10-1-2022

Impact of updated clinical practice guidelines on outpatient treatment for Clostridioides difficile infection and associated clinical outcomes

Erik R Dubberke  
*Washington University School of Medicine in St. Louis*

Justin T Puckett  
*COVIA Health Solutions*

Engels N Obi  
*Merck & Co, Inc*

Sachin Kamal-Bahl  
*COVIA Health Solutions*

Kaushal Desai  
*Merck & Co, Inc*

See next page for additional authors

Follow this and additional works at: [https://digitalcommons.wustl.edu/oa_4](https://digitalcommons.wustl.edu/oa_4)

Part of the Medicine and Health Sciences Commons

Please let us know how this document benefits you.

**Recommended Citation**

Dubberke, Erik R; Puckett, Justin T; Obi, Engels N; Kamal-Bahl, Sachin; Desai, Kaushal; Stuart, Bruce; and Doshi, Jalpa A, "Impact of updated clinical practice guidelines on outpatient treatment for Clostridioides difficile infection and associated clinical outcomes." Open Forum Infectious Diseases. 9, 10. ofac435 (2022).  
[https://digitalcommons.wustl.edu/oa_4/631](https://digitalcommons.wustl.edu/oa_4/631)
Authors
Erik R Dubberke, Justin T Puckett, Engels N Obi, Sachin Kamal-Bahl, Kaushal Desai, Bruce Stuart, and Jalpa A Doshi
Impact of Updated Clinical Practice Guidelines on Outpatient Treatment for *Clostridioides difficile* Infection and Associated Clinical Outcomes

Erik R. Dubberke,1 Justin T. Puckett,2 Engels N. Obi,3 Sachin Kamal-Bahl,2 Kaushal Desai,3 Bruce Stuart,4 and Jalpa A. Doshi5,6

1Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri, USA, 2COVIA Health Solutions, Lansdale, Pennsylvania, USA, 3Merck & Co, Inc, Rahway, New Jersey, USA, 4School of Pharmacy, University of Maryland, Baltimore, Maryland, USA, 5Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, and 6Leonard Davis Institute of Health Economics, Philadelphia, Pennsylvania, USA

**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* < 0.001 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* = 0.002) 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.
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).

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
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%               | 48.4%                 | 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<sup>b</sup> | 27.2%               | 29.4%                 | 24.8%        | 28.2%          |
| No. of recurrent CDI risk factors<sup>c</sup> |                     |                       |              |                |
| 1                                   | 70.2%               | 68.0%                 | 72.5%        | 68.9%          |
| 2                                   | 28.2%               | 30.3%                 | >26.0<sup>a</sup> | 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%          |
Supplementary Tables 5 and 6 at 8 weeks, both statistically significant at post period by 2.8 percentage points at 4 weeks and 3.9 points in sustained response, CDI recurrence rates rose over the pre/post periods (from 52.9% to 49.8%; \( P < .001 \)). For instance, even after adjusting the odds of fidaxomicin or vancomycin use relative to metronidazole use were significantly higher (odds ratio [OR], 3.91 [95% confidence interval {CI}, 3.62–4.21]) in the postguideline period versus preguideline period.

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 period 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.

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.

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% |
| Healthcare costs, mean (SD) | All-cause hospitalization in the 12 mo preindex | 3.7% | 4.0% | 3.2% | 3.2% |
| All-cause costs in the 12 mo preindex | $43,908 ($58,233) | $43,047 ($54,526) | $37,939 ($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.

*Per Centers for Medicare and Medicaid Services policy, results based on cell sizes ≥11 cannot be displayed.

*Patients 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.

*Age ≥65 years, CDI within past 6 months, immunocompromised.

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 Elixhausen 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.

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
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% vs 22.3%; \( P = .2158 \)) and 8-week (18.0% vs 19.7%; \( P = .0800 \)) intervals compared to vancomycin.
the fidaxomicin and vancomycin arms) are presented in
response rate was 30.0 percentage points higher (75.1% vs 45.1%;
clinical outcomes, and the real-world comparative
effectiveness of the first-line agents (fidaxomicin and vancomycin)
recommended in this update, in the elderly Medicare pop-
ulation. Our findings show that this guideline update led
clinicians to shift their choice of first-line agent from metroni-
dazole to vancomycin and substantially less so to fidaxomicin.
The shift was dramatic with relative rate declines in metronida-
ze 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 re-
current CDI episodes after the guideline publication. Finally,
we found better clinical outcomes in patients receiving fidaxo-
micin compared to vancomycin in both the initial and recur-
rent CDI setting.

Our findings on the changes in CDI treatment utilization af-
fter 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 in-
surance 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 de-
crease 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 im-
provement 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 re-
ponse 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 vi-
tue 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 differenc-
es in the clinical outcomes observed in our real-world study
were quite similar to those reported in the fidaxomicin ran-
donized trials [9, 10]. For example, the difference in 4-week
sustained response rates between fidaxomicin (71.7%) and van-
comycin (58.2%) in the initial CDI episode sample was 13.5% in
our real-world study and 10.5% in the fidaxomicin randomized

| Table 2. Unadjusted Clinical Outcomes, Pre– Versus Post–Guideline Update, Among Medicare Beneficiaries With Initial or Recurrent CDI Episode |
|------------------|-------|-------|------------------|
| Outcome          | Pre   | Post  | P value          |
| Initial CDI episode |      |       |                  |
| All patients with initial CDI episode | 7389  | 7746  |                  |
| Sustained response (4 wk) | 4205  | 4247  | 0.01             |
| Sustained response (8 wk) | 3907  | 3861  | 0.0002           |
| Among patients with a clinical resolution | 6097  | 6415  |                  |
| CDI recurrence (4 wk) | 1892  | 2168  | 0.001            |
| CDI recurrence (8 wk) | 2190  | 2554  | 0.0001           |
| Recurrent CDI episode |      |       |                  |
| All patient with recurrent CDI episode | 779   | 837   |                  |
| Sustained response (4 wk) | 447   | 437   | 0.0369           |
| Sustained response (8 wk) | 415   | 391   | 0.0084           |
| Among patients with a clinical resolution | 663   | 671   |                  |
| CDI recurrence (4 wk) | 216   | 234   | 0.3756           |
| CDI recurrence (8 wk) | 248   | 280   | 0.1064           |

CDI recurrence was calculated only among patients with evidence of clinical resolution. P values are based on y² test.

Abbreviation: CDI, Clostridioides difficile infection.

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

Recurrent CDI Episode Sample

There were 67 fidaxomicin users and 931 vancomycin users be-
fore 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 pa-
tients in the vancomycin group received prior vancomycin ther-
apy 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 = 0.0002) and the 8-week sustained response rate was 27.6 per-
centage points higher (66.5% vs 38.9%; P = 0.0012) 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 signi-
cificant (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
claims data, coding errors are possible. Medicare claims do not lacke negative CDI test results to confirm a patient’s diagnosis termine CDI severity and certain CDI risk factors; we therefore see whether this most recent update has further shifted treat ment for both initial and recurrent CDI episodes, with vanco date to IDSA guidelines for CDI treatment published in 2021 over vancomycin has also been acknowledged in the latest up 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 im possible 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

text

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)* |
|----------------------------------------------|--------------|------------|------------------------|----------------------|
| 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    |              |            |                        |                      |
| 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 (12.9–43.2)       | .0012                |
| Among patients with a clinical resolution    |              |            |                        |                      |
| CDI recurrence (4 wk)                        | b            | b          | −10.3 (−28.9 to 8.0)   | .292                 |
| CDI recurrence (8 wk)                        | b            | b          | −13.3 (−35.1 to 8.8)   | .255                 |

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

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

†Per 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 ran domized 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 siz es <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.

Downloaded from https://academic.oup.com/ofid/article/9/10/ofac435/6686548 by Washington University in St. Louis user on 23 November 2022
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 surveillance 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.

*Financial support.* This work was supported by Merck Sharp & Dohme Corporation, a subsidiary of Merck & Co, Inc, Rahway, New Jersey. The sponsor provided funds to COVIA Health Solutions for conducting the study and manuscript development.

*Potential conflicts of interest.* ERD reports research funding from Ferring and Pfizer, and serving as a consultant for Merck, Pfizer, Seres, and Summit. TTP and SKB are employees of COVIA Health Solutions, a consulting firm with clients in the biotechnology/pharmaceutical sector. BCS has served as a consultant for COVIA Health Solutions. ENO and KD are current employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. JAD reports research funding from Humana, Janssen, Merck, NIH, PAN Foundation, Regeneron, and Sanofi, and serving as an advisory board member or consultant for AbbVie, Acadia, Allergan, Catabasis, Janssen, Merck, Otsuka, and Takeda. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. All other authors have no potential conflict of interests to declare.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**

1. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. N Engl J Med 2020; 382:1320–30.
2. Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridioides difficile* infection incidence among hospitalized adults in the United States: 2001–2010. Am J Infect Control 2014; 42:1028–32.
3. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridioides difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1–48.
4. Kuntz JL, Baker JM, Kipnis P, et al. Utilization of health services among adults with recurrent *Clostridioides difficile* Infection: a 12-year population-based study. Infect Control Hosp Epidemiol 2017; 38:45–52.
5. Ghanotii SS, Salk K, Lairson DR, DuPont HL, Garey KW. Economic healthcare costs of *Clostridioides difficile* infection: a systematic review. J Hosp Infect 2010; 74:309–18.
6. Zhang S, Palazuelos-Munoz S, Baldells EM, Nair H, Chit A, Kyaw MH. Cost of hospital management of *Clostridioides difficile* infection in United States—a meta-analysis and modelling study. BMC Infect Dis 2016; 16:447.
7. Zhang D, Prabhu VS, Marcella SW. Attributable healthcare resource utilization and costs for patients with primary and recurrent *Clostridioides difficile* infection in the United States. Clin Infect Dis 2018; 66:1326–32.
8. Cohen SH, Gerding DN, Johnson S, et al. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America clinical practice guidelines for *Clostridioides difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010; 31:431–55.
9. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridioides difficile* infection. N Engl J Med 2011; 364:422–31.
10. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridioides difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12:281–9.
11. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis 2021; 73:e1029–44.
12. Clancy CJ, Buehrle D, Yu M, et al. Impact of revised Infectious Diseases Society of America and Society for Healthcare Epidemiology of America clinical practice guidelines on the treatment of *Clostridioides difficile* infections in the United States. Clin Infect Dis 2021; 72:1944–9.
13. Gentry CA, Campbell DL, Williams RJ. Outcomes associated with recent guideline recommendations removing metronidazole for treatment of non-severe *Clostridioides difficile* infection: a retrospective, observational, nationwide cohort study. Int J Antimicrob Agents 2021; 57:106282.
14. Asempe TE, Nicolau DP. *Clostridioides difficile* infection in the elderly: an update on management. Clin Interv Aging 2017; 12:1799–809.
15. Furuya-Kanamori L, McKenzie SJ, Yakob L, et al. *Clostridioides difficile* infection seasonality: patterns across hemispheres and continents—a systematic review. PLoS One 2015; 10:e0120730.
16. Ma J, Dubberke ER. Current management of *Clostridioides (Clostridium) difficile* infection in adults: a summary of recommendations from the 2017 IDSA/SHEA clinical practice guideline. Pol Arch Intern Med 2019; 129:189–98.
17. Crook DW, Walker AS, Keen Y, et al. Fidaxomicin versus vancomycin for *Clostridioides difficile* infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis 2012; 55(Suppl 2):S93–103.
18. Prohaska L, Mahmoudzafar Z, Shune L, et al. Retrospective evaluation of fidaxomicin versus oral vancomycin for treatment of *Clostridioides difficile* infections in patients undergoing hemodialysis or peritoneal dialysis. Clin Infect Dis 2012; 54:1956–62.
19. Cordes DE, Batke GP, Seibert JS, Sanger RN. The role of fidaxomicin in the treatment of *Clostridioides difficile* infection. Clin Ther 2016; 38:609–15.
20. Goldenberg SD, Brown S, Edwards L, et al. The impact of the introduction of fidaxomicin on the management of *Clostridioides difficile* infection in seven NHS secondary care hospitals in England: a series of local service evaluations. Eur J Clin Microbiol Infect Dis 2016; 35:251–9.
21. Gallacher JC, Kelly JP, Nalvakele B, Downham G, Trivedi M. Clinical and economic benefits of fidaxomicin compared to vancomycin for *Clostridioides difficile* infection. Antimicrob Agents Chemother 2015; 59:7007–10.
22. Polikova S, Krutowa M, Capek V, Sykorova B, Benes J. Fidaxomicin versus metronidazole, vancomycin and their combination for initial episode, first recurrence and severe *Clostridioides difficile* infection—an observational cohort study. Int J Infect Dis 2021; 102:226–33.