Background/Aims: To select appropriate empirical antibiotics, updates on the changes in pathogens are essential. We aimed to investigate the changes in pathogens and their antibiotic susceptibility in acute cholangitis (AC) with bacteremia over a period of 15 years. Furthermore, the efficacy of empirical antibiotic therapies and the risk factors predicting antibiotic-resistant pathogens (ARPs) were analyzed.

Methods: A total of 568 patients with AC and bacteremia who were admitted to Daegu Catholic University Medical Center from January 2006 to December 2020 were included. Their medical records were retrospectively reviewed. In addition, the data were grouped and analyzed at 3-year intervals under the criteria of Tokyo Guideline 2018.

Results: During the study period, 596 pathogens were isolated from blood cultures of 568 patients. The three most common pathogens were *Escherichia coli* (50.5%), *Klebsiella* species (24.5%), and *Enterococcus* species (8.1%). The proportion of vancomycin-resistant *Enterococci* (VRE) has increased since the mid-2010 (0.0% to 4.3%, p=0.007). There was emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) in 2018 to 2020, albeit not statistically significant (1.3%, p=0.096). Risk factors predicting ARP were healthcare-associated infection, history of previous biliary intervention, and the severity of AC. For patients with these aforementioned risk factors, imipenem was the most effective antibiotic and piperacillin-tazobactam was also effective but to a lesser degree (susceptibility rates of 92.1% and 75.0%, respectively).

Conclusions: The proportion of VRE has increased and CRE has emerged in AC. In addition, healthcare-associated infection, history of previous biliary intervention, and the severity of AC were independent risk factors predicting ARP. For patients with these risk factors, the administration of imipenem or piperacillin-tazobactam should be considered. (Gut Liver 2022;16:985-994)

Key Words: Cholangitis; Bacteremia; Anti-bacterial agents; Drug resistance, microbial; Carbapenem-resistant *Enterobacteriaceae*

**INTRODUCTION**

Acute cholangitis (AC) occurs when biliary stenosis results in cholestasis and biliary infection. Biliary stenosis elevates pressure within biliary system and flushes microorganisms or endotoxins from infected bile into systemic circulation. Thus, antibiotic therapy and biliary drainage are the mainstay of the management for AC. And previous studies have shown that both inadequate initial administration of antibiotics and delayed biliary drainage increase mortality.

In order to select appropriate empirical antibiotics, regional epidemiology and patterns of antibiotic resistance are important. And widely accepted rule for empirical therapy is that resistant organisms occurring in more than 10% to 20% of patients should be treated. In other words, it is considered that the acceptable susceptibility of empirical antibiotics should be 80% or more, and at least 70% or more.
The previous study from our institution showed that the proportion of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* did not change significantly during the period from 2006 to 2012 (36.7% in the first half vs 32.1% in the second half). On the other hand, Sung et al. reported a marked increase in ESBL-producing *E. coli* and *Klebsiella* strains among the causative pathogens of patients with biliary tract infections (BTIs) and bacteremia in the 2000s (2.3% in 2000 to 2004 and 43.9% in 2005 to 2009). And Lee et al. reported that the proportion of these organisms was 7.8% in the study on patients with severe AC from 2007 to 2009.

With time passage, both pathogens and antibiotic susceptibility may have changed, however, studies in the 2010s are limited. Therefore, the aim of this study was to investigate changes of causative pathogens and their antibiotic susceptibility in patients with AC and bacteremia over the last 15 years. Furthermore, clinical characteristics and clinical outcomes of patients with antibiotic-resistant pathogen (ARP) were evaluated. In addition, efficacy of empirical antibiotic therapies and risk factors predicting ARP were analyzed.

### MATERIALS AND METHODS

#### 1. Study population

A total of 4,044 patients with AC who were admitted to Daegu Catholic University Medical Center from January 2006 to December 2020 were eligible (Fig. 1). All cases were retrieved using the diagnostic code for AC (K830, K8030, and K8031) based on the Korean Standard Classification of Diseases, 8th revision. Exclusion criteria were as follows: (1) patients with negative blood culture results; (2) patients who did not fulfill the definite diagnostic criteria according to the updated Tokyo Guideline 2018 (TG18); (3) patients with other significant infectious diseases such as pneumonia or acute pyelonephritis; (4) patients suspected of having contaminated blood culture results; or (5) patients with insufficient medical records.

#### 2. Study design

This study was a retrospective, observational cohort study. Following data were collected from medical records: demographics, laboratory findings, etiology of AC, underlying disease, results of blood culture, antibiotic susceptibility, and administered antibiotics. In-hospital mortality, duration of fever, and length of hospitalization were used as variables for evaluating clinical outcome. This study was performed in compliance with the ethical guidelines of the revised Helsinki Declaration of 2013. The study protocol was reviewed and approved by the Institutional Review Board of Daegu Catholic University Medical Center (IRB number: CR-21-098). And the need for informed consent was waived since this study was performed retrospectively.

#### 3. Diagnosis and severity grading of AC

AC was diagnosed when systemic inflammation, cholestasis, and imaging evidence were all fulfilled according to the definite diagnostic criteria of the TG18. The severity of AC was classified into mild (grade 1), moderate (grade 2), and severe (grade 3) according to the TG18.

#### 4. Definitions

AC with bacteremia was defined as AC with at least one positive result of blood culture tests that were obtained at admission or within 24 hours of the onset of fever in hospitalized patients. Blood culture was considered as...
contaminated when the result was any of following microorganisms: (1) coagulate-negative Staphylococi, (2) Corynebacterium species (spp.), (3) Bacillus spp., or (4) Propionibacterium spp.13

ARPs included ESBL-producing Enterobacteriaceae, methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococci (VRE), multidrug-resistant (MDR) Acinetobacter spp., MDR Pseudomonas spp., and carbapenem-resistant Enterobacteriaceae (CRE). Acinetobacter spp. were considered MDR if they were resistant to all penicillins, all cephalosporins, ciprofloxacin, gentamicin, and imipenem.14 Pseudomonas spp. were considered MDR if they were resistant to at least three of the four following groups: (1) imipenem or meropenem; (2) cefepime or ceftazidime; (3) piperacillin-tazobactam; and (4) ciprofloxacin or levofloxacin.15

Healthcare-associated infections included community-onset and hospital-onset infection.16 Community-onset healthcare-associated infection was defined as infection having at least one of the following risk factors: (1) presence of invasive device at time of admission; (2) history of methicillin-resistant S. aureus infection or colonization; or (3) history of surgery, hospitalization, dialysis, or residence in long-term care facility in the 12 months preceding the culture date.17 Hospital-onset healthcare-associated infection was defined as infection having positive culture results, obtained 48 hours after admission.16

Initial failure rate was defined as the proportion of patients with pathogens resistant to initial empirical antibiotics. Final failure rate was defined as the proportion of patients who continued to receive inappropriate antibiotic therapy even after the causative pathogen was identified.

Drainage time was defined as the time (hours) from hospital visit to receiving biliary drainage procedures such as endoscopic retrograde cholangiopancreatography or percutaneous drainage. Previous biliary intervention was defined as any of following: (1) endoscopic retrograde biliary drainage (ERBD) or nasobiliary drainage; (2) endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilatation (EPBD); or (3) percutaneous transhepatic biliary drainage (PTBD).

The study period was divided into five groups (period 1 to period 5) at 3-year intervals from January 2006 to December 2020 in order to examine the trend of causative pathogens and antibiotic susceptibility.

5. Statistical analysis
Statistical analysis was performed using IBM SPSS Statistics for Windows version 19.0. (IBM Corp., Armonk, NY, USA). The chi-square or the Fisher exact test was used to compare categorical variables. Linear by linear association was used to examine trends. Since continuous variables were not normally distributed, they were described as medians with interquartile range and the Mann-Whitney U test was used to compare them. However, the mean was used as the representative value only when the median could not reveal the difference between the variables. Logistic regression model was used to determine risk factors predicting ARP. Statistical significance was defined as a p-value of <0.05 (two-tailed).

### Table 1. Changes of Isolated Pathogens over a Period of 15 Years

| Pathogen               | Period 1* (n=27) | Period 2 (n=47) | Period 3 (n=116) | Period 4 (n=171) | Period 5 (n=235) | Total (n=596) | p-value |
|------------------------|------------------|-----------------|------------------|------------------|------------------|---------------|---------|
| **Gram-negative**      |                  |                 |                  |                  |                  |               |         |
| Escherichia coli       | 12 (44.4)        | 27 (57.4)       | 63 (54.3)        | 79 (46.2)        | 120 (51.1)       | 301 (50.5)    | 0.725   |
| Klebsiella spp.        | 8 (29.6)         | 12 (25.5)       | 32 (27.6)        | 40 (23.4)        | 54 (23.0)        | 146 (24.5)    | 0.306   |
| Pseudomonas spp.       | 1 (3.7)          | 1 (2.1)         | 3 (2.6)          | 4 (2.3)          | 1 (0.4)          | 10 (1.7)      | 0.091   |
| Enterobacter spp.      | 2 (7.4)          | 1 (2.1)         | 3 (2.6)          | 7 (4.1)          | 10 (4.3)         | 23 (3.9)      | 0.829   |
| Citrobacter spp.       | 0                | 0               | 0                | 4 (2.3)          | 8 (3.4)          | 12 (2.0)      | 0.020   |
| Acinetobacter spp.     | 0                | 0               | 1 (0.9)          | 3 (1.8)          | 3 (1.3)          | 7 (1.2)       | 0.376   |
| **Gram-positive**      |                  |                 |                  |                  |                  |               |         |
| Enterococcus spp.      | 2 (7.4)          | 2 (4.3)         | 7 (6.0)          | 16 (9.4)         | 21 (8.9)         | 48 (8.1)      | 0.262   |
| Staphylococcus spp.    | 0                | 0               | 0                | 1 (0.6)          | 0                | 1 (0.2)       | 0.934   |
| Streptococcus spp.     | 0                | 1 (2.1)         | 2 (1.7)          | 3 (1.8)          | 5 (2.1)          | 11 (1.8)      | 0.598   |
| Anaerobes              | 0                | 0               | 0                | 3 (1.8)          | 0                | 3 (0.5)       | 0.886   |
| Others§                | 2 (7.4)          | 3 (6.4)         | 5 (4.3)          | 11 (6.4)         | 13 (5.5)         | 34 (5.7)      | 0.493   |

Data are presented as the number (%).

*The period from 2006 to 2020 was grouped into 3-year intervals and divided into period 1 through period 5; †Raoultella planticola, Aeromonas hydrophila, Serratia fonticola, Vibrio vulnificus, etc.
RESULTS

1. Changes of isolated pathogens and antibiotic susceptibility over a period of 15 years

During the study period, 596 pathogens were isolated from the blood cultures of 568 patients. The changes of isolated pathogens over 15 years were shown in Table 1. In all periods, *E. coli* (44.4% to 57.4%) was the most common pathogen, followed by *Klebsiella* spp. (23.0% to 29.6%), and *Enterococcus* spp. (4.3% to 9.4%). There was no significant change in microbial profile of antibiotic susceptible pathogens except for *Citrobacter* spp. (0.0% to 3.4%, p=0.020).

Table 2 shows changes of ARP during the study period. ESBL-producing *E. coli* was the most common pathogen (21.8%), followed by VRE (2.3%). The proportion of the total ARPs did not change significantly during the study period (Fig. 2). However, the proportion of VRE has been on the rise since the mid-2010s (0.0% to 4.3%, p=0.007). Although it was not statistically significant, the emergence of CRE was reported in period 5 (1.3%, p=0.096).

Comparison of antibiotic susceptibility results for each period was shown in Table 3. The susceptibility of ampicillin showed an increasing trend (p=0.038), nevertheless it was only less than 40%. All third-generation cephalosporins showed susceptibility between 60% and 70%. And the two most effective antibiotics were piperacillin-tazobactam and imipenem (87.9% and 96.5%, respectively) during the study period.

![Fig. 2. Changes in antibiotic-resistant pathogens over a period of 15 years.](image)

ESBL, extended-spectrum beta-lactamase.

### Table 2. Changes of Antibiotic-Resistant Pathogens over a Period of 15 Years

| Antibiotic-resistant pathogen | Period 1* | Period 2 | Period 3 | Period 4 | Period 5 | Total | p-value |
|------------------------------|-----------|----------|----------|----------|----------|-------|---------|
| ESBL-producing *Enterobacteriaceae* | 4 (14.8) | 11 (23.4) | 27 (23.3) | 40 (23.4) | 48 (20.4) | 130 (21.8) |         |
| VRE                          | 0         | 0        | 0        | 4 (2.3)  | 10 (4.3) | 14 (2.3) |         |
| CRE                          | 0         | 0        | 0        | 3 (1.3)  | 3 (0.5)  | 3 (0.5)  |         |
| MDR *Acinetobacter* spp.     | 0         | 0        | 1 (0.9)  | 0        | 0        | 1 (0.2)  |         |
| MDR *Pseudomonas* spp.       | 1 (3.7)   | 0        | 1 (0.9)  | 0        | 0        | 2 (0.3)  |         |
| MRSA                         | 0         | 0        | 0        | 1 (0.6)  | 0        | 1 (0.2)  |         |

Data are presented as the number (%). ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant *Enterococci*; CRE, carbapenem-resistant *Enterobacteriaceae*; MDR, multidrug resistant; spp., species; MRSA, methicillin-resistant *Staphylococcus aureus*.

*The period from 2006 to 2020 was grouped into 3-year intervals and divided into period 1 through period 5.

### Table 3. Changes of Antibiotic Susceptibility over a Period of 15 Years

| Antibiotics               | Period 1* | Period 2 | Period 3 | Period 4 | Period 5 | Total | p-value |
|---------------------------|-----------|----------|----------|----------|----------|-------|---------|
| Ampicillin                | 5 (20.8)  | 6 (14.6) | 32 (30.2) | 43 (28.3) | 86 (37.7) | 172 (31.2) | 0.038   |
| Cefotaxime                | 10 (66.7) | 29 (67.4) | 78 (67.8) | 107 (64.1) | 153 (65.9) | 377 (65.9) | 0.819   |
| Ceftriaxime               | 8 (53.3)  | 31 (70.5) | 78 (68.4) | 107 (65.2) | 156 (67.8) | 380 (67.0) | 0.517   |
| Cefepime                  | 22 (81.5) | 33 (71.7) | 80 (70.2) | 110 (67.1) | 163 (71.2) | 408 (70.3) | 0.534   |
| Ciprofloxacin             | 21 (77.8) | 18 (64.3) | 66 (71.7) | 113 (76.4) | 165 (78.6) | 383 (75.8) | 0.436   |
| Piperacillin-tazobactam   | 22 (88.0) | 28 (84.6) | 85 (91.4) | 131 (89.1) | 176 (85.9) | 442 (87.9) | 0.305   |
| Imipenem                  | 26 (96.3) | 44 (97.8) | 108 (95.6) | 160 (98.2) | 217 (95.6) | 555 (96.5) | 0.855   |

Data are presented as the number (%). The number of pathogens that were tested for antibiotic susceptibility is different for each cell. In addition, the number of pathogens susceptible to each antibiotic is shown in each cell.

*The period from 2006 to 2020 was grouped into 3-year intervals and divided into period 1 through period 5.
2. Comparison of baseline characteristics and clinical outcomes between antibiotic-resistant and non-resistant groups

The baseline characteristics and clinical outcomes between antibiotic-resistant and non-resistant groups are shown in Table 4. Of the 568 patients, 142 patients (25.0%) belonged to the antibiotic-resistant group. There was no significant difference in sex, comorbidity, etiology, laboratory findings, and drainage time between two groups. The most common cause of AC was biliary stone (n=421, 74.1%), followed by malignancy (n=115, 20.2%), and others (n=32, 5.6%). The distribution was the same in both groups. On the other hand, patients in the antibiotic-resistant group were older (78 years vs 75 years, p=0.008) and had a higher severity of AC according to TG18 (2.12 vs 1.92, p=0.012). In addition, in the antibiotic-resistant group, healthcare-associated infection and a history of previous biliary intervention were significantly more common (64.1% vs 38.0%, p<0.001 and 68.3% vs 40.4%, p<0.001, respectively). In particular, the proportions of both ERBD or PTBD and EST or EPBD were significantly higher in the antibiotic-resistant group (49.3% vs 29.6%, p<0.001 and 38.7% vs 25.6%, p=0.004, respectively). In the antibiotic-resistant group, initial failure rate and final failure rate were
significantly higher than non-resistant group (99.3% vs 9.2%, \( p<0.001 \) and 31.0% vs 4.0%, \( p<0.001 \), respectively). There was no significant difference between the two groups with respect to in-hospital mortality and duration of fever (7.7% vs 5.2%, \( p=0.351 \) and 1 day vs 1 day, \( p=0.564 \), respectively). However, patients in antibiotic-resistant group showed longer length of hospitalization than those in non-resistant group (8 days vs 6 days, \( p<0.001 \)).

3. Risk factors predicting ARP

Based on data of this study and results of several previous studies, multivariate regression analysis was performed using backward elimination with a history of previous biliary intervention, age, sex, etiology of malignancy, severity of AC, and healthcare-associated infection as independent variables. Severity of AC was reclassified into severe (grade 3 AC) and non-severe (grade 1 or 2 AC). The statistically significant results were shown in Table 5. Risk factors predicting ARP included healthcare-associated infection (odds ratio [OR], 1.961; 95% confidence interval [CI], 1.265 to 3.039; \( p=0.003 \)), a history of previous biliary intervention (OR, 2.399; 95% CI, 1.537 to 3.745; \( p<0.001 \)), and severe AC (OR, 1.624; 95% CI, 1.070 to 2.464; \( p=0.023 \)). In addition, we also performed multivariate regression analysis using ERBD or PTBD and EST or EPBD as independent variables instead of previous biliary intervention. And both variables did not show statistically significant results (OR, 1.421; 95% CI, 0.868 to 2.328; \( p=0.162 \) and OR, 1.242; 95% CI, 0.782 to 1.974; \( p=0.359 \), respectively).

4. Efficacy of empirical antibiotics according to risk factors

Table 6 shows comparison of antibiotic susceptibility according to risk factors. When there were any risk factors, the antibiotic susceptibility of ampicillin was 24.3% to 27.3%. And it was only 19.0% when there were all risk factors. All cephalosporins showed antibiotic susceptibility between 53.8% and 61.4% when there were any risk factors. Also, when there were all risk factors, it was only 40.0% to 43.8%. Under such conditions, imipenem and piperacillin-tazobactam showed susceptibilities of more than 80% (94.5% to 96.0% and 81.0% to 86.2%, respectively). For patients with all risk factors, antibiotic susceptibility was 92.1% for imipenem and 75.0% for piperacillin-tazobactam.

## DISCUSSION

The regional epidemiology and patterns of antibiotic resistance are important factors in selecting appropriate empirical antibiotics. And they vary from region to region. The previous studies on microbial profile in BTIs with bacteremia were summarized in Table 7. The proportion of causative pathogens varied between studies, but their distribution was similar. The most common Gram-negative bacteria were *E. coli* (20.5% to 52.3%), followed by *Klebsiella* spp. (14.1% to 21.0%), and the most common Gram-positive bacteria were *Enterococcus* spp. (11.3% to

### Table 5. Risk Factors Predicting Antibiotic-Resistant Pathogen

| Variable                              | OR (95% CI) | p-value |
|---------------------------------------|------------|---------|
| Previous biliary intervention*        | <0.001     |         |
| Yes                                   | 2.399 [1.537–3.745] | 0.003   |
| Healthcare-associated infection*      | 1.961 [1.265–3.039] | 0.023   |
| Disease severity†                     | 1.624 [1.070–2.464] | 0.023   |

OR, odds ratio; CI, confidence interval.
*Reference category; †Disease severity was classified according to the updated Tokyo Guideline 2018.

### Table 6. Comparison of Antibiotic Susceptibility According to Risk Factors

| Antibiotics                  | Grade 3 severity* | Previous biliary intervention | Healthcare-associated infection | All risk factors† |
|------------------------------|-------------------|-------------------------------|---------------------------------|------------------|
| Ampicillin                   | 45 (26.3)         | 72 (27.3)                     | 59 (24.3)                       | 12 (19.0)        |
| Cefotaxime                   | 101 (58.4)        | 151 (54.5)                    | 140 (53.8)                      | 26 (40.0)        |
| Cefazidime                   | 100 (58.8)        | 153 (55.6)                    | 142 (55.3)                      | 27 (42.2)        |
| Cefepime                     | 108 (61.4)        | 164 (59.0)                    | 151 (57.9)                      | 28 (43.8)        |
| Ciprofloxacin                | 106 (72.1)        | 162 (47.5)                    | 150 (48.2)                      | 27 (51.9)        |
| Piperacillin-tazobactam      | 125 (86.2)        | 194 (81.3)                    | 179 (81.0)                      | 39 (75.0)        |
| Imipenem                     | 166 (96.0)        | 259 (94.5)                    | 245 (94.6)                      | 58 (92.1)        |

Data are presented as the number (%). The number of pathogens that were tested for antibiotic susceptibility is different for each cell. In addition, the number of pathogens susceptible to each antibiotic is shown in each cell.
*Disease severity was classified according to the updated Tokyo Guideline 2018; †All risk factors included grade 3 severity, a history of previous biliary intervention, and healthcare-associated infection.
The proportion of ESBL-producing Enterobacteriaceae was between 4.6% and 10.0% and that of VRE was between 2.0% and 3.8%. On the other hand, in period 1 (2006 to 2008) of this study, the proportion of ESBL-producing Enterobacteriaceae was 14.8% and it increased to 23.4% in the early 2010s, which was in line with the global trend of increasing human intestinal ESBL-producing Enterobacteriaceae. However, since 2010s, it has been maintained at the 20% range in this study. To our knowledge, there have been no studies investigating changes of the proportion of ESBL-producing Enterobacteriaceae among causative pathogens isolated from blood culture of BTIs in the 2010s. Jang et al. investigated the proportion of ESBL-producing Enterobacteriaceae in BTIs in Korea using carbapenem prescription records as the surrogate and showed that overall percentage of BTIs treated with carbapenems was 2.4%, with increasing annual trend. However, the ratio did not change much in recent years, with 3.2% in 2014, 3.3% in 2015, and 3.0% in 2016. Therefore, although additional studies are needed, the increase of ESBL-producing Enterobacteriaceae in AC is considered to have reached a plateau in the 2010s. This is probably because the concerns about ESBL-producing Enterobacteriaceae have been emphasized in several previous studies, which has prompted healthcare providers to be alert and reduce the overuse of antibiotics. 

However, since 2015, the proportion of VRE has been increasing and CRE has emerged in this study. CRE has disseminated globally since it was first reported in the early 1990s. It is resistant to most antibiotics, which limits treatment options, and has a higher mortality rate and a longer hospitalization compared to susceptible strains. Similarly, since the first VRE was identified in the England, it has spread worldwide and is associated with higher mortality. Although the proportion of VRE and CRE among the total causative pathogens was not high (4.3% and 1.3% in period 5, respectively) in this study, these pathogens should be considered when patients have risk factors predicting ARP.

Recent studies showed that risk factors associated with mortality in patients with AC were etiology of malignancy, bacteraemia, insufficient drainage, and disease severity. And use of inappropriate antibiotics was also significant risk factor in patients with bacteremia. However, in this study, there was no statistically significant difference between the two groups with respect to in-hospital mortality and duration of fever although the patients in the antibiotic-resistant group were older, had higher severity of AC, and antibiotic failure rate than those in the non-resistant group. This was probably because biliary drainage was per-
formed within 24 hours in both groups. According to the TG18, the two axes of treatment for AC are biliary drainage and antibiotics.1 And the importance of biliary drainage is emphasized as severity of AC increases.1 Our findings indirectly support the importance of biliary drainage. The length of hospitalization, the last parameter of clinical outcomes, was significantly longer in the antibiotic-resistant group. This can be explained by the fact that there are very few oral alternatives to antibiotics used for ARPs.

Antibiotic resistance is directly related to overuse of antibiotics, because antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind as a result of natural selection.29 In previous studies on BTIs, risk factors associated with antibiotic resistance were nosocomial infection, indwelling biliary drainage, previous antibiotic use within 90 days, male sex, Charlson comorbidity index ≥5, and healthcare-associated infection.10,18-29 Similarly, healthcare-associated infection and a history of previous biliary intervention were risk factors predicting ARP in this study. And both factors may be linked by a history of antibiotic use. On the other hand, severity of AC was newly identified as a risk factor in this study. Since previous studies did not evaluate severity of AC according to TG18, further studies are needed.

Interestingly, in this study, although a history of ERBD or PTBD appeared to be more useful than that of EST or EPBD, both variables were not statistically significant to predict ARP. It suggests that ARP can be predicted better when a history of biliary intervention, which lead to alteration in the normal anatomy of biliary tract, is considered along with a history of indwelling catheter. In this regard, Schneider et al.30 reported that biliary intervention including both percutaneous and endoscopic cholangiography increased antibiotic resistance. And Goo et al.31 have suggested that previous biliary intervention including EST can make a larger inoculum of bacterobilia, which may contribute the acquisition of ARPs in the condition of biliary tract obstruction. However, the acquisition of ARPs according to types of biliary intervention is beyond the purpose of this study and researches are also limited. Therefore, additional researches are needed.

According to the TG18, empirical antibiotics are recommended differently depending on severity of AC and the presence or absence of healthcare-associated infection.2 Piperacillin-tazobactam, cefepime, ceftazidime, and carbapenem are recommended for patients with healthcare-associated infection and grade 3 community-acquired infection. Of these four antibiotics, imipenem was the most effective when all risk factors predicting ARP were present. Furthermore, coverage for VRE should be considered if Gram-positive bacteria are identified under such conditions. As mentioned above, it is important to avoid unnecessary administration of antibiotics to prevent antibiotic resistance. In this regard, the possibility of using piperacillin-tazobactam as an alternative to carbapenems has been reported in previous studies.18,32 In this study, imipenem was the most effective antibiotic in patients with all risk factors predicting ARP. However, piperacillin-tazobactam also showed a relatively effective susceptibility of about 80% (81.0% to 86.2%), when only one risk factor was present, and 75.0% even when all risk factors were present. Therefore, piperacillin-tazobactam can be considered as an alternative to carbapenems if the patient’s condition is not critical and early biliary drainage, which is another axis of treatment, is possible.

This study has several limitations. First, there were uncontrolled factors such as blood culture technique, initial management, and choice of antibiotics because it was a retrospective study. Second, because the number of pathogens included in each period was different, results could be over or underestimated. Third, this study was conducted at a single tertiary medical center. Therefore, it is difficult to generalize the results of this study. Fourth, in order to select appropriate antibiotics in actual clinical practice, both blood culture and bile culture tests are considered, but bile culture results were not investigated in this study. However, it was because it is difficult to distinguish the actual causative pathogens from colonization in bile culture. And, although it was a single tertiary medical center study, a relatively large number of patients were included compared to other studies, and they were systematically analyzed according to TG18.

In summary, the proportion of total ARPs in AC with bacteremia did not increase in the 2010s. However, the proportion of VRE has been increasing and CRE has become a new threat. This study also showed that healthcare-associated infection, severity of AC, and a history of previous biliary intervention were independent risk factors predicting ARP. And for patients with these risk factors, imipenem is the most effective antibiotic but piperacillin-tazobactam is relatively effective. Therefore, in order to reduce the overuse of carbapenems, piperacillin-tazobactam can be considered as an alternative to carbapenems in AC, especially if early biliary drainage is possible. In addition, if Gram-positive bacteria are identified in such patients, coverage for VRE should be considered.

CONFLICTS OF INTEREST

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

Study concept and design: H.G.K., J.H. Data acquisition: H.T.J. Data analysis and interpretation: H.T.J., J.E.S., H.G.K., J.H. Drafting of manuscript: H.T.J. Critical revision of the manuscript for important intellectual content: J.E.S., H.G.K., J.H. Statistical analysis: H.T.J., J.E.S., J.H. Administrative, technical, or material support: J.H. Study supervision: H.G.K., J.H.

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