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MAJOR ARTICLE

The Addition of Intravenous Metronidazole to Oral Vancomycin is Associated With Improved Mortality in Critically Ill Patients With *Clostridium difficile* Infection

Kristina E. E. Rokas,[1] James W. Johnson,[1] James R. Beardsley,[1] Christopher A. Ohl,[2] Vera P. Luther,[2] and John C. Williamson[1]

[1]Department of Pharmacy, Wake Forest Baptist Medical Center, and [2]Wake Forest University School of Medicine, Winston-Salem, North Carolina

Background. The optimal therapy for critically ill patients with *Clostridium difficile* infection (CDI) is not known. We aimed to evaluate mortality among critically ill patients with CDI who received oral vancomycin (monotherapy) vs oral vancomycin with intravenous (IV) metronidazole (combination therapy).

Methods. A single-center, retrospective, observational, comparative study was performed. Patients with a positive *C. difficile* assay who received oral vancomycin while bedded in an intensive care unit (ICU) between June 2007 and September 2012 were evaluated. Patients meeting ≥3 of the following criteria were included: albumin <2.5 g/dL, heart rate >90 bpm, mean arterial pressure <60 mmHg, white blood cell count ≥15 000 cells/mL, age >60 years, serum creatinine ≥1.5 times baseline, or temperature ≥100.4°F. Patients in the combination therapy group received IV metronidazole within 48 hours after initiating vancomycin. Patients <18 years or with unrelated gastrointestinal disease were excluded. The primary outcome was in-hospital mortality. Patients were matched using Acute Physiology and Chronic Health Evaluation II scores.

Results. Eighty-eight patients were included, 44 in each group. Patient characteristics were similar although more patients in the combination group had renal disease. Mortality was 36.4% and 15.9% in the monotherapy and combination therapy groups, respectively ($P = .03$). Secondary outcomes of clinical success, length of stay, and length of ICU stay did not differ between groups.

Conclusions. Our data are supportive of the use of combination therapy with oral vancomycin and IV metronidazole in critically ill patients with CDI. However, prospective, randomized studies are required to define optimal treatment regimens in this limited population of CDI patients.

Keywords. *Clostridium difficile* infection; vancomycin; metronidazole; mortality; sepsis.

Clostridium difficile infections (CDI) have generated a significant burden on the healthcare system and are linked to 14 000 deaths per year in the United States [1]. The increasing prevalence of the fluoroquinolone-resistant BI/NAP1/027 epidemic strain of *C. difficile*, which has been shown to cause more severe disease than historical strains, has contributed to increased morbidity and mortality [2, 3]. The attributable mortality rate of CDI at 30 days and 1 year after diagnosis was estimated at 6.9% and 16.7%, respectively, which was noted during outbreaks with the NAP1 strain [2, 4, 5]. In addition, it has been estimated that management of CDI costs US hospitals $3.2 billion annually [5].

The Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) developed recommendations to distinguish severity of CDI [6]. Patients presenting with an initial *C. difficile* episode with a white blood cell (WBC) count of ≥15 000 cells/mL or serum creatinine ≥1.5 times baseline are categorized as having severe disease.

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Correspondence: John C. Williamson, PharmD, Wake Forest Baptist Medical Center, Department of Pharmacy, Winston-Salem, NC 27157 (johnwill@wakehealth.edu).

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The recommended treatment for severe disease is oral vancomycin (BI recommendation). Patients with life-threatening megacolon, ileus, hypotension, or shock are categorized as having severe, complicated disease. The recommended treatment for severe, complicated disease is oral vancomycin plus intravenous (IV) metronidazole (CIII recommendation). This recommendation is based on expert opinion. There are presently no data to support a preferred regimen for critically ill patients with CDI requiring admission to an intensive care unit (ICU). The purpose of our study was to evaluate mortality among critically ill patients with CDI who received oral vancomycin (monotherapy) vs oral vancomycin with IV metronidazole (combination therapy).

METHODS

Subjects and Study Design

A single-center, retrospective, observational, comparative study was conducted among critically ill patients with CDI. This study was approved by the institutional review board of Wake Forest Baptist Medical Center. Patients with a positive *C. difficile* polymerase chain reaction or toxin assay who were admitted to an ICU between June 2007 and September 2012 were screened for inclusion. CDI was not required to be the attributable reason for ICU admission. However, at least 3 of the following seven criteria had to be present within 24 hours of CDI treatment initiation: albumin <2.5 g/dL, heart rate >90 bpm, mean arterial pressure (MAP) <60 mmHg, WBC count ≥15 000 cells/mL, age >60 years, serum creatinine ≥1.5 times baseline, or temperature ≥100.4°F (38°C). All patients received oral vancomycin as treatment of CDI. Patients in the combination therapy group received concurrent IV metronidazole for at least 72 hours started within 48 hours after oral vancomycin. Patients were excluded if they were <18 years of age or had unrelated gastrointestinal disease. Patients were matched 1:1 based on Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.

The primary outcome measure was in-hospital mortality. Secondary outcomes included clinical success at days 6, 10, and 21 (using predefined criteria), hospital length of stay (LOS) after CDI diagnosis, and length of ICU stay after CDI diagnosis. Multivariable analysis was performed to determine factors independently associated with survival.

Definitions

Clinical success was defined as improvement of diarrhea (a decrease in the number of stools and/or volume), absence of fever, WBC count <15 000 cells/mL, normalization of tachycardia (if present), and a MAP >60 mmHg without the use of vasopressors. Patients who died were counted as clinical failures. Patients were classified as immunosuppressed if they met any of the following criteria: absolute neutrophil count (ANC) <1000 cells/mm^3, receiving chronic immunosuppressive therapy (eg, chemotherapy, monoclonal antibody, corticosteroids, methotrexate, azathioprine), or human immunodeficiency virus-positive with a CD4 count <200 cells/mm^3. Antimicrobial risk for CDI was categorized using criteria published elsewhere [7]. A high-risk antimicrobial was defined as 2nd-, 3rd-, 4th-generation cephalosporin, fluoroquinolone, or lincosamide. A moderate-risk antimicrobial was defined as penicillin, penicillin combination, 1st-generation cephalosporin, macrolide, monobactam, or streptogramin. A low-risk antimicrobial was any other systemic antimicrobial.

Standardized case definitions were used to classify CDI exposures [8]. Health-care facility-onset health-care facility associated (HO-HCFA) CDI was defined as CDI symptom onset >48 hours after admission to a HCF. Community-onset HCFA (CO-HCFA) CDI was defined as CDI symptom onset in the community or ≤48 hours after admission to a HCF, given that symptom onset was <4 weeks from the last discharge from a HCF. Indeterminate disease was defined as CDI symptom onset in the community but discharge from the same or another HCF occurred 4–12 weeks prior to symptom onset. Patients with symptom onset in the community and without discharge from a HCF in the previous 12 weeks were assigned community associated CDI (CA-CDI).

Statistical Analysis

Comparisons between groups were analyzed using chi-square or Fisher's exact test for categorical data. Mann–Whitney *U* test and Student *t* test were used for ordinal and continuous data, depending on distribution of the data. A 2-sided *P* value of <.05 was considered statistically significant. Logistic regression was used to determine factors independently associated with survival. WBC counts were adjusted using a square root transformation to make the data more normally distributed than the original data. A full model was then fit with variables with univariate *P* values <.20. Additionally, the effect of MAP was added as a control in the initial model. A final model was fit by removing nonsignificant effects singularly until only significant variables ($P < .05$) remained.

RESULTS

Patient Characteristics

Of the 187 patients who were prescribed oral vancomycin and admitted to an ICU, 88 patients failed to meet 3 of 7 criteria for establishing critical illness, leaving 99 patients who met study criteria. Of these, 88 patients were matched based on APACHE II score, 44 patients in each treatment group. Patient characteristics of the study population are shown in Table 1. Patients in the combination therapy group were more likely to have

Table 1. Patient Characteristics

Characteristic	Monotherapy (n = 44)	Combination (n = 44)	*P* Value
Age, y, mean (SD)	60.5 (15.3)	60.9 (14.8)	.90
Male gender	20 (45.5)	16 (36.4)	.52
Year of CDI treatment			.43
2007	1 (2.3)	3 (6.8)	
2008	4 (9.1)	1 (2.3)	
2009	4 (9.1)	3 (6.8)	
2010	5 (11.4)	2 (4.5)	
2011	16 (36.4)	15 (34.1)	
2012	14 (31.8)	20 (45.5)	
APACHE II score, mean (SD)	26.4 (6.9)	26.8 (6.9)	.80
Albumin, g/dL, median (range)	2.09 (1.0–3.6)	1.85 (1.0–3.3)	.06
Heart rate, beats per minute, median (range)	107 (54–152)	113 (58–168)	0.51
White blood cell count, cells/mm^3, median (range)	13.8 (0.1–151.8)	20.2 (0.2–143.2)	.004
Mean arterial pressure, mmHg, median (range)	65 (43–140)	59 (44–125)	.025
Temperature, °F, median (range)	101.1 (95.6–103.5)	100.9 (94.5–104.6)	.30
Serum creatinine, mg/dL, median (range)	1.5 (1.0–4.2)	1.6 (0.65–5.3)	.41
Charlson comorbidity index, mean (SD)	5.2 (2.7)	5.9 (2.4)	.22
Comorbidities			
Cancer	18 (40.9)	15 (34.1)	.66
Chronic pulmonary disease	10 (22.7)	11 (25.0)	1.0
Myocardial infarction	3 (6.8)	7 (15.9)	.31
Congestive heart failure	2 (4.5)	7 (15.9)	.16
Cerebrovascular disease	5 (11.4)	3 (6.8)	.71
Peripheral vascular disease	4 (9.1)	6 (13.6)	.74
Diabetes	8 (18.2)	15 (34.1)	.15
Moderate to severe renal disease	9 (20.5)	24 (54.5)	.002
Chronic hepatitis	3 (6.8)	1 (2.3)	.62
Immunosuppressed	13 (29.5)	10 (22.7)	.63
Neutropenia	8 (18.2)	3 (6.8)	.20
Chronic immunosuppressive medication(s)	3 (6.8)	6 (13.6)	.48
HIV-positive with CD4 count <200 cells/mm^3	2 (4.5)	1 (2.3)	1.0
Bedded or transferred to ICU within 24 h CDI diagnosis	40 (90.9)	43 (97.7)	.36
ICU location			.55
Medical	16 (36.4)	20 (45.5)	
Surgical	13 (29.5)	12 (27.3)	
Oncology	11 (25.0)	6 (13.6)	
Neurology	3 (6.8)	2 (4.5)	
Cardiology	1 (2.3)	2 (4.5)	
Trauma	0	2 (4.5)	
Reason for ICU admission			.83
CDI	14 (31.8)	12 (27.3)	
Respiratory failure	11 (25.0)	13 (29.5)	
Sepsis	8 (18.2)	10 (22.7)	
Cardiac	2 (4.5)	2 (4.5)	
Post-operative	1 (2.3)	2 (4.5)	
Renal failure	1 (2.3)	2 (4.5)	
Other	7 (15.9)	3 (6.8)	
CDI classification			.11
HO-HCFA	38 (86.4)	30 (68.2)	
CO-HCFA	4 (9.1)	7 (15.9)	
CA-CDAD	0 (0)	0 (0)	
Indeterminate	2 (4.5)	7 (15.9)	

Table 1 continued.

Characteristic	Monotherapy (n = 44)	Combination (n = 44)	*P* Value
Initial episode of CDI	40 (90.9)	35 (79.5)	.23
Presence of ileus	1 (2.3)	4 (9.1)	.36
Concomitant proton pump inhibitor	28 (63.6)	32 (72.7)	.49
Concomitant antimicrobials[a]			
High-risk	29 (65.9)	29 (65.9)	1.00
Moderate-risk	27 (61.4)	34 (77.3)	.17
Low-risk	42 (95.5)	37 (84.1)	.16
Received intravenous immune globulin	0	0	NS
Received vancomycin per rectum	2 (4.5)	8 (18.2)	.09

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CA-CDAD, community-associated *Clostridium difficile*-associated disease; CDI, *Clostridium difficile* infection; CO-HCFA, community-onset-health care facility-associated; HIV, human immunodeficiency virus; HO-HCFA, healthcare facility-onset-health care facility-associated; ICU, intensive care unit; NS, not significant; SD, standard deviation.

[a] High-risk: 2nd-, 3rd-, or 4th-generation cephalosporin, fluoroquinolone, or lincosamide; Moderate-risk: penicillin, penicillin combination, 1st-generation cephalosporin, macrolide, monobactam, or streptogramin; Low-risk: any other systemic antimicrobial.

moderate to severe renal disease (20.5% vs 54.5%, $P = .002$). More patients in the combination therapy group received concurrent vancomycin per rectum, but this did not reach statistical significance (2 vs 8, $P = .09$). Only one patient who received vancomycin per rectum died, and this patient received combination therapy.

The percentage of patients meeting each of the predefined severity criteria are displayed in Figure 1. Despite matching on APACHE II scores, patients in the combination therapy arm met more severity criteria than patients in the monotherapy arm. Thirty patients in the monotherapy group and 37 patients in the combination therapy group met at least 4 of 7 severity criteria (68.2% vs 84.1%, $P = .08$). Sixteen and 24 patients met at least 5 of 7 severity criteria, respectively (36.4% vs 54.5%, $P = .09$). A higher percentage of patients in the combination therapy group had a WBC count ≥15 000 cells/mm^3 (43.2% vs 68.2%, $P = .03$) and were hypotensive (36.4% vs 56.8%, $P = .05$) within 24 hours of initiation of study treatment. When

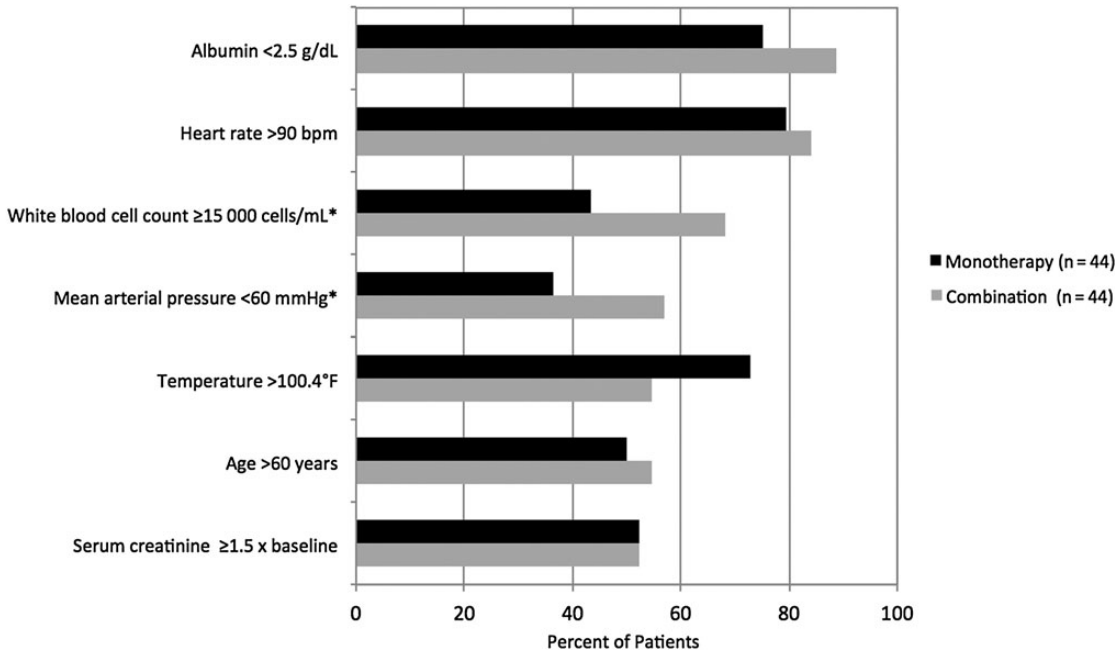

Figure 1. Percent of patients meeting criteria for critical illness in monotherapy and combination therapy groups; *$P \leq .05$.

Table 2. Treatment Outcomes

Outcome	Monotherapy (n = 44)	Combination (n = 44)	*P* Value
In-hospital mortality	16 (36.4)	7 (15.9)	.03
Time to death, days, median (range)	21 (5–174)	15 (6–32)	.23
Clinical success			
Day 6	9 (20.5)	6 (13.6)	.57
Day 10	27 (61.4)	25 (56.8)	.83
Day 21	33 (75.0)	37 (84.1)	.43
Length of stay after CDI diagnosis, days, median (range)[a]	20.5 (10–64)	18.0 (6–166)	.99
Length of ICU stay after CDI diagnosis, days, median (range)[a]	9 (4–60)	11.0 (3–68)	.93

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: CDI, *Clostridium difficile* infection; ICU, intensive care unit.

[a] Analysis excluded patients who died.

analyzed as continuous data (Table 1), patients in the combination therapy group had a higher median WBC count (13.8 vs 20.2 cells/mm^3, $P = .004$) and a lower MAP (65 vs 59 mmHg, $P = .025$).

Outcomes

Table 2 displays results of outcome measures. In-hospital mortality was higher in the monotherapy group compared to the combination therapy group; 16 patients died in the monotherapy group, whereas 7 patients died in the combination therapy group (36.4% vs 15.9%, $P = .03$). Nine patients (20.5%) in the monotherapy group compared to 6 patients (13.6%) in the combination therapy group met criteria for clinical success by day 6 of therapy ($P = .57$). At day 6, improvement in diarrhea occurred in 47.7% and 52.3% of patients in the monotherapy and combination therapy groups, respectively ($P = .67$). Similarly, there were no differences in clinical success rates at days 10 and 21. Length of stay (median 20.5 vs 18.0 days, $P = .99$) and length of ICU stay after CDI diagnosis (median 9.0 vs 11.0 days, $P = .93$) did not differ between the 2 groups. Four patients (9.1%) in the monotherapy group compared to 3 patients (6.8%) in the combination therapy group had recurrent CDI ($P = 1.0$). Multivariable analysis revealed 2 factors independently associated with survival, receiving concurrent IV metronidazole and albumin (Table 3). For albumin, survival was associated with increasing albumin values.

Antibiotic Regimens

Initial oral vancomycin dose did not differ significantly between the 2 groups. Most patients received oral vancomycin 125 mg every 6 hours, 79.5% and 59.0% in the monotherapy and combination therapy groups, respectively. Other vancomycin doses prescribed were either 250 mg every 6 hours or 500 mg every 6 hours. Oral vancomycin dose was modified during therapy in 18.2% in the monotherapy group compared to 25% in the combination therapy group ($P = .44$). All dosing modifications were among the aforementioned doses. Median duration of oral vancomycin was 15.0 days (range 6–39) in the monotherapy group and 15.5 days (6–59) in the combination therapy group ($P = .15$). Of the patients receiving IV metronidazole in combination, 25.0% received 500 mg every 6 hours, 72.7% received 500 mg every 8 hours, and 2.3% received 250 mg every 6

Table 3. Factors Associated With Survival

	Univariate		Multivariable Model	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Charlson Comorbidity Index	1.01 (.84, 1.21)	.93		
Albumin	0.91[a] (.82, .99)	.041	0.87[a] (.78, .97)	.011
WBC count	1.04 (.84, 1.29)	.72		
Mean arterial pressure	1.11 (.88, 1.40)	.38		
Absence of ileus	1.44 (.15, 13.6)	.75		
Received vancomycin per rectum	3.53 (.42, 29.6)	.24		
Immunocompromised	0.56 (.20, 1.58)	.28		
Neutropenic	0.37 (.10, 1.34)	.13		
Chronic immunosuppressive medication	0.40 (.10, 1.63)	.19		
AIDS	0.69 (.06, 8.08)	.77		
ICU location	NA	.88		
Reason for ICU admission	NA	.73		
Received IV metronidazole	3.02 (1.10, 8.33)	.033	4.54 (1.48, 14.0)	.008

Abbreviations: CI, confidence interval; ICU, intensive care unit; IV, intravenous; NA, no association; OR, odds ratio; WBC, white blood cell.

[a] Per decrease by 0.1 mg/dL.

hours. The median duration of IV metronidazole was 12.5 days (range 3–33). Only one patient received colectomy as part of CDI management (combination therapy group).

DISCUSSION

The specific aim of our study was to evaluate the difference in mortality among critically ill patients who received monotherapy or combination therapy. In the 2010 SHEA and IDSA guideline, the recommendation to add IV metronidazole is based on expert opinion [6]. The European Society of Clinical Microbiology and Infectious Diseases recently published recommendations for management of CDI but did not include specific recommendations on the use of combination therapy [9]. To our knowledge, the present study is the first to evaluate monotherapy vs combination therapy in critically ill patients with CDI. We found that mortality is higher in patients who receive monotherapy.

IV metronidazole for CDI has not been well studied. Small trials and anecdotal evidence suggest IV metronidazole alone may have efficacy [10, 11], but this evidence is not sufficient to support routine use of IV metronidazole alone in the treatment of CDI. The advantage of combination therapy observed in our study could be attributable to the dual route of IV and oral administration. Gut dysmotility in critically ill patients may inhibit delivery of oral vancomycin to the colon, thereby limiting its effectiveness. Achieving therapeutic metronidazole concentrations at the site of CDI may still occur with IV therapy because it is not dependent on gastrointestinal transit. For this reason, IV metronidazole should not be substituted with oral metronidazole when used as combination therapy.

Zar and colleagues evaluated clinical cure at day 6 in a study of oral metronidazole compared with oral vancomycin [12]. Among patients with severe disease who received oral vancomycin, clinical cure was 97%. However, of the 31 patients who received oral vancomycin for severe disease, only 2 patients were hospitalized in the ICU, which limits the applicability of these results to the treatment of critically ill patients.

One factor that has the potential to influence mortality associated with CDI is immune suppression. There were more immunocompromised patients in the monotherapy group (13 vs 10). The combination therapy group had more patients on chronic immunosuppressive medication whereas the monotherapy group had more neutropenic patients. Multivariable analysis did not find an association between types of immune suppression and mortality. Cancer is another factor to consider, and there were more patients with cancer in the monotherapy group (18 vs 15). This may have influenced how many patients were housed in an Oncology ICU, which also was a greater number in the monotherapy group. However, in our hospital, the most critically ill oncology patients are transferred to the Medicine ICU, and there were more of these patients in the combination therapy group. Similarly, multivariable analysis failed to identify ICU location as a predictor of survival.

Although mortality was lower in the combination therapy group, a difference between treatment groups in the number of patients meeting the definition of clinical success was not observed. Clinical success was similar between the groups at all time points evaluated (6, 10, and 21 days). In addition, the overall clinical success rates were relatively low; only 20.5% in the monotherapy group and 13.6% in the combination therapy group achieved clinical success by day 6. The authors acknowledge that the definition for clinical success used in this study may not be appropriate for evaluating response to CDI treatment in this patient population, and this may account for the discrepancy between clinical success and mortality. Many critically ill patients who get CDI are not critically ill only because of CDI. Underlying comorbidities in addition to CDI can contribute to their level of illness. For instance, it is possible patients could have had another reason besides CDI to exhibit tachycardia (part of clinical success criteria) which may not have resolved with effective CDI treatment. This is supported by the much higher rates of improvement in diarrhea at day 6 compared with the rates of clinical success.

This study was not designed to determine the cause of death or the extent to which CDI contributed to death among patients who died during their hospitalization. Although the median time to death for each treatment group was similar, the range was rather large for the monotherapy group (5–174 days). These data are not normally distributed, and 174 days represents an outlier result. Although death at 174 days is not as likely to be directly attributable to CDI, it is difficult to know how much early events in a hospitalization impact the ultimate disposition of any given patient.

It is noteworthy that more patients in the combination therapy group received vancomycin per rectum (8 vs 2). Even though the multivariable analysis did not identify receipt of per rectum vancomycin as an independent predictor of survival, the use of vancomycin by this route would afford the same proposed benefit as IV metronidazole by ensuring delivery of antibiotic to the site of infection. Although this study was not designed to assess the impact of per rectum vancomycin, the study's findings suggest possible benefit and support future efforts to study this treatment in the critically ill population.

Critically ill patients represent a unique subgroup within the 'severe disease' category of current guidelines. Within guidelines, categorization as severe CDI can be based on laboratory data alone (eg, WBC count or serum creatinine), but these criteria may not adequately represent the severity of disease present in a critically ill patient. As such, the terms "severe disease" and "critically ill" as they relate to CDI may not be appropriately interchangeable. Consideration of other factors is important when deciding who should get concurrent IV metronidazole. Such factors include admission to an ICU, advanced age, temperature

>38.3°C, low serum albumin, and evidence of hemodynamic instability (tachycardia and hypotension) [12–15]. To be classified as critically ill in our study, patients had to receive CDI treatment in an ICU and meet at least 3 of 7 severity of illness criteria. Having at least 3 of these criteria was chosen arbitrarily; however, a majority of patients in each group met more than 3 criteria. This method of assigning critically ill status has not been previously validated, and so this is considered a limitation to the study.

There are limited data regarding the preferred dosing regimen of oral vancomycin for critically ill patients with CDI. The SHEA/IDSA guideline recommends 125 mg every 6 hours for most patients, but for patients with ileus, toxic megacolon, hypotension, or shock the recommended dose of oral vancomycin is 500 mg every 6 hours [6]. Abdominal distention is considered an indication for the 500 mg dose in another set of guidelines [16]. This seems reasonable as abdominal distention is considered a sign of potential ileus. Even with consistent recommendations to administer the higher dose for patients with severe, complicated CDI, the evidence to support this recommendation is lacking. In our study, different oral vancomycin doses were used in both groups. The effect of vancomycin dose on clinical outcomes is unknown. Available literature suggests there is no difference in clinical outcomes between low- and high-dose regimens [17–19]. In addition, vancomycin 125 mg every 6 hours achieves fecal concentrations that far exceeds the necessary amount needed to inhibit *C. difficile* [20, 21]. Gonzales et al noted lower fecal concentrations during the first 24 hours of treatment; however, concentrations were still well above the MIC_{90} of *C. difficile* (1 mg/L), and clinical significance of this finding is unknown [21]. Likewise, there is no evidence to support a higher dose for critically ill patients with CDI, although there is potential for gut dysmotility in this patient population.

Our study is not without other limitations. The retrospective study design instills reliance on accurate documentation in the medical record and limits interpretation of outcomes that are not completely objective. Although efforts were made to match the groups, lack of randomization imparts risk that the groups may not be drawn from the same population. There is particular risk of confounding by indication; assignment according to treatment may be inherently biased because a relationship may exist between choice of treatment and certain medical conditions or health outcomes. The small sample size of this study undermines statistical power and decreases the likelihood of accurate results. However, this study represents the largest study of critically ill, ICU patients with CDI. We evaluated management of CDI in a limited subgroup of patients where practice guidelines lack sufficient evidence to support treatment recommendations.

Clostridium difficile infections have generated a significant burden on the healthcare system contributing to elevated healthcare costs and mortality. Based on our findings, critically ill patients with CDI who require admission to an ICU may benefit from combination therapy with oral vancomycin and IV metronidazole. It is important to emphasize that these results are best applied in the care of the most severely ill patients with CDI. Prospective, randomized studies to define optimal treatment regimens in critically ill patients with CDI are warranted.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

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.

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