ORIGINAL ARTICLE

TRANSPLANT INFECTIOUS DISEASE

Comparison of short-course antibiotic therapy of 6 or less days with a longer treatment in patients with cholangitis after liver transplantation

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Abstract

Objectives: Stenosis of the biliary anastomosis predisposes liver graft recipients to bacterial cholangitis. Antibiotic therapy (AT) is performed according to individual clinical judgment, but duration of AT remains unclear.

Methods: All liver graft recipients with acute cholangitis according to the Tokyo criteria grade 1 and 2 after endoscopic retrograde cholangiography (ERC) were included. Outcome of patients treated with short AT (<7 days) was compared to long AT (>6 days). Recurrent cholangitis (RC) within 28 days was the primary end point.

Results: In total, 30 patients were included with a median of 313 (range 34–9849) days after liver transplantation until first proven cholangitis. Among 62 cases in total, 51/62 (82%) were graded as Tokyo-1 and 11/62 (18%) as Tokyo-2. Overall median duration of AT was 6 days (1–14) with 36 cases (58%) receiving short AT and 26 (42%) receiving long AT. RC was observed in 10 (16%) cases, without significant difference in occurrence of RC in short versus long AT cases. CRP and bilirubin were significantly higher in patients with long AT, while low serum albumin and low platelets were associated with risk of RC.

Conclusion: A shorter antibiotic course than 7 days shows good results in selected, ERC-treated patients for post-transplantation biliary strictures.

KEYWORDS
biliary stricture, liver transplantation, multidrug resistance, recurrent cholangitis, short-course antibiotic therapy

1 | INTRODUCTION

Bacterial cholangitis is a common complication after liver transplantation (LT). It is mostly caused by an impaired flow of the bile into the intestine, which leads to stasis and, consequently, infection of the common bile duct and the biliary system.[1] Two forms of biliary stenosis facilitating stasis can be distinguished. On the one hand, biliary anastomosis stenosis (BAS) is a defined stricture of the extrahepatic bile duct. On the other hand, nonanastomotic biliary stricture may appear as uni- or multifocal destruction of the biliary tree, most often due to intermitting ischemia. This is therefore commonly termed ischemic-type biliary lesion (ITBL), leading to intrahepatic as well as extrahepatic strictures.[2,3] Both forms may aggravate over time and facilitate cholangitis during long-term LT aftercare.[4]

Ensuring sufficient flow of the infected bile is mandatory. This is usually performed via internal drainage using endoscopic retrograde cholangiography (ERC) and most often including plastic stent insertion, and possibly balloon dilation in few cases.[1,5] To resolve the infection, the second therapeutic cornerstone is adequate antibiotic therapy (AT). Selection of antibiotics depends on the expected range of pathogens, that is, mostly *Enterobacteriaceae*.[1,6] While risk factors for the occurrence of BAS and ITBL have been well established, less is known about recurrent cholangitis (RC).[4,5] In line with this lack of reliable clinical data, optimal duration of AT in LT recipients with cholangitis is unclear to date. The previous standard of duration for non-LT patients had been at least 7 days, and extension to 14 days had been recommended in case of Gram-positive bacteremia.[7] Moreover, there are no data on whether AT should be extended in immunosuppressed individuals. Recent studies assessing the length of AT, however, suggested that much shorter courses of antibiotics such as three to 4 days are feasible and safe.[8–10] Moreover, brevity of AT is of high importance in order to avoid occurrence of multidrug-resistant organisms (MDROs) in this vulnerable population.[11] However, due to immunosuppression in LT recipients, one must be careful not to over-shorten AT. In this context, the aim of the current study was to assess the feasibility of short AT up to 6 days in comparison with AT of 7 or more days.

2 | PATIENTS AND METHODS

2.1 | Data curation

This is a retrospective study including all patients admitted to a tertiary German liver transplant center between 2008 and 2019. Screening was performed in an endoscopic database containing all ERC cases between 2008 and 2018 (Figure 1). The follow-up period ended by December 31, 2019. Cases of cholangitis were screened by searching for the German terms *pus, putrid(e), eiter, eitrig(e)*, and/or turbid bile and/or fluoroscopic evidence of cholestasis and/or endoscopic diagnosis of cholangitis within all ERC reports. From these results, cases fulfilling the according laboratory Tokyo criteria for cholestasis and systemic inflammation were retrieved.[6] Ultimately, cases which were not classifiable as cholangitis according to the judgment of two
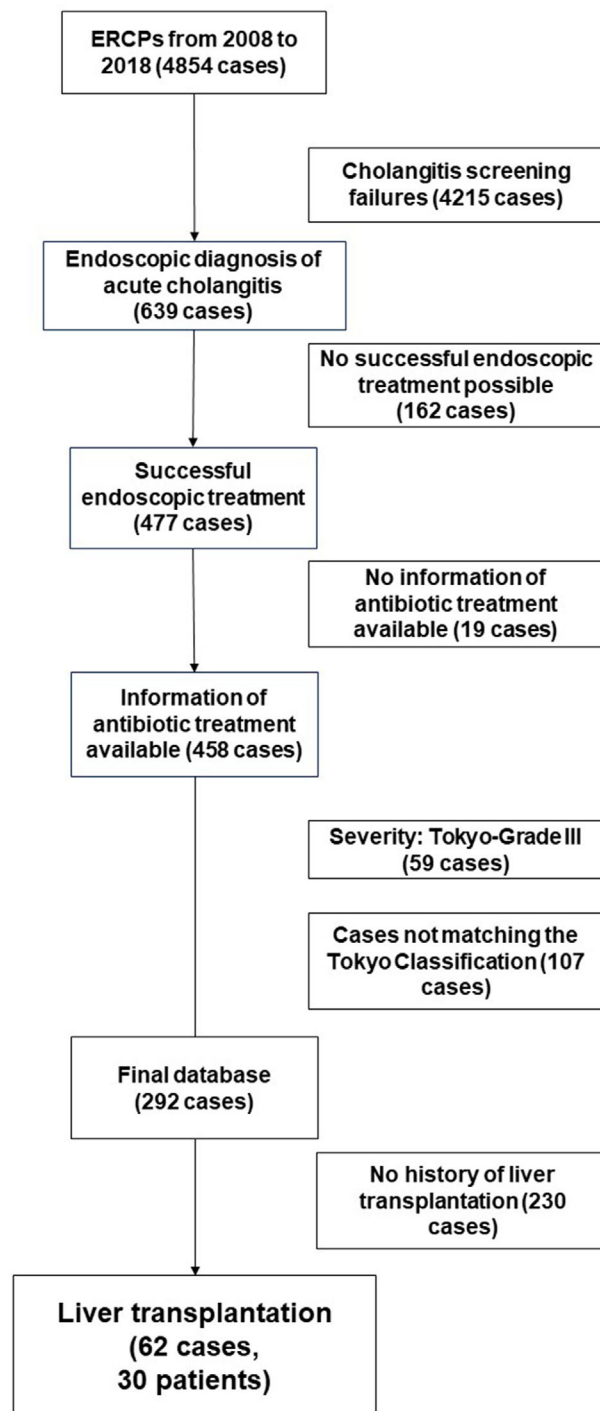

FIGURE 1 Flowchart of the screening and enrollment algorithm for the present study

independent investigators were manually removed. Then, electronic charts of patients with proven acute cholangitis were evaluated, including biometrical, clinical, and microbiological data as well as ATs. Due to homogeneity of the cohort, patients treated with percutaneous drainage were not included. Moreover, patients with infectious foci that may not be easily sanitized—such as liver abscesses or permanent biliary leakage—were not considered for the present study (Figure 1).

The database was anonymized throughout, and ethical approval was obtained prior study initiation (file number 74/19).

2.2 | Case definition and clinical endpoint

Inclusion criteria for the present study were (A) history of LT, (B) age of 18 or more years, and (C) presence of cholangitis of grade 1 or 2, according to the Tokyo criteria.[1,6] Cases with grade 3 cholangitis were excluded since these patients may be septic and therefore often require longer AT. Moreover, they have a higher risk of developing additional sources of infection, which likely prolongs AT in cholangitis. The Tokyo criteria have defined cholangitis as an acute bacterial infection of the biliary tree stemming from biliary stasis, resulting in all of the following three: (1) abnormal imaging (cholestasis or evidence of common bile duct obstacle, such as stone, cast, stent etc.); (2) jaundice and/or elevated liver enzymes (ALT, AP, AST, GGT, and/or bilirubin; Table 2); and (3) systemic inflammation (fever and/or shaking/chills and/or increased c-reactive protein [CRP] and/or leukocytes). Tokyo grade 1 is a mild cholangitis not fulfilling criteria of grade 2 (at least two criteria of: Leukocytosis > 12/L or < 4/L; Fever > 39°C; Age > 75y; Bilirubin > 5 mg/dl; Albumin < 2,5 mg/dl) or grade 3 (cholangitis with organ dysfunction of at least one organ: need of catecholamines; clouding of consciousness; pulmonary failure; renal failure; hepatic failure; failure of coagulation). Laboratory findings were assessed at the day of presentation. Only patients with definite diagnosis of cholangitis (fulfilling all three criteria) were included to minimize the risk of including "false positive" cases. Due to missing data in the majority of cases, procalcitonin was not included in the analysis. Duration of AT was assessed starting the day of ERC, which was considered the time point of adequate drainage, and duration of AT before ERC was delineated separately. All cases receiving antibiotics for up to 6 days were defined as short-course antibiotics (short AT, SAT), and all cases with longer duration of therapy were defined as long-course (long AT, LAT). A 6-day cut-off was chosen based upon the existing evidence in patients with cholangitis without immunosuppression.[10] Duration of sequential oral treatment was included in the treatment duration. The switch to oral treatment was based on the expertise of the treating physician.

Primary end point of the study was occurrence of RC, which was defined as an episode of cholangitis within 28 days after a previous episode of cholangitis. To minimize inclusion of patients with cholangitis due to occlusion of a stent, we did not assess RC later than 28 days. MDROs were defined as multidrug-resistant Gram-negative bacteria (MDRGN) or Vancomycin-resistant enterococci (VRE), as proposed by the current nomenclature earlier.[12] In particular, MDRGN are defined as *Enterobacterales* with extended spectrum beta-lactamase phenotype as well as *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* resistant against Piperacillin, any 3rd/4th generation cephalosporin, and fluoroquinolones.

2.3 | Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were presented as medians with ranges, or as means with interquartile ranges, as appropriate. The Wilcoxon–Mann-Whitney-*U*-test and the chi-Square-test were used for comparisons at baseline. Independent risk factors for RC were calculated using uni- and multivariate Cox-regression with a generalized estimating equation approach, which accounts for correlations arising of multiple events on the same patient. Results were expressed as log-hazard ratios (log-HR) with 95%-confidence intervals. Time to RC in days was used as time-dependent variable. Importantly, survival was not an end point in the current study. All tests were two-sided, and a *p*-value ≤ .05 was considered as significant. Statistical analysis was conducted using R version 4.0.4 (R Core Team (2021), R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study population

In the present study, 30 individuals with biliary stricture following LT were included, with BAS being the underlying pathology in 23/30 (77%) patients and ITBL in 7/30 (23%) patients. Among these patients, altogether 62 cases of acute cholangitis according to the Tokyo criteria were included (Figure 1). Thereof, 60/62 (97%) had been considered as clinically significant and required AT. The median time from LT to cholangitis was 313 (range 34–9849) days. Mean age was 52 years, 77% of the patients were male. The majority of the patients had an end-to-end anastomosis (57%). BAS and ITBL were the underlying biliary pathologies in 23 (77%) and seven (23%) patients, respectively. Fifty-one (82%) cases were graded as Tokyo-1 and 11 (18%) as Tokyo-2. Clinical characteristics are shown in Table 1.

3.2 | Index and secondary episodes

We then compared first, that is, index episodes of cholangitis, with consecutive episodes, regarding to Tokyo grading, baseline systemic inflammation and bilirubin, and likelihood of RC. Index and consecutive episodes were comparable in all these terms, meaning that no difference in severity and treatment success could be detected (*p* > .1). Median (minimum, maximum) duration from discharge to RC was 11 (5, 17) days.

3.3 | Treatment of cholangitis

Mean time from hospital admission to ERC was 22.5 h, and stenting was performed in 58/62 (94%) instances. In the majority of cases, two stents were placed (*n* = 27 cases), followed by one (*n* = 14), three (*n* = 11), and four stents (*n* = 6; Table 2). Antibiotics were administered periprocedurally (i.e., before, during, or immediately after ERC), however 12 patients had received antibiotics at least 1 day prior ERC. Overall median duration of AT was 6 (range 1–14) days in the entire cohort (Figure 2A). SAT was administered in 36 (58%) cases with a median duration of 5 days (range 1–6), and LAT in 26 cases

TABLE 1 Baseline characteristics of the 30 patients included

Characteristics at liver transplant (n = 30)	
Age at LT (years)	52 ± 10.1
Male sex	23 (77%)
MELD score	16.8 ± 8.7
Type of biliary anastomosis	
End-to-end	17 (57%)
Side-to-side	8 (27%)
Not otherwise specified	5 (17%)
Biliary pathology	
Biliary anastomosis stenosis	23 (77%)
Ischemic-type biliary lesion	7 (23%)
Etiology of liver disease before liver transplant*	
Alcohol	4 (13%)
Autoimmune hepatitis	2 (7%)
Cryptogenic cirrhosis	2 (7%)
Hepatitis B+D	6 (20%)
Hepatitis C	13 (43%)
Others**	3 (13%)
*Thereof with hepatocellular carcinoma****	7 (23%)
Comorbidities	
Arterial hypertension	15 (50%)
Chronic kidney disease	14 (47%)
Coronary artery disease	5 (17%)
Diabetes mellitus	11 (37%)

Note: Categorical variables are given in absolute numbers (percentages), and numerical variables are given in mean ± standard deviation.

Abbreviations: LT, liver transplantation; MELD score, model of end-stage liver disease score.

*All 30 patients were transplanted due to liver cirrhosis.

**Other underlying diseases comprised one case patient each with hepatitis B, nonalcoholic steatohepatitis, primary biliary cirrhosis, and noncirrhotic HBV-associated HCC, respectively.

***Among six patients with HCC, Hepatitis C was the underlying disease in three patients, Hepatitis B in two patients, and alcohol and Hepatitis B+D was present in one patient, respectively.

(42%), with a median AT of 8 days (range 7–14). Of note, baseline CRP and total bilirubin were significantly higher in patients with LAT (Table 2). In patients with BAS, mean AT was slightly longer than in ITBL patients (6.4 ± 2.96 vs. 4.9 ± 1.93 days, p = .058; Figure 2B). Carbapenems (n = 20/62, 32%), fluoroquinolones (n = 18, 29%), piperacillin/tazobactam (n = 14, 23%), and cephalosporines (n = 10, 16%) were classes of initially administered AT, and duration of therapy did not differ between these types of antibiotics. In two cases, a carbapenem was combined with a fluoroquinolone. Adjustment of AT was necessary in 4/62 (6%) cases. AT could be switched to oral administration in 29/62 cases (47%) to facilitate earlier discharge.

3.4 | Microbiological testing

Blood cultures were taken in 27 cases (44%). The majority of cultures (24/27, 89%) was sterile. Two blood cultures (7%) were positive for Gram-negative bacteria, and one was polymicrobial (4%). Colonization with MDRO was present in six patients with cholangitis. Among those, MDRGN were the predominant pathogen (17 cases, 27%), and five cases (8%) were positive for VRE. Remarkably, all cases with VRE were also positive for MDRGN (Table S2).

3.5 | Recurrent Cholangitis

In total, RC was observed in 10/62 cases (16%), of whom 5/36 (14%) were in the SAT and 5/26 (19%) in the LAT group (p > .2). Two cases with RC (20%) arose from ITBL and eight cases from BAS (80 %; p > .2). Median AT was 6.5 days (range 4–14) in cases developing RC as opposed to 6 days (range 1–11) in cases without subsequent RC (p > .2). None of the patients with positive blood cultures developed RC. Among the four patients in whom adjustment of AT was necessary, one developed RC in the further course. Inter-

TABLE 2 Clinical characteristics of cholangitis cases grouped by duration of antibiotic therapy. Numerical variables are represented by mean values ± SD

	Cholangitis episodes in 30 patients			
	All (n = 62)	Short AT ≤ 6d (n = 36)	Long AT ≥d 7 (n = 26)	p-Value
Age, mean ± SD	55.5 ± 9.93	53.9 ± 11.2	57.7 ± 7.5	>.2
Sex, male, n (%)	50 (80.7)	28 (80.00)	22 (81.5)	>.2
Severity, n (%)				
Tokyo Grade I	51 (82.3)	29 (80.6)	22 (84.6)	>.2
Tokyo Grade II	11 (17.7)	7 (19.4)	4 (15.4)	>.2
Body temperature (°C)	37.8 ± 1.11	37.6 ± 1.15	38.0 ± 1.03	>.2
Leucocytes/ml	6.2 ± 3.3	5.6 ± 2.8	7.0 ± 3.9	>.2
Thrombocytes/μl	150 ± 87	149 ± 99	152 ± 70	>.2
CRP (mg/dl; ULN = 0.5)	5.4 ± 5.0	4.2 ± 4.0	6.9 ± 5.6	.007
Creatinine (mg/dl)	1.61 ± 1.06	1.79 ± 1.30	1.37 ± 0.54	>.2
International normalized ratio (INR)	1.22 ± 0.26	1.18 ± 0.17	1.28 ± 0.35	>.2
Total bilirubin (mg/dl; ULN = 1.4)	2.8 ± 4.1	2.2 ± 4.1	3.7 ± 4.0	.0418
Albumin (g/dl)	5.5 ± 0.6	5.8 ± 0.6	5.0 ± 0.5	>.2
Alkaline phosphatase (U/l)	354 ± 483	357 ± 585	349 ± 291	>.2
gamma-Glutamyltransferase (U/l)	486 ± 566	470 ± 567	507 ± 576	>.2
Aspartate-aminotransferase (U/l)	74 ± 86	77 ± 84	70 ± 90	>.2
Alanine-aminotransferase (U/l)	67 ± 73	76 ± 87	57 ± 48	>.2
Time from admission to ERC (h)	22.5 ± 34.8	18.5 ± 28.3	27.6 ± 41.9	>.2
Stent obstruction, n (%)	18 (29.0)	9 (25.0)	9 (34.6)	>.2
ERC				
Papillotomy, n (%)	1 (1.61)	0 (0.00)	1 (3.8)	>.2
Stenting, n (%)	58 (93.5)	33 (94.2)	25 (92.6)	>.2
Balloon dilatation, n (%)	1 (1.6)	1 (2.8)	0	>.2
Stent material (new stent)				
Plastic, n (%)	57 (91.9)	33 (91.2)	24 (92.3)	>.2
Metal, n (%)	1 (1.6)	0	1 (3.8)	n/a
Antibiotics				
Piperacillin/Tazobactam, n (%)	14 (22.6)	6 (16.7)	8 (30.8)	>.2
Cephalosporin, n (%)	10 (16.1)	6 (16.7)	4 (15.4)	>.2
Carbapenem, n (%)	20 (32.3)	11 (30.6)	9 (34.6)	>.2
Fluoroquinolone, n (%)	18 (29.0)	11 (30.6)	7 (26.9)	>.2
Metronidazole, n (%)	4 (6.4)	1 (2.8)	3 (11.5)	>.2
Vancomycin/ Teicoplanin/ Tigecycline/ Linezolid, n (%)	8 (12.9)	4 (11.1)	4 (15.4)	>.2
Recurrent cholangitis within 28 days, n (%)	10 (16.1)	5 (13.9)	5 (19.2)	>.2

Abbreviations: CRP, creative protein; SD, standard deviation; ULN, upper limit of normal.

estingly, five (50%) of RC cases had previously been treated with a carbapenem. Importantly, all 62 cases could be discharged, resulting in a survival rate of 100%. Low serum albumin (HR = 0.06, $p < .0001$) and low thrombocytes (HR = 0.98, $p = .012$) were independent risk factors for RC. MDRO colonization, however, was equally distributed across both groups and did not increase the risk for RC (Table S2).

3.6 | Recurrence in patients with early or late-onset cholangitis

Upon LT, biliary stenosis may remodel over time and immunosuppression is often tapered over the course of the first year. However, no difference in cholangitis and RC within the first year after LT was observed: 27/62 cases of cholangitis (44%, comprising 17 patients)
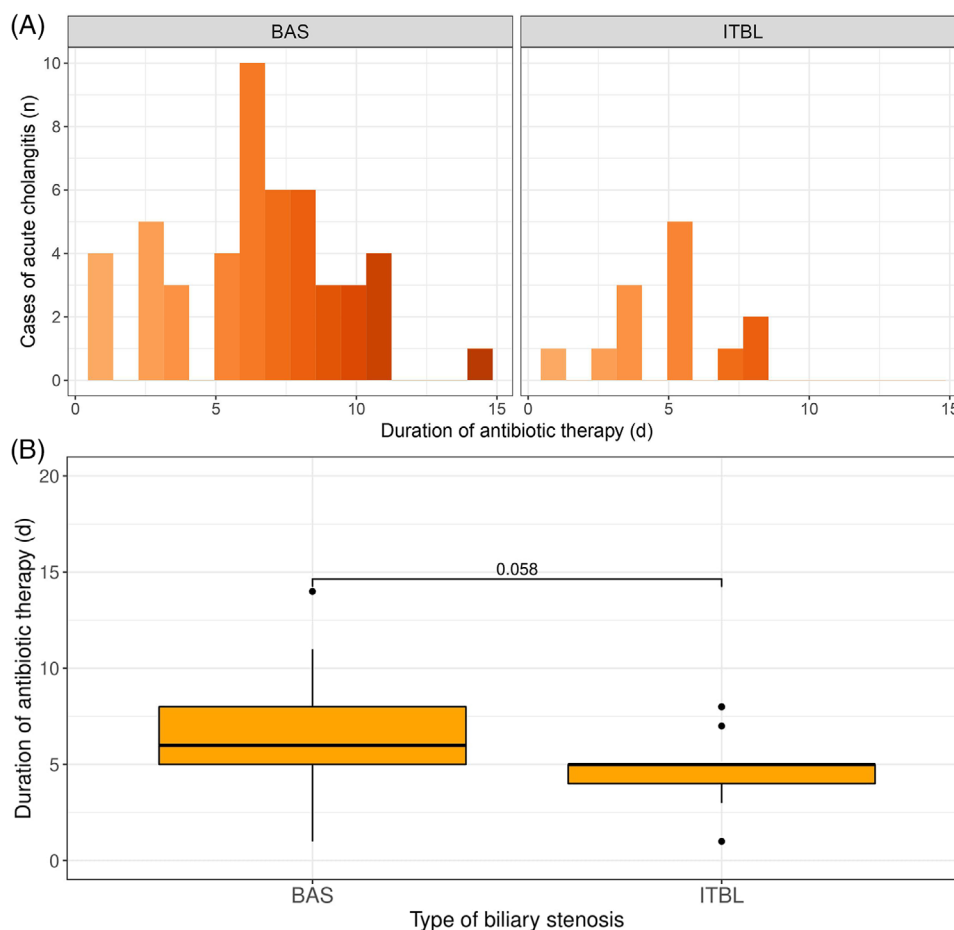
FIGURE 2 (A) Histograms of cholangitis due to biliary anastomosis stenosis (BAS) or ischemic-type biliary lesion (ITBL), sorted by duration of antibiotic therapy (AT) in days. (B) Boxplot of AT duration between cases of cholangitis with BAS or with ITBL

occurred within 1 year after LT, while the remaining 35/62 cases (56%, $p > .2$, comprising 19 patients) were observed more than 1 year after LT. Likewise, RC was equally distributed, with five cases per each group.

4 | DISCUSSION

Optimal length of AT is of high importance for patients after LT, as insufficient duration might lead to reinfection. On the other hand, excessive exposure to antibiotics might contribute to the development of MDRO. To date, treatment duration of patients with cholangitis after LT is based on clinical expertise due to a lack of data and guideline recommendations for this specific situation. Aim of the current study was to address this unmet need and to retrospectively evaluate the impact of SAT in comparison to LAT on the occurrence of RC.

The majority of patients in this study underwent SAT without developing an RC. This result needs to be interpreted with caution, as only 10 cases reached the primary end point, and the power of the statistical analysis was therefore limited. However, current evidence regarding the length of AT for cholangitis in general is still weak.[10] In detail, AT conducted for three (96 patients, retrospective[9]; and 18 patients, prospective[13]), five (80 patients, restrospective[14]; and 16 patients,

randomized-controlled[15]), and 10 (91 patients, retrospective[16]) days has been described as sufficient in resolving cholangitis; the latter in case of Gram-negative bacteremia. In line with the latter study, none of the patients with bacteremia in the present study developed RC, suggesting even complicated cases were not subject to overtreatment. As ours are the first data in patients with cholangitis after LT, the results of this study should encourage to further address this unmet clinical need in prospective trials.

At our center, no standardized protocol defining length of AT had been at hand during the study. In uncomplicated courses of cholangitis in non-LT patients, AT is carried out 4–7 days following successful biliary drainage, while longer therapies are usually held available for cases with inadequate empiric AT or complicated courses. In patients with LT, however, duration may need to be extended due to immunosuppression according to the clinician's choice. In the given population, we therefore defined cases with 6 or less days of AT after adequate drainage as SAT.

In the present study, 47% of the patients could be switched to oral fluoroquinolones and subsequently discharged. This demonstrates that oral intake of AT is a feasible approach in LT patients with cholangitis. Notably, an up-to-date assessment of MDRO burden is an important aspect in choosing AT, since failure of initial AT might lead

to longer and complicated courses. At our institution, all LT patients undergo aftercare solely at our center and are thereby regularly tested for MDRO.[11]

Only albumin and low platelets were identified as independent risk factors. There is no obvious biological relationship between these parameters and the event of RC. However, low serum albumin often reflects a reduced nutrition status including a limited immune system and is associated with inflammation.[17] The low platelet count might reflect a portal hypertension caused by a relapse of the underlying liver disease, which might contribute to the development of RC. It needs to be addressed that a lower quality of the graft might contribute to RC as well, although this factor is difficult to objectify. Likewise, individual posttransplant anatomy might be of more relevance to the occurrence of RC than duration of antibiotic treatment. These considerations are underlined by a higher value of CRP and bilirubin in the LAT group, indicating that structural differences could have existed in both groups.

Some limitations of the study need to be addressed. First, to ensure an unbiased approach, we evaluated all episodes of cholangitis among included patients, and hence multiple episodes of a single patient could be included. Although we chose this approach, the number of episodes was limited. However, this study still resembles the largest sized cohort to our knowledge. Second, due to its retrospective nature, the study is merely descriptive, and prospective data are warranted to validate potential treatment recommendations. Third, the study exclusively included nonseptic patients with Grade 1 or 2 cholangitis; hence patients with Grade 3 cholangitis are not represented. Fourth, Tokyo criteria have two limitations in patients after LT, since these are immunosuppressed and, furthermore, may be subject to chronic elevation of liver enzymes such as GGT or AP. However, all cases included in this study received AT. By combining ERC imaging with Tokyo criteria, our screening algorithm therefore reliably lead to enrollment of clinically significant cases.

5 | CONCLUSION

In conclusion, the current study provides first data suggesting that AT likely can be shorter for selected patients with ERC-treated cholangitis and Tokyo classification grade 2 or lower after LT. Systemic inflammation, bilirubin, albumin, and platelet count should be considered when choosing length of AT. This important finding may help to encourage clinicians to choose shorter courses of treatment as well as bringing prospective and confirmatory studies underway. Such studies are needed to determine the value of antibiotics after resolution of fever and at most 7 days in case of bacteremia.

CONFLICT OF INTEREST
The authors declare no conflict of interest related to the current work.

AUTHOR CONTRIBUTIONS
Study design: Dirk Walter. *Data collection*: Philip G. Ferstl, Alexander Queck, Katharina Bremer, Nina Weiler, and Martin-W. Welker. *Data interpretation*: Philip G. Ferstl, Alexander Queck, Nina Weiler, Mate Knabe, and Dirk Walter. *Writing of manuscript*: Philip G. Ferstl, Alexander Queck, Martin-W. Welker, Jonel Trebicka, Michael Hogardt, and Dirk Walter. *Statistical analysis*: Philip G. Ferstl, Katharina Bremer, Natalie Filmann, Jonel Trebicka, and Dirk Walter. *Critical review of the manuscript*: Oliver Waidmann, Mate Knabe, Wolf O. Bechstein, Volkhard A. J. Kempf, Stefan Zeuzem, Jonel Trebicka, Mireen Friedrich-Rust, and Dirk Walter.

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REFERENCES
1. 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. https://doi.org/10.1002/jhbp.518
2. Buis CI, Verdonk RC, Van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 1: radiological features and risk factors for early vs. late presentation. *Liver Transpl*. 2007;13(5):708-718. https://doi.org/10.1002/lt.21166
3. Verdonk RC, Buis CI, van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 2: management, outcome, and risk factors for disease progression. *Liver Transpl*. 2007;13(5):725-732. https://doi.org/10.1002/lt.21165
4. Larghi A, Tringali A, Rimbaş M, et al. Endoscopic management of benign biliary strictures after liver transplantation. *Liver Transpl*. 2019;25(2):323-335. https://doi.org/10.1002/lt.25358
5. Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. *Transpl Int*. 2011;24(4):379-392. https://doi.org/10.1111/j.1432-2277.2010.01202.x
6. 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. https://doi.org/10.1002/jhbp.509
7. Gomi H, Solomkin JS, Takada T, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2013;20(1):60-70. https://doi.org/10.1007/s00534-012-0572-0
8. Doi A, Morimoto T, Iwata K. Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study. *Clin Microbiol Infect*. 2018;24(11):1184-1189. https://doi.org/10.1016/j.cmi.2018.01.021
9. Satake M, Yamaguchi Y. Three-day antibiotic treatment for acute cholangitis due to choledocholithiasis with successful biliary duct drainage: a single-center retrospective cohort study. *Int J Infect Dis*. 2020;96:343-347. https://doi.org/10.1016/j.ijid.2020.04.074
10. Tinusz B, Szapáry L, Paládi B, et al. Short-course antibiotic treatment is not inferior to a long-course one in acute cholangitis: a

systematic review. *Dig Dis Sci*. 2019;64(2):307-315. https://doi.org/10.1007/s10620-018-5327-6

11. Ferstl PG, Filmann N, Heilgenthal EM, et al. Colonization with multidrug-resistant organisms is associated with in increased mortality in liver transplant candidates. *PLoS One*. 2021;16(1):e0245091. https://doi.org/10.1371/journal.pone.0245091

12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-281. https://doi.org/10.1111/j.1469-0691.2011.03570.x

13. 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. https://doi.org/10.1007/s00535-011-0451-5

14. van Lent AU, Bartelsman JF, Tytgat GN, Speelman P, Prins JM. Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract. *Gastrointest Endosc*. 2002;55(4):518-522. https://doi.org/10.1067/mge.2002.122334

15. Limmathurotsakul D, Netinatsunton N, Attasaranya S, Ovartlarnporn B. An open-labeled, randomized controlled trial comparing between short duration and standard 14 days antibiotic treatments for acute cholangitis in patients with common bile duct stone afte successful endoscopic biliary drainage. A preliminary report. *Gastrointest Endosc*. 2014;79:AB251.

16. 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. https://doi.org/10.1016/j.ijid.2016.12.018

17. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr*. 2019;43(2):181-193. https://doi.org/10.1002/jpen.1451

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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