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BRIEF REPORT

Does Adjunctive Tigecycline Improve Outcomes in Severe-Complicated, Nonoperative *Clostridium difficile* Infection?

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Severe *Clostridium difficile* infection is associated with a high rate of mortality; however, the optimal treatment for severe-complicated infection remains uncertain for patients who are not candidates for surgical intervention. Thus, we sought to evaluate the benefit of adjunctive tigecycline in this patient population using a retrospective cohort adjusted for propensity to receive tigecycline. We found that patients who received tigecycline had similar outcomes to those who did not, although the small sample size limited power to adjust for comorbidities and severity of illness.

Keywords. *Clostridium difficile*; severe *Clostridium difficile*; tigecycline.

Clinical *Clostridium difficile* infection (CDI) ranges from mild diarrheal illness to fulminant and life-threatening infection. The Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) CDI guideline defines severe-complicated infection if hypotension, shock, colonic ileus, or toxic megacolon is present [1]. Clinical manifestations of CDI are primarily attributable to exotoxins A and B, which mediate colitis and diarrhea. In vivo, toxin production levels correlate with disease severity [2].

Treatment of mild to moderate and severe CDI has been studied in randomized controlled trials; however, little data are available to guide management of severe-complicated infection, particularly in nonsurgical candidates. The SHEA/IDSA guideline recommendations for medical therapy include vancomycin, 500 mg by mouth or by nasogastric tube 4 times daily, plus metronidazole, 500 mg intravenously 3 times daily. If a complete ileus is present, rectal administration of vancomycin may be considered (CIII level of evidence) [1, 3].

Despite improvements, mortality rates in patients with severe-complicated disease exceed 30% [4]. Colectomy is a potentially life-saving intervention; however, validated indications for the use of colectomy do not exist [1, 4]. Ileostomy with colonic lavage is another promising surgical intervention [5]. Unfortunately, many patients have multiple comorbidities and/or develop severe sepsis attributable to severe-complicated CDI precluding operative intervention.

Standard antimicrobial treatment options are limited: oral vancomycin may have limited efficacy in this population with a nonfunctional gastrointestinal tract, and the efficacy of metronidazole against *C difficile* is suboptimal [6, 7]. Clinical trials of novel agents, such as tolevamer, have been disappointing [8]. Although fecal microbiota transplantation (FMT) is a promising investigational treatment for recurrent and refractory CDI, prospective data in severe-complicated disease are limited, and FMT will likely have to be coupled with pathogen-directed treatments that reduce toxin production and control the proliferation of *C difficile* [9]. Surgical colectomy is often curative; however, many patients may not be eligible given underlying comorbidities or goals of care. The limitation of current available therapies creates an urgent need for alternatives that address all of these challenges.

Tigecycline possesses several qualities that suggest potential utility in the treatment of severe-complicated CDI. First, it is an intravenous—rather than oral—agent and thus would be expected to achieve therapeutic concentrations in the colon even in the setting of gastrointestinal tract nonmotility. In addition, tigecycline has excellent in vitro activity against the organism, the ability to achieve high concentrations in the gut, and, as an inhibitor of bacterial protein synthesis, inhibition of toxin production [10, 11]. Animal models of disease and case-report level data in human subjects also suggest a benefit [12–15]. Thus, we sought to evaluate the effectiveness of tigecycline in reducing in-hospital mortality in patients with severe-complicated CDI who were not surgical candidates.

METHODS

A retrospective cohort study was performed at a single, tertiary care facility in Boston with 300–400 new diagnoses of *C difficile* carriage or infection annually. Patients with CDI confirmed by toxin enzyme immunoassay or deoxyribonucleic acid amplification assay from September 2009 to June 2012 were included. Severe-complicated CDI was defined by presence of at least one of the following: intensive care unit (ICU) level of care, sepsis, ileus, elevated serum lactate (>2.5 mmol/L), white blood cell count (WBC) 50 000 cells/μL, hemodynamic instability, severe

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abdominal pain or rigidity, imaging with megacolon or confluent pseudomembranous colitis on colonoscopy. Mortality risk was assessed using a modified age, renal disease, and cancer (ARC) comorbidity score [16].

Patients receiving adjunctive tigecycline plus standard *C difficile* agents (vancomycin orally and/or rectally plus metronidazole) were compared with cohort patients who received guideline-driven CDI management. The primary end point was in-hospital mortality. Of note, at the beginning of our study period, the Antimicrobial Stewardship Team at Beth Israel Deaconess Medical Center suggested oral vancomycin plus intravenous metronidazole for patients with severe complicated disease as standard practice. In 2011, a multidisciplinary clinical treatment guideline was introduced to institutionalize these recommendations (Supplement A). In the clinical treatment pathway, infectious diseases consultations, surgical consultation, and receipt of tigecycline were listed as "considerations" for additional management in patients with severe, complicated disease.

A propensity score was derived from variables determined a priori to be likely associated with the receipt of tigecycline. Factors in the propensity score included the following: sex, age >65 years, serum creatinine >1.2 mg/dL, body mass index >30 kg/m^2, ICU admission, WBC <4000 or >11 000 cells/μL, previous CDI, concurrent infection, receipt of non-CDI antibiotics (exclusive of tigecycline) within 1 week of CDI diagnosis, and admission to a medical service.

The propensity score and receipt of tigecycline were included as predictor variables in a logistic regression model predicting in-hospital mortality. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Approval was obtained from the institution's Committee on Clinical Investigation before data collection and analysis.

RESULTS

A total of 641 patients with CDI were identified during the study period. Of these, 98 had severe-complicated disease; 8 underwent colectomy and did not meet study criteria. Of the 90 eligible patients, 21 (23%) received adjunctive tigecycline and 69 (77%) did not (see Table 1 for baseline characteristics of the cohort). The majority of patients were classified as severe-complicated infection due to ICU admission for the reason of CDI (61% in the tigecycline group and 75% in the standard care group).

The in-hospital mortality rate among tigecycline recipients was 14% versus 23% in controls (unadjusted odds ratio [OR], 0.55; 95% confidence interval [CI], 0.14–2.12). No significant difference in modified ARC score between groups was detected. Causes of death in the tigecycline group (3) included multiorgan system failure (2) and progressive deterioration of unclear etiology (1). One patient was discharged to hospice care after resolution of CDI due to advanced age and other comorbid conditions.

After adjusting for propensity score, no statistically significant difference in in-hospital mortality was detected in the multivariable model when comparing those patients receiving adjunctive tigecycline and those receiving standard therapy alone (OR, 0.71; 95% CI, 0.16–3.24). C-statistic of the propensity score model was 0.79.

DISCUSSION

Tigecycline is a protein synthesis inhibitor that reduces bacterial toxin production and has excellent in vitro activity against *C difficile* [17]. Because CDI is a toxin-mediated disease, tigecycline has a theoretical benefit for improving outcomes in patients with severe-complicated CDI. Animal models of disease have demonstrated a role for tigecycline for reducing toxin production and improving survival, and recent studies suggest that tigecycline monotherapy may be superior to standard agents for patients with severe disease [12, 15, 18].

Despite these potential advantages of tigecycline for CDI management, published experience in human subjects is limited, particularly for patients with the most severe clinical illness. In this population, few case reports suggest a role [13, 14, 18, 19]. A recent retrospective cohort study investigating tigecycline for severe CDI found higher rates of clinical cure, less complicated courses, and a reduction in CDI sepsis in patients who received tigecycline monotherapy versus standard treatments [20]. Our study expands upon this concept by evaluating the impact of tigecycline in a small cohort of patients with severe, complicated disease who were nonsurgical candidates. In this population, we found no statistical benefit to the addition of tigecycline to the standard of care in our facility. However, we were limited in our ability to assess the impact of severity of illness and comorbid conditions given the small size of the cohort. In particular, we had an insufficient sample size to assess risk of mortality by the reason for classification as severe-complicated infection because the majority of our patients were classified as severe-complicated due to ICU admission for CDI.

Tetracycline-derived antibiotics, such as doxycycline, have been shown to have less potential to cause CDI than other types of antimicrobials [21]. Thus, tigecycline may also be a reasonable option for patients with CDI and concomitant non-CDI bacterial infections. However, the potential lack of harm from tigecycline vis-a-vis CDI and potential benefit accrued by tigecycline replacing other antibiotics associated with poorer CDI-related outcomes must be carefully weighed against other data demonstrating lower efficacy for tigecycline for treating other types of severe infections [22]. Given the high mortality of patients with severe-complicated CDI who are nonsurgical candidates, the balance of risks and benefits may lean towards considering tigecycline as a potential adjunctive agent while alternate promising strategies, such as FMT, are considered.

Table 1. Patient Characteristics

Patient Characteristics	Tigecycline ± Standard of Care (n = 21)	Standard of Care (n = 69)	*P* Value
Demographics			
Age (years, median, interquartile range)	75 (52–81)	77 (58–85)	.24
Male, n (%)	9 (42.9)	27 (39.1)	.76
Patient Factors			
Previous CDI, n (%)	5 (23.8)	7 (10.1)	.14
Body mass index >30, n (%)	7 (33.3)	23 (33.3)	1.0
Active malignancy, n (%)	5 (23.8)	18 (26.1)	.83
Bone marrow transplant, n (%)	1 (4.8)	1 (1.5)	.41
Solid organ transplant, n (%)	3 (14.3)	4 (5.8)	.35
Inflammatory bowel disease, n (%)	0 (0)	9 (13.0)	.08
Glucocorticoid use, n (%)	3 (14.3)	11 (15.9)	1.0
Admission Information			
Service, n (%)			.10
Medicine	20 (95.2)	54 (78.3)	
Other	1 (4.8)	15 (21.7)	
Intensive care unit admission, n (%)	14 (66.7)	54 (78.3)	.38
Intensive care unit admission for CDI, n (%)	13 (61.9)	52 (75.4)	.23
Mechanical ventilation, n (%)	7 (33.3)	13 (18.8)	.23
Pressor therapy, n (%)	8 (38.1)	26 (37.7)	.97
White Blood Cell Count, Range (%)			
<4	3 (14.3)	6 (8.7)	.43
4–11	Reference group	Reference group	
>11	16 (76.2)	47 (68.1)	.48
Serum creatinine >1.2 mg/dL, n (%)	13 (61.9)	34 (49.3)	.31
Modified ARC Score			.75
0–3	10 (47.6)	28 (40.6)	
4–7	11 (52.4)	40 (58.0)	
>8	0 (0)	1 (1.4)	
Concurrent infection, n (%)	12 (57.1)	25 (36.2)	.13
Bloodstream infection	4 (19.0)	6 (8.7)	.23
Intra-abdominal infection	4 (19.0)	1 (1.4)	.01
Urinary tract infection	4 (19.0)	11 (15.9) 10	.74
CAP/HCAP/HAP	1 (4.7)	(14.5)	.45
Ventilator-associated pneumonia	1 (4.7)	3 (4.4)	1.0
Complicated skin and soft tissue infection	2 (9.5)	1 (1.4)	.13
Receipt of non-CDI antibiotics within 1 week of CDI diagnosis, n (%)	16 (76.2)	55 (79.7)	.73
Infectious diseases consult, n (%)	21 (100)	17 (24.6)	<.001
Gastroenterology consult, n (%)	8 (38.1)	14 (20.3)	.10
Endoscopy, n (%)	3 (14.3)	5 (7.2)	.38
Surgery consult or primary surgical service, n (%)	16 (76.1)	23 (33.3)	<.001
Treatment, n (%)			
Vancomycin, oral administration	21 (100)	59 (85.5)	.11
Vancomycin, rectal administration	10 (47.6)	13 (18.8)	.02
Metronidazole	21 (100)	66 (95.6)	1.0
Intravenous immunoglobulin	3 (14.3)	0 (0)	.01
Cholestyramine	2 (9.5)	4 (5.8)	.62

Abbreviations: ARC, age, renal disease, and cancer; CAP, community-acquired pneumonia; CDI, *Clostridium difficile* infection; HAP hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia.

The major limitation of our study is its small sample size limiting our power. Given concern for confounding by indication because those who were sicker may be more likely to receive adjunctive therapy, we used a propensity score model to account for this concern as much as was feasible. Our sample size additionally limited (1) our ability to account for variation in the standard of care agents used as well as (2) our ability to assess for differences in mortality based on the timing of receipt or duration of use of adjunctive tigecycline. A second limitation is that all of the patients who received tigecycline also received infectious diseases consultations, which has been demonstrated in a variety of clinical syndromes to improve outcomes [23, 24].

Because the 2 factors were universally associated, we were not able to determine the independent effect of each.

CONCLUSIONS

In this largest study to date, we found no difference in in-hospital mortality when adjunctive tigecycline was added to guideline-driven regimens among patients with severe-complicated CDI who were deemed not to be surgical candidates. However, we also did not detect harm associated with receipt of tigecycline. Larger randomized controlled trials will be needed to fully elucidate the role of tigecycline as an adjunctive agent for the management of severe-complicated CDI.

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.

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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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