JAMA Internal Medicine | Original Investigation

Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With *Clostridium difficile* Infection

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IMPORTANCE Metronidazole hydrochloride has historically been considered first-line therapy for patients with mild to moderate *Clostridium difficile* infection (CDI) but is inferior to vancomycin hydrochloride for clinical cure. The choice of therapy may likewise have substantial consequences on other downstream outcomes, such as recurrence and mortality, although these secondary outcomes have been less studied.

OBJECTIVE To evaluate the risk of recurrence and all-cause 30-day mortality among patients receiving metronidazole or vancomycin for the treatment of mild to moderate and severe CDI.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, propensity-matched cohort study evaluated patients treated for CDI, defined as a positive laboratory test result for the presence of *C difficile* toxins or toxin genes in a stool sample, in the US Department of Veterans Affairs health care system from January 1, 2005, through December 31, 2012. Data analysis was performed from February 7, 2015, through November 22, 2016.

EXPOSURES Treatment with vancomycin or metronidazole.

MAIN OUTCOMES AND MEASURES The outcomes of interest in this study were CDI recurrence and all-cause 30-day mortality. Recurrence was defined as a second positive laboratory test result within 8 weeks of the initial CDI diagnosis. All-cause 30-day mortality was defined as death from any cause within 30 days of the initial CDI diagnosis.

RESULTS A total of 47 471 patients (mean [SD] age, 68.8 [13.3] years; 1947 women [4.1%] and 45 524 men [95.9%]) developed CDI, were treated with vancomycin or metronidazole, and met criteria for entry into the study. Of 47 147 eligible first treatment episodes, 2068 (4.4%) were with vancomycin. Those 2068 patients were matched to 8069 patients in the metronidazole group for a total of 10 137 included patients. Subcohorts were constructed that comprised 5452 patients with mild to moderate disease and 3130 patients with severe disease. There were no differences in the risk of recurrence between patients treated with vancomycin vs those treated with metronidazole in any of the disease severity cohorts. Among patients in the any severity cohort, those who were treated with vancomycin were less likely to die (adjusted relative risk, 0.86; 95% CI, 0.74 to 0.98; adjusted risk difference, −0.02; 95% CI, −0.03 to −0.01). No significant difference was found in the risk of mortality between treatment groups among patients with mild to moderate CDI, but vancomycin significantly reduced the risk of all-cause 30-day mortality among patients with severe CDI (adjusted relative risk, 0.79; 95% CI, 0.65 to 0.97; adjusted risk difference, −0.04; 95% CI, −0.07 to −0.01).

CONCLUSIONS AND RELEVANCE Recurrence rates were similar among patients treated with vancomycin and metronidazole. However, the risk of 30-day mortality was significantly reduced among patients who received vancomycin. Our findings may further justify the use of vancomycin as initial therapy for severe CDI.

JAMA Intern Med. 2017;177(4):546-553. doi:10.1001/jamainternmed.2016.9045
Published online February 6, 2017.

Supplemental content

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During the past 2 decades, *Clostridium difficile* infection (CDI) has progressed from a relatively uncommon hospital-acquired infection to a major contributor to morbidity and mortality inside and outside the hospital.[1-5] In 2011, there were approximately 450 000 incident and 83 000 recurrent CDIs in the United States,[6] many of which were managed by primary care physicians in the outpatient setting. The treatment of CDI is largely guideline driven.[7-9] Current guidelines recommend metronidazole hydrochloride as initial therapy for most cases of mild to moderate CDI. Although an early clinical trial found no difference in cure rates between vancomycin hydrochloride and metronidazole,[10] subsequent observational data and clinical trials suggest that metronidazole is inferior to vancomycin for primary clinical cure, especially in severe cases.[11-13] Most recently, an analysis of mirror trials by Johnson et al[11] found that patients treated with metronidazole had a nearly 10% lower probability of achieving cure than patients treated with vancomycin (81.1% vs 72.7%; $P = .02$).

Beyond the question of clinical cure, important downstream outcomes, such as recurrence and mortality, should be taken into consideration when choosing an initial therapy. *Clostridium difficile* infection is a serious infection that significantly affects the quality of patients' lives.[14] Recurrence of CDI after successful resolution of the initial episode occurs in approximately 15% to 50% of patients depending on patient factors, such as age and immune status.[11,15] Rates of all-cause 30-day mortality as high as 38% have been reported.[16] Although evidence is mixed,[11,15] clinical trial data suggest that metronidazole and vancomycin may result in similar rates of recurrence.[11,12] Risk of mortality after treatment is not well understood, but one small study[17] indicates that patients who receive vancomycin may have lower rates of all-cause mortality vs patients receiving metronidazole (7.4% vs 13.5%). However, our understanding of how treatment choice affects downstream outcomes remains incomplete.

The objective of this study was to improve on the existing evidence by evaluating the risk of recurrence and all-cause 30-day mortality among patients receiving metronidazole or vancomycin for the treatment of mild to moderate and severe CDI in a multiyear comparative effectiveness study within the US Department of Veterans Affairs (VA). The VA serves more than 5 million patients each year,[18] providing access to longitudinal data on an unprecedented number of CDI cases in inpatient, long-term care, and outpatient settings. We hypothesized that patients receiving vancomycin would have better downstream outcomes than patients receiving metronidazole regardless of CDI severity.

Key Points

Question Does vancomycin hydrochloride result in fewer recurrences or lower risk of mortality compared with metronidazole hydrochloride for patients with *Clostridium difficile* infection?

Findings In this propensity-matched cohort study, no difference was found in the risk of recurrence between patients treated with vancomycin vs metronidazole. Among patients with severe infections, those treated with vancomycin had a significantly lower risk of death than patients treated with metronidazole.

Meaning Vancomycin should be first-line therapy for patients with severe *C difficile* infection.

Methods

Study Design and Participants

We conducted a retrospective, propensity-matched cohort study of patients treated for CDI in the VA Healthcare System from January 1, 2005, through December 31, 2012. Data analysis was performed from February 7, 2015, through November 22, 2016. Eligible patients included those with CDI as measured by the Centers for Disease Control and Prevention laboratory-identified definition[19] based on a laboratory test result that indicated the presence of *C difficile* toxin or toxin gene in a stool sample. From 2005 through 2009, enzyme immunoassay was the predominant testing method. In 2010, one-third of VA laboratories used polymerase chain reaction alone,[20] and by 2012 that number had increased to 59%.[21] Patients were excluded if they did not receive metronidazole or oral vancomycin or if they received both metronidazole and oral vancomycin within 2 days before or after CDI diagnosis. Patients may have experienced more than one episode of CDI, and we included only the first episode that met the study eligibility criteria whether it was an incident or recurrent case. Information was collected on patient demographics, comorbidities, health care utilization, CDI history, laboratory values, and medication use from the Corporate Data Warehouse, the VA's clinical data repository. Data were accessed through the VA Informatics and Computing Infrastructure.

This study was reviewed and approved by the University of Utah Institutional Review Board and the Research and Development Committee of the VA Salt Lake City Health Care System. Waivers of consent and authorization were granted by the University of Utah Institutional Review Board and the Veterans Affairs Salt Lake City Health Care System Research and Development Committee. Study data were not deidentified.

Study Data

The primary exposure in this study was treatment of CDI with oral vancomycin or metronidazole. To capture all oral vancomycin use, we identified and included intravenous vancomycin compounded and administered orally. Analogous to an intention-to-treat analysis in a randomized clinical trial,[22,23] patients were classified according to the initial treatment they received, defined as 2 days before or after the CDI diagnosis. There was no minimum treatment duration. Inpatient treatment data were obtained from the bar code medication administration system.[24] Outpatient treatment was identified using pharmacy prescription fill data.

The outcomes of interest were recurrent CDI and all-cause 30-day mortality. Recurrent CDI was defined as another positive laboratory test result for *C difficile* more than 14 days but 56 days or fewer after the initial diagnosis date.[25]

All-cause 30-day mortality was defined as death from any cause within 30 days of the CDI diagnosis. Death data were obtained from the VA Vital Status file, which contains mortality information from the Veterans Benefits Administration, Social Security Administration, and Center for Medicare & Medicaid Services.

Basic demographic and clinical information was extracted for each patient. Underlying comorbidity at baseline was measured using the Charlson Comorbidity Index-Elixhauser score in the year before the CDI diagnosis.[26] Intensity of health care exposure was assessed using the number of hospitalizations in the year before diagnosis. Characteristics of the CDI episode collected included the episode type (primary incident, recurrent, or secondary incident), location of diagnosis, and epidemiologic classification (community acquired, health care acquired, or community-onset health care associated).[25] Severity of CDI was defined according to criteria in the joint practice guidelines of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA).[7] Patients with leukocytosis (white blood cell count ≥15 000/μL [to convert to $\times 10^9$/L, multiply by 0.001]) or elevated serum creatinine level 1.5 times or more than the baseline value (defined as the mean serum creatinine value in the 90 days before CDI) within 4 days of the CDI diagnosis date were considered to have severe CDI. Patients with normal white blood cell counts and kidney function less than 1.5 times their baseline value were considered to have mild to moderate CDI, and those without sufficient information to classify the severity of the episode were considered to have unknown severity. The use of other agents for the treatment or prevention of CDI (rifaximin, nitazoxanide, or toxin-binding compounds) was also recorded.

Statistical Analysis

To make the treatment groups as similar as possible, we used propensity score matching. First, logistic regression was used to estimate the probability of receiving vancomycin as a function of the following baseline characteristics: year of diagnosis, diagnosis in the intensive care unit, Charlson Comorbidity Index-Elixhauser score, number of hospitalizations in the past year, age, diagnosis in a health care facility, incident vs recurrent episode, antibiotics at diagnosis, sepsis within the past 7 days, and proton pump inhibitors, chemotherapy, or immunosuppressive medications in the past 30 days. These factors were chosen as candidate true confounders or risk factors for death or recurrence.[27] Next, 3 separate propensity-matched cohorts were generated by selecting up to 4 patients in the metronidazole group for each patient in the vancomycin group using a greedy matching algorithm and a caliper width of 0.2 SD of the logit of the propensity score.[28] The any severity cohort contained all patients who were matched regardless of severity. The second cohort comprised matched patients with mild to moderate CDI, and the third cohort comprised matched patients with severe CDI. The distributions of propensity scores before and after matching were visually inspected to ensure a reasonable area of common support (eFigure 1 through eFigure 6 in the Supplement). Balance between treatment groups was assessed using standardized differences and was considered similar if less than 0.10 (eFigure 7 through eFigure 10 in the Supplement).

To determine whether treatment choice significantly influenced the risk of recurrence or all-cause mortality, we constructed a series of multivariable models. Relative risks (RRs) and risk differences (RDs) for the effect of initial treatment choice on recurrence and all-cause 30-day mortality were estimated in each cohort separately using Poisson regression with robust sandwich covariance estimation (modified Poisson regression).[29-31] All 6 models were fit using generalized estimating equations assuming the independent correlation structure to account for clustering of patients within individual VA health care systems (stations). The outcome models included the same covariates as the propensity score model to improve the robustness of estimates and increase precision. All analyses were preplanned. Statistical procedures were performed using SAS statistical software, version 9.2 (SAS Institute Inc) except for the modified Poisson regressions, which were implemented in STATA software, version 14 (StataCorp). All hypothesis tests assume a 2-sided $\alpha = .05$.

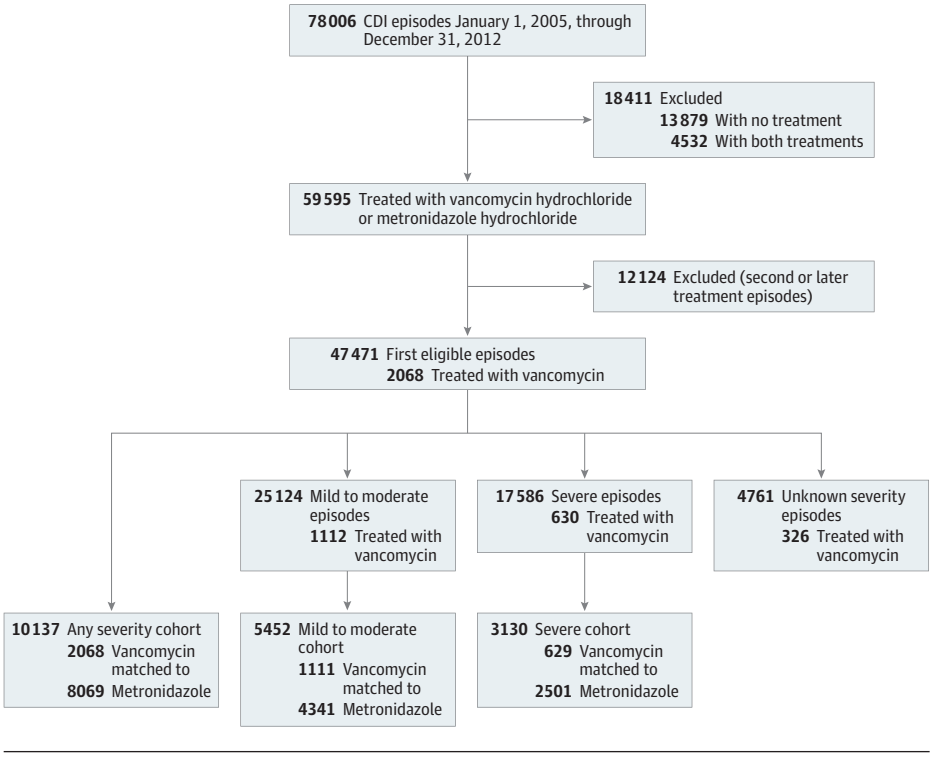
Results

From January 1, 2005, to December 31, 2012, a total of 47 471 patients (mean [SD] age, 68.8 [13.3] years; 1947 females [4.1%] and 45 524 males [95.9%]) developed CDI, were treated with vancomycin or metronidazole, and met criteria for entry into the study (**Figure 1**). During the study period, the number of first treated cases classified as severe decreased from 7432 (40.3%) in 2005 to 5138 (30.5%) in 2012. The number of patients treated with vancomycin increased from 147 (2.0%) in 2005 to 428 (8.3%) in 2012 (eFigure 11 in the Supplement). Of those 47 471 patients with first eligible treatment episodes, 2068 (4.4%) received vancomycin as initial therapy. Vancomycin was used among 1112 patients (4.4%) with mild to moderate CDI, 630 (3.6%) with severe CDI, and 326 (6.8%) with CDI of unknown severity.

Table 1 gives the baseline clinical and demographic characteristics of patients for each treatment group by episode severity cohort. Because of the 1:4 matching algorithm, 2068 patients (20.4%) in the any severity group, 1111 (20.4%) in the mild to moderate group, and 629 (20.1%) in the severe group received vancomycin. Overall, the propensity score matching resulted in well-balanced cohorts. The use of nitazoxanide, rifaximin, toxin-binding agents, and fidaxomicin was uncommon, and use was similar between patients treated with vancomycin and metronidazole for all severity groups (eTable in the Supplement).

A total of 7449 of 45 661 patients (16.3%) presenting with incident CDI and 191 of 837 patients (22.8%) presenting with recurrent CDI developed recurrence. The unadjusted risks of recurrence were similar between patients with mild to moderate and severe CDI (**Figure 2**). The all-cause 30-day mortality rates were 10.2% for any severity CDI, 6.7% for mild to moderate CDI, and 18.9% for severe CDI (Figure 2). A crude comparison of recurrence rates between patients receiving

Figure 1. Eligibility and Selection of Patients Treated for *Clostridium difficile* Infection (CDI) in the US Department of Veterans Affairs Health System, January 1, 2005, Through December 31, 2012



Flowchart of patient selection into the study. From 47 471 initially eligible patients, 10 137 were included in the any severity cohort. After excluding patients with unknown severity, 5452 patients were included in the mild to moderate cohort and 3130 patients were included in the severe cohort.

vancomycin and metronidazole found no statistically or clinically significant difference across all CDI severity groups. Overall, patients who received vancomycin had a lower risk of mortality compared with patients treated with metronidazole (8.6% vs 10.6%, $P = .01$).

This difference was largely driven by a 4.5% (15.3% vs 19.8%, $P = .01$) reduction in absolute risk of mortality among patients with severe CDI being treated with vancomycin compared with those treated with metronidazole. There was no statistically significant difference in the risk of mortality by treatment group among patients with mild to moderate CDI (65 of 1111 [5.9%] for the vancomycin group vs 299 of 4341 [6.9%] for the metronidazole group, $P = .22$).

Table 2 gives the results of the multivariable modified Poisson regression models. Vancomycin did not reduce the risk of recurrence compared with metronidazole among any of the CDI severity subgroups. Among patients in the any severity cohort, those who were treated with vancomycin were less likely to die (adjusted RR, 0.86; 95% CI, 0.74 to 0.98; adjusted RD, -0.02; 95% CI, -0.03 to -0.01). No significant difference was found in the risk of mortality between treatment groups among patients with mild to moderate CDI, but vancomycin significantly reduced the risk of all-cause 30-day mortality among patients with severe CDI (adjusted RR, 0.79; 95% CI, 0.65-0.97; adjusted RD, -0.04; 95% CI, -0.07 to -0.01). The number needed to treat with vancomycin to prevent 1 death among patients with severe CDI is approximately 25.

Discussion

Treatment of infections due to *C difficile* has changed remarkably little since it was first identified as the main pathogenic cause of pseudomembranous colitis in the late 1970s.[32] Although vancomycin was the first agent found to be effective for the treatment of CDI,[33] metronidazole quickly became the drug of choice because of concerns about the cost of branded vancomycin tablets and the possible emergence of vancomycin resistance among *Enterococcus*.[34,35] Although early clinical trial data indicated that metronidazole was noninferior to vancomycin for the treatment of CDI,[10] further trials found that vancomycin is superior to metronidazole,[11] especially for severe CDI.[12] Evidence continues to emerge[11-13] that primary cure rates with metronidazole and vancomycin are lower than previously expected based on early trial data.[10] However, the consequences of these treatment failures are often overlooked and underestimated. Specifically, downstream outcomes, such as recurrence and mortality, are major concerns for patients with CDI. Comparative effectiveness studies such as this one can help to address this critical gap in our knowledge of CDI treatment. We report the results of a large comparative effectiveness study to evaluate treatment of CDI with metronidazole or vancomycin and subsequent risk of recurrence and 30-day all-cause mortality.

Recent qualitative work indicates that patients with CDI live in persistent fear of developing recurrent infection.[14]

Table 1. Baseline Clinical and Demographic Characteristics of Patients Treated for CDI With Vancomycin Hydrochloride or Metronidazole Hydrochloride in the US Department of Veteran Affairs Health System, 2005-2012[a]

	Any Severity Cohort		Mild to Moderate Cohort		Severe Cohort	
Characteristic	Vancomycin	Metronidazole	Vancomycin	Metronidazole	Vancomycin	Metronidazole
Patient Characteristics						
No. of patients	2068 (20.4)	8069 (79.6)	1111 (20.4)	4341 (79.6)	629 (20.1)	2501 (79.9)
Age, median (IQR), y	70.0 (18.5)	70.0 (19.3)	68.8 (18.3)	68.9 (19.1)	70.2 (18.9)	71.0 (19.4)
Sex						
Female	102 (4.9)	342 (4.2)	55 (5.0)	226 (5.2)	26 (4.1)	78 (3.1)
Male	1966 (95.1)	7727 (95.8)	1056 (95.0)	4115 (94.8)	603 (95.9)	2423 (96.9)
Charlson Comorbidity Index-Elixhauser score, median (IQR)	2.0 (3.0)	2.0 (3.0)	2.0 (3.0)	2.0 (3.0)	2.0 (4.0)	2.0 (3.0)
No. of hospitalizations in the past year, median (IQR)	2.0 (3.0)	2.0 (4.0)	2.0 (3.0)	2.0 (4.0)	3.0 (4.0)	3.0 (4.0)
Sepsis in the past 7 d						
Yes	180 (8.7)	683 (8.5)	78 (7.0)	302 (7.0)	82 (13.0)	354 (14.2)
No	1888 (91.3)	7386 (91.5)	1033 (93.0)	4039 (93.0)	547 (87.0)	2147 (85.9)
Dialysis in the past 30 d						
Yes	108 (5.2)	447 (5.5)	52 (4.7)	207 (4.8)	44 (7.0)	164 (6.6)
No	1960 (94.8)	7622 (94.5)	1059 (95.3)	4134 (95.2)	585 (93.0)	2337 (93.4)
Prior episodes of CDI						
None	1722 (83.3)	7493 (92.9)	920 (82.8)	4034 (92.9)	549 (87.3)	2343 (93.7)
1	300 (14.5)	521 (6.5)	163 (14.7)	278 (6.4)	72 (11.4)	142 (5.7)
2	40 (1.9)	44 (0.6)	24 (2.2)	21 (0.5)	7 (1.1)	13 (0.5)
≥3	6 (0.3)	11 (0.1)	4 (0.4)	8 (0.2)	1 (0.2)	3 (0.1)
Episode Characteristics						
Location of CDI diagnosis						
Outpatient	737 (35.6)	2795 (34.6)	418 (37.6)	1587 (36.6)	57 (9.1)	226 (9.0)
Inpatient or LTC	1331 (64.4)	5274 (65.4)	693 (62.4)	2754 (63.4)	572 (90.9)	2275 (91.0)
CDI diagnosis in the ICU						
Yes	193 (9.3)	751 (9.3)	70 (6.3)	274 (6.3)	123 (19.6)	518 (20.7)
No	1875 (90.7)	7318 (90.7)	1041 (93.7)	4067 (93.7)	506 (80.5)	1983 (79.3)
Episode type						
Primary incident	1718 (83.1)	7245 (89.8)	921 (82.9)	3894 (89.7)	544 (86.5)	2284 (91.3)
Recurrent	248 (12.0)	243 (3.0)	131 (11.8)	104 (2.4)	64 (10.2)	54 (2.2)
Secondary incident	102 (4.9)	581 (7.2)	59 (5.3)	343 (7.9)	21 (3.3)	163 (6.5)
CDI epidemiologic classification						
Hospital acquired	656 (31.7)	2841 (35.2)	337 (30.3)	1468 (33.8)	259 (41.2)	1088 (43.5)
Community-onset health care associated	863 (41.7)	3174 (39.3)	470 (42.3)	1741 (40.1)	338 (53.7)	1292 (51.7)
Community acquired	549 (26.6)	2054 (25.5)	304 (27.4)	1132 (26.1)	32 (5.1)	121 (4.8)
Maximum baseline white blood cell count, in thousands, median (IQR), /μL	11.7 (9.2)	11.6 (8.6)	9.2 (4.8)	9.2 (4.8)	19.4 (9.4)	19.2 (8.4)
Baseline serum creatinine, median (IQR), mg/dL	1.12 (0.68)	1.14 (0.73)	1.10 (0.65)	1.12 (0.71)	1.19 (0.82)	1.19 (0.85)
Maximum serum creatinine, median (IQR), mg/dL	1.20 (0.92)	1.28 (0.97)	1.10 (0.74)	1.11 (0.70)	1.50 (1.40)	1.60 (1.60)
Medication History						
PPI in the past 30 d						
Yes	1617 (78.2)	6320 (78.3)	875 (78.8)	3410 (78.6)	525 (83.5)	2090 (83.6)
No	451 (21.8)	1749 (21.7)	236 (21.2)	931 (21.5)	104 (16.5)	411 (16.4)
Non-CDI antibiotics on day of diagnosis						
Yes	591 (28.6)	2398 (29.7)	254 (22.9)	1036 (23.9)	327 (52.0)	1298 (51.9)
No	1477 (71.4)	5671 (70.3)	857 (77.1)	3305 (76.1)	302 (48.0)	1203 (48.1)

(continued)

Table 1. Baseline Clinical and Demographic Characteristics of Patients Treated for CDI With Vancomycin Hydrochloride or Metronidazole Hydrochloride in the US Department of Veteran Affairs Health System, 2005-2012[a] (continued)

Characteristic	Any Severity Cohort		Mild to Moderate Cohort		Severe Cohort	
	Vancomycin	Metronidazole	Vancomycin	Metronidazole	Vancomycin	Metronidazole
Immunosuppressants in the past 30 d						
Yes	166 (8.0)	634 (7.9)	100 (9.0)	406 (9.4)	40 (6.4)	169 (6.8)
No	1902 (92.0)	7435 (92.1)	1011 (91.0)	3935 (90.6)	589 (93.6)	2332 (93.2)
Chemotherapy in the past 30 d						
Yes	237 (11.5)	921 (11.4)	148 (13.3)	596 (13.7)	67 (10.7)	293 (11.7)
No	1831 (88.5)	7148 (88.6)	963 (86.7)	3745 (86.3)	562 (89.3)	2208 (88.3)

Abbreviations: CDI, *Clostridium difficile* infection; ICU, intensive care unit; IQR, interquartile range; LTC, long-term care; PPI, proton pump inhibitor.

SI conversion factors: To convert white blood cell counts to $\times 10^9$/L, multiply by 0.001; creatinine to micromoles per liter, multiply by 88.4.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

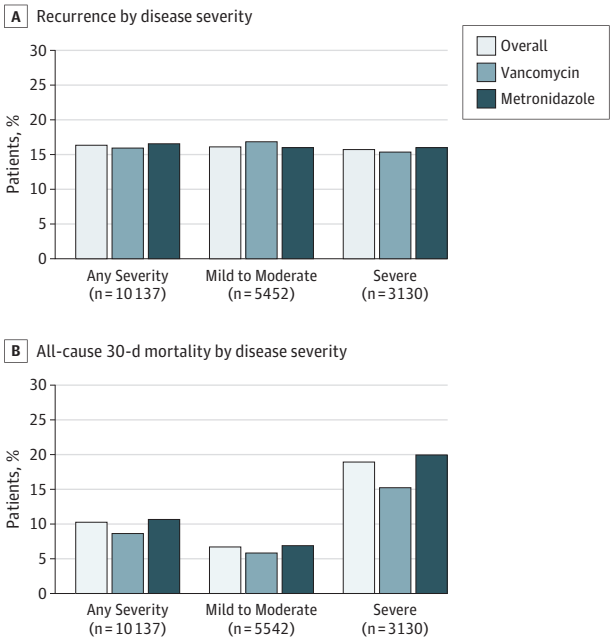
Approximately 16% of patients in our study developed recurrent infection, similar to the 15% to 35% reported in the literature.[36] Severity of CDI infection did not appear to influence the risk of recurrence, in contrast with another study[12] that found that the risk of recurrence is greater among patients with severe infections.

Clostridium difficile infection disproportionately affects patients with high comorbidity burden and immunocompromising conditions. As such, death is common among patients with CDI. A previous systematic review[16] suggests that approximately 26% of inpatients across 20 published studies died within 30 days of a CDI diagnosis. In our study, mortality rates were 6.8% for patients with mild to moderate CDI and 19.3% for patients with severe CDI. One possible explanation for the lower mortality estimates compared with published estimates is the mix of low-mortality outpatients (2.6%) with higher-mortality inpatients (14.3%) in our study.

We observed that patients with severe CDI treated with vancomycin were approximately 20% less likely to die of any cause within 30 days than patients treated with metronidazole. This RR reduction translates to an absolute risk reduction of 4% (95% CI, 1%-7%). Conversely, there was no difference in the risk of 30-day mortality between vancomycin and metronidazole among patients with mild to moderate CDI. Although existing evidence is limited, our findings are similar to those of a study by Takahashi et al,[17] which revealed that mortality among patients with CDI treated with vancomycin was approximately 6% lower than patients treated with metronidazole (7.4% vs 13.5%).

Despite strong evidence and clinical practice guidelines to support vancomycin treatment for severe CDI,[7-9,11,12] it remains an underused treatment option. In our study, 4% to 6% of patients initially received vancomycin despite 42% of episodes being classified as severe. Notably, vancomycin use increased over time, likely in response to the publication of the trial by Zar et al[12] in 2007 and the SHEA/IDSA guidelines recommending vancomycin for severe CDI in 2010.[7] Despite the increase in vancomycin use during the study period, half of the patients with severe CDI did not receive vancomycin in 2012. Our results are in accordance with previous findings, which indicate that vancomycin is used in 15% or less of all patients with CDI[37,38] and that patients with severe CDI are no more likely to receive vancomycin than patients with mild to moderate CDI unless an active antimicrobial stewardship protocol is in place to give oral vancomycin to patients with severe CDI.[38]

Figure 2. Unadjusted Risks of Recurrence and All-Cause 30-Day Mortality for Patients With Vancomycin Hydrochloride and Metronidazole Hydrochloride Stratified by Disease Severity Cohort



A, Patients treated with vancomycin and metronidazole had similar risks of recurrence across disease severity cohorts. B, Among patients with severe *Clostridium difficile* infection, those treated with vancomycin were less likely to die compared with patients treated with metronidazole.

Strengths and Limitations

Our study was observational in nature and as such is subject to a number of limitations. Patients were not randomized to treatment groups and therefore may have differed on important characteristics that could have influenced their outcomes. Although propensity score matching is an accessible

Table 2. Adjusted RRs and RDs of Recurrence and Mortality for Patients Treated With Vancomycin Hydrochloride Compared With Metronidazole Hydrochloride[a]

Cohort	No. of Patients	Recurrence		30-d Mortality	
		RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Full cohort (any severity)	10 137	0.98 (0.87 to 1.10)	0.00 (−0.02 to 0.02)	0.86 (0.74 to 0.98)	−0.02 (−0.03 to −0.01)
Mild to moderate subcohort	5452	1.07 (0.93 to 1.15)	0.01 (−0.01 to 0.03)	0.91 (0.72 to 1.14)	−0.01 (−0.02 to 0.01)
Severe subcohort	3130	0.96 (0.76 to 1.23)	−0.01 (−0.04 to 0.03)	0.79 (0.65 to 0.97)	−0.04 (−0.07 to −0.01)

Abbreviations: RD, risk difference; RR, relative risk.

[a] All models fit using generalized estimating equations to account for clustering within Veterans Affairs station. All estimates are adjusted for intensive care unit at the time of *Clostridium difficile* infection, Charlson Comorbidity Index–Elixhauser score, hospitalizations in the past year, age at *C difficile* infection diagnosis, inpatient or long-term care patient at diagnosis, episode type, receipt of chemotherapy, immunosuppressive medications or proton pump inhibitor in the prior 30 d, dialysis in the prior 30 days, antibiotics on the day of *C difficile* infection diagnosis, and sepsis in the past 7 days.

and useful tool to balance patients on measured confounders, the possibility of unmeasured confounding remains. Treatment for CDI can change over time, and we did not measure treatment changes that occurred outside the initial window, which could have resulted in misclassification of exposure. However, only 7% of patients had a change in therapy within 14 days after their CDI diagnosis. In addition, our results are analogous to the familiar intention-to-treat analyses and allow comparison of our findings with those reported in clinical trials of CDI treatments. During the study period, bar code medication administration capture may have been imperfect, especially in the emergency department. Because most patients received several days of treatment, we anticipate capturing most patients after admission or through outpatient pharmacy records for those not admitted. Medications received outside the VA system, including over-the-counter medications, were not captured. Finally, our definition of CDI (including recurrence) is based on the presence of a positive laboratory test result for CDI, which may have resulted in the inclusion of some patients colonized with *C difficile* without clinically relevant infection or patients whose symptoms were attributable to other conditions. However, all the patients in our study received oral vancomycin or metronidazole within 2 days of their laboratory test, minimizing the likelihood of including a large number of patients without true CDI. Detecting test of cure is a concern with identifying recurrence. We anticipate that test-of-cure rates would not differ between patients treated with vancomycin vs metronidazole. We were also unable to exclude polymerase chain reaction–positive, toxin-negative patients, which may have contributed to misclassification and a possible underestimation of treatment effects.

Our study also has a number of notable strengths. This is the largest study to date to compare vancomycin and metronidazole in a real-world setting and 1 of the few studies focused on downstream outcomes of CDI. Most cases of CDI occur outside the hospital, and information on CDI outcomes in these settings is sparse. The VA health care system affords the unique opportunity of following up a large number of patients with CDI in the inpatient, outpatient, or long-term care settings across the nation. Unlike many smaller studies, the large sample size allowed us to detect small but clinically meaningful differences in mortality between treatment groups.

Conclusions

Our results build on existing evidence that vancomycin may be preferable to metronidazole, particularly for patients with severe disease. Although the excess treatment costs of vancomycin relative to metronidazole and the concern for vancomycin-resistant *Enterococcus* will likely remain barriers, improved clinical cure and mortality rates may warrant reconsideration of current prescribing practices. One approach to minimizing the effects of increasing vancomycin use is to target vancomycin treatment to patients with severe disease. Future research should focus on balancing improved outcomes with economic and resistance considerations.

ARTICLE INFORMATION

Accepted for Publication: December 1, 2016.

Published Online: February 6, 2017. doi:10.1001/jamainternmed.2016.9045

Author Contributions: Dr Stevens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Stevens, Nelson, Khader, Samore, Rubin.
Acquisition, analysis, or interpretation of data: Stevens, Schwab-Daugherty, Jones, Brown, Greene, Croft, Neuhauser, Glassman, Goetz, Samore, Rubin.
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Obtained funding: Samore, Rubin.
Administrative, technical, or material support: Schwab-Daugherty, Khader, Jones, Samore, Rubin.
Study supervision: Samore, Rubin.

Conflict of Interest Disclosures: None reported.

Funding/Support: This material is based on work supported in part by Center of Innovation grant 13-414 (Dr Samore, principal investigator) and Career Development Award 11-210 (Dr Nelson, principal investigator) from the US Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the US Department of Veterans Affairs or the US government.

Meeting Presentation: This study was presented in part at the International Conference on Prevention and Infection Control; June 18, 2015; Geneva, Switzerland.

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