Impact of Tigecycline on *C. difficile* Outcomes: Case Series and Propensity-Matched Retrospective Study

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ABSTRACT

This case series and propensity-matched cohort study on the use of tigecycline in *Clostridioides difficile* infection (CDI) evaluated the effect of tigecycline on 30-day mortality. Adjusted for ATLAS Score, hypotension, treatment time period, and serum lactate, tigecycline did not significantly improve 30-day mortality (odds ratio: 0.89; 95% confidence interval: 0.25–3.12; \( P = 0.853 \)). A randomized controlled trial is needed to determine efficacy and safety of tigecycline in severe or refractory CDI.

KEYWORDS *Clostridioides difficile*, tigecycline

*Clostridioides difficile* infection (CDI) remains potentially lethal in an unacceptably large proportion of inpatients (1). Tigecycline has been used off-label as adjunctive treatment in severe or refractory CDI (2); however, there are no randomized controlled trials to date supporting its use. While some case reports (3–5) and limited retrospective analyses suggest higher rates of CDI cure with tigecycline (6), other observational studies have failed to demonstrate any statistically significant benefit while adjusting for confounding factors (7–9), and some suggest increased rates of mortality and colectomy (10). Furthermore, tigecycline does not appear to reduce CDI recurrence (3, 9, 11), and excess all-cause mortality is associated with tigecycline for non-CDI indications (12, 13).

A retrospective case series analysis and propensity-matched cohort study were conducted at University of Virginia (UVA) Hospital to evaluate hospitalized adult patients with *C. difficile* infection administered >1 dose of tigecycline during treatment. This study received approval...
TABLE 1 Baseline characteristics of full and propensity-matched CDI cohorts

| Characteristic                  | Full cohort | Propensity matched |
|--------------------------------|-------------|--------------------|
|                                |             | No tigecycline     | Tigecycline | No tigecycline | Tigecycline | P value |
|                                | (N = 3,273) | N = 28             |            | N = 140       | N = 28      |         |
| Age (Mean (SD))                | 60.7 (16.5) | 56.1 (12.9)         | 0.0704     | 56.0 (17.8)   | 56.1 (12.9) | 0.982   |
| Gender                         |             |                    |            | No tigecycline | Tigecycline |         |
| Male                           | 1,643 (50.2%) | 18 (64.3%)        | 0.195      | 90 (64.3%)    | 18 (64.3%)  | 1       |
| Race                           |             |                    |            | No tigecycline | Tigecycline |         |
| White                          | 2,617 (80.0%) | 23 (82.1%)         | 0.969      | 122 (87.1%)   | 23 (82.1%)  | 0.538   |
| African American               | 594 (18.1%)  | 5 (17.9%)          |            | 16 (11.4%)    | 5 (17.9%)   |         |
| Asian                          | 15 (0.5%)    | 0 (0%)             |            | 0 (0%)        | 0 (0%)      |         |
| Other                          | 47 (1.4%)    | 0 (0%)             |            | 2 (1.4%)      | 0 (0%)      |         |
| Ethnicity                      |             |                    |            | No tigecycline | Tigecycline |         |
| Hispanic                       | 36 (1.1%)    | 0 (0%)             | 0.966      | 1 (0.7%)      | 0 (0%)      | 0.571   |
| Hypotension                    |             |                    |            | No tigecycline | Tigecycline |         |
| SBP <90                        | 1,202 (36.7%) | 15 (53.6%)         | 0.1        | 75 (53.6%)    | 15 (53.6%)  | 1       |
| Pressors                       | 314 (9.6%)   | 8 (28.6%)          | **0.00229** | 35 (25.0%)    | 8 (28.6%)   | 0.874   |
| Ileus or megacolon             | 1,104 (33.7%) | 8 (28.6%)         | 0.708      | 41 (29.3%)    | 8 (28.6%)   | 1       |
| Intensive care unit            | 385 (11.8%)  | 5 (17.9%)          | 0.483      | 25 (17.9%)    | 5 (17.9%)   | 1       |
| NHSN Classification            |             |                    |            | No tigecycline | Tigecycline |         |
| CO-CDI                         | 1,189 (36.3%) | 6 (21.4%)          | 0.157      | 29 (20.7%)    | 6 (21.4%)   | 0.904   |
| CO-HCFA-CDI                    | 575 (17.6%)  | 8 (28.6%)          |            | 46 (32.9%)    | 8 (28.6%)   |         |
| HO-CDI                         | 1,509 (46.1%) | 14 (50.0%)        |            | 63 (46.4%)    | 14 (50.0%)  |         |
| Comorbidities                  |             |                    |            | No tigecycline | Tigecycline |         |
| CHF                            | 441 (13.5%)  | 3 (10.7%)          | 0.714      | 21 (15.0%)    | 3 (10.7%)   | 0.714   |
| PVD                            | 308 (9.4%)   | 0 (0%)             | 0.132      | 15 (10.7%)    | 0 (0%)      | 0.132   |
| Dementia                       | 67 (2.0%)    | 1 (3.6%)           | 1          | 0 (0%)        | 1 (3.6%)    | 0.384   |
| COPD                           | 563 (17.2%)  | 5 (17.9%)          | 1          | 31 (22.1%)    | 5 (17.9%)   | 0.719   |
| Rheum                          | 117 (3.6%)   | 0 (0%)             | 0.556      | 2 (1.4%)      | 0 (0%)      | 1       |
| Diabetes                       | 863 (26.4%)  | 8 (28.6%)          | 0.962      | 41 (29.3%)    | 8 (28.6%)   | 1       |
| Renal                          | 634 (19.4%)  | 8 (28.6%)          | 0.325      | 45 (32.1%)    | 8 (28.6%)   | 0.882   |
| Cancer                         | 717 (21.9%)  | 9 (32.1%)          | 0.283      | 51 (36.4%)    | 9 (32.1%)   | 0.829   |
| AIDS                           | 15 (0.5%)    | 0 (0%)             | 1          | 0 (0%)        | 0 (0%)      | 1       |
| Charlson Comorbidity Index     | 1.77 (1.38)  | 1.68 (1.35)        | 0.731      | 2.12 (1.52)   | 1.68 (1.35) | 0.157   |
| Recurrence                     |             |                    |            | No tigecycline | Tigecycline |         |
| Initial                        | 2.718 (83.0%) | 22 (78.6%)        | 0.0538     | 102 (72.9%)   | 22 (78.6%)  | 0.547   |
| 1                              | 371 (11.3%)  | 3 (10.7%)          |            | 25 (17.9%)    | 3 (10.7%)   |         |
| 2                              | 105 (3.2%)   | 2 (7.1%)           |            | 6 (4.3%)      | 2 (7.1%)    |         |
| 3                              | 47 (1.4%)    | 0 (0%)             |            | 3 (2.1%)      | 0 (0%)      |         |
| 4                              | 22 (0.7%)    | 0 (0%)             |            | 3 (2.1%)      | 0 (0%)      |         |
| 5                              | 10 (0.3%)    | 1 (3.6%)           |            | 1 (0.7%)      | 1 (3.6%)    |         |
| White blood cell count (cells/μL) |           |                    |            | No tigecycline | Tigecycline |         |
| Mean (SD)                      | 14.4 (10.8)  | 22.5 (28.5)        | 0.15       | 20.9 (17.1)   | 22.5 (28.5) | 0.785   |
| Creatinine (mg/dL)             | 2.15 (2.29)  | 2.91 (2.40)        | 0.112      | 2.89 (2.31)   | 2.91 (2.40) | 0.972   |
| Albumin (mg/dL)                | 2.66 (0.712) | 2.24 (0.636)       | **0.00274** | 2.44 (0.707)  | 2.24 (0.636) | 0.164   |
| Lactate (mg/dL)                | 2.38 (2.19)  | 3.92 (4.83)        | 0.182      | 3.20 (2.87)   | 3.92 (4.83) | 0.541   |
| Mean (SD)                      | 1.830 (55.9%) | 19 (67.9%)        | 0.282      | 94 (67.1%)    | 19 (67.9%)  | 1       |
| Non-CDI antibiotics during treatment |       |                    |            | 449 (13.7%)   | 7 (25.0%)   |         |
| Immunosuppression              | 449 (13.7%)  | 7 (25.0%)          | 0.148      | 37 (26.4%)    | 7 (25.0%)   |         |
| Antimotility use               | 169 (5.2%)   | 4 (14.3%)          | <0.001     | 14 (10.0%)    | 4 (14.3%)   | 0.715   |

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from UVA Internal Review Board (no. 20082). Inpatient episodes with a CDI diagnosis (based on positive C. difficile PCR; GeneXpert; Cepheid) were identified between March 2011 and April 2021 (Fig. 1) and stratified into two treatment periods (2011–2016 and 2017–2021) marked by implementation of computerized decision support tool in December 2016 (14) and updated 2017 CDI management guidelines (15). Patients <18 years, with > 5 prior recurrent episodes, or who did not receive active treatment (oral vancomycin, IV/oral metronidazole, or tigecycline) were excluded.

Baseline clinical data, including laboratory measurements within ±48 h of the positive PCR, and outcome data were gathered electronically from the UVA Clinical Data Warehouse. Modified Charlson Comorbidity Index was calculated using International Classification of Diseases coding data (16, 17). ATLAS/Zar Scores were measured at diagnosis (18, 19). Analyses were performed using statistical software R, version 4.0.4 (R Core Team, Vienna, Austria) with 'comorbidity,' 'MatchIt,' and 'gee' packages.

Baseline characteristics of each cohort are in Table 1. In the full cohort, tigecycline-treated patients had significantly higher pressor and antimotility agent use, lower albumin, and higher ATLAS and Zar Scores. A significantly higher proportion of tigecycline cases occurred after 2016. The propensity-matched cohort showed no significant differences in baseline characteristics.

The case series was manually compiled by investigator E. C. Phillips using REDCap data capture tools hosted at UVA (20, 21). Cases were stratified into categories of nonsevere, severe, and fulminant infection based on current CDI management guideline criteria (15). Twenty-eight cases of tigecycline treatment were identified among 26 individuals. Seven out of twenty-eight (25%) cases were classified as nonsevere, 12/28 (43%) as severe, and 9/28 (32%) as fulminant infection. Tigecycline was given for an average 7.3 (range: 0.5–27.5; standard deviation: 6.1) days. In the nonsevere/severe groups, tigecycline was used primarily as salvage therapy (Table 2). Mortality was highest in the fulminant group, and recurrence rates were equivalent among surviving patients in the severe and fulminant groups. Tigecycline was used exclusively for CDI in 18/28 (64%) cases, CDI plus another infection in 4/28 (14%) cases, and primarily for another infection (examples include pneumonia, intrabdominal abscess, Enterobacter sepsis, and urinary tract infection) in 6/28 (21%) cases.

The primary outcome was 30-day all-cause mortality. Secondary outcomes were in-hospital mortality attributable to CDI, colectomy, or diverting ileostomy due to CDI, CDI recurrence,
and length of stay. Chart reviews by investigator G. R. Madden identified 130/179 (72.6%) deaths and 15/18 (83.3%) colectomies or ileostomies attributable to CDI. Propensity scores were estimated using a logistic regression model, with tigecycline therapy as the outcome. Nearest neighbor matching was performed at 5:1 control:case ratio to optimize covariate balance and statistical power. The effect of tigecycline on the outcomes of interest was evaluated in the logistic regression, with and without adjusting for baseline characteristics. Repeated CDI episodes were accounted for using the generalized estimating equation method.

Unadjusted 30-day mortality was higher among tigecycline-treated patients (4/28 [14.3%] tigecycline versus 173/3,273 [5.3%] nontigecycline; $P < 0.001$). Compared with propensity-matched controls, mortality in the tigecycline group was not statistically different (4/28 [14.3%] tigecycline versus 12/140 [16.4%; $P = 1.00$]. After risk adjustment in the propensity-matched cohort, tigecycline did not significantly improve 30-day mortality (Table 3; odds ratio: 0.89; $P = 0.853$); however, this is limited by small case numbers.

Univariate and multivariable analyses of the secondary outcomes are shown in Table 4. Adjusted coefficients for tigecycline were significantly greater than zero for both total length of stay and length of stay following CDI diagnosis, indicating significantly longer lengths of stay with tigecycline. Colectomy/diverting ileostomy due to CDI, hospital mortality attributable to CDI, and subsequent recurrence were all not significantly associated with tigecycline in the univariate and multivariable analyses.

Although nonsignificant, the *Clostridium difficile*-associated mortality in the later study period (2017–2021) was higher. This may be in part due to the aforementioned decision support tool, which led to 41% fewer tests and proportionally fewer cases with subclinical infection or colonization; therefore, the proportion of cases in the later period was not only higher, but also likely more severe (14).

There are several potential explanations for why tigecycline may not be effective adjunct therapy in CDI. Although not available clinically, oral tigecycline may be preferable to intravenous administration due to high protein binding in the bloodstream (22). Additionally, the FDA noted that most deaths from early clinical trials were related to progression of an under-

### Table 2: Outcomes of tigecycline treatment for CDI from case series

| Outcome | Nonsevere infection | Severe infection | Fulminant infection |
|---------|---------------------|-----------------|--------------------|
| Avg length of tigecycline therapy | 7.4 days (range 0.5–13.6) | 7.75 days (range 2.5–20.3) | 7.7 days (range 0.5–27.5) |
| Tigecycline used as initial, salvage, or nondirected therapy* | Salvage | Salvage | |
| In-hospital mortality | 2 of 7 (29%) | 2 of 12 (17%) | 5 of 9 (56%) |
| 90-day mortality | 2 of 7 (29%) | 2 of 12 (17%) | 6 of 9 (67%) |
| Recurrences at 30 days | 0 | 2 | 1 |
| Recurrences at 90 days | 0 | 5 | 1 |
| Total recurrences | 5 (in 2/5 [40%] surviving patients) | 5 (in 5/10 [50%] surviving patients) | 1 (in 1/2 [50%] surviving patients who reached follow-up) |

*Initial therapy is defined as tigecycline use within 7 days from day 0: the earliest of the date of positive stool test, the start of directed antimicrobial therapy, or the start of tigecycline therapy. Salvage therapy is defined as tigecycline use after 7 days from day 0. An equals sign indicates that tigecycline was used as initial, salvage, or nondirected therapy in an equal number of cases.

### Table 3: Impact of tigecycline from the multivariable logistic regression with generalized estimating equation method*

| Variable | Odds ratio | 95% CI | $P$ |
|----------|------------|--------|-----|
| Tigecycline | 0.89 | 0.25–3.12 | 0.853 |
| ATLAS Score | 1.33 | 1.03–1.72 | 0.026 |
| Hypotension | 1.93 | 0.66–5.61 | 0.227 |
| 2017–2021 (vs. 2011–2016) | 1.76 | 0.72–4.31 | 0.216 |
| Lactate $\geq$ 2.0 mg/dL | 2.54 | 1.01–6.38 | 0.047 |

*P values in bold-faced type are considered to be significant. CI, confidence interval.
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Tigecycline for adjunctive *Clostridium difficile* treatment should be carefully weighed against delay in pursuing potentially life-saving aggressive measures such as surgical intervention. A randomized controlled trial is needed to better characterize the role, if any, of tigecycline in the treatment of severe, fulminant, and/or refractory *Clostridium difficile* infection.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grants K23 AI163368 (to G.R.M.) and AI145322 (to C.A.W.) and National Center for Advancing Translational Sciences Grants UL1 TR003015 and KL2 TR003016 (to G.R.M. and J.Z.M.).

All authors report no conflicts of interest relevant to this article.

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