A Propensity-Matched Analysis Between Standard Versus Tapered Oral Vancomycin Courses for the Management of Recurrent *Clostridium difficile* Infection

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**Background.** This study was conducted to compare clinical outcomes of oral vancomycin courses without taper versus oral vancomycin courses with taper for treatment of recurrent *Clostridium difficile* infection (CDI).

**Methods.** This investigation was a multicenter, retrospective, propensity score-matched analysis study using a Veterans Health Administration national clinical administrative database. Adult patients who were treated for recurrent CDI from any Veterans Affairs Medical Center between June 1, 2011 and October 31, 2016 were included if they were treated with oral vancomycin with or without a tapering regimen. The 2 groups were matched by next-nearest approach from a propensity score formula derived from independent variables associated with the selection of a taper regimen.

**Results.** Propensity score matching resulted in 2 well-matched groups consisting of 226 episodes of patients treated with a vancomycin taper regimen and 678 episodes treated by vancomycin regimen without taper. No difference was found for the primary outcome of 180-day recurrence (59 of 226 [26.1%] for taper regimens versus 161 of 678 [23.8%], *P* = .48). A secondary outcome of 90-day all-cause mortality met statistical significance, favoring a taper regimen (5.31% vs 9.29%, *P* = .049); however, secondary outcomes of 90-day recurrence and 180-day all-cause mortality were not different.

**Conclusions.** Vancomycin taper regimens did not provide benefit over vancomycin regimens without taper in preventing additional CDI recurrence in patients with first or second recurrent episodes in this propensity score-matched analysis.

**Keywords.** *Clostridium difficile*; recurrence; vancomycin taper.

*Clostridium difficile* is a toxigenic anaerobic Gram-positive bacilli that causes a diarrheal illness commonly referred to as CDI [1]. The illness is linked to a substantial burden of morbidity, mortality, and resource utilization [2, 3]. Several characteristics, such as spore formation, allow the organism to be horizontally transferred between patients and healthcare workers [4]. Numerous factors have been associated with CDI development; chief among these is precedent use of antibiotics, which is thought to disrupt the microbiome of the gastrointestinal tract creating an environment for *C difficile* to proliferate [5]. Other risk factors include advanced age, prolonged hospitalization, and recent cancer chemotherapy [5]. Trends in the prevalence of many of these variables may have contributed to an increased incidence and severity of CDI witnessed in the past 2 decades [6–8].

Complicating efforts to manage CDI, current treatment strategies lead to unacceptable rates of failure and/or recurrence. Guideline-driven therapy of first episodes is based on high level evidence, centering on oral vancomycin or metronidazole [5]. Failure rates often approach 10%, and recurrence occurs in an additional 20%–30% of patients [5, 9, 10]. Furthermore, for those who have recurrent disease, multiple recurrent episodes can follow. The evidence available to guide recommendations for treatment of recurrent episodes is poor [5, 11]. One of these approaches for treatment of recurrence is the use of a slowly tapered vancomycin regimen over several weeks after a standard course of therapy [12, 13]. The purpose of this multicenter, clinical, administrative database study was to compare the outcomes of an oral vancomycin course without taper versus an oral vancomycin course with taper for treatment of recurrent CDI.

**METHODS**

**Study Design and Patients**

This investigation was a retrospective, nationwide, propensity score-matched analysis study of patients ≥18 years of age treated for recurrent CDI from any Veterans Affairs Medical Center (VAMC) between June 1, 2011 and October 31, 2016. Approval for the conduct of the study was obtained from the University of Oklahoma Institutional Review Board, Oklahoma City VA Health Care System Research and Development Committee, and the Veterans Health Administration (VHA) Corporate...
Data Warehouse (CDW). Patients were included in this study if the patient had the following: (1) a positive result from the facility’s pertinent VAMC test for presence of *C difficile* toxin (positive enzyme immunoassay [EIA] or positive polymerase chain reaction [PCR] for toxigenic *C difficile*); (2) a documented first or second recurrence of CDI; and (3) begun treatment within 72 hours of positive toxin result with a 7- to 21-day course of vancomycin OR a more prolonged course known as a “vancomycin taper.” A vancomycin taper was defined as a course of therapy that continues for at least 21 days and involves a declining vancomycin dose. Documentation of the first or second recurrent CDI case was defined as follows: (1) a positive test outcome (positive EIA or positive PCR for toxigenic *C difficile*) with the pertinent VAMC test for presence of *C difficile* toxin, preceded within the previous 90 days by (2) a positive test outcome with the pertinent VAMC test for presence of *C difficile* toxin. Concomitant intravenous or oral metronidazole beginning within 72 hours of the oral vancomycin initiation was allowed for inclusion. Exclusion criteria consisted of cases with the following: evident intent to prescribe less than 7 days of therapy, fecal transplant treatment, or discharge diagnosis, surgical report, or radiologic report consistent with toxic megacolon. Patients with conversion to alternative therapy before 72 hours of therapy initiation were also excluded from analysis. De-escalation was only allowed in the vancomycin 7- to 21-day course group, defined as initiation of oral vancomycin for ≥72 hours with conversion to intravenous or oral metronidazole monotherapy for the remainder of CDI treatment. A severe episode was defined as a baseline leukocytosis with a white blood cell count ≥15,000 cells/mL and/or a serum creatinine level ≥1.5 times the premorbid level consistent with current guidelines [5]. Clinical failure of CDI therapy was defined as any switch ≥72 hours after initiation of therapy through 14 days, except for cases of de-escalation.

The outcome of recurrence of CDI was defined as follows: (1) a positive test outcome with the pertinent VAMC test for presence of *C difficile* toxin (positive EIA or positive PCR for toxigenic *C difficile*) and (2) treatment with any antimicrobial directed at CDI within 180 days of the index case. Given the comparison of vancomycin regimens differing only by the continuation or lack of a tapered regimen, only cases that successfully completed therapy without clinical failure within the first 14 days were included.

Data were collected through the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database across the VHA. The VHA consists of 132 acute care VAMCs, each with active ambulatory care services and over 800 community-based outpatient clinics [14]. The VHA maintains the CDW, a central clinical and administrative relational database containing comprehensive electronic medical record information from each VAMC. Researchers, upon obtaining approval through a rigorous information security process, can access the VINCI workspace on the VHA intranet servers through a secure gateway. Patients are automatically assigned a de-identified patient identification number (“PatientSID”) within VINCI, making them unidentifiable to the investigators. Baseline demographic data, current and past diagnosis codes, admission and discharge data, laboratory values, vital signs, date of birth, date of death, administration data for each inpatient unit dose antibiotic given, and prescription data for each outpatient antibiotic given were collected (refer to Table 1 for detailed listing).

**Statistical Methods**

Patients who met inclusion criteria were analyzed to determine univariate variables associated with the selection of a tapered vancomycin regimen. A nominal logistic multivariate analysis to determine independent variables associated with the selection of a tapered vancomycin regimen was conducted using univariate variables with a *P* value of .1 or less. From this multivariate analysis, a formula was created to calculate a propensity score for each individual. Vancomycin regimens without taper were then matched to vancomycin tapered regimens by propensity score match, next-nearest approach, using a 3:1 ratio [15]. Assuming a 35% combined clinical failure/recurrence rate for the 7- to 21-day vancomycin course group, at least 134 patients needed to be analyzed in each arm to find a 20% combined clinical failure/recurrence rate for the vancomycin taper group to be statistically different, assuming α = 5% and β = 0.2.

The primary endpoint was CDI recurrence within 180 days of the positive test for *C difficile* toxin for the index case. The secondary outcomes include the following: 90-day CDI recurrence and 90-day and 180-day all-cause mortality. To validate the primary endpoint results of the propensity score-matched groups, univariate variables that identified factors with *P* ≤ .10 associated with 180-day recurrence were entered into nominal logistic multivariate analysis (along with treatment group) to describe independent variables associated with the primary endpoint. In addition, a Cox proportional hazards model was used with these variables to characterize time to recurrence.

**RESULTS**

Oral vancomycin orders were temporally identified in 5979 first or second recurrent CDI episodes. There were 1844 episodes excluded from analysis. Vancomycin therapy duration of less than 7 days was found in 575 episodes, and vancomycin therapy duration of >21 days without any tapering of dose was found in 1013 patients. The initial vancomycin dose regimen was unclear for 110 patients. Of the remaining 4281 episodes, failure was seen in 146 (3.41%) episodes. Therefore, 4135 first or second recurrence episodes of CDI treated by oral vancomycin were included. Of these, 3908 episodes included a vancomycin course without taper, and 227 episodes included a vancomycin course with taper. Only 31 nontaper courses had de-escalation to metronidazole. The paired columns on the left side of Table 1
### Table 1. Comparative Baseline Demographic Characteristics of the All Episodes and Propensity Score-Matched Episodes by Treatment Regimen Group

| Baseline Variable                        | All Episodes (n = 227) | Standard Regimen (n = 3908) | Propensity Score-Matched Episodes (n = 226) | Standard Regimen (n = 678) | P  |
|-----------------------------------------|------------------------|----------------------------|---------------------------------------------|-----------------------------|----|
| Age, mean (SD)                          | 68.8 (12.5)            | 69.7 (13.0)                | 69.0 (12.2)                                | 67.6 (13.4)                 | .27|
| Male gender, no. (%)                    | 208 (93.7)             | 3632 (94.4)                | 208 (94.1)                                 | 622 (92.8)                  | .65|
| Race, no. (%)                           |                        |                            |                                             |                             | .12|
| White                                   | 181 (79.7)             | 2865 (73.3)                | 181 (80.1)                                 | 515 (76.0)                  |    |
| African American                        | 23 (10.1)              | 601 (15.6)                 | 23 (10.2)                                  | 86 (12.7)                   |    |
| Hispanic                                | 11 (4.85)              | 168 (4.30)                 | 11 (4.87)                                  | 33 (4.87)                   |    |
| Native American                         | 0 (0)                  | 24 (0.610)                 | 0 (0)                                      | 4 (0.590)                   |    |
| Other/Unknown                           | 12 (5.29)              | 250 (6.40)                 | 11 (4.98)                                  | 37 (5.45)                   |    |
| First recurrence episode, no. (%)       | 155 (68.3)             | 3107 (79.5)                | <.0001                                     | 155 (68.6)                  |    |
| Second recurrence episode, no. (%)      | 72 (31.7)              | 801 (20.5)                 | <.0001                                     | 71 (31.4)                   |    |
| Inpatient status, no. (%)               | 87 (38.3)              | 2703 (69.2)                | <.0001                                     | 87 (38.5)                   |    |
| Total daily dose of initial regimen, no. (%) | 0.049                  |                            |                                             |                            | .94|
| 500 mg                                  | 180 (79.5)             | 2911 (74.5)                | 179 (79.2)                                 | 544 (80.2)                  |    |
| 1000 mg                                 | 37 (16.3)              | 660 (16.9)                 | 37 (16.4)                                  | 105 (15.5)                  |    |
| 2000 mg                                 | 10 (4.40)              | 337 (8.62)                 | 10 (4.42)                                  | 29 (4.28)                   |    |
| Concomitant CDI therapy*, no. (%)       | 12 (5.29)              | 489 (12.5)                 | .0003                                      | 12 (5.31)                   |    |
| Comorbidities, no. (%)                  |                        |                            |                                             |                             | .02|
| Respiratory                             | 82 (36.1)              | 1655 (42.4)                | 82 (36.3)                                  | 263 (38.8)                  |    |
| Renal/genitourinary                     | 133 (58.6)             | 2375 (60.8)                | 133 (58.8)                                 | 362 (53.4)                  |    |
| Cardiovascular                          | 162 (71.4)             | 3090 (79.1)                | 162 (71.7)                                 | 478 (70.5)                  |    |
| Gastrointestinal                        | 113 (49.8)             | 1893 (48.4)                | 113 (50.0)                                 | 286 (42.2)                  |    |
| Hepatic                                 | 35 (15.4)              | 629 (16.1)                 | 35 (15.5)                                  | 107 (15.8)                  |    |
| Musculoskeletal                         | 75 (33.0)              | 1544 (39.5)                | 75 (33.2)                                  | 236 (33.3)                  |    |
| Neurologic                              | 73 (32.2)              | 1511 (38.7)                | 73 (32.3)                                  | 214 (31.6)                  |    |
| Dermatologic                            | 55 (24.2)              | 1085 (27.7)                | 55 (24.3)                                  | 149 (22.0)                  |    |
| Metabolic/endocrinologic                | 141 (62.1)             | 2585 (66.2)                | 141 (62.4)                                 | 384 (56.8)                  |    |
| Hematologic                             | 84 (37.0)              | 1776 (45.4)                | .012                                       | 84 (37.2)                   |    |
| Immunologic/rheumatologic              | 19 (8.4)               | 272 (6.96)                 | .43                                        | 19 (8.4)                    |    |
| Psychiatric                             | 107 (47.1)             | 1824 (46.7)                | .89                                        | 107 (47.4)                  |    |
| Neoplastic                              | 59 (26.0)              | 889 (22.8)                 | .27                                        | 59 (26.1)                   |    |
| Laboratory analyses, no. (%)            |                        |                            |                                             |                             | .69|
| Hyponatremia                            | 36 (15.9)              | 2062 (30.9)                | <.0001                                     | 36 (15.9)                   |    |
| Hypernatremia                           | 1 (0.440)              | 6 (9.20)                   | .72                                        | 1 (0.440)                   |    |
| Hypokalemia                             | 54 (23.8)              | 1305 (33.4)                | .0021                                      | 54 (23.9)                   |    |
| Hyperkalemia                            | 12 (5.29)              | 369 (9.44)                 | .024                                       | 12 (5.31)                   |    |
| Hypochloremia                           | 23 (10.1)              | 731 (18.7)                 | .0005                                      | 23 (10.2)                   |    |
| Hyperchloremia                          | 20 (8.81)              | 749 (19.2)                 | <.0001                                     | 20 (8.85)                   |    |
| Low carbon dioxide                      | 41 (18.1)              | 1169 (29.9)                | <.0001                                     | 41 (18.1)                   |    |
| Elevated carbon dioxide                 | 5 (2.20)               | 213 (5.45)                 | .017                                       | 5 (2.21)                    |    |
| Hypoglycemia                            | 7 (3.08)               | 629 (16.1)                 | .41                                        | 7 (3.10)                    |    |
| Hyperglycemia                           | 89 (39.2)              | 1962 (50.2)                | .0012                                      | 89 (39.4)                   |    |
| Elevated serum creatinine               | 50 (22.0)              | 1256 (32.1)                | .0010                                      | 50 (22.1)                   |    |
| Anemia                                  | 121 (53.3)             | 2926 (74.9)                | <.0001                                     | 120 (53.1)                  |    |
| Thrombocytopenia                        | 40 (17.6)              | 901 (23.1)                 | .051                                       | 40 (17.7)                   |    |
| Leukopenia                              | 19 (8.37)              | 319 (8.16)                 | .91                                        | 19 (8.41)                   |    |
| Leukocytosis                            | 59 (26.0)              | 1687 (43.2)                | <.0001                                     | 59 (26.1)                   |    |
| Neutropenia                             | 3 (1.32)               | 49 (1.25)                  | .93                                        | 3 (1.33)                    |    |
| Leukocytosis >15 000 cells/mm²           | 26 (11.4)              | 1026 (26.5)                | <.0001                                     | 26 (11.5)                   |    |
| Elevated serum creatinine above 1.5 times baseline | 29 (12.8) | 845 (21.6) | .0008                                      | 29 (12.8)                   |    |
| Severe episode, no. (%)                 | 9 (3.96)               | 375 (9.60)                 | .0016                                      | 9 (3.96)                    |    |

Abbreviations: CDI, Clostridium difficile infection; SD, standard deviation.

*Metronidazole or fidaxomicin.
describe the baseline characteristics of the 4135 episodes by type of regimen. Appropriate univariate variables from Table 1 (ie, those with \( P \leq .1 \)) were placed into the multivariate logistic regression model. Independent variables associated with the selection of a taper regimen included second recurrence episode (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.33–2.43; \( P < .001 \)), outpatient treatment (OR, 2.55; 95% CI, 1.81–3.60; \( P < .001 \)), hyperchloremia (OR, .562, 95% CI, .315–.967; \( P = .037 \)), and leukocytosis >15,000 cells/mm\(^3\) (OR, .574; 95% CI, .323–.963; \( P = .035 \)).

Propensity scores were successfully computed for every episode except for 1 taper episode with missing data. Therefore, the 3:1 nearest neighbor matched cohort included 226 vancomycin taper episodes and 678 episodes without vancomycin taper. The median duration of vancomycin taper courses was 43.0 days (interquartile range [IQR], 32.8–57.0), compared with 15.0 days (IQR, 11.0–15.0). None of the episodes without taper were de-escalated to metronidazole. Figure 1 describes the propensity score distribution before and after matching. The paired columns on the right of Table 1 provide a comparison of baseline variables between the 2 propensity-matched groups. The 2 groups did not have statistically significant differences for any baseline variable except for gastrointestinal comorbidity (50.0% in the taper regimen group vs 42.2% in the group without taper, \( P = .041 \)). The mean age of the predominately male population was 68.8 ± 12.5 years, with a high incidence of comorbid conditions. First recurrences comprised 70.5% of the episodes; some 37.4% of the episodes were initially treated as inpatients, 80.0% of episodes were initially treated with a 500-mg total daily dose of oral vancomycin, and only 4.76% of episodes were classified as severe.

Table 2 presents the primary and secondary outcomes for the propensity score-matched groups. No difference was found for the primary outcome (ie, 180-day recurrence) nor for the secondary outcome (ie, 90-day recurrence) (\( P > .05 \)). Taper regimens were associated with a lower 90-day all-cause mortality (5.31% vs 9.29%, \( P = .050 \)), but there was no difference in 180-day all-cause mortality. The 90-day all-cause mortality in patients receiving taper who had a recurrent episode of CDI was 3.77% vs 8.46% (2 of 53 and 11 of 130, respectively; \( P = .22 \)) in patients not receiving a tapered regimen, whereas mortality was 5.78% and 9.49% (10 of 173 and 52 of 548, respectively; \( P = .11 \)), respectively, for patients who did not have recurrent CDI.

Univariate variables in the propensity score-matched cohort associated with 180-day recurrence included inpatient setting (44.6% with recurrence vs 35.1% without recurrence, \( P = .012 \)), renal/genitourinary (60.9% vs 52.8%, \( P = .034 \)), dermatologic (28.8% vs 20.8%, \( P = .024 \)), hematologic (45.4% vs 36.0%, \( P = .012 \)) and immunologic/rheumatologic comorbidities

**Table 2. Outcomes of the Propensity Score-Matched Groups**

| Outcome                        | Taper Regimen \( (n = 226) \) | Standard Regimen \( (n = 678) \) | \( P \) |
|-------------------------------|-------------------------------|----------------------------------|-------|
| **Primary Outcome**           |                               |                                  |       |
| Recurrence within 180 days, no. (%) | 59 (26.1)                    | 161 (23.8)                      | .48   |
| **Secondary Outcomes**        |                               |                                  |       |
| Recurrence within 90 days, no. (%) | 53 (23.4)                    | 130 (19.2)                      | .17   |
| Death within 90 days, no. (%)  | 12 (5.31)                     | 63 (9.29)                       | .050  |
| Death within 180 days, no. (%) | 23 (10.2)                     | 86 (12.7)                       | .31   |
(9.55% vs 4.97%, $P = .018$), hypokalemia (28.6% vs 19.7%, $P = .007$), low hemoglobin (58.6% vs 49.0%, $P = .012$), and serum creatinine $\geq 1.5$ times baseline (18.6% vs 11.6%, $P = .0091$). These variables, along with treatment group, concomitant therapy (7.73% vs 4.53%, $P = .077$), respiratory (43.6% vs 36.4%, $P = .056$), and cardiovascular (75.9% vs 69.2%, $P = .052$) comorbiditites, were placed into nominal logistic multivariate analysis to determine independent variables associated with recurrence.

No variable, including treatment group, was found to be an independent variable associated with 180-day recurrence in the propensity score-matched cohort. The mean number of days to recurrence was lower in the taper group than the group without taper (43.3 days vs 60.1 days, $P < .001$). Cardiovascular comorbidity (risk ratio, 1.36; 95% CI, 1.02–1.81; $P = .035$) and taper regimen (risk ratio, 1.56; 95% CI, 1.21–2.00; $P < .001$) reached statistical significance in the Cox proportional hazards fit.

Concomitant metronidazole therapy occurred in a small proportion of episodes (5.31%); 8 (18.6%) of 43 severe cases received concomitant metronidazole compared with 40 (4.65%) of 861 nonsevere cases ($P < .001$). Recurrence occurred in 14 (29.2%) of 48 episodes with concomitant therapy compared with 210 (24.5%) of 856 episodes without concomitant therapy ($P = .48$). Mortality at 90 days was 5 (10.4%) of 48 patients with concomitant therapy compared with 70 (8.18%) of 856 patients without concomitant therapy ($P = .60$).

**DISCUSSION**

The 2010 *C difficile* treatment guidelines from the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology (SHEA) recommend treating first recurrence of CDI with the same regimen used for the initial episode [5]. Oral vancomycin in a tapered and/or pulsed regimen is recommended for treatment of the second recurrence of CDI; however, this recommendation is based on limited data. To our knowledge, only 2 reports describe patient cohorts given a vancomycin taper or pulse regimen; both with retrospective uncontrolled data. Tedesco et al. [12] reported no further recurrences in a case series of 22 patients with multiple CDI recurrences who received tapering doses of vancomycin over 42 days after a follow-up ranging from 2 to 12 months. More recently, McFarland et al. [13] described various strategies for treating recurrent CDI in a post hoc analysis arising from 2 multicenter, double-blind, placebo-controlled trials evaluating a *Saccharomyces boulardii* preparation. Recurrence rates for “low” (n = 48), “medium” (n = 14), and “high” (n = 21) nontaper oral vancomycin dose groups were 54%, 71%, and 43%, respectively, whereas a separate group receiving a taper regimen (n = 29) had a 31% recurrence rate. No baseline evaluation was done to describe comparability of the groups.

To our knowledge, the current project is the first robust attempt to compare the use of a prolonged vancomycin taper to a standard course of vancomycin without taper, utilizing a propensity score-matched methodology to produce 2 groups with similar baseline demographics, comorbidities, laboratory abnormalities, and severity of disease. Our study population of patients across the VHA consisted of predominately older patients with multiple comorbidities, consistent with a high prevalence of healthcare experiences and a fair representation of patients at risk for recurrence [3, 5]. In this comparison, no difference in the primary outcome, 180-day recurrence, was seen between those receiving the prolonged vancomycin tapered regimen and those not receiving the tapered regimen. A secondary outcome of 90-day all-cause mortality reached statistical significance, favoring the tapered regimens, although the 180-day all-cause mortality was similar. Data did not seem to suggest that differences in 90-day all-cause mortality were related directly to CDI recurrence, because a numerically higher incidence of mortality occurred in both treatment groups for patients who did not have CDI recurrence. The overall low all-cause mortality rate in this population of advanced age and having multiple comorbidities could be attributed to the low incidence of episodes classified as severe in both propensity score-matched groups.

An interesting observation from the current study was the considerable amount of patients who received therapy concordant with current guidelines for first recurrence but discordant for second recurrence. First recurrence episodes should be treated with the same regimen as the patient’s initial episode, ie, nontaper regimens of vancomycin or metronidazole (or vancomycin plus metronidazole for severe, complicated episodes) [5]. Vancomycin taper regimens are recommended only in second or subsequent CDI recurrences. In the current study, 3107 (95.2%) of 3262 regimens were concordant nontaper regimens in first recurrence episodes where vancomycin was used, whereas 801 (91.7%) of 873 patients with a second recurrence who were treated with vancomycin received discordant nontaper regimens (Table 1). One explanation for seemingly discordant treatment is that clinicians may have different perspectives on what constitutes a recurrent episode; our study limited the definition to a positive toxigenic *C difficile* within 90 days of the index case, whereas in clinical practice some may have more strict or relaxed definitions for recurrence, which may alter their perception as to what “number” episode a possible CDI might be. Another contributing factor may be the perceived strength of (or lack thereof) the evidence supporting a particular recommendation.

Limitations of this study included the nonrandomized, retrospective nature and its reliance on clinical administrative database records. Clinical and laboratory diagnostic methods used in clinical practice to determine the presence of *C difficile* active disease versus asymptomatic (or no) carriage have significant sensitivity and specificity concerns. Only patients with watery, loose, or unformed stool should have specimens sent for testing [5].
Due to our inability to record symptoms, which could harm the sensitivity and specificity of our CDI episode or recurrence definitions, we were left to assume that if a patient had a positive laboratory test for the presence of toxigenic *C. difficile* and CDI treatment was begun, the clinician appropriately diagnosed symptomatic CDI. Even with appropriate specimen collection, EIA and PCR-based toxigenic tests have suboptimal sensitivity and specificity [5, 16]. The EIA testing procedures are rapid, but have less sensitivity and specificity than the optimal, but rarely clinically available, stool culture. Available PCR-based toxigenic tests have a different primary concern; their ability to detect toxin is so sensitive that there may be a problem of overdiagnosing CDI in either asymptomatic patients or patients with non-CDI symptomatic etiologies. Our protocol, similar to most available data on CDI treatment, relies on these less than optimal tests to select patients with CDI [17–19]. The possibility that asymptomatic patients may have been included in the study, together with a different definition of clinical failure (due to the nature of available data), could have accounted for the lower failure rate in our study compared with other studies. Dosing and duration standardization was not possible due to the retrospective nature of the study. The role of concomitant therapy could not be characterized significantly due to the small proportion of patients receiving concomitant metronidazole. The index episode of first recurrence must have been preceded by a positive toxigenic test for *C. difficile* within 90 days prior, deemed the initial episode; however, we did not confirm that patients with this initial episode of a positive test were treated as an active CDI case. Most studies of CDI recurrence define recurrence as within 30, 60, or 90 days, so the generalizability of our primary outcome could be questioned. However, our justification for extending our recurrence definition out to 180 days was the prolonged duration of tapered regimens, often extending therapy to as much as 10 weeks.

**CONCLUSIONS**

Although a vancomycin tapering strategy did not provide benefit in preventing additional CDI recurrence in patients with first or second recurrent episodes in this analysis, evidence to support other strategies for reducing multiple recurrences, such as fidaxomicin, fecal microbiota transplantation, and the novel human monoclonal antibody bezlotoxumab, have become available since the publication of the 2010 IDSA/SHEA guidelines [17, 18, 20, 21]. Any updated guidelines will no doubt review these developments and recommendations for the management of recurrent CDI will likely be revised.

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