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MAJOR ARTICLE

Predictors of Mortality Among a National Cohort of Veterans With Recurrent *Clostridium difficile* Infection

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Background. Though recurrent *Clostridium difficile* infection (CDI) is common and poses a major clinical concern, data are lacking regarding mortality among patients who survive their initial CDI and have subsequent recurrences. Risk factors for mortality in patients with recurrent CDI are largely unknown.

Methods. Veterans Affairs patients with a first CDI (stool sample with positive *C. difficile* toxin(s) and ≥2 days CDI treatment) were included (2010–2014). Subsequent recurrences were defined as additional CDI episodes ≥14 days after the stool test date and within 30 days of the end of treatment. A matched (1:4) case–control analysis was conducted using multivariable conditional logistic regression to identify predictors of all-cause mortality within 30 days of the first recurrence.

Results. Crude 30-day all-cause mortality rates were 10.6% for the initial CDI episode, 8.3% for the first recurrence, 4.2% for the second recurrence, and 5.9% for the third recurrence. Among 110 cases and 440 controls, 6 predictors of mortality were identified: use of proton pump inhibitors (PPIs; odds ratio [OR], 3.86; 95% confidence interval [CI], 2.14–6.96), any antibiotic (OR, 3.33; 95% CI, 1.79–6.17), respiratory failure (OR, 8.26; 95% CI, 1.71–39.92), congitive dysfunction (OR, 2.41; 95% CI, 1.02–5.72), nutrition deficiency (OR, 2.91; 95% CI, 1.37–6.21), and age (OR, 1.04; 95% CI, 1.01–1.07).

Conclusions. In our national cohort of Veterans, crude mortality decreased by 44% from the initial episode to the third recurrence. Treatment with antibiotics, use of PPIs, and underlying comorbidities were important predictors of mortality in recurrent CDI. Our study assists health care providers in identifying patients at high risk of death after CDI recurrence.

Keywords. *Clostridium difficile* infection; mortality; predictors; recurrent disease; Veterans Affairs.

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacterium that causes infectious diarrhea ranging in severity from mild to life-threatening [1]. Disease recurrence and decreased survival are important concerns related to *Clostridium difficile* infection (CDI). It is estimated that *C. difficile* is responsible for at least half a million cases of infection in the United States annually [2]. The estimated number of first recurrences of CDI each year is 83 000, and the estimated number of deaths is 29 300 [2]. Symptomatic first recurrence after resolution of the primary CDI episode occurs in 20%–30% of patients, usually within 30 days after treatment cessation [3–5]. *Clostridium difficile* infection mortality estimates vary widely in the literature, with rates ranging from less than 5% to more than 20% in severe cases [6, 7]. A review of 27 studies found that the CDI-associated mortality rate was 6% within 3 months of diagnosis [8]. Previous work has identified several risk factors for mortality in patients with CDI [9–12]. Older age, non-CDI antibiotic use concomitantly or after CDI treatment, and presence of underlying comorbid conditions are among the most frequently reported mortality risk factors [9, 10].

Despite the common and growing concern of recurrent disease over the past decade, data are lacking regarding mortality rates among patients who survive their initial CDI episode and have subsequent recurrences [5]. The few previously reported mortality estimates among those with disease recurrence vary widely from approximately 5% to greater than 35%, likely due to the different patient populations studied and significant variations in follow-up for death from 30 days to 1 year post-recurrence [13–16]. Moreover, although some studies suggest that recurrence may increase risk of death, others suggest that recurrence may not increase risk of death and mortality rates may actually decrease as recurrences accrue [13, 15–18]. Finally, independent predictors of mortality among patients with CDI recurrence are largely unknown. Knowledge of these factors could improve the management of patients with recurrent disease and limit unfavorable outcomes. Thus, we sought to describe crude mortality rates of subsequent CDI episodes and identify independent predictors of mortality among our national cohort of Veterans with recurrence of *Clostridium difficile* infection.

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METHODS

Data Sources

We used data from national Veterans Affairs (VA) databases for this work. Corporate Data Warehouse (CDW), Medical SAS, and Decision Support System (DSS) data were accessed through the VA Informatics and Computing Infrastructure (VINCI). Our cohort included patients from 128 VA facilities nationally.

Study Population

We developed a national cohort of adult Veterans (≥18 years) with an initial CDI episode (no CDI episodes in the year prior) treated during an inpatient admission or outpatient encounter at a VA facility from May 1, 2010, to December 30, 2014. We defined a CDI episode as a positive stool sample for *C. difficile* toxin(s) and receipt of at least 2 days of standard CDI treatment (oral [PO] or intravenous [IV] metronidazole, PO or rectal [PR] vancomycin, or fidaxomicin) [1, 19]. Use of a minimum treatment window of at least 2–3 days of CDI therapy (regardless of dosing frequency) has been used previously in several studies for CDI identification and minimum CDI treatment exposure [17, 20, 21]. Although a CDI testing method was not available in the data source, the use of the nucleic acid amplification test for CDI diagnostic testing among VA facilities has increased from 33% in 2010 to 54% in 2012 to 81% in 2015 [22]. The initial episode was the first episode of CDI during the study period. First recurrence, second recurrence, and third recurrence were defined as subsequent CDI episodes at least 14 days after the positive stool test date and within 30 days of the end of treatment of the prior occurrence [23–25]. An interval of at least 14 days is commonly used to distinguish new recurrent episodes from prior CDI episodes [2, 26].

Study Design

We described the all-cause mortality rate by episode number. Mortality was defined as death from any cause within 30 days of the end date of CDI treatment of the prior CDI episode. We also conducted a case–control analysis in our cohort of patients with a first recurrence of CDI to identify independent predictors of all-cause mortality. Cases were defined as patients who died from any cause within 30 days of the end of treatment of recurrence. Controls were survivors at 30 days from the end of treatment of recurrence and were matched to cases on year, facility, and severity. Four controls were matched to each case. *Clostridium difficile* infection severity was defined as severe if the closest white blood cell count was $>15 \times 10^3/\mu L$ or the serum creatinine was >1.5 g/dL within 7 days of CDI treatment, nonsevere if the white blood cell count was $\leq 15 \times 10^3/\mu L$ and the serum creatinine was ≤1.5 g/dL, or unknown otherwise [27]. In our overall cohort of patients with CDI, >96% of white blood cell count (n = 42 298) and serum creatinine (n = 40 261) levels were obtained within 2 days of treatment.

Potential predictors assessed were based on clinical relevance and/or previously described predictors of poor outcomes [1, 28–31]. Potential predictors included demographics, treatment characteristics, current comorbidities and medical history, aggregate comorbidity burden using the Charlson Comorbidity Index, laboratory results, current and previous health care exposures, and concurrent and previous medication exposures. We defined CDI treatment as metronidazole PO or IV monotherapy, vancomycin PO or PR monotherapy, vancomycin and metronidazole combination therapy, or fidaxomicin alone or in combination with vancomycin and/or metronidazole. We compared metronidazole monotherapy with all other treatment options due to the high frequency of metronidazole monotherapy in our cohort. International Classification of Diseases, 9th Revision (ICD-9), diagnosis and procedure codes were used to identify the presence of current and previous disease states and procedures. Current comorbidities were defined as disease states that occurred during the index CDI admission (inpatient) or 30 days before the CDI episode (outpatient) and medical histories were defined as those that occurred in the year before the CDI episode. Clinical Classifications Software (CCS) for ICD-9 codes was used to categorize diagnoses and procedures into broader disease states [32]. Medication exposures assessed included antibiotics, gastric acid suppressants, immunosuppressants, laxatives, and supplemental medications (probiotics, binding agents, rifampin, rifaximin, nitazoxanide, and bacitracin). Medication exposures were assessed before CDI treatment (30 days prior for immunosuppressants and antibiotics and 7 days for gastric acid suppressants, histamine receptor 2 antagonists [H2RA], or proton pump inhibitors [PPIs]), during CDI treatment, and 30 days after CDI treatment. The window for assessment of exposure to medications was selected based on clinical relevance or previous work [3, 9, 31].

Statistical Analysis

We calculated descriptive statistics, including number, percentage, mean (standard deviation), and median (interquartile range). Differences in clinical characteristics and crude mortality rates by episode number were analyzed using the chi-square test or Fisher exact test for categorical data and the Student *t* test or Wilcoxon rank-sum test for continuous data, as appropriate. We also analyzed differences between cases and controls and used backward, manual, stepwise conditional logistic regression to identify independent predictors of mortality [33]. All variables with a *P* value of less than .10 from univariate analysis were included in subsequent multivariable analysis [33]. Variables were then removed in a stepwise fashion from the multivariable models until all remaining variables were significantly associated with the outcome ($P < .05$) [33]. Multicollinearity was assessed using the correlation matrix of the final model and variance inflation factor values [33, 34]. All variables in our final multivariable model had a variance inflation factor value of <3, indicating lack of multicollinearity. All statistical analyses were performed with SAS (version 9.2; SAS Institute Inc., Cary, NC).

The Institutional Review Board and the Research and Development Committee of the Providence Veterans Affairs Medical Center approved this study protocol before the study was initiated.

RESULTS

We identified 49 064 initial episodes of CDI, 2521 episodes of first recurrence, 409 episodes of second recurrence, and 68 episodes of third recurrence over our 5-year study period. The mean age of patients with an initial CDI episode (SD) was 66.2 (14.1) years. Mean age (SD) increased with each subsequent occurrence: 68.5 (13.1) years for first recurrence, 70.7 (13.4) years for second recurrence, and 73.2 (13.9) years for third recurrence. The majority of initial episodes (69.7%, n = 34 177) were treated in the outpatient setting. Significantly more episodes were treated in the outpatient setting for the initial episode as compared with the first recurrence (58%, n = 1462); however, with each subsequent recurrence, the percentage of patients treated in the outpatient setting remained stable (56.5% second recurrence, 55.9% third recurrence). Thirty-four percent of initial CDI episodes were severe (n = 16 806). The severity of most cases of recurrence was unknown (95.1% first, 97.6% second, 100% third recurrence). The crude 30-day all-cause mortality rate was 10.6% for the initial episode (n = 5214), 8.3% for first recurrence (n = 208), 4.2% for second recurrence (n = 17), and 5.9% for third recurrence. Crude 30-day all-cause mortality was significantly higher for the initial episode vs first recurrence ($P < .001$) and first recurrence vs second recurrence ($P = .004$).

We identified 110 cases who died within 30 days of end of treatment of the first recurrence and 440 surviving controls matched on year, facility, and severity. Characteristics of cases and controls are described in Table 1. The mean age (SD) of cases was 73.1 (12.5) years, and that of controls was 66.9 (13.1) years. Treatment in the outpatient setting (49.1% cases vs 65.0% controls) and metronidazole monotherapy treatment (40.9% cases vs 71.4% controls) were less common in cases as compared with controls. Table 2 lists the 6 independent predictors of 30-day all-cause mortality identified. Medication exposures predictive of mortality included use of proton pump inhibitors within 7 days before CDI treatment (odds ratio [OR], 3.86; 95% confidence interval [CI], 2.14–6.96) and any non-CDI antibiotic use during CDI treatment (OR, 3.33; 95% CI, 1.79–6.17). For comorbidities and medical history, current respiratory failure (OR, 8.26; 95% CI, 1.71–39.92), current congitive dysfunction (OR, 2.41; 95% CI, 1.02–5.72), and medical history of nutrition deficiency (OR, 2.91; 95% CI, 1.37–6.21) were predictive of mortality. Age was also a predictor of mortality (OR, 1.04; 95% CI, 1.01–1.07).

DISCUSSION

This study is the first to identify independent predictors of mortality among a national cohort of Veterans who already experienced an initial and subsequent first recurrence of CDI. Although several prior studies have studied the risk factors for mortality in patients with CDI, to our knowledge, ours is the first to focus specifically on evaluating predictors of mortality in patients with a first recurrence of CDI. From the time of the first recurrence of CDI (second CDI episode per patient), we followed patients to determine whether they died and then identified predictors of death.

In addition to identifying predictors, our study described crude mortality rates by subsequent episode. Our results are supported by another recent VA analysis among 30 326 VHA beneficiaries nationally, which also found higher 30-day mortality rates among those with initial disease (21%) than those with recurrent disease (11% with first recurrence and 7% with second recurrence) [35]. Another study among 1527 adults diagnosed with CDI in a hospital in Canada described decreasing mortality rates with subsequent CDI episodes (10.9% initial, 7.6% first recurrence, 7.0% second recurrence, 5.7% third recurrence) [16]. Possible explanations for decreased mortality with recurrent disease include a survival bias among patients who survive an initial episode, earlier disease detection and treatment among those who recur as compared with those with initial disease, and host-adaptive immune response changes [35]. Another possible explanation for findings may be related to the difficulties in distinguishing symptomatic recurrent CDI from those with alternative etiologies for continued diarrhea. A retrospective review of 117 patients referred for treatment for presumed recurrent CDI found that 25% did not actually have CDI but had an alterative diagnosis, usually postinfectious inflammatory bowel syndrome [36].

Similar to our findings, previous studies have demonstrated that older age and comorbid conditions are independent risk factors for mortality in patients with CDI [9, 11, 12]. A systematic review that included 30 studies demonstrated that increasing age and underlying comorbid conditions, including both individual conditions (specifically malignancy, chronic renal failure, and coronary artery disease) and aggregate Charlson score, were among the most commonly reported risk factors for mortality in patients with CDI [9]. One of the major reasons for an increased risk of poor outcomes, including mortality, in older patients and/or those with serious comorbid conditions may be a decreased ability to mount an adequate immune response to the *C. difficile* toxin [37]. Age has been recognized as a risk factor for both development of CDI and CDI-related death [28]. A recent study that used the US 2011 Nationwide Inpatient Sample (NIS) database and included more than 77 000 CDI hospitalizations found that progressive increase in age was an independent predictor of CDI-associated in-hospital mortality, especially in patients age 81–100 years (OR, 4.12; 95% CI, 3.39–4.99) as compared with those age 18–40 years [38]. Previous work evaluating predictors of complicated CDI (death, need for colectomy, shock, perforation, or megacolon within 30 days) in patients diagnosed in a hospital in Quebec, Canada,

Table 1. Patient Characteristics, 30-Day All-Cause Mortality

	Cases With 30-d All-Cause Mortality (n = 110)	Controls Without 30-d All-Cause Mortality (n = 440)
Age, mean (SD), y[c]	73.1 (12.5)	66.9 (13.1)
Male gender, n (%)	109 (99.1)	419 (95.2)
White race, n (%)	80 (72.7)	326 (74.1)
Hispanic ethnicity, n (%)	7 (6.4)	23 (5.2)
Married, n (%)	48 (43.6)	180 (40.9)
Treatment setting, n (%)[c]		
Acute care	46 (41.8)	140 (31.8)
Long-term care	10 (9.1)	14 (3.2)
Outpatient	54 (49.1)	286 (65.0)
CDI treatment, n(%)[c]		
Metronidazole PO/IV monotherapy	45 (40.9)	314 (71.4)
Metronidazole monotherapy	45 (40.9)	314 (71.4)
PO monotherapy	28 (25.5)	251 (57.0)
IV monotherapy	17 (15.5)	63 (14.3)
Vancomycin PO monotherapy	26 (23.6)	74 (16.8)
Metronidazole PO/IV & vancomycin PO	39 (35.5)	50 (11.4)
CDI treatment duration, median (IQR), d	7 (11–4)	8 (4–15)
Charlson comorbidity score, median (IQR)[c]	3 (0–5)	1 (0–4)
Current comorbidities, n (%)[a]		
Abdominal pain	<5	27 (6.1)
Alcoholic disorder	8 (7.3)	26 (5.9)
Atherosclerosis	15 (13.6)	61 (13.9)
Bacterial infection (unspecified site)	8 (7.3)	34 (7.7)
Cerebrovascular disease	<5	8 (1.8)
Chronic renal disease	21 (19.1)	63 (14.3)
Chronic obstructive pulmonary disease	16 (14.5)	58 (13.2)
Diabetes mellitus	12 (10.9)	70 (15.9)
Esophageal disorder	6 (5.5)	25 (5.9)
Fever of unknown origin	<5	14 (3.2)
Heart failure[c]	21 (19.1)	49 (11.1)
Hypertension	24 (21.8)	96 (21.8)
Liver disease	9 (8.2)	22 (5.0)
Myocardial infarction	<5	6 (1.4)
Nutrition deficiency[c]	20 (18.2)	23 (5.2)
Osteoarthritis	<5	10 (2.3)
Peptic ulcer disease	<5	<5
Peripheral vascular disease	5 (4.5)	18 (4.1)
Pulmonary heart disease[c]	8 (7.3)	9 (2.0)
Respiratory failure[c]	18 (16.4)	16 (3.6)
Solid organ cancer	16 (14.5)	49 (11.1)
Surgery/medical complication	6 (5.5)	12 (2.7)
Medical history, n (%)[b]		
Abdominal pain	8 (7.3)	50 (11.4)
Alcoholic disorder	10 (9.1)	43 (9.8)
Atherosclerosis[c]	38 (34.5)	104 (23.6)
Bacterial infection (unspecified site)	20 (18.2)	76 (17.3)
Cognitve dysfunction[c]	21 (19.1)	30 (6.8)
Cerebrovascular disease	6 (5.5)	17 (3.9)
Chronic renal disease	27 (24.5)	87 (19.8)
Chronic obstructive pulmonary disease	30 (27.3)	95 (21.6)
Diabetes mellitus	28 (25.5)	126 (28.6)
Esophageal disorder	24 (21.8)	82 (18.6)
Fever of unknown origin	6 (5.5)	29 (6.6)
Heart failure[c]	30 (27.3)	78 (17.7)
Hypertension	55 (50.0)	181 (41.1)
Liver disease	17 (15.5)	46 (10.5)

Table 1. *Continued*

	Cases With 30-d All-Cause Mortality (n = 110)	Controls Without 30-d All-Cause Mortality (n = 440)
Myocardial infarction	5 (4.5)	14 (3.2)
Nutrition deficiency[c]	30 (27.3)	39 (8.9)
Osteoarthritis	13 (11.8)	40 (9.1)
Peptic ulcer disease	5 (4.5)	12 (2.7)
Peripheral vascular disease	11 (10.0)	49 (11.1)
Pulmonary heart disease	7 (6.4)	21 (4.8)
Solid organ cancer	26 (23.6)	72 (16.4)
Surgery/medical complication	14 (2.7)	36 (8.2)
Medication exposures, n (%)		
Non-CDI antibiotic use, 30 d before *Clostridium difficile* infection treatment[c]	93 (84.5)	314 (71.4)
Non-CDI antibiotic use, during *Clostridium difficile* infection treatment[c]	82 (74.5)	213 (48.4)
Non-CDI antibiotic use, 30 d after *Clostridium difficile* infection treatment	36 (32.7)	154 (35.0)
Histamine receptor 2 antagonist use, 7 d before *Clostridium difficile* infection treatment	11 (10.0)	28 (6.4)
Proton pump inhibitor use, 7 d before *Clostridium difficile* infection treatment[c]	68 (61.8)	156 (35.5)
Histamine receptor 2 antagonist use, 30 d after *Clostridium difficile* infection treatment	7 (6.4)	49 (11.1)
Proton pump inhibitor use, 30 d after *Clostridium difficile* infection treatment	42 (38.2)	165 (37.5)
Probiotic use, 30 d after *Clostridium difficile* infection treatment	5 (4.6)	36 (8.2)
Immunosuppressant use, 30 d after *Clostridium difficile* infection treatment	13 (11.8)	55 (12.5)
Hospitalization, prior 90 d, n (%)	88 (80.0)	342 (77.7)
Long-term care admission, prior 90 d, n (%)[c]	11 (10.0)	20 (4.6)
Recurrent CDI in hospital setting, n (%)	57 (51.8)	155 (35.2)
Length of stay, median (IQR), d[c]	13 (8–21)	7 (4–13)

Current comorbidities and medical histories were defined using Clinical Classification Software for ICD-9.

Abbreviations: CDI, *Clostridium difficile* infection; IQR, interquartile range; IV, intravenous; PO, oral.

[a]Current comorbidities were defined as diagnoses that occurred during the index CDI admission (inpatient) or 30 days before the CDI episode (outpatient).

[b]Medical histories were defined as diagnoses that occurred in the year before the CDI episode.

[c]$P < .05$.

during 1991–2005 with first recurrence identified older age as a strong predictor [14].

Several comorbid conditions have been previously identified as predictors of mortality in patients with CDI [13, 38]. Our work demonstrated that respiratory failure, cognitive dysfunction, and nutrition deficiency were all independent predictors of mortality. Respiratory failure has been previously identified as an independent predictor of mortality in patients with fulminant *C. difficile* colitis [39]. Intensive care unit admission and acute renal failure were among the among the strongest predictors of CDI-associated in-hospital mortality identified in the study of CDI hospitalizations using 2011 NIS data, and although we did not identify these conditions as independent predictors, respiratory failure may represent a related surrogate marker [38]. Functional decline has previously been associated with severe CDI, and dependency in activities of daily living has been associated with long-term mortality in very old patients with CDI [40, 41]. The diagnosis codes for cognitive dysfunction include delirium, dementia, and amnestic and other cognitive disorders [32]. To our knowledge, nutrition deficiency has not been previously identified as an independent predictor; however, conditions that may cause or be related to various nutrition deficiencies have been identified as independent predictors of mortality, such as enteral tube feeding and inflammatory bowel disease [38, 42, 43]. Although enteral tube feeding and inflammatory bowel disease are not included in the codes for nutrition deficiency, nutrition deficiency codes capture a broad spectrum of nutritional conditions, such as unspecified protein-calorie malnutrition, other malnutrition, cachexia, and vitamin deficiencies [32]. It is possible that some enteral tube feeding diets may lead to nutrition deficiencies in the colon and resultant disruption on the colonic microbiota [42]. Additionally, the mortality risk has consistently been shown to be higher in CDI patients with inflammatory bowel disease, a

Table 2. Independent Predictors of 30-Day All-Cause Mortality

Predictor	Adjusted Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Medications used before *Clostridium difficile* infection treatment			
Proton pump inhibitor (within 7 d before)	3.86	2.14	6.96
Concurrent medications used during *Clostridium difficile* infection treatment			
Any antibiotic[a]	3.33	1.79	6.17
Current comorbidities			
Respiratory failure	8.26	1.71	39.92
Medical history			
Nutrition deficiency	2.91	1.37	6.21
Cognitve dysfunction	2.41	1.02	5.72
Demographics			
Age[b]	1.04	1.01	1.06

Adjusted odds ratios are estimated from multivariate analysis of the data. The final multivariate logistic regression model included 11 variables, including all predictive variables listed in the table above (odds ratio >1) and also the following variables with odds ratios <1: clindamycin use within 30 days before *Clostridium difficile* infection treatment, histamine receptor 2 antagonist use within 30 days after *Clostridium difficile* infection treatment, medical history of respiratory failure, metronidazole monotherapy for *Clostridium difficile* infection vs all other treatments, and treatment duration.

[a]Any antibiotic included any antibiotic not used for the treatment of *Clostridium difficile* infection, including the following antibiotic classes/agents: 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]Age represents a discrete variable for each year of age.

population at risk for a number of nutrition deficiencies [38, 43].

Although several individual conditions were associated with CDI, aggregate comorbidity burden was not identified as an independent predictor. Most previous work has identified the Charlson Comorbidity Index as an independent predictor of mortality; however, similar to our findings, other studies have not identified the Charlson Comorbidity Index as an independent predictor of mortality or poor outcomes [9, 42, 44]. The performance of aggregate comorbidity scores in predicting mortality is largely dependent on the underlying characteristics of the population under study [45, 46]. Additionally, scores developed specifically to predict risk of death associated with CDI have been found to outperform Charlson comorbidity scores. As such, future work developing such a score in the Veteran population is warranted [38].

Another potential factor associated with mortality supported by our findings is continued disruption in the normal colonic microbiota [37]. We found that concurrent use of any non-CDI antibiotic and use of proton pump inhibitors within 7 days before CDI treatment were independent risk factors for mortality. Antibiotic use is a well-established risk factor for the development of incident and recurrent CDI, and there is also evidence of an association between continued non-CDI antibiotic use and poor outcomes in patients with CDI [10, 47–50]. Continued use of antibiotics following CDI diagnosis (OR, 2.01; 95% CI, 1.01–3.99) was the strongest predictor of complicated CDI (death or need for colectomy within 30 days after CDI onset) identified in a hospital-based study [10]. In a single study among 421 patients at an academic, urban, tertiary care hospital in the United States, longer courses of antibiotics during the index CDI hospitalization were significantly associated with mortality within 180 days [13]. It is important to note that ongoing non-CDI active antibiotic therapy may be necessary and unavoidable in patients with concomitant infections in addition to their CDI, and both infections together may increase their risk of death. There are several studies that link PPI use with CDI recurrence, and there is even limited evidence that gastric acid suppression is associated with increased odds of death in patients with CDI [9, 51]. However, PPIs are commonly given to patients who are severely ill, have a number of serious comorbid conditions, and are frequently exposed to antibiotics [10, 52]. The effect of PPIs on death may differ depending on these factors.

There are limitations to this work. Our definition of CDI does not distinguish between symptomatic episodes and asymptomatic carriage. We attempted to include only patients treated for CDI by requiring at least 2 days of standard CDI treatment [17, 20, 21]. In an attempt to include the most severely ill patients who could not tolerate any medications by mouth, we included patients treated with intravenous metronidazole only [1]. Additionally, accurate identification of recurrent disease from administrative data is very challenging [53]. Previous work has shown that the performance of diagnosis codes, laboratory data, or medication data used alone to accurately identify recurrent disease was poor, and performance only improved moderately when used in combination [53]. We were unable to perform chart reviews to confirm the diagnosis of CDI recurrence in our cohort. Our work is thus limited in that we are not able to determine if the reduction in crude mortality rates that we observed among those with recurrences was due to continued symptoms of diarrhea due to alterative etiologies, such as postinfectious inflammatory bowel syndrome, vs true recurrent infection. Another limitation is that we are unable to account

for possible treatment or care received outside the VA system; therefore, we may have underestimated certain exposures, in particular over-the-counter proton pump inhibitors, histamine receptor 2 antagonists, and probiotics, or misclassified recurrence if patients were treated in non-VA settings. Our definition of severity is limited in that it was based in part on a single-serum creatinine level near CDI treatment initiation and laboratory values to determine severity were missing in a majority of our study population. We selected severity a priori as a matching factor in our statistical analysis plan as it is a known predictor of poor outcomes. We only assessed poor outcomes up to 30 days after CDI treatment, and there is thus the potential for underestimation of recurrence and death that occurred after that follow-up period. Most patients have recurrence within 30 days; however, 20% of patients may have another episode of CDI within 180 days of CDI treatment cessation [54]. We considered several risk factors for mortality in patients with CDI that have been previously described; however, there may be other known and unknown risk factors that were not included in our study. Additionally, the accuracy of using ICD-9 codes for identifying comorbidities and previous medical histories varies by disease state. Thus, our predictive analysis is limited by the variables included in the model. Generalizability to the general population may be limited.

CONCLUSIONS

In our national cohort of Veterans with CDI, crude mortality decreased by 44% from the initial episode to the third recurrence. Treatment with antibiotics, use of PPIs, and underlying comorbidities were important predictors of mortality within 30 days of the end of treatment of CDI recurrence. Our data are among the first to investigate predictors of mortality in patients with an initial episode and subsequent recurrence and will assist health care providers in identifying patients at high risk of mortality after a first recurrence of CDI.

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