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Original Article

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Abstract

Purpose: The most recent published guidelines on *Clostridium difficile*–associated diarrhea (CDAD) developed by the Infectious Diseases Society of America (IDSA) were released in 2017 and outline its treatment based on severity of the disease and recurrence; however, a clear first-line agent has not been recommended specifically for severe CDAD. **Methods:** This retrospective chart review was approved by the institutional review board and consisted of three community hospitals and one academic medical center. To be included, patients need to meet criteria for severe CDAD and receive at least 72 hours of therapy. Patients received either oral vancomycin or fidaxomicin, in addition to other therapies for CDAD, and differences in outcomes such as cost obtained from a common charge center, rates of recurrence, time to recurrence as measured at time of positive to negative polymerase chain reaction (PCR) test, and mortality were assessed. **Results:** Of the 147 patients, 74 patients received fidaxomicin and 73 patients received oral vancomycin. The average hospitalization cost for patients receiving fidaxomicin was $129,338.69 and for patients receiving vancomycin was $153,563.81 ($P = .26$). Recurrence rates were lower with fidaxomicin compared with vancomycin (6.8% vs 17.6%; $P = .047$), and time to recurrence was longer with fidaxomicin versus vancomycin, but not statistically significant (96.8 $\pm$ 45.9 days vs 63.2 $\pm$ 66.9 days; $P = .321$). Mortality, length of stay in the intensive care unit, and overall length of stay were similar between the two therapies. **Conclusions:** In the treatment of severe CDAD, recurrence rates were lower and time to recurrence was higher with fidaxomicin compared with oral vancomycin. A clear financial benefit has yet to translate from these known findings.

Keywords
fidaxomicin, severe *Clostridium difficile*–associated diarrhea, hospitalization cost, recurrence, oral vancomycin

Introduction

Clostridium difficile–associated diarrhea (CDAD) involves 450,000 to 700,000 patient cases per year, contributes to an increased hospital stay of 2.8 to 6.4 days, and costs approximately $3,006 to $15,397 per hospitalization, subsequently leading to a cost to the health care system of $4.8 billion per year.[1-3] The symptoms and complications associated with CDAD range from pseudomembranous colitis to ileus or toxic megacolon and potentially the need for colectomy.[1,2] In addition, the incremental risk of death associated with CDAD is approximately 5% to 11%.[4] Risk factors for developing CDAD include patients who are elderly, have received proton pump inhibitors, have received chemotherapy, possess concomitant human immunodeficiency virus (HIV), or have received broad-spectrum antibiotics. The highest risk groups are oncology patients or patients receiving hematopoietic stem-cell transplants.[1-3,5,6]

The most recent guidelines on CDAD developed by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) were updated in 2017 and outline the treatment of CDAD based on severity of the disease and recurrence. The panel defined severe CDAD as patients presenting with leukocytosis ($\geq$15,000 cells/mm^3) or serum creatinine level $\geq$1.5 times the premorbid level. Initial treatment for severe disease involves oral vancomycin at a dose of 125 mg 4 times daily

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for 10 to 14 days or fidaxomicin 200 mg oral twice daily for 10 days. If ileus, shock, or megacolon is noted, the CDAD is then defined as severe, complicated disease and vancomycin at a dose of 500 mg by mouth or nasogastric tube, plus metronidazole 500 mg intravenously every 8 hours, is recommended; however, fidaxomicin is not recommended for this use.[1]

Fidaxomicin (Dificid)[7] is a macrocyclic antibiotic that was approved by the Food and Drug Administration for the treatment of CDAD in 2011.[7] The mechanism by which fidaxomicin kills *C difficile* is through inhibition of the bacteria's RNA polymerase that is involved in protein synthesis. Fidaxomicin has a limited spectrum of activity against microbes; it possesses bactericidal activity against Gram-positive anaerobes, including *C difficile*. Similar to oral vancomycin, fidaxomicin produces extremely low concentrations in the serum and undetectable concentrations in the urine, demonstrating that it is not systemically absorbed.[7-10] Specifically, this agent falls into the treatment of recurrence, based on expert reviews and clinical data; however, there is little evidence on the treatment of severe CDAD.[11-13] Finally, the agent is immensely expensive; however, if clinical endpoints such as recurrence rates and time to recurrence are better with fidaxomicin, it may off-set the financial implications for utilizing the agent.

This study was conducted to evaluate the financial utility of fidaxomicin compared with oral vancomycin in the setting of severe CDAD, given the lack of data available on the subject.

Methods

This was a retrospective chart review conducted from January 1, 2012, to December 31, 2014, of patients admitted to the hospital and identified with a positive *C difficile* test at 3 community hospitals and 1 academic medical center in a single health system. After patients were determined to have a positive test result, they were screened for inclusion criteria. To be included in the study, patients must have received 72 hours of medication, met criteria for severe CDAD as established by the IDSA/SHEA guidelines, and been $\geq$18 years of age. Patients were excluded if they had diverticulitis, Crohn disease, ulcerative colitis, or irritable bowel syndrome. After patients met criteria for inclusion, they were assigned to groups based on which CDAD therapy they received for $>$72 hours. If a patient was switched to another therapy or received $<$72 hours, they were excluded.

Baseline characteristics were collected from initiation of CDAD therapy to classify patient's disease severity, in addition to established risk factors for developing CDAD, such as broad-spectrum antibiotics within the last 90 days or concurrent, previous chemotherapy and/or radiation within the last 90 days, immunosuppression (HIV or solid organ transplant), and advanced age (age $>$64 years). Adjunctive therapies for CDAD such as rifaximin, intravenous immunoglobulin, tigecycline, metronidazole, rectal vancomycin, and stool transplant were collected and quantified. These therapies could be used specifically for CDAD or other conditions the patient had during their encounter. The primary outcome of this study was to compare the associated hospital charges for patients receiving fidaxomicin versus oral vancomycin. Financial reports were obtained and included charges to patients for room stay, the use of mechanical ventilation or supplemental oxygen, medications including as-needed medications, radiological scans, and laboratory tests. Secondary outcomes were length of stay (LOS), intensive care unit (ICU) admission, ICU LOS, episodes of recurrence, time to recurrence, and mortality. Patients were classified as having recurrence if they were subsequently readmitted with a positive *C difficile* test. Statistical tests that were used to analyze baseline characteristics and study outcomes were the chi square, Fisher exact test, or Student *t* test where appropriate by means of the SPSS software. The primary outcome of cost was assessed for normal distribution and analyzed with a Student *t* test. The secondary outcomes were also assessed for normal distribution and analyzed with chi-square or Fisher exact test where appropriate for nominal data, and Mann-Whitney *U* or a Student's *t* test for continuous variables where appropriate based on distribution. The study received institutional review board approval through the University of Tennessee and did not receive any financial grants or support from outside sources.

Results

Overall, 377 patients were screened for inclusion with 147 meeting inclusion criteria. Of the 147 patients meeting inclusion criteria, 73 patients received vancomycin and 74 patients received fidaxomicin as their primary CDAD treatment (see Figure 1). Baseline demographics between the two groups were similar in regard to characteristics (Table 1), risk factors (Table 2), and adjunctive therapies (Table 3); however, there were a larger number of African American patients, patients with larger WBC elevations, solid organ transplant recipients, and prior receipt of broad-spectrum antibiotics in the oral vancomycin arm compared with the fidaxomicin arm. On average, patients were middle-aged, African American, and female. Furthermore, patients were most likely to have chronic kidney disease, been on a form of hemodialysis, and received concurrent broad-spectrum antibiotics. There were no differences between the two treatment groups in regard to adjunctive therapies that may have made an impact on a patient's eradication of *C difficile*.

The primary outcome of hospital charges incurred to patients during their hospitalization was lower with fidaxomicin compared with oral vancomycin ($54,172.96 $\pm$ 53,385 vs $64,138.09 $\pm$ 54,542.84); however, this finding was not statistically significant ($P = .26$) (Table 4). The LOS for the patient's hospitalization (22.6 days vs 21.5 days; $P = .82$) and ICU LOS (10.4 days vs 13.0 days; $P = .95$) were no different between patients receiving fidaxomicin versus oral

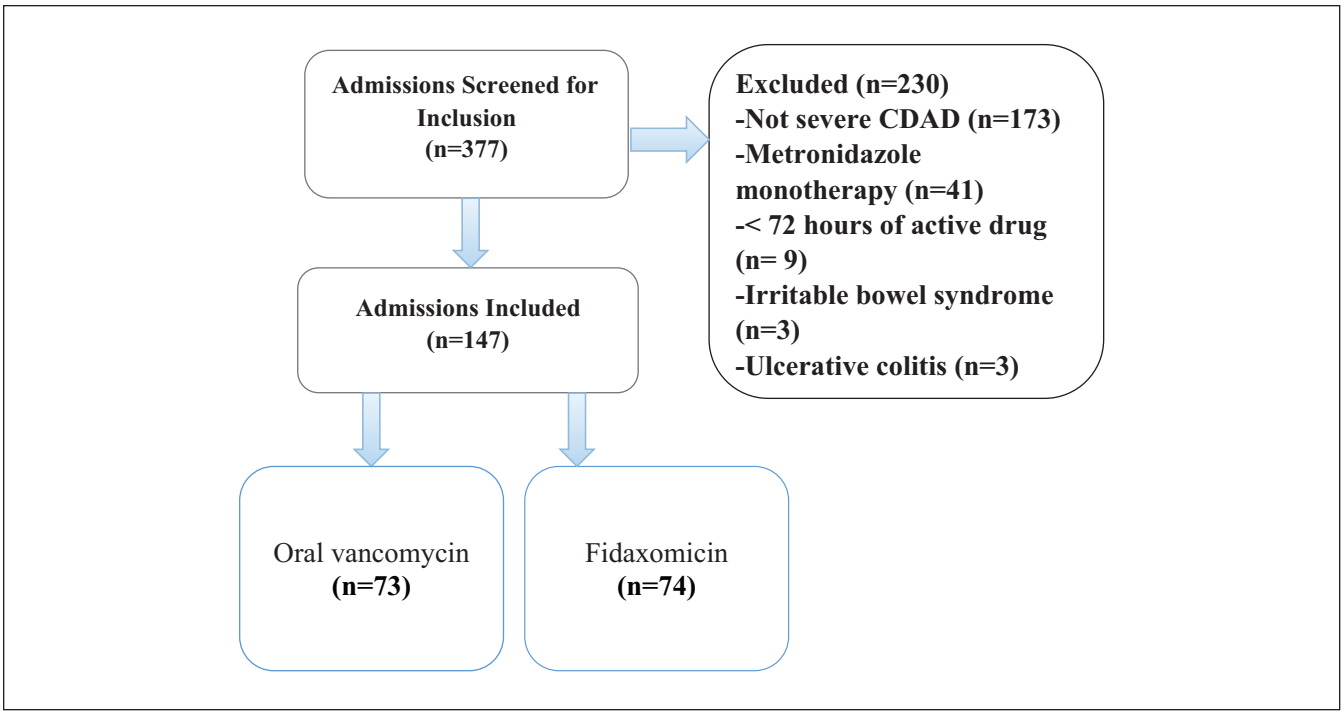

Figure 1. Patient allocation.
Note. CDAD = *Clostridium difficile*–associated diarrhea.

Table 1. Baseline Demographics.

Demographics	Oral vancomycin (n = 73)	Fidaxomicin (n = 74)	*P* value
Age (years, SD)	61 ± 17	58 ± 19	.31
Female (n, %)	38 (52)	40 (54)	.89
African American (n, %)	51 (70)	41 (55)	.09
White blood cell count (cells/mm^3, SD)	19.6 ± 15.4	15.4 ± 10.5	.06
Serum creatinine (mg/dL, SD)	3.0 ± 2.7	3.4 ± 3.3	.42
Ileus (n, %)	4 (5.5)	1 (1.4)	.21
Dialysis (n, %)	15 (20.5)	17 (23)	.84
Chronic Kidney Disease (n, %)	26 (35.6)	18 (24.3)	.15

vancomycin, respectively. With respect to reducing recurrence and prolonging the eradication of *C difficile*, fidaxomicin was found to be more effective than oral vancomycin in the setting of severe CDAD. The incidence of recurrence was 6.8% with fidaxomicin (5 of 74 patients) and 17.6% with oral vancomycin (13 of 73 patients), which was a statistically significant finding ($P = .047$). The time to recurrence of *C difficile* infection was longer with fidaxomicin compared with oral vancomycin (96.8 ± 45.9 days vs 63.2 ± 66.9 days; $P = .321$). Finally, there was no difference in mortality between the two treatments with 9 deaths in the oral vancomycin group and 7 deaths in the fidaxomicin group ($P = .6$).

Discussion

This was a retrospective chart review comparing fidaxomicin with oral vancomycin in the setting of severe CDAD. Since its approval in 2011, fidaxomicin utilization has evolved from a second-line agent to a concomitant option for the first-line treatment of CDAD alongside oral vancomycin. After reviewing the published data for treatment of severe CDAD, or now fulminant CDAD as defined by the update, there is still minimal data for this specific indication, and even less regarding monetary benefits.[1,10] A cost-effective analysis conducted by Nathwani and colleagues took the known outcomes from previous studies with fidaxomicin and CDAD and attempted to determine whether these outcomes also benefited patients and the health care system financially.[11] The investigators utilized a 1-year time horizon Markov model to determine incremental cost-effectiveness ratios that were further determined by adjusted cost per quality-adjusted life years and cost per recurrence avoided. Overall, the final analysis found similar total costs for fidaxomicin and vancomycin but differences in clinical outcomes that

Table 2. Risk Factor Demographics.

Risk factor	Oral vancomycin (n = 73)	Fidaxomicin (n = 74)	*P* value
Human immunodeficiency virus (n, %)	2 (2.7)	2 (2.7)	1
Malignancy (n,%)	10 (13.7)	13 (17.6)	.65
Solid organ transplant (n,%)	9 (12.3)	5 (6.8)	.28
Hematopoetic stem cell (n, %)	0	1 (1.4)	1
Prior chemotherapy (n, %)	2 (2.7)	4 (5.4)	.68
Previous broad-spectrum antibiotics (n, %)	10 (13.7)	4 (5.4)	.1
Broad-spectrum antibiotics (n, %)	57 (78.1)	52 (70.3)	.35

Table 3. Adjunctive Therapies.

Treatment	Oral vancomycin (n = 73)	Fidaxomicin (n = 74)	*P* value
Metronidazole (n, %)	51 (69.9)	43 (58.1)	.17
Rifaximin (n, %)	1 (1.4)	1 (1.4)	1
Intravenous immunoglobulin (n, %)	0	0	NA
Stool transplant (n, %)	0	1 (1.4)	1
Tigecycline (n, %)	13 (17.8)	18 (24.3)	.42
Probiotics (n, %)	13 (17.8)	13 (17.6)	1

Table 4. Study Outcomes.

Outcome	Oral vancomycin (n = 73)	Fidaxomicin (n = 74)	*P* value
Length of stay (days, SD)	21.5 ± 15.7	22.6 ± 37.1	.82
ICU admissions (n, %)	46 (63)	36 (48.7)	.1
ICU length of stay (days, SD)	13.0 ± 10.7	10.4 ± 7.9	.95
Recurrence (n, %)	13 (17.8)	5 (6.8)	.047
Time to recurrence (days, SD)	63.2 ± 64.3	96.8 ± 41.0	.0002
Mortality (n, %)	9 (12.3)	7 (9.5)	.6

Note. ICU = intensive care unit.

resulted in benefits in incremental cost-effectiveness ratios for severe CDAD and in patients with multiple recurrences. From the captured charges to patients, we found an average cost of $54,172.96 ± 53,385 compared with an average cost of $64,138.09 ± 54,542.84, which was not statistically significant. This is a different finding from the cost-effective analysis; however, it should be noted the large degree of standard deviation that makes these results difficult to apply.

The first study of fidaxomicin published by Louie and colleagues excluded patients with severe CDAD and attempted to establish efficacy for fidaxomicin in the highly virulent strains of *C difficile* (NAP1/BI/027).[12] The investigators enrolled 629 patients, with 548 patients overall that experienced a clinical cure and based on that, were evaluable for recurrence. The patients in the study were predominantly older females who were treated as outpatients. Overall, the study found that fidaxomicin was associated with lower rates of recurrence when compared with oral vancomycin (15.4% vs 25.3%; $P = .005$). The difference with rates of recurrence, however, was lost when examined in the group of patients who had data available on NAP1/BI/027, with similar rates of recurrence between fidaxomicin and vancomycin (24.4% vs 23.6%). When this outcome was analyzed in other strains of *C difficile*, the rates of recurrence were lower with fidaxomicin compared with vancomycin (7.8% vs 25.5%; $P < .001$) and the relative risk for recurrence in these strains was 3.3 times higher with patients receiving vancomycin. A study by Cornely and colleagues was conducted to determine whether there were benefits to using fidaxomicin in various subpopulations over oral vancomycin.[13] From the large population pulled from the registry the investigators utilized, 91 patients with severe CDAD were evaluable for rates of recurrence and 124 similar patients were evaluable for response rates. In terms of rates of recurrence in severe CDAD, fewer patients experienced recurrence of CDAD with fidaxomicin compared with oral vancomycin (4/48 patients, 8.3% vs 14/43 patients, 32.6%; P = N/A). There were also more patients with fidaxomicin achieving longer

sustained response rates compared with oral vancomycin (44/63 patients, 69.8% vs 29/61 patients, 47.5%; $P = .012$). This large analysis also did not find differences in treatment outcomes between fidaxomicin and oral vancomycin in the BI/027 strains as well.[12] Our analysis found similar results in regard to rates of recurrence favoring fidaxomicin over oral vancomycin (6.8 % vs 17.6%; $P = .047$) in the setting of severe CDAD. Because our institution does not test for the NAP1/BI/027 strain at the time, we were not able to analyze whether this would impact outcomes in the setting of severe CDAD. From the second analysis, it appears that the strain of *C difficile* does not impact the outcomes of therapy in severe CDAD.

There are several limitations to this study that need to be considered in light of these findings. The first is that this was a small retrospective study performed at multiple hospitals within a single health system. Including patients at other health care systems would increase the applicability of our results; however, it also introduces a potential confounder in consistent standard of care. Patients were screened for severe or fulminant CDAD to be included in the study, but other markers such as the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) or Sequential Organ Failure Assessment (SOFA) might have been beneficial to analyze as baseline demographics. At our institution, we do not routinely test for specific strains of *C difficile*; therefore, these data were not available to be analyzed. Previous studies have also assessed the role of fidaxomicin in highly virulent strains such as NAP1/BI/027, which have shown no difference between fidaxomicin and oral vancomycin, making this limitation negligible.[11-13] The data that we obtained to assess any cost differences associated with the two treatments were also only reflective of the charges to the patient and would not be reflective of real-world pharmacoeconomics and may have led to the large standard deviations in that analysis. Finally, we were unable to assess compliance in patients who were discharged on outpatient therapy due to the retrospective nature of the study, nor the presence of signs or symptoms of recurrence in the outpatient setting.

Conclusion

The role of fidaxomicin in CDAD is mostly clear in that it reduces the incidence of recurrence and provides a prolonged response; however, the role of fidaxomicin in severe CDAD has yet to be determined. This retrospective analysis demonstrated that there is no financial benefit with using fidaxomicin in severe CDAD, but there might be a role in reducing the rates of recurrence. Further studies are needed in general, as well as pharmacoeconomic analysis, to determine whether the differences in recurrence can impact future hospitalizations and thus reducing cost.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KOC, MSG and JU were consultants for Cubist.

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