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Association of short-course antimicrobial therapy and bacterial resistance in acute cholangitis: Retrospective cohort study

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Authors
Sakue Masuda[1], Ryuhei Jinushi[2], Yoshinori Imamura[3], Jun Kubota[1], Karen Kimura[1], Kento Shionoya[1], Makomo Makazu[1], Ryo Sato[1], Makoto Kako[1], Masahiro Kobayashi[1], Haruki Uojima[4], Kazuya Koizumi[1]

Institutions
1 Gastroenterology, Shonan Kamakura General Hospital, Kamakura, Japan
2 Gastroenterology, Saitama Medical University International Medical Center, Hidaka, Japan
3 Division of Medical Oncology/Hematology, Department of Medicine, Kobe University, Kobe, Japan
4 Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Sagamihara, Japan

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70469 Stuttgart, Germany

Corresponding author
Dr. Sakue Masuda, Shonan Kamakura General Hospital, Gastroenterology, Kanagawa , 247-8533 Kamakura, Japan
sakue.masuda@tokushukai.jp

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ABSTRACT

Background and study aims Although the number of resistant bacteria tends to increase with prolonged antimicrobial therapy, no studies have examined the relationship between the duration of antimicrobial therapy and increase in the number of resistant bacteria in acute cholangitis. We hypothesized that the short-term administration of antimicrobial agents in acute cholangitis would suppress bacterial resistance.

Patients and methods This was a single-center, retrospective, observational study of patients with acute cholangitis admitted between January 2018 and June 2020 who met the following criteria: successful biliary drainage, positive blood or bile cultures, bacteria identified from cultures sensitive to antimicrobials, and subsequent cholangitis recurrence by January 2022. The patients were divided into two groups: those whose causative organisms at the time of recurrence became resistant to the antimicrobial agents used at the time of initial admission (resistant group) and those who remained susceptible (susceptible group). Multivariate analysis was used to examine risk factors associated with the development of resistant pathogens. Multivariate analysis investigated antibiotics used with the length of 3 days or shorter after endoscopic retrograde cholangiopancreatography (ERCP) and previously reported risk factors for the development of bacterial resistance.

Results In total, 89 eligible patients were included in this study. There were no significant differences in patient background or ERCP findings between the groups. The use of antibiotics, completed within 3 days after ERCP, was associated with a lower risk of developing bacterial resistance (odds ratio, 0.17; 95% confidence interval, 0.04–0.65; P= 0.01).

Conclusions In acute cholangitis, the administration of antimicrobials within 3 days of ERCP may suppress the development of resistant bacteria.

Introduction

Antibiotic resistance is a growing problem worldwide, with antibiotic-resistant infections associated with increased morbidity, mortality, and healthcare costs [1, 2]. In the United States, antibiotic-resistant infections lead to approximately 35,000 deaths annually [2]. Mitigating antimicrobial drug resistance encompasses strategies such as drug discovery and the control of antimicrobial drug-resistant pathogen development. Given the protracted research timelines and substantial expenses involved in drug discovery, controlling the development of antimicrobial drug-resistant pathogens is imperative [1, 3].

The risk factors for developing infections caused by antimicrobial drug-resistant pathogens include a history of antimicrobial exposure [4, 5]. Other risk factors include exposure to medical devices and healthcare workers [1, 5, 6, 7, 8, 9, 10], regular use of proton pump inhibitors (PPIs) [11], implantation of biliary stents [12, 13], and prior endoscopic sphincterotomy (EST) [14, 15]. Moreover, the long-term administration of antimicrobial agents, especially in patients with pneumonia, poses a risk for the emergence of multidrug-resistant bacteria [16, 17, 18, 19]. Therefore, global recommendations advocate for the short-term administration of antimicrobial agents [20, 21]. Acute cholangitis (AC), the second or fourth most prevalent cause of community-acquired bacteremia [22, 23], stands as one of the most common diseases necessitating antimicrobial therapy. However, no study has explored the potential association between antimicrobial resistance and the duration of antimicrobial therapy recommended by the current AC guidelines.

The Tokyo Guidelines 2018 (TG18), the most prominent AC guideline, recommend a 4- to 7-day course of antibiotic therapy following biliary drainage; however, robust evidence substantiating the requisite duration for curing AC remains elusive [24]. Recent studies suggested that a 1- to 3-day course or less of antibiotic therapy following biliary drainage is a reasonable duration for antibiotic administration to cure AC [25, 26, 27, 28]; thus, Dutch guidelines recommended a 3-day regimen after biliary drainage [29]. Moreover, the French Infectious Disease Society (SPILF) proposed the reduction of antimicrobial therapy duration to 3 days if successful drainage was achieved, including those with bacteremia [20]. Once the source of infection is controlled by biliary drainage, bacteremia is likely to resolve, potentially obviating the need for further antibiotic therapy [30].

Shortening the administration of such antibiotics may effectively mitigate the development of resistant bacteria in patients with AC. Nevertheless, whether a shortened course of antimicrobial therapy, as opposed to the TG18 recommendation, indeed diminishes the emergence of resistant organisms remains enigmatic. Therefore, we hypothesized that administering antimicrobial therapy for up to 3 days following endoscopic retrograde cholangiopancreatography (ERCP) could mitigate the emergence of resistant organisms in AC patients. To explore this hypothesis, we analyzed the duration of previous antimicrobial therapy in two distinct groups: patients with recurrent AC in whom resistant bacteria emerged and those in whom susceptible bacteria emerged. By investigating this relationship, we aimed to ascertain whether a treatment duration shorter than the standard duration recommended by TG18 may be necessary to suppress the emergence of resistant bacteria in patients with AC.

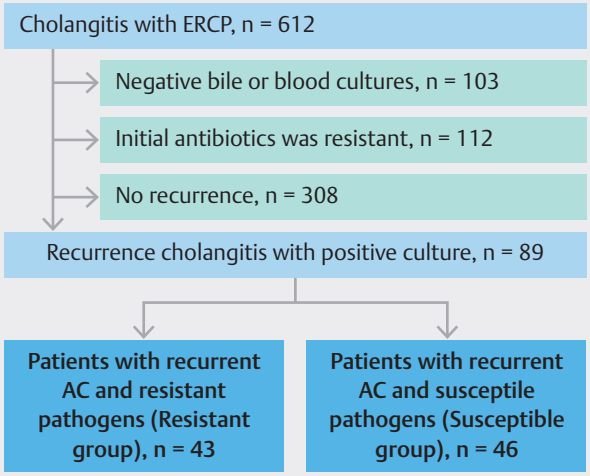
Patients and methods

Study population

This retrospective cohort study was conducted at the Shonan Kamakura General Hospital in Japan. The medical records of patients treated at the hospital between January 2018 and June 2020 were searched to identify patients with AC who obtained positive results on blood or bile culture tests; the patients successfully underwent ERCP and were infected with organisms that were susceptible to the administered antimicrobials. Patients who experienced AC recurrence by January 2022 and obtained positive blood or bile culture test results at that time were included in the final analysis. The patients were divided into two groups at the time of recurrence: those in whom the causative organisms had become resistant to the antimicrobials administered at the time of initial admission (resistant group) and those in whom the organisms remained susceptible (susceptible group). This dichotomy enabled the researchers to investigate whether the duration of antimicrobial treatment during the initial AC was correlated with the acquisition of resistance by the causative organisms during the relapse AC (▶ **Fig. 1**).

Blood cultures were collected prior to the antibiotic administration, while bile cultures were collected immediately after ERCP. We employed interpretive standards from the Clinical and Laboratory Standards Institute (CLSI) for minimal inhibitory concentration (MIC) or zone diameter testing to identify susceptible or resistant organisms [31].

In our hospital, ampicillin/sulbactam, cefmetazole, ceftriaxone, piperacillin/tazobactam, meropenem, and ciprofloxacin are typically used as initial treatments. Mild cases were primari-



▶ **Fig. 1** Flow diagram. ERCP, endoscopic retrograde cholangiopancreatography; AC, acute cholangitis

ly treated with cefmetazole, with other antibiotics administered based on severity and results of previous cultures.

If plastic stent implantation was required during ERCP, one or two 7F stents were generally implanted. Self-expandable metallic stents measuring 10 and 8 mm in diameter were implanted in the common bile duct and hilar regions, respectively.

Research items

Data on the patient background, ERCP findings, antimicrobials used, duration of administration, and blood and bile culture results at initial admission were collected. We also investigated the antimicrobial agents used, blood and bile culture results, and clinical characteristics at the second admission to assess for recurrent cholangitis.

According to the results of previous studies exploring the risks of developing resistant bacteria, we also investigated the incidence of PPI use [11], implantation of biliary stents [12, 13], history of EST [14, 15], and exposure to medical devices and healthcare workers [1, 5, 6, 7, 8, 9, 10].

We also investigated the history of antimicrobial administration for other infections not related to this study from the time of initial disease onset to the time of cholangitis recurrence. If any pertinent information was not available from the electronic medical record, we contacted the patient, his or her family, the nursing home in which he or she resided, or the attending physician by telephone to inquire about the antimicrobial administration history from the initial onset to the recurrence of cholangitis.

To the best of our knowledge, no existing study has reported long-term antimicrobial therapy as a risk factor for the development of resistant organisms in patients with AC. However, a relationship between long-term antimicrobial therapy and the development of resistant organisms was reported in patients with other infectious diseases [16, 17, 32]. Therefore, we investigated the factors involved in the development of resistant organisms in patients with recurrent cholangitis, including long-term antimicrobial therapy.

Definitions

The diagnosis and assessment of cholangitis severity were based on the TG18 guidelines [33]. The duration of hospitalization was defined as the number of days from admission to discharge or death. The duration of antimicrobial therapy was investigated, with 4 to 7 days after ERCP as the standard treatment period according to the TG18 guidelines and within 3 days after ERCP as the short-term treatment period.

Cholangitis is frequently attributed to polymicrobial infection. Blood cultures exhibit low sensitivity and may fail to detect the causative organism, whereas bile cultures possess low specificity and may detect enteric bacteria that are unrelated to the causative organisms. This discrepancy complicates the accurate identification of the causative organism of cholangitis. Therefore, in this study, all identified bacteria were regarded as causative organisms.

The development of resistant organisms in recurrent cholangitis was defined as follows. Organisms identified from the blood and bile cultures were susceptible to antimicrobials administered during the initial hospitalization. On the second admission, owing to the recurrence of AC, the bacteria identified from the blood and bile cultures had developed resistance to the antimicrobial agent administered during the initial admission. Resistance to the initial antibiotics was defined as in vitro resistance to these antibiotics, with antibiotic efficacy determined in accordance with the CLSI interpretive standards for MIC or zone diameter testing [31].

Statistical analyses

The Mann-Whitney U test was used to compare non-normally distributed continuous variables, while the $\chi 2$ test or Fisher's exact test was used to compare categorical variables. Multivariate analysis was performed using logistic regression and included antibiotics used within 3 days after ERCP in addition to the reported risk factors for the development of bacterial resistance. "Regular use of PPI," "first ERCP in their life," "EST performed during the initial hospitalization," "antibiotics within 3 days after ERCP," "piperacillin/tazobactam," and "history of antimicrobial administration from the initial onset to the recurrence of cholangitis" were included in the multivariate analysis as independent variables.

Notably, the "history of antimicrobial administration from the initial onset to the recurrence of cholangitis," a facet seldom explored in previous studies to our knowledge, seems to be an important independent variable signifying the interaction between patients and medical interventions or antimicrobial agents. Piperacillin/tazobactam is the most frequently used broad-spectrum antibacterial agent in our hospital. Previous studies considered "bile duct stent placement from initial admission to second admission" as a risk factor for the development of resistant pathogens [12, 13]. However, these studies were single-center, retrospective studies; did not include the period of antimicrobial administration, which is an important risk factor for the development of bacterial resistance, in the multivariate analysis; or did not sufficiently investigate the antimicrobial exposure history. Therefore, "bile duct stent placement from initial admission to second admission" was excluded from the multivariate analysis in favor of a more pivotal factor. A sensitivity analysis was performed using more independent variables, including "bile duct stent placement from initial admission to second admission."

A two-tailed P <0.05 was considered significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander, designed to allow additional biostatistical functions [34].

Results

Patient characteristics

▶ **Table 1** summarizes the patient characteristics. The data from 89 patients with recurrent AC and positive blood or bile culture results were analyzed. Of these, 43 patients (48.3%) had causative organisms that developed resistance to the administered antimicrobials at the time of initial admission (resistant group),

▶ **Table 1** Patient characteristics.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Age, median (IQR)	83.00 (74.00, 86.00)	77.50 (70.00, 85.00)	0.17
Age > 80 years, n (%)	26 (60.5)	21 (45.7)	0.2
Sex ratio	Male 19: Female 24	Male 27: Female 19	0.21
Cause of cholangitis, n (%)			
Malignant stricture	18 (41.9)	18 (39.1)	0.94
Bile duct stone	18 (41.9)	21 (45.7)	
Benign stricture	3 (7.0)	4 (8.7)	
Other	4 (9.3)	3 (6.5)	
Stent obstruction, including malignant and benign, n (%)	12 (27.9)	18 (39.1)	0.37
Severity, n (%)			
Mild	19 (44.2)	18 (39.1)	0.67
Moderate	19 (44.2)	22 (47.8)	0.83
Severe	5 (11.6)	6 (13.0)	>0.99
Underlying medical conditions, n (%)			
CKD	3 (7.0)	1 (2.2)	0.35
CHF	3 (7.0)	2 (4.3)	0.67
LC	2 (4.7)	1 (2.2)	0.61
DM	6 (14.0)	8 (17.4)	0.77
Malignant tumor	18 (41.9)	18 (39.1)	0.83
Hemodialysis	1 (2.3)	0 (0.0)	0.48
Gastrostomy	0 (0.0)	0 (0.0)	1
Constant placement of urinary catheter	0 (0.0)	0 (0.0)	1
Aspiration pneumonia	0 (0.0)	0 (0.0)	1
Residence nursing home	9 (20.9)	7 (15.2)	0.58
Immunosuppressant user	2 (4.7)	3 (6.5)	>0.99
Regular use of PPI	20 (46.5)	21 (45.7)	>0.99

Some cases overlapped.
CKD, chronic kidney disease; CHF, chronic heart failure; DM, diabetes mellitus; IQR, interquartile range; LC, liver cirrhosis; PPI, proton pump inhibitor.

while 46 (51.7%) had organisms that remained susceptible (susceptible group). No significant differences were observed between the two groups in terms of age, sex, cause of cholangitis, severity of cholangitis, underlying medical conditions, nursing home residence, or PPI use.

ERCP findings

▶ **Table 2** outlines the ERCP findings during the initial admission. No significant differences were found between the groups in terms of ERCP treatment history, technical success rates of biliary drainage, ERCP drainage procedures, or complications.

Antimicrobials used on initial and second admission

▶ **Table 3** summarizes the antibiotics administered during the initial admission. Cefmetazole (CMZ) and ampicillin/sulbactam and piperacillin/tazobactam (PIPC/TAZ) were the most commonly used antibiotics. CMZ was predominantly used in the resistant group (51.2%) and PIPC/TAZ in the susceptible group (52.2%).

▶ **Table 4** summarizes the antibiotics administered during the second admission. CMZ, ampicillin/sulbactam, and PIPC/TAZ were the most commonly used antibiotics. CMZ was predominantly used in the resistant group (51.2%) and PIPC/TAZ in the susceptible group (47.8%). Approximately half of patients in both groups received the same antimicrobials during their initial and second hospitalizations.

Characteristics of antimicrobial use on initial admission

▶ **Table 5** summarizes the characteristics of antimicrobial use. No significant differences were observed between the two groups according to the time from first physician contact to antibiotic administration. However, the resistant group had a significantly longer duration of antimicrobial therapy compared with the susceptible group (median, 6 vs. 5 days, respectively; $P = 0.04$). Additionally, the resistant group had a longer antimicrobial therapy duration following ERCP (median, 6 vs. 5 days, respectively; $P = 0.02$), along with a reduced proportion of patients receiving a shorter dosing regimen (within 3 days after ERCP) (9.3% vs. 30.4%; $P = 0.02$).

Laboratory findings regarding microbial cultures on initial and second admission

The laboratory findings regarding the microbial cultures from patients during the initial admission are summarized in ▶ **Table 6**. The proportions of patients with sampling blood and bile cultures were 74.4% and 93.0% in the resistant group and 71.7% and 97.8% in the susceptible group, respectively. The proportions of patients with positive results on blood and bile culture tests were 37.2% and 90.7% in the resistant group and 39.1% and 97.8% in the susceptible group, respectively. No significant differences were observed in the proportion of patients with positive results on blood or bile culture tests. *Escherichia coli*, *Klebsiella* spp., and *Enterococcus* spp. were the most commonly detected pathogens. *Enterococcus* spp. in bile cultures was detected more frequently in the susceptible group than in the resistant group.

The laboratory findings of the microbial cultures from the patients during the second admission are summarized in ▶ **Table 7**. The proportions of patients with sampling blood and bile cultures were 44.2% and 97.7% in the resistant group and 47.8% and 100% in the susceptible group, respectively. The propor-

▶ **Table 2** ERCP findings.

	Resistant group n = 43	Susceptible group n = 46	*P* value
First ERCP in their life, n (%)	21 (48.8)	13 (28.3)	0.053
EST, n (%)			0.17
EST was performed in the past	19 (44.2)	29 (63.0)	
EST performed during initial hospitalization	16 (37.2)	10 (21.7)	
No EST was performed	5 (11.6)	2 (4.3)	
Choledochojejunostomy	3 (7.0)	5 (10.9)	
ERCP drainage procedure, n (%)			0.79
Stent placement	27 (62.8)	30 (65.2)	
Self-expandable metallic stent	10 (37.0)	5 (15.7)	
Plastic stent	17 (63.0)	25 (83.3)	
ENBD	1 (2.3)	0 (0.0)	
Stone extraction	13 (30.2)	15 (32.6)	
Other	2 (4.7)	1 (2.2)	
Technical success of ERCP	42 (97.7)	45 (97.8)	>0.99
Technical success of biliary drainage procedure	43 (100)	46 (100)	1
Complications*, n (%)			
Pancreatitis	2 (4.7)	0 (0.0)	0.23
Bleeding	0 (0.0)	1 (2.2)	>0.99
Perforation	0 (0.0)	0 (0.0)	1
Cholecystitis	4 (9.3)	0 (0.0)	>0.99
No complications	38 (88.4)	45 (97.8)	0.1

EST, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography; ENBD, endoscopic nasobiliary drainage
*One case overlapped.

▶ **Table 3** Antimicrobials used on initial admission.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Cefmetazole, n (%)	22 (51.2)	11 (23.9)	0.01
Piperacillin/tazobactam, n (%)	5 (11.6)	24 (52.2)	<0.01
Ampicillin/sulbactam, n (%)	11 (25.6)	6 (13.0)	0.18
Ceftriaxone, n (%)	4 (9.3)	1 (2.2)	0.19
Meropenem, n (%)	1 (2.3)	3 (6.5)	0.62
Ciprofloxacin, n (%)	0 (0.0)	1 (2.2)	>0.99
Vancomycin, n (%)	0 (0.0)	1 (2.2)	>0.99
Others	1 (2.3)	0 (0.0)	0.48

One patient in the resistant group and one in the susceptible group were administered two antimicrobial agents.

▶ **Table 4** Antimicrobials used on second admission.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Cefmetazole, n (%)	22 (51.2)	12 (26.1)	0.02
Piperacillin/tazobactam, n (%)	7 (16.3)	22 (47.8)	< 0.01
Ampicillin/sulbactam, n (%)	4 (9.3)	8 (17.4)	0.36
Ceftriaxone, n (%)	3 (7.0)	2 (4.3)	0.67
Meropenem, n (%)	3 (7.0)	1 (2.2)	0.35
Ciprofloxacin, n (%)	4 (9.3)	1 (2.2)	0.19
Vancomycin, n (%)	0 (0.0)	0 (0.0)	N/A
Other, n (%)	0 (0.0)	0 (0.0)	N/A
Use of same antimicrobials on initial and second hospitalizations, n (%)	21 (48.8)	26 (56.5)	0.53

tions of patients with positive results on blood and bile culture tests were 20.9% and 97.0% in the resistant group and 19.6% and 100% in the susceptible group, respectively. No significant differences were observed in the proportion of patients with positive results on positive blood or bile culture tests. *Escherichia coli*, *Klebsiella* spp., and *Enterococcus* spp. were the most common pathogens. *Enterococcus* sp. and *Enterobacter* sp. in bile cultures were more frequently detected in the resistant group than in the susceptible group. *Klebsiella* spp. and anaerobes in bile culture were detected more frequently in the susceptible group than in the resistant group.

Clinical features associated with the second hospitalization

▶ **Table 8** summarizes the clinical features during the second admission. There was no significant difference in the duration until recurrence of AC between the two groups. The administered antimicrobials were less effective in the resistant group than in the susceptible group (11.6% vs. 76.1%, *P* <0.01). However, no significant differences were found between the two groups in terms of in-hospital mortality due to cholangitis or duration of hospitalization. In the process of bacteria develop-

▶ **Table 5** Characteristics of antimicrobial use.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Time from first physician contact to antibiotic administration, median hours (IQR)	3.0 (2.0–5.0)	4.0 (2.0–7.0)	0.61
Total duration of antimicrobial therapy, median days (IQR)	6.0 (5.0–10.5)	5.0 (4.0–8.0)	0.04
Antimicrobial duration after ERCP, median days (IQR)	6.0 (5.0–10.5)	5.0 (3.0–7.0)	0.02
Antimicrobial agents used within 3 days after ERCP, n(%)	4 (9.3)	14 (30.4)	0.02
Total duration of antimicrobial therapy in patients with positive results on blood culture tests, median days (IQR)	8.00 [5.75–11.00]	6.50 [4.25–10.00]	0.31
Antimicrobial duration after ERCP in patients with positive results on blood culture tests, median days (IQR)	8.00 [5.00–11.00]	6.00 [4.00–10.00]	0.3
Antimicrobial agents used within 3 days after ERCP in patients with positive results on blood culture tests, n(%)	0 (0.0)	3 (16.7)	0.23

IQR, interquartile range; ERCP, endoscopic retrograde cholangiopancreatography.

ing resistance to antimicrobials, it was more common to observe a phenomenon of microbial substitution than the original causative bacteria acquiring resistance directly.

Association between antimicrobial therapy within 3 days after ERCP and development of bacterial resistance

Multivariate analysis showed that the use of antibiotics, completed within 3 days after ERCP, was associated with a lower risk of developing bacterial resistance (odds ratio [OR]: 0.17, 95% confidence interval [CI]: 0.04–0.65; $P = 0.01$) (▶ **Table 9**).

PIPC/TAZ also emerged as a factor linked to a low incidence of resistant bacteria. No significant differences were noted in other parameters such as “regular use of PPI”, “first ERCP in their life”, “EST performed during the initial hospitalization”, and “history of antimicrobial administration from the initial onset to the recurrence of cholangitis.”

A sensitivity analysis was also performed using more independent variables, including “age over 80,” “bile duct stent placement from initial admission to second admission”, “residence nursing home”, and “cefmetazole used on initial admission.” We decided to include cefmetazole, which was the most frequently used narrow-spectrum antimicrobial agent in this study, in the sensitivity analysis. The results in this sensitivity analysis mirrored those of the main analysis, with “antibiotics used within 3 days after ERCP” and “PIPC/TAZ used on initial admission” extracted as independent inhibitors (**Supplementary file 1**).

Discussion

This study primarily investigated whether a treatment duration shorter than the duration recommended by the TG18 guidelines (4–7 days after ERCP) affected the development of resistant pathogens that caused AC. The multivariate analysis included “antimicrobial therapy within 3 days after ERCP” in addition to the established risk factors for bacterial resistance development. The results showed a significantly low odds ratio and suggested that a 3-day antimicrobial therapy or less during the initial AC may have suppressed the development of resistant organisms when cholangitis recurred. To the best of our knowledge, no study has examined the association between short-course antimicrobial therapy during initial cholangitis and the development of resistant organisms during recurrent cholangitis. Moreover, few previous studies reporting the occurrence of resistant organisms in cholangitis have mentioned the duration of antimicrobial therapy.

Reuken et al. investigated whether the total duration of antimicrobial therapy (14 days) for AC was associated with resistant organisms and concluded that it had no discernible impact [12]. However, in other severe infections and ventilator-associated pneumonia, the incidence of resistant organisms increased as the duration of antimicrobial therapy increased, which was consistent with the findings of our study [16, 17, 18, 19]. Another study reported that the hazard ratio for the emergence of resistant organisms increased by 1.04 for every additional day of exposure to β-lactam antibiotics [19]. Therefore, the overutilization of antimicrobial agents contributes to the proliferation of resistant organisms [35]. The absence of an association between the duration of antimicrobial administration and the emergence of resistant organisms observed in Reuken et al.’s study may be attributed to the extended predefined duration of “14 days.” Resistant organisms might have emerged in groups with a treatment duration of less than 14 days, which was almost as frequently as those with a treatment duration of 14 days or more.

Another novelty of this study is that the results of blood and bile cultures of patients with recurrent AC were compared with the blood and bile cultures of those with initial AC. Previous studies examining the relationship between AC and resistant organisms only relied on the data from a single culture. To the best of our knowledge, no study has compared the cultures obtained during the initial AC episode and those from recurrent AC, as conducted in this study [12, 13, 14, 15]. In bile cultures

▶ **Table 6** Laboratory findings from microbial cultures on initial admission.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Blood culture, n (%)			
Sampling a blood culture	32 (74.4)	33 (71.7)	0.82
Positive rate	16 (37.2)	18 (39.1)	0.9
Pathogens			
Escherichia coli	8 (18.6)	10 (21.7)	0.88
Klebsiella sp.	6 (14.0)	4 (8.7)	0.74
Enterococcus sp.	0 (0.0)	2 (4.3)	0.57
Enterobacter sp.	1 (2.3)	1 (2.2)	0.91
Citrobacter sp.	0 (0.0)	0 (0.0)	0.82
Streptococcus sp.	1 (2.3)	1 (2.2)	0.91
Pseudomonas sp.	0 (0.0)	0 (0.0)	0.82
Anaerobes	0 (0.0)	2 (4.3)	0.57
Others	1 (2.3)	1 (2.2)	0.91
Bile culture, n (%)			
Sampling a bile culture	40 (93.0)	45 (97.8)	0.35
Positive rate	39 (90.7)	45 (97.8)	0.19
Pathogens			
Escherichia coli	18 (41.9)	21 (45.7)	0.83
Klebsiella sp.	17 (39.5)	16 (34.8)	0.67
Enterococcus sp.	11 (25.6)	22 (47.8)	0.05
Enterobacter sp.	5 (11.6)	6 (13.0)	>0.99
Citrobacter sp.	2 (4.7)	6 (13.0)	0.27
Streptococcus sp.	10 (23.3)	5 (10.9)	0.16
Pseudomonas sp.	1 (2.3)	1 (2.2)	>0.99
Anaerobes	2 (4.7)	6 (13.0)	0.27
Other	5 (11.6)	2 (4.3)	0.26

▶ **Table 7** Laboratory findings of microbial cultures on second admission.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Blood culture, n (%)			
Sampling a blood culture	19 (44.2)	22 (47.8)	0.83
Positive rate	9 (20.9)	9 (19.6)	0.85
Pathogens			
Escherichia coli	4 (9.3)	4 (8.7)	0.95
Klebsiella sp.	1 (2.3)	4 (8.7)	0.51
Enterococcus sp.	3 (7.0)	2 (4.3)	0.78
Enterobacter sp.	0 (0.0)	1 (2.2)	0.91
Citrobacter sp.	0 (0.0)	0 (0.0)	0.83
Streptococcus sp.	0 (0.0)	0 (0.0)	0.83
Pseudomonas sp.	0 (0.0)	0 (0.0)	0.83
Anaerobes	1 (2.3)	1 (2.2)	0.91
Other	0 (0.0)	0 (0.0)	0.83
Bile culture, n (%)			
Sampling a bile culture	42 (97.7)	46 (100.0)	0.48
Positive rate	42 (97.7)	46 (100.0)	0.48
Pathogens			
Escherichia coli	16 (37.2)	22 (47.8)	0.39
Klebsiella sp.	12 (27.9)	24 (52.2)	0.03
Enterococcus sp.	32 (74.4)	20 (43.5)	<0.01
Enterobacter sp.	9 (20.9)	3 (6.5)	0.04
Citrobacter sp.	8 (18.6)	8 (17.4)	0.89
Streptococcus sp.	3 (7.0)	7 (15.2)	0.32
Pseudomonas sp.	5 (11.6)	3 (6.5)	0.37
Anaerobes	1 (2.3)	8 (17.4)	0.03
Other	2 (4.7)	8 (17.4)	0.09

derived from the resistant group at the time of AC recurrence, the rate of *Enterococcus* spp. detection was higher than that in bile cultures from the initial AC episode. Consequently, if the duration of antibiotic administration following ERCP during the initial episode of cholangitis exceeds 4 days, the likelihood of encountering *Enterococcus* spp. upon recurrence tends to be higher, compared with the cases where the administration period is only ≤3 days. However, the number of patients in whom *Enterococcus* spp. was one of the treatment-resistant pathogens was insufficient for multivariate analysis; therefore, a detailed study of *Enterococcus* spp. was not possible.

One major limitation of this study is its single-center, retrospective nature, which led to insufficient adjustment for confounding factors. For example, the PIPC/TAZ use rate was higher in the susceptible group. Based on the multivariate analysis, PIPC/TAZ use was associated with a lower likelihood of resistant bacterial development. However, the risk of bacterial resistance related to the use of other antimicrobials has not been examined; to the best of our knowledge, no study has reported the

▶ **Table 8** Clinical features associated with second hospitalization.

	Resistant group n = 43	Susceptible group n = 46	*P* value
Duration to AC recurrence, median weeks (IQR)	16.0 (6.0, 40.5)	20.0 (8.0, 51.5)	0.63
Bile duct stent placement from initial admission to second admission	28 (65.1)	30 (65.2)	> 0.99
History of antimicrobial administration from the initial onset to the recurrence of cholangitis, n (%)	14 (32.6)	9 (19.6)	0.23
Mechanisms of resistance to initial antimicrobials*, n (%)			
Microbial substitution	39 (90.7)		
The same bacteria as before resistance developed	6 (14.0)		
Cases in which the antimicrobials used during the second admission were effective, n (%)	5 (11.6)	35 (76.1)	< 0.01
Technical success of ERCP, n (%)	42/42† (100.0)	46/46 (100.0)	1
In-hospital mortality due to cholangitis, n (%)	1 (2.3)	0 (0.0)	0.48
Duration of hospitalization, median days (IQR)	8.0 (5.5, 13.5)	6.5 (5.0, 9.0)	0.21

*One case overlapped.
†One patient did not undergo ERCP as he was in the terminal stage of cholangiocarcinoma.
AC, acute cholangitis; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range.

▶ **Table 9** Multivariate analysis of the risk factors for the development of bacterial resistance.

	Resistant group n = 43	Susceptible group n = 46	Odds ratio	Confidence interval	*P* value
Regular use of PPI, n (%)	20 (46.5)	21 (45.7)	1.64	0.56–4.77	0.36
First ERCP in their life, n (%)	21 (48.8)	13 (28.3)	1.12	0.18–6.92	0.91
EST performed during initial hospitalization, n (%)	16 (37.2)	10 (21.7)	1.04	0.15–7.02	0.97
History of antimicrobial administration from the initial onset to the recurrence of cholangitis, n (%)	14 (32.6)	9 (19.6)	2.54	0.74–8.78	0.14
Antibiotics completed within 3 days after ERCP, n (%)	4 (9.3)	14 (30.4)	0.17	0.04–0.65	0.01
Piperacillin/tazobactam used on initial admission, n (%)	5 (11.6)	24 (52.2)	0.09	0.02–0.33	<0.01

ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; PPI, proton pump inhibitor

difference in the incidence of resistant bacteria associated with PIPC/TAZ use. A difference in the incidence of resistant bacteria depending on the type of antimicrobial agent used is possible [19, 36]; however, several studies that compared antibiotics head to head found no evidence that the type of antibiotic contributed to the development of bacterial resistance [37]. Furthermore, although we confirmed that the patients were receiving regular PPI prescriptions at the time of admission, we were unable to accurately assess the impact of PPI due to the lack of data on the treatment duration or adherence prior to admission. Therefore, a multicenter prospective study is needed to validate the results of this study, a plan for which is in development.

Second, this study exceeded the commonly advised limit of one-tenth of the event count for the number of independent variables included in the multivariate analysis, as stipulated by the events per variable (EPV) rule. Specifically, our model incorporated six independent variables against an event count of 43. This deviation from the EPV rule potentially increases the risk of overfitting, which might lead to biased estimates and may affect the generalizability and reliability of the findings. Despite this limitation, we explored the complex relationships among the variables and to gain preliminary insights. Future studies with a larger event count are warranted to validate our findings.

Conclusions

In conclusion, the administration of antimicrobials within 3 days after ERCP may suppress the development of resistant bacteria in patients with AC. Furthermore, in cases of AC requiring more than 4 days of antimicrobial therapy, the possibility of *Enterococcus* spp. as the causative organism at the time of recurrence should be considered. In addition, in alignment with the reports of previous studies on other infectious diseases, clinicians treating cholangitis should avoid the unnecessary use of antimicrobial agents.

Although the current international guideline, TG18, recommends a standard post-ERCP antimicrobial therapy period of 4 to 7 days, several recent studies have shown that clinical outcomes are not inferior when the duration of therapy is 1 to 3 days. The present study is significant in that it presents the possibility that an antimicrobial treatment duration of 3 days or less after ERCP may reduce the risk of the development of resistant pathogens.

Conflict of Interest

The authors declare that they have no conflict of interest.

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