CONCISE COMMUNICATION

Comparison of 3 Severity Criteria for *Clostridium difficile* Infection

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Effective severity criteria are needed to guide management of *Clostridium difficile* infection (CDI). In this retrospective study, outcomes were compared between patients with mild-moderate versus severe CDI according to 3 different severity criteria: those included in the 2010 Society for Healthcare Epidemiology of America/Infectious Diseases Society of America guidelines, those from a recent clinical trial, and our hospital-specific guidelines.

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Clostridium difficile infection (CDI) can produce a variable clinical course ranging from mild diarrhea to severe infection with fulminant colitis and septic shock.[1] The emergence of highly virulent strains of *C. difficile* over the past decade, particularly the epidemic BI/NAP1/027 strain, has been linked to increased disease prevalence and severity[2,3] as well as higher rates of treatment failure with metronidazole.[4,5]

Recent studies readdressing management strategies for CDI found higher rates of treatment failure with metronidazole retrospectively[6] and improved outcomes with oral vancomycin, compared with metronidazole, prospectively[7] in patients who met criteria for severe infection only. Subsequently, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) issued revised clinical practice guidelines for CDI management recommending metronidazole for mild-moderate disease and vancomycin for severe disease.[8] The various severity criteria used to guide treatment selection in these publications were based on risk factors for severe CDI previously identified in the literature and expert opinion and, to our knowledge, have not been systematically evaluated. In this study, we compare 3 different severity criteria for CDI, including those in the 2010 SHEA/IDSA guidelines.

METHODS

This study included all adult patients with CDI between 2009 and 2010 at 2 hospitals in New York City, a 700-bed academic tertiary care center and a 200-bed community hospital. For all patients, diagnosis was confirmed by testing fecal samples using enzyme immunoassay (Wampole TOX A/B) or polymerase chain reaction (Cepheid Xpert). Data were collected by reviewing medical, laboratory, and pharmacy records. Only the first episode of CDI during the study period was considered; patients who did not receive at least 2 days of treatment with metronidazole or oral vancomycin while hospitalized or who could not be stratified because of missing data were excluded. The study protocol was approved by the institutional review board of Columbia University Medical Center.

Patients were retrospectively stratified into mild-moderate or severe disease categories using data obtained on the CDI diagnosis date according to 3 different severity criteria: hospital-specific guidelines created by experts at our institution,[9] criteria included in the 2010 SHEA/IDSA guidelines,[8]

TABLE 1. Three Different Severity Criteria for *Clostridium difficile* Infection (CDI)

Severity criteria	Mild-moderate disease	Severe disease
Hospital-specific guidelines[9]	≥3 diarrheal stools/day; may be accompanied by mild or moderate abdominal discomfort, elevated WBC count, and fever	Mild-moderate criteria plus at least 1 of the following: At least 3 of the following: temperature >38.3°C, WBC count >20,000 cells/mm^3, albumin level <2.5 g/dL, age ≥65 years, ICU admission; *OR* endoscopically or histologically confirmed pseudomembranous colitis; *OR* toxic megacolon, perforation, colectomy, or septic shock requiring ICU admission and pressors
SHEA/IDSA guidelines[8]	WBC count <15,000 cells/mm^3 *AND* serum creatinine <1.5 × baseline	WBC count ≥15,000 cells/mm^3 *OR* serum creatinine ≥1.5 × baseline; Severe, complicated CDI: hypotension or shock, ileus, or megacolon
Zar criteria[a]	<2 points	2 or more points

NOTE. ICU, intensive care unit; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America; WBC, white blood cell.

[a] Based on the clinical trial conducted by Zar et al.[7] One point is given for each of the following: age >60 years; temperature >38.3°C; albumin level <2.5 mg/dL; WBC count >15,000 cells/mm^3. Two points are given for endoscopic evidence of pseudomembranous colitis and treatment in the ICU.

TABLE 2. Patient Characteristics

Characteristic	All patients with CDI (n = 364)	Patients treated with metronidazole (n = 253)	Patients treated with vancomycin (n = 111)	P
Male sex	172 (47)	123 (49)	49 (44)	.50
Age ≥65 years	208 (57)	130 (51)	78 (70)	.001
ICU at time of diagnosis	81 (22)	37 (15)	44 (40)	<.001
Positive by PCR	263 (72)	178 (70)	85 (77)	.27
Chronic comorbidities by organ system				
Cardiac disease	118 (33)	72 (29)	46 (41)	.02
Pulmonary disease	97 (27)	62 (25)	35 (32)	.21
Diabetes mellitus	139 (38)	99 (39)	40 (36)	.66
Gastrointestinal/liver disease	57 (16)	41 (16)	16 (14)	.78
Renal disease	84 (23)	62 (25)	22 (20)	.40
Malignancy	52 (14)	38 (15)	14 (13)	.66
Solid organ transplant recipient	55 (15)	39 (15)	16 (14)	.93
Concomitant use of acid-suppressing medication	256 (70)	179 (71)	77 (69)	.89
Gastrointestinal surgery within the past 6 months	55 (15)	40 (16)	15 (14)	.69
Use of chemotherapy within the past month	19 (5)	13 (5)	6 (5)	1.0
Use of immunosuppressant medications	133 (37)	92 (36)	41 (37)	1.0
Temperature >38.3°C	32 (9)	18 (7)	14 (13)	.13
WBC count ≥15,000 cells/mm^3	122 (34)	60 (24)	62 (56)	<.001
WBC count ≥20,000 cells/mm^3	60 (17)	21 (8)	40 (36)	<.001
Serum creatinine ≥1.5 × baseline	76 (21)	39 (16)	37 (33)	<.001
Serum albumin <2.5 g/dL (n = 354)	98 (28)	56 (23)	42 (38)	.01
Outcome				
Death within 7 days	23 (6)	9 (4)	14 (13)	.002
Colectomy	1 (0.3)	0 (0)	1 (1)	.67
Pathologically confirmed pseudomembranes	3 (0.8)	0 (0)	3 (3)	.05
Septic shock within 48 hours	24 (7)	7 (3)	17 (15)	<.001
ICU admission within 48 hours	50 (14)	20 (8)	30 (27)	<.001
Death within 30 days	57 (16)	23 (9)	34 (31)	<.001

NOTE. CDI, *Clostridium difficile* infection; ICU, intensive care unit; PCR, polymerase chain reaction; WBC, white blood cell.

and a severity score used in the randomized clinical trial by Zar et al[7] (Table 1).

After stratification by initial treatment regimen, outcomes were compared among patients according to their disease severity designation. Patients who received a combination of metronidazole and vancomycin were included in the vancomycin group. The primary outcome measure was a composite of death or need for colectomy within 7 days of CDI diagnosis. For convenience, patients who met the primary outcome were labeled as having a "poor outcome," whereas patients who did not were labeled as having a "good outcome."

Proportions of patients with good versus poor outcomes were compared using Pearson's χ^2 or Fisher's exact test as appropriate. P values of less than .05 were considered to be statistically significant for all comparisons. All statistical analyses were performed using Predictive Analytics Software Statistics 18.0 (SPSS).

RESULTS

During the study period, 398 patients with CDI were identified; 3 pediatric patients, 19 patients not treated in the hospital, and 12 patients with missing data were excluded. Ultimately, 364 patients were included in the analyses. Patient characteristics and outcomes are presented in Table 2. Most patients (70%) were initially treated with metronidazole; 12% received vancomycin, and 18% were given a combination of metronidazole and vancomycin and were included in the vancomycin group.

Overall, 24 (7%) of 364 patients met the primary outcome and were labeled as having a poor outcome; 23 patients died within 7 days of CDI diagnosis, and 1 patient underwent colectomy. Compared with those who received metronidazole, patients treated with vancomycin were significantly more likely to be older than 65 years or have a white blood cell (WBC) count greater than or equal to 15,000 cells/mm^3, el-

TABLE 3. Proportion of Poor Outcomes by Disease Severity in Patients Treated with Metronidazole or Vancomycin

	Metronidazole treatment, no. (%) of patients (n = 253)			Vancomycin treatment, no. (%) of patients (n = 111)		
Severity criteria	Mild-moderate disease	Severe disease	P	Mild-moderate disease	Severe disease	P
Hospital-specific guidelines (n= 364)	7/223 (3)	2/30 (7)	.29	4/57 (7)	11/54 (20)	.05
SHEA/IDSA guidelines (n = 364)	1/161 (1)	8/92 (9)	.002	0/28 (0)	15/83 (18)	.01
Zar criteria[7] (n = 364)	2/154 (1)	7/99 (7)	.03	0/31 (0)	15/80 (19)	.01

NOTE. IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America.

evated serum creatinine level greater than or equal to 1.5 × baseline, or albumin level less than 2.5 g/dL. They were also more likely to have a poor outcome, require intensive care unit (ICU) admission, or develop sepsis within 48 hours of CDI diagnosis.

Only 23% of patients were classified as having severe CDI by hospital-specific guidelines, compared with 48% by SHEA/IDSA guidelines and 49% by Zar criteria; the difference between hospital-specific guidelines and the other 2 criteria was significant ($P < .001$ for both comparisons). Although 54% of patients who had a poor outcome were categorized as having severe CDI by hospital-specific guidelines, 96% and 92% of patients with a poor outcome had severe disease according to SHEA/IDSA guidelines and Zar criteria, respectively.

As shown in Table 3, regardless of treatment regimen, patients who met criteria for severe disease were more likely to have a poor outcome than a good outcome. Among patients treated with metronidazole, this difference was significant using SHEA/IDSA guidelines and Zar criteria only; poor outcomes did not differ significantly between patients categorized as having mild-moderate versus severe disease by hospital-specific guidelines.

Patients found to have severe disease were most likely to meet the following individual components of each of the severity criteria: for hospital-specific guidelines, older age (74%), ICU admission (69%), or complications such as toxic megacolon or septic shock (63%) were most common; for SHEA/IDSA guidelines, higher WBC count (70%) was more frequent than elevated serum creatinine level (43%); and for Zar criteria, older age (82%) and higher WBC count (60%) were most common. Patients often met more than 1 severity criterion.

DISCUSSION

To our knowledge, this is the first study to present a comparison of severity criteria for CDI and evaluate the ability of these criteria to identify patients who are at risk for having a poor outcome and may benefit from treatment with vancomycin. Upon retrospective stratification using 3 different severity criteria, we found that patients with severe CDI were significantly more likely to have a poor outcome, which suggests that each of the criteria met this primary goal.

In a recent systematic review of 26 studies assessing risk factors for poor outcomes in patients with CDI, 59% and 46% of studies found WBC count and serum creatinine level, respectively, to be associated with mortality; advanced age and low serum albumin level were also found by several studies to be associated with mortality.[10] Although our study was not primarily designed to compare the individual components of each severity criteria, we did find that elevated WBC count, elevated creatinine level, and older age were common among patients designated as having severe disease, in addition to other expected markers for complicated disease, such as pseudomembranous colitis, septic shock, or ICU admission.

Because our hospital-specific guidelines had more stringent criteria for severe disease, a larger proportion of patients in the mild-moderate category went on to have a poor outcome; this suggests that these guidelines may need to be reevaluated. SHEA/IDEA guidelines and Zar criteria identified similar proportions of patients as having mild-moderate and severe disease, and few patients with mild-moderate disease had a poor outcome. As the criteria included in SHEA/IDSA guidelines are streamlined, easily applied in the clinical setting, and supported by previous studies of risk factors for severe CDI, their preferred use would seem justified on the basis of the results of this study.

Because of the study's retrospective study design and limited number of adverse outcomes, we were unable to determine which patient groups were most likely to benefit from vancomycin use. Future assessments of severity criteria for CDI should be performed prospectively.

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