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Characteristics of Patients With Initial *Clostridioides difficile* Infection (CDI) That Are Associated With Increased Risk of Multiple CDI Recurrences

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Background. Because interventions are available to prevent further recurrence in patients with recurrent *Clostridioides difficile* infection (rCDI), we identified predictors of multiple rCDI (mrCDI) in adults at the time of presentation with initial CDI (iCDI).

Methods. iCDI was defined as a positive *C difficile* test in any clinical setting during January 2018–August 2019 in a person aged ≥ 18 years with no known prior positive test. rCDI was defined as a positive test ≥ 14 days from the previous positive test within 180 days after iCDI; mrCDI was defined as ≥ 2 rCDI. We performed multivariable logistic regression analysis.

Results. Of 18 829 patients with iCDI, 882 (4.7%) had mrCDI; 437 with mrCDI and 7484 without mrCDI had full chart reviews. A higher proportion of patients with mrCDI than without mrCDI were aged ≥ 65 years (57.2% vs 40.7%; $P < .0001$) and had healthcare (59.1% vs 46.9%; $P < .0001$) and antibiotic (77.3% vs 67.3%; $P < .0001$) exposures in the 12 weeks preceding iCDI. In multivariable analysis, age ≥ 65 years (adjusted odds ratio [aOR], 1.91; 95% confidence interval [CI], 1.55–2.35), chronic hemodialysis (aOR, 2.28; 95% CI, 1.48–3.51), hospitalization (aOR, 1.64; 95% CI, 1.33–2.01), and nitrofurantoin use (aOR, 1.95; 95% CI, 1.18–3.23) in the 12 weeks preceding iCDI were associated with mrCDI.

Conclusions. Patients with iCDI who are older, on hemodialysis, or had recent hospitalization or nitrofurantoin use had increased risk of mrCDI and may benefit from early use of adjunctive therapy to prevent mrCDI. If confirmed, these findings could aid in clinical decision making and interventional study designs.

Clostridioides difficile infection (CDI) is a common healthcare-associated gastrointestinal infection, with an estimated >400 000 incident infections occurring annually in the United States [1]. Rates of recurrence vary, but generally, up to 25% of patients with an initial CDI (iCDI) may experience recurrent CDI (rCDI), with the majority of first recurrences occurring within 8 weeks of the initial episode [2]. rCDI is associated with significant morbidity and mortality, with 2.5 times higher hospital admission rate, 4 times longer hospital stay, and 33% higher all-cause mortality rate than iCDI [3, 4]. The economic burden of rCDI is also substantial; the attributable healthcare costs have been estimated to be \$10 850 per recurrent episode [5].

Recent advancements in CDI treatment have focused on prevention of rCDI in adults, particularly multiple recurrences

(≥ 2 rCDI). Although antibiotics alone, including extended or tapering courses, can be used to treat or prevent a first or subsequent recurrence, fecal microbiota transplantation (FMT) or live biotherapeutic products (REBYOTA or VOWST) following antibiotic therapy are currently recommended for the management of a second or subsequent recurrence [6–8]. Another adjunctive therapy for prevention of a first or subsequent recurrence includes bezlotoxumab, a human monoclonal antibody that binds to *C difficile* toxin B [9]. Despite the availability of these interventions to prevent multiple rCDI (mrCDI), little is known regarding which patients are at increased risk for mrCDI. We sought to describe the epidemiology of mrCDI across geographically diverse U.S. sites and identify predictors of mrCDI in adults at the time of presentation with iCDI.

METHODS

Surveillance Population and Case Definition

The Centers for Disease Control and Prevention's Emerging Infections Program (EIP) conducts population-based surveillance for CDI in 35 counties in 10 states (California, Colorado,

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Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) [10]. Laboratories serving the catchment areas reported all positive *C difficile* tests to EIP site staff. iCDI was defined as a positive *C difficile* molecular or toxin assay in any clinical setting during January 2018–August 2019 in a catchment-area resident aged ≥ 18 years with no prior positive test reported to EIP. rCDI was defined as a positive test ≥ 14 days from the previous positive test, whereas mrCDI was defined as a second or subsequent rCDI episode, within 180 days after iCDI.

Data Collection and Epidemiologic Classification

An initial chart review was performed by trained EIP site staff using a standardized case report form on all patients with iCDI from 8 EIP sites and on a random sample of patients from 2 sites with the largest surveillance population (Colorado and Georgia). Based on chart review, iCDI was epidemiologically classified as community onset if the *C difficile*-positive stool was collected as an outpatient or within 3 days of hospital admission; hospital onset if the positive stool was collected >3 days after hospital admission; or long-term care facility (LTCF) onset if the positive stool was collected in a LTCF or from a LTCF resident. Per routine surveillance protocol, all community-onset patients and a random 10% to 20% of healthcare facility-onset patients (ie, hospital onset and LTCF onset) underwent a subsequent full chart review to collect additional

healthcare and medication exposures, comorbidities, and clinical course (Figure 1). All medication exposures (eg, antibiotics) were limited to the 12 weeks before iCDI; no information about subsequent antibiotics, other than those used in the treatment of iCDI, was collected. State death registries were used to obtain mortality within 180 days after iCDI.

Community-onset iCDI was further classified as community-associated if there was no documentation of an overnight stay in a healthcare facility in the preceding 12 weeks. All other community-onset iCDI that did not meet this criterion were classified as community-onset healthcare facility-associated (COHCFA), and, along with hospital-onset and LTCF-onset iCDI, were considered healthcare-associated iCDI.

Statistical Analysis

We used descriptive statistics to summarize rCDI data among all patients. To identify predictors of mrCDI, we restricted the analysis to patients who had a full chart review. Chi-square and Fisher exact tests (where applicable) were used to assess the associations between risk factors and patient groups with or without mrCDI (ie, ≤ 1 rCDI). We also calculated mrCDI attack rates and unadjusted relative risks for selected risk factors. Multiple imputation was performed for the race variable (18.9% of cases missing) and ethnicity variable (23.6% of cases missing) using the fully conditional specification method based on age, sex, epidemiologic classification,

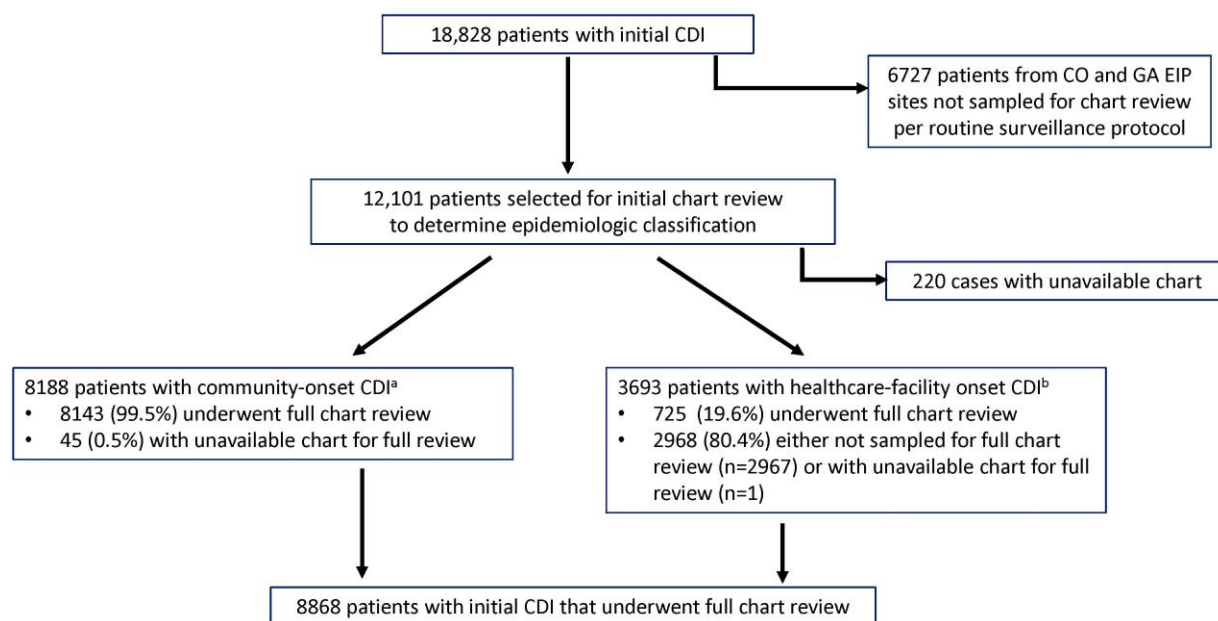


Figure 1. Flow diagram depicting the selection of patients with initial *Clostridioides difficile* infection for chart review and inclusion in the analysis. Abbreviations: CDI, *Clostridioides difficile* infection; EIP, Emerging Infections Program. ^aPatients with community-onset CDI who underwent a full chart review were less likely than those without a chart review to be community-associated (71.0% vs 93.3%; $P = .004$), but there were no differences in the proportion who were female ($P = .10$), aged ≥ 65 y ($P = .93$), or who had multiple recurrent CDI ($P = 1.00$) or died within 180 d of initial CDI ($P = .69$). ^bPatients with healthcare facility-onset CDI (ie, hospital-onset or long-term care facility onset CDI) who had a full chart review were less likely than those without a chart review to be long-term care facility-onset (32.7% vs 38.5%; $P = .004$), but there were no differences in the proportion who were female ($P = .19$), aged ≥ 65 y ($P = .32$), or who had multiple recurrent CDI ($P = .51$), or died within 180 d of initial CDI ($P = .48$).

EIP site, and year [11]. Because our objective was to identify risk factors of patients who were at risk of mrCDI, regardless of when the recurrences occurred during the follow-up period, we used a logistic regression model instead of survival analysis. The following candidate variables were determined a priori to be potentially associated with mrCDI and were entered into an initial multivariable logistic regression model: age, sex, race/ethnicity, selected comorbidities and healthcare and medication exposures, hospitalization, intensive care unit (ICU) admission, and iCDI treatment. We also adjusted for healthcare facility onset status to account for the sampling of cases for full chart review. To reduce the number of variables in the model, we selected candidate variables with a P value $<.1$ in the initial model for inclusion in the final model. Patients without mrCDI who had died within 180 days of their iCDI were excluded from these models because they did not have a chance to develop mrCDI.

We performed a sensitivity analysis excluding patients with a single recurrence from the models (ie, comparing patients with mrCDI with patients without recurrence). We performed a second sensitivity analysis evaluating death as another outcome, where patients with mrCDI or those who had died within 180 days of iCDI were compared with patients without mrCDI who had survived.

Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated for the models. A 2-tailed P value $<.05$ was considered statistically significant. SAS statistical software version 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all analyses. Datasets used for this analysis included 2018 surveillance data as of 17 November 2020 and 2019 surveillance data as of 12 October 2021.

Patient Consent Statement

This study was reviewed and approved by the Centers for Disease Control and Prevention institutional review board (see 45 C.F.R. part 46; 21 C.F.R. part 56.) and was deemed either nonresearch or received institutional review board approval with a waiver of informed consent in EIP sites. This activity did not include factors necessitating patient consent.

RESULTS

Description of mrCDI

Of 18 828 patients with iCDI, 15 367 (81.6%) had no rCDI, 2579 (13.7%) had a single rCDI, and 882 (4.7%) had mrCDI, ranging from 2 to 5 rCDI per patient within 180 days following iCDI (Table 1). Among patients with rCDI, 32.9% had their recurrent CDI episodes diagnosed at different laboratories. Of the 882 patients with mrCDI, 702 (79.6%) had 2 recurrences, 146 (16.6%) had 3 recurrences, 31 (3.5%) had 4 recurrences, and 3 (0.3%) had 5 recurrences. The median time between each subsequent recurrence varied slightly (Table 1), with an overall median of 43 days (interquartile range, 27–65 days).

Table 2 shows the proportion of patients with subsequent recurrences by their baseline characteristics. Patients aged ≥ 65 years at the time of their iCDI, compared with other age groups ($P \leq .01$), and patients with COHCFA or LTCF-onset iCDI, compared with community-associated or hospital-onset iCDI ($P < .01$), were more likely to have any number of rCDI during the 180-day follow-up period. Hispanic patients of any race and non-Hispanic White patients were more likely than other racial/ethnic groups to have up to 2 or more rCDI ($P < .01$). Patients with a toxin-positive iCDI were also more likely than those with a toxin-negative iCDI (ie, nucleic acid amplification test [NAAT] positive only) to have up to 2 or more rCDI ($P < .01$).

Predictors of mrCDI

A full chart review was performed on 8868 patients with iCDI (Figure 1). Among those with data available, 97.7% (8063/8257) had documentation of diarrhea. Of the 8868 patients, 437 (4.9%) subsequently had mrCDI and 8431 (95.1%) did not have mrCDI. Of the 8431 patients without mrCDI, 947 (11.2%) had died within 180 days after iCDI. A comparison of the patients who had died and those who had survived is shown in Supplementary Table 1.

Table 3 compares the 437 patients with subsequent mrCDI to the 7484 patients without mrCDI (6326 patients without recurrence and 1158 with a single recurrence) who had survived the 180-day period after iCDI. A higher percentage of patients with mrCDI than those without mrCDI were aged ≥ 65 years at

Table 1. Timing of Recurrent CDI From the Initial and Previous CDI Episodes

	All Patients With Initial CDI		
	N = 18 828 No. (%)	Days From Initial CDI Median (IQR)	Days From Previous CDI Median (IQR)
First recurrence	3461 (18.4)	37 (25–65)	37 (25–65)
Second recurrence	882 (4.7)	84 (60–117)	44 (27–67)
Third recurrence	180 (1.0)	118.5 (97–148)	43 (27–61)
Fourth recurrence	34 (.2)	140 (118–160)	39 (26–51)
Fifth recurrence	3 (.02)	152 (150–174)	37 (36–41)

Abbreviations: CDI, *Clostridioides difficile* infection; IQR, interquartile range.

Table 2. Frequency of Recurrent CDI Among Patients With Initial CDI by Their Baseline Characteristics

Patient Characteristics at Time of Initial CDI	No. (%) ^a	Percent of Subgroup ^b							
		≥1 rCDI	P Value	≥2 rCDI	P Value	≥3 rCDI	P Value	≥4 rCDI	P Value
Patients with initial CDI	18 828 (100.0)	18.4		4.7	...	1.02	...
Age group, y (n = 18 828)	<.01	...	<.01	...	<.0101
18–44	3771 (20.0)	13.8		2.951	...
45–64	5952 (31.6)	17.7		4.171	...
≥65	9105 (48.4)	20.7		5.8	...	1.33	...
Sex (n = 18 828)09271526
Male	7895 (41.9)	17.8		4.581	...
Female	10 933 (58.1)	18.8		4.8	...	1.02	...
Epidemiologic classification of initial CDI (n = 11 881) ^c	<.01	...	<.01	...	<.01	...	<.01
CA	5825 (49.0)	17.9		4.391	...
COHCFA	2363 (19.9)	24.2		6.7	...	1.43	...
HO	2312 (19.5)	14.0		3.271	...
LTCFO	1381 (11.6)	23.2		6.2	...	1.77	...
Race/ethnicity (n = 11 586) ^d	<.01	...	<.011053
Hispanic, any race	1105 (9.5)	20.1		5.2	...	1.14	...
Non-Hispanic, White race	7583 (65.5)	21.0		5.4	...	1.32	...
Non-Hispanic, other race ^e	2898 (25.0)	17.4		3.982	...
Diagnostic test result for initial CDI (n = 10 153) ^f	<.01	...	<.011744
Toxin-positive	4970 (49.0)	21.0		5.9	...	1.22	...
NAAT positive/toxin negative	5183 (51.1)	17.1		4.0	...	1.02	...

Abbreviations: CA, community-associated; COHCFA, community-onset healthcare facility-associated; EIP, Emerging Infections Program; HO, hospital-onset; LTCFO, long-term care facility onset; NAAT, nucleic acid amplification test; rCDI, recurrent *Clostridioides difficile* infection.

^aDisplays column percentages.

^bDisplays row percentages.

^cExcludes 6947 patients, of whom 220 (3.2%) had incomplete documentation of healthcare exposures in their medical records and 6727 (96.8%) were not selected by Georgia and Colorado EIP sites for chart review.

^dExcludes 7242 patients, of whom 3052 (42.1%) were missing race/ethnicity data from the laboratory line list or medical records and 4190 (57.9%) were not selected by Georgia and Colorado EIP sites for chart review.

^eAll non-Hispanic, non-White patients were grouped into a single category because of small numbers. These included patients of Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races.

^fExcludes 8675 patients diagnosed by NAAT alone or as part of a multistep algorithm where the toxin result was not available.

the time of their iCDI (57.2% vs 40.7%; $P < .0001$) and had healthcare-associated (42.6% vs 30.4%; $P < .0001$) and toxin-positive (33.6% vs 26.6%; $P = .003$) iCDI, although toxin-positivity status was known for <60% of patients. They were also more likely than those without mrCDI to have underlying conditions, including chronic kidney disease (22.0% vs 14.4%; $P < .0001$), diverticular disease (15.6% vs 11.2%; $P = .006$), and hematologic or solid tumor malignancy (17.9% vs 14.1%; $P = .03$). Healthcare and medication exposures in the 12 weeks preceding iCDI were also more common in patients with than without mrCDI, including prior hospitalization (39.6% vs 26.9%; $P < .0001$), long-term care facility stay (9.0% vs 4.9%; $P = .0002$), chronic hemodialysis (6.3% vs 3.0%; $P = .0001$), surgery (16.0% vs 12.1%; $P = .02$), antibiotic use (77.3% vs 67.3%; $P < .0001$), proton-pump inhibitor use (38.7% vs 33.0%; $P = .02$), and immunosuppressant use (30.6% vs 25.5%; $P = .02$). Patients with mrCDI were also more likely than those without mrCDI to have received treatment for their iCDI (97.8% vs 95.4%; $P = .02$). A separate comparison of patients with mrCDI to those without recurrence and to those with a single recurrence is shown in [Supplementary Table 2](#).

The initial multivariable model to identify predictors of mrCDI is shown in [Supplementary Table 3](#). In the final multivariable analysis, age ≥65 years at the time of iCDI (aOR, 1.91; 95% CI, 1.55–2.35), chronic hemodialysis (aOR, 2.28; 95% CI, 1.48–3.51), hospitalization (aOR, 1.64; 95% CI, 1.33–2.01), and nitrofurantoin use (aOR, 1.95; 95% CI, 1.18–3.23) in the 12 weeks preceding iCDI were significantly associated with experiencing mrCDI within 180 days following iCDI ([Table 4](#)).

Attack rates of mrCDI among patients with iCDI by selected risk factors are shown in [Supplementary Table 4](#). The mrCDI attack rate among patients with iCDI who were aged ≥65 years, receiving chronic hemodialysis, or had prior hospitalization or nitrofurantoin use ranged from 7.6% to 11.0%. Among 1300 patients with 2 or more of these risk factors, the mrCDI attack rate was 10.2%.

In the first sensitivity analysis, we excluded patients from the comparator group that had a single recurrence and found the same variables remained significantly associated with mrCDI ([Supplementary Tables 5 and 6](#)). In the second sensitivity analysis that included death as an outcome, the following were significant predictors of mrCDI or death within 180 days after

Table 3. Comparison of Characteristics Between Patients With and Without Multiple Recurrent CDI

Patient Characteristics at Time of Initial CDI	Patients With mrCDI N = 437 No. (%)	Patients Without mrCDI N = 7484 ^a No. (%)	P Value
Age group, y	<.0001
18–44	53 (12.1)	1896 (25.3)	
45–64	134 (30.7)	2546 (34.0)	
≥65	250 (57.2)	3042 (40.7)	
Sex62
Male	164 (37.5)	2898 (38.7)	
Female	273 (62.5)	4586 (61.3)	
Race/ethnicity004
Hispanic, any race	32 (7.3)	611 (8.2)	
Non-Hispanic, White race	271 (62.0)	3988 (53.3)	
Non-Hispanic, other race ^b	49 (11.2)	968 (12.9)	
Unknown race or ethnicity	85 (19.5)	1917 (25.6)	
Epidemiologic classification of initial CDI	<.0001
Community-associated	251 (57.4)	5209 (69.6)	
Healthcare-associated	186 (42.6)	2275 (30.4)	
Community-onset healthcare-facility associated	158 (36.2)	1782 (23.8)	
Hospital-onset	17 (3.9)	348 (4.7)	
Long-term care facility-onset	11 (2.5)	145 (1.9)	
Diagnostic test result for initial CDI003
Toxin-positive	147 (33.6)	1993 (26.6)	
NAAT-positive/toxin-negative	106 (24.3)	2225 (29.7)	
Unknown toxin status	184 (42.1)	3266 (43.6)	
Select underlying conditions	
Charlson comorbidity index ≥1	289/431 (67.1)	4170/7400 (56.4)	<.0001
Cardiac disease	62/431 (14.4)	862/7400 (11.7)	.09
Chronic kidney disease	95/431 (22.0)	1068/7400 (14.4)	<.0001
Chronic liver disease	20/431 (4.6)	365/7400 (4.9)	.79
Chronic pulmonary disease	82/431 (19.0)	1286/7400 (17.4)	.38
Diabetes mellitus	102/431 (23.7)	1602/7400 (21.7)	.32
Diverticular disease	67/431 (15.6)	827/7400 (11.2)	.006
Hematologic or solid tumor malignancy	77/431 (17.9)	1043/7400 (14.1)	.03
Hematopoietic stem cell or solid organ transplant	13/431 (3.0)	194/7400 (2.6)	.62
Inflammatory bowel disease	33/431 (7.7)	471/7400 (6.4)	.29
Prior healthcare exposures ^c	
Hospitalization	172/434 (39.6)	1995/7413 (26.9)	<.0001
Long-term acute care hospital stay	3/434 (.7)	16/7412 (.2)	.08
Long-term care facility stay	39/434 (9.0)	361/7410 (4.9)	.0002
Emergency room visit	130/434 (30.0)	1944/7412 (26.2)	.09
Observational unit stay	11/431 (2.6)	152/7407 (2.1)	.48
Chronic hemodialysis	27/432 (6.3)	219/7411 (3.0)	.0001
Surgery	69/432 (16.0)	895/7412 (12.1)	.02

Table 3. Continued

Patient Characteristics at Time of Initial CDI	Patients With mrCDI N = 437 No. (%)	Patients Without mrCDI N = 7484 ^a No. (%)	P Value
Any of the above	256/433 (59.1)	3474/7413 (46.9)	<.0001
Prior medication exposures ^c	
Any antibiotic	327/423 (77.3)	4883/7260 (67.3)	<.0001
Select antibiotic classes:	
Beta-lactam/beta-lactamase inhibitor combinations	136/423 (32.2)	1815/7260 (25.0)	.001
Carbapenems	18/423 (4.3)	192/7260 (2.6)	.05
Cephalosporins	156/423 (36.9)	2082/7260 (28.7)	.0003
Clindamycin	50/423 (11.8)	719/7260 (9.9)	.20
Fluoroquinolones	83/423 (19.6)	1174/7260 (16.2)	.06
Macrolides	20/423 (4.7)	335/7260 (4.6)	.91
Nitrofurantoin	18/423 (4.3)	157/7260 (2.2)	.005
Penicillins	22/423 (5.2)	470/7260 (6.5)	.30
Proton-pump inhibitor	164/424 (38.7)	2384/7221 (33.0)	.02
Immunosuppressant	129/421 (30.6)	1837/7215 (25.5)	.02
Clinical course	
Hospital admission ^d	194 (44.4)	3039/7471 (40.7)	.12
Intensive-care unit stay ^e	8/434 (1.8)	174/7467 (2.3)	.51
Receipt of treatment for initial CDI	405/414 (97.8)	6603/6921 (95.4)	.02
Metronidazole only	91/414 (22.0)	1459/6915 (21.1)	.67
Oral/rectal vancomycin	312/414 (75.4)	5092/6915 (73.6)	.44
Fidaxomicin	8/414 (1.9)	117/6915 (1.7)	.71

Any missing response to a variable is excluded from the denominator.

Abbreviations: CDI, *Clostridioides difficile* infection; mrCDI, multiple recurrent *Clostridioides difficile* infection; NAAT, nucleic acid amplification test.

^aExcludes 947 patients who had died within 180 d of initial CDI diagnosis.

^bAll non-Hispanic, non-White patients were grouped into a single category because of small numbers. These included patients of Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races.

^cDuring the 12 wks prior to initial CDI diagnosis.

^dHospitalized at the time of or within 6 d following initial CDI diagnosis.

^eAdmitted to the intensive care unit on the day of or within 6 d following initial CDI diagnosis.

iCDI: aged ≥65 years at the time of iCDI; healthcare-facility onset iCDI; cardiac disease; chronic liver disease; chronic kidney disease; hematologic or solid tumor malignancy; hematopoietic stem cell or solid organ transplant; chronic hemodialysis; hospitalization, LTCF stay, surgery, immunosuppressant use, and beta-lactam/beta-lactamase inhibitor combination use in the 12 weeks preceding iCDI; and hospitalization and ICU admission at the time of or within 6 days following iCDI (Supplementary Tables 7 and 8).

DISCUSSION

In our large multisite analysis, 5% of patients with iCDI experienced mrCDI (2 or more recurrences) in the subsequent 180 days. By using population-based surveillance, which encompassed inpatient and outpatient settings, we were able to

Table 4. Final Multivariable Model: Characteristics of Initial CDI Associated With Developing Multiple Recurrent CDI

Patient Characteristics at Time of Initial CDI	Adjusted Odds Ratio (95% CI)	P Value
≥65 y of age	1.91 (1.55–2.35)	<.0001
Race/ethnicity	...	
Hispanic, any race	.89 (.60–1.31)	.55
Non-Hispanic, White race	Referent	-
Non-Hispanic, Other race ^a	.75 (.55–1.02)	.07
Healthcare-facility onset initial CDI	.73 (.49–1.09)	.13
Inflammatory bowel disease	1.46 (.99–2.15)	.05
Chronic hemodialysis	2.28 (1.48–3.51)	.0002
Prior hospitalization ^b	1.64 (1.33–2.01)	<.0001
Prior LTACH stay ^b	2.96 (.82–10.67)	.10
Prior nitrofurantoin use ^b	1.95 (1.18–3.23)	.009

Abbreviation: CDI, *Clostridioides difficile* infection; CI, confidence interval; LTACH, long-term acute-care hospital.

^aAll non-Hispanic, non-White patients were grouped into a single category because of small numbers. These included patients of Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races.

^bDuring the 12 wks before initial CDI diagnosis.

identify recurrent episodes diagnosed by different laboratories in a third of the patients who experienced rCDI. We found the frequency of recurrences was highest among patients aged ≥65 years or who had an initial COHCFA or LTCF-onset CDI. We also found that older age, receipt of chronic hemodialysis, recent hospitalization, and nitrofurantoin use were independent risk factors for mrCDI. The presence of 2 or more of these risk factors resulted in an mrCDI attack rate of 10.2%.

Several factors associated with advanced age might increase the risk of mrCDI, including impairment of the immune system from a decline in the quantity or function of antibody-producing and innate immune cells [12]. The inability to mount an adequate immune response to an initial episode of CDI increases the risk for recurrence [13, 14]. Intestinal microbiota can also change with age, resulting in reduced species diversity and smaller inhibitory effect on *C difficile* growth [15, 16]. Additionally, older patients are more likely to have underlying comorbidities and frequent antibiotic use that can contribute to the risk of mrCDI. Furthermore, they are also more likely to have frequent and prolonged hospitalizations and be admitted to LTCFs [17], all of which can lead to repeated exposures to *C difficile*.

We also found chronic hemodialysis to be a risk factor for mrCDI. A previous study found chronic kidney disease to be independently associated with mrCDI but did not specifically evaluate end-stage renal disease [18]. Data regarding recurrent CDI are limited among patients with end-stage renal disease, but 1 study reported a recurrence rate of 23.6% [19] and another study identified chronic dialysis as an independent risk factor for rCDI [20]. Similar to the older population, patients with end-stage renal disease have impairment of their immune system and frequent antibiotic use [21], which can contribute to

the risk of mrCDI. Importantly, they also regularly encounter the healthcare environment for maintenance hemodialysis, which could lead to continued *C difficile* exposure. In fact, CDI outbreaks have been associated with outpatient dialysis facilities [22], where the physical layout, commonly an open floorplan with patients placed in close proximity to one another, and challenges with environmental cleaning and disinfection can lead to *C difficile* transmission [23].

Interestingly, we did not find an increased risk of mrCDI among patients with iCDI who had recent immunosuppressant use or another underlying condition that could result in an impaired immune system, such as hematologic or solid organ malignancy or transplant (Table 4). However, the immunological effect of immunosuppressive drugs is variable, and we did not collect information on duration of use that could impact risk of mrCDI.

We also assessed whether recent antibiotic exposure before iCDI might increase subsequent risk of mrCDI, given that gut microbiome disruption from antibiotic use can persist for several weeks to months. We included antibiotic classes with high or moderate CDI risk (Supplementary Table 3) [24, 25], as well as nitrofurantoin because of 1 study that found nitrofurantoin use before iCDI was a risk factor for a first recurrence [26]. Surprisingly, only nitrofurantoin use was associated with mrCDI in our study, even though it is not known to significantly affect bowel flora and has comparatively lower risk of CDI than other antibiotics [27]. The significant association with nitrofurantoin might reflect cumulative exposure to antibiotics for treatment or prevention of recurrent urinary tract infections (UTIs), including continued antibiotic use after iCDI. An increased risk of CDI has been shown in older patients receiving long-term antibiotic prophylaxis for UTIs [28]. Alternatively, it could reflect a propensity to mrCDI in patients who experience UTIs that is not related to antibiotic exposure. Separately, we also found that recent hospitalization among patients with iCDI was associated with mrCDI, which could be a marker for generally sicker patients with comorbid conditions who might be more likely to be readmitted and exposed to antibiotics.

We conducted a sensitivity analysis with either mrCDI or death as an outcome because emerging data suggest that FMT can reduce 90-day mortality among patients with rCDI [29]. Several significant risk factors for 180-day mrCDI or mortality were identified among patients with iCDI, with the strongest associations seen with older age, hospitalization, and ICU admission (≥2 times the odds of having either outcome), suggesting that investigations of FMT or live biotherapeutic products might prioritize studying these patients.

If confirmed, our findings could help guide patient selection in interventional trials of patients with iCDI to prevent rCDI. Although bezlotoxumab is indicated to reduce rCDI in patients receiving antibiotic treatment for iCDI who are at high risk of rCDI, both REBYOTA and VOWST are currently solely

indicated for the prevention of mrCDI following rCDI. Potential settings in which to conduct these clinical trials would be places with longitudinal electronic medical records, including antibiotic exposures, such as the Veterans Health Administration, health maintenance organizations, or localities with highly functional health information exchanges. Such patients could be randomized to receive an intervention at the time of iCDI and followed electronically for extended outcomes.

Our study has several limitations. First, because the case definition was based on a laboratory diagnosis, it is possible recurrence could have been overestimated if some patients were colonized, had repeat testing without resolution of symptoms, or had a positive result for a test of cure rather than a true recurrence. Conversely, intensity of *C. difficile* testing varies among institutions [30], and recurrence could have been underestimated if clinicians did not retest for *C. difficile* when clinically indicated or patients sought care outside the surveillance catchment area. Second, >40% of iCDI cases were diagnosed with NAAT alone or as part of an algorithm where the toxin enzyme immunoassay result was not available, thus limiting our ability to evaluate toxin-positivity status as a predictor of mrCDI. Third, we could have underestimated risk factors for mrCDI if there was incomplete documentation of exposures or parts of the medical chart were unavailable for review. Although intervening antibiotics (ie, following iCDI or rCDI but before mrCDI) are an important risk factor for rCDI, we limited exposures to those before iCDI; future studies could assess the additional risk from intervening antibiotics on the outcome of mrCDI because those might be additional points to introduce interventions. Fourth, we did not adjust *P* values for multiple comparisons; however, the significant *P* values were several magnitudes smaller than .05 and would likely have remained significant had we used adjusted *P* values. Last, because of the sampling of healthcare-facility onset cases for full chart review, our data may not be representative of that patient population. However, an increasing proportion of CDI are now community onset [1].

In summary, we found 5% of patients with iCDI had up to 5 recurrences over the subsequent 180 days. Patients with iCDI who were older, on chronic hemodialysis, had recent hospitalization or nitrofurantoin use had increased risk of mrCDI and may benefit from early use of adjunctive therapy to prevent mrCDI. Confirmation of these findings could aid in clinical decision making and interventional study designs. Further efforts to improve the identification of patients at risk of mrCDI may require novel approaches, including exploring the use of biomarkers or gut metabolites to predict CDI recurrence.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the

authors, so questions or comments should be addressed to the corresponding author.

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