

Antimicrobial therapy of 3 days or less is sufficient after successful ERCP for acute cholangitis

United European Gastroenterology Journal

2020, Vol. 8(4) 481–488

© Author(s) 2020



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/2050640620915016

journals.sagepub.com/home/ueg



Sylke Haal^{1,2}, Britt ten Böhmer¹, Sebastiaan Balkema³,
Annekatrien CTM Depla⁴, Paul Fockens¹, Jeroen M Jansen⁵,
Sjoerd D Kuiken⁵, Boris I Liberov⁶, Ellert van Soest⁷,
Jeanin E van Hooft¹, Elske Sieswerda⁸ and Rogier P Voermans¹

Abstract

Background: Recommendations for the duration of antimicrobial therapy in cholangitis after successful endoscopic biliary drainage vary. The aim of this study was to compare the occurrence of local infectious complications in patients with acute cholangitis treated with antibiotics for 3 days or less compared with 4 days or more.

Methods: We performed a retrospective multicentre study in seven hospitals in the Netherlands. Patients who received a successful biliary drainage by endoscopic retrograde cholangio-pancreatography because of cholangitis due to common bile duct stones between 2012 and 2017 were included. The primary outcome was the occurrence of a local infectious complication within 3 months of endoscopic retrograde cholangio-pancreatography. Secondary outcomes included *Clostridioides difficile* infection, total length of hospital stay and all-cause mortality.

Results: A total of 426 patients with cholangitis were identified and 296 patients met all inclusion criteria. Therapy duration was ≤ 3 days in 137 patients (46.3%). During follow-up, 41 patients (13.9%) developed a local infectious complication. Occurrence of infectious complications did not differ between the two groups ($p = 0.32$). No patient developed *Clostridioides difficile* infection. Median hospital stay was 6 days (interquartile range 4–8 days) in the short antibiotic group compared with 7 days (interquartile range 5–9 days) in the long group ($p = 0.03$). Four (1.4%) patients died during follow-up, all were treated for ≥ 4 days ($p = 0.13$).

Conclusions: Antimicrobial therapy of 3 days or less seems to be sufficient after successful biliary drainage in patients with acute cholangitis. Randomized trials should confirm our findings.

Keywords

Acute cholangitis, treatment duration, antimicrobial stewardship

Received: 6 January 2020; accepted: 24 February 2020

¹Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology and Metabolism, Amsterdam, Netherlands

²Department of Internal medicine, Spaarne Gasthuis, Hoofddorp, Netherlands

³Department of Gastroenterology, Dijklander Ziekenhuis, Hoorn, Netherlands

⁴Department of Gastroenterology, MC Slotervaart, Amsterdam, Netherlands

⁵Department of Gastroenterology and Hepatology, OLVG, Amsterdam, Netherlands

⁶Department of Internal medicine, Zaans Medisch Centrum, Zaandam, Netherlands

⁷Department of Gastroenterology, Spaarne Gasthuis, Hoofddorp, Netherlands

⁸Department of Medical Microbiology and Infection Control, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Corresponding author:

Sylke Haal, Amsterdam UMC, Location AMC, Meibergdreef 9, Amsterdam, 1105 AZ, Netherlands.

Email: s.haal@amsterdamumc.nl

Key summary

Summarise the established knowledge on this subject

- Acute cholangitis is treated with endoscopic biliary drainage and antimicrobial therapy.
- Optimal duration of antimicrobial therapy is unknown in cholangitis.
- Recommendations regarding the duration of antimicrobial therapy in cholangitis after successful endoscopy biliary drainage vary from 3 to 10 days.

What are the significant and/or new findings of this study?

- Antimicrobial therapy of ≤ 3 days is sufficient after successful biliary drainage.

Introduction

Patients with common bile duct stones (CBD) are at risk of developing acute cholangitis and subsequent sepsis.¹ The combination of biliary drainage by endoscopic retrograde cholangio-pancreatography (ERCP) and antimicrobial therapy is the cornerstone of treatment of acute cholangitis.^{2,3} However, the optimal duration of antimicrobial therapy is unclear, because there is limited research conducted on this matter.⁴⁻⁹ Consensus-based recommendations on antimicrobial treatment duration in current (inter) national guidelines therefore vary from 3 days or less up to 10 days.¹⁰⁻¹³ Unnecessary prolonged antimicrobial therapy increases risk of mortality and side-effects, such as diarrhoea and colitis due to *Clostridioides difficile* infection.^{14,15} Prolonged hospital stay causes an extra financial burden on the healthcare system. In addition, overuse of antibiotics fuels the development of resistance, which is already a major issue worldwide.¹⁶⁻¹⁸ The national sepsis guideline in the Netherlands is most progressive on antimicrobial therapy duration in cholangitis, with a recommended therapy duration of 3 days or less after successful biliary drainage.¹⁹ This recommendation was based on one retrospective study.⁷ International guidelines recommend longer treatment durations.^{10,11,13,20,21} We hypothesized that antimicrobial therapy duration of 3 days or less is sufficient after successful biliary drainage in patients with acute cholangitis. We therefore performed a retrospective multicentre study to compare the occurrence of a local infectious complication in cholangitis patients treated with antibiotics for 3 days or less compared with those treated for 4 days or more. Secondary aims were to compare occurrence of *C. difficile* infection, total length of hospital stay and all-cause mortality.

Methods

Study design

We performed a retrospective multicentre study in seven hospitals in the region of Amsterdam. The study was approved by the Medical Ethics Review Committee of the Amsterdam Medical Center in Amsterdam on 20 March 2017; reference number: W17_100# 17.120. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. For this type of study (retrospective) formal written consent was not required. After approval we identified all patients who underwent an ERCP for cholangitis due to CBD stones between January 2012 and January 2017 from endoscopy databases (Endobase; Olympus Medical System Europe, Hamburg, Germany or HIX; Chipsoft, Amsterdam, Netherlands). Participating centres existed of one tertiary care center, four teaching hospitals, and two non-teaching hospitals. Data regarding infectious complications were retrospectively retrieved from electronic patient records.

Patients

Patients were included if they had suffered from cholangitis due to CBD stones and were over 18 years of age at the time the cholangitis occurred. Cholangitis was defined according to the updated Tokyo Guidelines.²² Treatment had to include successful drainage of the biliary tract by means of an ERCP. Successful drainage was defined by total clearance of stones or successful placement of a biliary stent if not all stones could be removed. Patients could be included multiple times if they suffered from more than one episode of cholangitis with a minimum interval of at least 3 months. Exclusion criteria were any other etiology of

cholangitis than bile duct stones such as primary sclerosing cholangitis, benign or malignant biliary obstruction or biliary stent dysfunction. Patients were also excluded if they suffered from a cholangitis as a result of ERCP, a concomitant cholecystitis, or post-ERCP perforation. Furthermore, patients were excluded if they received percutaneous or surgical drainage, or when they used maintenance antibiotic therapy for any other reason at the time cholangitis was diagnosed. Patients that died within 3 days after initial ERCP or lost to follow-up within 3 months after initial ERCP were excluded as well. The rationale for excluding patients who died within 3 days after initial ERCP is that these patients never had the chance to be treated for more than 3 days.

Data collection

We reviewed the ERCP report and electronic medical records of all potential patients. We collected data on patient demographics, severity of cholangitis according to the Tokyo Guidelines,²² blood culture pathogens, ERCP details, antimicrobial therapy details (type, duration) and the development of infectious complications.

Study outcome

The primary outcome was the occurrence of a local infectious complication. An infectious complication was defined as the need for antibiotics within 3 months after ERCP. We reported results per episode of cholangitis. Local infectious complications included recurrent cholangitis, cholecystitis, liver abscess, infected portal vein thrombosis and other infections that could be related to the primary cholangitis episode. Secondary outcomes included the occurrence of *C. difficile* infection, total length of hospital stay and all-cause mortality within 3 months. Hospital stay was defined as the number of days from the day of admission to the day of discharge or date of death.

Statistical methods

Patients were categorised in two groups according to the duration of antimicrobial therapy (intravenous and/or oral administration) after ERCP: 3 days or less/4 days or more. Descriptive statistics were used to describe the population. Continuous variables with a normal distribution were summarized using means and standard deviations (SD), whereas medians and interquartile ranges (IQR) were used for skewed distributions. Categorical variables were summarized using numbers and percentages. Patient characteristics were

compared using the independent samples *t*-test or Mann Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. The primary outcome was compared using the Chi-squared test. Total length of hospital stay was categorized to short (7 days or less) and long (8 days or more). Univariate logistic regression analysis was used to evaluate associations between potential confounders and primary and secondary outcomes. To adjust for potential confounding, we performed multiple logistic regression analysis including clinically relevant predictors. To obtain stability in our model we planned to have a minimum of 10 events per variable. For all missing values, we planned to run a best-worse-case scenario. A *p* value of 0.05 or smaller was considered to imply statistical significance and all reported *p* values are two-sided. Analyses were performed in SPSS statistics 24.

Results

Study population

A total of 426 patients with cholangitis due to CBD stones were retrieved from local databases by reviewing endoscopy reports; of which 296 patients met study eligibility criteria. Most patients ($n = 123$) were excluded, because the duration of antimicrobial therapy was unknown or because they were lost to follow-up within 3 months after ERCP. Other reasons for exclusion were: concomitant cholecystitis ($n = 3$), death within 3 days after first episode of cholangitis ($n = 2$), post-ERCP perforation ($n = 1$) and the presence of a second infection that extended antimicrobial therapy ($n = 1$). Baseline characteristics of the included study population are summarized in Table 1. The mean age of the study population was 72.7 (SD 14.1) years, 144 (48.6%) patients were male, and most patients (69.6%) suffered from a cholangitis grade II. In 48 patients (16.2%) a stent was placed to achieve adequate drainage during ERCP, due to incomplete removal of gallstones. Seven patients developed a mild post-ERCP pancreatitis; no severe post-ERCP pancreatitis occurred. The short antimicrobial therapy group (≤ 3 days) consisted of 137 patients (46.3%), and the long group (≥ 4 days) of 159 patients (53.7%). There were some differences between the two groups. Patients who received antibiotics for ≥ 4 days more frequently experienced a grade III cholangitis (18 patients (11.3%) vs five patients (3.6%); $p = 0.03$), underwent the ERCP sooner after admission (1 day (IQR 1–2 days) vs 2 days (IQR 1–4 days); $p < 0.01$) and were more likely

Table 1. Baseline characteristics of the study population.

	≤3 days AB n=137 (%)	≥4 days AB n=159 (%)	P value
Age, mean SD	71.4 (15.1)	73.8 (13.0)	0.14
Male gender	67 (48.9)	77 (48.4)	0.94
Relevant comorbidity ^a			
– Diabetes	25 (18.2)	33 (20.8)	0.59
– COPD	16 (11.7)	14 (8.8)	0.41
– Immunodeficiency ^b	1 (0.7)	1 (0.6)	0.92
Previous cholecystectomy, n (%)	32 (23.4)	43 (27.0)	0.47
Tokyo severity score			0.03
– Grade I	36 (26.3)	31 (19.5)	
– Grade II	96 (70.1)	110 (69.2)	
– Grade III	5 (3.6)	18 (11.3)	
Timing ERCP after admission, median in days (IQR)	2 (1–4)	1 (1–2)	<0.01
Papillotomy	126 (92.0)	148 (93.1)	0.72
Stent used to retrieve adequate drainage	20 (14.6)	28 (17.6)	0.48
Positive blood culture ^c	62 (45.3)	98 (61.6)	<0.01
Treatment centre			0.06
– Tertiary care hospital	23 (16.8)	13 (8.2)	
– Teaching hospital	68 (49.6)	93 (58.5)	
– Non-teaching hospital	46 (33.6)	53 (33.3)	

^aEach patient could have multiple comorbidities.

^bImmunodeficiency: drug induced or as the result of an infection with human immunodeficiency virus (HIV).

^cEach blood culture could contain multiple bacteria.

COPD: chronic obstructive pulmonary disease; ERCP: endoscopic retrograde cholangiopancreatography; IQR: interquartile range; AB: antibiotics.

to have a positive blood culture (98 patients (61.6%) vs 62 patients (45.3%); $p < 0.01$).

The five most frequently isolated microorganisms were: *Escherichia coli* (67.5%), *Klebsiella* spp. (24.4%), *Streptococcus* spp. (8.1%), *Enterococcus* spp. (4.4%) and *Enterobacter* spp. (3.8%). In two patients (1.3%) an anaerobic pathogen was found, *Clostridium perfringens* and *Bacteroides fragilis* (Supplemental Table 1). Empirical antibiotic treatment regimens consisted mostly of piperacillin/tazobactam (16.6%), ceftriaxone plus metronidazole (14.2%), amoxicillin/clavulanic acid (14.2%), ceftriaxone plus gentamicin (11.8%), ceftriaxone (11.8%), amoxicillin/clavulanic acid plus gentamicin (11.5%) or amoxicillin/clavulanic acid plus ciprofloxacin (10.8%; Supplemental Table 1). The total median duration of antimicrobial therapy (before and after ERCP) was 4 days (IQR 3–6 days) in the short group and 7 days (IQR 6–10 days) in the long group. After ERCP, the median duration was 4 days (IQR 2–6 days, range 0–20 days) in the total study population, 2 days (IQR 1–3 days) in the short group and 6 days (IQR 4–7 days) in the long group. All patients except for one received antibiotics before ERCP. Patients treated in a tertiary care hospital tend to receive antibiotics for 3 days or less (23 out of 36; 63.9%) more often, compared with patients treated in a teaching hospital (68 out of 161; 42.2%)

and non-teaching hospital (46 out of 99; 46.5%); $p = 0.06$.

Primary outcome: Infectious complications

As demonstrated in Table 2, 41 (13.9%) patients developed a local infectious complication during follow-up. Infectious complications occurred in 16 of 137 patients (11.7%) receiving antibiotics for ≤3 days and in 25 of 159 patients (15.7%) receiving antibiotics for ≥4 days. The occurrence of a local infectious complication did not differ between the two treatment groups ($p = 0.32$). The most common local infection was recurrent cholangitis, which occurred in 28 patients (9.5%). Six patients (2.0%) experienced cholecystitis, two patients (0.7%) developed a liver abscess and two patients (0.7%) an infected portal vein thrombosis. As shown in Table 3, potential confounders (age, gender, relevant comorbidity, previous cholecystectomy, Tokyo severity score, timing of ERCP, papillotomy, stent placement, positive blood culture and treatment centre) were not significantly associated with infectious complications in univariate logistic regression analysis. In multiple logistic regression analysis with adjustment for Tokyo severity score and positive blood culture, antimicrobial therapy duration remained un-associated with the occurrence of an infectious complication (adjusted

Table 2. Primary and secondary outcomes.

	Total	≤3 days AB n=137 (%)	≥4 days AB n=159 (%)	P value
Local infectious complication	41 (13.9)	16 (11.7)	25 (15.7)	0.32
Type of complication				
– Recurrent cholangitis	28 (9.5)	10 (7.3)	18 (11.3)	
– Cholecystitis	6 (2.0)	3 (2.2)	3 (1.9)	
– Liver abscess	2 (0.7)	1 (0.7)	1 (0.6)	
– Infected portal vein thrombosis	2 (0.7)	1 (0.7)	1 (0.6)	
– Other ^a	3 (1.0)	1 (0.7)	2 (1.3)	
<i>Clostridioides difficile</i> infection	0			
Hospital stay, median in days (IQR)	6 (4–9)	6 (4–8)	7 (5–9)	0.03
Hospital stay ≤7 days	186 (62.8)	95 (69.3)	91 (57.2)	0.04
Mortality	4 (1.4)	0	4 (2.5)	0.13

^aOther: infected necrotizing pancreatitis, infected hematoma, spontaneous bacterial peritonitis.

IQR: interquartile range; AB: antibiotics.

Table 3. Association between patient characteristics and local infectious complication.

	No infectious complication n=255 (%)	Infectious complication n=41 (%)	Unadjusted OR (95% CI)	P value
Age, mean SD	72.9 (14)	71.2 (14.5)	0.99 (0.97–1.02)	0.48
Male gender	122 (47.8)	22 (53.7)	1.26 (0.65–2.45)	0.49
Relevant comorbidity ^a				
– Diabetes	49 (19.2)	9 (22)	1.18 (0.53–2.64)	0.68
– COPD	23 (9)	7 (17.1)	2.08 (0.83–5.21)	0.12
– Immunodeficiency ^b	2 (0.8)	0	NA	1
Previous cholecystectomy, n (%)	67 (26.3)	8 (19.5)	0.68 (0.30–1.55)	0.36
Tokyo severity score				0.75
– Grade I	57 (22.4)	10 (24.4)	reference	
– Grade II	177 (69.4)	29 (70.2)	0.93 (0.43–2.03)	
– Grade III	21 (8.2)	2 (4.9)	0.54 (0.11–2.69)	
Timing ERCP after admission, median in days (IQR)	2 (1–3)	2 (1–3)	0.98 (0.83–1.15)	0.79
Papillotomy	236 (92.5)	38 (92.7)	1.02 (0.29–3.61)	0.98
Stent used to retrieve adequate drainage	41 (16.1)	7 (17.1)	1.08 (0.45–2.59)	0.87
Positive blood culture ^c	135 (52.9)	25 (61)	1.39 (0.71–2.73)	0.34
Treatment centre				0.31
– Tertiary care hospital	28 (11)	8 (19.5)	reference	
– Teaching hospital	141 (55.3)	20 (48.8)	0.50 (0.20–1.24)	
– Non-teaching hospital	86 (33.7)	13 (31.7)	0.53 (0.20–1.41)	

^aEach patient could have multiple comorbidities.

^bImmunodeficiency: drug induced or as the result of an infection with human immunodeficiency virus (HIV).

^cEach blood culture could contain multiple bacteria.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; ERCP: endoscopic retrograde cholangiopancreatography; IQR: interquartile range; OR: odds ratio.

odds ratio (aOR) 95% confidence interval (CI) 0.71 (0.36–1.41); Table 4).

Secondary outcomes: *C. difficile* infection, hospital stay and all-cause mortality

No patient developed *C. difficile* infection. As shown in Table 2, median hospital stay was 6 days (IQR 4–8 days)

Table 4. Association between antimicrobial therapy duration and local infectious complication.

	OR (95% CI)	P value
Antimicrobial therapy duration (≤3 days vs ≥4 days)		
Unadjusted	0.71 (0.36–1.39)	0.32
Adjusted ^a	0.71 (0.36–1.41)	0.33

^aAdjusted for Tokyo severity score and positive blood culture.

CI: confidence interval; OR: odds ratio.

Table 5. Association between patient characteristics and hospital stay.

	Hospital stay ≤7 days <i>n</i> =186 (%)	Hospital stay ≥8 days <i>n</i> =109 (%)	Unadjusted OR (95% CI)	<i>P</i> value
Age, mean SD	69.8 (15.3)	77.5 (10)	0.95 (0.93–0.97)	<0.01
Male gender	95 (51.1)	48 (44)	1.33 (0.83–2.13)	0.24
Relevant comorbidity ^a				
– Diabetes	37 (19.9)	21 (19.3)	1.04 (0.57–1.89)	0.90
– COPD	18 (9.7)	12 (11)	0.87 (0.40–1.87)	0.72
– Immunodeficiency ^b	1 (0.5)	1 (0.9)	0.58 (0.04–9.42)	0.71
Previous cholecystectomy, <i>n</i> (%)	49 (26.3)	26 (23.9)	1.14 (0.66–1.98)	0.64
Tokyo severity score				0.08
– Grade I	48 (25.8)	19 (17.4)	reference	
– Grade II	128 (68.8)	78 (71.6)	0.65 (0.36–1.19)	
– Grade III	10 (5.4)	12 (11)	0.33 (0.12–0.89)	
Timing ERCP after admission, median in days (IQR)	1 (1–2)	3 (1–5)	0.65 (0.56–0.76)	<0.01
Papillotomy	175 (94.1)	98 (89.9)	1.79 (0.75–4.27)	0.19
Stent used to retrieve adequate drainage	26 (14)	22 (20.2)	0.64 (0.34–1.20)	0.17
Positive blood culture ^c	87 (46.8)	72 (66.1)	0.45 (0.28–0.74)	<0.01
Treatment centre				<0.01
– Tertiary care hospital	29 (15.6)	7 (6.4)	reference	
– Teaching hospital	112 (60.2)	49 (45)	0.55 (0.23–1.35)	
– Non-teaching hospital	45 (24.2)	53 (48.6)	0.21 (0.08–0.51)	

^aEach patient could have multiple comorbidities.

^bImmunodeficiency: drug induced or as the result of an infection with human immunodeficiency virus (HIV).

^cEach blood culture could contain multiple bacteria.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; ERCP: endoscopic retrograde cholangiopancreatography; IQR: interquartile range; OR: odds ratio.

in the short antibiotic group compared with 7 days (IQR 5–9 days) in the long antibiotic group ($p = 0.03$). In the short antibiotic group, more patients were discharged within 7 days (95 patients (69.3%) vs 91 patients (57.2%); $p = 0.04$). The results of the univariate logistic regression analysis are shown in Table 5. Younger age, early timing of ERCP, the lack of a positive blood culture and treatment centre were significantly associated with a short hospital stay (≤ 7 days). In multiple logistic regression analysis with adjustment for age, Tokyo severity score, timing ERCP, positive blood culture and treatment centre, short antimicrobial therapy duration (≤ 3 days) remained associated with a short hospital stay (aOR (95% CI) 2.48 (1.33–4.62); Table 6). Four (1.4%) patients died during follow-up, all were treated for 4 days or more; $p = 0.13$ (Table 2). Only one of them had developed an infectious complication.

Discussion

In this retrospective multicentre study, we did not observe a difference in the occurrence of infectious complications in patients with acute cholangitis treated with antibiotics for 3 days or less compared with 4 days or more. Furthermore, a shorter therapy duration was

Table 6. Association between antimicrobial therapy duration and short hospital stay.

	OR (95% CI)	<i>P</i> value
Antimicrobial therapy duration (≤ 3 days vs ≥ 4 days)		
Unadjusted	1.67 (1.03–2.69)	0.038
Adjusted ^a	2.48 (1.33–4.62)	0.004

^aAdjusted for age, Tokyo severity score, timing ERCP, positive blood culture, treatment center.

CI: confidence interval; ERCP: endoscopic retrograde cholangiopancreatography; OR: odds ratio.

associated with shorter hospitalization and did not seem to affect all-cause mortality.

Our results are in line with earlier published work.^{4,7} Van Lent et al. also suggested that 3 days of antibiotics after ERCP would be sufficient. In their retrospective study ($n = 80$), including all aetiologies of cholangitis, such as primary sclerosing cholangitis and stent obstruction in hilar obstructions, the overall rate of recurrent cholangitis was 24%. The percentage of patients with an episode of recurrent cholangitis was not statistically different among patients with a short (≤ 3 days), medium (4–5 days) or long (> 5 days) course of antibiotics. Kogure et al. performed a small prospective study ($n = 18$) in which they investigated a fever-based

approach for the treatment of acute cholangitis. Administration of antibiotics was stopped, when the body temperature of $<37^{\circ}\text{C}$ was maintained for 24 hours. This approach resulted in a median therapy duration of 3 days. The authors suggested that this approach is safe and effective because no infectious complications occurred during follow-up of 4 weeks. Furthermore, shorter antimicrobial treatment duration is also indirectly supported by randomized controlled trials in general (non-cholangitis) intra-abdominal infections, which showed that shorter therapy duration after adequate source control is feasible and safe.^{20,21,23}

Our study is the largest and first multicentre study that supports that 3 days of antibiotics might be sufficient to treat cholangitis patients after adequate drainage. Moreover, we are the first to include a homogenous study population only including the far most common etiology of cholangitis. Furthermore, the percentage of missing data was low. We only had to deal with 40 missing values of the variable ‘blood culture’. We reported the results of the best-case scenario, in which all missing blood cultures were considered negative.

Our study showed that more than half of patients with cholangitis and successful drainage in several Dutch hospitals are treated with antibiotics for more than 3 days. The motivation for the deviation of our national guidelines was not available in the majority of cases. It is likely that the wide range of therapy duration was at least partially based on the different recommendations of (inter)national guidelines, ranging from a 4–10 day course of antibiotics after successful drainage. A positive blood culture seemed to influence the decision of the clinician to continue antibiotics for more than 3 days after successful drainage was achieved, as did the severity of the infection. However, in our study, positive blood culture as well as severity of cholangitis were not associated with the development of an infectious complication.

The above-mentioned results should be interpreted taking into account some uncertainties. First, the main reason for exclusion was unknown antimicrobial therapy duration and lack of follow-up of at least 3 months. This may have led to selection bias and potential overestimation of infectious complications, assuming patients lost to follow-up more frequently had an uncomplicated course of cholangitis. Another limitation is that our retrospective data indicated that confounding by indication was present; that is, more severely sick patients, demonstrated by Tokyo grade III cholangitis and/or positive blood culture, received a longer course of antibiotics. However, as mentioned earlier, both factors were not associated with the development of an infectious complication, nor were other patient characteristics. In addition, we were not able to adjust our analyses for adequacy of empirical therapy, which could have led to

misclassification of the intervention. We also lacked information about the timing of the development of the infection. Another important limitation is that the multiple logistic regression analysis of the primary outcome resulted in a wide confidence interval. This means we lacked the power to fully exclude a higher risk on infectious complications after a short antimicrobial treatment. Therefore, prospective studies are needed to confirm our results. Furthermore, we have limited the study population to patients who suffered from cholangitis due to CBD stones and received adequate source control. To improve internal validity, it was a conscious choice to include a homogeneous group of patients, even though it reduced the generalizability of our results in view of other, less common aetiologies of cholangitis. In addition, all-cause mortality was rare and only 1.4%. This finding is probably the result of the relatively low number of grade III cholangitis patients included in our study, which also reduces the generalizability of our results. Finally, it remains unclear whether a local infectious complication is the result of ongoing underlying disease/inadequate source control, rather than insufficient treatment with antimicrobial therapy. Given the high number of patients, we expect that these patients, if present, are equally distributed over both groups.

Conclusion

This study indicates that antimicrobial therapy of 3 days or less is sufficient after successful drainage of the biliary tract in patients with acute cholangitis due to CBD stones. Prospective studies are needed to confirm our results to ensure evidence-based and harmonized guideline recommendations on antimicrobial therapy duration in cholangitis patients. This could ultimately lead to a large decrease in unnecessary antibiotic administration, hospital stay and associated adverse events.

Declaration of conflicting interests

The authors declared no potential conflicts of interest for the research, authorship, and/or publication of this article.

Ethics Approval

The study was approved by the Medical Ethics Review Committee of the Amsterdam Medical Center in Amsterdam on March 20, 2017; reference number: W17_100# 17.120. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution’s human research committee.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent

For this type of study (retrospective) formal written consent was not required.

References

- Kimura Y, Takada T, Strasberg SM et al. TG13 current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci* 2013; 20(1): 8–23.
- Miura F, Okamoto K, Takada T et al. Tokyo Guidelines 2018: Initial management of acute biliary infection and flowchart for acute cholangitis. *J Hepatobiliary Pancreat Sci* 2018; 25(1): 31–40.
- van den Hazel SJ, Speelman P, Tytgat GN et al. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. *Clin Infect Dis* 1994; 19(2): 279–286.
- Kogure H, Tsujino T, Yamamoto K et al. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. *J Gastroenterol* 2011; 46(12): 1411–1417.
- Park TY, Choi JS, Song TJ et al. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. *Digestive Dis Sci* 2014; 59(11): 2790–2796.
- Uno S, Hase R, Kobayashi M et al. Short-course antimicrobial treatment for acute cholangitis with Gram-negative bacillary bacteremia. *Int J Infect Dis* 2017; 55: 81–85.
- van Lent AU, Bartelsman JF, Tytgat GN et al. Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract. *Gastrointest Endosc* 2002; 55(4): 518–522.
- Doi A, Morimoto T, Iwata K. Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: A retrospective cohort study. *Clinical Microbiol Infect* 2018; 24(11): 1184–1189.
- Tinusz B, Szapary L, Paladi B et al. Short-course antibiotic treatment is not inferior to a long-course one in acute cholangitis: A systematic review. *Digestive Dis Sci* 2019; 64(2): 307–315.
- Gomi H, Solomkin JS, Schlossberg D et al. Tokyo Guidelines 2018: Antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci* 2018; 25(1): 3–16.
- Mazuski JE, Tessier JM, May AK et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surgical Infect* 2017; 18(1): 1–76.
- Rhodes A, Evans LE, Alhazzani W et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017; 43(3): 304–377.
- Solomkin JS, Mazuski JE, Bradley JS et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50(2): 133–164.
- Riccio LM, Popovsky KA, Hranjec T et al. Association of excessive duration of antibiotic therapy for intra-abdominal infection with subsequent extra-abdominal infection and death: A study of 2,552 consecutive infections. *Surgical Infect* 2014; 15(4): 417–424.
- Tamma PD, Avdic E, Li DX et al. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Int Med* 2017; 177(9): 1308–1315.
- Bell BG, Schellevis F, Stobberingh E et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014; 14: 13.
- Marston HD, Dixon DM, Knisely JM et al. Antimicrobial resistance. *JAMA* 2016; 316(11): 1193–1204.
- Sartelli M, Weber DG, Ruppe E et al. Antimicrobials: A global alliance for optimizing their rational use in intra-abdominal infections (AGORA). *WJES* 2016; 11: 33.
- Dutch Working Party on Antibiotic Policy (SWAB). SWAB guidelines for: Antibacterial therapy of adult patients with Sepsis. Available at: [https://www.swab.nl/swab/cms3.nsf/uploads/65FB380648516FF2C125780F002C39E2/\\$FILE/swab_sepsis_guideline_december_2010.pdf](https://www.swab.nl/swab/cms3.nsf/uploads/65FB380648516FF2C125780F002C39E2/$FILE/swab_sepsis_guideline_december_2010.pdf). (2010, accessed March 2017).
- Rattan R, Allen CJ, Sawyer RG et al. Patients with complicated intra-abdominal infection presenting with sepsis do not require longer duration of antimicrobial therapy. *J Am Coll Surg* 2016; 222(4): 440–446.
- Sawyer RG, Claridge JA, Nathens AB et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *New England J Med* 2015; 372(21): 1996–2005.
- Kiryama S, Kozaka K, Takada T et al. Tokyo Guidelines 2018: Diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2018; 25(1): 17–30.
- Hassinger TE, Guidry CA, Rotstein OD et al. Longer-duration antimicrobial therapy does not prevent treatment failure in high-risk patients with complicated intra-abdominal infections. *Surgical Infect* 2017; 18(6): 659–663.