Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 8: 1–7

DOI: 10.1177/2050312120930898
journals.sagepub.com/home/smo
SAGE

Analysis of the impact of secondary prophylaxis on *Clostridioides difficile* recurrence in critically ill adults

Kathryn A Connor and Kelly M Conn

Abstract

Introduction: *Clostridioides* (formerly *Clostridium*) *difficile* infection recurrence in patients re-exposed to antibiotics for treatment of a non-*Clostridioides difficile* infection is high at approximately 33%. Low-dose per os vancomycin (e.g. 125 mg q12 h) or metronidazole (e.g. 500 mg intravenous/per osq8 h) may help prevent recurrences, but study of secondary prophylaxis in critically ill patients is needed.

Objectives: To determine whether critically ill adults receiving low-dose per os vancomycin for secondary *Clostridioides difficile* infection prophylaxis have fewer recurrences of *Clostridioides difficile* infection in 90 days compared with patients receiving metronidazole for secondary *Clostridioides difficile* infection prophylaxis or control (no secondary prophylaxis).

Methods: This was a retrospective, two-center, observational study in a large academic medical center and affiliated community hospital. Included patients had a history of *Clostridioides difficile* infection within 1 year of receiving antibiotics for clinical care. We compared patients receiving secondary prophylaxis with vancomycin or metronidazole and control patients; in addition, an unplanned fourth group (vancomycin/metronidazole combination) was identified and analyzed. The primary outcome was *Clostridioides difficile* infection recurrence within 90 days of a course of broad-spectrum antibiotic therapy. Fisher's exact, analysis of variance, and Kruskal–Wallis tests were used to compare *Clostridioides difficile* infection recurrence with prophylaxis group and additional contributing factors.

Results: Eighty-two patients were included: 38 control (46.3%), 20 metronidazole (24.4%), 17 vancomycin (20.7%), and 7 combination (8.5%). Ten of 82 patients (12.2%) had at least one *Clostridioides difficile* infection recurrence; 8/38 patients in the control group (21.1%), 1/7 patients in the combination group (14.3%), 1/17 patients in the per os vancomycin group (5.9%), and 0/20 in the metronidazole group (0%; $p = 0.073$). As a post hoc secondary analysis, the three prophylaxis groups were coalesced into one group and compared with control (4.5% vs 21%; $p = 0.039$). Additional factors (e.g. age, obesity, immunosuppression, acid suppression) were not significantly associated with *Clostridioides difficile* infection recurrence or with prophylaxis group.

Conclusion: There was no difference in *Clostridioides difficile* infection recurrence between prophylaxis groups, however, given the low recurrence rate, prospective evaluation with a larger sample of critically ill patients is necessary.

Keywords

Antibiotics, clinical pharmacy, diarrhea, evidence-based practice, infectious diseases, vancomycin

Date received: 24 February 2020; accepted: 11 May 2020

Introduction

The Centers for Disease Control and Prevention (CDC) states that prevention of *Clostridioides* (formerly *Clostridium*) *difficile* infections (CDIs) is a national priority, as they are associated with high morbidity, mortality, and cost.[1] CDIs were estimated to cause nearly 500,000 infections in the United States in 2011, with about 83,000 of these patients experiencing at least one recurrence and 29,000 associated deaths.[2] Recurrence rates for health care-associated CDI have been reported to vary from 5% to 50%, with an average of 20%, with the risk of recurrence increasing with subsequent episodes of CDI.[3,4] Recurrent CDI is an emergent concern, especially in vulnerable critically ill patients, and these infections

Department of Pharmacy Practice and Administration, Wegmans School of Pharmacy, St. John Fisher College, Rochester, NY, USA

Corresponding author:
Kathryn A Connor, Department of Pharmacy Practice and Administration, Wegmans School of Pharmacy, St. John Fisher College, 3690 East Avenue, Rochester, NY 14618, USA.
Email: kaconnor@sjfc.edu

pose challenges in treatment and an ongoing risk of transmission when symptoms recur. Current prevention efforts focus on minimizing modifiable risks, and providing appropriate antimicrobial stewardship, infection control, and environmental management, with limited data evaluating pharmacologic prevention.

The risk of CDI recurrence in patients who are treated for their initial CDI and recover, but subsequently receive broad-spectrum antibiotics for a different infection (e.g. pneumonia) is high at approximately 33%.[5] The administration of low-dose per os (PO) vancomycin (e.g. 125 mg q12 h) or PO/intravenous (IV) metronidazole (e.g. 500 mg q8 h) may help to prevent recurrences in these high-risk patients by making conditions less favorable to develop CDI while receiving subsequent antibiotics. The mechanism by which PO vancomycin or PO/IV metronidazole may help prevent CDI recurrence while receiving subsequent antibiotics is unclear, but for PO vancomycin may involve reduction of cytotoxin production when *C. difficile* burden in the gut is low, while minimizing disruption to the normal gut flora.[5] At our medical center at the time of this study, interest in these two drugs for secondary CDI prophylaxis arose due to their validity as treatment options for CDI, their availability and cost at our sites, and the low concern for adverse sequelae with short-term use.

Study of secondary CDI prophylaxis in an intensive care unit (ICU) setting is greatly needed. There are no reported prospective studies, and no specific evaluation in critically ill patients, leaving the role, efficacy, and safety of secondary CDI prophylaxis, both short and long terms, largely undefined in this complex population.[5–7] At the University of Rochester Medical Center (URMC), our critical care teams have commonly prescribed secondary CDI prophylaxis to patients, as in many other institutions nationally, mainly based on their own clinical judgment given the limited body of evidence. Thus, this study evaluated the impact of secondary CDI prophylaxis on CDI recurrence in critically ill patients receiving broad-spectrum antibiotics. The purpose of this study was also to assess the effects of other risk factors on *C. difficile* recurrence after an episode of *C. difficile* with subsequent antibiotic exposure. This study was conducted to evaluate the association between low-dose vancomycin secondary prophylaxis and the risk of recurrent CDI in adult critically ill patients receiving broad-spectrum antibiotics when compared with PO/IV metronidazole or no prophylaxis."

Materials and methods

We performed a retrospective, two-center, observational cohort study in a mixed population of critically ill adult patients receiving non-CDI antibiotics and secondary CDI prophylaxis (PO vancomycin or metronidazole) or control. This study was approved by and conducted in compliance with requirements of the UR Institutional Review Board, and informed consent was waived. Adult patients were eligible if they were admitted to an ICU for ⩾ 72 h at either of two urban teaching hospitals within URMC: a large academic medical center (Strong Memorial Hospital, which has 886 beds, with about 100 adult ICU beds) or an affiliated community hospital (Highland Hospital, which has approximately 260 beds, with 14 adult ICU beds). Patients were included if they had a history of CDI within the past year and subsequently received broad-spectrum systemic antibiotics to treat a known or suspected non-CDI for ⩾48 h. CDI was defined as diarrhea or loose stools with presence of *C. difficile* toxin as determined by cytotoxin assay, enzyme-linked immunoassay, the empiric provision of a course of CDI treatment, or direct visualization of pseudomembranous colitis within 90 days of study inclusion. Broad-spectrum antibiotic regimens included ⩾ 1 of the following: a fluoroquinolone, cephalosporin, macrolide, penicillin, aminoglycoside, clindamycin, beta-lactam/beta-lactamase inhibitor combination, carbapenem, trimethoprim–sulfamethoxazole, daptomycin, linezolid, aztreonam, and/or IV vancomycin. All agents in the respective antibiotic classes were included as applicable; please see Appendix 1 for specific antibiotics included. "Broad-spectrum" therapy was defined by the standard already set by the CDC's *National Healthcare Safety Network* list of identified broad-spectrum antimicrobial agents, and in consultation with our institutional Infectious Disease Clinical Pharmacy Specialists.[8] Only the most recent course of broad-spectrum antibiotics was included if there was more than one eligible course. The date range for inclusion was January 1, 2011 (when the electronic medical record was first being utilized at both institutions) through December 31, 2017. Patients were excluded if they were being treated for a known or suspected active CDI or if they died within 72 h of receiving broad-spectrum antibiotics. The primary outcome was CDI recurrence within 90 days of receiving broad-spectrum antibiotics. Patients were followed out to 90 days within the URMC electronic medical record system. We compared patients receiving PO vancomycin to patients receiving metronidazole IV or PO or control patients receiving no secondary prophylaxis. Patients had to receive vancomycin or metronidazole prophylaxis for at least 50% of their non-CDI antibiotic regimen to be included. An unexpected fourth prophylactic group (vancomycin and metronidazole combination) was identified and included in the analysis. Patients who appeared to be receiving metronidazole only for the indication of anaerobic coverage and not necessarily for secondary CDI prophylaxis were included in the metronidazole cohort. A first or subsequent recurrence of CDI was defined as diarrhea or loose stools with presence of *C. difficile* toxin as determined by cytotoxin assay, enzyme-linked immunoassay, the empiric provision of a subsequent course of CDI treatment, or direct visualization of pseudomembranous colitis within 90 days of study inclusion. The medical center follows a consistent *C. difficile* testing policy, involving a two-step approach, starting with the enzyme

immunoassay (EIA, formerly Alere, subsequently acquired by Abbott)/glutamate dehydrogenase (GDH) and then reflexing to polymerase chain reaction (PCR; Cepheid GeneXpert®) if the sample is EIA negative, but GDH positive. Patient demographics and CDI recurrence data were collected, including presence of immunosuppression (immunosuppressive conditions or drugs, including solid organ transplant, cancer, human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE), corticosteroids, and chemotherapy), dates and frequency of CDI, broad-spectrum antibiotic regimens used and their durations, prophylactic antibiotic regimens used and their durations, and death or discharge within 90 days. We designed this study to be as practical and applicable as possible to clinical practice in our region in the following ways: (1) by the comparison of the three different prophylactic groups, (2) including all eligible adult critically ill patients since the inception of our electronic medical record system at two large affiliated teaching hospitals (3) utilizing common CDI diagnostic definitions and testing criteria (4) using limited exclusion criteria. An electronic report was generated to identify eligible patients, and manual data collection from the electronic medical record was mainly conducted by K.A.C. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at UR Medicine. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.[9]

All statistical analyses were completed using Statistical Package for the Social Sciences (SPSS) Statistics (v24, SPSS Inc.) and Microsoft (MS) Excel. Descriptive statistics were used to summarize baseline demographics and clinical data. Continuous and ordinal data were assessed for normality; analysis of variance (ANOVA) was used to compare age and body mass index (BMI) between prophylaxis groups and Kruskal–Wallis test was used to compare time since previous *C. difficile* episode, duration of antibiotics, hospital length of stay, and ICU length of stay between groups. All other categorical variables were compared between prophylaxis groups using Fisher's exact test: this includes the primary outcome (CDI recurrence), sex (male vs female), race (white, African American, other/not reported), hospital admission (academic vs community), number of previous episodes (1, 2, 3, 4, and 5), resident of long-term care, ICU service (medical, surgical, burn/trauma, cardiac, and pediatric), concomitant use of a proton pump inhibitor (PPI) or a histamine-2 receptor antagonist (H2RA), immunosuppression, infectious disease team consult, transfer from a long-term care facility.[4,10–13] Sample size for this study (three groups: for each of the two prophylaxis groups and one control group), using a *C. difficile* recurrence rate of approximately 30%[5] in the control group was determined to be 36 per group, or 62 per group, to detect a 15% and 20% difference between all three groups, respectively, using an alpha level of .05 and power of 80%. A fourth group that was not anticipated by investigators was added, and was not included in our pre-study sample anticipated.

Results

Four hundred ninety-four mixed critically ill adult patients were screened for this study. Two hundred two patients met inclusion criteria, and 120 of those were excluded because they had a known or suspected active *C. difficile* infection at the time broad-spectrum antibiotics were started or died within 72 h of receiving broad-spectrum antibiotics. Eighty-two mixed critically ill adult patients were included in this study, and patients were mainly older white men with one prior episode of CDI, admitted to the medical ICU (MICU) of a large academic hospital, who were not being followed by an infectious disease team. Patients were largely admitted for respiratory failure or infections, and were being treated with non-CDI antibiotics mainly for pneumonia and sepsis. Most patients (49/82, 59.8%) were receiving more than one class of broad-spectrum antibiotics. Furthermore, a portion of patients (24/82, 29.3%) had a history of more than one episode of CDI, and most (60/82, 73.2%) were discharged alive. Baseline characteristics were similar between the study cohorts (Table 1), with the exception of patients in the community hospital receiving less secondary CDI prophylaxis overall. Thirty-eight patients (46.3%) received no secondary CDI prophylaxis, 20 (24.4%) received IV or PO metronidazole, 17 patients (20.7%) received PO vancomycin, and 7 (8.5%) received a combination of PO vancomycin and IV or PO metronidazole. There was no evidence of prior clinical failures or antimicrobial allergies or intolerances that influenced the choice of secondary prophylaxis regimens. The specific secondary prophylaxis regimens are described further in Table 2, but patients predominantly received PO vancomycin 125 mg q12 h or PO/IV metronidazole 500 mg q8 h. For the primary outcome of CDI recurrence, 10/82 patients (12.2%) had at least one CDI recurrence; 8/38 patients in the control group (21.1%), 1/7 patients in the combination group (14.3%), 1/17 patients in the PO vancomycin group (5.9%), and 0/20 in the metronidazole group (0%; $p = 0.073$). Of the two patients who recurred while receiving secondary CDI prophylaxis, one patient received a combination of PO vancomycin 125 mg q6 h and PO metronidazole 500 mg q8 h and had a history of only one prior episode of *C. difficile*. The other patient who recurred received PO vancomycin 125 mg q12 h and had a history of two prior episodes of *C. difficile*. Four patients in the control group (50%) had two recurrences each. No patient in this study had more than two recurrences within the 90 day follow-up period, and no patient that received any pharmacologic secondary prophylaxis regimen recurred more than one time

Table 1. Comparison of baseline and demographic characteristics by prophylaxis group (n = 82).

	PO Vancomycin (n = 17)	Metronidazole (n = 20)	Combination (n = 7)	Control (n = 38)	P-value
Primary outcome: CDI recurrence	1 (5.9)	0 (0.0)	1 (14.3)	8 (21.1)	0.073
Age, years, mean (SD)	60.3 (15.2)	59.7 (14.7)	54.7 (19.8)	56.9 (15.3)	0.776
Sex, male, N (%)	14 (82.4)	12 (60.0)	3 (42.9)	19 (50.0)	0.119
Race, N (%)					
White	16 (94.1)	13 (65.0)	6 (85.7)	28 (73.7)	0.277
African American	0 (0.00)	5 (25.0)	1 (14.3)	8 (21.1)	
Other/not reported	1 (5.9)	2 (10.0)	0 (0.0)	2 (5.3)	
Hospital admission, N (%)					
Academic	11 (64.7)	20 (100.0)	7 (100.0)	26 (68.4)	0.004
Community	6 (35.3)	0 (0.0)	0 (0.0)	12 (31.6)	
BMI (mean, SD)	26.5 (3.7)	27.0 (7.0)	28.0 (10.2)	28.6 (8.6)	0.768
Number of previous CDI episodes, median (IQR)	1 (1–2)	1 (1–1)	1 (1–2)	1 (1–2)	0.193
Immunosuppression, N (%)	5 (29.4)	9 (45.0)	4 (57.1)	18 (47.4)	0.568
Resident of long-term care, N (%)	6 (35.3)	3 (15.0)	3 (42.9)	14 (36.8)	0.295
ICU service (predominate), N (%)					
Medical	10 (58.8)	9 (45.0)	4 (57.1)	29 (76.3)	0.190
Surgical	2 (11.8)	8 (40.0)	2 (28.6)	4 (10.5)	
Burn/trauma	3 (17.6)	2 (10.0)	1 (14.3)	3 (7.9)	
Cardiac	2 (11.8)	1 (5.0)	0 (0.0)	1 (2.6)	
Pediatric[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	
Hospital length of stay, days, median (IQR)	20 (13.0–92.5)	36 (13.5–101.3)	66 (10–165.0)	35 (17.8–88.3)	0.801
ICU length of stay, days, median (IQR)	9 (4.5–41.0)	11.5 (5.0–26.3)	8 (4.0–25.0)	12.5 (6.0–39.8)	0.820
Discharged alive, N (%)	12 (70.6)	17 (85.0)	6 (85.7)	27 (71.1)	0.617
Had infectious disease team consult, N (%)	5 (29.4)	3 (15.0)	2 (28.6)	7 (18.4)	0.659
Concomitant use of acid suppression (PPI or H2RA), N (%)	8 (47.1)	14 (70.0)	5 (71.4)	31 (81.6)	0.080
Duration of systemic antimicrobial therapy, days, median (IQR)	8 (5.0–12.5)	7.0 (5.0–10.5)	12.0 (7.0–35.0)	8.5 (5.8–14.3)	0.35
Time since previous CDI, days, median (IQR)	42.0 (25.5–159.5)	74.0 (24.0–169.0)	73.0 (14.0–75.0)	114.0 (61.0–195.5)	0.07

PO: per os; CDI: *Clostridium difficile* infection; SD: standard deviation; BMI: body mass index; IQR: interquartile range; ICU: intensive care unit; PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist.
[a]This was an adult patient in the pediatric ICU.

within this timeframe. As a post hoc secondary analysis, the three prophylaxis groups were coalesced into one and compared with control with the intent of comparing any form of potential secondary prophylaxis with no prophylaxis. The recurrence of CDI was 2 of 44 (4.5%) with any prophylaxis and 8 of 38 (21%) in the control group (p = 0.039). Additional contributing factors, including age, time since previous episode, duration of antibiotics, immunosuppression, obesity, transfer from a long-term care facility, and the use of acid suppressing drugs (H2RA and PPIs) were not significantly associated with CDI recurrence or with prophylaxis group.

Discussion

Recurrent CDI is a pervasive, significant clinical concern, especially in complex, vulnerable critically ill patients. The provision of secondary CDI prophylaxis has become commonplace in our and other institutions, despite the lack of rigorous study in any population, and no clear evidence of benefit in general inpatients. Our two-center, retrospective study demonstrated that CDI recurrence does not differ between the groups (critically ill adults receiving PO vancomycin, metronidazole, or combination therapy, or control patients receiving no secondary prophylaxis).

Of note, an unexpected fourth group (vancomycin/metronidazole combination) was identified and analyzed. We thought this was an interesting finding to report, based on decisions that clinicians were making at the time of patient treatment. To our knowledge, there is no literature to support the use of combination therapy as secondary CDI prophylaxis in critically ill patients, and there was not a protocol in place at our institution that would have recommended combination therapy. Two of the seven patients (28.6%) were being followed by our transplant infectious disease team at

Table 2. Summary of secondary prophylaxis regimens (n = 82).

None (control), N (%)	38 (46.3)
Metronidazole	20 (24.4)
IV	11 (55)
500 mg q8 h	10 (90.9)
500 mg q12 h	1 (9.1)
PO	9 (45)
500 mg q8 h	6 (66.6)
500 mg q6 h	2 (22.2)
250 mg q6 h	1 (11.1)
PO vancomycin	17 (20.7)
125 mg q12 h	7 (41.2)
125 mg q6 h	5 (29.4)
250 mg q6 h	4 (23.5)
125 mg q24 h	1 (5.9)
Combination	7 (8.5)
PO vancomycin 125 mg q12 h IV metronidazole 500 mg q8 h	5 (71.4)
PO vancomycin 125 mg q12 h + PO metronidazole 500 mg q8 h	1 (14.3)
PO vancomycin 125 mg q6 h + PO metronidazole 500 mg q8 h	1 (14.3)

IV: intravenous; PO: per os.

the time, and all of the combination therapy patients were admitted to the academic hospital. In addition, in a post hoc secondary analysis, a statistically significant result was found when the three secondary prophylaxis groups were coalesced into a single group receiving any form of secondary prophylaxis compared with control. This suggests that any form of prophylaxis may be more effective than no prophylaxis, and this may be a hypothesis worthy of further exploration.

This study emphasizes the challenging and common clinical question that arises when patients with a recent or persistent history of CDI require subsequent antibiotics, as there is little data to guide clinical practice regarding the provision of secondary prophylaxis, and many unanswered questions remain.[4,14] To our knowledge, based on an extensive literature search and a review of information from clinicaltrials.gov, ours is the first known study to evaluate the role of secondary CDI prophylaxis in a critically ill patient population, and there are no ongoing trials evaluating CDI secondary prophylaxis specifically in the ICU setting. Of note, in our study, metronidazole-containing regimen groups had higher proportions of being in the surgical ICU. That said, we are not aware of any published studies evaluating metronidazole specifically for CDI secondary prophylaxis, in critically ill patients or otherwise. Three other retrospective studies have evaluated the role of oral vancomycin secondary prophylaxis compared with no secondary prophylaxis in general adult inpatients, and did not specifically exclude critically ill patients.[5–7] Our overall recurrence rate of 12.2% was most similar to the rate of 10% reported by Caroff and colleagues who found no consistent benefit of PO vancomycin secondary prophylaxis, although patients with only one prior CDI episode may benefit.[7] The two earlier retrospective studies did find an apparent benefit of oral vancomycin secondary prophylaxis. As referred to in the introduction, Carignan and colleagues noted a CDI recurrence rate of about 33% in patient diagnosed from 2003 to 2011, although their control group generally had lower rate of >1 CDI recurrence prior to admission. They also found that oral vancomycin significantly lowered the likelihood of subsequent recurrence in patients with a history of recurrent CDI, but did not improve recurrence rates among patients with only one prior CDI episode. The study by Van Hise and colleagues found a general benefit for oral vancomycin in reducing recurrent CDI.[6] Differences in study methodology may account to some extent for the discordant results between studies. We were unable to determine whether secondary prophylaxis was protective against subsequent CDI recurrences, potentially due to the low event rate and small sample size and subsequent high risk of a type II error.

For the first time, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)'s Clinical Practice Guidelines for *Clostridium difficile* Infection, published in 2018, address the issue of the provision of secondary CDI prophylaxis to patients.[4] These guidelines state that, despite limited evidence, consideration may be given to the administration of low-dose vancomycin (e.g. 125 mg daily) or fidaxomicin (e.g. 200 mg daily) in this situation. Our medical center does not use fidaxomicin for CDI secondary prophylaxis, and we are not aware of published evidence to support this practice. Other strategies that have been explored to reduce CDI recurrences, such as probiotics, fecal microbiota transplant, and bezlotoxumab, are also not employed routinely in our critically ill patients.[4,15] When weighing the decision of whether to initiate secondary CDI prophylaxis, clinicians should assess factors such as the length of time from previous CDI treatment, the number and severity of previous CDI episodes, and the health status of the patient (e.g. underlying frailty).[4] The most likely time for a CDI recurrence to occur is within several weeks of stopping the CDI treatment, although patients may be at risk for recurrence for at least several months afterward.[16,17]

We believe that this was a well-designed, real-world study with reasonable external validity that was conducted in a challenging patient population evaluating an important clinical issue. A specific strength of our study was the 90-day surveillance period to assess patients for *C. difficile* recurrence, as patients are still at risk for developing CDI for up to 3 months after stopping antibiotic therapy, and this longer timeframe maximized the observation of recurrences.[16,17] To exclude patients who may have received an inadequate duration of secondary prophylaxis, only patients who received secondary CDI prophylaxis for $\geqslant$50% of the duration of concomitant broad-spectrum antibiotics were included.[5] In

addition, our study is generalizable to different institutions that may have different CDI testing protocols, due to its limited exclusion criteria and the inclusion of all available patients from two affiliated teaching hospitals.

Our study was inherently limited by the retrospective, observational design and the relatively small sample size within a particularly complex patient population. There were some confounding factors that were not specifically accounted for when evaluating the risk of recurrent CDI (e.g. severity of illness, serum albumin, recent gastro intestinal (GI) surgery). Our study was underpowered given that we did not meet our sample size goal, and observed a low effect size (8.6%) and recurrence rates. Our small sample size also limits our ability to conduct multivariable analyses to control for multiple factors. A future multisite study with a larger sample size would be a reasonable next step. The study cohorts were not matched, and we did not classify the severity of CDI or the appropriateness of treatment. There were also inconsistent dosing strategies and unknown factors that may have led to the prescribing of secondary prophylaxis, which was to be expected, given that there was no formal guidance in place at the time to inform clinical decision-making. Another source of potential bias was the inclusion of only the most recent course of broad-spectrum antibiotics, since the need for repeated courses of antibiotic therapy may influence the risk of CDI. Our concern was that the repeated inclusion of the same patient would introduce an even greater bias and lack of independence in statistical testing. We did not assess the potential long-term benefit or adverse effects of secondary prophylaxis, including the incidence of colonization or subsequent infections (e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), or resistant gram-negative organisms). Furthermore, CDI recurrence event rates were low, limiting statistical evaluation. Also, we cannot rule out that some recurrences may have been relapses or involved inflammatory colitis, and our microbiology lab does not routinely test for resistant *C. difficile* strains, so that data were unavailable retrospectively. Finally, it is possible that hospital admission setting played a role in the recurrence of CDI based on bivariate analysis; however, we conducted a post hoc analysis that included control for it; hospital admission (setting) was not statistically significant ($p = 0.618$). Although this was not a factor that we anticipated needing further exploration for, we now recognize the role that future studies should have to include this confounder."

Conclusion

This was an exploratory, retrospective study of secondary CDI prophylaxis in mixed critically ill patients that does not support the routine use of secondary CDI prophylaxis. However, given the low CDI recurrence rate, evaluation with a larger, more diverse sample of critically ill patients, ideally prospectively, is necessary to fully assess the risk-versus-benefit profile of this intervention, and before any form of secondary prophylaxis can be recommended as the standard of care in the ICU. Clinicians should continue to focus on antimicrobial stewardship and other known preventive methods until robust data supporting secondary prophylaxis becomes available.

Acknowledgements

This study is part of the American College of Clinical Pharmacy's Mentored Research Investigator Training (MeRIT) Program. A preliminary analysis was presented as a poster in October 2018 at the ACCP Annual Meeting in Seattle, WA, and a final analysis was presented as a poster in May 2019 at the ACCP Virtual Poster Symposium. K. Connor is grateful to the ACCP Critical Care Practice and Research Network for awarding her a MeRIT scholarship to support her participation in the MeRIT program, her MeRIT mentors C. Haas and J. Hatton Kolpek, and Alixandra Mann, 2019 Pharm. D. candidate, for her assistance with data collection.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the University of Rochester Research Subjects Review Board, STUDY00001578.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Informed consent was not sought for the present study because of the retrospective nature of the study, and minimal risk of harm. The exact wording regarding the waiver of informed consent from our institutional IRB-approved protocol is as follows: Process of Consent—A waiver of informed consent will be requested. A waiver of HIPAA authorization will also be requested. This study is a retrospective study and, therefore, it is not feasible to obtain consent. The study poses minimal risk to patients. Direct patient involvement is not needed in the study and information will only be gathered from pre-existing data in the patients' medical record. Study data will be shared with co-investigators, but not with patients, and only de-identified analysis of the data will be shared outside of the research team.

ORCID iD

Kathryn A Connor https://orcid.org/0000-0002-3755-5435

References

1. Centers for Disease Control and Prevention. Nearly half a million Americans suffered from Clostridium difficile infections in a single year, http://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html (accessed 7 March 2019).
2. Lessa FC, Winston LG and McDonald LC. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; 372: 2368–2370.

3. Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of Clostridium difficile colitis in Quebec, Canada. *Clin Infect Dis* 2005; 40: 1591–1597.
4. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66: 987–994.
5. Carignan A, Poulin S, Martin P, et al. Efficacy of secondary prophylaxis with vancomycin for preventing recurrent Clostridium difficile infections. *Am J Gastroenterol* 2016; 111(12): 1834–1840.
6. Van Hise N, Bryant A, Hennessey E, et al. Efficacy of oral vancomycin in preventing recurrent Clostridium difficile infection in patients treated with systemic antimicrobial agents. *Clin Infect Dis* 2016; 63: 651–653.
7. Caroff DA, Menchaca JT, Zhang Z, et al. Oral vancomycin prophylaxis during systemic antibiotic exposure to prevent Clostridiodes difficile infection relapses. *Infect Control Hosp Epidemiol* 2019; 40(6): 662–667.
8. CDC. Antimicrobial use and resistance module (AUR), https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf (accessed November 25, 2019).
9. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42(2): 377–381.
10. D'Agostino RB Sr, Collins SH, Pencina KM, et al. Risk estimation for recurrent Clostridium difficile infection based on clinical factors. *Clin Infect Dis* 2014; 58(10): 1386–1393.
11. Hu MY, Katchar K, Kyne L, et al. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. *Gastroenterology* 2009; 136(4): 1206–1214.
12. Ma GK, Brensinger CM, Wu Q, et al. Increasing incidence of multiply recurrent Clostridium difficile infection in the United States: a cohort study. *Ann Intern Med* 2017; 167: 152–158.
13. Shin JH and Warren CA. Collateral damage during antibiotic treatment of C. difficile infection in the aged host: insights into why recurrent disease happens. *Gut Microbes* 2017; 8: 504–510.
14. Leedahl DD, Personett HA, Nagpal A, et al. Prevention of Clostridium difficile infection in critically ill adults. *Pharmacotherapy* 2019; 39: 399–407.
15. Brown CC, Manis MM, Bohm NM, et al. Oral vancomycin for secondary prophylaxis of Clostridium difficile infection. *Ann Pharmacother* 2019; 53(4): 396–401.
16. Hensgens MP, Goorhuis A, Dekkers OM, et al. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. *J Antimicrob Chemother* 2012; 67(3): 742–748.
17. Johnson S. Editorial commentary: potential risks and rewards with prophylaxis for Clostridium difficile infection. *Clin Infect Dis* 2016: 63; 654–655.

Appendix 1. Specific antibiotic agents included in study.

Class	Agents (arranged alphabetically)
Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin
Cephalosporins	Cefazolin, cefepime, ceftaroline, ceftriaxone, cephalexin
Macrolides	Azithromycin
Penicillins	Amoxicillin, nafcillin
Aminoglycosides	Tobramycin
Beta lactam/beta lactamase-inhibitor combinations	Piperacillin–tazobactam, Ticarcillin–clavulanic acid
Carbapenems	Ertapenem, imipenem–cilastatin, meropenem