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ORIGINAL SCIENTIFIC REPORT

Antibiotics May be Safely Discontinued Within One Week of Percutaneous Cholecystostomy

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Abstract

Background For patients with acute cholecystitis managed with percutaneous cholecystostomy (PC), the optimal duration of post-procedural antibiotic therapy is unknown. Our objective was to compare short versus long courses of antibiotics with the hypothesis that patients with persistent signs of systemic inflammation 72 h following PC would receive prolonged antibiotic therapy and that antibiotic duration would not affect outcomes.

Methods We performed a retrospective cohort analysis of 81 patients who underwent PC for acute cholecystitis at two hospitals during a 41-month period ending November 2014. Patients who received short ($\leq$7 day) courses of post-procedural antibiotics were compared to patients who received long (>7 day) courses. Treatment response to PC was evaluated by systemic inflammatory response syndrome (SIRS) criteria. Logistic and linear regressions were used to evaluate associations between antibiotic duration and outcomes.

Results Patients who received short ($n = 30$) and long courses ($n = 51$) of antibiotics had similar age, comorbidities, severity of cholecystitis, pre-procedural vital signs, treatment response, and culture results. There were no differences in recurrent cholecystitis (13 vs. 12%), requirement for open/converted to open cholecystectomy (23 vs. 22%), or 1-year mortality (20 vs. 18%). On logistic and linear regressions, antibiotic duration as a continuous variable was not predictive of any salient outcomes.

Conclusions Patients who received short and long courses of post-PC antibiotics had similar baseline characteristics and outcomes. Antibiotic duration did not predict recurrent cholecystitis, interval open cholecystectomy, or mortality. These findings suggest that antibiotics may be safely discontinued within one week of uncomplicated PC.

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Introduction

When acute cholecystitis is managed with cholecystectomy and complete source control is obtained, prolonged postoperative antibiotic therapy is not warranted [1–3]. When patients with acute cholecystitis are too ill to tolerate surgery, they may be managed by decompressing the biliary tree with a percutaneous cholecystostomy (PC) tube. However, the optimal duration of antibiotic therapy following PC is unknown [4]. Ongoing gallbladder wall inflammation may not be mitigated by PC, especially in the context of gangrenous cholecystitis [5]. Even with a PC tube in place, the patient remains at risk for recurrent cholecystitis, particularly in the presence of calculi [6]. Faced with these challenges and a lack of evidence-based recommendations, patients may be subjected to unnecessarily prolonged antibiotic regimens. Previous work has shown that excessive antibiotic administration propagates multi-drug-resistant organisms [7–9], increases *Clostridium difficile* infection rates [10], and increases health care costs [11, 12]. Therefore, prudent antibiotic management following percutaneous cholecystectomy has the potential to make a significant impact.

The purpose of this study was to compare short ($\leq$7 day) courses of antibiotics to long (>7 day) courses of antibiotics for patients managed with PC for acute cholecystitis. We hypothesized that patients with persistent systemic toxicity 72 h following PC would be more likely to receive prolonged antibiotic therapy and that antibiotic duration would not affect rates of recurrent cholecystitis, subsequent operative management strategies, or mortality.

Methods

We conducted a retrospective analysis of 81 patients who underwent PC for acute cholecystitis at two hospitals (a tertiary academic center and Veterans Affairs hospital) from June 1, 2011 to November 1, 2014. PC was performed by the transhepatic or transperitoneal route and was guided by computed tomography or ultrasound imaging. Patients age $\geq$18 and meeting the TG13 Tokyo definition of acute cholecystitis (right upper quadrant mass, pain, or tenderness along with fever, leukocytosis, elevated C-reactive protein, or imaging findings characteristic of acute cholecystitis) [13] were included. Patients transferred from outside institutions after endoscopic, radiographic, or surgical interventions on the biliary tree and those with concomitant cholangitis or gallstone pancreatitis were excluded. Patients were also excluded if PC was not technically successful, defined as cannulation of the gallbladder with aspiration of bile and/or purulence within three attempts [14]. Patients who died while on antibiotic therapy were excluded in order to ensure that antibiotic duration would not be confounded by early deaths. At both hospitals, cholecystostomy was offered as an alternative to cholecystectomy for high-risk surgical candidates with acute cholecystitis. The decision to perform cholecystostomy was reached through a shared decision-making process involving the patient and the treating physicians and was made on a case-by-case basis.

Data were retrospectively collected from the electronic medical record. Severity of acute cholecystitis was defined by the TG13 Tokyo guidelines (Grade I: mild, Grade I: moderate, Grade III: severe) [13]. Systemic inflammatory response syndrome (SIRS) criteria were defined as described by Davies and Hagen [15]. Clinical improvement was defined as resolution of the SIRS response, discontinuation of vasopressors, or discharge home within 72 h of PC. Clinical decline was defined as development of a new SIRS response or a new vasopressor requirement within 72 h of PC. The 72-hour time point to measure SIRS criteria was based on methods and results from previous studies [16–19]. Microbiologic culture data were recorded for each patient. Recurrent acute cholecystitis was defined as a new episode of acute cholecystitis occurring after a 48-h period in which the patient was off antibiotics and did not meet SIRS criteria. Decisions regarding duration of antibiotic therapy were at the discretion of the attending surgeon. Antibiotic therapy for $\leq$7 days was defined as a short course; antibiotic therapy for >7 days was defined as a long course. The 7-day cutoff allowed for comparison of more evenly sized groups (short course: $n = 30$; long course: $n = 51$). Differences in group sizes hindered analysis of a 5-day cutoff (short course: $n = 20$; long course: $n = 61$) or 3-day cutoff (short course: $n = 12$; long course: $n = 79$).

Statistical analysis was performed using SPSS (version 23, IBM, Armonk, NY). Normally distributed continuous variables were compared by one-way analysis of variance (reported as mean $\pm$ standard deviation), non-normally distributed continuous variables were compared by the Kruskal–Wallis test (reported as median [interquartile range]), and discrete variables were compared by Fisher's exact test [reported as n (%)]. Correlations between antibiotic duration and salient outcomes were assessed by Pearson's r. The ability of antibiotic duration to predict discrete and continuous outcome variables was determined with logistic and linear regressions as appropriate. Significance was set at $\alpha = 0.05$, and confidence intervals for regression variables were set at 95%.

Table 1 Patient characteristics

	≤7d antibiotics $n = 30$	>7d antibiotics $n = 51$	p
Age (years)	65 ± 20	70 ± 12	0.214
Male	17 (57%)	38 (75%)	0.139
Charlson comorbidity index	4.0 ± 2.4	4.4 ± 2.5	0.440
Calculous cholecystitis	25 (83%)	41 (80%)	0.742
TG13 severity grade	1.9 ± 0.6	1.8 ± 0.8	0.678
Days from admission to PC	2 [1–4]	2 [1–5]	0.857
At the time of PC			
Temperature (°C)	37.5 ± 0.8	37.2 ± 0.5	0.060
Heart rate	97 ± 15	93 ± 18	0.356
Respiratory rate	22 ± 4	21 ± 4	0.415
WBC count ($\times 10^9$/L)	17.2 ± 7.3	14.2 ± 7.3	0.075
SIRS	23 (77%)	27 (53%)	0.030*
Vasopressor infusion	1 (3%)	5 (10%)	0.409
72 h after PC			
Temperature (°C)	37.0 ± 0.5	37.2 ± 0.5	0.445
Heart rate	80 ± 14	83 ± 11	0.352
Respiratory rate	18 ± 3	19 ± 2	0.832
WBC count ($\times 10^9$/L)	10.1 ± 5.7	9.7 ± 5.8	0.781
SIRS	4 (13%)	7 (14%)	0.931
Vasopressor infusion	1 (3%)	0	0.375
Clinical improvement	23 (77%)	34 (67%)	0.452
Discharged home	9 (30%)	16 (31%)	0.897
Clinical decline	0	2 (4%)	0.528

*$p < 0.05$ was considered significant

Data are presented as mean ± standard deviation, n (%), or median [interquartile range]

TG13 revised Tokyo guidelines, *PC* percutaneous cholecystostomy, *WBC* white blood cell, *SIRS* systemic inflammatory response syndrome

Results

There were no significant differences in the baseline characteristics of patients who received ≤7 days of antibiotic therapy and those that received >7 days of antibiotic therapy (Table 1). The two groups had similar age (65 vs. 70 years), Charlson comorbidity index (4.0 vs. 4.4), severity of acute cholecystitis (1.9 vs. 1.8), and clinical response to PC. Compared to the university hospital, patients managed at the Veterans Affairs hospital were older (73 vs. 65 years, $p = 0.019$), more likely to be male (93 vs. 53%, $p < 0.001$), and had higher Charlson comorbidity index scores (5.1 vs. 3.8, $p = 0.015$). VA and university hospital patients had similar rates of acalculous cholecystitis (17 vs. 20%, $p > 0.999$) and TG13 cholecystitis severity grade (1.8 vs. 1.8, $p = 0.953$). Acute cholecystitis was the admitting diagnosis in 73% of all patients. Patients who received ≤7 days of antibiotics were more likely to meet SIRS criteria at the time of PC (77 vs. 53%), though rates of SIRS were equal between groups 72 h after PC (13 vs. 14%). Of the four patients in the short-course group (13%) who had SIRS 72 h after PC, three patients (10%) still had SIRS at five days, and two patients (6%) had SIRS at 7 days. Of the seven patients (14%, $p = 0.931$) in the long-course group who had SIRS 72 after PC, three patients (6%, $p = 0.665$) still had SIRS at 5 days, and one (2%, $p = 0.552$) had SIRS at seven days. Of the three patients in the entire study population who had SIRS seven days following PC, two patients died within 30 days.

There were no differences in microbiologic findings between groups (Table 2). Seventy-seven out of 81patients (95%) had a bile culture performed, and 53 (69%) of these specimens contained bacteria (Table 2). There was a higher incidence of positive bile cultures in the prolonged antibiotic group, though the difference was not statistically significant (73 vs. 53%, $p = 0.094$). The most commonly isolated organisms were *Escherichia coli, Klebsiella* species, and *Enterococcus faecalis.* Thirty-seven percent of all specimens were polymicrobial. Compared to patients with a positive bile culture, patients with a negative bile culture had similar rates of SIRS at the time of PC (64 vs. 62%, $p > 0.999$) and SIRS 72 h after PC (28 vs. 16%, $p = 0.308$). Twelve patients (15%) had a bloodstream infection. In ten of these twelve patients (83%), the same

Table 2 Microbiology findings

	≤7d antibiotics $n = 30$	>7d antibiotics $n = 51$	p
Bile culture performed	28 (93%)	49 (96%)	0.624
Positive bile culture	16 (53%)	37 (73%)	0.094
Bile culture organisms			
Escherichia coli	4 (13%)	15 (29%)	0.113
Klebsiella species	4 (13%)	14 (27%)	0.174
Enterococcus faecalis	7 (23%)	10 (20%)	0.780
Streptococcus viridans	2 (7%)	4 (8%)	0.845
Coagulase negative-*Staphylococcus*	2 (7%)	3 (6%)	0.887
Candida species	0	5 (10%)	0.152
β-hemolytic *Streptococcus*	0	3 (6%)	0.292
Serratia marcescens	1 (3%)	1 (2%)	0.701
Pseudomonas aeruginosa	0	2 (4%)	0.528
Clostridium perfringens	0	2 (4%)	0.528
Aeromonas hydrophila	0	2 (4%)	0.528
Other (MRSA, MSSA, *Pantoea, Diphtheroids, Prevotella, Citrobacter*)	3 (10%)	3 (6%)	0.665
Polymicrobial bile culture	9 (30%)	21 (41%)	0.350
Blood culture performed	20 (67%)	35 (69%)	0.855
Positive blood culture	4 (13%)	8 (16%)	0.773
Same organism in blood and bile	3 (10%)	7 (14%)	0.584
Non-biliary infection	9 (30%)	15 (29%)	0.955
Two or more non-biliary infections	2 (7%)	2 (4%)	0.624

Data are presented as *n* (%)

MRSA methicillin-resistant *Staphylococcus aureus, MSSA* methicillin-sensitive *Staphylococcus aureus*

organism was isolated in blood and bile cultures. There were no cases in which culture results required escalation or broadening of antibiotic therapy.

There was no significant difference in the proportion of patients with a non-biliary infection between the short-course and long-course groups (30 vs. 29%, $p > 0.999$). The proportion of patients who had two or more non-biliary infections was also similar between groups (7 vs. 4%, $p = 0.624$). Therefore, it seems unlikely that non-biliary infectious had a significant influence on the observed duration of antibiotic therapy between groups. There were no significant differences in the percentage of patients who had a stool culture to detect *Clostridium difficile* between short-course and long-course groups (23 vs. 14%, $p = 0.363$). There was one positive *Clostridium difficile* stool culture, which occurred in a patient in the long-course group (0 vs. 2%, $p > 0999$). There were no significant differences in the frequency of multi-drug-resistant infections for short-course and long-course groups (20 vs. 20%, $p > 0.999$). None of these infections occurred more than one calendar day after PC, and 75% of these cases involved a multi-drug-resistant organism in the bile culture.

Seventy-five patients (93%) had at least one follow-up clinic visit or subsequent hospital admission. The incidence of recurrent cholecystitis was similar between patients who received ≤7 days of antibiotic therapy (13%) and those that received >7 days of antibiotic therapy (12%). The two groups also had similar initial hospital length of stay, and rates of drain removal, interval cholecystectomy, requirement for open/converted to open cholecystectomy, and mortality at 30 days and one year (Table 3). A greater proportion of patients managed at the university hospital underwent interval cholecystectomy, though the difference was not statistically significant (49 vs. 27%, $p = 0.062$). Duration of antibiotic therapy did not have any significant associations with relevant outcomes by Pearson's correlation, logistic regression, or linear regression (Table 4).

To address the possibility that outcomes were affected by disproportionate allocation of patients with a favorable clinical trajectory to the group that received a short-course of antibiotics, we performed a sensitivity analysis by excluding all patients who had SIRS at the time of PC, remained in the hospital 72 h after PC, and did not have SIRS at 72 h. This analysis excluded 15 patients in the short-course group and 16 patients in the long-course group. All parameters in Table 3 were assessed in the sensitivity analysis; there were no significant differences between groups. Short-course and long-course groups had

Table 3 Outcomes

	≤7d antibiotics $n = 30$	>7d antibiotics $n = 51$	p
Initial hospital length of stay (days)	8 [4–12]	6 [3–13]	0.750
Recurrent acute cholecystitis	4 (13%)	6 (12%)	0.836
Median days to recurrent cholecystitis	75 [63–331]	51 [15–75]	0.257
Drain removal	24 (80%)	40 (78%)	0.867
Median days to drain removal	45 [31–79]	53 [36–78]	0.698
Cholecystectomy	12 (40%)	21 (41%)	0.917
Laparoscopic	5 (17%)	10 (20%)	0.741
Open or converted to open	7 (23%)	11 (22%)	0.741
Median days to cholecystectomy	80 [52–204]	57 [35–83]	0.163
Mortality within 30 days of PC	2 (7%)	1 (2%)	0.552
Mortality within one year of PC	6 (20%)	9 (18%)	0.776

Data are presented as median [interquartile range] or n (%)

MDR multi-drug-resistant, *PC* percutaneous cholecystostomy

Table 4 Associations between antibiotic duration and outcomes

	Pearson correlation	OR or β coefficient	95% CI	p
Recurrent acute cholecystitis	−0.05	0.97	0.86–1.10	0.638
Hospital length of stay	0.00	0.00	−0.69–0.68	0.996
Open/converted to open cholecystectomy	0.05	1.02	0.89–1.18	0.769
Mortality within 30 days of PC	−0.11	0.89	0.71–1.12	0.329
Mortality within one year of PC	0.08	1.04	0.94–1.15	0.482

Discrete variables were analyzed by logistic regression and reported as OR; hospital length of stay was analyzed by linear regression and reported as β coefficient

OR odds ratio, *CI* confidence interval, *PC* percutaneous cholecystostomy

similar hospital length of stay [6 (3–25) vs. 6 (3–10) days, $p = 0.537$], and similar rates of recurrent cholecystitis (7 vs. 11%, $p > 0.999$), drain removal (87 vs. 77%, $p = 0.702$), and cholecystectomy (47 vs. 46%, $p > 0.999$).

Discussion

Our data indicate that decisions regarding antibiotic therapy following PC for acute cholecystitis were arbitrary and that prolonged courses of antibiotics provided no benefit. We hypothesized that sicker patients would receive more than one week of antibiotics, and this was not the case. In fact, the group of patients who received ≤7 days of antibiotics had higher initial rates of SIRS, but improved over time such that the two groups had evenly matched SIRS criteria 72 h following PC. Microbiology data demonstrated that the groups had similar biliary and non-biliary infections, though there was a trend toward increased incidence of positive bile cultures in the prolonged antibiotic group, which may have affected decisions regarding antibiotic therapy [20–22]. There was a high degree of fidelity between organisms isolated from the blood and bile in patients with bloodstream infection. As expected, hospital length of stay and long-term outcomes were unaffected by antibiotic duration.

Rates of recurrent acute cholecystitis in this study were on the low end of the 10–41% range reported in the literature [6, 23–27]. This may be due to a combination of two factors: 7% of patients in this study had no documented follow-up in our system, and 19% had acalculous cholecystitis and were therefore at low risk of recurrent cholecystitis [28–31]. Cases of acalculous cholecystitis were included because ultrasound is only 84% sensitive (95% CI 76–92) in detecting cholelithiasis, and so many patients diagnosed with acalculous cholecystitis may actually have gallstones [32]. Also, inclusion of cases of presumed acalculous cholecystitis increased the sample size and allows our findings to be generalized to a broader population of all patients with acute cholecystitis.

The major limitations of this study are its retrospective design, small sample size. A larger study would reduce the likelihood of type II errors and allow for an adequately powered analysis of an even shorter duration of antibiotic

therapy, e.g., 1–3 days. Unfortunately, there was no precedent for duration of antibiotic therapy following cholecystostomy tube placement in the literature prior to this study, and so the 7-day cutoff was based on our own practice patterns. Duration of antibiotic therapy was also analyzed as a continuous variable to decrease the likelihood that the 7 day cutoff concealed a true difference in outcomes for short versus long antibiotic therapy. Although immediate discontinuation of antibiotics following PC has not been studied, a short course of post-PC antibiotics seems prudent on the grounds that acute cholecystitis primarily involves inflammation of the gallbladder wall rather than its contents, and so decompression of the biliary tree may not address all aspects of the underlying pathophysiology [33]. In particular, a gangrenous necrotic gallbladder wall may be a source of ongoing inflammation and infection following PC [5]. Patients with this condition may be best managed by early cholecystectomy rather than extended antibiotic therapy [34]. Future studies should focus on appropriate selection of patients for PC and seek to determine whether even shorter courses of antibiotics are equally safe and effective.

Patients who received short ($\leq$7 day) versus long (>7 day) courses of antibiotics following PC for acute cholecystitis had similar baseline characteristics, clinical response to PC, short-term outcomes, and long-term outcomes. Antibiotic duration was not predictive of recurrent cholecystitis, interval open cholecystectomy, or mortality. These findings suggest that antibiotics may be safely discontinued within one week of PC. Future studies should determine the efficacy of even shorter antibiotic courses (e.g., 1–3 days).

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