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Cancel that PICC line order; cholecystostomy tube and short course of antibiotics

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A B S T R A C T

Background: Current guidelines do not specifically address optimal antibiotic duration following cholecystostomy. This study compares outcomes for short-course (<7 days) and long-course (≥7 days) antibiotics post-cholecystostomy.
Methods: This was a retrospective review of cholecystostomy patients (≥18 years) admitted (1/1/2007-12/31/2017) to one healthcare system.
Results: Overall, 214 patients were studied. Demographics were similar, except short-course patients had higher Charlson Comorbidity Index ($p < 0.0001$). There were no intergroup differences in tachycardia (22.5%[short-course] vs 23.3%[long-course]) or leukocytosis (67.1%[short-course] vs 64.4%[long-course]) at drain placement nor time to normalization for pulse, temperature or leukocytosis. There were no differences regarding *Clostridium Difficile* infection (5.0%[short-course] vs 1.6%[long-course]) or cholecystitis recurrence (8.8%[short-course] vs 10.9%[long-course]). No differences were observed regarding gallbladder-related unplanned readmissions (30-day:18.8%[short-course] vs 17.2%[long-course]; 90-day: 20.0%[short-course] vs 25.8%[long-course]). There were no 30- or 90-day mortality differences (overall mortality: 18.3%).
Conclusion: Post-cholecystostomy outcomes were comparable between short-course and long-course antibiotics, consistent with emerging literature supporting short-course antibiotics for intra-abdominal infection with source control.

Introduction

Cholecystectomy is the standard of care for cholecystitis; however, some patients are unable to undergo surgery due to critical illness or comorbidities that pose a prohibitive risk. Cholecystostomy tube placement has been shown to be a safe and effective way to bridge this cohort until they clinically improve for surgery or as definitive treatment in some patients.[1–5]

While cholecystostomy has gained acceptance as a non-surgical treatment strategy, there is a paucity of literature to guide duration of concurrent antibiotic therapy. The Tokyo Guidelines suggested four to seven days of antibiotics following source control.[6] However, this guideline is only for severe cholecystitis and does not include cholecystostomy in its consideration of source control. Similarly, the STOP-IT trial's findings may not be applicable to cholecystostomy. While it suggested that four days of antibiotics are sufficient for intra-abdominal infection after adequate source control, including either surgery or percutaneous drainage, only a small minority (10.8%) were biliary infections and it is unknown if any were treated with cholecystostomy.[7] Among the few reports examining cholecystitis and cholecystostomy, a small retrospective study recently suggested that antibiotics could be safely discontinued within seven days.[8] Therefore, the present study aims to validate the sufficiency of short-course antibiotics by comparing patient outcomes among those managed with short- or long-course antibiotics following cholecystostomy placement for cholecystitis.

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Methods

This was a retrospective study approved by the Institutional Review Board of Geisinger Health, which granted a waiver of informed consent due to the retrospective design. All adults (age $\geq$ 18 years) admitted (January 1, 2007 through December 31, 2017) to a single healthcare system who received a cholecystostomy tube for cholecystitis were eligible. To assess antibiotic duration for cholecystitis treated with cholecystostomy, any patient with a positive urine or sputum culture during the admission was excluded. Individuals who expired prior to the completion of the prescribed antibiotic course were excluded due to incomplete data.

There is no institutional guideline for the duration of antibiotics following cholecystostomy placement. Antibiotics were prescribed at the discretion of the attending surgeons, internists, intensivists and infectious disease specialists. Patients were categorized according to total (inpatient and outpatient) antibiotic duration: short-course (<7 days) or long-course ($\geq$7 days), consistent with previous work.[8] Time to normalization for key markers for infection following drain placement was assessed. The pulse, temperature and white blood cell (WBC) count immediately prior to drain placement served as the initial levels for trending analysis. Normalization was defined as follows: pulse <100 beats per minute, temperature $\leq$98.6 °F, WBC <10.9 K/μL. Inconsistent ordering practices precluded the assessment of lactate.

Comorbid conditions were assessed using the Charlson Comorbidity Index, as defined previously.[9] Categorical data were represented as frequency with percentages and analyzed using χ^2 tests or Fisher's exact test as appropriate. Continuous variables were described as mean (±standard deviation) and analyzed using two sample t-tests. Continuous variables that followed a non-normal distribution were described as median (interquartile range) and analyzed using Wilcoxon rank sum tests. Time to event data were visualized using Kaplan-Meier curves and analyzed using log-rank tests. All analyses were performed using SAS 9.4 (Copyright 2013 SAS Institute Inc. Cary, NC) and $p < 0.05$ was considered statistically significant.

Results

In total, 290 patients underwent cholecystostomy tube placement with 214 patients meeting final inclusion criteria. Most patients (131, 61.2%) were treated with long-course antibiotics (mean 12.1 ± 5.0 days, median: 11[9,14] days). The remaining patients received short-course antibiotics (mean 3.6 ± 1.7 days, median: 4 [2,5] days).

There were no differences between short-course and long-course groups regarding patient age (74.7 ± 14.7 vs 72.0 ± 16.1 years), gender (female: 41% vs 32.8%), or body mass index (29.7 ± 6.7 vs 29.6 ± 6.8 kg/m^2). However, short-course patients had significantly more comorbidities (median Charlson Comorbidity Index 2[0, 5] vs 0[0,2], $p < 0.0001$).

Overall, there was no difference among groups regarding the type of cholecystitis ($p = 0.69$; Table 1) with most patients treated for calculous cholecystitis (166, 77.6%). Antibiotic therapy was varied and tailored according to the bile culture, if performed (105 patients). No intra-group differences were observed in the incidence of positive culture ($p = 0.07$; Table 1) or the resultant organisms (all $p > 0.05$). The most common organisms were *Escherichia coli* (short-course: 6 patients, long-course: 14), *Enterococcus* (short-course: 1 patient, long-course: 12), and *Klebsiella pneumoniae* (short-course: 3 patients, long-course: 7).

There was no significant difference in the use of monotherapy or combination therapy between short-course and long-course antibiotics with respect to the primary inpatient regimen ($p = 0.38$; Table 1). The most common monotherapy agents were pipercillin-tazobactam (short-course: 21 patients, long-course: 47) and ampicillin-sulbactam (short-course: 14 patients, long-course: 18). The most common combination therapies consisted of ceftriaxone with metronidazole (short-course: 25 patients, long-course: 23) or ciprofloxacin with metronidazole (short-course: 17 patients, long-course: 34).

The timing of cholecystostomy tube placement did not significantly differ between groups (median 2 [1, 3] vs 2 [1, 4] days from admission; Table 1). At the time of drain placement, short-course and long-course patients did not differ in key markers for inflammation and infection, including leukocytosis or tachycardia; however, long-course had significantly more febrile patients (57.4% vs 40.0%; Table 1). Notably, there was no difference in time to normalization for pulse, temperature or WBC count (Fig. 1). Approximately half of each group underwent a tube cholangiogram at some point and no differences were found in patency of the cystic or common bile duct.

For the index admission, there was no difference in the hospital length of stay (LOS) between groups ($p = 0.07$; Table 1). The long-course cohort had a higher incidence of patients requiring hospitalization in the intensive care unit (ICU; 29.8% vs 15.7%, $p = 0.02$; Table 1), though there was no difference in the ICU LOS among these patients ($p = 0.85$; Table 1). While the incidence of shock requiring vasopressor support was comparable between groups, the short-course cohort remained on vasopressors significantly longer (median 6[2, 9] vs 3[1,5] days, $p = 0.02$; Table 1). There was no difference in the incidence of acute kidney injury or the development of a *Clostridium Difficile* infection following cholecystostomy placement ($p = 0.21$ and $p = 0.99$, respectively; Table 1).

With respect to post-discharge outcomes, there was no difference in the incidence of recurrent acute cholecystitis or development of a *Clostridium Difficile* infection between groups ($p = 0.62$ and $p = 0.21$, respectively; Table 1). There was no significant difference between groups for readmission at the 30- or 90-day mark for any unplanned readmission or gallbladder-related unplanned readmission (Table 1). The overall mortality rate was 18.3% and there was no difference in mortality between groups at the 30- or 90-day mark (Table 1).

Discussion

Clinicians across medical and surgical specialties have recognized the importance of optimizing antibiotic duration to balance infection control with the risk of antibiotic resistance. Emerging literature suggests short-course antibiotics are sufficient for intra-abdominal infections with source control,[7] even if sepsis is present.[10] Nonetheless, little evidence is currently available to guide antibiotic stewardship specifically for patients with cholecystostomy, a population of patients who may require special consideration due to potential comprise from critical illness or a high burden of comorbid disease.

First and foremost, in a retrospective study of antibiotic duration it is essential to assess patient selection bias; summarized in the presumption that long-course antibiotics were given to more severely ill patients. The long-course group did demonstrate a higher percentage of patients requiring ICU hospitalization. The short-course group, however, had a greater comorbidity burden and remained on vasopressors significantly longer. Critically, there were no intergroup differences in tachycardia and leukocytosis at the time of drain placement nor time to normalization for pulse, temperature or WBC count. Ultimately, the data do not suggest that long-course antibiotics were given to more severely ill patients. Rather, the data suggest that antibiotic duration was likely

Table 1
Characteristics and outcomes of patients receiving cholecystostomy.

	Short Course Antibiotics (<7 days)		Long Course Antibiotics (≥7 days)		p value
	N = 83		N = 131		
	n	%	n	%	
Reason for Cholecystostomy					0.97
Calculous Cholecystitis	67	80.7	106	80.9	
Acalculous Cholecystitis	16	19.3	25	19.1	
Primary Inpatient Antibiotic Therapy					0.38
Monotherapy	38	45.8	68	51.9	
Combination Therapy	45	54.2	63	48.1	
Hospital Day of Drain Placement (days) [median (IQR)]	2 (1, 3)		2 (1, 4)		0.43
Markers of Infection at Drain Placement					0.07
Leukocytosis (≥10.9 K/uL)	47	67.1	74	64.4	0.70
Tachycardia (>100 bpm)	16	22.5	27	23.3	0.91
Febrile (>98.6 °F)	28	40.0	66	57.4	0.02
Bile Culture Assessed at Drain Placement	44	54.2	61	61.6	
Positive Culture	(14/44)		(38/61)		0.07
Post-Drain Placement Outcomes					
Tube Study					0.64
Patent	29	34.9	36	27.5	
Obstructed	4	4.8	9	6.9	
Other	15	18.1	23	17.6	
Not Tested	35	42.2	63	48.1	
Duration of Drain (days) [median (IQR)]	59 (33, 122)		57 (38, 97)		0.69
Index Admission Outcomes					
LOS [median (IQR)]	6 (4, 12)		7 (5, 14)		0.07
ICU Hospitalization (yes/no)	13	15.7	39	29.8	0.02
ICU LOS (days) [median (IQR)]	7 (6, 12)		8 (4, 15)		0.85
Requirement of Intubation	9	10.8	24	18.3	0.14
Requirement of Vasopressors (Shock)	8	9.6	19	14.5	0.30
Duration (days) [median (IQR)]	6 (2, 9)		3 (1, 5)		0.02
Acute Kidney Injury	20	24.1	42	32.1	0.21
Clostridium Difficile Infection	1	1.2	2	1.5	0.99
Post-Discharge Outcomes[a]					
Operation					0.16
Laparoscopic Cholecystectomy	20	25.0	48	37.5	
Laparoscopic to Open Cholecystectomy	10	12.5	7	5.4	
Open Cholecystectomy	3	3.8	3	2.3	
Other[b]	1	1.3	1	0.8	
None	46	57.5	69	53.9	
Recurrence of acute cholecystitis	7	8.8	14	10.9	0.62
Clostridium Difficile Infection	4	5.0	2	1.6	0.21
Any Unplanned Readmission					
30 Day	25	31.3	37	28.9	0.69
31–90 Day	31	38.8	46	35.9	0.65
Gallbladder-Related Unplanned Readmission					
30 Day	15	18.8	22	17.2	0.75
31–90 Day	16	20.0	33	25.8	0.35
Mortality					
30 Day	9	11.3	7	5.5	0.12
31–90 Day	9	11.3	13	10.2	0.79

Abbreviations: ICU, Intensive Care Unit; LOS, Length of Stay.
[a] Three patients were lost to follow-up in each group. Percentages reflect population of patients with follow-up data.
[b] Other operation includes laparoscopic drain placement following aborted cholecystectomy (short course) and exploratory laparotomy with drain placement (long course).

influenced by subjective factors and clinical examination parameters not readily observed retrospectively, similar to past reports.[8]

The present findings are consistent with a small, retrospective study examining post-cholecystostomy antibiotics, which also found that outcomes following short-course(<7 days) and long-course antibiotics did not differ in patient outcomes, including recurrent cholecystitis, *Clostridium Difficile* infection and mortality.[8] Notably, there was similar representation of acalculous cholecystitis (approximately 19%) in both studies.[8] The present findings supporting short-course antibiotics conflict with one previous report on long-term outcomes of cholecystostomy in Taiwan, which found that parental antibiotics for more than ten days reduced the likelihood of recurrent cholecystitis at the two-month and one-year marks.[1]

With validation that short-course antibiotics are not associated with adverse outcomes in the cholecystostomy population, it is prudent to further stratify antibiotic duration and identify the optimal length. More specifically, it is necessary to assess the recommendations of the STOP-IT trial,[7] which this study did not have the statistical power to do as only 35 patients received less than five days of antibiotics. Despite the STOP-IT trial including only a small portion of biliary infections and the inclusion of surgical source control, prescription patterns may have been influenced by the landmark trial as the majority of patients (65.7%) with less than five days of antibiotics were admitted after its publication in 2015.

There are several limitations to this study. The retrospective nature inherently relies upon accurate coding and complete documentation in the chart. This study was limited to a population treated within a single healthcare network, which does not have a standardized protocol for antibiotic therapy. It is also possible that

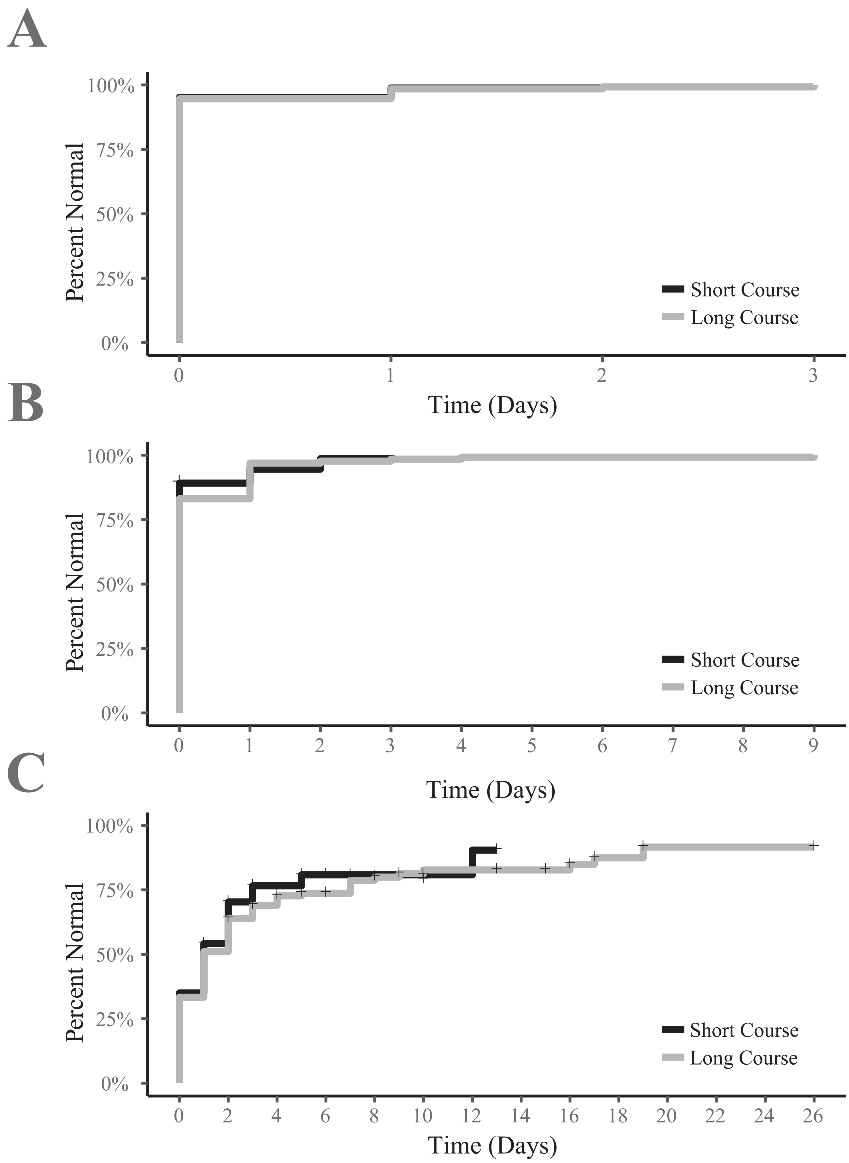

Fig. 1. Time to normalization for (A) pulse, (B) temperature, (C) white blood cell count following cholecystostomy tube placement.

patients within this population were readmitted outside this large healthcare network, though only 6 patients (2.8%) were lost to follow-up. While the sample size is limited, the present work examines a larger population than previously reported for cholecystitis patients treated with cholecystostomy,[2–4] including those who assess concurrent antibiotic usage.[1,8] The present population, though relatively large, was heterogenous in its etiology of cholecystitis. Future studies, ideally randomized and multi-institutional, should validate the efficacy of less than seven days of antibiotics for each type of cholecystitis, which this study did not have the statistical power to do, as other intra-abdominal infections have been successful with four days of antibiotics following source control.[7,10]

Conclusion

Across 11 years, 214 patients underwent cholecystostomy placement and completed a course of antibiotics, making this the largest study to date investigating antibiotics among cholecystostomy patients. Most patients were managed with long-course antibiotics with an average length of 12.1 days compared to an average of 3.6 days within the short-course group. There was no difference in time to normalization for inflammatory markers or post-discharge outcomes including recurrence of cholecystitis between the two groups. These findings provide further support that the use of short-course antibiotics following cholecystostomy tube placement for cholecystitis is safe and consistent with emerging literature supporting short-course antibiotics for intra-abdominal infection following source control.

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Disclosures/affiliations

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.10.044.

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