

ORIGINAL RESEARCH

Treatment of *Clostridioides difficile* Infection and Non-compliance with Treatment Guidelines in Adults in 10 US Geographical Locations, 2013–2015

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BACKGROUND: Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines describe recommended therapy for *Clostridioides difficile* infection (CDI).

OBJECTIVE: To describe CDI treatment and, among those with severe CDI, determine predictors of adherence to the 2010 IDSA/SHEA treatment guidelines.

DESIGN: We analyzed 2013–2015 CDI treatment data collected through the Centers for Disease Control and Prevention's Emerging Infections Program. Generalized linear mixed models were used to identify predictors of guideline-adherent therapy.

PATIENTS: A CDI case was defined as a positive stool specimen in a person aged ≥ 18 years without a positive test in the prior 8 weeks; severe CDI cases were defined as having a white blood cell count $\geq 15,000$ cells/ μ l.

MAIN MEASURES: Prescribing and predictors of guideline-adherent CDI therapy for severe disease.

KEY RESULTS: Of 18,243 cases, 14,257 (78%) were treated with metronidazole, 7683 (42%) with vancomycin, and 313 (2%) with fidaxomicin. The median duration of therapy was 14 (interquartile range, 11–15) days. Severe CDI was identified in 3250 (18%) cases; of 3121 with treatment data available, 1480 (47%) were prescribed guideline-adherent therapy. Among severe CDI cases, hospital admission (adjusted odds ratio [aOR] 2.48; 95% confidence interval [CI] 1.90, 3.24), age ≥ 65 years (aOR

1.37; 95% CI 1.10, 1.71), Charlson comorbidity index ≥ 3 (aOR 1.27; 95% CI 1.04, 1.55), immunosuppressive therapy (aOR 1.21; 95% CI 1.02, 1.42), and inflammatory bowel disease (aOR 1.56; 95% CI 1.13, 2.17) were associated with being prescribed guideline-adherent therapy.

CONCLUSIONS: Provider adherence to the 2010 treatment guidelines for severe CDI was low. Although the updated 2017 CDI guidelines, which expand the use of oral vancomycin for all CDI, might improve adherence by removing the need to apply severity criteria, other efforts to improve adherence are likely needed, including educating providers and addressing barriers to prescribing guideline-adherent therapy, particularly in outpatient settings.

KEY WORDS: infectious disease; decision-making; epidemiology; *Clostridioides difficile*.

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INTRODUCTION

Clostridioides difficile is a leading cause of US healthcare-associated infections,¹ causing an estimated 453,000 infections and 29,000 associated deaths in 2011.² *C. difficile* infection (CDI) increases 30-day mortality by 2.5-fold^{3,4} and is associated with higher healthcare expenditures^{5,6} and longer hospital length of stay.⁷

CDI symptoms range in severity from mild diarrhea to pseudomembranous colitis and can result in toxic megacolon and death. The Infectious Diseases Society of America (IDSA)

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and Society for Healthcare Epidemiology of America (SHEA) published CDI treatment guidelines in 2010.⁸ Metronidazole was recommended for an initial episode of mild to moderate disease, and oral vancomycin was recommended as first-line therapy for an initial episode of severe disease. These guidelines were updated in 2017 and now recommend oral vancomycin or fidaxomicin for all initial CDI, regardless of severity⁹ (Table 1).

Use of guideline-adherent therapy has been associated with improved clinical response, such as shorter time to symptom resolution.^{10,11} Despite the benefits of appropriate therapy, previous studies indicated low provider adherence to the 2010 treatment guidelines, particularly in patients with severe disease^{12–16}; however, these were single-center studies and did not determine factors associated with prescribing guideline-adherent treatment. We sought to describe CDI treatment, regardless of severity, across geographically diverse areas. We then examined a subset with severe CDI to determine provider adherence to and predictors of prescribing guideline-adherent CDI therapy.

METHODS

CDI Surveillance

The Centers for Disease Control and Prevention's (CDC) Emerging Infections Program (EIP) conducts population-based CDI surveillance in 35 counties in 10 states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee), comprising a total surveillance population of > 11 million persons.¹⁷ This surveillance activity underwent ethical review by CDC and all EIP sites and either was deemed non-research or received an institutional review board approval with a waiver of informed consent.

Case Identification and Data Collection

Laboratories serving the catchment areas reported all positive *C. difficile* tests to EIP staff. A CDI case was defined as a positive stool specimen (*C. difficile* toxin or molecular assay) obtained during 2013–2015 in a person aged ≥ 18 years without a positive test in the prior 8 weeks. An initial chart review was performed on all cases in 8 EIP sites and a random sample of cases in 2 EIP sites with the largest surveillance populations.¹⁸ Cases were classified as community-onset if a positive specimen was collected in an outpatient setting or within 3 days after hospital admission, or they were classified as healthcare facility-onset if a positive specimen was collected in a long-term care facility (LTCF), from a LTCF resident, or > 3 days after hospital admission. All community-onset cases and a 10% random sample of healthcare facility-onset cases underwent additional chart review using a standardized form to collect comorbidities, healthcare and medication exposures, clinical course, and outcomes. Community-onset cases were further classified as community-associated if there was no documented overnight stay in a healthcare facility in the preceding 12 weeks. All other cases were classified as healthcare-associated.

Severe Disease and Guideline-Adherent Therapy

The 2010 IDSA/SHEA guidelines defined severe CDI as white blood cell (WBC) $\geq 15,000/\mu\text{l}$ or serum creatinine level ≥ 1.5 times the premorbid level.⁸ Accordingly, we defined cases as severe if the WBC count was $\geq 15,000$ cells/ μl within 1 calendar day before or after stool collection. In 2015, the case abstraction form was modified to include WBC $\geq 15,000$ cells/ μl within 7 days before or after stool collection (Fig. 1). We were unable to use serum creatinine to define severe CDI as this information was not collected during chart review.

Cases that underwent treatment for severe CDI were clas-

Table 1 *Clostridioides difficile* Treatment Recommendations for Initial Episodes in Adults According to 2010 and 2017 Infectious Diseases Society of America/Society for Healthcare Epidemiology of America Guidelines

Guideline year	Treatment recommendations by disease severity
2010 ⁸	Mild/moderate* Severe [†] Severe-complicated [‡]
2017 ⁹	Non-severe [§] Severe Fulminant [‡]
	<ul style="list-style-type: none"> • Metronidazole 500 mg 3 times per day by mouth for 10–14 days • Vancomycin, 125 mg 4 times per day by mouth for 10–14 days • Vancomycin, 500 mg 4 times per day by mouth or nasogastric tube, plus metronidazole, 500 mg every 8 h intravenously. If complete ileus, consider adding rectal instillation of vancomycin. • Vancomycin 125 mg 4 times per day by mouth for 10 days OR • Fidaxomicin 200 mg by mouth 2 times per day for 10 days • If above agents are unavailable, metronidazole 500 mg by mouth 3 times per day for 10 days • Vancomycin 125 mg 4 times per day by mouth for 10 days OR • Fidaxomicin 200 mg by mouth 2 times per day for 10 days • Vancomycin 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 h) should be administered together with oral or rectal vancomycin particularly if ileus is present.

*White blood cell count < 15,000 cells/ μl and a serum creatinine level < 1.5 times the premorbid level

[†]White blood cell count $\geq 15,000$ cells/ μl or serum creatinine level ≥ 1.5 times the premorbid level

[‡]Hypotension or shock, ileus, or megacolon

[§]White blood cell count < 15,000 cells/ μl and a serum creatinine level < 1.5 mg/dl

White blood cell count $\geq 15,000$ cells/ μl or serum creatinine level > 1.5 mg/dl
mg milligrams

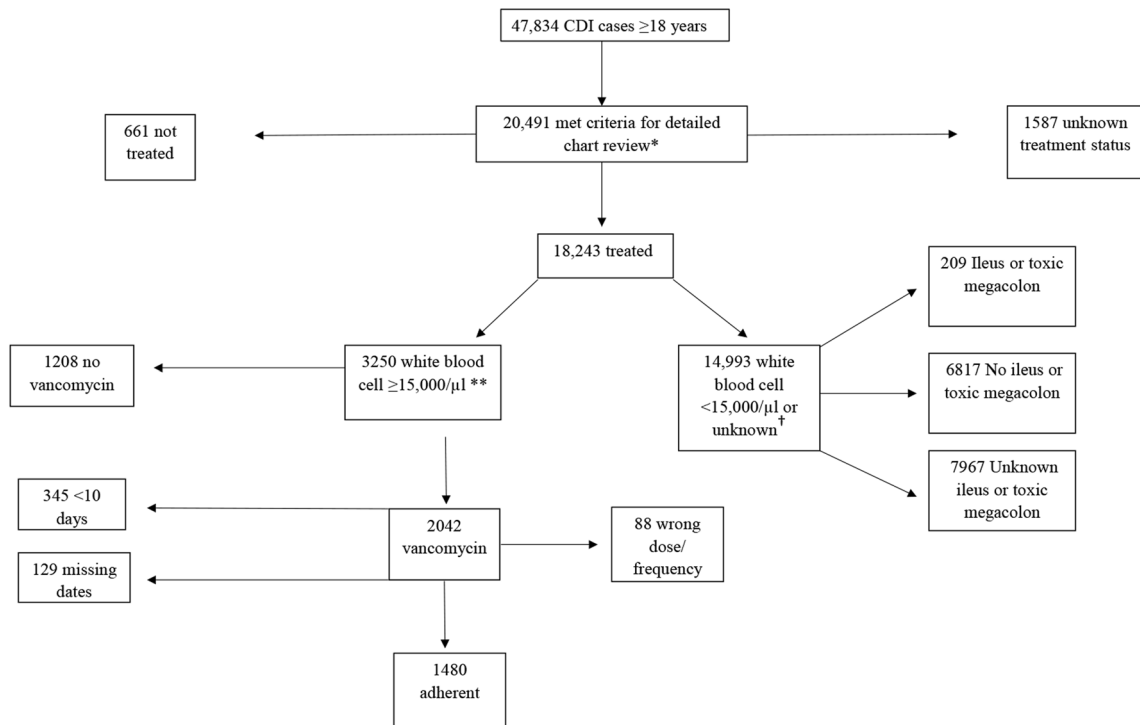


Figure 1 *Clostridioides difficile* infection cases, 2013–2015. Single asterisk symbol indicates community-onset and 10% of healthcare facility-onset CDI cases. Dagger symbol indicates white blood cell $\geq 15,000$ cells/ μl within 1 calendar day of stool specimen collection in 2013–2014, and within 7 calendar days of stool specimen collection starting in 2015. CDI, *Clostridioides difficile* infection

sified as being prescribed guideline-adherent or non-guideline-adherent therapy based on the 2010 IDSA/SHEA treatment guidelines (Table 1). If a case was prescribed vancomycin at a dose of at least 125 milligrams (mg) 4 times per day for 10 days, treatment was considered adherent. Since no cases were prescribed intravenous vancomycin, we did not include route of administration in the definition of adherent therapy. A gap in therapy > 48 h was considered cessation of therapy. If a patient died before receiving 10 days of therapy and if the case was started on vancomycin at the right dose and frequency within 48 h of specimen collection, treatment was considered adherent.

Statistical Analysis

Only cases with a full chart review were included in the analyses. Descriptive analyses were performed to summarize relevant variables and treatment data for all treated cases and for the subset with severe disease. Multiple imputation was performed for missing race (20% of cases) based on the distribution of known race by age, sex, and surveillance site.

Generalized linear mixed models were used to evaluate factors associated with prescription of guideline-adherent therapy. Unadjusted analyses were performed on demographics and other relevant case characteristics, including epidemiologic classification, location of stool collection, hospital admission, medications, and selected healthcare exposures in the prior 12 weeks. Charlson comorbidity index was calculated and included as an ordinal variable.¹⁹

All variables with a p value less than 0.20 in unadjusted analyses were included in the initial multivariable model. Backward selection was used to construct the final multivariable model, which included all variables with a p value < 0.05 . Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A 2-tailed p value < 0.05 was considered statistically significant. We performed a sensitivity analysis to evaluate factors associated with prescription of guideline-adherent therapy using an expanded definition of disease severity that included a CDI-associated complication (ileus, toxic megacolon, or colectomy) or intensive care unit (ICU) admission on the day of or following the *C. difficile*-positive specimen collection. All analyses were performed with SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Description of CDI Cases

Of 47,834 adult CDI cases, 20,491 (43%) cases had undergone full chart review. Among these cases, 18,243 (89%) were treated for CDI and 661 (3%) were not treated (Fig. 1); treatment data were not available for 1,587 (8%) cases. Among those treated, the median age was 63 (interquartile range (IQR) 48–76) years, 62% ($n = 11,292$) were female, and 52% ($n = 9,424$) were admitted to a hospital at the time of or within 7 days after stool collection (Table 2). Sixty-nine percent ($n = 12,542$) and 25% ($n = 4,502$) of the treated cases had received

Table 2 Description of *Clostridioides difficile* Infection Treated Cases ($n = 18,243$)

	Treated ($n = 18,243$) N (%) or median (IQR)
Age	
18–44	3953 (22)
45–64	5843 (32)
≥ 65 years	8447 (46)
Sex	
Male	6951 (38)
Female	11,292 (62)
Charlson comorbidity index	
0	6876 (38)
1–2	5430 (30)
≥ 3	5937 (32)
Inflammatory bowel disease	1230 (7)
Diverticular disease	1985 (11)
Hospital admission*	9424 (52)
Epidemiologic class	
Healthcare-associated	7309 (40)
Community-associated	10,932 (60)
Unknown 2 (<1)	
Location of stool collection	
Hospital/LTACH [†]	8682 (48)
Outpatient	7551 (41)
Emergency room/observation unit	1528 (8)
Long-term care facility	459 (3)
Other or unknown	23 (<1)
Medications in prior 12 weeks	
Antibiotics	12,542 (69)
Immunosuppressive	4502 (25)
unknown	23 (<1)
Healthcare exposures in prior 12 weeks [‡]	9884 (54)
CDI recurrence	2883 (16)
Colectomy	49 (<1)
All-cause 30-day mortality	417 (2)
ICU admission	642 (4)
Length of stay [§]	4 (2, 7)
WBC count ≤ 1000 cells/ μ l	134 (<1)
WBC count $\geq 15,000$ cells/ μ l	3250 (18)
Ileus or toxic megacolon	368 (2)
Pseudomembranous colitis	55 (<1)

*Admitted to acute care hospital at time of or within 7 days after stool collection

[†]Includes samples collected in emergency room or observation unit on the same day as acute care admission

[‡]Includes chronic hemodialysis, surgery, emergency room visit, hospital admission, residence in long-term care facility or skilled nursing facility, and observation unit admission in prior 12 weeks

[§]Length of stay indicates the time from CDI diagnosis to discharge
CDI *Clostridioides difficile* infection, ICU intensive care unit, LTACH long-term acute care hospital, WBC white blood cell

antibiotics or immunosuppressive medications, respectively, in the 12 weeks prior to CDI diagnosis. Eighteen percent ($n = 3250$) of the treated cases met the severe CDI definition; 159 (5%) of these had ileus or toxic megacolon within 5 days of specimen collection. Two hundred nine treated cases (1%) that did not meet the severe CDI definition had ileus or toxic megacolon. Those treated and not treated were similar regarding age, sex, race, and comorbidities. Treated cases were more likely to have been admitted to a hospital, had stool collected at a hospital, or had taken antibiotics in the prior 12 weeks.

Treatment

All CDI Cases. Metronidazole was the most common CDI treatment medication among all cases ($n = 14,257$, 78%) (Table 3). Five hundred milligrams was the most common starting dose ($n = 13,088$, 92%), and 83% ($n = 11,778$) were

Table 3 Description of *Clostridioides difficile* Infection Treatment Among All Treated Cases ($n = 18,243$) and a Subset with Severe Disease ($n = 3250$)

	All cases	Severe cases
	N (%)	N (%)
Any metronidazole	$N = 14,257$ (78)	$N = 2576$ (79)
Dose		
500 mg	13,088 (92)	2473 (96)
Other	535 (4)	61 (2)
Unknown	634 (4)	42 (2)
Frequency		
Three times a day	11,778 (83)	2130 (83)
Other	1797 (13)	403 (15)
Unknown	682 (4)	43 (2)
Route		
Oral	11,728 (82)	1508 (58)
Intravenous	2443 (17)	1060 (41)
Unknown	86 (<1)	8 (<1)
Any vancomycin	$N = 7683$ (42)	$N = 2042$ (63)
Doses		
125 mg	5077 (66)	1305 (64)
250 mg	1795 (23)	506 (25)
500 mg	444 (6)	194 (9)
Other	32 (<1)	9 (<1)
Unknown	335 (4)	28 (1)
Frequency		
Four times a day	6874 (89)	1895 (93)
Other	427 (6)	108 (5)
Unknown	382 (5)	39 (2)
Route		
Oral	7612 (99)	2013 (99)
Rectal	42 (<1)	24 (1)
Unknown	29 (<1)	5 (<1)
Any fidaxomicin	$N = 313$ (2)	$N = 64$ (2)
Doses		
200 mg	284 (91)	61 (95)
Other	4 (1)	0
Unknown	25 (8)	3 (5)
Frequency		
Two times a day	281 (90)	60 (94)
Three times a day	2 (<1)	0
Unknown	30 (10)	4 (6)
Route		
Oral	313 (100)	64 (100)
Any treatment	$N = 18,243$	$N = 3250$
Monotherapy		
Metronidazole	10,173 (56)	1162 (36)
Vancomycin	3576 (20)	626 (19)
Fidaxomicin	117 (<1)	10 (<1)
Combination therapy with metronidazole and vancomycin		
Any	4037 (22)	1405 (43)
Sequential	851 (5)	176 (5)
Metronidazole first	581 (3)	113 (3)
Vancomycin first	270 (1)	63 (2)
Overlap	3186 (17)	1229 (38)
≥ 2 days	2925 (16)	1141 (35)
Vancomycin taper	866 (5)	168 (5)
Probiotics	3223 (18)	701 (22)
Fecal microbiota transplant	89 (<1)	10 (<1)
Days from stool collection to therapy		
± 7 days	15,811 (87)	3019 (93)
± 2 days	13,117 (72)	2798 (86)
Days of therapy, median (IQR)	14 (11–15)	14 (11–17)

IQR interquartile range, mg milligrams

prescribed metronidazole 3 times per day. Metronidazole monotherapy was used in 56% ($n = 10,173$) of cases. Sixty-nine percent ($n = 7046$) of those prescribed only metronidazole were prescribed 500 mg 3 times per day for at least 10 days. Of the 31% of patients prescribed only metronidazole and who were not prescribed 500 mg 3 times per day for 10

days, 39% ($n = 1207$) were prescribed a different dose or frequency, 28% (880) were prescribed < 10 days of therapy, and 33% (1040) were missing dates to calculate duration of treatment.

Forty-two percent ($n = 7683$) of all treated cases were prescribed vancomycin. The most common starting doses were 125 mg in 66% ($n = 5077$) and 250 mg in 23% ($n = 1795$) of cases. Eighty-nine percent ($n = 6874$) were prescribed vancomycin 4 times per day. Twenty percent ($n = 3576$) were prescribed vancomycin only and 5% ($n = 866$) were treated with vancomycin tapers. Combination therapy (metronidazole and vancomycin) was used in 22% ($n = 4037$) of all treated cases.

Only 2% ($n = 313$) of treated cases were prescribed fidaxomicin, with < 1% ($n = 117$) prescribed fidaxomicin only. Ninety percent ($n = 281$) received 200 mg twice per day.

Most ($n = 13,117$, 72%) cases started therapy within 2 days of stool collection. The median length of all therapy was 14 (IQR 11–15) days. Probiotics were used in 3223 (18%) cases. Less than 1% ($n = 89$) of cases received a fecal microbiota transplant (FMT).

Severe CDI Cases. Of 3355 cases with severe disease, 3250 (97%) were treated for CDI, 53 (2%) were not treated, and 52 (1%) had unknown CDI treatment status. Forty-three percent of treated severe cases were prescribed a combination of medications; 626 (19%) were treated with vancomycin alone, and 1162 (36%) were treated with metronidazole only (Table 3). Of those treated for severe CDI, 129 (4%) were missing prescription dates to calculate duration of therapy. Of the 3121 treated cases with data to calculate duration, 1480 (47%) received guideline-adherent therapy. Of those who did not receive guideline-adherent therapy, 1208 (74%) were never started on vancomycin, 88 (5%) did not receive the recommended dose or frequency, and 345 (21%) received < 10 days of therapy (Fig. 1). Prescription of guideline-adherent therapy for severe cases was 44%, 45%, and 52% in 2013, 2014, and 2015, respectively.

Among 3355 severe cases, 2692 (80%) were community-onset, of whom 90% were hospitalized. Community-onset severe CDI patients who were hospitalized were more likely than those not hospitalized to receive guideline-adherent therapy (50% versus 25%; $p = 0.0001$).

Predictors of Guideline-Adherent Therapy Among Severe CDI Cases

In unadjusted analysis, age ≥ 65 years, higher Charlson comorbidity index, inflammatory bowel disease (IBD), healthcare-associated epidemiologic classification, antibiotics, and immunosuppressive therapy were significantly associated with prescription of guideline-adherent therapy (Table 4). In addition, hospital interactions, including hospital admission at the time of or within 7 days of stool collection and having stool collected in the hospital, were

significantly associated with prescription of guideline-adherent therapy.

In multivariable analysis, hospital admission (aOR 2.48; 95% CI 1.90, 3.24), age ≥ 65 years (aOR 1.37; 95% CI 1.10, 1.71), Charlson comorbidity index ≥ 3 (aOR 1.27; 95% CI 1.04, 1.55), immunosuppressive therapy (aOR 1.21; 95% CI 1.02, 1.42), and IBD (aOR 1.56; 95% CI 1.13, 2.17) were independently associated with prescription of guideline-adherent therapy among those with severe disease (Table 5).

Sensitivity Analysis. In unadjusted analysis, significant predictors of guideline-adherent therapy did not change when the definition of severity was expanded to include a CDI-associated complication or ICU admission. In multivariable analysis, antibiotic use in the prior 12 weeks was significantly associated with prescription of guideline-adherent therapy (aOR 1.19; 95% CI 1.01, 1.40) while age was no longer significantly associated with prescription of guideline-adherent therapy.

DISCUSSION

In this analysis of adult CDI patients from 10 different states during 2013–2015, more than 95% were treated, most commonly with metronidazole. Vancomycin, either alone or in combination with another medication, was used in 42% of patients overall and 63% of patients with severe CDI. Fidaxomicin was rarely used. In severe CDI patients, adherence to guideline-recommended therapy was low (47%). The most common type of provider non-adherence was not prescribing vancomycin, followed by not prescribing 10 days of vancomycin. Hospital admission was the most significant predictor for receiving guideline-adherent therapy for severe disease. Our findings of low adherence to guideline-recommended therapy for severe CDI have important implications given the recent publication of updated IDSA/SHEA CDI treatment guidelines that recommend either oral vancomycin or fidaxomicin for all initial non-severe and severe CDI episodes and raise concerns that adherence could continue to be poor in those with severe CDI.⁹

Metronidazole was the most commonly prescribed therapy among all CDI patients, with 78% prescribed metronidazole. We found a higher percentage of non-severe CDI patients were prescribed metronidazole alone (60%) than vancomycin alone (20%). Early studies demonstrated improved response to treatment with vancomycin in severe CDI, but were not definitive for non-severe CDI leading to the 2010 guideline recommendation for treating mild-moderate disease with metronidazole and severe disease with vancomycin.⁸ For example, in a 2007 study that compared oral metronidazole and oral vancomycin, 97% of patients with severe CDI were cured with oral vancomycin versus 76% with oral metronidazole ($p = 0.02$), but in those with mild CDI, cure rates were not statistically different: 90% with oral metronidazole and 98% with oral vancomycin ($p = 0.36$).¹⁰

Table 4 Unadjusted Analysis for Predictors of Being Prescribed Guideline-Adherent Therapy Among Severe *Clostridioides difficile* Infection Cases (n = 3121)*

	Non-guideline-adherent therapy (n = 1641) N (%)	Guideline-adherent therapy (n = 1480) N (%)	Unadjusted odds ratio (95% confidence interval)	p value
Sex				
Male	655 (40)	579 (39)	Reference	
Female	986 (60)	901 (61)	1.04 (0.90, 1.20)	0.63
Age (years)				
18–44	292 (18)	208 (14)	Reference	
45–64	484 (29)	382 (26)	1.12 (0.90, 1.41)	0.31
≥ 65	865 (53)	890 (60)	1.33 (1.21, 1.82)	< 0.001
Race				
White	1342 (82)	1240 (84)	Reference	
Non-white	299 (18)	240 (16)	0.87 (0.72, 1.06)	0.17
Charlson comorbidity index				
0	483 (29)	328 (22)	Reference	
1–2	536 (33)	502 (34)	1.37 (1.13, 1.65)	0.001
≥ 3	622 (38)	650 (44)	1.54 (1.29, 1.85)	< 0.001
Inflammatory bowel disease	80 (5)	98 (7)	1.39 (1.03, 1.89)	0.03
Diverticular disease	196 (12)	186 (13)	1.04 (0.84, 1.29)	0.72
Epidemiologic class				
Healthcare-associated	857 (52)	854 (58)	Reference	
Community-associated	784 (48)	626 (42)	0.80 (0.68, 0.91)	0.001
Location of stool collection				
Hospital/LTACH [†]	1329 (81)	1300 (88)	Reference	
Ambulatory and other locations [‡]	312 (19)	180 (12)	0.56 (0.45, 0.68)	< 0.001
Hospital admission [§]	1414 (86)	1395 (94)	2.73 (2.10, 3.55)	< 0.001
Admitted from home	1384 (84)	1242 (84)	0.96 (0.79, 1.16)	0.64
Medications in prior 12 weeks				
Antibiotics	1263 (77)	1185 (80)	1.24 (1.04, 1.48)	0.02
Immunosuppressive therapy	438 (27)	481 (33)	1.30 (1.11, 1.52)	0.001
Healthcare exposures in prior 12 weeks	1069 (65)	1016 (69)	1.19 (1.02, 1.38)	0.03

*Excludes patients with unknown duration of treatment, unknown treatment status, or who did not receive treatment

[†]Includes samples collected in emergency room or observation unit on the same day as acute care admission

[‡]Other locations include long-term care facilities

[§]Admitted to hospital at time of or within 7 days after stool collection

^{||}Includes chronic hemodialysis, surgery, ER visit, hospital admission, residence in long-term care facility or skilled nursing facility, or observation unit admission in prior 12 weeks

LTACH long-term acute care hospital

However, oral vancomycin is now considered to be superior to oral metronidazole for CDI treatment, regardless of disease

Table 5 Multivariable Analysis for Predictors of Being Prescribed Guideline-Adherent Therapy Among Severe *Clostridium difficile* Infection Cases (n = 3121)*

	Adjusted odds ratio (95% confidence interval)	p value
Age (years)		
18–44	Reference	
45–64	1.08 (0.86, 1.37)	0.51
≥ 65	1.37 (1.10, 1.71)	0.01
Charlson comorbidity index		
0	Reference	
1–2	1.19 (0.98, 1.45)	0.08
≥ 3	1.27 (1.04, 1.55)	0.02
Hospital admission [†]	2.48 (1.90, 3.24)	< 0.001
Inflammatory bowel disease	1.56 (1.13, 2.17)	0.01
Immunosuppressive therapy in prior 12 weeks	1.21 (1.02, 1.42)	0.03

*Excludes patients with unknown duration of treatment, unknown treatment status, or who did not receive treatment

[†]Admitted to hospital at time of or within 7 days after stool collection

severity, based on studies published after the 2010 guidelines. These studies have shown lower response rates to oral metronidazole than oral vancomycin for mild-moderate and severe CDI.^{11,20} The largest randomized, blinded comparison of metronidazole and vancomycin for CDI treatment showed vancomycin to be superior to metronidazole for all CDI patients with 81% vs 73% clinical success ($p = 0.02$).¹¹

In contrast to prior studies, which were smaller and largely single center,^{12–16} we were able to examine CDI treatment across multiple sites. Consistent with prior studies, we found that provider adherence to the 2010 treatment guidelines for severe CDI was low, with fewer than half of patients prescribed guideline-adherent therapy. Brown et al. found that approximately 35% of patients with severe CDI did not receive guideline-adherent therapy at a tertiary care county teaching hospital.¹² Similarly, at another institution, adherence to the 2010 treatment guidelines was 43% for all patients with CDI, 66% for those with mild-moderate disease, 25% for severe disease, and 36% for severe-complicated disease.¹⁴ In our analysis, more than two-thirds of patients with severe CDI

who were not prescribed adherent therapy were not prescribed vancomycin and a quarter were prescribed less than the recommended 10 days of therapy. Educating providers on starting vancomycin for the recommended duration of therapy may improve adherence with the new guidelines.

Probiotics were prescribed to a minority of all CDI cases (18%). Although a few studies have suggested that probiotics may be effective in CDI prevention,^{21,22} probiotics are not recommended for CDI treatment in either the 2010 or updated 2017 guidelines.^{8,9} Similarly, FMT was used in < 1% of all CDI cases; this is actually higher than expected given this was an analysis of only incident CDI, and FMT is a recommended therapy for only recurrent CDI.^{8,9}

Another medication used in only a few patients was fidaxomicin, with only 2% of patients prescribed any fidaxomicin and < 1% only fidaxomicin. A similarly low fidaxomicin usage rate of 1.98% was reported in Veteran Affairs Medical Centers during 2011–2015.²³ Fidaxomicin was approved by the US Food and Drug Administration for treatment of CDI in 2011,²⁴ and some providers may not have initially been familiar with this drug. However, we found no increase in its use from 2013 to 2015, whereas fidaxomicin use increased from 2011 to 2015 among Veteran Affairs Medical Centers,²³ suggesting provider adherence or awareness may be partly influenced by institutional policies. Fidaxomicin is more expensive than some of the other recommended medications and this may have limited its uptake by individual providers, institutions, and insurance companies and acceptability by patients.^{9,25}

Our findings have important implications for adherence to the new 2017 guidelines.⁹ We found inadequate use of oral vancomycin for severe disease despite it being guideline-recommended therapy as well as infrequent use of fidaxomicin and vancomycin monotherapy in general. These practices may reflect a lack of knowledge of guideline-recommended therapy or lack of provider confidence in the improved efficacy of vancomycin and fidaxomicin over metronidazole. It is possible that the new CDI treatment guidelines will actually improve provider adherence by simplifying treatment and removing the need for a provider to consider disease severity. However, our findings of low provider adherence to the 2010 treatment guidelines raise concerns about adherence to the updated guidelines. To ensure optimal patient outcomes, ongoing assessments of adherence and additional efforts to improve compliance may be needed.

Hospital admission was most strongly associated with receiving guideline-adherent therapy for severe disease even after controlling for age and comorbidities. It is unclear if this reflects the perception of providers that hospitalized patients are more ill or a lack of education of outpatient providers regarding CDI treatment guidelines. Barriers to obtaining oral vancomycin in the outpatient setting might also contribute to decreased use, including increased cost and limited availability at some pharmacies.^{9,26} Efforts to eliminate these barriers

as well as targeted education of providers may improve outpatient CDI management.

This analysis has some limitations. Incomplete documentation in the medical records and limited access to some outpatient records might have limited our ability to identify all relevant predictors of guideline-adherent therapy. When prescription information was available, we were unable to ascertain if patients took the medication as prescribed. We were only able to use WBC count to categorize severe disease (since serum creatinine was not collected), which could have underestimated the burden of severe CDI. However, we did perform a sensitivity analysis using an expanded definition of severity and results were similar to the primary analysis. Further, because we did not have creatinine data, we were unable to determine which patients had mild-moderate disease and therefore could not determine provider adherence to guideline-recommended therapy in this group of patients. In addition, we were not able to assess the association between prescription of guideline-adherent therapy and outcomes in patients with severe CDI, since mortality data was not collected on all patients. However, observational studies examining the effect of guideline-adherent CDI therapy on outcomes have shown mixed results,^{12,14,16,27} while randomized trials have primarily shown improved clinical response in those treated with vancomycin and no effect on recurrence and mortality.^{10,11} Lastly, we did not account for CDI overtreatment, which could also be associated with adverse outcomes.

In conclusion, we found that providers during 2013–2015 most commonly used metronidazole to treat CDI, whereas they infrequently used vancomycin monotherapy and fidaxomicin. Provider adherence to the 2010 guideline-recommended therapy for severe CDI was low. Targeted education, particularly of outpatient providers, and efforts to reduce barriers to prescribing and obtaining recommended medications may help increase awareness of and adherence to the updated CDI treatment guidelines.

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Conflict of Interest: D.N.G. is a member of the Scientific Advisory Boards of Merck, Rebiotix, Actelion, DaVolterra, and Summit; is a consultant for Pfizer, MGB Pharma, and Sanofi Pasteur; holds a research grant from Seres Therapeutics; and holds patents and technology for the prevention of CDI. G.K.D. serves on the Drug Safety Monitoring Board for a *C. difficile* treatment study by Seres. All other authors have no known conflicts of interest.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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