLUSIONS

This is one of the largest prospective cohort studies examining both patient-related out-

come and bacteriological growth patterns in patients undergoing ERCP. Because unnecessary antibiotic use has been linked with serious side-effects it is important to understand whether antibiotic prophylaxis can influence patient-oriented outcomes such as morbidity (i.e. postERCP cholangitis), mortality and hospital-stay.

We have compared these outcomes in a prospective manner in patients undergoing elective ERCP in our service. There were no significant differences with regard to procedure-related cholangitis rates or hospital stay between patients who received systemic antibiotics prior to their procedure compared to those who did not. Since there were only 6 cases of cholangitis reported and only 1 fatality in the whole study group (0.7%) data regarding 30-day mortality is not statistically relevant; however there seems to be no excess mortality because of lack of antibiotic prophylaxis.

The results of our bacteriological studies show similar growth patterns to those already reported (8-10), with *E. coli*, *Klebsiella* and *Enterococci* being the most frequently encountered microorganisms. There was no significant difference in the rate of bacteribilia between the two study groups. Antibiotic susceptibility was also similar to available published data, showing good susceptibility to amoxicillin, imipenem and gentamicin, with lower rates for ciprofloxacin and ceftriaxone. There was however a significant difference in susceptibility rates to ceftriaxone and ciprofloxacin between the two study groups, but this was not reflected in patient-related outcomes.

In our study, patients in the antibiotic group had higher bilirubin levels (7.1 mg/dL vs. 3.1 mg/dL, $p=0.001$ Mann Whitney U), but postERCP cholangitis developed only in case of incomplete biliary drainage, independent of bilirubin levels or antibiotic use. This is in accordance with data from a large study of ERCP related complications which failed to show a correlation between bilirubin levels, leucocyte levels or antibiotic use and post ERCP complications, including cholangitis (14). There was also a statistically significant difference in mean CRP levels in the two groups, but since cholangitis had been ruled out in all these cases we do not consider it clinically relevant.

The main limitation of this study is the fact that it is not a randomized controlled study. Also, duration of antibiotic exposure prior to

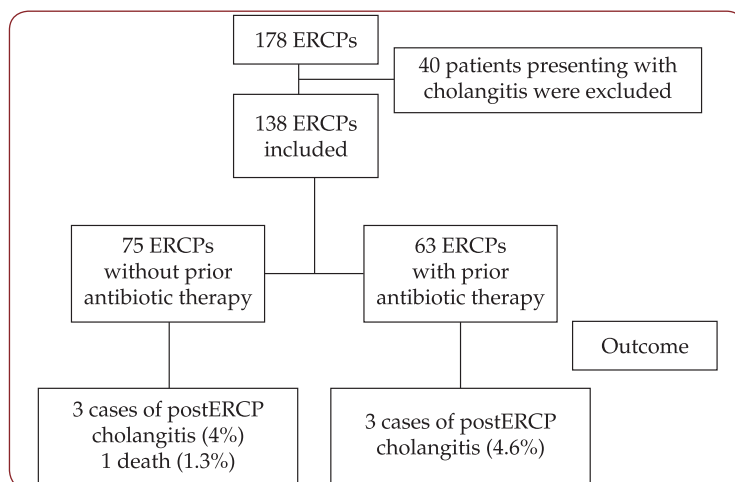


FIGURE 1. Flowchart of procedures included in the study and patient outcome according to the administration of systemic antibiotics prior to endoscopic retrograde cholangiopancreatography (ERCP).

Bacteria	Antibiotic group	Control group
<i>Escherichia coli</i>	25 (42%)	14 (27%)
<i>Enterococcus speciae</i>	8 (13%)	11 (21%)
<i>Klebsiella pneumoniae</i>	6 (10%)	4 (8%)
<i>Enterobacter speciae</i>	1 (2%)	3 (6%)
<i>Stafilococcus aureus</i>	0 (0%)	2 (4%)
<i>Proteus mirabilis</i>	2 (4%)	1 (2%)
<i>Streptococcus viridans</i>	0 (0%)	1 (2%)
<i>Pseudomonas aeruginosa</i>	3 (5%)	0 (0%)
Other	1 (2%)	1 (2%)
No growth	13 (22%)	15 (28%)

TABLE 2. Bacterial growth patterns in the bile aspirated from the two study groups.

Antibiotic	Susceptibility rates (%)		P
	Antibiotic prophylaxis	No antibiotic prophylaxis	
Amoxicillin	77.1%	82.6%	0.58
Ceftriaxone	55.6%	78.3%	0.03
Ciprofloxacin	58.3%	82.6%	0.025
Gentamicin	90.9%	90.7%	1
Imipenem	95.8%	100%	0.4

TABLE 3. Antibiotic susceptibility patterns of microorganism detected in the bile aspirates of the two study groups. Higher susceptibility rates to ceftriaxone and ciprofloxacin were determined for bile aspirates from patients without antibiotic prophylaxis.

ERCP as well as the type of antibiotic received were not homogenous and not included in the analysis. This was because the type and duration of antibiotic therapy prior to ERCP were likely to be influenced by non-medical factors such as referral from another center or delay of the elective procedure for various reasons. Another potential limitation of our study is the fact that we did not test for anaerobic bacteria. However, since anaerobic colonization of the bile ducts seems to be low (8,10), the addition-

al value of testing for anaerobic bacteria is limited. Also, we did not study antibiotic-related side effects, which might also influence the administration of prophylactic antibiotics prior to endoscopic procedures. However, given the large number of procedures included in this study, reflecting a wide variety of patients and situations, we believe the data we have obtained is robust and reflective of everyday practice in an endoscopy center.

In conclusion, antibiotic use prior to elective ERCP does not seem to improve patient-related outcomes such as morbidity, mortality or hospital stay or significantly alter the bacteriological profile of bile aspirates.

Conflict of interests: none declared.

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