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Fidaxomicin Therapy in Critically Ill Patients with *Clostridium difficile* Infection

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Fidaxomicin use to treat proven *Clostridium difficile* infection (CDI) was compared between 20 patients receiving care in critical care units (CCUs) and 30 patients treated on general medical floors. At baseline, the CCU patients had more initial CDI episodes, more severe and complicated disease, and more concurrent broad-spectrum antibiotic coverage. On multivariate analysis, the response to fidaxomicin therapy among the critically ill patients was comparable to that among patients in the general medical wards.

Clostridium difficile infection (CDI) is a serious complication in hospitalized patients undergoing transplantation and among those with low serum levels of immunoglobulin against bacterial exotoxins (1, 2). Patients who receive antineoplastic therapy and patients in critical care units (CCUs) are considered at additional risk for severe CDI (3), although this association has not been well established. A comprehensive meta-analysis of 11 clinical trials, which included 1,463 participants, showed that clinical response rates to commonly used drugs for the treatment of CDI were comparable. However, treatment with fidaxomicin resulted in significantly fewer early disease recurrences, which was in keeping with the results of two pivotal fidaxomicin trials (4–6). Importantly, this benefit was also observed in patients for whom systemic broad-spectrum antibiotics could not be discontinued during CDI therapy (7).

In our prior analysis, fidaxomicin was well tolerated in transplant recipients; we also observed a favorable potential for the preservation of the host microbiome, as supported by the low likelihood of intestinal colonization by drug-resistant bacteria and the subsequent low risk for potentially life-threatening infections (8). To date, randomized clinical trials of fidaxomicin have excluded patients with severe complicated CDI, various comorbidities, or life-threatening illness, so there has been little to guide optimum therapy in these highly vulnerable populations. With this in mind, we sought to assess the feasibility of fidaxomicin therapy in critically ill patients with CDI at our university hospital.

Study design and subjects. Fidaxomicin has been on the formulary at our 700-bed, acute care university hospital since September 2011. All adult patients (≥18 years) who received fidaxomicin therapy for at least 2 consecutive days between August 2011 and April 2014 were included in this analysis. The CDI cases were initially identified by using a microbiology laboratory database to find PCR results that were positive for the *C. difficile* toxin. The pharmacy database was queried for anti-CDI and other antimicrobial therapies. This retrospective study was undertaken after obtaining approval from the institutional review board.

Microbiology. *Clostridium difficile* infection was identified by PCR for bacterial exotoxin toxin B (Xpert *C. difficile*; Cepheid, Sunnydale, CA), and a gene link with the NAP1 strain was also assessed. Only unformed stool samples were tested.

Definitions. A diagnosis of CDI required a positive *C. difficile* PCR assay and the presence of a diarrheal illness, defined by the Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) guidelines as a decrease in consistency and an increase in the frequency of bowel movements to ≥3 stools per day. Disease severity was also classified according to IDSA/SHEA guidelines described elsewhere (9). Patients were considered critically ill if they required hospitalization in a critical care unit (CCU). The terms "*Clostridium difficile* infection" and "*C. difficile* disease" are used here interchangeably.

A response to therapy was defined as follows: (i) documentation in a nursing note that the patient produced well-formed or ≤3 soft bowel movements for 2 consecutive days or (ii) documentation by an infectious disease specialist that the patient responded successfully to anti-CDI therapy. Treatment failure was defined as (i) persistence of diarrhea, (ii) a need to change anti-CDI therapy, or (iii) increased severity of CDI-associated disease. Cases were reviewed independently by two investigators to validate the classification of disease severity, treatment response, and treatment failure. Patients were included for multiple episodes of CDI only if those episodes were separated by ≥3 months after completion of therapy for the prior episode. Secondary endpoints included infection recurrence within 30 days after the completion of treatment and death during hospitalization for a CDI episode.

Fidaxomicin was considered salvage therapy when it was administered to patients who had experienced a worsening of clinical symptoms or a lack of treatment response after ≥5 days of conventional CDI drug therapy with oral vancomycin, oral metronidazole, intravenous (i.v.) metronidazole, or any combination of these medications.

Statistical analysis. Categorical variables were analyzed using the chi-square or Fisher's exact test. Continuous variables were analyzed using Student's *t* test or the Mann-Whitney U test. A *P* value of <0.05 denoted statistical significance. Multivariate logis-

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TABLE 1 Clinical characteristics

Characteristic	Data for treatment courses in: All patients ($n = 50$)	Patients requiring CCU stay ($n = 20$)	Patients on general medicine floors ($n = 30$)	P
Age (mean [SD]) (yr)	61 (19)	57 (18)	64 (19)	0.294
Male patients (no. [%])	23 (46)	13 (65)	10 (33)	0.056
Comorbidity (no. [%])				
Diabetes mellitus	8 (16)	5 (25)	3 (10)	0.24
Malignancy	25 (50)	6 (30)	19 (63)	0.043
Liver disease	13 (26)	8 (40)	5 (17)	0.13
Chronic renal insufficiency	17 (34)	5 (25)	12 (40)	0.428
Cardiovascular disease	25 (50)	9 (45)	16 (53)	0.773
Transplant recipients (no. [%])	26 (52)	11 (55)	15 (50)	0.954
Corticosteroid/immunosuppressive medications (no. [%])	24 (48)	12 (60)	12 (40)	0.272
Length of stay (median [IQR]) (days)	19 (8–29)	17.5 (7–27)	18.5 (9–31)	0.428
CCU length of stay (median [IQR]) (days)	9 (6–20)	9.5 (6–21)	6[a]	0.26
Time from hospital admission to CDI (median [IQR]) (days)	2 (2–9)	3 (2–9)	2 (1–8)	0.127
CDI initial episode (no. [%])	23 (46)	14 (70)	9 (30)	0.013
NAP1 strain (no. of patients/total no. of patients [%])	21/49 (43)[b]	8/19 (42)	13/30 (43)	1
CDI severity at fidaxomicin start (no. [%])				
Mild to moderate	23 (52)	8 (40)	8 (60)	0.272
Severe	13 (26)	4 (20)	9 (30)	0.645
Severe complicated	11 (22)	8 (40)	3 (10)	0.031
Presence of pseudomembranous colitis/megacolon/pancolitis	13 (26)	9 (45)	4 (13)	0.645
Clinical measures at fidaxomicin start				
Albumin (median [IQR]; no. of patients) (g/dl)	2.5 (2–3); 38	2.1 (1.9–3.1); 17	2.6 (2.1–3.1); 21	0.281
WBC (cells/μl)	8.6 (5.5–15)	11.9 (7.2–16.8)	7.3 (4.8–12.5)	0.073
SCr (median [IQR]; no. of patients) (mg/dl)	1.2 (0.7–2.2); 49	1.4 (0.8–2.2); 20	1.0 (0.7–2.4); 29	0.5
Fever (no. [%])	8 (16)	5 (25)	3 (10)	0.24
Bowel movements per day (median [IQR]; no. of patients)	3 (2.5); 32	4 (2–5); 14	4 (2–6); 18	0.925
Hypotension/septic shock (no. [%])	8 (16)	7 (35)	1 (4)	0.005
Concurrent antibiotics (no. [%])	36 (72)	19 (95)	17 (56.7)	0.008
Penicillins	16 (32)	7 (35)	9 (30)	0.951
Cephalosporins	13 (26)	7 (35)	6 (20)	0.392
Carbapenems	14 (28)	10 (50)	4 (13.3)	0.012
Other	8 (16)	5 (25)	3 (10)	0.24

[a] Two patients stayed 6 days each in the CCU during their hospitalization, but not during the fidaxomicin treatment course.
[b] NAP1 status was unknown for one CCU patient.

TABLE 2 Factors associated with probability of lack of fidaxomicin treatment response

Characteristic	No. (%) of patients with: Treatment failure ($n = 18$)	Treatment response ($n = 32$)	Univariate, OR (95% CI); P value[a]	Multivariate, OR (95% CI); P value
Age > 60 yr	14 (77.8)	14 (43.8)	4.5 (1.21–16.72); 0.04	4.7 (0.9–23.4); 0.06
CDI due to NAP1 strain	10 (55.6)	11 (35.5)	2.3 (0.69–7.44); 0.3	1.5 (0.36–6.55); 0.6
Severe and severe complicated CDI	13 (72.2)	11 (34.4)	4.9 (1.4–17.56); 0.02	5.1 (1.02–25.46); <0.05
Fever when fidaxomicin therapy commenced	5 (27.8)	3 (9.4)	3.7 (0.77–17.94); 0.1	2.6 (0.27–25.48); 0.4
Fidaxomicin in combination with other anti-CDI drugs[b]	11 (61.1)	7 (21.9)	5.6 (1.58–19.87); 0.014	4.9 (0.95–25.43); 0.06
CCU level of care during fidaxomicin treatment	8 (44.4)	12 (37.5)	1.3 (0.412–4.31); 0.8	0.8 (0.12–3.74); 0.6

[a] OR, odds ratio; CI, confidence interval.
[b] Including metronidazole ($n = 9$), oral vancomycin ($n = 4$), or both ($n = 5$).

TABLE 3 Patients treated with fidaxomicin in CCUs

Age/gender[a]	CDI severity[b]	Comorbidities, transplant status, immunosuppresion[c]	Reason for CCU stay[d]	CDI episode (NAP1 status)[e]	Days from CCU admission to CDI diagnosis	Clinical presentation (fever)	WBC (cells/mm^3)[f]	SCr/Alb (mg/dl)[g]	Treatment[h]	Days to Fdx after CDI diagnosis	Fdx response	Days in CCU	In-hospital mortality
88/M	Sc	CVD	Sc CDI	Recurrent, 3rd ep (+)	1	Hypotension/shock (−)	16	0.9/1.9	[V, M][i], then [Fdx with V, M][j]	4	−[k,l]	21	−
54/M	Sc	HLD	Sc CDI	Initial (+)	0	Hypotension/shock, megacolon (−)	39.9	1.9/1.8	[V, M][i], then [Fdx with V, M][j]	7	−[k,m]	14	−
39/F	Sc	CKD, AH, OLT, steroids, tacrolimus	Sepsis	Initial (+)	2	(−)	21.1	2.9/1.8	[V, M][i], then [Fdx][j]	0	+	9	−
67/M	Sc	Lymphoma	RF, MV	Recurrent, 3rd ep (+)	0	Hypotension/shock (+)	3.4	1.7/2.1	[V, M][i], then [Fdx with V, M][j]	6	−[k,n,o]	8	+[n]
65/F	Sc	HBV cirrhosis, ESLD	ESLD, liver failure	Initial (−)	1	Hypotension/shock (+)	10	3.2/1.5	[V, M][i], then [Fdx with V, M][j]	3	−[k,o,p]	6	+[p]
79/M	Sc	CVD, COPD	Sc CDI	Recurrent, 3rd ep (+)	2	Hypotension/shock (+)	14.9	2/3.3	[V, M][i], then [Fdx with V, M][j]	18	+	19	+[u]
43/M	Sc	DM, ESLD, OLT, steroids, tacrolimus	Txp complications	Initial (+)	12	Hypotension/shock (+)	50.6	2.3/1.9	[V, M][i], then [Fdx][j]	0	−[k,n,o]	19	+[n]
25/M	Sc	CF, steroids	RF, MV	Initial (−)	7	Hypotension/shock (+)	28	0.5/2.7	[V, M][i], then [Fdx][j]	1	+	14	−
49/M	Mmd	CVD, DM, ESLD, OLT, steroids, tacrolimus	Txp complications	Initial (−)	1	(−)	4.6	0.9/4	[Fdx][i]	1	+	4	−
53/M	Mmd	HCC cirrhosis, ESLD, OLT, steroids, tacrolimus	Biliary sepsis	Initial (unknown)	1	(−)	8.1	0.7/3.7	[V][i], then [Fdx][j]	0	(5)	10	−
50/M	Mmd	CVD, DM, CKD, Buerger's Disease, EtOH cirrhosis, OLT, steroids, tacrolimus	SSTI	Initial (−)	1	(+)	7.2	2.3/2.1	[Fdx][i]	1	+	7	−
66/M	Mmd	CVD, DM, CKD, kidney txp, steroids, tacrolimus	Bacteremia	Initial (−)	1	(−)	4.2	1.2/2.5	[Fdx][i]	1	+	5	−
85/F	Mmd	CVD	Sepsis	Initial (+)	2 days prior CCU stay	Pseudomembranes, pancolitis (−)	5	0.7/2	[V, M][i], then [Fdx with M][j]	16	−[k,q]	27	−
60/F	Mmd	CVD, kidney txp, steroids, tacrolimus, MMF, everolimus, cyclosporine	Txp complications	Initial (−)	4	(−)	13.8	1.3/NA	[Fdx][i]	1	−[k,r]	7	−
61/F	Mmd	CVD, kidney txp, steroids, tacrolimus, MMF, everolimus, cyclosporine	Txp complications	Recurrent, 2nd ep (−)	1	(−)	9	0.7/NA	[Fdx][i]	2	+	22	−
41/F	Mmd	Metastatic melanoma, steroids	Metastatic melanoma	Recurrent, 2nd ep (−)	24 days prior CCU stay	(−)	7.2	0.6/3.4	[V][i], then [Fdx][j]	21	+	4	+[t]

62/M	S	HCC cirrhosis, short gut syndrome, OLT, steroids, MMF, tacrolimus	Liver failure	Initial (−)	3	(−)	17.1	1.2/2.8	[Fdx][i]	0	+	7	−
48/F	S	CKD, kidney txp, steropids, MMF, tacrolimus	Txp complications	Initial (+)	9	(−)	15.1	1.4/NA	[Fdx with M][i]	0	+	26	−
25/M	S	HCC cirrhosis, OLT, steroids, MMF, tacrolimus	Liver failure	Initial (−)	11	(−)	7.3	1.8/1.5	[Fdx with M][i]	1	+	27	−
83/M	S	CVD, DM, colon ca, CKD, hypothyroidism	Anemia and hyperkalemia	Recurrent, 3rd ep (−)	0	(−)	14.4	4.2/2.3	[Fdx][i]	0	−[k,s]	5	−

[a] M, male; F, female.
[b] Sc, severe complicated CDI; S, severe CDI; Mmd, mild to moderate CDI.
[c] CVD, cardiovascular disease; HLD, hyperlipidemia; CKD, chronic kidney disease; AH, autoimmune hepatitis; OLT, orthotopic liver transplant; HBV, hepatitis B virus; ESLD, end stage liver disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CF, cystic fibrosis; EtOH, ethyl alcohol; txp, transplant; MMF, mycophenolate mofetil; HCC, hepatocellular carcinoma; ca, cancer.
[d] Sc, severe complicated CDI; RF, respiratory failure; MV, mechanical ventilation; SSTI, skin and soft tissue infection.
[e] Ep, episode; +, yes; −, represents no.
[f] WBC, peripheral white blood cell count.
[g] SCr, serum creatinine; Alb, serum albumin.
[h] Fdx, fidaxomicin; V, vancomycin; M, metronidazole; NA, not available.
[i] Initial therapy.
[j] Salvage therapy.
[k] Persistent/worsening diarrhea.
[l] Requiring switch to V and M with treatment response.
[m] Requiring subtotal colectomy.
[n] Septic shock.
[o] In-hospital mortality.
[p] Acute respiratory distress syndrome.
[q] Required discharge on vancomycin.
[r] Requiring switch to M with treatment response.
[s] Requiring fecal transplant.
[t] Metastatic melanoma.
[u] Aspiration pneumonia.

tic regression was conducted to identify predictors of fidaxomicin treatment failure. Any variable with a *P* value of ≤0.3 in the univariate analysis was included in the multivariate analysis. The CCU level of care during fidaxomicin treatment was kept in the model as a variable of interest. All analyses were performed using SPSS version 20.

We assessed the efficacy of fidaxomicin in 48 patients with 50 discrete episodes of CDI. Twenty treatment courses of fidaxomicin were given to patients in the CCU; the baseline characteristics, disease severity, treatment courses, and outcomes in these patients were compared with those of the remaining CDI patients who received fidaxomicin on regular medical units. Table 1 summarizes the clinical characteristics of these patients. The median time to CDI diagnosis after admission to the CCU was 3 days (interquartile range [IQR], 2 to 9 days), and the median duration of stay was 9.5 days (IQR, 6 to 21 days). In the CCU and non-CCU patients, there were no significant differences in mean age (57 versus 64 years, respectively; $P = 0.3$), peripheral blood leukocytosis (11,900 versus 7,300 cells/μl, respectively; $P = 0.07$), serum creatinine levels (1.4 versus 1.0 mg/dl, respectively; $P = 0.5$), or serum albumin levels (2.1 versus 2.6 g/dl, respectively; $P = 0.3$). Half of the patients in each group had undergone solid organ or hematopoietic stem cell transplantation. With the exception of cancer diagnoses (30% in [CCU] versus 63% [non-CCU]; $P = 0.04$), all other medical comorbidities, including cardiovascular disease, diabetes mellitus, chronic kidney disease, and chronic liver disease, were comparable between the groups studied.

The rates of concurrent immunosuppressant therapy did not differ significantly between the two groups (60% [CCU] versus 40% [non-CCU]; $P = 0.272$). However, the patients in the CCU received fidaxomicin for initial CDI episodes more often than the patients in other medical units (70% versus 30%, respectively; $P = 0.01$). They also continued to receive broad-spectrum antibiotics during CDI therapy more often (95%) than the non-CCU patients (57%; $P = 0.008$); meropenem was the drug given to more patients in the CCU (50%) than in the non-CCU group (13.3%; $P = 0.012$).

The hypervirulent *C. difficile* NAP1 strain was evenly distributed among the two groups (40% [CCU] versus 43% [non-CCU]; $P = 0.5$). CDI severity when fidaxomicin therapy commenced was greater in CCU patients (40% with severe/severe complicated disease versus 10% in non-CCU patients; $P = 0.03$). The following are the various categories of disease severity observed in the CCU patients: mild-to-moderate disease ($n = 8$), severe disease ($n = 4$), and severe complicated CDI ($n = 8$).

In the CCU patients, salvage fidaxomicin therapy was less common than in the non-CCU patients (45% versus 63%, respectively; $P = 0.323$). Among the 9 CCU patients treated with fidaxomicin salvage therapy, prior treatment included oral vancomycin ($n = 2$) and oral vancomycin plus metronidazole ($n = 7$). The median time for initiation of fidaxomicin salvage therapy from the diagnosis of CDI was 6 days (IQR, 2 to 12 days) in CCU patients compared with 11 days (IQR, 5 to 20 days) in patients on general medicine units ($P = 0.069$). Of interest, only half of the fidaxomicin-treated patients in the CCU received it as single drug compared with 73.3% of non-CCU patients who received it alone ($P = 0.167$). The median duration of fidaxomicin therapy was 6 days (IQR, 5 to 15 days) in CCU patients, whereas it was 12 days (IQR, 6 to 22 days) in the non-CCU group ($P = 0.152$). However, it should be noted that this difference is influenced by the in-hospital mortality rate of 25% in the CCU patients compared to the 0% rate in the non-CCU patients ($P = 0.007$).

There were no drug-related adverse events noted during or after fidaxomicin therapy. The overall response rate was 60% in the CCU group compared with 67% in the non-CCU group ($P = 0.9$). Early (30-day) CDI recurrences were also comparable among the two groups (8% [CCU] versus 10% [non-CCU]; $P > 0.5$). Ten of 18 patients (55.5%) with fidaxomicin treatment failure were in the non-CCU group; 7 of these episodes were treated with additional anti-CDI therapy for a median of 10 days (IQR, 4 to 12 days). Of the 8 critically ill patients who experienced fidaxomicin treatment failure, 4 were given additional therapy at a median of 4 days (IQR, 2 to 10 days); 1 patient each required a colectomy and a fecal transplant on day 3 and 5 after fidaxomicin therapy, respectively. The overall response to fidaxomicin in patients with severe and severe complicated CDI was lower (46%) than the response in patients with mild-to-moderate CDI (81%; $P = 0.02$), and the response rate was not significantly different between those with NAP1 strains (52%) and non-NAP1 strains (71%; $P = 0.3$).

Table 2 presents the results of the multivariate analysis. Severe or severe complicated CDI episodes were associated with a high probability of fidaxomicin failure. Admission to a critical care unit for critical illness did not predict a failure to respond to fidaxomicin therapy. Patient characteristics, clinical features, and treatment outcomes among the 20 critically ill patients who received fidaxomicin are summarized in Table 3.

In this analysis, we found that the response to fidaxomicin therapy in critically ill patients with CDI was comparable to the response by patients receiving fidaxomicin on general medical units. The rate of early disease recurrence was also similar between the two groups. It was not unexpected that critically ill patients, as well as those with severe complicated CDI on general medicine units, experienced fewer successful outcomes following fidaxomicin therapy; nevertheless, our brief analysis underscores the feasibility of this drug in the treatment of CDI episodes for patients requiring a CCU stay (Table 2).

According to current guidelines, oral vancomycin and parenteral metronidazole form the mainstay of therapy for patients with severe and severe complicated CDI, and vancomycin retention enemas can be added for patients with paralytic ileus. However, an understanding of optimal treatment for these conditions remains limited, as patients with fulminant and life-threatening illnesses have traditionally not been included in clinical trials evaluating fidaxomicin or vancomycin therapy. One of the two clinical trials on fidaxomicin excluded CDI patients with evidence of hypotension or septic shock, among other criteria, and the other did not include those with fulminant disease (5, 6). Meanwhile, in a study of 69 patients which determined that oral vancomycin was superior to oral metronidazole for severe CDI, only 5 patients in the study required care in the CCU (10). It is clear that the optimal treatment approach to CDI in the critically ill remains uncertain.

As such, treatment paradigms require reassessment, especially in the era of expanding pharmacologic options. Many critically ill patients may have underlying compromised immune function, receive multiple courses of broad-spectrum antibiotics, and require prolonged durations of hospitalization; all of these factors place them at an increased risk for secondary health care-associated infection (11). Both metronidazole and vancomycin have the potential to alter host' microbiomes to promote colonization and

growth of drug-resistant bacteria and yeast (12). Fidaxomicin has a number of favorable attributes over conventional anti-CDI therapy, such as a narrow spectrum of antimicrobial activity which spares Gram-negative anaerobic and Gram-positive intestinal flora, bactericidal properties, and a high intraluminal drug concentration after oral administration that allows for a longer postantibiotic effect. These qualities may all play a role in the reduced risk for early infection recurrence noted in the pivotal trials (13, 14).

In this preliminary analysis, fidaxomicin was safe and appears promising for CDI therapy in critically ill patients. Further studies are needed to assess optimal treatment options in this patient population.

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