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Haley J. Appaneal
University of Rhode Island

Aisling R. Caffrey
University of Rhode Island, aisling_caffrey@uri.edu

See next page for additional authors

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Predictors of *Clostridium difficile* recurrence across a national cohort of Veterans in outpatient, acute and long-term care settings

Appaneal HJ[1], Caffrey AR[2], Beganovic M[2], Avramovic S[3], LaPlante KL[1].

[1] Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, and College of Pharmacy, University of Rhode Island, Kingston, RI.

[2] Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, and College of Pharmacy, University of Rhode Island, Kingston, RI.

[3] Health Administration and Policy, George Mason University, Fairfax, VA.

ABSTRACT

PURPOSE: The greatest challenge in treating *Clostridium difficile* infection (CDI) is disease recurrence, which occurs in about 20% of patients usually within 30 days of treatment cessation. We sought to identify independent predictors of first recurrence among a national cohort of Veterans with CDI.

METHODS: We conducted a case-control study among acute and long-term care Veterans Affairs (VA) inpatients and outpatients with a first CDI episode (positive stool sample for *C. difficile* toxin(s) and receipt of at least two days of CDI treatment) between 2010 and 2014. Cases experienced first recurrence within 30 days from the end of treatment. Controls were those without first recurrence matched 4:1 to cases on year, facility, and severity. Multivariable conditional logistic regression was used to identify predictors of first recurrence.

RESULTS: We identified 32 predictors of first recurrence among 974 cases and 3,896 matched controls. Significant predictors included medication use prior to (probiotics, fluoroquinolones, laxatives, 3rd/4th generation cephalosporins), during (1st/2nd generation cephalosporins, penicillin/amoxicillin/ampicillin, 3rd/4th generation cephalosporins), and after CDI treatment (probiotics, any antibiotic, proton pump inhibitors [PPIs], and immunosuppressants). Other predictors included current biliary tract disease, malaise/fatigue, cellulitis/abscess, solid organ cancer, and history of HIV, multiple myeloma, abdominal pain, and ulcerative colitis.

CONCLUSION: In our large national cohort of outpatient and acute and long-term care inpatients, treatment with certain antibiotics, PPIs, immunosuppressants, and underlying disease were among the most important risk factors for first CDI recurrence. Results highlight an important opportunity for antibiotic stewardship programs to not only target inappropriate antibiotic use but also unnecessary PPIs use, especially in patients with a history of CDI.

Keywords: *Clostridium difficile* infection, Veterans Affairs, recurrent disease**,** predictors

INTRODUCTION

Clostridium difficile is a gram-positive anaerobe that causes infectious diarrhea that can range in severity from mild to severe disease.[1] One of the greatest challenges in treating *Clostridium difficile* infection (CDI) effectively is the high recurrence rate. Reported CDI recurrence rates vary substantially from about 5% to as high as 50% due to differing prevalence in risk factors and definitions for recurrence between studies, however recurrence typically occurs in about 20% of patients.[2-5] Following the first recurrence, the risk of an additional episode of CDI increases to between 45% and 65%.[6] Recurrent CDI is challenging to treat and causes significant morbidity, mortality and reductions in quality of life.[7] Identifying those at highest risk for recurrence could allow for targeted initial CDI management and may improve patient outcomes.[2]

Several risk factors for CDI recurrence have been identified in the general population.[1, 8-11] Previously identified risk factors include, advanced age, use of certain medications, such as non-CDI active antibiotics, and gastric acid suppressants, as well as underlying comorbid or immunocompromising conditions.[1, 8-11] Previous studies have primarily focused on CDI diagnosed and treated in acute care settings. CDI has become increasingly common in community and long-term care settings and patients often receive care from multiple clinical settings.[12, 13] Current estimates suggest that community-associated CDI accounts for over 20% of cases.[14] Over 60% of cases of healthcare-associated CDI cases may have had onset in long-term care facilities.[13] This fragmented care for CDI among various settings poses a particular challenge for the accurate identification of recurrent disease, as the facility that treats the index episode often may not be the same facility that treats the recurrent episode.[15]

The Veterans Health Administration (VHA) is the United States' largest integrated health care system, with over 140 medical centers and 1,200 outpatient clinics and long-term care facilities.[16] Utilization of VA data provides the unique opportunity to study predictors of recurrent CDI among

patients diagnosed and treated across clinical settings. Moreover, the Veteran population is older, has poorer health status, more medical conditions, and higher medical resource use than the general population.[17] The risk for recurrence in Veterans may be different than in the general population highlighting the need for a comprehensive understanding of the predictors of first recurrence among Veterans with an initial CDI episode. Thus, our work sought to identify independent predictors of first recurrence among a national cohort of Veterans with CDI.

METHODS

The study was approved by the Institutional Review Board and the Research and Development Committee of the Providence Veterans Affairs Medical Center.

Patient Population and Study Design

We conducted a matched case-control study among adults (≥ 18 years) with a first CDI episode treated in Veterans Affairs (VA) facilities nationally from May 1, 2010 to December 30, 2014. The first episode of CDI was the first identified during the study period for each patient with no CDI episodes in the year prior to study inclusion.[18] A CDI episode was defined as a positive stool sample for *C. difficile* toxin(s) regardless of testing method (however the majority of testing throughout the VA is done through polymerase chain reaction) during an inpatient admission or an outpatient encounter and receipt of at least two days of standard CDI treatment (oral or intravenous [IV] metronidazole, oral or rectal vancomycin, or fidaxomicin).[1, 19] The use of the nucleic acid amplification test for CDI diagnostic testing among VA facilities increased from 33% in 2010 to 81% in 2015.[20] Similar to previous work, we used a window of at least two days of therapy (at least one dose of drug on two days regardless of frequency) to represent exposure.[21, 22] Two days was used to indicate real-world initiation of treatment, thus even if the episode represented colonization, it was being treated as an infection.

First recurrence was defined as a subsequent CDI episode (defined as a positive stool sample or diagnosis code 008.45 for CDI and at least two days of subsequent CDI treatment) at least 14 days after the positive stool test date and within 30 days of the end of treatment of the initial CDI occurrence. As above at least two days of therapy was required for exposure.[21, 22] We used an interval of at least 14 days to distinguish a new recurrent episode from the initial CDI episode similar to previous work.[2, 23] We assessed recurrence up to 30 days after treatment cessation as most recurrences occur within 1-3 weeks after the end of treatment.[2, 24, 25] Previous work has shown that the risk for recurrence is greatest 10 days after treatment cessation.[2] The definition of recurrence within 28 to 30 days of the end of CDI treatment is commonly used in clinical trials.[25-27] Recurrence within 30-days has been used in previous VA and non-VA studies.[28, 29] Cases were defined as patients that experienced 30-day first recurrence and controls were defined as those that did not experience 30-day first recurrence.

Controls were matched to cases with a 4 to 1 ratio, based on date of CDI episode (year), facility, and severity. CDI was defined as severe if the closest white blood cell count was >15 x 10^3/μL or the closest serum creatinine was >1.5 g/dL within 7 days of the index treatment date, non-severe if white blood cell count was $\leq$15 x 10^3/μL and serum creatinine $\leq$1.5 g/dL, or otherwise unknown.[30] Of patients with a white blood cell count (n=42,298) and serum creatinine (n=40,261) within 7 days, 96.3% and 96.0% were within 2 days of treatment, respectively.

Potential Predictors

We assessed 215 potential independent predictors of recurrence based on clinical relevance and/or previous work.[1, 8-11] All potential predictors assessed were selected a priori. Potential predictors included socio-demographics (age, gender, race, ethnicity, and marital status), CDI treatment, admitting source, current comorbidities and medical history (diagnosis codes) in the previous 365 days, current and previous infections, laboratory results, current and previous

surgeries and procedures, previous healthcare exposures, as well as medication exposures. All comorbidities, medical history, and infections were assessed from diagnosis codes using the Clinical Classifications Software (CCS) of the Agency for Healthcare Research and Quality (AHRQ).[31] CDI treatment was defined as metronidazole oral or IV monotherapy, vancomycin oral or rectal monotherapy, vancomycin and metronidazole combination therapy, or fidaxomicin alone or in combination with vancomycin and/or metronidazole. Due to the frequency of use of metronidazole monotherapy, we compared metronidazole monotherapy to all other treatment options combined as a binary variable. NAP1/027 strain was assessed based on the reported test name and results of the clinical specimen from the testing laboratory, where strain data was available. Strain was defined as hypervirulent or unknown/non-hypervirulent otherwise.

Medication exposures assessed included antibiotic agents/classes, gastric acid suppressants, immunosuppressant, laxatives, and supplemental medications. Antibiotic agents/classes exposure was assessed in the previous 30 days before CDI treatment, during CDI treatment, and 30 days after CDI treatment. Antibiotic exposures assessed were categorized as follows: aminoglycosides; amoxicillin or ampicillin / Beta-lactamase inhibitors; penicillin/amoxicillin/ampicillins; aztreonam; carbapenems; anti-staphylococcal pencillins, anti-pseudomonal pencillins/ Beta-lactamase inhibitors, $1^{st}/2^{nd}$ generation cephalosporins; $3^{rd}/4^{th}$ generation cephalosporins; clindamycin; fluoroquinolones, fosfomycin, glyco-/glycolipo-/lipopeptdes (except vancomycin oral/rectal), macrolides, nitrofurantoin, oxazolidinones, polymyxins, sulfamethoxazole/trimethoprim, quinupristin-dalfopristin, tetracyclines, and tigecycline. Any antibiotic use was defined as the presence of exposure to any of these agents/classes. Gastric acid suppressant use was assessed as histamine receptor 2 antagonists or proton pump inhibitor use in the previous 7 days before CDI treatment, during CDI treatment, and 30 days after CDI treatment. Immunosuppressant medication use was defined as corticosteroid, monoclonal antibody, antineoplastic, or transplantation agent use in the previous

30 days before CDI treatment, during CDI treatment, and 30 days after CDI treatment. Laxative use was assessed in the 2 days before CDI treatment. Supplemental medications included probiotics, binding agents (i.e. colestipol, cholestyramine), and rifampin or rifaximin in the 30 days before CDI treatment, during CDI treatment, and 30 days after CDI treatment. Windows for exposure to medications were selected based on clinical relevance or previous work.[3, 11, 32] Figure 1 presents a timeline of when predictors were assessed.

Statistical Analysis

All analyses were performed using SAS (SAS Institute Inc., Cary, NC, Version 9.2). Demographic and clinical characteristics of cases and controls were analyzed using chi-square or Fisher's exact tests for categorical data and Student's *t* test or the Wilcoxon rank sum test for continuous data, as appropriate. Independent predictors of first recurrence were identified utilizing backward manual stepwise conditional logistic regression models.[33] In univariate analyses, variables were included in the subsequent multivariable model at a p-value of less than 0.10.[33] Variables were then removed from the multivariable model in a stepwise fashion until all remaining variables within the final model demonstrated statistical significance (p-value <0.05).[33] Absence of collinearity between the variables in the final model was confirmed from tolerance and variance inflation.[33] Tolerance was above 0.1 and variance inflation was below 10 for all variables included in the model (highest variance inflation was 2.07).

Subgroup analyses were conducted to determine whether predictors varied by initial CDI severity (severe and non-severe) and treatment setting (acute care and outpatient).

RESULTS

We identified 49,064 patients with an initial CDI episode. The mean age of this cohort was 66.2 years (±14.1 SD), 93.5% were male (n=45,887), and 74.4% were white (n=36,524). Most patients

with initial CDI were treated in the outpatient setting (69.6%, n=34,146), followed by acute care (27.3%, n=13,396), and long-term care (2.1%, n=1,019). Of those with a first CDI treated in the outpatient setting, 56.5% had a VA hospital admission within prior 90 days and 60.3% had an antibiotic exposure within 30 days prior to CDI treatment. Initial treatment with metronidazole monotherapy (83.3%, n=40,868 [71.5% oral and 28.6% IV]) was most common, followed by vancomycin oral/rectal and metronidazole combination (9.7%, n=4,765), vancomycin monotherapy (6.9%, n=3,370). Severe CDI was observed in 34.3% (n=16,806) of patients and mild CDI in 50.4% (n=24,713). First recurrence within 30 days of the end of treatment occurred in 6.2% (n= 3,020) of patients with an initial CDI occurrence.

We identified 974 cases that experienced first recurrence and 3,896 controls matched on year, facility and severity that did not experience first recurrence. Severe CDI was observed in 36.8% of cases and controls, and mild CDI in 39.9% of cases and controls. As noted in Tables 1 and 2, several significant differences between cases and controls were observed, including differences in CDI treatment. Metronidazole monotherapy was used in 75.6% of cases (64% of which was oral) and 90% of controls (66% of which was oral).

Our final multivariate model was used to calculate adjusted odds ratios [OR] and identified 32 independent predictors of first recurrence of CDI in Veterans, which are listed in Table 3. Strong predictors included use of probiotics (odds ratio [OR] 4.62, 95% CI 2.37-8.98), fluoroquinolones (OR 3.35, 95% CI 2.58-4.34), laxatives (OR 2.35, 95% CI 1.21-4.58), and $3^{rd}/4^{th}$ generation cephalosporins (OR 2.04, 95% CI 1.49-2.79) prior to initial CDI treatment. Other predictors included medication use during the initial CDI treatment ($1^{st}/2^{nd}$ generation cephalosporins, OR 1.92, 95% CI 1.13-3.25; penicillin/amoxicillin/ampicillin, OR 1.70, 95% CI 1.06-2.71; and $3^{rd}/4^{th}$ generation cephalosporins, OR 1.54, 95% CI 1.13-2.11) and in the 30 days after CDI treatment (probiotics, OR 2.30, 95% CI 1.35-3.91; any antibiotic, OR 2.14, 95% CI 1.68-2.73; proton pump

inhibitors [PPI], OR 2.02, 95% CI 1.59-2.55, and immunosuppressants, OR 1.45, 95% CI 1.05-2.00).

Several current comorbidities and history of medical conditions were also identified as predictors: current biliary tract disease (OR 4.70, 95% CI 1.68-13.12), malaise/fatigue (OR 2.38, 95% CI 1.01-5.64), cellulitis/abscess (OR 1.797, 95% CI 1.03-3.15), solid organ cancer (OR 1.79, 95% CI 1.25-2.55), medical history of HIV (OR 3.32, 95% CI 1.26-8.78), multiple myeloma (OR 2.75, 95% CI 1.04- 7.27), abdominal pain (OR 2.47, 95% 1.65-3.70) ulcerative colitis (OR 2.14, CI 95% 1.01-4.57). White race was a significant predictor of first recurrence (OR 6.0, 95% CI 4.7-7.6).

Results of subgroup analyses by CDI severity and treatment setting can be found in the supplemental material. Use of probiotics and fluoroquinolones prior to initial CDI treatment, use of any antibiotic and PPI after CDI treatment, a principal diagnosis of CDI, and white race remained significant predictors of first recurrence in all subgroups assessed.

DISCUSSION

Our study identified important independent predictors of first recurrence among our national cohort of Veterans with initial CDI. Our study includes patients with CDI diagnosed and treated in various healthcare settings, including both acute and long-term care inpatients and outpatients, and focuses on the Veteran population. While several studies have assessed predictors of recurrence in patients with CDI, data on recurrence predictors among the Veteran population are limited.[3, 11, 28, 32, 34]

Antibiotic use is a well-established risk factor for recurrent CDI.[3, 11, 32] Our results confirm that antibiotic use before, during, and after treatment of the initial CDI episode were strongly associated with recurrence. It is thought that antibiotic use during and after CDI treatment alters

the recovering colonic microbiota and contributes to an increased risk for CDI recurrence.[35] Three meta-analyses and/or systematic reviews have shown that continued antibiotic use during and/or after CDI treatment are among the most common risk factors for recurrence.[3, 11, 32] We also confirmed that gastric acid suppression was associated with an increased risk of recurrence among Veterans. Gastric acid suppression is thought to increase the risk of infection through allowing increased passage of *C. difficile* spores beyond the stomach leading to infection.[11, 36] Previous studies have demonstrated an increased risk of CDI recurrence associated with PPI use and to a lesser extent histamine 2 receptor antagonists (H2RA) use.[3, 11, 37, 38] We found that patients treated with PPIs after CDI treatment had an increased risk of CDI recurrence. Similar results were observed among another national cohort of 22,615 Veterans, which found prior antibiotic use and PPI use were predictors of 60-day CDI recurrence.[34]

Our results confirmed that several antibiotic classes used prior to (specifically, fluoroquinolones, 3rd-4th generation cephalosporins, penicillin/ amoxicillin/ or ampicillin, amoxicillin or ampicillin / beta-lactamase inhibitors, 1st -2nd generation cephalosporins, and glyco-/ glycolipo-/ lipopeptide) and during CDI treatment (specifically, 1st -2nd generation cephalosporins, penicillin/ amoxicillin/ or ampicillin, 3rd-4th generation cephalosporins, and glyco-/ glycolipo-/ lipopeptides) were associated with an increased risk of recurrence as was use of any antibiotic not used for the treatment of CDI (thus all antibiotics but metronidazole, vancomycin oral/rectal, or fidaxomicin) after CDI treatment. In the previously mentioned VA study, the only antibiotic class independently associated with 60-day recurrence was prior 3rd-4th generation cephalosporin use.[34] While we also identified prior 3rd-4th generation cephalosporin use as an independent predictor, the other classes we identified may be related to the differences in exposure periods assessed between the two studies (90 days prior versus 30-days prior, during, and after CDI treatment in our study).

Several studies have been conducted to evaluate the comparative risk of CDI associated with different antibiotic classes.[39-41] These studies have demonstrated the greatest risk with clindamycin, where odds ratios have been as high as 20 compared to no antibiotics. Agents most commonly associated with a moderate CDI risk include fluoroquinolones, carbapenems, cephalosporins, and penicillins. The frequency and duration of use must also be considered when evaluating risk estimates for different antibiotic classes. Despite the highest risk of CDI being associated with clindamycin in other studies, it was not an independent predictor of recurrence in our study, which may have been due to low utilization in our high-risk older patient population (4% of patients in the 30 days prior to CDI, 2% during CDI treatment, and 1% after CDI treatment). Similarly, carbapenem use was not a significant predictor of CDI recurrence and was used only used in 3%, 7%, and 4% of patients in the 30 days prior, during, and after CDI treatment, respectively. Fluoroquinolones were associated with the greatest risk of CDI recurrence in our study (OR 3.4, 95% CI 2.6-4.3); while the risk of CDI recurrence with other antibiotic classes were all similar to each other (ORs range ~1.5-2). Fluoroquinolones are among the most commonly used antibiotics, often inappropriately, and are associated with a moderate risk of CDI.[39, 42] In our study, approximately 11% of controls and 35% of cases were exposed to fluoroquinolones in the 30 days before the initial CDI episode. Our results call for additional efforts in discontinuing inappropriate antibiotics, particularly the overuse of fluoroquinolones, in situations where antibiotics are avoidable. It is also important to note that, not all antibiotics may confer an increased risk of recurrent CDI.[19] Among Veterans with spinal cord injury and disorder, tetracycline use was protective against recurrence.[19] In another non-VA study, patients that received doxycycline had a lower risk of CDI.[43] Further, future work should assess which concomitant antibiotics are most appropriate for patients in situations where antibiotics are necessary and unavoidable.

Probiotics, such as *Lactobacillus*, *Bifidobacteria*, or *Saccharomyces boulardii*, are thought to restore the colonic microbiota in the setting of recurrent CDI, however the role of these agents in treatment or prevention of recurrent CDI is unclear.[44] Initial studies suggested that probiotic use may decrease CDI recurrence when used as adjunctive treatment with vancomycin, however later trials did not confirm these findings.[45-47] We found that probiotic use prior to and after CDI treatment were actually associated with an increased risk for CDI recurrence (prior: OR 4.62, 95% CI 2.37-8.98, after: OR 2.30, 95% CI 1.35-3.91). A possible explanation for this unexpected finding is that patients at an increased risk for recurrence were recognized as such by physicians and were prescribed probiotics. For example, exposure to antibiotics, particularly higher risk agents such as fluoroquinolones, may have prompted physicians to prescribe probiotics potentially driving our findings.

We also found that laxative exposure prior to CDI treatment was a strong predictor of CDI recurrence, a relationship that has not been previously evaluated. However, receipt of a laxative has previously been identified as a predictor of development of CDI.[48] Since laxative use distorts the symptoms of CDI and positive stool samples among those exposed to laxatives may represent colonization versus true infection, we hypothesized laxative exposure prior to the initial CDI episode would not be a significant predictor of subsequent disease recurrence. Our somewhat discordant findings may be related to differences in CDI treatment and potential disease severity between cases and controls exposed to laxatives. Metronidazole monotherapy was used in only 60% of cases exposed to laxatives (n=30) as compared to 90% of controls exposed to laxatives (n=68). Standard practice and CDI treatment guideline recommendations at the time of our study supported the use of vancomycin over metronidazole for severe CDI episodes since metronidazole use has been associated with poorer outcomes and higher recurrence rates in patients with severe CDI episodes.[1, 49, 50] Thus, differences in CDI treatment patterns among

cases and controls exposed to laxatives may suggest that cases were sicker than controls possibly leading to increased recurrence among the cases exposed to laxatives.

Similar to previous findings we found that certain underlying current or previous (in the year prior) comorbid conditions and immunodeficiency were associated with CDI recurrence.[36, 51, 52] We found that current biliary tract disease and history of abdominal pain, enteritis and colitis, esophageal disorder, and nutrition deficiency were all predictors of recurrence. These conditions may be associated with dysfunction of the intestinal microbiota and/or reduced gastric acid secretion, which may contribute to *C. difficile* colonization, infection, and recurrence.[53] Patients with these conditions may take gastric acid suppressants or laxatives, but upon further investigation these medication exposures did not appear to be driving findings. Impaired immune response to *C. difficile* toxins has also been shown to contribute to an increased risk of CDI recurrence.[54] Immunosuppressant use after CDI treatment, current malaise and fatigue, and solid organ cancer, history of HIV infection, multiple myeloma, diabetes mellitus, and COPD were all risk factors for CDI. Immunologic impairment associated with these conditions may contribute to the higher risk of recurrence found in these patients. It is expected that some of these conditions, for example abdominal pain and malaise and fatigue, may correspond with CDI diagnosis as they are symptoms of CDI, and therefore were commonly reported in the time periods assessed.

Other notable predictors of recurrence identified were having a primary diagnosis of CDI and demographic factors. In a single center retrospective chart review, primary diagnosis of CDI was one of the most prevalent risk factors for CDI recurrence.[55] In the hospital setting, a primary diagnosis often represents the main reason for hospitalization. Therefore, this finding may be related to CDI severity, as patients with a primary diagnosis of CDI may have severe CDI symptoms that result in an inpatient hospitalization as compared to those with less severe symptoms.[55] For demographic factors, we found that white race as compared to non-white race

was strongly associated with an increased risk of first CDI recurrence (OR 6.0, 95% CI 4.7-7.6). In previous studies, associations between race and ethnicity and risk of recurrence have been inconsistent.[44, 56, 57] Upon further analysis our results do not appear to be driven by differences in CDI treatment and are unlikely due to regional differences as we matched at the facility level. Our findings could be due to differences in genetics, healthcare utilization or treatment patterns, or other factors.

Our study found that the rate of first recurrence within 30 days of the end of treatment was 6.2%. Our recurrence rates are lower than a recently published national VA study, which found that of 7,538 Veterans with a first CDI episode, 1,223 (16.2%) experienced recurrence within 60 days post-treatment.[34] Differences in rates of recurrence are likely due to differing definitions used to define CDI episodes (IC9-code and positive laboratory value versus positive laboratory value and CDI treatment in our study), differing lengths of follow-up to identify recurrence (60 days versus 30 days post treatment in our study), and different study periods (2002 to 2014 versus 2010 to 2014 in our study).[34] Our CDI recurrence rates would have been higher had we extended follow-up for recurrence. It has been reported that CDI recurrence occurs at a rate of 7% to 26% at 30 days.[18] A previous national VA study of 30,326 Veterans with first CDI reported rates of 30-day, 60-day, and 90-day recurrence by CDI type.[28] In this study, the majority of patients (60%, n=18,260) had health care facility onset CDI and those with health care facility onset CDI had the lowest rates of 30-day recurrence (7.2%). Recurrence rates only increased to 9.5% at 60 days and 10.6% at 90 days.

There are a few limitations to this work. We defined incident CDI, as the first episode during the study period, with no history of CDI in the year prior to that initial CDI episode. Therefore, the incident CDI may not represent the first episode ever for all patients. Our definition of *C. difficile* was based on laboratory results and did not include assessment of clinical symptoms (diarrhea),

and the potential for misclassification of CDI symptomatic episodes versus asymptomatic carriage exists. We did require receipt of at least two days of standard CDI treatment. This practice of combining drug and laboratory data has been used previously, however capturing only clinically relevant disease remains a challenge when using large datasets.[30] Vancomycin, metronidazole, and fidaxomicin given orally were the primary antibiotics given for treatment of CDI during our study period. However, in patients with an ileus who cannot tolerate oral medications, they may be given metronidazole IV or vancomycin rectal.[1] In order to avoid excluding the most severely ill patients, we allowed for metronidazole IV and vancomycin rectal monotherapy to meet our definition of "standard CDI treatment".[1] There is the potential for misclassification of true disease in asymptomatic patients with positive lab tests treated with metronidazole IV for another infection. Another limitation was that we are unable to account for possible treatment or healthcare outside the VA system. In particular, we are unable to account for any over-the-counter medication use not filled in VA pharmacies, such as PPI, H2RAs, and probiotics, and for patients that may have had their initial CDI or recurrence treated outside of the VA system.

Severity was selected a priori as a matching factor in the statistical analysis plan for this study as it is a known predictor of poor outcomes. However, our definition of severity is limited as we only had a single serum creatinine level near CDI treatment initiation, and thus could not assess change from baseline as recommended in the 2010 Infectious Diseases Society of America CDI guidelines which were the guidelines used during our study period (2010-2014).[1] Additionally, lab values were not available on all patients to assess severity. Only having one lab value at baseline, may have led to misclassification of patients into the "severe" category. Treatment patterns of cases and controls suggest this may be minimal as 37% of cases and controls were classified as severe, and about 36% of cases and 33% of controls were treated with options recommended by current guidelines for more severe disease (oral vancomycin, IV metronidazole, or combination therapy).[1] However, despite only 40% of cases and controls being categorized as "non-severe",

about 66% were treated with metronidazole oral monotherapy, suggesting an underestimation of non-severe disease.[1] We would not expect misclassification of severity to be differential by case control status. Strain type was also unknown for most patients.

As previously mentioned, had we extended the follow-up period for CDI recurrence, rates would have been higher. However, a priori we chose to study 30-day recurrence since previous work has demonstrated that CDI recurrence usually occurs within 30 days following the end of CDI treatment, with most cases occurring within 1-3 weeks after treatment.[2, 24, 25, 54, 58] Additionally, most clinical trials have assessed outcomes at 28 to 30 days from the end of treatment. A recent systematic review of CDI treatments in 24 randomized controlled trials reporting recurrence rates, found that follow-up time was between 21 and 30 days from end of treatment for all studies except one which reported outcomes at 56 days only.[59] While the length of follow-up used in clinical trials has been consistently within 4 weeks of treatment cessation, that of studies assessing risk factors for CDI recurrence has varied substantially.[3, 59] A systematic review of 33 studies which investigated risk factors for recurrent CDI found that recurrence definitions ranged from less than 21 days to over 180 days from the previous CDI episode.[3] Additionally, accurate identification of recurrent disease from administrative data is challenging.[15] Previous work has shown performance of diagnosis codes, laboratory data, or medication data used alone to accurately identify recurrent disease is poor, and performance only improved moderately when used in combination.[15]

Another limitation is that our results on the frequency of metronidazole use are reflective of the practice patterns as recommended by the 2010 IDSA guidelines. Since publication of these guidelines, several studies have demonstrated superiority of oral vancomycin over metronidazole.[60-62] As such current clinical practice and new 2017 guideline recommendations recommend oral vancomycin over metronidazole first line despite disease severity.[61, 63] The high

frequency of metronidazole use in our study cohort limited our ability to evaluate other standard CDI treatment options (vancomycin or fidaxomicin) individually. The generalizability of this work to the general population is limited, as the Veteran population consists primarily of older White males. There may be other unknown predictors that were not included in our study, or known predictors that we could not capture from our data source.

Similar to previous findings, treatment with non-CDI active antibiotics, PPIs, and immunosuppressants, as well as underlying comorbid and immunocompromising conditions were among the most important risk factors for recurrence. Knowledge of predictors could help to optimize management of initial CDI and lower risk of recurrence. Specifically, our results highlight an important opportunity for multidisciplinary providers to not just target inappropriate antibiotic use but also to reduce inappropriate use of PPIs, especially in patients with a history of CDI. As with antibiotics, PPIs are a grossly overused class of medications with important consequences, such as the increased risk for first recurrence.[64] Multidisciplinary providers should be aware of the changing clinical practice in CDI treatment and the increasing role vancomycin oral will play in the treatment of initial disease despite severity.

CONCLUSION

In our large national cohort of outpatient and acute and long-term care inpatients, treatment with antibiotics, PPIs, immunosuppressants and underlying disease were among the most important risk factors for first CDI recurrence. Results highlight an important opportunity for antibiotic stewardship programs to not only target inappropriate antibiotic use but also unnecessary PPI use, especially in patients with a history of CDI.

KEY POINTS:

- A national case-control study among acute, long-term care, and outpatient Veterans with a first CDI episode identified 32 predictors of first recurrence among 974 cases and 3,896 matched controls.
- Treatment with antibiotics, proton-pump inhibitors (PPIs), immunosuppressants, and underlying disease were among the most important risk factors for CDI recurrence identified.
- Results highlight an important opportunity for antibiotic stewardship programs to not only target inappropriate antibiotic use but also unnecessary PPIs and probiotic use, especially in patients with a history of CDI.

References

1. Cohen SH, Gerding DN, Johnson S et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-55.

2. Eyre DW, Walker AS, Wyllie D et al. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. *Clin Infect Dis*. 2012;55 Suppl 2:S77-87.

3. Deshpande A, Pasupuleti V, Thota P et al. Risk factors for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2015;36(4):452-60.

4. Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. *Lancet Infect Dis*. 2005;5(9):549-57.

5. Ramsay I, Brown NM, Enoch DA. Recent progress for the effective prevention and treatment of recurrent Clostridium difficile Infection. *Infect Dis (Auckl)*. 2018;11:1178633718758023.

6. McFarland LV. Alternative treatments for Clostridium difficile disease: what really works? *J Med Microbiol*. 2005;54(Pt 2):101-11.

7. Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. *J Infect*. 2009;58(6):403-10.

8. Surawicz CM, Brandt LJ, Binion DG et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013;108(4):478-98; quiz 99.

9. Keddis MT, Khanna S, Noheria A et al. Clostridium difficile infection in patients with chronic kidney disease. *Mayo Clin Proc*. 2012;87(11):1046-53.

10. Debast SB, Bauer MP, Kuijper EJ et al. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect*. 2014;20 Suppl 2:1-26.

11. Garey KW, Sethi S, Yadav Y et al. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. *J Hosp Infect*. 2008;70(4):298-304.

12. Centers for Disease C, Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54(47):1201-5.

13. Campbell RJ, Giljahn L, Machesky K et al. Clostridium difficile infection in Ohio hospitals and nursing homes during 2006. *Infect Control Hosp Epidemiol*. 2009;30(6):526-33.

14. Khanna S, Pardi DS, Aronson SL et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *Am J Gastroenterol*. 2012;107(1):89-95.

15. Wen J, Barber GE, Ananthakrishnan AN. Identification of recurrent Clostridium difficile infection using administrative codes: accuracy and implications for surveillance. *Infect Control Hosp Epidemiol*. 2015;36(8):893-8.

16. Department of Veterans Affairs, Office of the Actuary, Veteran Population Projection Model (VetPop) 2014; Veterans Benefits Administration; Veterans Health Administration, Office of the Assistant Deputy Under Secretary for Health for Policy and Planning. Available: https://www.va.gov/vetdata/docs/Quickfacts/Stats_at_a_glance_06_04_16.PDF. Accessed September 4, 2018.

17. Agha Z, Lofgren RP, VanRuiswyk JV et al. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. *Arch Intern Med*. 2000;160(21):3252-7.

18. Reveles KR, Lawson KA, Mortensen EM et al. National epidemiology of initial and recurrent Clostridium difficile infection in the Veterans Health Administration from 2003 to 2014. *PLoS One*. 2017;12(12):e0189227.

19. Ramanathan S, Johnson S, Burns SP et al. Recurrence of Clostridium difficile infection among veterans with spinal cord injury and disorder. *Am J Infect Control*. 2014;42(2):168-73.

20. Evans ME, Kralovic SM, Simbartl LA et al. Effect of a Clostridium difficile infection prevention initiative in veterans affairs acute care facilities. *Infect Control Hosp Epidemiol*. 2016;37(6):720-2.

21. Gomez-Simmonds A, Kubin CJ, Furuya EY. Comparison of 3 severity criteria for Clostridium difficile infection. *Infect Control Hosp Epidemiol*. 2014;35(2):196-9.

22. Stevens V, Concannon C, van Wijngaarden E et al. Validation of the chronic disease score-infectious disease (CDS-ID) for the prediction of hospital-associated clostridium difficile infection (CDI) within a retrospective cohort. *BMC Infect Dis*. 2013;13:150.

23. Lessa FC, Mu Y, Bamberg WM et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015;372(9):825-34.

24. Aas J, Gessert CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis*. 2003;36(5):580-5.

25. Cornely OA, Crook DW, Esposito R et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-9.

26. Louie TJ, Miller MA, Mullane KM et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422-31.

27. Cornely OA. Current and emerging management options for Clostridium difficile infection: what is the role of fidaxomicin? *Clin Microbiol Infect*. 2012;18 Suppl 6:28-35.

28. Reveles KR, Pugh MJV, Lawson KA et al. Shift to community-onset Clostridium difficile infection in the national Veterans Health Administration, 2003-2014. *Am J Infect Control*. 2018;46(4):431-35.

29. Thabit AK, Nicolau DP. An exploratory study to evaluate Clostridium difficile polymerase chain reaction ribotypes and infection outcomes. *Infect Drug Resist*. 2016;9:143-8.

30. Stevens VW, Nelson RE, Schwab-Daugherty EM et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile Infection. *JAMA Intern Med*. 2017;177(4):546-53.

31. Agency for Healthcare Research and Quality. Clinical Classifications Software (CCS), Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 2015. http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.

32. Abou Chakra CN, Pepin J, Sirard S et al. Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. *PLoS One*. 2014;9(6):e98400.

33. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York, NY: John Wiley & Sons, Inc 2000.

34. Reveles KR, Mortensen EM, Koeller JM et al. Derivation and validation of a Clostridium difficile Infection recurrence prediction rule in a national cohort of Veterans. *Pharmacotherapy*. 2018;38(3):349-56.

35. Peterfreund GL, Vandivier LE, Sinha R et al. Succession in the gut microbiome following antibiotic and antibody therapies for Clostridium difficile. *PLoS One*. 2012;7(10):e46966.

36. Evans CT, Safdar N. Current trends in the epidemiology and outcomes of Clostridium difficile Infection. *Clin Infect Dis*. 2015;60 Suppl 2:S66-71.

37. Kwok CS, Arthur AK, Anibueze CI et al. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol*. 2012;107(7):1011-9.

38. Tleyjeh IM, Abdulhak AB, Riaz M et al. The association between histamine 2 receptor antagonist use and Clostridium difficile infection: a systematic review and meta-analysis. *PLoS One*. 2013;8(3):e56498.

39. Deshpande A, Pasupuleti V, Thota P et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013;68(9):1951-61.

40. Vardakas KZ, Trigkidis KK, Boukouvala E et al. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016;48(1):1-10.

41. Brown KA, Khanafer N, Daneman N et al. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrob Agents Chemother*. 2013;57(5):2326-32.

42. Shively NR, Buehrle DJ, Clancy CJ et al. Prevalence of inappropriate antibiotic prescribing in primary care clinics within a Veterans Affairs Health Care System. *Antimicrob Agents Chemother*. 2018;62(8).

43. Doernberg SB, Winston LG, Deck DH et al. Does doxycycline protect against development of Clostridium difficile infection? *Clin Infect Dis*. 2012;55(5):615-20.

44. Shields K, Araujo-Castillo RV, Theethira TG et al. Recurrent Clostridium difficile infection: From colonization to cure. *Anaerobe*. 2015;34:59-73.

45. McFarland LV, Surawicz CM, Greenberg RN et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. *JAMA*. 1994;271(24):1913-8.

46. Pochapin M. The effect of probiotics on Clostridium difficile diarrhea. *Am J Gastroenterol*. 2000;95(1 Suppl):S11-3.

47. Lawrence SJ, Korzenik JR, Mundy LM. Probiotics for recurrent Clostridium difficile disease. *J Med Microbiol*. 2005;54(Pt 9):905-6.

48. Dubberke ER, Yan Y, Reske KA et al. Development and validation of a Clostridium difficile infection risk prediction model. *Infect Control Hosp Epidemiol*. 2011;32(4):360-6.

49. Rodriguez-Pardo D, Almirante B, Bartolome RM et al. Epidemiology of Clostridium difficile infection and risk factors for unfavorable clinical outcomes: results of a hospital-based study in Barcelona, Spain. *J Clin Microbiol*. 2013;51(5):1465-73.

50. Nelson RL, Kelsey P, Leeman H et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. *Cochrane Database Syst Rev*. 2011(9):CD004610.

51. McFarland LV. Update on the changing epidemiology of Clostridium difficile-associated disease. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5(1):40-8.

52. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. *Clin Infect Dis*. 2008;46 Suppl 1:S12-8.

53. Zanella Terrier MC, Simonet ML, Bichard P et al. Recurrent Clostridium difficile infections: the importance of the intestinal microbiota. *World J Gastroenterol*. 2014;20(23):7416-23.

54. Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? *Clin Microbiol Infect*. 2012;18 Suppl 6:21-7.

55. Majors D, Ellis P. Risk Factors for Recurrent Clostridium difficile infections and strategies to decrease readmissions in a community hospital. *Hosp Pharm*. 2015;50(11):1003-10.

56. VerLee KE, Finks JL, Wilkins MJ et al. Michigan Clostridium difficile hospital discharges: frequency, mortality, and charges, 2002-2008. *Public Health Rep*. 2012;127(1):62-71.

57. Ricciardi R, Rothenberger DA, Madoff RD et al. Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. *Arch Surg*. 2007;142(7):624-31; discussion 31.

58. Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol*. 2009;7(7):526-36.

59. Beinortas T, Burr NE, Wilcox MH et al. Comparative efficacy of treatments for Clostridium difficile infection: a systematic review and network meta-analysis. *Lancet Infect Dis*. 2018.

60. Johnson S, Louie TJ, Gerding DN et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-54.

61. Ooijevaar RE, van Beurden YH, Terveer EM et al. Update of treatment algorithms for Clostridium difficile infection. *Clin Microbiol Infect*. 2018.

62. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. *Cochrane Database Syst Rev*. 2017;3:CD004610.

63. 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.

64. McDonald EG, Jones J, Green L et al. Reduction of inappropriate exit prescriptions for proton pump inhibitors: A before-after study using education paired with a web-based quality-improvement tool. *J Hosp Med*. 2015;10(5):281-6.

Table 1. Clinical characteristics, current comorbidities, medical history of patients with first CDI occurrence by case-control status

	Cases of first recurrence (n = 974)	**Controls without first recurrence (n = 3,896)**	**P-value**
Age (years), mean (SD)	67.8 (±13.6)	64.8 (±13.9)	<0.001
Male gender	920 (94.5)	3,604 (92.5)	0.034
White race	730 (75.2)	1,617 (41.5)	<0.001
Hispanic ethnicity	33 (3.4)	263 (6.8)	<0.001
Married	427 (43.8)	1,557 (40.0)	0.028
CDI Severity			
Severe	358 (36.8)	1,432 (36.8)	
Non-severe	389 (39.9)	1,556 (39.9)	
Unknown	227 (23.3)	908 (23.3)	
Hypervirulent strain	55 (5.7)	259 (6.7)	0.255
CDI treatment[a]			<0.001
Metronidazole monotherapy	736 (75.6)	3,506 (90.0)	
Oral Route	625 (64.2)	2,586 (66.3)	
IV Route	111 (11.4)	920 (23.6)	
Vancomycin oral monotherapy	96 (9.9)	35 (0.9)	

Metronidazole Oral/IV & vancomycin Oral	142 (14.6)	343 (8.8)	
CDI treatment duration (days), mean (SD)	10.2 (±6.1)	8.4 (±6.2)	<0.001
Current comorbidities			
Biliary tract disease	25 (2.6)	39 (1.0)	<0.001
Malaise and fatigue	23 (2.4)	21 (0.5)	<0.001
Cellulitis or abscess	49 (5.0)	74 (1.9)	<0.001
Solid organ cancer	132 (13.6)	206 (5.3)	<0.001
Pneumonia	64 (6.6)	203 (5.2)	0.095
Medical history			
Heart failure	142 (14.6)	273 (7.0)	<0.001
Chronic respiratory disease	227 (23.3)	361 (9.3)	<0.001
Chronic renal disease	182 (18.7)	349 (9.0)	<0.001
Diabetes mellitus	270 (27.7)	451 (11.6)	<0.001

Cerebrovascular disease	51 (5.2)	76 (2.0)	<0.001
Alcoholic disorder	92 (9.5)	232 (6.0)	<0.001
Abdominal pain	85 (8.7)	125 (3.2)	<0.001
Osteoarthritis	126 (12.9)	161 (4.1)	<0.001
Atherosclerosis	238 (24.4)	349 (9.0)	<0.001
Esophageal disorder	209 (21.5)	316 (8.1)	<0.001
Nutrition deficiency	116 (11.9)	233 (6.0)	<0.001

Data are number (%) unless otherwise stated.

CDI= *Clostridium difficile* infection; SD= standard deviation

[a]Metronidazole monotherapy for *Clostridium difficile* infection was compared to all other *Clostridium difficile* infection treatments combined. This variable was removed from the multivariable model during the stepwise removal process and as such was not included in the final multivariate model (Table 3).

Table 2. Healthcare and medication exposures of patients with first CDI occurrence by case-control status

	Cases of first recurrence (n = 974)	**Controls without first recurrence (n = 3,896)**	**P-value**
Treatment setting			<0.001
Acute care	397 (40.8)	970 (24.9)	
Long term care	25 (2.6)	82 (2.1)	
Outpatient	552 (56.7)	2,844 (73.0)	
Veterans Affairs hospitalization, prior 90 days	686 (70.4)	2,249 (57.7)	<0.001
Veterans Affairs long-term care admission, prior 90 days	52 (5.3)	71 (1.8)	<0.001
Non-CDI active antibiotic use, 30 days before CDI treatment	578 (59.3)	2,335 (59.9)	0.737
Non-CDI active antibiotic use, during CDI treatment	503 (51.6)	2,473 (63.5)	<0.001
Non-CDI active antibiotic use, 30 days after CDI treatment	487(50.0)	1267 (32.5)	<0.001
Histamine receptor 2 antagonist use, 7 days before CDI treatment	58 (6.0)	346 (8.9)	.003
Proton pump inhibitor use, 7 days before CDI treatment	309 (31.7)	1390 (35.7)	0.021

Histamine receptor 2 antagonist use, 30 days after CDI treatment	121 (12.4)	325 (8.3)	<0.001
Proton pump inhibitor use, 30 days after CDI treatment	503 (51.6)	1,310 (33.6)	<0.001
Probiotic use, 30 days before CDI treatment	80 (8.2)	31 (0.8)	<0.001
Probiotic use, 30 days after CDI treatment	89 (9.1)	85 (2.2)	<0.001
Immunosuppressant use, 30 days before CDI treatment	145 (14.9)	509 (13.1)	0.136
Immunosuppressant use, 30 days after CDI treatment	256 (16.0)	327 (8.4)	<0.001
Length of stay (days), median (IQR)	8 (4-18)	9 (5-20)	0.04

Data are number (%) unless otherwise stated.

CDI= *Clostridium difficile* infection; IQR= interquartile range

Table 3. Independent predictors of first recurrence in patients with initial *Clostridium difficile* infection

Predictor	**Adjusted Odds Ratio (95% CI)**
Medications used within 30 days before CDI treatment	
Probiotic	4.62 (2.37-8.98)
Fluoroquinolone	3.35 (2.58-4.34)
Laxative (within 2 days before)	2.35 (1.21-4.58)
3rd-4th generation cephalosporin	2.04 (1.49-2.79)
Penicillin, amoxicillin or ampicillin	1.70 (1.07-2.70)
Amoxicillin or ampicillin / Beta-lactamase inhibitor	1.69 (1.08-2.66)
1st -2nd generation cephalosporin	1.68 (1.13-2.48)
Glyco-/ glycolipo-/ lipopeptide	1.54 (1.12-2.12)
Concurrent medications used during CDI treatment	
1st -2nd generation cephalosporin	1.92 (1.13-3.25)
Penicillin, amoxicillin or ampicillin	1.70 (1.06-2.71)
3rd-4th generation cephalosporin	1.54 (1.13-2.11)
Medications used within 30 days after CDI treatment	
Probiotic use	2.30 (1.35-3.91)
Any non-CDI active antibiotic[a]	2.14 (1.68-2.73)
Proton pump inhibitor	2.02 (1.59-2.55)
Immunosuppressant	1.45 (1.05-2.00)
Current comorbidities	
Biliary tract disease	4.70 (1.68-13.12)
Malaise and fatigue	2.38 (1.01-5.64)

Cellulitis or abscess	1.80 (1.03-3.15)
Solid organ cancer	1.79 (1.25-2.55)
Medical history	
HIV infection	3.32 (1.26-8.78)
Multiple myeloma	2.75 (1.04-7.27)
Abdominal pain	2.47 (1.65-3.70)
Regional enteritis and ulcerative colitis	2.14 (1.01-4.57)
Osteoarthritis	1.89 (1.32-2.71)
Atherosclerosis	1.84 (1.38-2.46)
Esophageal disorder	1.66 (1.23-2.23)
Nutrition deficiency	1.63 (1.15-2.30)
Diabetes mellitus	1.59 (1.21-2.09)
Chronic obstructive pulmonary disease	1.35 (1.01-1.82)
Clinical characteristics	
Principal diagnosis of CDI	4.06 (2.97-5.55)
Treatment duration of initial CDI episode	1.04 (1.02-1.06)
Demographics	
White race[b]	5.95 (4.66-7.61)

The adjusted odds ratios are estimated from multivariate analysis of the data. The final multivariate model included all predictive variables listed in the table above (odds ratio >1) and also the following variables with odds ratios <1: histamine receptor 2 antagonist use within 7 days before *Clostridium difficile* infection treatment, proton pump inhibitor use within 7 days before *Clostridium difficile* infection treatment, any non-CDI active antibiotic during *Clostridium difficile* infection treatment, current thyroid disorder, current pneumonia, medical history of a bacterial

infection (unspecified site), medical history of biliary tract disease, abnormal albumin level, nursing home admitting source, and Hispanic ethnicity .

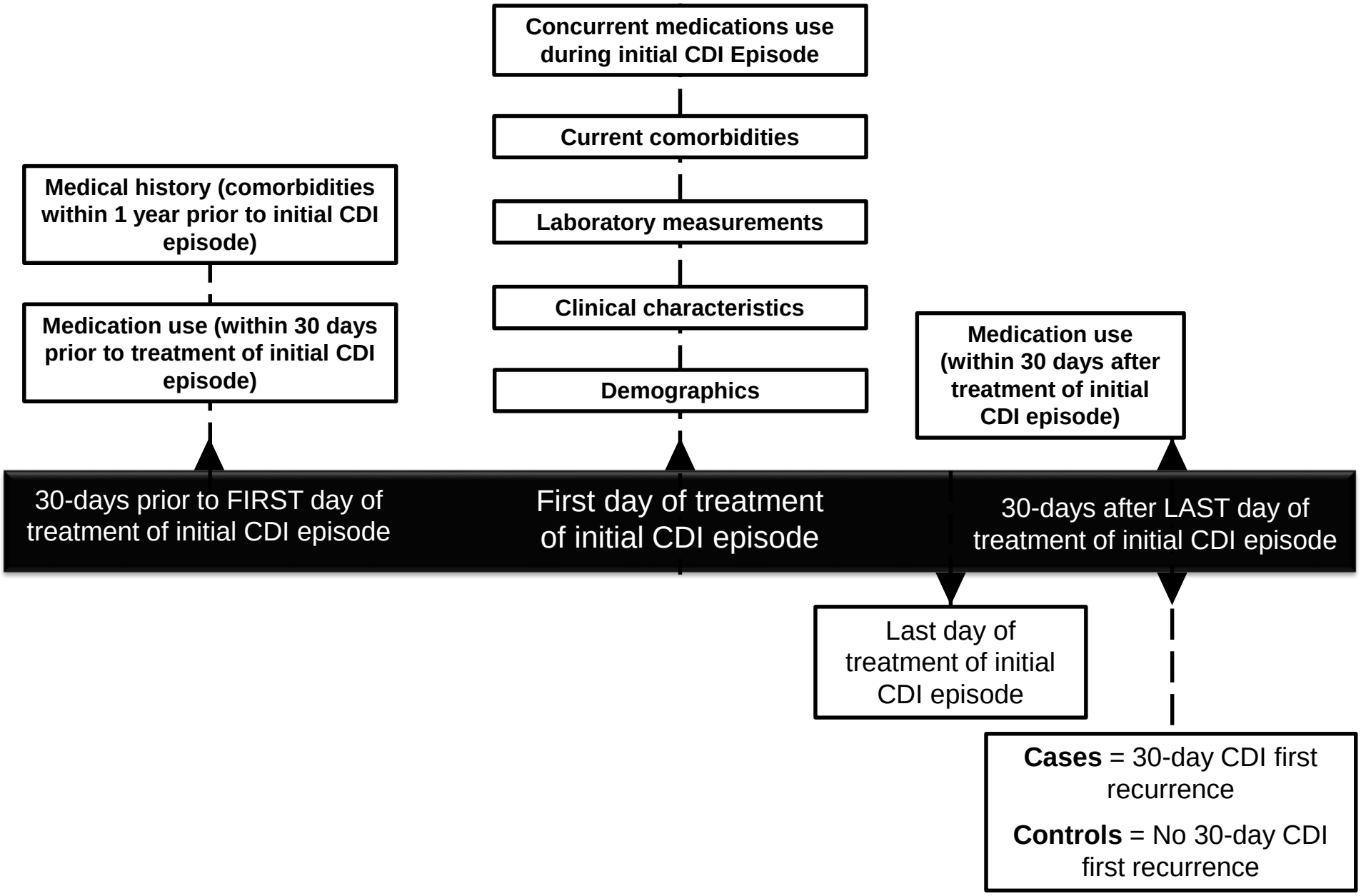
[a]Any antibiotic included any antibiotic not used for the treatment of CDI, including the following aminoglycosides, aztreonam, β-lactam/ β-lactamase inhibitor combinations, carbapenems, cephalosporins, clindamycin, fluoroquinolones, fosfomycin, glyco-/glycolipo-/lipopeptdes (except vancomycin oral/rectal), nitrofurantoin, macrolides, oxazolidinones, penicillins, polymyxins, sulfamethoxazole/trimethoprim, quinupristin-dalfopristin, tetracyclines, and tigecycline.

[b]White race was compared to all other non-white races.

CDI= *Clostridium difficile* infection

Figure 1. Timeline of when potential predictors for first CDI recurrence were assessed.

CDI= *Clostridium difficile* infection


Concurrent medications use during initial CDI Episode
Current comorbidities
Laboratory measurements
Clinical characteristics
Demographics
Medical history (comorbidities within 1 year prior to initial CDI episode)
Medication use (within 30 days prior to treatment of initial CDI episode)
Medication use (within 30 days after treatment of initial CDI episode)
30-days prior to FIRST day of treatment of initial CDI episode
First day of treatment of initial CDI episode
30-days after LAST day of treatment of initial CDI episode
Last day of treatment of initial CDI episode
Cases = 30-day CDI first recurrence
Controls = No 30-day CDI first recurrence