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Original Article

Impact of oral vancomycin treatment duration on rate of *Clostridioides difficile* recurrence in patients requiring concurrent systemic antibiotics

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Abstract

Background: There is a paucity of data guiding treatment duration of oral vancomycin for *Clostridiodes difficile* infection (CDI) in patients requiring concomitant systemic antibiotics.

Objectives: To evaluate prescribing practices of vancomycin for CDI in patients that required concurrent systemic antibiotics and to determine whether a prolonged duration of vancomycin (>14 days), compared to a standard duration (10–14 days), decreased CDI recurrence.

Methods: In this retrospective cohort study, we evaluated adult hospitalized patients with an initial episode of CDI who were treated with vancomycin and who received overlapping systemic antibiotics for >72 hours. Outcomes of interest included CDI recurrence and isolation of vancomycin-resistant *Enterococcus* (VRE).

Results: Among the 218 patients included, 36% received a standard duration and 64% received a prolonged duration of treatment for a median of 13 days (11–14) and 20 days (16–26), respectively. Patients who received a prolonged duration had a longer median duration of systemic antibiotic overlap with vancomycin (11 vs 8 days; $P < .001$) and significantly more carbapenem use and infectious disease consultation. Recurrence at 8 weeks (12% standard duration vs 8% prolonged duration; $P = .367$), recurrence at 6 months (15% standard duration vs 10% prolonged duration; $P = .240$), and VRE isolation (3% standard duration vs 9% prolonged duration; $P = .083$) were not significantly different between groups. Discontinuation of vancomycin prior to completion of antibiotics was an independent predictor of 8-week recurrence on multivariable logistic regression (OR, 4.8; 95% CI, 1.3–18.1).

Conclusions: Oral vancomycin prescribing relative to the systemic antibiotic end date may affect CDI recurrence to a greater extent than total vancomycin duration alone. Further studies are needed to confirm these findings.

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Clostridioides difficile infection (CDI) is common in the hospital setting, accounting for 15% of all healthcare-associated infections in the United States.[1] Based on data from the Centers for Disease Control Emerging Infections Program, the overall incidence rate of CDI in the United States in 2020 was 101.3 cases per 100,000 persons, with 51.2 cases being community-acquired and 50.1 cases being hospital-acquired.[2] Although the overall incidence of CDI has decreased over the last decade, the incidence of recurrent CDI has increased, highlighting the need to identify strategies to reduce recurrence.[3] Recurrent disease has been reported in 20%–35% of cases in the United States, with notable risk factors including advanced age, gastric acid suppressive therapy, infection with the hypervirulent NAP1/B1/027 strain, and most importantly, exposure to systemic antibiotics that may disrupt intestinal microflora and enable overgrowth of *C. difficile*.[3–7]

The pathogenesis of CDI involves disruption of the microbiome, and cessation of antibiotics in patients with active CDI is critical to restoring normal bowel flora and improving CDI-related outcomes. In a trial evaluating the effect of concomitant antibiotics on response to fidaxomicin or oral vancomycin for CDI, patients who received concomitant antibiotics had a lower clinical cure rate, extended time to resolution of diarrhea, and a higher recurrence rate compared to those who did not require antibiotics.[8] Nevertheless, antibiotics may remain necessary in

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patients with CDI due to new or persistent accompanying infections, and data to guide management in these circumstances are limited.[9]

Current practice guidelines recommend a 10-day course of fidaxomicin or oral vancomycin for initial episodes of CDI, but they do not offer a separate recommendation for patients receiving concomitant antibiotics for part, or for the entirety of, their CDI treatment course. The major trials that established this 10-day duration of therapy either did not comment on the use of concomitant antibiotics or permitted use for up to 7 days without defining which agents were used and for what duration.[10–13] In 3 small, retrospective studies evaluating the impact of prolonging CDI-active therapy in patients requiring concurrent antibiotics, no reduction in disease recurrence with extension was observed. However, these studies were limited by prevalent use of oral metronidazole as primary treatment for CDI, lack of description of CDI disease severity, and short duration of follow-up or loss to follow-up.[14–16]

Because CDI practice guidelines do not address duration of oral vancomycin treatment with concomitant systemic antibiotics that cannot be discontinued, vancomycin prescribing varies in this clinical scenario. It is unclear whether prolonging the duration of vancomycin in a high-risk cohort of hospitalized patients reduces the risk of disease recurrence. We evaluated vancomycin prescribing practices in patients with CDI who were continued on systemic antibiotics to determine whether prolonged durations of treatment beyond 14 days decrease the risk of CDI recurrence.

Methods

Study design

This was a retrospective cohort study of patients hospitalized with CDI between January 2017 and October 2022 at New York University Langone Health (NYULH) Manhattan campus (Tisch Hospital/Kimmel Pavilion), a 925-bed tertiary academic medical center. We obtained institutional review-board approval for this study. Patients were included if they were aged ≥18 years, had an initial episode of CDI confirmed by polymerase chain reaction (PCR), received treatment with oral vancomycin for at least 10 days, and required concomitant systemic antibiotics for >72 hours during vancomycin treatment while admitted. Patients were excluded if they were treated at any time with fidaxomicin or oral metronidazole for CDI or if they transitioned to hospice care or died during CDI treatment.

Institutional practice

Institutional policies are in place at NYULH that outline appropriate CDI testing requirements. The NYULH microbiology laboratory tests for CDI via polymerase chain reaction (PCR Xpert CD assay; Cepheid, Sunnyvale, CA) without a confirmatory enzyme immunoassay (EIA) to assess for toxin production. For this reason, diagnostic stewardship initiatives are in place to prevent false-positive results in patients colonized with CDI but not actively infected. These initiatives include rejection of formed stool specimens or samples sent within 30 days of a positive test, as well as rejection of samples sent within 24 hours of receipt of a bowel regimen, new tube feeds, or oral contrast media. Additionally, decision support within the Epic order (Epic, Verona WI) requires provider attestation that clinical suspicion for CDI is high and that the patient had 3 or more loose stools within 24 hours.

Guidelines also exist at NYULH to provide recommendations for CDI treatment and prevention in adults, but ultimately, decisions are at the discretion of the treating teams. Consistent with the Infectious Diseases Society of America (IDSA) guidelines, management of active CDI within the NYULH guideline is stratified based on disease severity and whether the episode is initial or recurrent.[17] Differing from IDSA guidelines, NYULH guidelines recommend a 10-day duration of vancomycin as first-line therapy over fidaxomicin for initial nonfulminant CDI episodes, and treatment may be extended in patients with slow clinical improvement. Recommendations for fulminant CDI are consistent with IDSA guidelines.[17] Additionally, discontinuation of all nonessential antibiotics is recommended, but no guidance is provided if this cannot be done due to accompanying infections. For prevention of recurrent episodes of CDI, patients at NYULH with a prior history of CDI who require exposure to systemic antibotics receive secondary prophylaxis with vancomycin 125 mg every 12 hours during antibiotic treatment and for 5 additional days after discontinuation of antibiotics.

Data collection and definitions

A list of patients hospitalized with CDI during the study period was obtained from an infection prevention and control (IPC) database of *C. difficile* events reported to the National Healthcare Safety Network (NHSN). This list was then matched to a list of patients who received concomitant antibiotics during concurrent admission, obtained from an Epic Clarity Reporting Database of patients on antibiotics. Finally, manual chart review of the electronic health record was utilized to further evaluate for inclusion and collect pertinent data. Baseline demographics, past medical history, risk factors for CDI such as acid suppressive therapy and immunocompromising conditions or medications, and CDI disease characteristics, including location of onset, severity, and clinical or laboratory markers at diagnosis were recorded. Location of CDI onset was defined consistent with NHSN definitions, stratified by community-onset, community-onset healthcare-facility associated, and hospital onset.[18] Individual categories of concomitant antibiotics received for at least 24 hours were collected and stratified based on risk of causing or exacerbating CDI, as previously categorized.[8] All treatments for CDI were captured, including vancomycin duration while admitted and after discharge, vancomycin dosing strategy, and use of adjunctive therapies including intravenous metronidazole, vancomycin retention enemas, tigecycline, and intravenous immunoglobulins. Dosing strategy was categorized as either treatment (125, 250, or 500 mg every 6 hours) or prophylaxis (125 mg every 12 hours), and tapered dosing was consistent with IDSA guideline recommendations.[17] Length of vancomycin therapy was categorized as either standard duration (10–14 days of treatment) or prolonged duration (>14 days of treatment).

Outcomes

The primary outcome was recurrence of CDI within 8 weeks of CDI treatment completion. Secondary outcomes included CDI recurrence, isolation of vancomycin-resistant *Enterococcus* (VRE), and mortality within 6 months of CDI treatment completion. Recurrence of CDI was defined by either retest (repeat positive PCR and clinical symptoms) or empiric retreatment (receipt of oral vancomycin or fidaxomicin treatment in the absence of a positive PCR test) because our institutional guidelines restrict the ordering of a repeat PCR within 30 days of a positive result. Isolation of VRE

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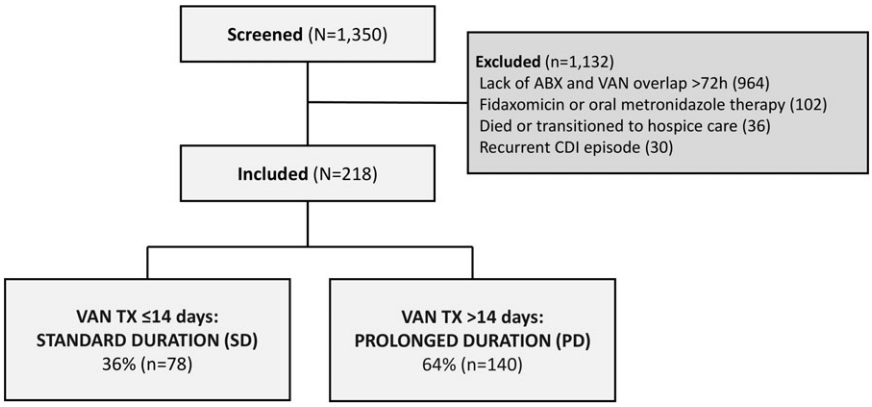

Figure 1. Patient screening and inclusion. Note. ABX, systemic antibiotics; VAN, oral vancomycin; CDI, *Clostridiodes difficile* infection; TX, treatment.

was captured by growth in clinical cultures or surveillance VRE stool screens recommended by hospital IPC policies for unique populations. Independent risk factors for CDI recurrence at 8 weeks were explored in a secondary analysis.

Statistical analysis

Categorical data are presented as frequencies, and continuous data are presented as medians and interquartile ranges (IQRs) for the full cohort, the standard-duration group, and the prolonged-duration group. Characteristics of patients receiving standard-duration treatment versus prolonged-duration treatment were compared using the χ^2 test and the Fisher exact test for categorical data and the Mann-Whitney *U* test for continuous data. Statistical significance was defined by a 2-sided $P < .05$. To identify risk factors for CDI recurrence within 8 weeks, a univariate analysis was conducted comparing patients who experienced recurrence to those who did not. To reduce omitted-variable bias, any patient, disease, or treatment characteristic with $P \leq .10$ on univariate analysis was subsequently evaluated on multivariate analysis to determine independent predictors of CDI recurrence. A Kaplan-Meier analysis of time to CDI recurrence according to treatment group was conducted using a log-rank test. Time at risk began with the day following completion of vancomycin treatment. Statistical analyses were conducted with SPSS Statistics version 28 software (IBM, Armonk, NY).[19]

Results

In total, 1,350 patients were screened for inclusion during the study period, of which 1,132 patients were excluded (Fig. 1). The primary reason for exclusion was lack of overlap between systemic antibiotics and oral vancomycin for >72 hours (n = 964). Among the 218 patients included, 78 (36%) received a standard duration and 140 (64%) received a prolonged duration. Patients in the standard-duration and prolonged-duration groups received vancomycin treatment for 13 (IQR, 11–14) days and 20 (IQR, 16–26) days, respectively ($P < .001$). Only 18 patients (8%) received vancomycin for 10 days.

Patient demographics and CDI characteristics are reported in Table 1. Most of the cohort was male (61%) with a median age of 65 years (IQR, 54–72) and a median Charlson comorbidity index of 4 (IQR, 2–6).[20] Also, 52% of the cohort was immunocompromised, characterized by solid organ or bone marrow transplant, human immunodeficiency virus (HIV), and/or immunosuppressant medication use, 41% had diabetes and 8% had end-stage renal disease requiring hemodialysis. There were no significant differences in past medical history between the groups. Most CDI cases were hospital-acquired (54%) and were classified as nonsevere (39%), followed by severe (36%) and fulminant (25%). Community-onset CDI was more prevalent in the standard-duration group (44% vs 30%; $P = .044$). The hypervirulent NAP1/B1/027 strain was detected in 22 patients (10%) in the total cohort, which was similar between groups. Intensive care unit (ICU) admission at any time during oral vancomycin treatment was required in 32% of patients in each group. An infectious diseases specialist was consulted in 69% of patients in the prolonged-duration group compared to 54% of patients in the standard-duration group ($P = .023$).

Systemic antibiotic characteristics are outlined in Table 2. Patients in the prolonged-duration group received concurrent antibiotics (overlapping with vancomycin treatment) for 15 days (IQR, 9–19), compared to 10 days (IQR, 8–12) in the standard-duration group ($P < .001$). Receipt of *any* high-risk antibiotics occurred in 66% of the cohort, with more carbapenem use in patients who received a prolonged duration of treatment (37% vs 21%; $P = .011$). Receipt of *only* low-risk antibiotics was uncommon overall (7%).

Table 3 summarizes CDI treatment characteristics. Although the vancomycin dosing strategy of 125 mg every 6 hours was used most frequently, 51 patients (23%) had at least 1 change in their dosing regimen during vancomycin treatment. The prolonged-duration group more commonly received vancomycin 500 mg every 6 hours (18% vs 6%; $P = .019$) and adjunctive IV metronidazole (42% vs 24%; $P = .009$). Vancomycin dose tapers and other CDI-active therapies were used infrequently. Upon completion of vancomycin treatment, step-down to prophylaxis occurred in 33% of patients in the standard-duration group compared to 19% in the prolonged-duration group ($P = .014$). Aggregate duration of vancomycin, which includes treatment, prophylaxis, and taper days, was significantly longer in the prolonged-duration group: 23 days (IQR, 18–32) versus 14 days (IQR, 13–20) ($P < .001$). Vancomycin prescribing relative to systemic antibiotic completion is displayed in Figure 2. Vancomycin was discontinued prior to antibiotics in 15 patients (7%), on the same day as antibiotics in 20 patients (9%), and after antibiotics in 183 patients (84%). Among patients who had vancomycin continued beyond antibiotic completion, most patients continued treatment dose (147 of 183, 80%) for a median of 6 days (IQR, 5–14) or prophylactic dose (30 of 183, 16%) for a median of 6 days (IQR, 5–22).

Outcome data are presented in Table 4. The primary outcome of CDI recurrence at 8 weeks occurred in 20 patients (9%) overall, 9

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Table 1. Patient Demographics and CDI Characteristics

Characteristic	Total (N=218), No. (%)[a]	Standard Duration (n=78), No. (%)[a]	Prolonged Duration (n=140), No. (%)[a]	*P* Value
Age, median y (IQR)	65 (54–72)	64 (57–72)	66 (53–73)	.988
Sex, male	132 (61)	49 (63)	83 (59)	.609
Weight, median kg (IQR)	70.2 (61.8–89)	72.9 (63.5–90.8)	68.4 (61–88.8)	.181
Body mass index, median kg/m^2 (IQR)	25.8 (22.3–30.3)	26.2 (22.3–31.3)	25.7 (22.3–30.1)	.519
Past medical history				
Charlson comorbidity index, median (IQR)	4 (2–6)	4 (3–6)	4 (2–6)	.384
Diabetes mellitus	89 (41)	33 (42)	56 (40)	.740
Moderate to severe liver disease	22 (10)	6 (8)	16 (11)	.380
Hemodialysis	17 (8)	7 (9)	10 (7)	.629
Inflammatory bowel disease	6 (3)	2 (3)	4 (3)	.899
Immunocompromised	114 (52)	42 (54)	72 (51)	.732
Immunosuppressant use only[b]	41 (36)	17 (41)	24 (33)	.443
Solid organ transplantation	35 (31)	11 (26)	24 (33)	.425
Bone marrow transplantation	35 (31)	13 (31)	22 (31)	.965
Human immunodeficiency virus	7 (6)	3 (7)	4 (6)	.733
Clinical and laboratory markers at CDI diagnosis				
Temperature >38°C	51 (23)	18 (23)	33 (24)	.934
WBC, median ×10^3/μL (IQR)	8.8 (3.1–14.9)	7.0 (2.5–12.3)	9.3 (4–15.5)	.113
Serum creatinine, median mg/dL (IQR)	0.94 (0.70–1.90)	1.00 (0.71–2.80)	0.91 (0.68–1.61)	.248
Serum albumin, g/dL, median (IQR)	2.9 (2.5–3.4)	2.9 (2.5–3.4)	2.9 (2.6–3.4)	.991
Bowel movements per day, median (IQR)	4 (2–7)	3 (2–5)	4 (3–7)	.141
Hospital onset	117 (54)	38 (49)	79 (56)	.274
Community onset	76 (35)	34 (44)	42 (30)	.044
CO-HFCA	25 (12)	6 (8)	19 (14)	.192
Nonsevere classification	85 (39)	30 (39)	55 (39)	.905
Severe classification	79 (36)	31 (40)	48 (34)	.422
Fulminant classification	54 (25)	17 (22)	37 (26)	.447
Shock	34 (16)	10 (13)	24 (17)	.399
Ileus	30 (14)	9 (12)	21 (15)	.477
Toxic megacolon or pseudomembranous colitis	5 (2)	2 (3)	3 (2)	1.000
NAP1/B1/027 strain	22 (10)	8 (10)	14 (10)	.952
Acid suppressive therapy	172 (79)	60 (77)	112 (80)	.594
Histamine-2 receptor antagonist	81 (37)	30 (39)	51 (36)	.766
Proton pump inhibitor	140 (64)	48 (62)	92 (66)	.538
Hospitalization characteristics				
Infectious diseases consultation	139 (64)	42 (54)	97 (69)	.023
ICU admission	70 (32)	25 (32)	45 (32)	.989
ICU length of stay, median d (IQR)	15 (5–32)	12 (4–49)	20 (9–31)	.512
Hospital LOS, median d (IQR)	17 (11–31)	15 (10–24)	18 (11–33)	.196
Hospital LOS after CDI diagnosis, median d (IQR)	13 (8–21)	11 (8–17)	15 (9–22)	.051

Note. CDI, *Clostridiodes difficile* infection; WBC, white blood cell; CO-HFCA, community-onset, healthcare-facility associated.
[a]Units unless otherwise specified.
[b]Immunosuppressants included antineoplastics, immunotherapy, and prednisone equivalents ≥20 mg for at least 2 weeks.

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Table 2. Systemic Antibiotic Characteristics

Antibiotic Characteristic	Total (N=218), No. (%)[a]	Standard Duration (n=78), No. (%)[a]	Prolonged Duration (n=140), No. (%)[a]	*P* Value
Duration of ABX, median d (IQR)	21 (12–35)	15 (10–22)	24 (14–41)	<.001
Duration ABX and VAN TX overlap, median d (IQR)	13 (8–17)	10 (8–12)	15 (9–19)	<.001
Antibiotic classification				
High-risk	144 (66)	48 (62)	96 (69)	.293
Carbapenem	68 (31)	16 (21)	52 (37)	.011
Third-generation cephalosporin	51 (23)	22 (28)	29 (21)	.210
Fluoroquinolone	40 (18)	13 (17)	27 (19)	.632
Fourth-generation cephalosporin	30 (14)	7 (9)	23 (16)	.126
Broad spectrum cephalosporin	5 (2)	0	5 (4)	.163
Clindamycin	1 (1)	0	1 (1)	1.000
Ceftaroline	0	0	0	. . .
Medium-risk	140 (64)	47 (60)	93 (66)	.362
Beta-lactam/beta-lactamase inhibitor	123 (56)	41 (53)	82 (59)	.391
Penicillin	15 (7)	5 (6)	10 (7)	.838
Macrolide	14 (6)	7 (9)	7 (5)	.251
First-generation cephalosporin	9 (4)	6 (8)	3 (2)	.072
Aztreonam	4 (2)	1 (1)	3 (2)	1.000
Second-generation cephalosporin	0	0	0	. . .
Low-risk	170 (78)	56 (72)	114 (81)	.100
Vancomycin	113 (52)	37 (47)	76 (54)	.332
Sulfamethoxazole/trimethoprim	57 (26)	20 (26)	37 (26)	.899
Aminoglycoside	22 (10)	6 (8)	16 (11)	.380
Metronidazole	21 (10)	5 (6)	16 (11)	.229
Linezolid	14 (6)	6 (8)	8 (6)	.568
Daptomycin	11 (5)	2 (3)	9 (6)	.335
Tetracyclines	6 (3)	2 (3)	4 (3)	1.000
Fosfomycin	3 (1)	0	3 (2)	.554
Polymyxin B	1 (1)	1 (1)	0	.358
Nitrofurantoin	1 (1)	0	1 (1)	1.000
Rifampin	1 (1)	0	1 (1)	1.000
Only received low-risk antibiotics	15 (7)	6 (8)	9 (6)	.724

Note. ABX, systemic antibiotics; VAN, oral vancomycin; TX, treatment (VAN 125–500 mg every 6 h).
[a]Units unless otherwise specified.

patients (12%) in the standard-duration group and 11 patients (8%) in the prolonged-duration group ($P = .367$). Among the 20 recurrences, 13 (65%) were confirmed by PCR (4 standard-duration and 9 prolonged-duration) and the remaining 7 were retreated in the absence of a positive PCR test (2 standard-duration and 5 prolonged-duration). CDI recurrence at 8 weeks was higher in patients with the NAP1/B1/027 strain than in patients with the standard strain: 6 of 22 (27%) versus 14 of 196 (7%), P = .008. When evaluating vancomycin prescribing relative to systemic antibiotic completion, there was no difference in CDI recurrence at 8 weeks among patients who continued vancomycin treatment after antibiotic discontinuation compared to vancomycin prophylaxis or taper after antibiotic discontinuation: 14 of 147 (10%) versus 2 of 36 (6%), P = .742. At 6 months, 26 patients (12%) had CDI recurrence, which was also similar between groups. We detected a numerically higher incidence of VRE isolated in patients who received prolonged duration; however, this was not statistically significant: 3% standard-duration versus 9% prolonged-duration ($P = .083$). All-cause mortality was 10% at 6 months: 12% standard-duration versus 9% prolonged-duration ($P = .477$).

A Kaplan-Meier analysis of time to 8-week recurrence did not demonstrate a significant difference based on oral vancomycin treatment duration (log rank test $P = .324$) (Fig. 3). In the multivariable logistic regression model, independent predictors of recurrence at 8 weeks included discontinuation of vancomycin (any dose: treatment, prophylaxis, or taper) prior to systemic antibiotic completion (OR, 4.8; 95% CI, 1.3–18.1), NAP1/B1/027 strain (OR,

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Table 3. CDI Treatment Characteristics

Treatment Characteristic	Total (N=218), No. (%)[a]	Standard Duration (n=78), No. (%)[a]	Prolonged Duration (n=140), No. (%)[a]	*P* Value
Duration of VAN TX, median d (IQR)	16 (14–22)	13 (11–14)	20 (16–26)	<.001
Dosing strategy[b]				
125 mg every 6 h	209 (96)	75 (96)	134 (96)	1.000
250 mg every 6 h	38 (17)	11 (14)	27 (19)	.334
500 mg every 6 h	30 (14)	5 (6)	25 (18)	.019
Adjunctive CDI therapies				
Intravenous metronidazole	78 (36)	19 (24)	59 (42)	.009
Intravenous immunoglobulin	12 (6)	4 (5)	8 (6)	1.000
Vancomycin retention enema	11 (5)	2 (3)	9 (6)	.335
Tigecycline	4 (2)	1 (1)	3 (2)	1.000
Receipt of taper	8 (4)	1 (1)	7 (5)	.264
Duration, median d (IQR)	19 (15–28)	40	16 (15–23)	.250
Receipt of PPX after completing CDI TX	52 (24)	26 (33)	26 (19)	.014
Duration, median d (IQR)	14 (6–24)	10 (6–31)	15 (7–21)	.854
Aggregate duration of VAN, median d (IQR)[c]	20 (15–29)	14 (13–20)	23 (18–32)	<.001

Note. CDI, *Clostridiodes difficile* infection; VAN, oral vancomycin; TX, treatment (VAN 125–500 mg every 6 h); PPX, secondary prophylaxis (VAN 125 mg every 12 h).
[a]All values are reported as no. (%) unless otherwise specified.
[b]51 (23%) patients had at least 1 change in their VAN TX dosing regimen.
[c]Aggregate duration included combined days of TX, PPX, and taper.

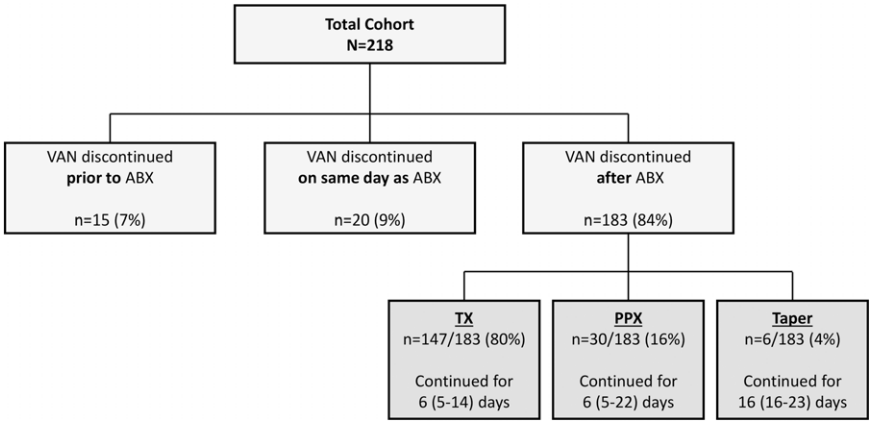

Figure 2. Prescribing patterns of VAN relative to the end date of ABX. Note. ABX, systemic antibiotics; VAN, oral vancomycin; TX, treatment (VAN 125–500 mg every 6 hours); PPX: secondary prophylaxis (VAN 125 mg every 12 hours).

4.7; 95% CI, 1.5–14.5), and circulatory shock (OR, 3.5; 95% CI, 1.2–0.1) (Supplementary Table 1 online). Duration of vancomycin treatment and aggregate duration of vancomycin did not impact risk of recurrence.

Discussion

In our analysis of a heterogeneous cohort of hospitalized patients receiving both oral vancomycin for CDI and concurrent systemic antibiotics for accompanying infections, vancomycin treatment was commonly extended beyond 14 days, but doing so did not reduce the risk of CDI recurrence within 8 weeks. Despite the IDSA guideline recommending a 10-day course of therapy for initial CDI episodes, real-world experience suggests that adherence to this guidance is low for patients who require concomitant antibiotics. In our study, only 36% of patients received CDI therapy for ≤14 days, which is similar to prior studies reporting that only 43%–47% of hospitalized patients received a standard treatment duration when also receiving concomitant antibiotics.[14–16] The median duration of vancomycin treatment in patients who had therapy prolonged was 20 days (IQR, 16–26), which is comparable to previously reported extended durations of 24–26 days.[14,15] Given the lack of available literature and treatment guidance from the IDSA for this population, we hypothesized reasons that clinicians may opt to prolong vancomycin treatment for CDI.

We detected notable differences between patients who received vancomycin for a standard versus a prolonged duration that may have affected prescribing decisions. Patients who received a prolonged duration appeared to have a higher severity of illness, evidenced by longer durations of overlapping antibiotics, more carbapenem use, and greater use of combination therapy directed toward CDI. Additionally, infectious disease service consultations

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Table 4. Outcomes

Outcome	Total (N=218), No. (%)[a]	Standard Duration (n=78), No. (%)[a]	Prolonged Duration (n=140), No. (%)[a]	*P* Value
CDI recurrence within 8 weeks	20 (9)	9 (12)	11 (8)	.367
Time to recurrence, median d (IQR)	19 (7–36)	9 (7–29)	27 (10–39)	.175
CDI recurrence within 6 mo	26 (12)	12 (15)	14 (10)	.240
Time to recurrence, median d (IQR)	27 (9–55)	17 (7–53)	31 (16–56)	.374
VRE isolation within 6 mo	14 (6)	2 (3)	12 (9)	.083
Time to VRE isolation, median d (IQR)	35 (15–56)	49 (44–51)	35 (12–65)	.791
Mortality within 6 mo	21 (100)	9 (12)	12 (9)	.477

Note. CDI: *Clostridiodes difficile* infection; VRE: vancomycin-resistant *Enterococcus*
[a]Units unless otherwise specified.

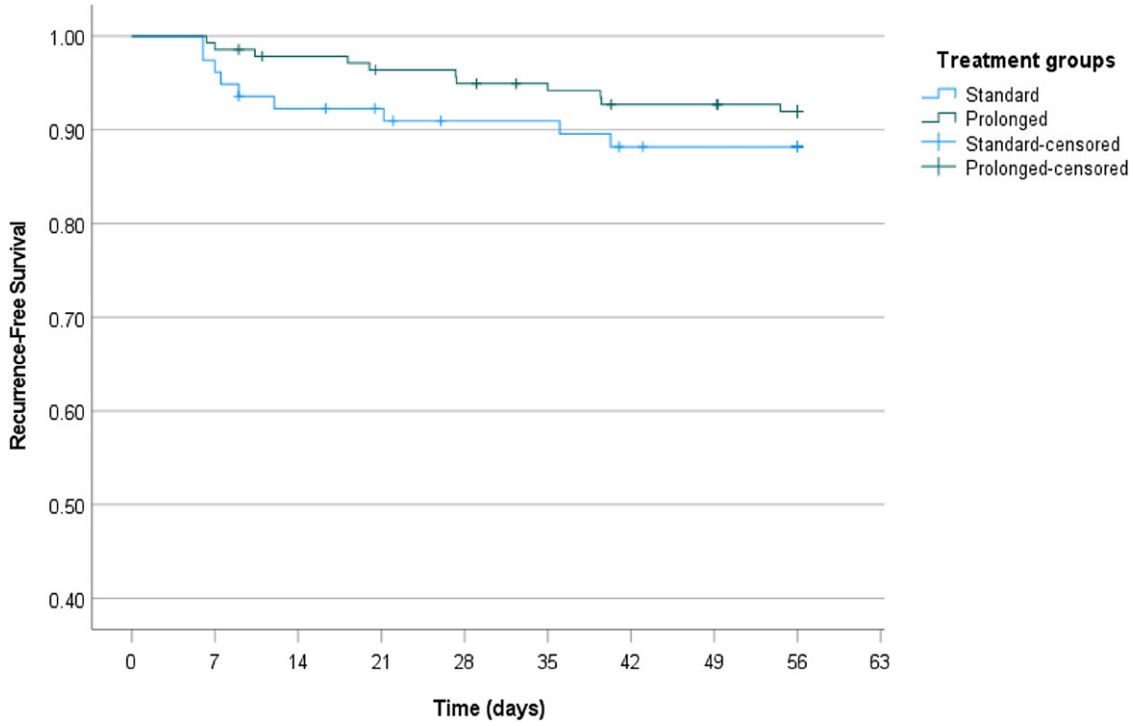

Figure 3. Recurrence-free 8-week survival curve. Cumulative proportion of patients with recurrence estimated using a Kaplan-Meier survival model and compared using the log-rank test ($P = .324$). Time at risk began with the day following completion of VAN TX. Note. VAN, oral vancomycin; TX, treatment (VAN 125–500 mg every 6 h).

were more commonly obtained in the prolonged-duration group, which may suggest more complex infections warranting specialist consultation. Likewise, these specialists may have directly influenced the decision to prolong vancomycin treatment, recognizing microbiome disruption as critical to disease pathogenesis and evolution. In contrast, patients who received a standard duration more often had community-acquired CDI, which has been associated with lower CDI severity and lower mortality.[21] Therefore, patient acuity and duration of concomitant antibiotics were likely the primary determinants of duration of vancomycin treatment.

The rates of CDI recurrence after vancomycin treatment completion in our cohort were low: 9% within 8 weeks and 12% within 6 months. Although recurrence was numerically lower at both time points in patients who received prolonged treatment, there was no significant difference compared to the standard-duration group. Our recurrence rates were lower than published studies evaluating patients with CDI requiring concomitant antibiotics, with rates reported to be 21% within 8 weeks and 16%–29% within 6 months.[14–16] There may be several reasons for this difference. Oral metronidazole was used for CDI in 30%–70% of patients included in prior studies, which has been demonstrated to be inferior to vancomycin for CDI in terms of clinical cure and recurrence.[14–16,22] Additionally, we evaluated only initial CDI episodes, whereas prior studies included patients with recurrent episodes who were at a significantly higher risk of subsequent recurrences.[3,6] Lastly, our institution recommends secondary prophylaxis for all patients with a history of CDI requiring exposure to systemic antibiotics, a strategy that markedly decreases disease recurrence.[23] Notably, the rate of VRE isolation within 6

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months of vancomycin treatment completion in our cohort was numerically higher in patients who received prolonged vancomycin treatment, a finding consistent with prior studies and abstracts.[15,16,24] Indeed, prolonged vancomycin tapers have been demonstrated to maintain VRE colonization compared to shorter courses due to persistent disruption of intestinal microbiota.[25] Strategies to decrease CDI recurrence must be balanced with the risk of VRE emergence, a well-documented consequence of vancomycin therapy.[26,27]

In our study, discontinuation of oral vancomycin prior to the completion of systemic antibiotics independently increased the risk of disease recurrence 5-fold. Thus, vancomycin prescribing relative to systemic antibiotics may implicate CDI recurrence to a greater extent than total vancomycin duration alone. This important finding questions the utility of continuing vancomycin *treatment* beyond a 10-day course and whether step-down to vancomycin *prophylaxis* may be a valuable strategy to minimize total drug exposure and disruption to colonic flora. If patients with CDI have clinical resolution of diarrhea at day 10 but require ongoing concomitant antibiotics, our data suggest that vancomycin therapy should be continued. Because gastrointestinal transit time affects the fecal pharmacokinetics of vancomycin, vancomycin administered less frequently (ie, every 12 or 24 hours) may provide enough protection if CDI diarrhea has resolved.[28] However, use of secondary prophylaxis in this population remains in equipoise and requires further study. Notably, prolonging vancomycin has been shown to delay recovery of indigenous microbiota responsible for colonization resistance to *C. difficile* compared to short-course vancomycin or fidaxomicin.[25] Future studies are needed to compare CDI prevention strategies after treatment completion in patients requiring continuation of antibiotics.

This study had several limitations. This small, single-center retrospective analysis depended on the accuracy of documentation in the electronic health record. Our study groups were well-balanced with respect to characteristics that most notably affect CDI recurrence, but we cannot exclude the possibility of other confounding variables that may have influenced our results. Our institution's practice of CDI testing via PCR without confirmatory EIA may have led to an overdiagnosis of events; however, diagnostic stewardship practices are in place to limit these occurrences. Due to the retrospective study design and inconsistent documentation, our ability to capture time to resolution of diarrhea was limited, which may have affected vancomycin treatment duration. Additionally, we hypothesized reasons that vancomycin treatment was prolonged, but we were unable to determine the exact rationale without querying prescribers. Step-down to vancomycin prophylaxis upon completion of vancomycin treatment was prevalent (24%), which may have affected the recurrence rate in our overall cohort. Also, we could not capture recurrent CDI events that may have occurred outside of the NYULH system. Lastly, we were unable to statistically power our analysis due to the anticipated small difference in the rate of the primary outcome between groups, based on prior data.[14–16,24]

In conclusion, we did not identify evidence to support prolonging the duration of oral vancomycin treatment beyond 10–14 days in all hospitalized patients with CDI requiring concomitant systemic antibiotics for accompanying infections. On the contrary, we found that discontinuation of any dosing regimen of vancomycin prior to antibiotic completion independently increased the risk of CDI recurrence at 8 weeks. Future prospective trials are warranted to explore these findings and to identify alternative risk reduction strategies.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2024.4

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