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Comparison of the Risk of Recurrent *Clostridioides Difficile* Infections Among Patients in 2018 Versus 2013

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Among persons with an initial *Clostridioides difficile* infection (CDI) across 10 US sites in 2018 compared with 2013, 18.3% versus 21.1% had ≥ 1 recurrent CDI (rCDI) within 180 days. We observed a 16% lower adjusted risk of rCDI in 2018 versus 2013 ($P < .0001$).

Keywords. *Clostridioides difficile*; infection; recurrent.

Recurrent *Clostridioides difficile* infection (CDI) is associated with substantial morbidity and mortality [1]. In a systematic review, the median recurrent CDI (rCDI) rate reported among US studies conducted before 2013 was 20.2% (range, 2.1%–64.0%) [2]. Most of these studies used an 8-week follow-up period. Since 2013, several factors might have impacted rCDI rates, including the following: the increased diagnostic use of nucleic acid amplification tests (NAATs) [3], which are highly sensitive but less specific for toxin-producing disease [4]; changes in CDI treatment [5]; and decreasing prevalence of ribotype 027, a strain associated with a higher risk of recurrence [3, 6]. To assess

for changes in rCDI, we compared 180-day rCDI rates among patients in diverse US sites with initial CDI in 2018 and 2013.

METHODS

Study Design

The Centers for Disease Control and Prevention's (CDC) Emerging Infections Program (EIP) conducts population-based CDI surveillance in 10 sites: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. Laboratories serving the surveillance catchment areas reported all positive *C. difficile* tests of catchment-area residents to EIP. An initial CDI was defined as a positive *C. difficile* molecular or toxin assay in a person aged ≥ 1 year with no prior positive test reported to EIP since CDI surveillance began in 2011. Recurrent CDI was defined as a positive test ≥ 14 days from the previous positive test within 180 days after initial CDI. State death registries were used to obtain 180-day mortality data.

Patient Consent Statement

The study protocol was approved by the CDC institutional review board (IRB) and was deemed nonresearch or received IRB approval with a waiver of informed consent in EIP sites. The study did not include factors necessitating patient consent.

Data Collection

A brief medical record review was performed for all patients with initial CDI from 8 EIP sites and for a random sample of patients with initial CDI from 2 EIP sites (Colorado and Georgia) [7]. Patients' initial CDI was classified as community-associated, community-onset healthcare facility-associated (CO-HCFA), hospital-onset, or long-term care facility (LTCF)-onset (see [Supplementary Material](#)). A subsequent comprehensive review of medical records to abstract clinical and treatment data was performed for community-associated and CO-HCFA patients and a random sample of hospital-onset and LTCF-onset patients.

Statistical Analysis

The χ^2 test was used to compare baseline characteristics of 2018 and 2013 patients. Multiple imputation analysis was performed for missing race and epidemiologic classification based on the distribution of known values among patients (see [Supplementary Material](#)). Sampling weights were constructed to accommodate the sampling performed in Georgia and Colorado using previously described methods [7] (see [Supplementary Material](#)).

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The Kaplan-Meier survival plot was used to visualize time-to-recurrence for both years, and the log-rank test was used to test the probability of recurrence within 180 days after initial CDI. Domain analysis using SAS's PROC SURVEYMEANS was performed to generate crude rCDI rates, and the SURVEYPHREG procedure was used to calculate crude rate ratios. An adjusted hazard ratio comparing rCDI in 2018 and 2013 was estimated with the SURVEYPHREG procedure using a Cox proportional hazards model on each imputed dataset. This model censored patient deaths, while adjusting for age, sex, race, and epidemiologic classification and incorporated sampling weights by site, year, age group, and sex. The Finite Population Correction Factor was applied to improve precision.

Because toxin-positive CDI is more likely than NAAT-positive-only CDI to have recurrence [8], we performed a sensitivity analysis including only toxin-positive patients from 9 of 10 EIP sites reporting toxin-positive patients in both years (see [Supplementary Material](#)). This allowed us to assess for changes in rCDI rates that were independent of changes in testing methods (ie, increased use of NAAT over toxin EIA).

Isolate Collection

A convenience sample of stool specimens was cultured for *C. difficile*. Recovered isolates underwent strain typing by capillary-based polymerase-chain-reaction ribotyping [9]; results were analyzed against a library of standard profiles using BioNumerics software (Applied Math, Austin, TX).

RESULTS

Of 26 003 patients, 12 283 (47.2%) and 13 720 (52.8%) patients had an initial CDI in 2018 and 2013, respectively. Among patients with data available, 5600 of 5959 (94.0%) patients in 2018 had documented diarrhea within 6 days before or after stool collection, and 5105 of 5710 (89.4%) patients in 2013 had documented diarrhea within 1 day before or after stool collection (symptoms beyond ± 1 day of stool collection were not abstracted in 2013). Fewer patients in 2018 compared with 2013 were ≥ 65 years old (45.5% vs 51.2%, $P < .0001$) and had hospital-onset (19.5% vs 24.7%) or LTCF-onset (10.3% vs 18.3%) CDI ($P < .0001$) ([Table 1](#)). A greater percentage of patients in 2018 than in 2013 had their initial CDI diagnosed by a laboratory that used NAAT (either alone or as part of a multistep algorithm) (90.9% vs 78.7%, $P < .0001$) and were treated with vancomycin (66.5% vs 32.0%, $P < .0001$) or fidaxomicin (1.3% vs 0.9%, $P = .04$).

Within 180 days of initial CDI, 2250 (18.3%) patients in 2018 had ≥ 1 recurrence, compared with 2889 (21.1%) patients in 2013 ($P < .0001$) ([Table 1](#)). The first recurrent episode was diagnosed at a different laboratory from the initial CDI for 28.5% and 31.2% of patients in 2018 and 2013, respectively.

A comparison of the subset of patients with rCDI in 2018 and 2013 is shown in [Supplementary Table 1](#).

As shown in [Supplementary Figure 1](#), the probability of rCDI was significantly different between 2018 and 2013 (log-rank test $P < .0001$). Site-specific Kaplan-Meier curves are depicted in [Supplementary Figure 2](#). The unadjusted 180-day rCDI rate was significantly lower in 2018 compared with 2013 for the overall sample and among the subsets of patients aged ≥ 65 years and with hospital- or LTCF-onset CDI ([Table 2](#)). The overall adjusted risk of 180-day rCDI was 16% lower in 2018 compared with 2013 ($P < .0001$) ([Supplementary Table 2](#)). In the sensitivity analysis, there was no difference in the adjusted risk of rCDI between the 2 years among toxin-positive cases ($P = .79$) ([Supplementary Table 3](#)).

Isolates from the initial CDI were available for 833 (6.8%) patients in 2018 and 1004 (7.3%) patients in 2013. Ribotype 027 was less frequently detected in 2018 compared with 2013 (8.3% vs 16.1%, $P < .0001$).

DISCUSSION

Our multisite study revealed a 16% reduction in the risk of 180-day rCDI in 2018 compared with 2013. Lower recurrence rates were observed among subsets of patients with known increased risk of recurrence, including those aged ≥ 65 years or with hospital-onset or LTCF-onset CDI. These findings indicate not only a significant reduction in illness but potentially substantial cost savings, given that healthcare costs attributable to rCDI have been estimated to be \$10 850 per case [10].

In a previous analysis, we did not find a change in the adjusted US burden estimates of first rCDI during 2011–2017 [3]. However, we previously did not censor for patient deaths, and we used an 8-week period instead of a 180-day period to assess for recurrence, which could have accounted for the difference.

We suspect a key driver of the decrease in rCDI in 2018 was the greater proportion of initial CDI cases in 2018 that were diagnosed with NAAT, which detects the presence of the toxin gene and not the toxin itself. Therefore, a larger proportion of patients in 2018 may have had mild disease or even colonization and would have had low risk of recurrence, resulting in less testing for rCDI. This hypothesis is supported by our sensitivity analysis, where we found no change in the 2013 and 2018 adjusted rCDI rates among the subset with toxin-positive initial CDI.

We cannot exclude the possibility that other factors might have also contributed to the overall decrease in rCDI, including a lower burden of initial hospital-onset and LTCF-onset CDI and fewer patients with ribotype 027 in 2018 than in 2013, as well as increased focus on reducing inappropriate diagnostic testing and improving antibiotic use [5, 11]. In addition, vancomycin and fidaxomicin were used more frequently in 2018 to

Table 1. Characteristics of Patients With Initial *Clostridioides difficile* Infection at 10 Emerging Infections Program Sites, 2018 and 2013

Characteristics	Overall N= 26 003	2018 Patients With Initial CDI n= 12 283	2013 Patients With Initial CDI n= 13 720	P Value
State	<.0001
California	1314 (5.1)	613 (5.0)	701 (5.1)	...
Colorado	6478 (24.9)	3356 (27.3)	3122 (22.8)	...
Connecticut	2237 (8.6)	981 (8.0)	1256 (9.2)	...
Georgia	6863 (26.4)	3213 (26.2)	3650 (26.6)	...
Maryland	2166 (8.3)	1020 (8.3)	1146 (8.4)	...
Minnesota	1236 (4.8)	661 (5.4)	575 (4.2)	...
New Mexico	1937 (7.5)	898 (7.3)	1039 (7.6)	...
New York	2065 (7.9)	851 (6.9)	1214 (8.9)	...
Oregon	334 (1.3)	74 (0.6)	260 (1.9)	...
Tennessee	1373 (5.3)	616 (5.0)	757 (5.5)	...
Sex02
Male	10 874 (41.8)	5227 (42.6)	5647 (41.2)	...
Female	15 129 (58.2)	7056 (57.5)	8073 (58.8)	...
Age, Years	<.0001
1–17	1367 (5.3)	771 (6.3)	596 (4.3)	...
18–44	4439 (17.1)	2252 (18.3)	2187 (15.9)	...
45–64	7576 (29.1)	3666 (29.9)	3910 (28.5)	...
≥65	12 621 (48.5)	5594 (45.5)	7027 (51.2)	...
Race ^a04
White	20 075 (77.2) [95% CI, 19 980 (76.6)–20 169 (77.8)]	9365 (76.2) [95% CI, 9292 (75.3)–9437 (77.1)]	10 710 (78.1) [95% CI, 10 637 (77.3)–10 783 (78.9)]	...
Black	4783 (18.4) [95% CI, 4669 (17.8)–4898 (19.0)]	2293 (18.7) [95% CI, 2203 (17.7)–2383 (19.6)]	2490 (18.1) [95% CI, 2417 (17.4)–2563 (18.9)]	...
Other	1145 (4.4) [95% CI, 1077 (4.1)–1213 (4.7)]	625 (5.1) [95% CI, 567 (4.5)–684 (5.6)]	520 (3.8) [95% CI, 496 (3.5)–544 (4.1)]	...
Epidemiologic classification of initial CDI ^b	<.0001
Community-associated	11 842 (45.5) [95% CI, 11 823 (45.0)–11 861 (46.1)]	6331 (51.5) [95% CI, 6319 (50.7)–6343 (52.4)]	5511 (40.2) [95% CI, 5493 (39.4)–5529 (40.9)]	...
Community-onset, healthcare-associated	4599 (17.7) [95% CI, 4573 (17.2)–4626 (18.1)]	2289 (18.6) [95% CI, 2277 (18.0)–2301 (19.3)]	2310 (16.8) [95% CI, 2292 (16.2)–2329 (17.4)]	...
Hospital-onset	5781 (22.2) [95% CI, 5762 (21.7)–5799 (22.7)]	2392 (19.5) [95% CI, 2382 (18.8)–2403 (20.2)]	3388 (24.7) [95% CI, 3377 (24.0)–3400 (25.4)]	...
Long-term care facility- onset	3781 (14.5) [95% CI, 3771 (14.2)–3791 (14.9)]	1271 (10.3) [95% CI, 1261 (9.8)–1280 (10.9)]	2510 (18.3) [95% CI, 2501 (17.7)–2519 (18.9)]	...
Diagnostic assay used by laboratories for initial CDI ^c	<.0001
Any NAAT use	21 957 (84.4)	11 165 (90.9)	10 792 (78.7)	...
Toxin EIA or cell cytotoxicity assay without routine NAAT use	2470 (9.5)	493 (4.0)	1977 (14.4)	...
Unknown	1576 (6.1)	625 (5.1)	951 (6.9)	...
Disease Severity or Complications of Initial CDI ^d
Occurrence of ileus, toxic megacolon, or colectomy	251/7247 (3.5)	133/2195 (6.1)	118/5052 (2.3)	<.0001
Hospitalization required among community-onset cases ^e	5301/13 691 (38.7)	2558/6556 (39.0)	2743/7135 (38.4)	.49
ICU admission within 6 days of stool collection	331/13 864 (2.4)	204/6717 (3.0)	127/7147 (1.8)	<.0001
Treatment of Initial CDI ^d
Any treatment	10 680/11 135 (95.9)	5492/5747 (95.6)	5188/5388 (96.3)	.05
Any oral or rectal vancomycin	5503/11 073 (49.7)	3778/5685 (66.5)	1725/5388 (32.0)	<.0001
Metronidazole only	4985/11 073 (45.0)	1624/5685 (28.6)	3361/5388 (62.4)	<.0001
Any fidaxomicin	122/11 073 (1.1)	74/5685 (1.3)	48/5388 (0.9)	.04

Table 1. Continued

Characteristics	Overall N= 26 003	2018 Patients With Initial CDI n= 12 283	2013 Patients With Initial CDI n= 13 720	P Value
Bezlotoxumab (adjunctive therapy)	2/11 073 (0.02)	2/5685 (0.04)	—	—
CDI Recurrence Within 180 Days
Any recurrence	5139 (19.8)	2250 (18.3)	2889 (21.1)	<.0001
Median days from initial CDI to first recurrence (IQR)	35 (23–61)	37 (25–66)	34 (23–58)	.0001
Single recurrence only	3741 (14.4)	1675 (13.6)	2066 (15.1)	.001
Multiple recurrences (≥2 CDI recurrences)	1398 (5.4)	575 (4.7)	823 (6.0)	<.0001
Death Within 180 Days
Died at any time	4636 (16.8)	1810 (14.7)	2553 (18.6)	<.0001
Median days from initial CDI to death (IQR)	36 (13–82)	38 (13–85)	34 (13–80)	.13
Died without CDI recurrence	3568 (13.7)	1535 (12.5)	2033 (14.8)	<.0001
Died after having ≥1 CDI recurrence	795 (3.1)	275 (2.2)	520 (3.8)	<.0001

Abbreviations: CDI, *Clostridioides difficile* infection; CI, confidence interval; EIA, enzyme immunoassay; ICU, intensive care unit; IQR, interquartile range; NAAT, nucleic acid amplification test. NOTE: Data are presented as no. (%) unless otherwise indicated. Missing responses to race and epidemiologic classification were estimated through multiple imputation. Weights were applied to incorporate the sampling design applied at the Georgia and Colorado sites.

^aRace was statistically imputed for 20.8% and 23.2% of the observed patients with initial CDI who underwent a medical-record review in 2018 and 2013, respectively.

^bEpidemiologic classification was statistically imputed for 1.6% and 0.7% of the observed patients with initial CDI who underwent a medical record review in 2018 and 2013, respectively.

^cThe 3 categories of diagnostic assays used by laboratories are mutually exclusive. Any NAAT includes cases with positive NAAT result or diagnosed by laboratories that routinely used NAAT alone or as part of a multistep algorithm. Toxin EIA or cell cytotoxicity assay includes cases diagnosed by laboratories that used either assay alone or in combination with glutamate dehydrogenase but did not routinely use NAAT. Unknown includes cases not known to have a positive NAAT result and were diagnosed by laboratories with unspecified or no routine testing method.

^dAny patient with missing information was excluded from the denominator.

^eIncludes community-associated CDI and community-onset healthcare facility-associated CDI.

treat initial CDI. Although both drugs can improve clinical response, only fidaxomicin has been shown to reduce risk of recurrence [12–14]. However, only 1.3% of patients were treated with fidaxomicin, which suggests that it was not a large driver of the decrease in rCDI. Other treatment factors, such as the decreasing use of metronidazole for initial CDI treatment and the growing use of oral vancomycin prophylaxis for secondary CDI prevention [15, 16], might have also contributed to the decrease in rCDI in 2018. Finally, we did not have access to any data before 2011, and it is possible that some patients classified as having an initial CDI episode in 2013 may have actually been experiencing a recurrence and may therefore be more likely to have a subsequent recurrence. Although less likely, this might be one explanation for the higher rCDI rate in 2013.

A strength of our study is that we accounted for patient mortality when determining recurrence rates. Another strength is that cases were identified through population-based surveillance, including CDI diagnosed in inpatient and outpatient settings, which allowed us to identify first recurrences that were diagnosed at a different laboratory from the initial episode in one third of the patients. In addition, by using a longer follow-up period than the 8-week period used for public health surveillance, our study reflected the real-world experience where a distinction between a subsequent incident versus recurrent episode is less clinically relevant.

Our study had several limitations. First, because we used only a laboratory diagnosis to define CDI, some patients may have been colonized or had a positive result for a test of cure rather than a true recurrence, particularly in 2013 when testing to document cure was more commonly performed even though it is not recommended [5]. To address this concern, we performed a chart review of the first recurrent episode for a subset of patients with initial CDI in 2013 who had undergone an initial comprehensive chart review. Approximately 22% of these patients were missing clinical data regarding their first recurrent episode (eg, missing chart); among the remaining patients with data available, all had diarrhea associated with their recurrent episode, suggesting that most of the positive recurrent test results in 2013 were likely true recurrent disease. Second, due to the higher frequency of NAAT testing in 2018, initial CDI cases identified in 2018 might not accurately reflect true disease with associated morbidity and mortality. However, we found that CDI-related complications (ileus, toxic megacolon, or colectomy), hospitalizations, and intensive-care unit admissions did not occur less frequently among patients in 2018 than in 2013 (Table 1), suggesting that a portion of the patients with initial CDI in 2018 did in fact have clinically significant disease. Third, we did not systematically capture positive tests of patients tested outside the catchment area, which might have led to an underestimation of rCDI. Fourth, the sampling of cases in Colorado and Georgia and missing values for race in the

Table 2. Unadjusted Age-, Sex-, Race-, and Epidemiologic Class-Specific *Clostridioides difficile* Recurrence Within 180 Days of Initial Diagnosis Among Patients in 10 Emerging Infections Program Sites, 2018 and 2013

Characteristic	2018		2013		2018 vs 2013	
	Rate ^a	95% CI	Rate ^a	95% CI	Rate Ratio	95% CI
Overall	1.32	1.27–1.38	1.69	1.63–1.75	0.79	.73–.85
Sex
Male	1.32	1.24–1.41	1.61	1.52–1.70	0.82	.73–.93
Female	1.32	1.25–1.40	1.75	1.67–1.83	0.77	.69–.85
Age, Years
1–17	0.87	.87–.88	1.11	1.11–1.11	0.80	.61–1.04
18–44	0.91	.80–1.02	0.96	.86–1.06	0.95	.76–1.18
45–64	1.19	1.09–1.29	1.38	1.28–1.48	0.86	.74–1.00
≥65	1.72	1.61–1.82	2.30	2.19–2.41	0.76	.69–0.84
Race ^b
White	1.40	1.32–1.48	1.79	1.68–1.89	0.79	.72–.86
Black	1.26	1.06–1.45	1.50	1.29–1.71	0.80	.64–.99
Other	1.09	0.79–1.39	1.08	.44–1.72	0.85	.56–1.31
Epidemiologic Classification of Initial CDI ^c
Community-associated	1.12	1.05–1.19	1.19	1.12–1.26	0.94	.84–1.07
Community-onset, healthcare-associated	1.84	1.68–1.99	1.80	1.65–1.95	1.00	.85–1.18
Hospital-onset	1.07	.94–1.19	1.71	1.57–1.84	0.63	.52–.76
Long-term care facility- onset	2.15	1.90–2.40	3.23	3.00–3.46	0.68	.57–.82

Abbreviations: CDI, *Clostridioides difficile* infection; CI, confidence interval.

NOTE: Missing responses to race and epidemiologic classification were estimated through multiple imputation. Weights were applied to incorporate the sampling design applied at the Georgia and Colorado sites.

^aDefined as number of cases per 1000 patient-days at risk for first CDI recurrence.

^bRace was statistically imputed for 20.8% and 23.2% of the observed patients with initial CDI who underwent a medical record review in 2018 and 2013, respectively.

^cEpidemiologic classification was statistically imputed for 1.6% and 0.7% of the observed patients with initial CDI who underwent a medical record review in 2018 and 2013, respectively.

medical records of one fifth of the patients could have increased uncertainty in our estimates. Finally, the convenience sample of isolates might not be representative of the overall prevalence of ribotype 027.

CONCLUSIONS

As the epidemiology of CDI continues to evolve and novel therapies are introduced [17], continued monitoring of rCDI is needed to guide prevention and treatment efforts.

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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