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Risk Factors of Post Endoscopic Retrograde Cholangiopancreatography Bacteremia

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Background/Aims: Bacteremia following endoscopic retrograde cholangiopancreatography (ERCP) is a severe complication, but the risk factors for this condition have not yet been clearly determined. Thus, the aim of this study was to investigate the risk factors of post-ERCP bacteremia. **Methods:** Among patients who underwent ERCP from June 2006 to May 2009, we selected patients without any signs of infection prior to the ERCP procedures. Of these patients, we further selected those who experienced bacteremia after ERCP as well as two-fold age and sex-matched controls who did not experience bacteremia after ERCP procedures. We compared clinical, laboratory and technical aspects between these two groups. **Results:** There were 70 patients (3.1%) who developed bacteremia after ERCP. In the multivariate analysis, a history of previous liver transplantation, an elevated serum alkaline phosphatase level and an endoscopic retrograde biliary drainage procedure were independent risk factors of post-ERCP bacteremia (p=0.006, p=0.001, and p=0.004, respectively). The microbiologic analysis revealed the presence of gram-negative organisms in 80% of the cases, and 11 patients had infections with bacteria expressing extended spectrum β-lactamases. Pseudomonas infection was significantly more common in patients who received liver transplantation as compared to patients without transplantation (p=0.014). **Conclusions:** A history of liver transplantation, elevated serum alkaline phosphatase levels and endoscopic retrograde biliary drainage procedure were independent risk factors of post-ERCP bacteremia and require additional attention in future studies. **(Gut Liver 2013;7:228-233)**

Key Words: Bacteremia; Endoscopic retrograde cholangiopancreatography; Liver transplantation; Alkaline phosphatase; Endoscopic retrograde biliary drainage

INTRODUCTION

Therapeutic endoscopic procedures in pancreatobiliary tract have been challenged in many years, and the development towards to high techniques made it possible to expand the role of endoscopic retrograde cholangiopancreatography (ERCP). However, ERCP are still invasive procedures, therefore there are always chances of post-ERCP complications including infection, bleeding, pancreatitis, and perforation.[1] The cholangitis and sepsis following ERCP are severe complications and they occur in up to 0.5% to 3.0% of cases.[1-5] The actual incidence of post-ERCP bacteremia remains unknown; investigators have reported the incidence of bacteremia as low as 2.2% and up to 21% in different populations.[6-9]

There has been much effort to find the high risk group of post-ERCP bacteremia. Several previous studies showed that patients with obstructed bile ducts are at highest risk of developing septic complications following ERCP, especially when the drainage was not complete.[3,10,11] And poorly disinfected duodenoscopy was considered as a risk factor of post-ERCP bacteremia especially in *Pseudomonas aeruginosa* infection.[12] However, since ERCP procedure is not frequently performed compared to the gastroscopy or colonoscopy, there is no sufficient data about post-ERCP bacteremia. Moreover, most of the studies were performed several decades ago, thus underlying diseases, causative microorganisms and procedure techniques have been changed. Therefore, the aim of this study is to investigate the risk factors of post-ERCP bacteremia on the basis of recent case-control study.

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MATERIALS AND METHODS

1. Study patients

The patients who underwent ERCP at Seoul National University Hospital from June 1, 2006 to May 31, 2009 were firstly selected in this study. We further selected the patients who experienced bacteremia after ERCP procedures among patients who did not show bacteremia before ERCP. Inclusion criteria is as follows: 1) patients who did not have any evidence of bacteremia before ERCP including patients without any symptom or sign of bacteremia with normal laboratory findings for the diagnostic ERCP or patients who had jaundice or right upper quadrant pain suggesting diseases like stone impaction or malignant obstruction but who did not have any signs of fever >38.0°C and who did not have positive blood culture results prior to ERCP, 2) patients who were not treated with antibiotics prior to ERCP, 3) patients who showed positive blood culture results within 5 days after ERCP, and 4) patients with positive culture results of definite pathogens were included. Patients with other infection such as pneumonia and urinary tract infection were excluded. Patients with culture results of possible contamination like isolation of coagulase negative staphylococcus in only one blood culture bottle were also excluded.

Then, the 2-fold age and sex matched patients who showed no evidence of cholangitis and no evidence of bacterial growth in the culture before and after ERCP were enrolled as controls.

2. Clinical data and laboratory test

Both of the patients and controls group were analyzed in terms of clinical, laboratory, and technical aspects of ERCP procedures. In our ERCP data base, we originally made thorough description along the procedure and kept records for each patient besides formal reports (previous endoscopic sphincterotomy [EST] state, methods of EST, number of attempts during EST, methods of biliary drainage, types of accessories used during the ERCP procedure, approximation of volume amount in dye injection, existence of periampullary diverticulum, underlying disease, cause of disease upon ERCP and other clinical factors, etc.). Medical records of these patients were reviewed thoroughly based on electronic medical records system and our procedure data base as well. Institutional Review Board approval was obtained for this study.

Clinical information included indications for ERCP, primary diagnoses, and comorbid diseases such as hypertension, diabetes, ischemic heart disease, congestive heart failure, cerebrovascular accident, chronic kidney disease, liver cirrhosis, liver transplantation, and malignancies.

The following blood test results before ERCP were reviewed; white blood cell count (normal range, 4,000/mm^3 to 10,000/mm^3), bilirubin (normal range, 0.2 to 1.2 mg/dL), alkaline phosphatase (ALP; normal range, 0 to 40 IU/L), C-reactive protein (normal range, 0 to 0.5 mg/dL), and amylase (normal range, 60 to 180 U/L). The isolation of microorganisms from blood cultures and the susceptibilities to antibiotics were also identified.

In technical aspects, ERCP was performed by therapeutic duodenoscopy (TJF-240, JF-240, TJF-200, or JF-200; Olympus, Tokyo, Japan). Therapeutic ERCP was defined when EST, or any drainage procedure of pancreatic or bile duct had been carried out. Details of procedures were also reviewed as follows; biliary or pancreas cannulations, EST methods, endoscopic retrograde biliary drainage (ERBD), endoscopic nasobiliary drainage (ENBD) and usage of accessories in stone removal (balloon or basket). Procedure related complications such as pancreatitis, bleeding and perforation were also reviewed. Post-ERCP pancreatitis was diagnosed when serum amylase levels elevated more than three times of the normal limit with notable persistent abdominal pain for more than 24 hours after ERCP. Significant bleeding was defined as a requirement of a blood transfusion of more than two units or when patients needed an embolization or urgent operation.

3. Statistical analysis

Statistical analysis was performed with SPSS for Windows version 17.0K (SPSS Korea, Seoul, Korea). The Student t-test and Pearson's chi-square test were used to calculate the statistical significances of different clinical, laboratory, and endoscopic variables. Multivariate analyses were performed to identify independent factors associated with post-ERCP bacteremia by using stepwise logistic regression model. The p-values <0.05 were considered statistically significant.

RESULTS

1. Baseline and follow-up clinical characteristics

Among 2,236 patients who underwent ERCP during study period, we selected 70 patients with post-ERCP bacteremia and age-sex matched 140 controls as mentioned in methods section. One hundred and thirty-two patients (62.9%) were male and median age was 61 years (range, 35 to 81 years). The baseline characteristics are outlined in Table 1. Malignancy, especially biliary tract cancer (p<0.001) and hepatocellular carcinoma (p=0.043) occupied significantly more proportions in the patients with bacteremia. Among the benign diseases, biliary stricture after liver transplantation was significantly higher in patients with post-ERCP bacteremia (p<0.001). In the laboratory findings, patients in post-ERCP bacteremia group showed significantly higher serum levels of bilirubin (p=0.033) and ALP (p<0.001).

2. Comorbidities

Table 2 shows comorbid diseases of patients with and without post-ERCP bacteremia. The incidence of hypertension, diabetes, ischemic heart disease, congestive heart failure, cerebrovascular accident, chronic kidney disease, liver cirrhosis, chronic obstruc-

Table 1. Baseline Characteristics of the Patients

Characteristic	Bacteremia (-) (n=140)	Bacteremia (+) (n=70)	p-value
Age, median (range), yr	61 (35-80)	61 (35-81)	0.989
Male sex	88 (63)	44 (63)	1.000
Primary diagnosis for ERCP			
Tumorous conditions	45 (32)	32 (46)	0.056
Pancreas cancer	21 (15)	8 (11)	0.479
Biliary tract cancer	7 (5)	18 (26)	<0.001
Hepatocellular carcinoma	1 (1)	4 (6)	0.043
Other metastatic cancers in liver	6 (4)	2 (3)	0.722
IPMN	11 (8)	0 (0)	0.017
Nontumorous conditions	95 (68)	38 (54)	0.054
Common bile duct stone	47 (34)	17 (24)	0.168
Cholecystitis	8 (6)	2 (3)	0.502
Pancreatitis	13 (9)	1 (1)	0.038
Benign stricture	10 (7)	20 (29)	<0.001
With liver transplantation	2 (1)	12 (17)	<0.001
Without liver transplantation	8 (6)	8 (11)	0.141
Laboratory findings			
White blood cell >5,900 mm^3*	57 (41)	32 (46)	0.555
Bilirubin >1.2 mg/dL*	76 (54)	49 (70)	0.033
Alkaline phosphatase >115 IU/L*	54 (39)	55 (79)	<0.001
C-reactive protein >1.16 mg/L*	112 (85)	55 (79)	0.329
Amylase >90 IU/L*	15 (11)	8 (11)	1.000

Data are presented as number (%).
ERCP, endoscopic retrograde cholangiopancreatography; IPMN, intraductal papillary mucinous neoplasm.
*Data are presented as medians.

tive pulmonary disease, acquired immune deficiency syndrome, and lymphoma showed no significant difference between the two groups. However, we could find that prior liver transplantation (p<0.001) and malignant biliary obstruction (p=0.003) were significantly associated with post-ERCP bacteremia.

3. Endoscopic interventions

Table 3 shows details of ERCP procedures in both groups. In control group, 60.7% of patients underwent therapeutic ERCP whereas 90.0% of patients underwent therapeutic ERCP in bacteremia group with a statistically significant difference (p<0.001). Biliary cannulation was not associated with post-ERCP bacteremia (p=0.397). ERBD (p<0.001) and EST including both of standard EST and needle knife EST (p=0.006) increased the risk

Table 2. Differences in Comorbid Diseases between Patients with and without Post Endoscopic Retrograde Cholangiopancreatography Bacteremia

	Bacteremia (-) (n=140)	Bacteremia (+) (n=70)	p-value
Hypertension	33 (24)	16 (23)	0.908
Diabetes	32 (23)	21 (30)	0.261
Ischemic heart disease	6 (4)	1 (1)	0.428
Congestive heart failure	2 (1)	3 (3)	0.602
Cerebrovascular accident	6 (4)	1 (1)	0.428
Chronic kidney disease	3 (2)	3 (4)	0.403
Liver cirrhosis	19 (14)	8 (11)	0.662
Liver transplantation	3 (2)	12 (17)	<0.001
COPD	1 (1)	2 (3)	0.260
AIDS	1 (1)	0 (0)	1.000
Lymphoma	0 (0)	1 (1)	0.333
Malignancy	44 (31)	34 (49)	0.015
With biliary obstruction	29 (21)	28 (40)	0.003
Without biliary obstruction	15 (11)	6 (9)	0.626

Data are presented as number (%).
COPD, chronic obstructive pulmonary disease; AIDS, acquired immune deficiency syndrome.

Table 3. Differences in Endoscopic Findings between Patients with and without Post Endoscopic Retrograde Cholangiopancreatography (ERCP) Bacteremia

	Bacteremia (-) (n=140)	Bacteremia (+) (n=70)	p-value
Therapeutic	85 (61)	63 (90)	<0.001
Diagnostic	55 (39)	7 (10)	<0.001
Procedures			
Biliary cannulation	109 (78)	58 (83)	0.397
Pancreas cannulation	68 (49)	18 (26)	0.001
Volume of contrast media injected, median (range), mL	15 (8-22)	18 (5-26)	0.087
Previous state of EST	18 (13)	9 (13)	1.000
Endoscopic sphincterotomy	58 (41)	43 (61)	0.006
ERBD	24 (17)	34 (49)	<0.001
ENBD	3 (2)	2 (3)	1.000
Balloon dilatation	26 (19)	18 (26)	0.231
Stone removal	30 (21)	18 (26)	0.486
Post-ERCP complication			
Perforation	0 (0)	1 (1)	0.333
Significant bleeding	0 (0)	1 (1)	0.333
Pancreatitis	0 (0)	2 (3)	0.110

Data are presented as number (%).
EST, endoscopic sphincterotomy; ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic nasobiliary drainage.

Table 4. Multivariate Analyses Performed Using a Stepwise Logistic Regression Model to Identify Risk Factors for Post Endoscopic Retrograde Cholangiopancreatography Bacteremia

	p-value	HR (95% CI)
Liver transplantation	0.006	8.66 (1.89-39.75)
Elevated serum alkaline phosphatase level*	0.001	3.55 (1.71-7.34)
Endoscopic retrograde biliary drainage	0.004	2.95 (1.42-6.15)
Pancreatitis	0.068	0.14 (0.02-1.16)

HR, hazard ratio; CI, confidence interval.
*Alkaline phosphatase ≤115 IU/L vs alkaline phosphatase >115 IU/L.

of bacteremia after ERCP. However, balloon dilatation (p=0.231) and basket stone extraction (p=0.486) did not show any significant association with post-ERCP bacteremia. Also, previous state of EST (p=1.000) and amount of dye injection (p=0.087) reflecting the pressure of bile duct which is very important in pathogenesis of cholangitis were not significantly different between two groups.

4. Multivariate analysis

Multivariate analysis was done to evaluate the risk factors which were significantly associated with post-ERCP bacteremia in univariate anlaysis (Table 4). These factors were as followings; laboratory findings (bilirubin, ALP), comorbidities (malignancies, liver transplantation history), type of ERCP (diagnostic versus therapeutic), and types of intervention (pancreas cannulation, EST, and ERBD). History of liver transplantation (hazard ratio [HR], 8.66; 95% confidence interval [CI], 1.89 to 39.75), elevated ALP due to cholestasis (HR, 3.55; 95% CI, 1.71 to 7.34), and ERBD procedure (HR, 2.95; 95% CI, 1.42 to 6.15) were the independent risk factors for post-ERCP bacteremia.

5. Isolation of microorganism

The microorganisms were isolated from the blood cultures of the patients with post-ERCP bacteremia and the results were in Fig. 1. Five patients (7%) had multiple organisms among the 70 patients with post-ERCP bacteremia. Gram-positive bacteria occupied 20%, and gram-negative bacteria occupied 80%. The most common microorganism was *Escherichia* which occupied in 23 patients (32%) and *Klebsiella* was the second common bacterial genus isolated in 13 patients (17%). Others were as follow: *Pseudomonas, Stephomonas, Enterococcus, Enterobacter*, and *Bacillus*. There was the total of 11 patients who had extended spectrum β-lactamase (ESBL) bacteremia: *Escherichia* six patients, *Klebsiella* three patients, and *Stephomonas* in two patients.

Pseudomonas infection was significantly more common in patients who received liver transplantation (p=0.014) than who did not receive liver transplantation, however *Escherichia* (p=0.738) and *Klebsiella* (p=1.000) were not.

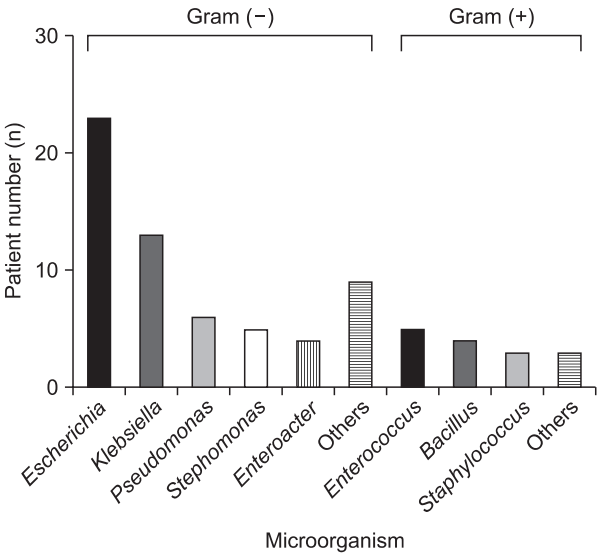

Fig. 1. Isolation of microorganisms. The most common microorganisms among the isolated gram-negative bacteria were Escherichia, which was present in 23 patients (32%), and *Klebsiella*, which was the second most common bacterial genus and was isolated in 13 patients (17%). The other bacteria isolated included *Pseudomonas*, *Stephomonas*, *Enterococcus*, *Enterobacter*, and *Bacillus*.

DISCUSSION

In this study, we found that the incidence of post-ERCP bacteremia was 3.1%, and we also found that history of liver transplantation, elevated serum ALP, and ERBD procedures were independent risk factors of post-ERCP bacteremia.

The number of liver transplantations performed per year has been increasing steadily, and the post-transplantation population is growing.[13] Biliary complications such as bile leakage, stricture, and choledocholithiasis are reported from 13.2% to 66.6% after liver transplantation and these are the major causes of morbidity and mortality in liver transplanted patients.[14-17] ERCP is widely used for both the diagnostic and therapeutic purposes in these patients. Though, there is a tendency to use minimal immunosuppressive agent, the patients with liver transplantation definitely are more vulnerable to the infection.[13,18,19] As our data showed that the history of liver transplantation was an independent risk factor for the post-ERCP bacteremia, this group of patients should be paid much attention after the ERCP procedures. Interestingly, *Pseudomonas* bacteremia was significantly more common in patients who received liver transplantation than who did not. *Pseudomonas* infection has been known as one of major cause of bacterial infection after liver transplantation, and biliary tract problem has been known to be associated with *Pseudomonas* infection.[20,21] The finding of this study also suggests the consistent results. Therefore, we should consider *Pseudomonas* infection when we choose antibiotics for

the patients who received liver transplantation when post-ERCP *Pseudomonas* bacteremia is suspicious.

Elevated ALP level due to cholestasis was also an independent predictor of post-ERCP bacteremia. This shows consistent results from the previous study suggesting biliary obstruction as a risk factor of post-ERCP bacteremia. The reason is that biliary obstruction can cause ascending bacterial infection.[4,22] Though, bilirubin also reflects the biliary obstruction, it was not an independent predictor of post-ERCP bacteremia in the multivariate analysis. It might be because serum ALP is a more sensitive marker of bile duct obstruction than serum bilirubin. ALP can be elevated in the small peripheral duct obstruction even though bilirubin is still in the normal range.

ERBD was also an independent risk factor among the procedural aspects in ERCP. As ERBD procedures are used to drain the biliary obstruction, this can be explained in the same context of elevated ALP as a risk factor of post-ERCP bacteremia. ENBD is also performed in pursuing bile drainage, however the number of patients who got ENBD procedures was too small to evaluate the effect of ENBD on post-ERCP bacteremia.

The incidence of microorganisms cultured after ERCP is similar to other studies reporting biliary tract infection; *Escherichia* and *Klebsiella* were the most common micooragnism isolated.[23] The rate of ESBL producers was over 20% in these organisms. This high rate of ESBL producers in these organisms implies the necessity of broad spectrum antibiotics coverage when traditional antibiotics effect is not sufficient to control infection.[24]

As this study is the retrospective study, selection bias might have somewhat affected the results. However, we selected definite bacteremia group and nonbacteremia group according to the strict criteria, and we matched age, sex, and time of procedure between two groups to lower the effect of those confounding factors. Additionally this study has strength in that it shows recent trend of post-ERCP bacteremia reflecting recent underlying diseases like stricture after liver transplantation and recent incidence of microorganisms causing post-ERCP bacteremia. Also, this study focused on the every single possible risk factor in terms of host factors (underlying disease, comorbidities), laboratory factors and technical factors in the process of evaluation.

Here we showed that history of liver transplantation, elevated serum ALP level due to cholestasis and ERBD procedures as independent risk factors of post-ERCP bacteremia. In addition, gram-negative bacteria were main cause of post-ERCP bacteremia and *Pseudomonas* infection was especially high in patients who received liver transplantation. As a result, clinical attention might be needed more to the high risk group of post-ERCP bacteremia and we could consider using appropriate antibiotics for those patients with further investigation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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