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Impact of Updated Clinical Practice Guidelines on Outpatient Treatment for *Clostridioides difficile* Infection and Associated Clinical Outcomes

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Background. The 2017 Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) *Clostridium (Clostridioides) difficile* infection (CDI) guideline update recommended treatment with fidaxomicin or vancomycin for CDI. We aimed to examine outpatient CDI treatment utilization before and after the guideline update and compare clinical outcomes associated with fidaxomicin versus vancomycin use.

Methods. A pre-post study design was employed using Medicare data. CDI treatment utilization and clinical outcomes (4- and 8-week sustained response, CDI recurrence) were compared between patients indexed from April–September 2017 (preguideline period) and those indexed from April–September 2018 (postguideline period). Clinical outcomes associated with fidaxomicin versus vancomycin were compared using propensity score–matched analyses.

Results. From the pre- to postguideline period, metronidazole use decreased (initial CDI: 81.2% to 53.5%; recurrent CDI: 49.7% to 27.6%) while vancomycin (initial CDI: 17.9% to 44.9%; recurrent CDI: 48.1% to 66.4%) and fidaxomicin (initial CDI: 0.87% to 1.63%; recurrent CDI: 2.2% to 6.0%) use increased significantly ($P < .001$ for all). However, clinical outcomes did not improve. In propensity score–matched analyses, fidaxomicin versus vancomycin users had 4-week sustained response rates that were higher by 13.5% (95% confidence interval [CI], 4.0%–22.9%; $P = .0058$) and 30.0% (95% CI, 16.8%–44.3%; $P = .0002$) in initial and recurrent CDI cohorts, respectively. Recurrence rates were numerically lower for fidaxomicin in both cohorts.

Conclusions. Vancomycin use increased and metronidazole use decreased after the 2017 guideline update. Fidaxomicin use increased but remained low. Improved outcomes associated with fidaxomicin relative to vancomycin suggest benefits from its greater use in Medicare patients.

Keywords. *Clostridioides difficile* infection; fidaxomicin; Medicare; metronidazole; vancomycin.

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in adults [1–3] and is associated with significant morbidity, mortality, and healthcare utilization and costs [4–7]. Historically, the standard of care for treating CDI was limited to vancomycin or metronidazole [8]. Fidaxomicin (Difcid), was approved by the United States (US) Food and Drug Administration in May 2011, offering a new treatment option [9, 10]. As evidence on CDI treatments accumulated, major changes in CDI treatment guidelines

were introduced. In the 2017 update to the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) clinical practice guidelines, metronidazole was demoted from a first-line agent for nonsevere CDI [3]. Vancomycin and fidaxomicin were recommended as first-line agents for initial or recurrent CDI episodes. The guidelines were recently updated in June 2021 with fidaxomicin as the sole recommended first-line agent and vancomycin as an alternative agent [11].

Despite these guideline changes, limited data exist on their impact on treatment utilization and clinical outcomes. Clancy et al [12] found that use of vancomycin and fidaxomicin increased considerably whereas metronidazole use decreased in the 18 months following publication of the 2017 guidelines update compared to the 18 months before. Gentry et al [13] did not find an improvement in clinical outcomes after the shift away from metronidazole as the preferred treatment option. However, clinical outcomes were not examined in this study. Furthermore, no study has exclusively examined the impact in elderly patients, who are disproportionately affected by CDI [14].

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Using real-world claims data for elderly Medicare beneficiaries with CDI treated in the outpatient setting, we aimed to (1) evaluate changes in CDI treatment utilization and clinical outcomes before versus after the 2017 IDSA guidelines update among patients with initial and recurrent CDI and (2) compare clinical outcomes in elderly Medicare beneficiaries receiving fidaxomicin versus vancomycin as first-line treatment for initial and recurrent CDI. Study findings should help inform CDI disease management strategies in the outpatient setting and serve as a useful benchmark while we wait for data to accumulate to evaluate the more recent 2021 IDSA CDI guideline update.

METHODS

Study Design and Data Source

A pre-post study design was employed for the first study aim. For the second study aim, we conducted a propensity score (PS)-matched analysis of the pooled pre- and postguideline cohorts treated with fidaxomicin versus vancomycin. The study used 2016–2018 claims data from the Medicare program, the largest source of health insurance for the elderly in the US (additional background on the Medicare data is available in the [Supplementary Materials](#)). The data included claims for patients with fee-for-service Medicare Part A and B-covered medical claims as well as Medicare Part D prescription drug claims.

Study Samples

[Figure 1](#) shows the schematic used to identify the base sample of initial CDI episode patients from which the recurrent CDI episode sample was generated. Subjects were selected based on the first outpatient claim with a CDI diagnosis (*International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]* code A047.xx) between 1 April 2017 and 30 September 2017 (preguideline cohort) and between 1 April 2018 and 30 September 2018 (postguideline cohort). The first diagnosis identified was classified as the initial CDI diagnosis. The postguideline period duration was limited and only incorporated the year 2018 since those were the latest data available at the time of the study. Identical April–September time periods in the pre- and postguideline cohorts correspond to those used by Furuya-Kanamori et al [15] and were intended to capture seasonality in CDI infection rates.

Given the limitations inherent with administrative claims data, several sample inclusion/exclusion criteria were necessary to ensure all patients included had complete data available to conduct the planned analyses, had a new episode of CDI, and had clear evidence of receiving a CDI treatment so as to allow the assessment of clinical outcomes using claims-based definitions. Hence, sample selection for the pre- and postguideline cohorts was restricted to patients with outpatient claims because inpatient Medicare claims do not list medications needed to ascertain CDI treatment regimens. Dates for the first

observed outpatient CDI claims were designated as index dates from which clinical outcomes were tracked. Patients were included if they were at least 66 years of age and had continuous Medicare fee-for-service coverage for 12 months before and 3 months after their index dates (or until death). Additional selection criteria included absence of CDI in the 12 weeks prior to index date (to ensure initial CDI episode) and evidence of CDI prescription fill (vancomycin, fidaxomicin, or metronidazole) during follow-up. Patients were excluded if they were hospitalized between the index date and first CDI prescription fill date, had evidence of first CDI prescription fill occurring >7 days after index CDI diagnosis date, received multiple prescriptions for the same or different CDI treatments on the first CDI prescription fill date, or received >15 or <10 days' supply on their first CDI prescription fill ([Supplementary Tables 1 and 2](#)). Preguideline observations were excluded for patients selected in both the pre- and postguideline cohorts to avoid repeated observations ([Supplementary Table 1](#)).

From the pre- and postguideline cohorts of patients with an initial CDI episode as outlined above, we selected a subset of patients with 4-week CDI recurrence (definition shown in “Outcome Variables”) and applied additional selection criteria (see [Supplementary Tables 3 and 4](#) for additional selection criteria) to derive the recurrent CDI pre- and postguideline cohorts. For the second study aim (the PS-matched analysis), we limited our analysis to vancomycin and fidaxomicin users and pooled them across the pre- and postguideline cohorts to maximize sample sizes.

Outcome Variables

Outcomes were assessed over a 3-month follow-up period for both the pre- and postguideline cohorts. These included first CDI prescription filled (ie, metronidazole, vancomycin, or fidaxomicin) on or after the index date and 4-week and 8-week sustained response and CDI recurrence rates. Sustained response was defined as having evidence of clinical resolution (no additional CDI treatment or hospitalization with a diagnosis of CDI before or within 1 day after the supply of the first CDI prescription is exhausted) and no evidence of CDI recurrence. CDI recurrence was defined as any evidence of a new CDI treatment or hospitalization with a diagnosis of CDI within 4 weeks (or 8 weeks) of the date of completion of the index CDI prescription among patients with clinical resolution.

Other Variables

Covariates captured included demographic characteristics (age, sex, race/ethnicity, census region, and metropolitan status), Medicare Part D plan coverage, low-income subsidy status, plan type, CDI-related costs in the 12 months before the index date, and clinical factors believed to influence CDI drug selection and recurrence rates. The clinical variables included CDI history, evidence of compromised immunity, Elixhauser

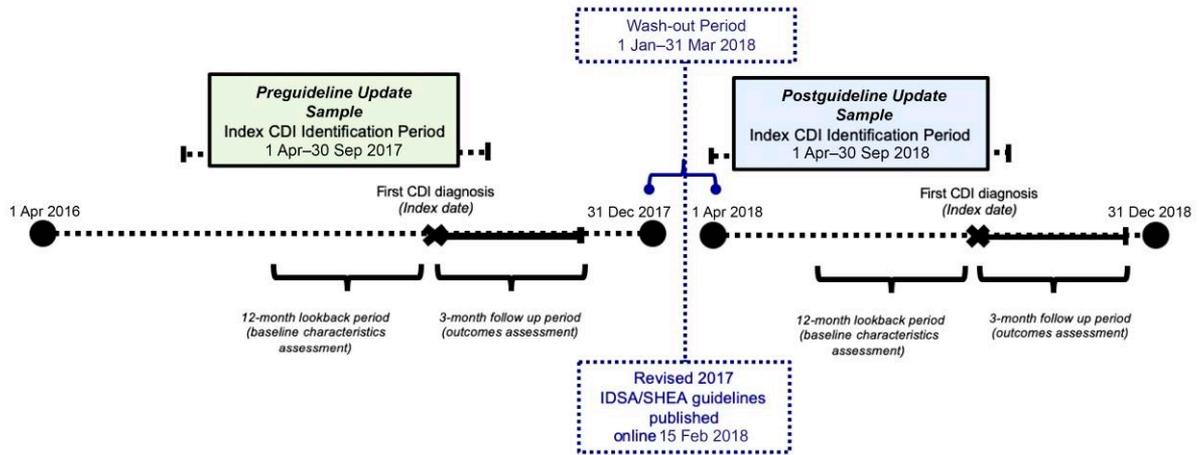


Figure 1. Sample selection schematic. Abbreviations: CDI, *Clostridioides difficile* infection; IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America.

comorbidities, renal impairment, hepatic impairment, Crohn disease/ulcerative colitis, solid tumors, and medication use (antibiotics, gastric acid suppressors, laxatives, and nonsteroidal anti-inflammatory drugs).

Statistical Analysis

The first study aim entailed descriptive and multivariable logistic regression analyses comparing rates of first-line CDI treatment utilization, sustained response, and CDI recurrence in the pre- and postguideline cohorts, in the initial and recurrent CDI samples. The key independent variable of interest in the logistic regression models was patient membership in the post- (vs pre-) guideline cohort. The models also included the above-listed sociodemographic and clinical covariates that may be associated with CDI drug selection, sustained response, and recurrence rates (see [Supplementary Tables 5–8](#) for a detailed list of covariates).

For the second aim, PS-matched analyses were used to compare clinical outcomes between fidaxomicin and vancomycin users. Separate PS models were estimated for the initial and recurrent CDI samples. Multivariable logistic regression was used to estimate the propensity for being a fidaxomicin user (vs vancomycin user) as a function of various combinations of demographic and clinical variables designed to achieve the best balance between the groups in the combined initial CDI episode sample and recurrent episode sample (see [Supplementary Tables 9 and 10](#) for detailed list of covariates). After generating the propensity scores, fidaxomicin users were matched 1:1 with vancomycin users using a nearest-neighbor matching approach with caliper widths set at 0.20 of the standard deviation of the logit of the propensity scores. Plots of the distribution of the propensity scores in the fidaxomicin and vancomycin groups were assessed to evaluate

common support before and after matching ([Supplementary Figures 1–4](#)). Balance between the matched samples was assessed based on whether the Cohen standardized difference (D) was <10 . We were unable to achieve acceptable balance on some covariates (ie, Cohen $D >10$); we adjusted for this remaining imbalance by estimating the clinical outcomes using logistic regressions among the PS-matched samples that included only the unbalanced variables (ie, Part D benefit type in the initial CDI episode PS-matched sample; sex, region, and Part D benefit type for recurrent CDI episode PS-matched sample) as covariates in the regression models.

RESULTS

Changes in Treatment Utilization and Clinical Outcomes Before and After Guideline Update

Initial CDI Sample

There were 7389 and 7746 patients with an initial CDI episode in the pre- and postguideline periods, respectively ([Supplementary Tables 1 and 2](#)). Both cohorts were similar in characteristics ([Table 1](#)). Both cohorts were primarily White and primarily female. Approximately 40% of both cohorts were aged 66–74 years and $>50\%$ of both cohorts had ≥ 5 Elixhauser comorbidities. Approximately two-thirds of both cohorts had exposure to moderate to high-CDI-risk antibiotics. Significant proportions had renal impairment and cancer. The top panel in [Figure 2](#) shows CDI treatment utilization by choice of first-line agent in the pre- and postguideline cohorts. Preguideline, 81.2% of CDI patients were treated with metronidazole, which dropped to 53.5% in the postguideline period (relative change [RC], -34.1% ; $P < .001$). Most of the 27.7 percentage point decline in metronidazole shifted to vancomycin (17.9% [preguideline period] to 44.9% [postguideline period]; RC, $+150.2\%$; $P < .001$). Fidaxomicin use (0.87% in the preguideline period) increased

Table 1. Sample Characteristics by First-Line *Clostridioides difficile* Infection (CDI) Treatment Pre- and Post-Guideline Update, Among Medicare Beneficiaries With an Initial or Recurrent CDI Episode

Characteristic	Initial CDI Episode		Recurrent CDI Episode	
	Pre (n = 7389)	Post (n = 7746)	Pre (n = 779)	Post (n = 837)
Age				
66–74	41.2%	41.4%	42.7%	40.0%
75–84	37.7%	39.4%	38.5%	42.7%
≥85	21.1%	19.2%	18.7%	17.3%
Sex				
Male	32.3%	32.0%	32.5%	34.5%
Female	67.7%	68.0%	67.5%	65.5%
Race				
White	92.1%	93.1%	93.6%	95.2%
Black	3.8%	3.4%	3.3%	2.6%
Hispanic	1.0%	0.9%	a	a
Other	3.2%	2.6%	a	a
Census region				
Northeast	19.5%	20.3%	21.7%	19.4%
Midwest	27.9%	27.5%	30.2%	28.7%
South	34.6%	34.2%	31.2%	34.2%
West	18.1%	18.0%	16.9%	17.8%
Metropolitan status				
Urban	76.8%	77.0%	77.7%	76.5%
Rural	23.2%	23.0%	22.3%	23.5%
Part D LIS status				
Full or partial LIS	21.5%	19.9%	19.5%	15.8%
Non-LIS	78.5%	80.1%	81.5%	84.2%
Part D drug benefit type				
Basic alternative	24.4%	24.7%	26.1%	24.5%
Enhanced alternative	44.5%	45.4%	43.8%	44.7%
Defined standard benefit	15.4%	15.3%	13.5%	14.6%
Other	15.7%	14.6%	16.7%	16.2%
No. of Elixhauser comorbidities in the 12 mo preindex				
0	2.5%	2.6%	4.7%	2.5%
1–2	15.7%	14.7%	18.1%	17.7%
3–4	21.2%	21.4%	24.6%	22.3%
≥5	60.7%	61.3%	52.5%	57.5%
Recurrent CDI risk factors				
CDI within past 6 mo	4.1%	4.2%	3.9%	4.2%
Compromised immunity in the 12 mo preindex ^b	27.2%	29.4%	24.8%	28.2%
No. of recurrent CDI risk factors^c				
1	70.2%	68.0%	72.5%	68.9%
2	28.2%	30.3%	>26.0% ^a	29.7%
3	1.6%	1.6%	a	1.3%
Key comorbidities in the 12 mo preindex				
Renal impairment	28.1%	28.4%	26.1%	27.5%
Hepatic impairment	12.4%	13.9%	87.3%	87.8%
Crohn disease or ulcerative colitis	5.0%	5.5%	4.7%	4.5%
Cancer	21.9%	22.7%	20.3%	24.3%
Solid tumor	19.9%	20.3%	18.5%	20.9%
Hematologic malignancy	3.4%	3.8%	3.2%	4.7%
HSCT or SOT	2.5%	2.8%	2.6%	2.6%
Recent history of medication use in the 3 mo preindex				
Antibiotics	68.2%	67.8%	73.3%	70.4%
Moderate- to high-risk antibiotics	63.9%	63.3%	69.7%	67.0%
Low-risk antibiotics	4.3%	4.5%	3.6%	3.3%
Gastric acid suppression	48.8%	48.9%	46.2%	47.9%

Table 1. Continued

Characteristic	Initial CDI Episode		Recurrent CDI Episode	
	Pre (n = 7389)	Post (n = 7746)	Pre (n = 779)	Post (n = 837)
Laxatives	6.2%	6.5%	5.8%	7.3%
NSAIDs	23.0%	24.1%	21.4%	23.7%
Hospitalization				
All-cause hospitalization in the 12 mo preindex	49.1%	48.7%	46.0%	46.0%
CDI-related hospitalization in the 12 mo preindex	3.7%	4.0%	3.2%	3.2%
Healthcare costs, mean (SD)				
All-cause costs in the 12 mo preindex	\$43 908 (\$58 233)	\$43 047 (\$54 526)	\$37 839 (\$50 002)	\$40 340 (\$54 712)
CDI-related costs in the 12 mo preindex	\$1231 (\$8645)	\$1172 (\$6770)	\$875 (\$5516)	\$1223 (\$8595)

Abbreviations: CDI, *Clostridioides difficile* infection; HSCT, hematopoietic stem cell transplant; LIS, low-income subsidy; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SOT, solid organ transplant.

^aPer Centers for Medicare and Medicaid Services policy, results based on cell sizes <11 and/or exact values for cell sizes ≥11 that may permit calculation of a cell size <11 cannot be displayed.

^bPatients were classified as having compromised immunity if they were a transplant recipient or had evidence of human immunodeficiency virus/AIDS, immunosuppressive agent use, chemotherapy use, or hematological malignancy.

^cAge ≥65 years, CDI within past 6 months, immunocompromised.

by 0.8 percentage points (RC, +87.8%; $P < .001$), but its overall utilization rate remained low in the postguideline period (1.63%).

Descriptive statistics for the clinical outcomes associated with CDI treatment in the pre- and postguideline periods are presented in Table 2. Over the pre/post periods, 4-week sustained response rates dropped 2.1 percentage points (from 56.9% to 54.8%; $P = .01$) and 8-week sustained response dropped 3.1 percentage points (from 52.9% to 49.8%; $P = .0002$). Together with declines in sustained response, CDI recurrence rates rose over the pre/post period by 2.8 percentage points at 4 weeks and 3.9 points at 8 weeks, both statistically significant at $P < .05$. Multivariable logistic regressions confirmed these descriptive findings (Supplementary Tables 5 and 6). For instance, even after adjustment the odds of fidaxomicin or vancomycin use relative to metronidazole use were nearly 4-fold higher (odds ratio [OR], 3.91 [95% confidence interval {CI}, 3.62–4.21]) in the postguideline versus preguideline period. Similarly, even after adjustment, the odds of having a 4-week sustained response were significantly lower (OR, 0.93 [95% CI, .87–.99]) and the odds of having a 4-week CDI recurrence were significantly higher (OR, 1.13 [95% CI, 1.05–1.22]) in the post- versus preguideline period.

Recurrent CDI Sample

There were 779 and 837 people in our recurrent CDI sample in the pre- and postguideline periods, respectively (Supplementary Tables 3 and 4). As with the initial CDI episode samples, there was little change in characteristics between the pre- and postguideline cohorts (Table 1). Relative to the initial CDI sample, the pre- and postguideline cohorts in the recurrent episode sample were somewhat younger and exhibited slightly lower prevalence of Elixhauser comorbidities and CDI risk factors but were far more likely to suffer from hepatic impairment. In fact, >87% of all recurrent patients had evidence of hepatic impairment. The bottom panel of Figure 2 reports drug utilization rates for these patients.

As in the initial CDI sample, the largest fraction of recurrent patients used metronidazole (49.7%) in the preguideline period, virtually the same as for vancomycin users (48.1%). Postguideline, metronidazole use dropped by from 49.7% to 27.6% (RC, –44.4%; $P < .001$), whereas vancomycin use increased from 48.1% to 66.4% (RC, +38.0%; $P < .001$). Fidaxomicin use increased by 3.8 percentage points (from 2.2% to 6.0%; RC, +173.7%; $P < .001$) and its overall use remained low in the postguideline period.

Sustained response rates were lower in the postguideline period (52.2% [4 weeks] and 46.7% [8 weeks]) compared to the preguideline period (57.4% [4 weeks] and 53.3% [8 weeks]) in the recurrent CDI sample (Table 2). For the CDI recurrence outcome, the increases were 2.3 percentage points at 4 weeks (from 32.6% to 34.9%) and 4.3 points (from 37.4% to 41.7%) at 8 weeks, but neither result was statistically significant. Multivariable logistic regression analyses confirmed these descriptive findings (Supplementary Tables 7 and 8). For instance, even after adjustment, the odds of fidaxomicin or vancomycin use relative to metronidazole use were significantly higher (OR, 1.75 [95% CI, 1.37–2.23]) in the postguideline versus preguideline period. Similarly, even after adjustment, the odds of having a 4-week sustained response were significantly lower (OR, 0.77 [95% CI, .62–.96]) and the odds of having a 4-week CDI recurrence were not significantly different (OR, 1.24 [95% CI, .96–1.60]) in the postguideline versus preguideline period.

Comparison of Clinical Outcomes for Fidaxomicin Versus Vancomycin Initial CDI Episode Sample

There were 190 fidaxomicin users and 4800 vancomycin users before PS matching in our initial CDI episode sample. A 1:1 match was found for all 190 fidaxomicin users. Patient characteristics for the matched sample in the PS analysis (190 subjects in both the fidaxomicin and vancomycin groups) are presented in Supplementary Table 9. Key findings from these logistic

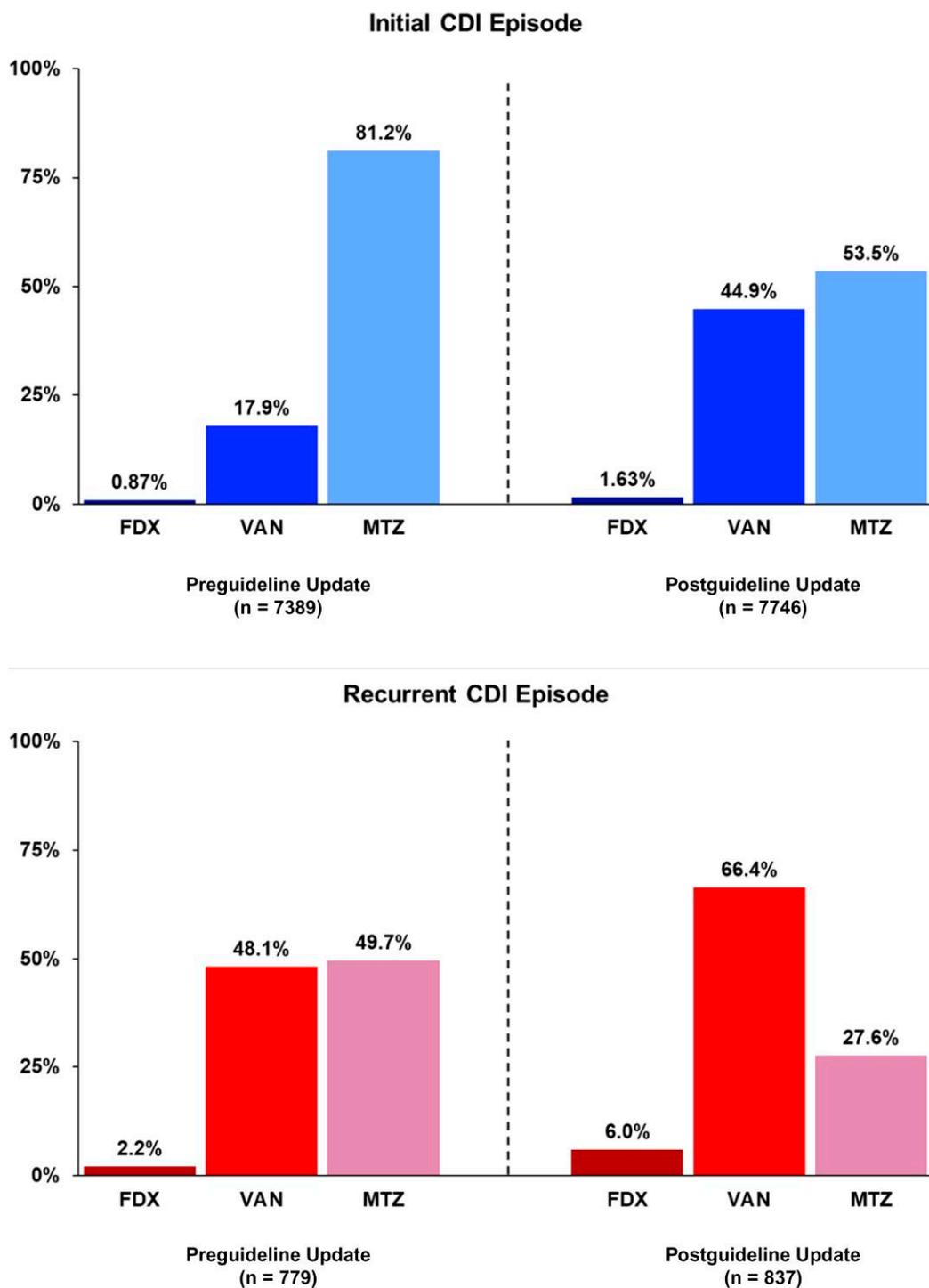


Figure 2. First-line use of *Clostridioides difficile* infection (CDI) treatments, pre- vs post-guideline update, among Medicare beneficiaries with an initial or recurrent CDI episode. $P < .001$ for all results, based on χ^2 test. Abbreviations: CDI, *Clostridioides difficile* infection; FDX, fidaxomicin; MTZ, metronidazole; VAN, vancomycin.

regression models are shown in Table 3. For patients in their initial CDI episode, fidaxomicin was associated with a 4-week sustained response that was 13.5 percentage points higher compared to vancomycin (71.7% vs 58.2%; $P = .0058$) and a 8-week

sustained response rate 13.2 percentage points higher (63.2% vs 50.0%; $P = .0114$) compared to vancomycin (Table 3). Rates of CDI recurrence for patients in their initial CDI episode were numerically lower for fidaxomicin in both the 4-week (20.6%

Table 2. Unadjusted Clinical Outcomes, Pre- Versus Post-Guideline Update, Among Medicare Beneficiaries With Initial or Recurrent CDI Episode

Outcome	Pre		Post		P Value
	No.	(%)	No.	(%)	
Initial CDI episode					
All patients with initial CDI episode	7389	...	7746	...	
Sustained response (4 wk)	4205	(56.9)	4247	(54.8)	.01
Sustained response (8 wk)	3907	(52.9)	3861	(49.8)	.0002
Among patients with a clinical resolution	6097	...	6415	...	
CDI recurrence (4 wk)	1892	(31.0)	2168	(33.8)	.001
CDI recurrence (8 wk)	2190	(35.9)	2554	(39.8)	<.0001
Recurrent CDI episode					
All patient with recurrent CDI episode	779	...	837	...	
Sustained response (4 wk)	447	(57.4)	437	(52.2)	.0369
Sustained response (8 wk)	415	(53.3)	391	(46.7)	.0084
Among patients with a clinical resolution	663	...	671	...	
CDI recurrence (4 wk)	216	(32.6)	234	(34.9)	.3756
CDI recurrence (8 wk)	248	(37.4)	280	(41.7)	.1064

CDI recurrence was calculated only among patients with evidence of clinical resolution. P values are based on χ^2 test.

Abbreviation: CDI, *Clostridioides difficile* infection.

[fidaxomicin] vs 29.0% [vancomycin]) and 8-week (31.3% [fidaxomicin] vs 38.9% [vancomycin]) comparisons, but the results were not statistically significant.

Recurrent CDI Episode Sample

There were 67 fidaxomicin users and 931 vancomycin users before PS matching in our initial CDI episode sample. A 1:1 match was found for all 67 fidaxomicin users. Patient characteristics for the best-matched sample in the PS analysis (67 subjects in both the fidaxomicin and vancomycin arms) are presented in [Supplementary Table 10](#). In the recurrent CDI episode sample, about 66% of patients in the fidaxomicin group and 60% of patients in the vancomycin group received prior vancomycin therapy for their initial CDI episode. For patients receiving fidaxomicin in their recurrent CDI episode, the 4-week sustained response rate was 30.0 percentage points higher (75.1% vs 45.1%; $P = .0002$) and the 8-week sustained response rate was 27.6 percentage points higher (66.5% vs 38.9%; $P = .0012$) compared to those receiving vancomycin ([Table 3](#)). Rates of CDI recurrence were numerically lower for fidaxomicin in both the 4-week and 8-week comparisons, but the results were not statistically significant (which also did not permit reporting of the absolute rates per Centers for Medicare and Medicaid Services [CMS] policy).

DISCUSSION

This study provides a comprehensive evaluation of the impact of the 2017 IDSA/SHEA guideline update on drug utilization and clinical outcomes, and the real-world comparative

effectiveness of the first-line agents (fidaxomicin and vancomycin) recommended in this update, in the elderly Medicare population. Our findings show that this guideline update led clinicians to shift their choice of first-line agent from metronidazole to vancomycin and substantially less so to fidaxomicin. The shift was dramatic with relative rate declines in metronidazole use of 34% for initial CDI episodes and 42% for recurrent CDI episodes. We also found no corresponding improvement in sustained response and CDI recurrence in either initial or recurrent CDI episodes after the guideline publication. Finally, we found better clinical outcomes in patients receiving fidaxomicin compared to vancomycin in both the initial and recurrent CDI setting.

Our findings on the changes in CDI treatment utilization after the 2017 guideline update in the Medicare population have been reported in other patient populations. Clancy et al [12] used US antibiotic prescription claims data across multiple insurance segments and found that vancomycin and fidaxomicin use increased, whereas use of metronidazole decreased in the 18 months following publication of the 2017 guideline update compared to 18 months before. While the Clancy et al study did not examine clinical outcomes, our study found that the decrease in metronidazole use and an increase in the utilization of vancomycin, one of the first-line treatments recommended in the 2017 guideline update, was not accompanied by an improvement in clinical outcomes. There are 3 potential reasons for these mixed findings. First, in post-hoc analysis ([Supplementary Figure 5](#)), we found that the sustained response rates and recurrence rates associated with vancomycin were very similar to those associated with metronidazole in our real-world study sample of elderly Medicare patients. Second, fidaxomicin, found to have significantly better clinical outcomes, had utilization rates that were too low to impact changing population-level clinical outcomes between the pre- and postguideline periods. In other words, had there been a greater shift to fidaxomicin prescribing after the 2017 guideline update, we might have observed improved outcomes for the study sample as a whole in the postguideline period. Third, the CDI cases included in these analyses were nonsevere by virtue of needing to limit the population to patients treated in the outpatient setting based on prescription data availability. The greatest benefit of vancomycin over metronidazole is for initial cure of more severe CDI episodes [16].

Our findings suggesting that fidaxomicin was superior to vancomycin in achieving sustained response is supported in prior literature [9, 10, 17–20]. Strikingly, the absolute differences in the clinical outcomes observed in our real-world study were quite similar to those reported in the fidaxomicin randomized trials [9, 10]. For example, the difference in 4-week sustained response rates between fidaxomicin (71.7%) and vancomycin (58.2%) in the initial CDI episode sample was 13.5% in our real-world study and 10.5% in the fidaxomicin randomized

Table 3. Clinical Outcomes Among Propensity Score–Matched Medicare Beneficiaries With *Clostridioides difficile* Infection (CDI) Initiating Fidaxomicin Versus Vancomycin for an Initial or Recurrent CDI Episode With Regression Controlling for Unbalanced Variables

Outcome	Fidaxomicin	Vancomycin	Difference, % (95% CI)	P Value (Clustered) ^a
Initial CDI episode				
All patients with initial CDI episode	n = 190	n = 190		
Sustained response (4 wk)	71.7%	58.2%	13.5 (4.0–22.9)	.0058
Sustained response (8 wk)	63.2%	50.0%	13.2 (3.1–23.4)	.0114
Among patients with a clinical resolution	n = 141	n = 141		
CDI recurrence (4 wk)	20.6%	29.0%	–8.4 (–18.4 to 1.6)	.101
CDI recurrence (8 wk)	31.3%	38.9%	–7.6 (–18.9 to 3.7)	.1893
Recurrent CDI episode				
All patients with recurrent CDI episode	n = 67	n = 67		
Sustained response (4 wk)	75.1%	45.1%	30.0 (16.8–44.3)	.0002
Sustained response (8 wk)	66.5%	38.9%	27.6 (12.0–43.2)	.0012
Among patients with a clinical resolution	n = 40	n = 40		
CDI recurrence (4 wk)	^b	^b	–10.3 (–28.9 to 6.9)	.292
CDI recurrence (8 wk)	^b	^b	–13.3 (–35.1 to 8.8)	.255

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

^aP values are based on logistic regressions with robust standard errors for clustering by matched pair.

^bPer Centers for Medicare and Medicaid Services policy, results based on cell sizes <11 and/or exact values for cell sizes ≥11 that may permit calculation of a cell size <11 cannot be displayed.

trials [9]. Furthermore, a meta-analysis of data from these randomized trials conducted by Crook et al [17] found that fidaxomicin was also superior in reducing CDI symptoms and CDI recurrence. We also observed an absolute difference in the 4-week CDI recurrence rates (–8.4% in initial CDI episodes [20.6% for fidaxomicin and 29.0% for vancomycin] and –10.3% [data not reported due to CMS policy restricting cell sizes <11] in the recurrent CDI episodes) that was in favor of fidaxomicin but did not reach statistical significance, possibly due to small sample sizes. Again, the absolute reduction in CDI recurrence was similar to the randomized trials. While it should be noted that some observational studies conducted in certain high-risk groups [18, 19] have not found a meaningful difference in outcomes between fidaxomicin and vancomycin, several other observational studies conducted by Goldenberg et al [20], Gallagher et al [21], and Polivkova et al [22] have demonstrated fidaxomicin's superiority over vancomycin in treating CDI. The evidence on the superiority of fidaxomicin over vancomycin has also been acknowledged in the latest update to IDSA guidelines for CDI treatment published in 2021 [11], which now recommends fidaxomicin as first-line treatment for both initial and recurrent CDI episodes, with vancomycin an acceptable alternative. Future research is necessary to see whether this most recent update has further shifted treatment patterns toward fidaxomicin and its associated impact on clinical outcomes.

Our study has several limitations. As with all administrative claims data, coding errors are possible. Medicare claims do not report laboratory values or microbiological data necessary to determine CDI severity and certain CDI risk factors; we therefore lacked positive CDI test results to confirm a patient's diagnosis

or patient symptoms to document active infection. In addition, the codes used to identify outcomes and other variables in our claims-based study are not validated; thus, the study is prone to measurement error. To the extent there are systematic differences in any of these factors across the fidaxomicin versus vancomycin groups, it may have resulted in unmeasured confounding of our study findings. We were also unable to assess any CDI diagnoses that may have occurred outside of our study period. Furthermore, it is important to note that our study only examined CDI diagnosed in the outpatient setting, a necessary limitation in order to link drug treatment to initial diagnosis, limiting our results to nonsevere CDI. Thus, findings may not be generalizable to other care settings and severe CDI. Our study sample excluded patients who had multiple prescriptions for CDI treatment on their index date or had a prescription with a supply of <10 days or >15 days. These patients were not receiving treatment consistent with guidelines and were excluded to permit a more robust evaluation of the impact of treatment guidelines on outcomes. Finally, given that the guidelines were published and available to all clinicians in the country, it was impossible to establish a contemporaneous control group. Thus, some of the treatment utilization changes we observed may be due to other factors; however, the magnitude of the changes in vancomycin and metronidazole use were large and occurred over such a short period of time that any explanation other than the guidelines update appears implausible.

We conclude that the 2017 IDSA guideline update for CDI treatment led to considerable increases in vancomycin use and decreases in metronidazole use in the months immediately following publication in 2018. Fidaxomicin use increased but remained low. Our findings regarding better outcomes

associated with fidaxomicin in treating both initial and recurrent CDI suggest benefits from its greater use in the Medicare population and support the 2021 change in IDSA guidance recommending fidaxomicin over vancomycin.

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.

Notes

Patient consent. This study was an analysis of secondary insurance claims data and thus informed consent was not feasible. This study was deemed exempt from Pearl Institutional Review Board review and received both a waiver of informed consent and waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization.

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