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Addition of anaerobic coverage for treatment of biliary tract infections: a propensity score-matched cohort study

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Objectives: To evaluate whether additional antibiotics that target anaerobes, including *Bacteroides* spp., are associated with improved clinical outcomes in patients with biliary tract infections (BTIs).

Methods: This was a retrospective propensity score-matched cohort of adults aged ≥18 years with BTIs, admitted to hospital between 1 April 2015 and 30 March 2021. Eligible patients treated with antibiotics that provided coverage of anaerobes were compared with those treated with comparable regimens without anaerobic coverage. The primary outcome was a composite of mortality within 30 days or relapse within 90 days of source control or completion of antibiotics. Secondary outcomes included length of stay (LOS), duration of antibiotic therapy and adverse drug reactions. ORs were calculated using a weighted generalized linear regression model with propensity-score matching.

Results: Among 398 patients included, 209 were treated without anaerobic coverage and 189 with anaerobic coverage. After propensity-score matching, there was no significant difference in primary outcome between propensity-matched patients who received additional anaerobic coverage and those who did not [adjusted OR (aOR) 1.23; 95% CI 0.69–2.22)]. Those with anti-anaerobic coverage had longer LOS (aOR 4.85; 95% CI 1.68–13.98) and longer duration of antibiotic treatment (aOR 4.14; 95% CI 2.61–6.57) than those who did not receive additional anaerobic therapy, but not more adverse drug reactions (aOR 1.01; 95% CI 0.97–1.05).

Conclusions: Omitting anti-anaerobic antibiotics may be a safe antimicrobial stewardship intervention. However, a randomized controlled trial may be warranted to definitively conclude whether additional anaerobic coverage in BTI treatment is necessary.

Introduction

Biliary tract infections (BTIs), including acute cholecystitis and ascending cholangitis, are a common reason for hospitalization, accounting for significant morbidity and mortality in hospitalized patients.[1–4] Appropriate and timely antimicrobial therapy is vital in reducing complications and preventing mortality, especially when sepsis is suspected.[5,6] The most recent Tokyo guidelines and IDSA guidelines for treatment of cholecystitis and cholangitis in adults recommend empirical treatment with first-, second- or third-generation cephalosporins alone in mild–moderate cases.[3,7] These recommendations are based on a small number of randomized controlled trials published before the mid-1990s that compared clinical and microbiological cure in patients treated with antimicrobial agents that are no longer available (e.g. mezlocillin, perfloxacin) or broad antibiotic regimens (e.g. cefepime, ampicillin plus gentamicin), which are scarcely used for treatment of cholecystitis and cholangitis in current practice.[8–12] Nevertheless, the addition of metronidazole or other antibiotics that contain additional anaerobic coverage (such as those that target *Bacteroides* spp.) is only recommended in these guidelines when patients have anaerobic bacteraemia or when there is evidence or suspicion of biliary–enteric anastomoses.[3,7]

Despite these recommendations, the exclusion of metronidazole for treatment of BTIs has not been consistently applied across institutions.[12] In the era of antimicrobial stewardship in which judicious use of antimicrobials is increasingly emphasized, optimizing treatment regimens is a priority to improve patient outcomes,

reduce healthcare-associated costs, prevent the development of antimicrobial resistance and decrease antibiotic-associated adverse drug reactions. Our study aimed to evaluate whether additional anaerobic coverage affects clinical outcomes in patients with acute cholecystitis or cholangitis, in order to streamline future quality improvement initiatives and improve patient care. We hypothesized that regimens lacking anaerobic coverage would lead to similar rates of mortality and infection relapses compared with those that include anaerobic coverage.

Materials and methods

Study setting, design and participants

This study was conducted at Sunnybrook Health Sciences Centre in Toronto, Canada, which is a tertiary care academic hospital with 678 acute care beds. This was a retrospective propensity score-matched cohort study of adults (aged ≥18 years) with BTIs, admitted between 1 April 2015 and 30 March 2021. Eligible patients were identified by specific hepatobiliary diagnostic codes (Table S1, available as Supplementary data at *JAC-AMR* Online) provided by Health Data Records during the study period. The local antimicrobial stewardship database, SPIRIT (Stewardship Program Integrating Resource Information Technology)[13] was used to identify patients who were treated with an antibiotic regimen ≥72 h. Those who received an antibiotic that was effective against anaerobes including *Bacteroides* spp. ≥72 h were considered as having received anaerobic coverage.

Patients with anaerobic bacteraemia, biliary–enteric anastomoses, presence of other conditions that required treatment or prophylaxis with concurrent antibiotics, and those discharged on antibiotics with anaerobic coverage after being treated without anaerobic coverage during admission were excluded from the study. Patients who received piperacillin/tazobactam or a carbapenem regimen for ≥72 h were also excluded, because prolonged duration of these agents are likely to be used in patients with more severe illness or history of MDR pathogens.

Study outcomes

The primary outcome was a composite of mortality within 30 days, or relapse within 90 days of source control or completion of antimicrobial management if medical management only was used. Relapse was defined as documentation of signs and symptoms compatible with BTIs and treatment with antibiotics. Secondary outcomes included hospital length of stay (LOS), duration of antibiotic therapy and adverse drug reactions attributed to antibiotic therapy.

Data collection

The electronic medical record was reviewed to confirm patient eligibility and to extract outcomes, comorbidities, laboratory parameters, surgical procedures and adverse drug reactions. Patient demographics, LOS, ICU admissions, antibiotic prescription data and microbiology results were extracted from SPIRIT.

Statistical analysis

Continuous and categorical variables were expressed using the Mann–Whitney *U*-test and Student's *t*-test, respectively. Optimal full match using a propensity score was performed to balance the baseline characteristics between treatment groups. The propensity score model incorporates 21 covariates associated with either recurrent BTIs or mortality in the literature or based on clinical judgement.[4,14,15] These covariates included age, gender, specific hepatobiliary diagnostic codes, malignancy, admission to ICU, presence of biliary stent on admission, history of congestive heart failure, hypertension, diabetes, chronic kidney disease, pancreatitis, liver disease, immunosuppression, positive biliary fluid or blood cultures, history of BTIs, history of hepato-pancreato-biliary cancers, elevated WBC count, elevated ALT or alkaline phosphatase, elevated bilirubin, presence of fever on admission, and whether a source control procedure was performed. Optimal full matching is a method that uses subclasses formed by one treated subject and one or more control subjects or one control subject and one or more treated subjects, in a way that minimizes the interclass distances in the matched sample. This matching method assigns weights to every subject within each subclass, thereby allowing for all patients to be included in the final sample size. Compared with other propensity score-matching methods such as 'nearest-neighbour' matching, optimal full matching minimizes the average distance across any matched pairs, and improves generalizability by including all patients within the sample.[16] Balance between groups was assessed using standardized mean differences and was considered similar when less than 0.1. The marginal OR for the primary outcome and secondary outcomes were calculated using a weighted generalized linear regression model.

Sensitivity analyses were performed by conducting the analysis on patients with positive cultures only, as well as excluding patients who did not have a history of hepato-pancreato-biliary cancers. All statistical analysis was conducted using the R Project software (version 4.0.5).[17]

Sample size calculation

In comparison with a recent report of a 20.6% treatment failure rate in patients with BTIs treated with anaerobic coverage, we used a more conservative estimate of 15% for the baseline event rate in our study. To determine if there is a difference in the primary outcome between the two treatment groups with a 95% confidence, and 80% power, we calculated that we would require 143 patients in each group.[18,19]

Ethics

This study received institutional approval by the Sunnybrook Research Ethics Board on 5 May 2021 (Project Identification Number: 4870).

Results

Study population

A total of 1446 patients were screened for eligibility (Figure 1) during the study period. After applying exclusion criteria, 398 were included in the analysis; 209 (53%) patients were treated without anaerobic coverage and 189 (47%) were treated with anaerobic coverage.

The demographic and clinical characteristics of patients prior to the propensity-score analysis in the two treatment groups

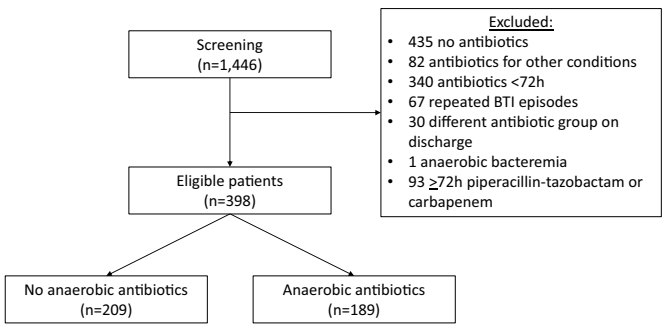

Figure 1. Study flow diagram.

are described in Table 1. Compared with patients treated without anaerobic coverage, patients treated with anaerobic coverage were older (71 ± 16 versus 63 ± 19 years; $P < 0.001$), more likely to be male (56.6% versus 43.1%; $P = 0.009$), more likely to be admitted to the ICU (8.5% versus 3.3%; $P = 0.049$), had more malignancies (30.7% versus 15.8%; $P < 0.001$), hepato-pancreato-biliary cancers (16.9% versus 5.3%; $P < 0.001$), diabetes (29.1% versus 18.7%; $P = 0.02$), chronic kidney disease (10.1% versus 4.3%; $P = 0.041$), stents (19.6% versus 3.3%; $P < 0.001$), temperatures >38°C (46.0% versus 20.1%; $P < 0.001$), history of BTIs (25.9% versus 6.2%; $P < 0.001$) and more likely to have positive biliary fluid or blood cultures (12.2% versus 5.7%; $P = 0.037$). The most common bacterium isolated from blood cultures in either group was *Escherichia coli* ($n = 7$ in those treated without anaerobic coverage; $n = 10$ in those treated with anaerobic coverage), followed by *Klebsiella pneumoniae* ($n = 3$ in those treated without anaerobic coverage; $n = 4$ in those treated with anaerobic coverage). No anaerobic organisms were isolated from blood or bile cultures.

Most patients ($n = 198$; 94.7%) treated without anaerobic coverage received a cephalosporin ± ampicillin, whereas the addition of metronidazole to the same regimen was most used for the patients in the anaerobic coverage group ($n = 119$; 63%).

Primary outcome

All patients ($n = 398$) were included after optimal full matching was applied. Post-matching, 13 covariates (age, gender, ICU admission, history of BTIs, pancreatitis, liver disease, malignancy, history of hepato-pancreato-biliary cancers, hypertension, chronic renal failure, presence of stent, elevated bilirubin and elevated ALT or alkaline phosphatase) had a standardized mean difference (SMD) of <0.1, indicating adequate balance between treatment groups. However, eight covariates had an SMD of >0.1 (Figure S1).

In the primary outcome analysis, 2 (1%) patients who were treated with additional anaerobic coverage died and 25 (13.2%) had a relapse of their infection. In comparison, no patients in the group without anaerobic coverage died, but 8 (3.8%) were readmitted for treatment of biliary tract infections. The unadjusted analysis showed that anaerobic coverage was associated with increased odds of death or relapse (OR 4.19; 95% CI 1.85–9.47) (Table 2). However, with propensity matching there was no significant difference in primary outcome between those who received additional anaerobic coverage and those who did not [adjusted OR (aOR) 1.23; 95% CI 0.69–2.22] (Table 2).

Secondary outcomes

Patients treated with antibiotics that did not provide anaerobic coverage had a median (IQR) LOS of 3 (3–5) days and a mean (SD) duration of antibiotic therapy of 3.9 ± 1.5 days, whereas those treated with an anaerobic regimen had a median (IQR) LOS of 5 (3–7) days and a mean (SD) duration of antibiotic therapy of 5.5 ± 3.1 days. After propensity-score matching, patients who received anaerobic coverage had a significantly longer LOS and duration of antibiotic therapy (aOR 4.85; 95% 1.68–13.98 and aOR 4.14; 95% CI 2.61–6.57, respectively) (Table 2).

Nine patients treated with anaerobic coverage and two patients treated without anaerobic coverage developed *Clostridioides difficile* infection, while only one patient in the study (treated without anaerobic coverage) experienced a rash attributed to their antibiotic regimen. There was no significant difference in adverse drug reactions (combined rate of *C. difficile* infections and rashes) between the two groups in the adjusted analyses (aOR 1.01; 95% CI 0.97–1.05) (Table 2).

Sensitivity analysis

After excluding patients who had negative blood cultures (Table S2), there was still no significant difference in the primary outcome between patients who received additional anaerobic coverage and those who did not (aOR 2.1; 95% CI 0.08–52.65). Similarly, when looking specifically at patients who had hepato-pancreato-biliary cancers (Table S2), there was no significant differences in the primary outcome between groups (aOR 13.44; OR 0.51–354.40).

Discussion

Our study shows that in patients with BTIs, additional antibiotics that target anaerobic organisms including *Bacteroides* spp. are not associated with a statistically significant difference in mortality or relapse compared with regimens that do not cover these anaerobes. International guidelines have consistently supported the addition of anti-anaerobic coverage for treatment of BTIs in certain circumstances, despite those recommendations being formed on the basis of studies that used agents that are no longer marketed and combinations that may be considered broad by current standards (e.g. ampicillin plus aminoglycosides).[2,3,7] In addition, the effect of antimicrobial therapy on mortality outcomes is unlikely to reflect current practice due to advances in surgical techniques over the last 30 years, which have decreased fatality of BTIs 5-fold.[20,21] Our findings underscore the limited utility of additional anti-anaerobic antibiotics in regimens that already provide adequate treatment of the most commonly encountered bacteria in BTIs.

In patients screened for study inclusion, only one patient had anaerobic bacteraemia, which is in agreement with prior evidence showing that *Bacteroides fragilis* is not commonly encountered in biliary tract or blood samples of patients with cholecystitis or cholangitis.[2,3,15,22,23] The most frequently isolated organisms in blood cultures from our patient sample were *E. coli* ($n = 17$; 53%) *and K. pneumoniae* ($n = 7$; 22%), which also aligns with previously reported epidemiological studies examining the microbiology of patients with BTI.[23–25]

To our knowledge, there are only two recent trials that have examined clinical outcomes in patients with BTIs who were treated with antibiotics that do and do not cover anaerobic organisms such as *Bacteroides* spp.[19,26] Lee *et al.*[26] prospectively excluded metronidazole from standard therapy in adults with acute cholecystitis and compared findings to a historical cohort of 338 patients who were treated with a regimen that included metronidazole. They found that there was no difference in the rate of overall mortality or cholangitis-related mortality between the patients who received metronidazole and those who did not (1.2% versus 0.5%; $P = 0.34$% and 0.9% versus 0%; $P = 0.15$, respectively). Similarly, Wu *et al.*[19] conducted a propensity score-adjusted multivariable analysis on 87 Taiwanese patients with BTIs and showed that the treatment failure rate

Table 1. Baseline characteristics

	No anaerobic coverage $N=209$	Anaerobic coverage $N=189$	*P* value	ASD prior to propensity-score matching	ASD after propensity-score matching
ICD-10 code, (%)			<0.001	0.6724	0.1459
81–81.9 Cholecystitis	67 (32.1)	66 (34.9)			
80.0–80.11 Calculus of gallbladder with cholecystitis	91 (43.5)	30 (15.9)			
80.4–80.41 Calculus of bile duct with cholecystitis	24 (11.5)	10 (5.3)			
83–83.08 Cholangitis	13 (6.2)	43 (22.8)			
80.3–80.31 Calculus of bile duct with cholangitis	9 (4.3)	17 (9.0)			
83.1 Obstruction of bile duct without calculus	4 (1.9)	13 (6.9)			
82.2, 83.2 Perforation of bile duct or gallbladder	1 (0.5)	8 (4.2)			
82.8, 83.8 Other specified diseases of biliary tract	0 (0.0)	2 (1.0)			
Age, mean (SD)	63.11 (18.50)	71.19 (16.27)	<0.001	0.4965	0.0787
Female, *n* (%)	119 (56.9)	82 (43.4)	0.009	0.2734	0.0638
Positive cultures, *n* (%)	12 (5.7)	23 (12.2)	0.037	0.1966	0.1794
Bile cultures	0 (0.0)	3 (13.0)[a]			
Bacteraemia	12 (100)	20 (87.0)			
E. coli	7 (58.3)	10 (50.0)			
Klebsiella spp.	3 (25.0)	4 (20.0)			
Other/polymicrobial	2 (16.6)	6 (30.0)			
ICU admission, *n* (%)	7 (3.3)	16 (8.5)	0.049	0.1838	0.0499
Past medical history, *n* (%)					
History of BTIs	13 (6.2)	49 (25.9)	<0.001	0.4497	0.0291
Liver disease	5 (2.4)	11 (5.8)	0.138	0.1464	0.0548
Pancreatitis	10 (4.8)	7 (3.7)	0.776	0.0572	0.0895
Congestive heart failure	11 (5.3)	11 (5.8)	0.982	0.0238	0.1525
Hypertension	90 (43.1)	97 (51.3)	0.122	0.1653	0.0799
Immunosuppression	8 (3.8)	14 (7.4)	0.18	0.1367	0.2955
Malignancy	33 (15.8)	58 (30.7)	0.001	0.3230	0.0911
Hepato-pancreato-biliary cancers	11 (5.3)	32 (16.9)	<0.001	0.3111	0.0159
Diabetes	39 (18.7)	55 (29.1)	0.02	0.2298	0.1082
Chronic renal failure	9 (4.3)	19 (10.1)	0.041	0.1911	0.0433
Presence of stent on admission	7 (3.3)	37 (19.6)	<0.001	0.4090	0.0533
Source control procedure	183 (87.6)	134 (70.9)	<0.001	0.3668	0.1846
Laboratory parameters					
WBC <4 or >10 $\times 10^9$ cells/L, *n* (%)	120 (57.4)	121 (64.0)	0.214	0.1376	0.1095
Temperature >38°C, *n* (%)	42 (20.1)	87 (46.0)	<0.001	0.5204	0.1219
Bilirubin >20 μmol/L, *n* (%)	108 (51.7)	108 (57.1)	0.321	0.1105	0.0026
ALT >31 U/L or alkaline phosphatase >120 U/L, *n* (%)	108 (51.7)	108 (57.1)	0.321	0.1105	0.0005
Main antibiotic regimen[b]					
First- or third-generation cephalosporin ± ampicillin	198	0	<0.001		
First- or third-generation cephalosporin ± ampicillin plus metronidazole	0	119	<0.001		
Fluoroquinolone monotherapy	11	1	0.014		
Fluoroquinolone plus metronidazole	0	16	<0.001		
Piperacillin/tazobactam (<72 h)	0	13	<0.001		

Continued

Table 1. *Continued*

	No anaerobic coverage $N=209$	Anaerobic coverage $N=189$	*P* value	ASD prior to propensity-score matching	ASD after propensity-score matching
Amoxicillin/clavulanic acid	0	38	<0.001		
Carbapenem (<72 h)	0	1	0.96		

ASD, absolute standardized difference.
[a]*E. coli*, *Mycobacterium fortuitum*, *Staphylococcus aureus*.
[b]Defined as the antimicrobial regimen that comprised the longest duration within a treatment course.

Table 2. Primary and secondary outcomes before and after propensity-score matching

	OR (95% CI)[a]	aOR (95% CI)[a]
Mortality (within 30 days) or relapse (within 90 days)	4.19 (1.85–9.47)	1.23 (0.69–2.22)
Secondary outcomes		
LOS, mean (SD)	6.79 (2.70–17.10)	4.85 (1.68–13.98)
Antibiotic duration, mean (SD)	5.15 (3.23–8.23)	4.14 (2.61–6.57)
Adverse drug reactions	3.43 (0.92–12.88)	1.01 (0.97–1.05)

[a]OR calculated with anaerobic coverage as the intervention group and treatment without anaerobic coverage as the reference group.

was not significantly different between the group that received anaerobic coverage and the group that did not (20.6% versus 16.7%; $P=0.677$). Although limited by its sample size, these studies both support our results and contribute to the growing body of evidence that the addition of anaerobic coverage for treatment of BTIs is unnecessary. Unlike the findings by Wu *et al.*,[19] which showed no difference in total duration of antibiotics between the groups that received definitive therapy with and without anaerobic coverage (13.2 ± 5.0 and 13.1 ± 5.7 days respectively; $P=0.913$), our study found that anaerobic coverage was associated with a significantly longer duration of therapy and longer LOS. It is possible that this finding is a result of the remaining imbalance between covariates in the two treatment groups even after propensity-score matching, owing to possible higher complexity of patients in the anaerobic group rather than a true biological reason for the difference. Despite this, there was no significant difference in adverse drug reactions between the two treatment groups in our cohort, possibly owing to the low rate of side effects associated with metronidazole,[27] which was the main anaerobic agent used for coverage of *Bacteroides* spp. ($n=135$; 71.4%).

Despite this existing evidence[19,26] and recommendations by international guidelines,[3,7] our study identified that using anaerobic antibiotics for BTIs is a common practice in our institution as 47% of patients included in this study received anaerobic coverage. This emphasizes the importance of this study to provide a contemporary evaluation of the utility of this practice.

This was the first report of sufficient sample size to address a clinically important question regarding additional anaerobic antimicrobial treatment in patients with BTIs. In addition, patient covariates were better balanced by using a propensity-score matching method, which is known to reduce indication bias and lead to an improvement in the precision of the effect of additional anaerobic coverage on the primary outcome.[28]

Our study had several limitations. First, despite using propensity-score matching to balance the baseline characteristics between groups, several covariates remained unbalanced after matching. This could have resulted in residual selection bias between the two patient groups at the time when treatment regimens were selected during their admissions. It is also possible that there were other unmeasured confounders due to the retrospective nature of this study. To definitively confirm or refute the hypothesis that anaerobic coverage does not affect survival outcomes in patients with BTIs, a randomized controlled trial may be warranted. Additionally, although we used all available patients in the statistical analysis, there can be a loss in precision due to the assigned weights in the optimal full matching method. On the other hand, including all of the patients within the sample may help increase generalizability of the study to more patients receiving antibiotic treatment for BTIs. Another limitation is the likelihood that the results of the sensitivity analyses were underpowered given the presence of the wide CIs. Moreover, this was a single-centre study and therefore patients who may have been readmitted to other centres with BTIs would not have been captured during screening. This limits the generalizability of our findings and could have led to a potential underestimation of our primary outcome frequency. However, we estimate those cases to be few as the hospital-catchment area would remain consistent for those readmitted patients. Finally, it is important to note that although there were no anaerobic organisms isolated in our study, the true number and type of anaerobes implicated in BTIs may be underestimated due to the low yield of anaerobes grown in cultures outside of ideal anaerobic collection and growth techniques.[29] Even though our study aimed to reflect the common approaches to sampling of organisms implicated in BTIs, which included anaerobic blood cultures, further studies incorporating strict anaerobic detection techniques of biliary samples may be beneficial. In conclusion, the outcomes of patients who receive anaerobic coverage for treatment of BTIs do not differ significantly from those without the additional coverage. Omitting anti-anaerobic antibiotics may be a safe antimicrobial stewardship intervention. However, a randomized controlled trial may be warranted to definitively conclude whether additional anaerobic coverage in BTI treatment is necessary.

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Transparency declarations

None to declare.

Author contributions

M.S., M.E., P.W.L. and N.D. were involved in the conceptualization of the study, design of the methodology, and contributed to the final data analysis and interpretation. M.S. conducted the data collection and drafted the manuscript. All authors contributed to the revision of the manuscript and approve of the final version submitted.

Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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