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Original Scientific Paper

THE USE OF MICROBIOLOGICAL AND LABORATORY DATA IN THE CHOICE OF EMPIRICAL ANTIBIOTIC THERAPY IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY – THE ROLE OF LOCAL ANTIBIOGRAMS

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SUMMARY – Antibiotic therapy is indicated during acute cholecystitis. However, in the treatment of uncomplicated cholelithiasis, prophylactic use of antibiotics is controversial. Microbiological and laboratory data are the basis for the choice of antibiotic treatment. However, monitoring and updating local antibiograms is important because they ensure effective therapy in the given clinical environment. The study included 110 consecutive patients who underwent laparoscopic cholecystectomy, divided into the group of uncomplicated cholelithiasis (n=60) and the group of acute cholecystitis (n=50). Preoperative data included age, sex, body mass index, leukocytes, C-reactive protein, and ultrasound examination. Bile samples for bacteriological testing were obtained under aseptic conditions during the surgery. Cultures were evaluated for aerobic, anaerobic and fungal organisms using routine tests. After the surgery, gallbladder specimens were sent for histopathological examination. In the group of uncomplicated cholelithiasis, 6/60 positive samples were found, and in the group of acute cholecystitis, there were 25/50 positive microbiological findings. *Citrobacter* sp. and *Enterococcus faecalis* predominated in the group of uncomplicated cholelithiasis, and *Escherichia coli, Enterococcus faecalis, Proteus mirabilis* and *Citrobacter* sp. in the group of acute cholecystitis. Antibiotics were administered to 49/50 patients with acute cholecystitis and to 32/60 patients with uncomplicated cholelithiasis. Cefazolin was the most frequently used antibiotic and also the most resistant antibiotic. To conclude, the administration of antibiotics in elective patients is not justified. The results of this study indicate that third-generation cephalosporin or ciprofloxacin + metronidazole should be administered in mild and moderate acute cholecystitis, and fourth-generation cephalosporin + metronidazole in severe acute cholecystitis in this local setting. The appropriate use of antibiotic agents is crucial and should be integrated into good clinical practice and standards of care.

Key words: *Acute cholecystitis; Laparoscopic cholecystectomy; Bile; Antibiotic prophylaxis*

Introduction

Laparoscopic cholecystectomy is the gold standard in the treatment of symptomatic chole-cystolithiasis[1].

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During acute cholecystitis, antibiotic therapy is indicated. The recommended antibiotics are piperacillin/tazobactam or cephalosporin +/- metronidazole for moderate and severe acute cholecystitis[2]. A blood or bile culture is also recommended[3]. However, in the treatment of uncomplicated cholelithiasis, prophylactic use of antibiotics is controversial, although the latest studies state that the perioperative prophylactic administration of antibiotics should be recommended

in order to prevent postoperative infective complications[4].

In healthy individuals, bile is considered to be sterile[5], but gallstone disease might lead to bacterial colonization. Culture-based studies report bacteria in 9% to 54% of patients with gallstone disease without infection[5,6] , with the prevalence of gram-negative bacteria, *Escherichia* sp., *Klebsiella* sp. and *Enterobacter* sp., which account for 60.4% of the isolated bacteria[5,7].

Bactobilia is a risk factor for a poor outcome. Microbiological studies are the basis of selection of antibiotic treatment because inappropriate empirical antibiotic therapy is an independent factor related to mortality[8]. The monitoring and updating of local antibiograms is very important because they result in effective therapy in a given clinical environment[2]. Therefore, we undertook a study to determine the predominant bacterial flora in bile, with antibiogram determination, in uncomplicated cholelithiasis and acute cholecystitis.

Patients and Methods

This prospective, cohort study was performed at the Department of Surgery, Tuzla University Clinical Center. All patients gave their informed consent for participation in the study. The principles of the Declaration of Helsinki were followed during the study. The study included 110 consecutive patients who underwent laparoscopic cholecystectomy during a six-month period. Patients were divided into two groups, as follows: group of uncomplicated cholelithiasis (n=60) and group of acute cholecystitis (n=50).

Preoperative data included age, sex, body mass index, leukocytes, C-reactive protein, and ultrasound examination. Bile samples for bacteriological testing were obtained under aseptic conditions during the surgery. Cultures were carefully evaluated for aerobic, anaerobic and fungal organisms using routine tests. After the surgery, gallbladder specimens were sent for histopathological examination.

Statistical analysis

The Kolmogorov-Smirnov test was used to define normal and non-normal distributions of variables. The χ^2 analysis and Fisher exact test were used to compare two groups for qualitative data, as appropriate, and Student's t-test (for normal variables) or Mann-U test (for non-normal variables) for quantitative data. For multivariate analysis, the logistic regression technique was applied. A probability of 0.05 or less was accepted as statistically significant. SPSS version 23 (SPSS, Inc., Chicago, IL, USA) was used on all statistical analyses.

The predictive potential of each variable of interest for predicting a positive biopsy culture was evaluated by the Receiver Operating Characteristics (ROC) curve calculation. The cut-off value of each variable was determined using the Youden index formula. The area under the ROC curve was also calculated for each particular variable. The level of statistical significance was set at $p<0.05$.

Results

In the group of uncomplicated cholelithiasis, 6/60 positive samples were found, whereas in the group of acute cholecystitis there were 25/50 positive microbiological findings. In the group of acute cholecystitis, *Escherichia coli, Enterococcus faecalis*, *Proteus mirabilis* and *Citrobacter* sp. predominated, whereas in the uncomplicated cholelithiasis group, *Citrobacter* sp. and *Enterococcus faecalis* were the most common isolates (Fig. 1).

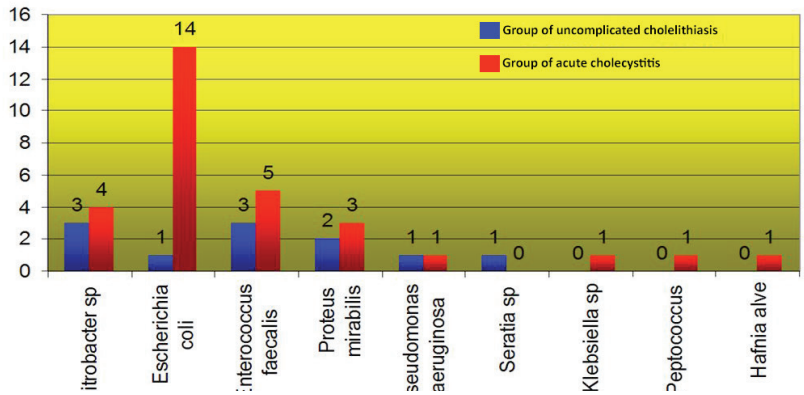

Fig. 1. Distribution of bacteria in the groups with uncomplicated cholelithiasis and acute cholecystitis.

Antibiotics were administered to 49/50 patients with acute cholecystitis and to 32/60 patients with uncomplicated cholelithiasis. However, the duration of antimicrobial therapy for acute cholecystitis was 7 days *versus* one day in the group with uncomplicated cholelithiasis. The antibiotic most frequently used in both groups was cefazolin, which was also the most resistant antibiotic (Fig. 2).

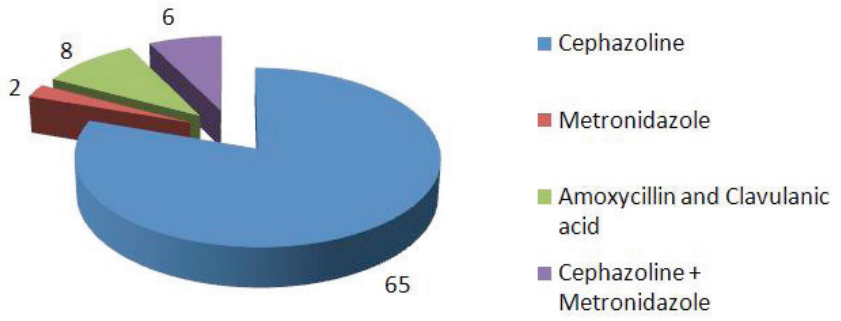

Fig. 2. Distribution of most resistant antibiotics in positive bile culture.

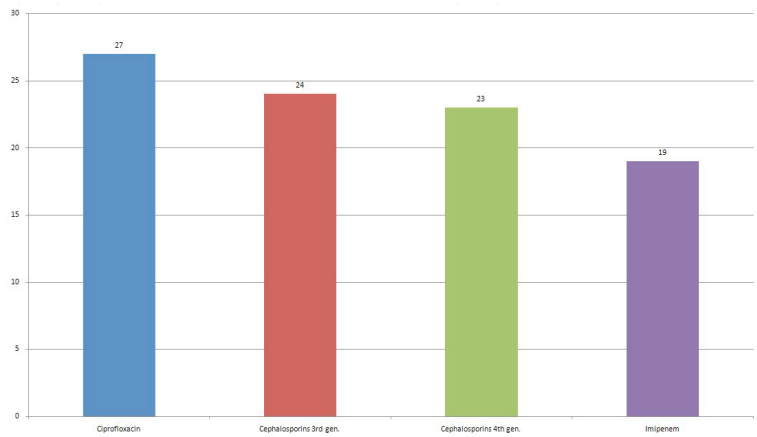

Fig. 3. Distribution of the most sensitive antibiotics in patients with positive bile culture.

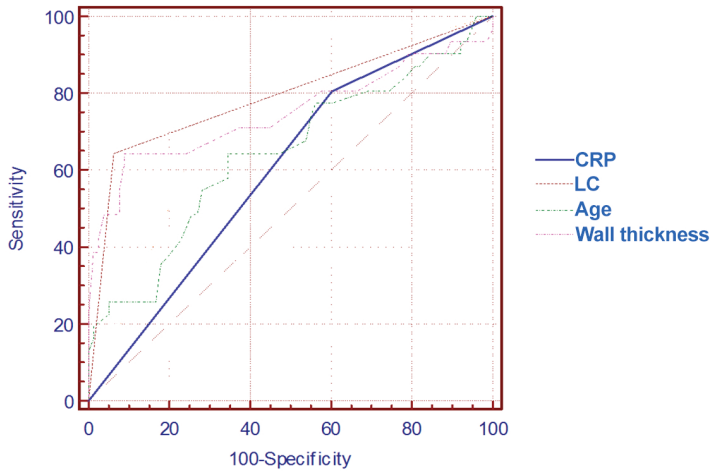

Fig. 4. ROC curve for individual predictors of positive bile culture.

ROC = Receiver Operating Characteristics; CRP = C-reactive protein; LC = laparoscopic cholecystectomy

Distribution of antibiotics revealed that third- and fourth-generation ciprofloxacin and cephalosporin were the most sensitive antibiotics in patients with positive bile culture (Fig. 3).

According to the ROC curves and areas below the ROC curve, it may be concluded that leukocyte values and thickness of the gallbladder wall had the greatest predictive power for a positive culture (Fig. 4, Table 1).

Table 1. Results of ROC curve analysis of individual predictors of positive bile culture

Variable	Correlation factor	p
Age	0.2349	0.014
Wall thickness	0.4723	0.0001
Increased leukocyte count	0.6235	0.0001
Increased C-reactive protein	0.1942	0.043

ROC = Receiver Operating Characteristics

Discussion

Monitoring and updating local antibiograms are critical to provide effective therapy in the clinical setting. Moreover, bile should be sent for culture in all cases of acute cholecystitis except for those with mild symptoms[2]. Bactobilia is one of the most important causes of acute cholecystitis, and the use of targeted antibiotic therapy is crucial[9]. In this study, the gram-negative bacteria *Escherichia coli, Proteus mirabilis* and *Citrobacter* sp., and *Enterococcus faecalis* as a gram-positive bacterium predominated in the group of acute cholecystitis. In previous studies, *Escherichia coli, Enterococcus* and *Klebsiella* were predominant pathogens in positive cultures[6,7]. Gram-negative bacteria are typically found in the intestinal flora and probably colonize the gallbladder ascending from the duodenum[6].

In the group of uncomplicated cholelithiasis, the culture was positive in 10% of cases. In other studies, a positive bile culture is reported in up to 18% of cases of elective cholecystectomy[7]. Gram-negative *Citrobacter* sp. and gram-positive *Enterococcus faecalis* were predominant. In this group, antibiotics were administered in 32/60 cases.

The administration of antibiotics in elective cholecystectomy is contradictory. It has been shown that the use of prophylactic antibiotics is effective in reducing the incidence of superficial but not deep surgical site infections in a low-risk patient[10]. However, the majority of randomized studies and a meta-analysis did not show any significant difference in the rate of postoperative complications between prophylactic groups and non-prophylactic groups[4,6]. The large-scale administration of antibiotics in the elective group in our study was not justified, as only 10% of bile samples were positive.

However, considering the rate of antibiotic resistance in the group of acute cholecystitis and the most frequently administered antibiotic, we see that the most frequently administered antibiotic was cefazolin, which showed the highest rate of resistance. Other studies report that amoxicillin/clavulanate, cefuroxime and ampicillin[9] have the highest resistance rates. That is why local antibiogram monitoring is very important.

Yet, if we look at the distribution of the most sensitive antibiotics in patients with positive bile cultures, we can see that these were third- and fourth-generation cephalosporin and ciprofloxacin, which were not administered. However, care should be taken because increase in the administration of third-generation cephalosporin is associated with a high rate of resistance to *Escherichia coli* in neighboring countries[11].

Most guidelines do not include specific coverage of *Enterococcus*, except for Tokyo Guidelines, which recommend vancomycin in severe cholecystitis[2,12].

In earlier studies, the predictive factors of bactobilia were advanced age and high inflammatory markers, such as C-reactive protein[13,14]. It is interesting that in this study, advanced age was not a factor, but wall thickness and a raised leukocyte count were.

The results of this study should be interpreted in the light of some of its limitations. First, this was a single-center study, which only covered a six-month period, with a small number of patients and a lack of information on the type and number of gall stones. Second, the data available did not permit us to classify patients according to the Tokyo severity grading or acute cholecystitis classification, making this study population less comparable to other studies. Third, we considered the ROC curve for all patients with bile culture, but we did not divide them into elective and acute ones.

To conclude, the administration of antibiotic in elective patients is not justified. The results of this study indicate that third-generation cephalosporin or ciprofloxacin + metronidazole should be administered in

mild and moderate acute cholecystitis, and fourth-generation cephalosporin + metronidazole for severe acute cholecystitis in this local setting. The appropriate use of antibiotic agents is crucial and should be integrated into good clinical practice and standards of care[15].

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Sažetak

UPOTREBA MIKROBIOLOŠKIH I LABORATORIJSKIH NALAZA U IZBORU EMPIRIJSKE ANTIBIOTSKE TERAPIJE U BOLESNIKA PODVRGNUTIH LAPAROSKOPSKOJ KOLECISTEKTOMIJI – ULOGA LOKALNIH ANTIBIOGRAMA

F. Pašić i *S. Delibegović*

Antibiotska terapija je indicirana u liječenju akutnog kolecistitisa. Međutim, u liječenju nekompliciranе kolelitijaze profilaktična upotreba antibiotika je proturječna. Mikrobiološki i laboratorijski podaci su osnova za izbor antibiotske terapije. Stoga su nadzor i lokalni antibiogrami vrlo važni, jer daju djelotvornu terapiju u datom kliničkom okruženju. U istraživanje je bilo uključeno 110 bolesnika koji su podvrgnuti laparoskopskoj kolecistektomiji. Bolesnici su podijeljeni u dvije skupine: skupina s nekompliciranom kolelitijazom (n=60) i skupina s akutnim kolecistitisom (n=50). Prijeoperacijski podaci su uključivali dob, spol, indeks tjelesne mase, leukocite, C-reaktivni protein te ultrasonografski pregled. Uzorci žuči za bakteriološka testiranja uzeti su pod aseptičkim uvjetima tijekom kirurškog zahvata te evaluirani na aerobnu i anaerobnu floru i fungalne organizme primjenom rutinskih testova. Nakon kirurškog zahvata uzorci žučnog mjehura poslani su na patohistološku analizu. U skupini s nekompliciranom kolelitijazom pronađeno je 6/60 pozitivnih nalaza, a u skupini s akutnim kolecistitisom 25/50 pozitivnih mikrobioloških nalaza. U skupini s nekompliciranom kolelitijazom prevladavali su *Citrobacter* sp. i *Enterococcus faecalis*, a u skupini s akutnim kolecistitisom *Escherichia coli, Enterococus faecalis, Proteus mirabilis, Citrobacter* sp. U skupini s nekompliciranom kolelitijazom antibiotici su davani u 32/60 slučajeva, a u skupini s akutnim kolecitistisom u 49/50 slučajeva. Najčešće primijenjeni antibiotik bio je cefazolin, koji je bio također i najrezistentniji antibiotik. Može se zaključiti da davanje antibiotika elektivnim bolesnicima nije opravdano. Rezultati ove studije upućuju na to da u ovom kliničkom okruženju cefalosporin treće generacije ili ciprofloksacin + metronidazol treba davati kod blagog i umjerenog akutnog kolecistitisa, a u teškim slučajevima cefalosporin četvrte generacije + metronidazol. Primjerena upotreba antibiotika je presudna i treba biti integralni dio dobre kliničke prakse i standardne skrbi.

Ključne riječi: *Akutni kolecistitis; Laparoskopska kolecistektomija; Žuč; Antibiotska profilaksa*