

## RESEARCH ARTICLES

# CHARACTERISTICS OF BILIARY BACTERIAL COLONIZATION AND BACTEREMIA FOLLOWING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

## ENDOSKOPIK RETROGRAD KOLANJİOPANKREATOGRAFİYİ TAKİP EDEN BİLİYER BAKTERİYEL KOLONİZASYON VE BAKTERİYEMİNİN ÖZELLİKLERİ

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### ABSTRACT

**Purpose:** Biliary infection and septicemia are probable fatal complications of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy that may compromise their benefits. The aim of this study was to investigate which patients are more susceptible to the infectious complications following ERCP in a specific era, and to identify the type of pathogens involved and the appropriate antibiotics for these microorganisms. **Methods:** Bile (during ERCP) and blood samples (before and right after ERCP) were obtained in 37 patients (21 females, 16 males, mean age 54) and cultured for aerobic and anaerobic bacteria. The pathogens identified, the antibiograms obtained, and the relationship of the type of endoscopic procedure and the final diagnosis with the type of infectious complication were evaluated. **Results:** Biliary bacterial colonization was observed in 28 (76%) patients. The majority of the identified microorganisms were Gram-negative bacilli. Biliary bacterial colonization were seen more frequently in therapeutic ERCP patients (n: 24) than in diagnostic ERCP patients (n: 13) (p: 0.05). Bacteremia was observed in 7 cases, with no significant difference between diagnostic and therapeutic ERCP patients. Biliary bacterial colonization was more frequent in patients with abnormal ERCP findings than in those with normal ERCP (p<0.05). Bacteremia was also significantly more frequent in patients with biliary obstruction (p<0.05). **Conclusion:** Infectious complications are more likely to occur in patients with biliary obstruction and in those who undergo therapeutic ERCP procedures. The vast majority of the pathogens (most of them were Gram-negative bacilli) identified are susceptible to ciprofloxacin, ofloxacin and imipenem. We think that appropriate use of prophylactic antibiotics in ERCP can reduce the rate of infectious complications, especially in patients with a high risk.

**Key Words:** Biliary Infection, Bacteremia, ERCP.

### ÖZET

**Amaç:** Biliyer enfeksiyonlar ve sepsisemi, ERCP ve sfinkterotomünün olası komplikasyonlarından olup bu işlemlerin faydalarını riske atarlar. Bu çalışmanın amacı, belirli bir dönemde, ERCP sonrası enfeksiyöz komplikasyonlara hangi tip hastaların daha yatkın olduğunu, rol oynayan patojen etkenleri ve bunlar için en uygun antibiyotikleri araştırmaktır. **Yöntem:** 37 hastanın (21 kadın, 16 erkek, yaş ortalaması 54) kan (ERCP'den önce ve hemen sonra) ve safra örnekleri (ERCP sırasında) alınıp aerobik ve anaerobik bakteriler için kültürlerle ekildi. Belirlenen patojenler, elde edilen antibiogramlar, endoskopik işlem ve son tanı ile enfeksiyöz komplikasyonun ilişkisi gözden geçirildi. **Bulgular:** 28 (%76) hastada biliyer enfeksiyon gözlemlendi. Belirlenen mikroorganizmaların çoğunluğu Gram negatif basillerdi. Biliyer enfeksiyonlar, terapötik ERCP hastalarında (n: 24), diagnostik ERCP hastalarına (n: 13) oranla daha sık görüldü (p: 0.05). Bakteriemi de biliyer obstrüksiyonlu hastalarda anlamlı olarak daha sıkı (p: 0.05). **Sonuç:** Enfeksiyöz komplikasyonlar en sık olarak biliyer obstrüksiyonlu ve terapötik ERCP uygulanan hastalarda oluşmaktadır. Belirlenen patojenlerin büyük kısmı (çoğunluğu Gram negatif idi) ciprofloksasin, ofloksasin ve imipeneme hassastır. ERCP'de profilaktik antibiyotiklerin, özellikle yüksek riskli hastalarda uygun kullanımının, enfeksiyöz komplikasyonların oranını düşürebileceğine inanıyoruz.

**Anahtar Kelimeler:** Biliyer Enfeksiyon, Bakteriemi, ERCP.

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is the most complex endoscopic procedure for the endoscopy unit, with special equipment and trained personnel required. It has evolved from a purely diagnostic tool to a sophisticated treatment procedure since its introduction to the medical field. The indications for ERCP have become fewer in recent years due to the widespread use of noninvasive imaging techniques, but endoscopic biliary sphincterotomy (ES) has become a common and minimally invasive procedure in the management of biliary and pancreatic disorders (1-3). However, both ERCP and ES have severe complications that compromise their benefits (4-6). The complications of ERCP/ES are well known and large prospective and retrospective series have defined the incidence of complications. The patient populations are heterogeneous and definitions of complications are variable in these series. Depending primarily on the definitions used, the incidence of complications varies widely (2,4,7,8). ERCP-induced pancreatitis, hemorrhage, cholangitis and perforation are the major complications of ERCP/ES.

Cholangitis after ERCP is an infrequent but important complication and a cause of morbidity (6,8). It probably results primarily from failure to achieve drainage in patients with total or partial obstruction of the biliary tree or the pancreatic duct (6,8). Acute cholecystitis is another septic event known to occur following ERCP (5,6). These complications may result in serious and fatal complications, such as abscesses and septicemia (6,8-11).

The expertise of endoscopists in therapeutic procedures is reported to be the main determinant in the prevention of these severe infectious complications, combined with antibiotic prophylaxis for biliary obstruction (6). Proper disinfection of the endoscopes and catheters used during the procedure is also important in preventing contamination (6,10,12). Prophylactic antibiotic use is still controversial (5,6,8), because the incidence of bacteremia and the spectrum of active pathogens specified in different studies vary widely (9-11).

The aim of this study was to identify the types of pathogens involved in infectious biliary

complications of ERCP, and to specify the frequency of biliary bacterial colonizations and bacteremia following ERCP in a specific era. The relationship of the type of endoscopic procedure and the final diagnosis with the type of infectious complication is also evaluated.

## PATIENTS AND METHODS

*Patients:* Thirty-seven consecutive patients (21 females and 16 males) were enrolled in the study, regardless of the indication for ERCP. Patients who had undergone ERCP previously or who had been on antibiotics in the previous 10 days for any reason were excluded.

*Procedure:* Specialized gastroenterologists experienced in ERCP performed the procedures. Following appropriate premedication, using an Olympus TCF-20 duodenoscope the ampulla of Vater was exposed and 40 mg of hyosine - N - butyl bromide was administered intravenously, thereafter. During cannulation of the common bile duct, a small amount of contrast material was gradually infused to visualize the biliary tract with simultaneous radioscopic scanning. When the catheter was proved to be inside the common bile duct, injection of the contrast material was terminated. Bile was gradually aspirated through the catheter. The first 2-3 ml was discarded and 5 ml of the subsequent sample was injected into aerobic and anaerobic culture bottles and immediately sent to the microbiology laboratory. The procedure was completed as necessary according to the indication of ERCP.

Before and immediately after the ERCP, 20 ml of blood was drawn for serum amylase and lipase levels and for blood cultures. Blood samples for complete blood count, sedimentation and routine biochemical analysis were drawn before the procedure only.

*Cultures:* Bact/Alert culture bottles, used for the blood and bile cultures, were placed in an automatic Bact/Alert (Organon Tecnika) blood culture system. When growth occurs an automatic positive signal is received. In these situations the material taken from these bottles was directly dyed with Gram stain. Cultivation was also performed on blood agar, eosin methylene blue and chocolate agar. Aerobic and anaerobic incubation was performed according to the bottle in which growth occurred, and thus identification of the bottles in which growth occurred was possible. The culture in which no

growth had occurred within one week was considered negative.

Statistical analysis: A Yates corrected chi-square test and when needed Fisher's Exact test were used for the statistical evaluation of the results. *p* values <0.05 was considered significant.

## RESULTS

Mean age of the patients was 54 (20-83). Thirteen patients underwent diagnostic ERCP, while in 24 patients the procedure was therapeutic. Endoscopic sphincterotomy was performed in 21 patients. The other therapeutic procedures were stone extraction in 6 patients, nasobiliary drainage in 5, pigtail stent placement in 2 and balloon dilatation in 1 (Table 1).

Biliary bacterial colonization was observed in 28 (76%) of the 37 patients in the study group. The number of microorganisms cultured was 1 in 18 patients (64%), 2 in 7 patients (25%) and 3 in 3 (11%) patients. *E. coli* and *Enterococcus* species were the most frequently observed agents (Table 2).

The total number of identified

Table-1: Age (year) characteristics of the patients and procedures

|                           |            |
|---------------------------|------------|
| Median age                | 54 (20-83) |
| Sex (F:M)                 | 21/16      |
| Diagnostic ERCP           | 13         |
| Therapeutic ERCP          | 24         |
| Endoscopic sphincterotomy | 21         |
| Stone extraction          | 6          |
| Nasobiliary drainage      | 5          |
| Pigtail stent placement   | 2          |
| Balloon dilatation        | 1          |

microorganisms was 41. Of these agents, 33 (80%) were Gram-negative bacilli and 8 (20%) were Gram-negative cocci (Table 2).

Biliary bacterial colonization was seen in 22 (92%) patients who underwent therapeutic ERCP and in 6 (46%) patients who underwent diagnostic ERCP. The frequency of biliary bacterial colonization in patients who underwent therapeutic ERCP was significantly higher than in those who underwent diagnostic ERCP (*p*<0.05) (Table 3).

Bacteremia was observed in 7 (19%) cases. *S. aureus* and coagulase-negative staphylococci were the most frequently identified bacteria in blood cultures. Of the 9 organisms detected, 8 (89%) were Gram-positive cocci and 1 (11%) was a Gram-negative bacillus. Multiple organisms were detected in 2 patients (29%) (Table 2). There was no statistically significant difference between the number of patients with bacteremia after diagnostic and therapeutic procedures (Table 3). Bacterial growth was observed from days 4 to 7 in bile cultures and from days 2 to 7 in blood cultures.

ERCP findings were normal in 8 (22%) patients. Five of them had a past history of cholecystectomy and the major complaint in all was right upper quadrant pain. Biliary bacterial colonization was found in 5 (25%) of these patients, while the number of patients with biliary bacterial colonization in the 29 patients with abnormal findings was 26 (89.6%). When these results were compared, it was observed that biliary bacterial colonization was more frequent

Table-2: Microorganisms identified in patients with positive bile and blood cultures \*

| MICROORGANISM                        | BILE CULTURE<br>(Positive in 28 patients) | BLOOD CULTURE<br>(Positive in 7 patients) |           |         |
|--------------------------------------|-------------------------------------------|-------------------------------------------|-----------|---------|
|                                      |                                           | Pre-ERCP                                  | Post-ERCP | Total   |
| <b><u>Gram-Negative Bacillus</u></b> |                                           |                                           |           |         |
| Escherichia coli                     | 14 (50%)                                  | -                                         | -         | -       |
| Klebsiella pneumoniae                | 6 (21%)                                   | -                                         | 1 (14%)   | 1 (14%) |
| Pseudomonas aeruginosa               | 3 (11%)                                   | -                                         | -         | -       |
| Proteus mirabilis                    | 2 (7%)                                    | -                                         | -         | -       |
| Enterobacter cloacae                 | 2 (7%)                                    | -                                         | -         | -       |
| Citrobacter diversus                 | 2 (7%)                                    | -                                         | -         | -       |
| Citrobacter freundii                 | 2 (7%)                                    | -                                         | -         | -       |
| Providencia stuartii                 | 1 (4%)                                    | -                                         | -         | -       |
| Providencia rettgeri                 | 1 (4%)                                    | -                                         | -         | -       |
| <b><u>Gram-Positive Coccus</u></b>   |                                           |                                           |           |         |
| Enterococcus species                 | 7 (25%)                                   | -                                         | 1 (14%)   | 1 (14%) |
| Staphylococcus aureus                | 1 (4%)                                    | 1 (4%)                                    | 2 (29%)   | 3 (43%) |
| Coagulase negative staphylococcus    | -                                         | 1 (4%)                                    | 2 (29%)   | 3 (43%) |
| Streptococcus pneumoniae             | -                                         | -                                         | 1 (14%)   | 1 (14%) |

\*Multiple organisms found in bile cultures of 10 patients (36%) and in blood cultures of 2 patients (29%).

Table-3: Relationship between the ERCP procedure and positive bile and blood cultures.

|                                      | Diagnostic ERCP<br>(n=13) | Therapeutic ERCP<br>(n=24) |
|--------------------------------------|---------------------------|----------------------------|
| patients with positive bile culture  | 6 (46%)                   | 22 (92%)                   |
| patients with positive blood culture | 2 (15%)                   | 5 (21%)                    |
| Pre-ERCP                             | -                         | 2 (8%)                     |
| Post- ERCP                           | 2 (15%)                   | 3 (13%)                    |

Table-4: ERCP-based diagnosis of the patients with positive bile and blood cultures.

| ERCP diagnosis        | Patients<br>n (%) | Bile<br>culture<br>n (%) | Blood culture     |                    | Total<br>n (%) |
|-----------------------|-------------------|--------------------------|-------------------|--------------------|----------------|
|                       |                   |                          | Pre-ERCP<br>n (%) | Post-ERCP<br>n (%) |                |
| Normal                | 8 (22%)           | 2 (25%)                  | -                 | 1 (13%)            | 1 (13%)        |
| Cholecystolithiasis   | 11 (30%)          | 9 (82%)                  | -                 | 2 (18%)            | 2 (18%)        |
| Choledocholithiasis   | 8 (22 %)          | 8 (100%)                 | 2 (25%)           | 1 (13%)            | 3 (38%)        |
| Malignancy            | 2 (5%)            | 2 (100%)                 | -                 | 1 (50%)            | 1 (50%)        |
| Bile duct stricture   | 1 (3%)            | 1 (100%)                 | -                 | -                  | -              |
| Chronic pancreatitis  | 2 (5%)            | 2 (100%)                 | -                 | -                  | -              |
| Pancreatic pseudocyst | 1 (3%)            | 1 (100%)                 | -                 | -                  | -              |
| Papillary fibrosis    | 2 (5%)            | 1 (50%)                  | -                 | -                  | -              |
| Recurrent cholangitis | 2 (5%)            | 2 (100%)                 | -                 | -                  | -              |
| TOTAL                 | 37 (100%)         | 28 (76%)                 | 2 (5%)            | 5 (14%)            | 7 (19%)        |

in the latter group ( $p<0.05$ ) (Table 4).

There were 13 patients with biliary obstruction in the study group and bacteremia was observed in 5 (39%) of these 13 patients and in 2 (8%) of the remaining 24 patients. When these results were compared the difference was statistically significant ( $p<0.05$ ), indicating that bacteremia is more frequent in patients with biliary obstruction. In 6 (86%) patients with bacteremia, bile cultures were positive.

When the antibiograms for Gram-negative bacilli in bile cultures were evaluated, the most efficient antibiotics were determined to be ciprofloxacin, ofloxacin, imipenem, amikacin, ceftazidime and sulbactam-cefoperazone according to their intensity, in descending order of importance. Microorganisms in hemoculture were susceptible to ciprofloxacin, ofloxacin, imipenem, amikacin, ceftazidime, sulbactam-cefoperazone and vancomycin.

Clinical complications developed in 4 (11%) patients (cholangitis in 2 patients, cholecystitis and pancreatitis in 1 patient and perforation, cholangitis-cholecystitis and sepsis in 1 patient). These patients were among the 6 patients in whom adequate biliary drainage could not be provided after ERCP. Statistical analysis revealed that the possibility of complications occurring is significantly higher in patients without adequate biliary drainage after ERCP ( $p<0.001$ ). The serum pancreatic amylase and

lipase levels increased threefold or more in 10 patients (27%).

## DISCUSSION

Large prospective studies have been published in the medical literature about the frequency and type of complications following ERCP/ES (4-7,12). Infectious complications of ERCP play an important role in the total morbidity and mortality rates of the procedure, because cholangitis is a major cause of sepsis in patients who undergo ERCP/ES (1-3,9-12). Although microorganisms can be found in bile cultures after ERCP/ES without causing clinically manifest complications, the high mortality rates in patients with septicemia due to cholangitis as a complication of ERCP/ES indicate the importance of infectious complications (13-15). The use of prophylactic antibiotics is still controversial, but it is advised in patients with biliary obstruction and in whom sufficient drainage cannot be provided after ERCP/ES (5,7,12,17).

Biliary bacterial colonization occurs most frequently when an obstructed duct system has been contaminated with contrast medium injected during ERCP but the obstruction could not be released (12). This complication, which may cause fatal sepsis, may be caused by contaminated endoscopes and equipment. Despite careful cleaning and disinfection of the

endoscopes and other equipment, nosocomial contamination still remains an important problem.

In our study bile cultures were positive in 28 (76%) patients and multiple microorganisms were detected in 10 (36%) patients, with *E. coli* and *Enterococcus* species being the most frequently observed agents. In addition, all of the microorganisms identified in this study were Gram-negative bacilli or cocci. In previous studies, similar results such as the frequency of multi-agent infections and the types of the most frequently identified microorganisms were reported (10,13,18-20), indicating that in the last decade and a half, the same microorganisms have been the main cause of infectious complications of ERCP/ES and there has been no major change in this area.

Another finding in our study is that the number of patients with biliary bacterial colonization is higher in the therapeutic ERCP group than in the diagnostic ERCP group (22 patients and 6 patients, respectively), with a statistically significant difference. When this finding is combined with the finding that clinical complications develop mostly in patients in whom adequate biliary drainage cannot be provided after ERCP, it can be concluded that the risk of infectious complications is higher in patients with biliary obstruction who have undergone therapeutic ERCP. This finding supports the results of Mollison et al. (16). They reported that there was a strong association between therapeutic procedures and sepsis and therapeutic procedures and bacteremia (16).

Bacteremia was observed in 7 patients (19%) in our study, and 8 (89%) of the 9 microorganisms detected were Gram-positive cocci (*S. aureus* and coagulase-negative staphylococci were the most frequent). Multiple organisms were detected in 2 patients (29%). Quite different results have been reported concerning the frequency of bacteremia after ERCP (10,14,16,21). Kullman et al. studied the occurrence of bacteremia in association with diagnostic or therapeutic ERCP. They observed bacteremia in 19% of their procedures. Complication rates associated with bacteremia were 15% after diagnostic procedures and 27% after therapeutic procedures, with a statistically significant difference (14). Although the rates of

bacteremia were similar in their study, there was a difference between the rates of bacteremia after therapeutic and diagnostic procedures in our study. This difference may be because of the smaller number of patients in our study compared to that in the study by Kullman et al.

Deviere et al. reported a rate of bacteremia of 0.16% after diagnostic ERCP and 3.4% after therapeutic ERCP (13). It is possible that methodological differences caused this difference. Considering that up to 80% of septic complications develop within several hours of the procedure (10), even this may explain the extensive variations in the bacteremia rates because the time when the samples are collected differ in different studies (in some samples were collected during ERCP and in others about 15 minutes after ERCP or at the time when septic findings were seen). The use of prophylactic antibiotics also causes less frequent infectious complications (12,22).

In the present study, the Gram-negative bacilli isolated from bile cultures were more susceptible to ciprofloxacin, ofloxacin, imipenem, amikacin, ceftazidime and sulbactam-cefoperazone. The efficacy of cephalosporins and amikacin on the Gram-positive cocci found in bile was less than 50%. Pathogens cultured in blood were susceptible to ciprofloxacin, ofloxacin, imipenem, amikacin, ceftazidime, sulbactam-cefoperazone and vancomycin, with an efficacy rate of 90% or more. The type of microorganisms identified in our study were similar to the findings in previous studies (11,16) (Gram-negative enteric bacteria in biliary bacterial colonization and oro-pharyngeal bacteria in bacteremia); however, antibiotic susceptibilities varied. Although there have been no studies published evaluating prophylaxis in ERCP, antibiotic prophylaxis was used in these studies and may be the cause of the antibiotic susceptibility differences.

In our study, the low number of patients with sepsis in spite of the high biliary bacterial colonization and bacteremia rate may be attributable to the fact that drainage was achieved in a very short time in most of the patients and to the relatively small number of patients in the study group. Although the clinical incidence of sepsis development after ERCP was quite low in previous studies (0.5-2%), it has a fatal prognosis

in 10-22% of cases (9,10,16,18). This is an important indication of the significance of infectious complications. The sole observation of bacteria in bile and blood cultures does not seem to have any clinical importance. Therefore, the existence of clinical findings (fever, hypotension, shock) should be considered of greatest importance (9,10,13,15).

ERCP still has its place as a diagnostic and effective therapeutic modality, even in the era of MRCP. The infectious complications of the procedure, however, are potentially fatal. Our results indicate that infectious complications are more likely to occur in patients with pancreatobiliary pathologies causing biliary obstruction, which need therapeutic ERCP procedures. Patients are especially prone to biliary infection or bacteremia if the obstructed biliary duct cannot be released during ERCP. Therefore, due precautions must be taken to provide biliary drainage in cases of biliary obstruction. Our results also support the finding that the most frequently encountered microorganisms in biliary infections after ERCP are of enteric origin, while those found in bacteremia originate from oropharyngeal flora. The vast majority of the agents causing biliary infection or bacteremia are susceptible to ciprofloxacin, ofloxacin and imipenem. We think that appropriate use of prophylactic antibiotics can reduce the risk of infectious complications, especially in patients with a high risk of infectious complications.

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