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Randomized trial of prophylactic antibiotics for endoscopic retrograde cholangiopancreatography in patients with biliary obstruction

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Competing interests

The antibiotic used in this trial (Pacetin®) was provided by JW Pharmaceutical, Seoul, Korea. However, this trial was designed and conducted independently of JW Pharmaceutical, and the authors declare no conflicts of interest.

Abstract

Background

The incidence of post ERCP infections is reported to be up to 18% in patients with biliary obstruction. Antibiotic prophylaxis may reduce the risk of infectious complications after ERCP; however, the clinical value of prophylactic antibiotics in ERCP remains controversial.

Methods

We conducted a double-blind, placebo-controlled, randomized trial to investigate whether the use of prophylactic antibiotics would reduce infectious complications after ERCP in patients with biliary obstruction. We randomly assigned patients in a 1:1 ratio to receive either a single dose of 1 g intravenous cefoxitin or normal saline as a placebo 30 min before undergoing ERCP. The primary outcome was the incidence of infectious complications after ERCP.

Results

We enrolled 378 patients, and 189 patients were assigned to each group. The risk of infectious complications after ERCP was 2.8% (5 of 176 patients) in the antibiotic-prophylaxis group and 9.8% (17 of 173 patients) in the placebo group (risk ratio, 0.29; 95% confidence interval [CI], 0.11 to 0.74, *P*=0.0073). The incidence rates of bacteremia were 2.3% (4 of 176 patients) and 6.4% (11 of 173 patients), respectively (risk ratio, 0.36; 95% CI, 0.12 to 1.04; *P*=0.0599). The incidence rate of cholangitis was 1.7% (3 of 176 patients) in the antibiotic-prophylaxis group and 6.4% (11 of 173 patients) in the placebo group (risk ratio, 0.27; 95% CI, 0.08 to 0.87; *P*=0.0267).

Conclusions

Antibiotic prophylaxis before ERCP in patients with biliary obstruction resulted in a significantly lower risk of infectious complications, especially cholangitis, than placebo (ClinicalTrials.gov trial number NCT02958059).

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for the diagnosis and treatment of patients with biliary obstruction.(1) Since several procedures, including cannulation of the ampulla of Vater, endoscopic sphincterotomy, extraction of stones or sludges in bile ducts, intraductal biopsies, and palliative stenting are performed using ERCP for patients with biliary obstruction, ERCP is considered a high-risk procedure that can cause various complications. Infection is the most common complication associated with pancreatitis and bleeding, accounting for 10% of deaths from complications after ERCP.(2-5) The incidence rate of post ERCP infection, including bacteremia, cholangitis, and cholecystitis, is reported to be approximately 5%, but it increases to 18% in the setting of biliary obstruction.(2, 6-8)

In addition to the infectious complications from the procedure itself, patients undergoing ERCP are also susceptible to duodenoscope-related transmission of infection because of the challenge of duodenoscope reprocessing.(5, 9) In 2015, a post ERCP carbapenem-resistant Enterobacteriaceae (CRE) infection outbreak occurred at a medical center in the United States. Seven patients were infected with multidrug-resistant bacteria, and two of them died. The Centers for Disease Control and Prevention in the United States has announced that this outbreak of CRE infection after ERCP was associated with a contaminated duodenoscope. A subsequent meta-analysis, including 15 studies and 13,112 samples, revealed that the contamination rate of reprocessed patient-ready duodenoscopes was 15.25%.(10)

The clinical value of prophylactic antibiotics in preventing infectious complications after ERCP remains controversial. Several randomized controlled studies have reported that the prophylactic use of antibiotics reduced the incidence of bacteremia, but not cholangitis.(11-14) A meta-analysis of seven trials and a total of 1,389 patients showed that prophylactic antibiotics did not significantly prevent ERCP-induced cholangitis in unselected patients.(15) However, in studies of patients with suspected biliary obstruction, prophylactic antibiotics showed potential preventive effects on post ERCP cholangitis.(13, 16, 17) A Cochrane Database of Systematic Review, including nine randomized trials and 1,573 patients, has reported that prophylactic antibiotics reduce bacteremia and seem to prevent post ERCP cholangitis and septicemia, but the effect is less evident in patients with uncomplicated ERCP.(18) Based on these results, major international endoscopic societies, including American Society for Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy (ESGE), and the British Society of Gastroenterology (BSG), do not recommend periprocedural antibiotic prophylaxis in ERCP except for the cases of anticipated incomplete biliary drainage and for severely immunocompromised patients.(19-21) However, due to the low quality of evidence, the level of recommendation is not strong, and further studies on high-risk patient groups are required.(22)

We designed this single-center, double-blind, placebo-controlled, randomized trial (Prophylactic Antibiotics in ERCP for Biliary Obstruction [PAEBO]) to investigate whether the use of prophylactic antibiotics (intravenous cefoxitin [second generation cephalosporin] 1 g, once 30 min before ERCP) would reduce the infectious complications after ERCP in patients with biliary obstruction.

Methods

Trial patients

The PAEBO trial was approved by the Institutional Review Board of the Yonsei University Medical Center (number 4-2015-0596). Patients were recruited at the Yonsei University Severance Hospital (Seoul, Korea) between April, 2017 and February, 2021. Patients whose biliary obstruction was radiologically confirmed using either computed tomography (CT) or magnetic resonance imaging (MRI) and aged > 19 years were eligible for inclusion and were scheduled to undergo ERCP for the diagnosis and treatment of radiologically confirmed biliary obstruction. Patients were ineligible if they were under 19 years of age, pregnant, allergic to beta-lactam antibiotics, or did not consent to this trial. Patients were also excluded from the trial if there was any evidence of infection (leukocytosis [white blood cells (WBC)] $\geq$ 11,000/mm^3, fever ($\geq$38 °C), and history of empiric antibiotics for any kind of infection) within 72 h prior to ERCP. Written informed consent was obtained from all patients before randomization. This study was registered at ClinicalTrials.gov (NCT02958059).

Trial design

The enrolled patients were randomly assigned in a 1:1 ratio to receive either antibiotics or normal saline as a placebo 30 min before the ERCP procedure. In collaboration with an infectious disease specialist, we chose cefoxitin, a second-generation cephamycin antibiotic, as a prophylactic antibiotic based on the recommendations for prophylaxis in biliary tract surgery or invasive procedures.(23-25) We analyzed the results of antibiotic susceptibility tests for common bile bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, etc.), which were commonly detected in patients' blood cultures after ERCP in the same hospital for the last 2 years (2015 to 2017) and confirmed that cefoxitin would be effective against most of the detected strains. The antibiotic mixture (1 g of cefoxitin [Pacetin®, JW Pharmaceutical, Seoul, Korea] in 10 mL of normal saline) or placebo (10 mL of normal saline) was prepared in the same syringe with the same label and administered to the patient through the same route by a pharmacist who was blinded to the contents of the syringe. In all these processes, the assigned group of patients was unknown to the trial staff, endoscopists, and patients. During ERCP, the complete biliary drainage was defined as the resolution of the radiologically confirmed biliary obstructive lesion. After the ERCP procedure was completed, blood samples were collected for culture from all the enrolled patients as soon as possible after confirming the patient's recovery from moderate sedation during the procedure.

Outcome measures

The primary outcome was the incidence of infectious complications after ERCP, including bacteremia, cholangitis, and cholecystitis. Blood samples were collected from all enrolled patients within 24 hours after ERCP and bacteremia was diagnosed when any of the bacterial strains were detected within 5 days of the culture of blood samples. Culture results of possible contamination like isolation of coagulase negative staphylococcus in only one blood culture bottle were excluded. Post ERCP cholangitis was diagnosed as the presence of three or more of the following four clinical features: aggravated right upper quadrant abdominal pain, pyrexia (>38.0 °C according to ear thermometry), inflammatory signs (WBC count > 10,400/μL or C-reactive protein > 8 mg/L or aggravated if they were already higher than the upper normal limit (UNL) before the procedure), jaundice (total

bilirubin > 2.0 mg/dL or aggravated if it was already higher than the UNL before the procedure), or abnormal liver function (gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 1.5 × UNL or aggravated if they were already higher than the UNL before the procedure). Post ERCP cholecystitis was diagnosed using additional radiologic tests, including abdominal ultrasonography or computed tomography, when there were clinically suspicious features. These criteria were derived from Tokyo guidelines.(26) The incidence of each infectious complication was measured as a secondary outcome. In addition, the incidence of ERCP complications other than infection, such as bleeding and pancreatitis, were also analyzed as secondary outcomes. Post ERCP pancreatitis was diagnosed when the patient developed symptoms of acute pancreatitis (i.e., abdominal pain) in addition to elevation of pancreatic enzymes.(27)

Statistical analysis

The planned sample size of 400 patients was estimated using an inequality test for two independent proportions (PASS version 12, NCSS, LLC, Utah, USA) to provide 80% power to detect a relative difference between groups in the risk of infectious complications (risk ratio, 0.50)(14, 18) under the assumption of a two-sided P value of 0.05 and a 10% dropout rate. All analyses were performed in accordance with the intention-to-treat principle. Continuous variables were tested for normal distribution using the D' Agostino–Pearson normality test and analyzed using either an unpaired t-test or the Mann–Whitney U test according to the result. For categorical variables, we used either the Fisher's exact test or chi-square test according to the expected frequency of each cell for statistical analysis. The Koopman asymptotic score was used to calculate the confidence interval for the relative risk ratio. Statistical analyses were performed using Prism software V.8.4.3 (GraphPad, La Jolla, California, USA). P<0.05 was considered significant.

Results

Trial population

From April, 2017 to February, 2021, 400 patients were assessed for eligibility, and 378 patients underwent randomization. A total of 189 patients were assigned to receive antibiotic prophylaxis and 189 to receive a placebo. After withdrawal and exclusion, 176 patients in the antibiotic prophylaxis group and 173 patients in the placebo group were included in the outcome analysis. The patient enrollment, randomization, follow-up, and reasons for exclusion are summarized in **Figure 1**.

The baseline characteristics of the patients were similar between the antibiotic prophylaxis and placebo groups (**Table 1)**. Over 70% of the patients in each group showed symptoms, including jaundice, fever, chills, abdominal pain, and general weakness, and more than 70% of them had never undergone ERCP before. Malignant biliary obstruction was 44.9% in the antibiotic-prophylaxis group and 50.1% in the placebo groups. In addition, malignant hilar obstruction was 15.3 % in the antibiotic-prophylaxis group and 10.4% in the placebo group. There were no significant differences in ERCP procedures, including total procedure time, amount of contrast dye used, procedures performed during ERCP, and the result of biliary drainage, between the antibiotic prophylaxis and placebo groups (**Table 2**). Complete biliary drainage was performed successfully in the majority of the patients, with a success rate of 91.5% in the antibiotic-prophylaxis group and 90.9% in the placebo group.

Primary outcome

The incidence rate of infectious complications after ERCP was 2.8% (5 of 176 patients) in the antibiotic-prophylaxis group and 9.8% (17 of 173 patients) in the placebo group (risk ratio, 0.29; 95% confidence interval [CI], 0.11 to 0.74, *P*=0.0073) (**Table 3**).

Secondary outcomes

The incidence rate of bacteremia diagnosed with blood cultures within 24 h after ERCP was 2.3% (4 of 176 patients) in the antibiotic-prophylaxis group, as compared with 6.4% (11 of 173 patients) in the placebo group (risk ratio, 0.36; 95% CI, 0.12 to 1.04; *P*=0.0599). The median time interval from ERCP to blood culture was 1 h and 1 min (interquartile range [IQR] of 59 min). There was no significant difference in the time interval of blood culture between the two groups (median time interval ± IQR, 59 min ± 51 min in the antibiotic-prophylaxis group and 1 h 3 min ± 1 h 3 min in the placebo group; *P*-value = 0.2231). Furthermore, there was also no significant difference in the time interval between patients with and without bacteremia (median time interval ± IQR, 56 min ± 1 h 8 min and 1 h 1 min ± 57 min, respectively; *P*-value = 0.9570). Notably, of the 15 patients diagnosed with post-ERCP bacteremia, 10 (66.7%) developed septicemia and required treatment. The incidence rate of cholangitis diagnosed using the Tokyo guideline-based criteria was 1.7% (3 of 176 patients) in the antibiotic-prophylaxis group and 6.4% (11 of 173 patients) in the placebo group (risk ratio, 0.27; 95% CI, 0.08 to 0.87; *P*=0.0267). Only one patient in the trial who was assigned in the placebo group was diagnosed with post ERCP cholecystitis. Two patients in the antibiotic prophylaxis group and six patients in the placebo group showed multiple infectious complications. Other outcomes, including post ERCP bleeding and pancreatitis, did not differ between the two groups (**Table 3**). The bacterial species identified in patients diagnosed with bacteremia are presented in **Table 4**.

Subgroup analyses

We analyzed the primary and secondary outcomes in each subgroup divided according to the cause of biliary obstruction: malignant or benign. We found that fewer patients in the antibiotic-prophylaxis group than in the placebo group suffered from infectious complications, regardless of the cause of biliary obstruction, and a statistically significant difference was confirmed in the incidence of cholangitis in the benign disease group (*P*=0.0421) (**Table S1**).

We also confirmed that in patients with successfully performed biliary drainage by ERCP, prophylactic antibiotics significantly lowered the incidence of post-ERCP infectious complications (risk ratio, 0.29; 95% CI, 0.11 to 0.74; *P*=0.0077) (**Table S2**). In the analysis of all patients, the incidence rate of bacteremia and cholangitis was reduced in the antibiotic-prophylaxis group compared to the placebo group, of which the incidence of cholangitis showed a statistically significant difference (risk ratio, 0.27; 95% CI, 0.08 to 0.88; *P*=0.0279).

Risk factor analyses

In the placebo group, repeated ERCP (risk ratio 2.57; 95% CI, 1.06 to 6.02; *P*=0.0566) and performing procedures inducing mechanical damage to the bile ducts during ERCP, such as stone removal (risk ratio 2.15; 95% CI, 0.89 to 5.23; *P*=0.0931) and balloon dilatation (risk ratio 2.23; 95% CI, 0.93 to 5.31; *P*=0.0741), had tendency toward increasing the risk of infectious complications after ERCP (**Figure 2**).

In the antibiotic-prophylaxis group, we evaluated the risk factors associated with post-ERCP infectious complications. However, due to the relatively low incidence of post-ERCP infectious complications in this group (2.8%), we were unable to identify any significant risk factors specific to this group (**Figure S1**).

Adverse events

There were no serious adverse events related to ERCP in either group, except for the primary, secondary, and other outcomes described above. There were no cases of anaphylaxis or serious allergic reactions to antibiotics (Pacetin®) in the antibiotic prophylaxis group. There was no mortality from any causes in this trial.

Discussion

In this large, single-center, double-blind, placebo-controlled, randomized trial, we found that the use of prophylactic antibiotics before ERCP in patients with biliary obstruction resulted in a significantly lower risk of infectious complications, especially cholangitis, than placebo. We found that prophylactic antibiotics lowered post ERCP infectious complications regardless of the cause of biliary obstruction. Furthermore, even in cases of performing successful biliary drainage by ERCP, we found that the use of prophylactic antibiotics significantly lowered the incidence of infectious complications. Since there was no difference in the etiology or intervention between the antibiotic prophylaxis and placebo groups, this trial is considered suitable to demonstrate the efficacy of prophylactic antibiotics in patients with biliary obstruction.

Several randomized controlled studies have reported conflicting results regarding the efficacy of prophylactic antibiotics in ERCP. Although the biliary obstruction is a major risk factor for biliary infections and is also considered to be a risk factor for infectious complications after ERCP, the preventive effect of prophylactic antibiotics has not been clearly demonstrated because large-scale prospective trials have not been

conducted on patients with biliary obstruction. Under these circumstances, since two clinical factors, incomplete biliary drainage and severe neutropenia, have been reported to predict the benefit of antibiotic prophylaxis in patients undergoing ERCP,(28, 29) the current guidelines, including guidelines from ASGE, ESGE, and BSG, do not recommend periprocedural antibiotic prophylaxis in ERCP, except in cases of anticipated incomplete biliary drainage and in severely immunocompromised patients. However, existing trials supporting the current guidelines were conducted decades ago and conducted on heterogeneous patient population. Here, we conducted a large-scale randomized trial with only patients with radiologically confirmed biliary obstruction but without overt infection. Our findings clearly demonstrate that the use of prophylactic antibiotics before ERCP significantly reduces the incidence of infectious complications, particularly bacteremia and cholangitis. Moreover, considering that the majority of the patients in our study (> 90%) achieved complete biliary drainage, our results indicate that prophylactic antibiotics are beneficial not only for patients with anticipated incomplete biliary drainage but also for those with complete biliary drainage. These findings challenge the rationale behind recommending prophylactic antibiotics solely in cases of anticipated incomplete biliary drainage, as suggested by current guidelines.

The appropriate use of pre-procedural prophylactic antibiotics is crucial for achieving favorable patient outcomes. However, it is important to exercise caution to avoid improper overuse of prophylactic antibiotics as they can contribute to the emergence of multidrug-resistant (MDR) bacterial infections within the community. Recent reports have indicated an increasing detection rate of MDR bacteria in cases of biliary infection, particularly among patients who received antibiotic prophylaxis before ERCP.(30) Therefore, although our study provides evidence for the necessity of prophylactic antibiotics in patients with biliary obstruction, it is important to conduct multi-center randomized controlled trials including regions where ERCP-related MDR outbreaks have been reported to establish general recommendations regarding the use of prophylactic antibiotics before ERCP in all patients with biliary obstruction.

In this trial, blood sampling for culture was performed on patients immediately after confirming their recovery from moderate sedation during the ERCP procedure. It is important to note that not all blood samples were obtained from patients at the exact same time interval after ERCP. Therefore, the rates of bacteremia could potentially vary depending on the timing of blood culture. However, the majority of the patients underwent blood sampling for culture within 2 h after ERCP. Furthermore, there was no significant difference in the time interval of blood culture between the two groups and between patients with and without bacteremia. These findings suggest that the results would not have been significantly distorted due to differences in blood culture timing.

Additionally, since the pre-procedural blood sample was not obtained in this study, it was challenging to accurately differentiate whether the bacteremia identified in the post-ERCP blood culture was preexisting latent infection or developed as a result of the procedure. To minimize the possibility of latent infection, this study was conducted on patients who did not exhibit any signs or symptoms of infection within 72 h before undergoing ERCP, considering the relatively short latent period of biliary infection. However, this inclusion criterion alone may not completely exclude the possibility of latent infection. Nonetheless, even if some patients have a latent infection from biliary obstruction before ERCP, the administration of pre-procedure antibiotics can serve as a broad prophylactic measure to prevent latent infection from progressing to overt infection.

This study has several limitations. Although duodenoscope contamination is one of the etiologies of post-ERCP infection, any additional analyses to validate duodenoscope contamination or to identify specific strains associated with different etiologies was not performed in this study. Furthermore, this trial was large enough to demonstrate the clinical benefit of prophylactic antibiotics on preventing infectious complications after ERCP in patients with biliary obstruction, but not enough to demonstrate the preventive benefits in subgroups. Only four immunocompromised patients, taking immunosuppressive agents after liver transplantation, were enrolled, and all of them were randomized to the antibiotic prophylaxis group. Among them, no patients suffered from infectious complications after ERCP; therefore, the effectiveness of prophylactic antibiotics in immunocompromised patients recommended by the existing guidelines could not be confirmed. In addition, this trial was conducted at a single medical center in Korea by several endoscopists, so there is a risk of ethnical bias or operator bias. However, since all registered patients have undergone ERCP at the same center, standardized intervention could be performed and considering that the incidence of post ERCP infectious complications in this trial was lower than previously reported incidence, the performed ERCP is considered to have been conducted by experienced endoscopy experts.

In conclusion, in this large, single-center, double-blind, placebo-controlled, randomized trial, we found that the use of prophylactic antibiotics with cefoxitin before ERCP in patients with biliary obstruction significantly lowered the incidence of infectious complications compared with the use of placebo regardless of the complete drainage of obstructed bile juice. This result conflicts with the existing guidelines suggesting antibiotic prophylaxis before ERCP only in cases of anticipated incomplete biliary drainage or in severely immunocompromised patients. We suggest reconsidering the use of prophylactic antibiotics when performing ERCP in patients with biliary obstruction.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Yonsei University Medical Center (number 4-2015-0596). All patients gave their written informed consent.

Competing interests

The antibiotic used in this trial (Pacetin®) was provided by JW Pharmaceutical, Seoul, Korea. However, this trial was designed and conducted independently of JW Pharmaceutical, and the authors declare no conflicts of interest.

Data sharing

The trial protocol and deidentified participant data collected for this trial is available from the corresponding author M.J.C. upon reasonable request.

Funding

The antibiotic used in this trial (Pacetin®) were provided by JW Pharmaceutical, Seoul, Korea. No other funding sources were available.

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Variables	Antibiotic Prophylaxis (*N*=176)	Placebo (*N*=173)	*P*-value
Age (years)	65.1 ± 13.4	66.5 ± 12.0	0.6834
Sex			0.1729
Male	91 (51.7)	102 (59.0)	
Female	85 (48.3)	71 (41.0)	
Underlying disease	128 (72.7)	131 (75.7)	0.5225
HTN	77 (43.8)	87 (50.3)	
DM	46 (26.1)	55 (31.8)	
Heart disease	11 (6.3)	19 (11.0)	
Liver disease	7 (4.0)	5 (2.9)	
s/p liver transplantation	4 (2.3)	0 (0.0)	
COPD	0 (0.0)	2 (1.2)	
Malignancies	28 (15.9)	24 (13.9)	
Primary sclerosing cholangitis	1 (0.6)	0 (0.0)	
Others	49 (27.8)	54 (31.2)	
Previous ERCP			0.8613
No	137 (77.8)	136 (78.6)	
Yes	39 (22.2)	37 (21.4)	
Reason for ERCP			0.9051
Diagnostic	62 (35.2)	62 (35.8)	
Therapeutic	114 (64.8)	111 (64.2)	
Initial clinical manifestations			0.8275
Asymptomatic	46 (26.1)	47 (27.2)	
Symptomatic	130 (73.9)	126 (72.8)	
Laboratory tests before ERCP			
WBC ($x10^3/\mu L$)	6.37 ± 1.88	6.60 ± 2.27	0.4537
Total bilirubin (mg/dL)	3.9 ± 5.2	4.4 ± 6.0	0.3507
γ-GT (IU/L)	550.0 ± 573.6	526.9 ± 550.4	0.8570
ALP (IU/L)	265.7 ± 267.2	297.2 ± 275.6	0.2132
AST (IU/L)	111.6 ± 131.1	122.3 ± 216.3	0.6855
ALT (IU/L)	134.6 ± 165.7	137.6 ± 172.7	0.7127
CRP (mg/L)	13.3 ± 23.1	14.3 ± 29.5	0.2839
Reason for biliary obstruction			0.2634
Benign	97 (55.1)	85 (49.1)	
Post-LT anastomosis site stricture	4 (2.3)	0 (0.0)	
Malignancy	79 (44.9)	88 (50.1)	
Malignant hilar obstruction	27 (15.3)	18 (10.4)	0.1698

Data are presented as n (%) or mean ± standard deviation.

HTN; hypertension, DM; diabetes mellitus, COPD; chronic obstructive pulmonary disease, ALP; Alkaline phosphatase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; c-reactive protein, IU; international unit.

Patients with post-LT anastomosis site strictures are also included in benign biliary obstruction.

Table 1. Characteristics of the Trial Patients at Baseline

Table 2. ERCP Procedure Characteristics

Variables	Antibiotic Prophylaxis (*N*=176)	Placebo (*N*=173)	*P*-value
Total procedure time (minute)	19.0 ± 9.9	19.1 ± 11.0	0.5812
Contrast dye (mL)	15.8 ± 11.4	16.5 ± 12.8	0.7769
Performed procedure during ERCP			
Cannulation of bile duct	169 (96.0)	167 (94.9)	0.8017
Cannulation of pancreatic duct	26 (14.8)	20 (11.4)	0.3751
Bile duct sphincterotomy	130 (73.9)	123 (69.9)	0.5630
Pancreatic duct sphincterotomy	2 (1.1)	4 (2.3)	0.4457
Stone removal	77 (43.8)	69 (39.2)	0.4642
Balloon dilatation	57 (32.4)	58 (33.0)	0.8208
Bile duct stent insertion	94 (53.4)	101 (57.4)	0.3496
Plastic stent	81 (46.0)	83 (47.2)	
Metal stent	11 (6.3)	17 (9.7)	
ENBD	2 (1.1)	1 (0.6)	
Pancreatic duct stent insertion	14 (8.0)	8 (4.5)	0.2006
Plastic stent	13 (7.4)	8 (4.5)	
ENPD	1 (0.6)	0 (0.0)	
Biopsy/Cytology of bile duct	54 (30.7)	46 (26.1)	0.3979
Biopsy/Cytology of pancreatic duct	2 (1.1)	4 (2.3)	0.4457
Ampullectomy	2 (1.1)	2 (1.1)	>0.9999
Biliary drainage result			0.8281
No drainage	9 (5.1)	9 (5.1)	
Complete	161 (91.5)	160 (90.9)	
Incomplete	6 (3.4)	4 (2.3)	

Data are presented as n (%) or mean ± standard deviation.
ENBD; endoscopic nasobiliary drainage, ENPD; endoscopic nasopancreatic drainage.

Variables	Antibiotic Prophylaxis (*N*=176)	Placebo (*N*=173)	† Risk Ratio (95% CI)	*P*-value
Primary outcome: Infectious complications after ERCP	5 (2.8)	17 (9.8)	0.29 (0.11 – 0.74)	****0.0073**
Secondary outcomes				
Bacteremia	4 (2.3)	11 (6.4)	0.36 (0.12 – 1.04)	0.0599
Cholangitis	3 (1.7)	11 (6.4)	0.27 (0.08 – 0.87)	***0.0267**
Cholecystitis	0 (0.0)	1 (0.6)	0.00 (0.00 – 3.76)	0.4957
Other outcomes				
Bleeding	1 (0.6)	2 (1.2)	0.49 (0.06 – 3.72)	0.6207
Pancreatitis	13 (7.4)	9 (5.2)	1.42 (0.64 – 3.17)	0.4012

Data are presented as n (%) or mean ± standard deviation.

† Risk ratios are presented for binary outcomes; values of less than 1 favor antibiotic prophylaxis.

Two patients in the antibiotic-prophylaxis group and 6 patients in the placebo group showed multiple infectious complications. Statistically significant values are indicated in bold and asterisk (*). ***P*<0.01; **P*<0.05.

Table 3. Primary, Secondary, and Other Outcomes

Group	Species	N (%)
Antibiotic Prophylaxis	**Gram-negative bacteria**	2 (50.0)
	Escherichia coli	1 (25.0)
	Klebsiella pneumoniae	1 (25.0)
	Gram-positive bacteria	3 (75.0)
	Enterococcus faecalis	3 (75.0)
Placebo	**Gram-negative bacteria**	7 (63.6)
	Escherichia coli	5 (45.5)
	Klebsiella oxytoca	2 (18.2)
	Gram-positive bacteria	7 (63.6)
	Staphylococcus hominis	1 (9.1)
	Streptococcus sanguinis	1 (9.1)
	Streptococcus gallolyticus subspecies pasteurianus	1 (9.1)
	Enterococcus faecalis	3 (27.3)
	Enterococcus casseliflavus	1 (9.1)

Data are presented as n (%).
In one patient in each group, two or more strains were detected.

Table 4. Identified bacterial species in patients with bacteremia

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Figure Legends

Figure 1. Trial profile. Summarized flow of enrollment, randomization, follow-up, and outcomes.

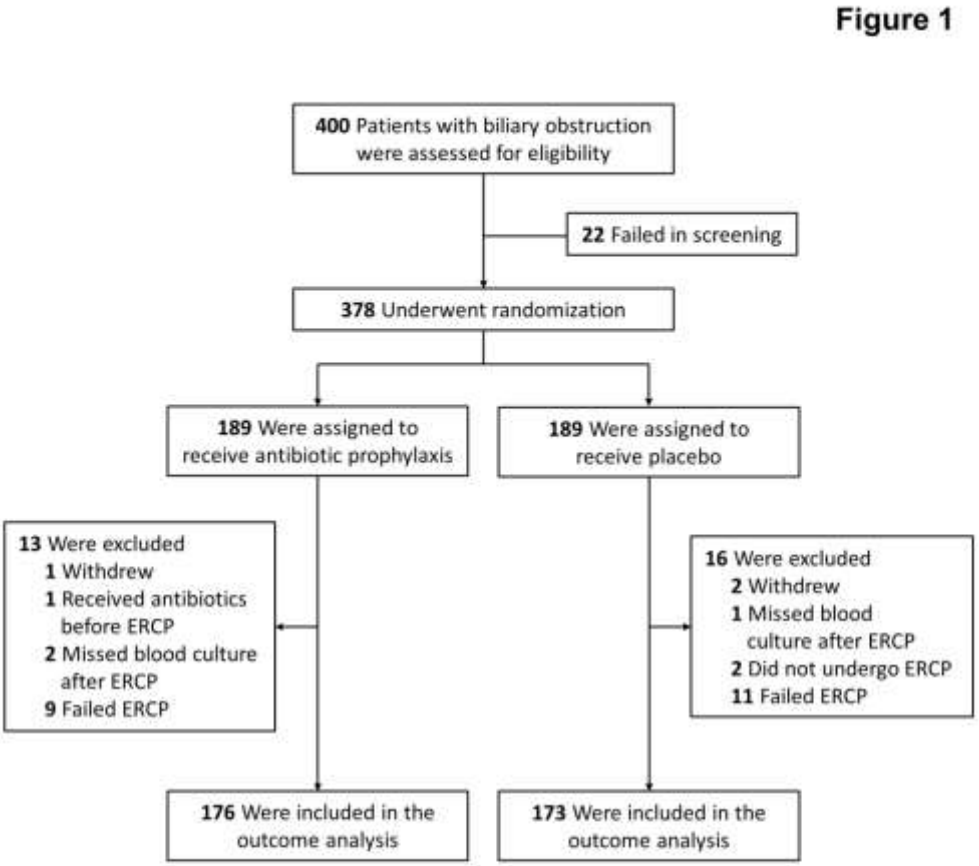

Figure 2. Risk factor analysis for post-ERCP infectious complications. In placebo group, clinical factors and procedure-related factors were included in the analysis.