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Evaluating Risk Factors for Clinical Failure Among Tigecycline-Treated Patients

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Purpose: Clinical trials have documented that tigecycline has a higher mortality risk than other treatments; it continues to be widely used for various infections in real-world settings, where its associated risk factors for clinical failure are understudied.

Patients and Methods: This retrospective analysis included a prospective 2019–2021 cohort of tigecycline-treated patients, excluding those with multiple infection sites. We assessed the outcomes on day 28, with clinical failure defined by mortality, persistent initial infection symptoms, or the requirement for continued antimicrobial treatment. Multivariable logistic regression was used for the outcome analysis.

Results: Of 253 patients included in the study, 94 experienced clinical failure. The infection foci included pneumonia (46.3%), bloodstream infection (BSI) (25.3%), and skin/soft tissue infections (10.3%). There were no significant differences in high-dose tigecycline administration or monotherapy rates between patients with favorable outcomes and those with clinical failure. A higher Charlson comorbidity index (adjusted odds ratio [aOR] = 1.20, $P = 0.001$), Pitt bacteremia score (aOR = 1.25, $P = 0.007$), and BSI (aOR = 3.94, $P < 0.001$) were significant predictors of clinical failure. Concomitant use of *Pseudomonas aeruginosa*-active fluoroquinolone (aOR = 1.97, $P = 0.03$) and carbapenem (aOR = 2.20, $P = 0.01$) was linked to increased clinical failure.

Conclusion: Multiple comorbidities, BSI, and higher Pitt bacteremia scores are associated with increased risk of clinical failure in tigecycline-treated patients. These results suggest clinicians should consider alternatives to tigecycline for patients with these risk factors. When administering tigecycline, vigilant monitoring is indicated to manage potential clinical failures.

Keywords: clinical response, predictors, tigecycline

Introduction

Tigecycline is a glycycline antibiotic with broad-spectrum activity against gram-positive and gram-negative bacteria and anaerobes. It was approved for the treatment of community-acquired pneumonia, complicated skin and skin structure infections (cSSSI), and complicated intra-abdominal infections (cIAI) by the US Food and Drug Administration (FDA) in 2005.[1] In in vivo studies, tigecycline was effective against multiple drug-resistant organisms (MDRO) and is listed as a potential antibiotic against infection by carbapenem-resistant *Enterobacterales* under the guidance of the Infectious Diseases Society of America.[2] With the guidance of the Infectious Disease Society of Taiwan, tigecycline could be an alternative treatment for pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* and the recommended treatment for complicated intra-abdominal infections due to vancomycin-resistant *Enterococci*.[3] Despite off-label drug use, tigecycline is frequently prescribed to patients with MDRO-induced hospital-acquired pneumonia, ventilator-associated pneumonia, and bloodstream infections (BSI).[4] However, tigecycline has been reported to increase mortality compared with other regimens.[5–7] In the warning box for tigecycline, the FDA has imposed that it should be reserved for situations where alternative treatments are unsuitable.[8] Tigecycline remains an important treatment option in the emerging MDRO era.[2] However, studies on the factors influencing tigecycline treatment responses are relatively scarce.

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Observational studies focusing on cIAI and cSSSI have indicated that younger patients, although not reaching statistical significance, demonstrate a tendency toward improved clinical responses.[9] A study on *A. baumannii* pneumonia showed that a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score predicted clinical failure.[10] Tigecycline monotherapy has been associated with a higher mortality rate than combination therapy with tigecycline, as demonstrated in a meta-analysis.[11]

This study evaluated the factors influencing treatment response to tigecycline in a real-life cohort. Understanding these factors may facilitate clinicians in determining more suitable candidates for tigecycline treatment and in identifying those for whom tigecycline may not be appropriate.

Materials and Methods

This study was a retrospective analysis of a prospectively enrolled cohort from the National Taiwan University Hospital (NTUH) database. As one of Taiwan's largest medical centers, the NTUH offers over 2600 beds. The study protocol was approved by the Research Ethics Committee of NTUH (approval number: 202012286RIND). Since this was an observational study involving minimal risk to patients and did not include sensitive populations or topics, the Committee granted a waiver of informed consent. Patient data were de-identified, ensuring confidentiality, and all procedures adhered to the principles of the Declaration of Helsinki.

Patients older than 20 years who received tigecycline treatment for at least two days from July 1, 2019, to December 31, 2021, were included in the study. Tigecycline is commonly used to treat carbapenem-resistant Enterobacteriaceae infections. To avoid possible confounding factors, patients who received ceftazidime-avibactam or colistin during the index hospitalization were excluded. The focus of the infection was identified based on the discharge diagnosis. Patients with multiple infection foci were excluded to accurately assess the factors influencing tigecycline treatment outcomes. Clinical characteristics, such as age, sex, body weight, daily dose of tigecycline, antibiotic regimens, intensive care unit admission, and use of mechanical ventilation, were retrieved from the NTUH database. The underlying comorbidities were evaluated using the Charlson comorbidity index. The severity of the infections was assessed using the Quick SOFA score, Pitt Bacteremia Score, and APACHE II score. Tigecycline therapy with a daily dose exceeding 100 mg, such as 75 mg or 100 mg every 12 h, was defined as high-dose tigecycline therapy. As tigecycline lacks activity against *Pseudomonas aeruginosa*, we recorded whether patients received tigecycline in combination with aminoglycosides, anti-Pseudomonas beta-lactams, or anti-Pseudomonas carbapenems.

The date of tigecycline therapy initiation was recorded on the first day of the study. The outcomes were evaluated on day 28. Favorable outcomes encompassed both clinical cure and improvement. We defined clinical cure as discharge in a surviving state or discontinuation of antibiotic. A response to antibiotic therapy with resolution of initial infection symptoms was classified as clinical improvement. Conversely, clinical failure meant cases where patients either passed away, exhibited persistent initial infection symptoms, or required continued antimicrobial treatment.

Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. For continuous variables, the differences between groups were analyzed using the two-sample Student's *t*-test. In all analyses, two-sided *P*-values less than 0.05 were considered statistically significant. Multivariable logistic regression was used for the outcome analysis. Variables that exhibited a *P*-value less than 0.1 in univariable regression were included in the multivariable analysis. Multivariable models were developed using backward stepwise minimization based on Akaike's Information Criterion. Variables with *P*-values less than 0.05 were retained in the final multivariable model. Statistical analyses were performed using Stata software (v. 17; StataCorp, College Station, TX, USA).

Results

During the study period, 1485 patients aged > 20 years were treated with tigecycline and 704 patients remained after excluding 781 patients exposed to colistin and ceftazidime-avibactam Further exclusion of patients with multiple infectious foci resulted in a final cohort of 253 patients. The mean (standard deviation) age of this cohort was 65.3 (16.3) years. Among these patients, 111 were admitted to the intensive care unit, and the mean Pitt bacteremia score was 1.1 (1.7). The most commonly identified infection foci were pneumonia (46.3%), BSI (25.3%), and skin and soft tissue infections (10.3%).

In the study cohort, 159 patients had favorable outcomes, while 94 patients had clinical failure. The clinical characteristics of the patients with favorable outcomes and those with clinical failure are summarized in Table 1. Patients with a favorable outcome, compared with those with clinical failure, were younger (mean age 63.1 vs 69.1 years, $P = 0.004$), had a lower Charlson comorbidity index (4.7 vs 6.1, $P < 0.001$), and a lower Pitt bacteremia score (0.8 vs 1.6, $P < 0.001$). Patients with clinical failure exhibited a higher proportion of mechanical ventilation (33% vs 16.4%, $P = 0.002$) and BSI (50% vs 18.9%, $P < 0.001$). There was no significant difference in the proportion of patients who received a high dose of tigecycline between those with favorable outcomes and those with clinical failure (11.3% vs 18.1%, $P = 0.13$). No significant difference in monotherapy rates was observed between patients with favorable outcomes and those with clinical failure (4.4% vs 3.2%, $P = 0.63$).

In the study cohort, 243 patients received concomitant antimicrobial agents and tigecycline, whereas 10 patients were treated exclusively with tigecycline monotherapy. The proportion of patients receiving monotherapy was similar in the favorable outcome group (4.4%) and poor outcome group (3.2%, $P = 0.63$). However, patients with clinical failure had higher exposure to concomitant antimicrobial therapy with *P. aeruginosa*-active fluoroquinolone (81.9% vs 74.8%, $P = 0.001$) and *P. aeruginosa*-active carbapenem (52.1% vs 37.1%, $P = 0.02$) compared with patients with a favorable outcome.

Multivariable logistic regression was performed to identify the predictive factors, controlling for confounding factors associated with clinical failure (Table 2). The analysis identified significant predictors of clinical failure, including a higher Charlson comorbidity index (adjusted odds ratio [aOR] = 1.20, $P = 0.001$), greater disease severity by Pitt

Table 1 Univariable Comparison of Tigecycline-Treated Patients with Favorable Outcomes and Clinical Failure

	Favorable Outcomes (N = 159)	Clinical Failure (N = 94)	*P*-value
Characters			
Mean age	63.1 (16.9)	69.1 (14.6)	0.004
Male	90 (56.6)	53 (56.4)	0.97
Mean body mass index (kg/m^2)	23 (5.9)	22.3 (4.2)	0.28
Charlson comorbidity score	4.7 (2.9)	6.1 (2.7)	<0.001
Cardiovascular disease	27 (17.0)	23 (24.5)	0.15
Malignant disease	44 (27.7)	40 (42.6)	0.02
Renal disease	20 (12.6)	21 (22.3)	0.04
Hepatic disease	22 (13.8)	10 (10.6)	0.46
Diabetes mellitus	33 (20.8)	21 (22.3)	0.77
qSOFA score	1.2 (1.0)	1.7 (1.0)	<0.001
Pitt bacteremia score	0.8 (1.6)	1.6 (1.9)	<0.001
APACHE II score	17.1 (6.5)	22.6 (9.6)	0.003
ICU admission	63 (39.6)	48 (51.1)	0.08
Mechanical ventilation	26 (16.4)	31 (33)	0.002
High-dose tigecycline	18 (11.3)	17 (18.1)	0.13
Infection focus			
Pneumonia	78 (49.1)	39 (41.5)	0.24
Bloodstream infection	30 (18.9)	47 (50)	<0.001
Urinary tract infection	16 (10.1)	2 (2.1)	0.02
Intra-abdominal infection	12 (7.5)	3 (3.2)	0.16
Soft tissue infection	23 (14.5)	3 (3.2)	0.004
Antibiotic strategy			
Monotherapy	7 (4.4)	3 (3.2)	0.63
Concomitant antibiotics			
Aminoglycosides	19 (11.9)	10 (10.6)	0.75
Pseudomonas aeruginosa-active fluoroquinolone	37 (23.3)	40 (42.6)	0.001
Pseudomonas aeruginosa-active beta-lactam	119 (74.8)	77 (81.9)	0.19
Pseudomonas aeruginosa-active carbapenem	59 (37.1)	49 (52.1)	0.02

Notes: Data are presented as mean (standard deviation) for continuous variables and as N (%) for categorical variables.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; qSOFA, Quick SOFA sc.

Table 2 Multivariable Logistic Regression Analysis of Predictive Factors for Clinical Failure in Tigecycline-Treated Patients

Predictors	Odds Ratio (95% Confidence Interval)	*P*-value[a]
Charlson comorbidity index	1.20 (1.08–1.33)	0.001
Pitt bacteremia score	1.25 (1.06–1.47)	0.007
Bloodstream infection	3.94 (2.06–7.54)	<0.001
Concomitant *Pseudomonas Aeruginosa*-Active Fluoroquinolone	1.97 (1.07–3.63)	0.03
Concomitant *Pseudomonas aeruginosa*-active carbapenem	2.20 (1.21–3.99)	0.01

Note: [a]Estimated area under the ROC curve = 0.79.

bacteremia score (aOR = 1.25, $P = 0.007$), and the presence of BSI (aOR = 3.94, $P < 0.001$). Additionally, patients receiving concomitant *P. aeruginosa*-active fluoroquinolone (aOR = 1.97, $P = 0.03$) and concomitant *P. aeruginosa*-active carbapenem (aOR = 2.20, $P = 0.01$) were more likely to experience clinical failure.

Discussion

This study identified several key factors associated with clinical failure in patients treated with tigecycline. Our findings indicate that patients with more comorbidities and more severe disease, are at an increased risk of clinical failure. Moreover, BSI, independently predicted a higher likelihood of clinical failure in these patients. Contrary to expectations, our data did not demonstrate a correlation between high-dose tigecycline administration and favorable outcomes, nor did they establish a clear association between tigecycline monotherapy and clinical failure. Multivariable logistic regression showed that a higher Charlson comorbidity index (aOR = 1.20, $P = 0.001$), greater disease severity by Pitt bacteremia score (aOR = 1.25, $P = 0.007$), and a BSI focus (aOR = 3.94, $P < 0.001$) were significant predictors of clinical failure.

The association of higher clinical failure rates with multiple comorbidities and severe infection aligns with expectations and has been corroborated by previous studies on tigecycline treatment outcomes. Older patients and those with elevated APACHE II scores have consistently been identified as being at a higher risk of tigecycline treatment failure.[9,10] Our findings are in line with those of previous studies demonstrating that patients with multiple comorbidities and high infection severity, as measured by the Pitt bacteremia score, have a higher likelihood of clinical failure. Although originally developed to predict mortality in cases of bacteremia, the Pitt bacteremia score has also been demonstrated to effectively predict mortality in patients with infections that do not involve bacteremia.[12] This underscores the need for vigilant monitoring of treatment responses when tigecycline is administered to such patients.

Tigecycline, approved in 2005 for the treatment of community-acquired pneumonia, cSSSI, and cIAI, has been associated with increased mortality rates compared with other treatments, particularly in off-label applications such as hospital-acquired pneumonia.[5] Clinical trials have also linked baseline bacteremia to higher mortality in patients receiving tigecycline,[6] leading the FDA to recommend its use only when no alternatives are available.[8] As a time-dependent pattern of bactericidal activity against several gram-positive and gram-negative organisms,[13] tigecycline reaches a serum concentration of 0.403 mg/L under standard dosing.[14] This concentration may be sufficient for treating BSI caused by pathogens such as gram-positive cocci with low minimum inhibitory concentrations (MICs),[15] but it may be inadequate for gram-negative bacilli, including *K. pneumoniae* and *A. baumannii*. Despite being less effective than other regimens for treating BSI in clinical settings, tigecycline continues to be used in real-world scenarios.[16,17] However, its effectiveness in treating *A. baumannii* bacteremia has been debated.[18] Recent large cohort studies have suggested that tigecycline may be as effective as other treatments for carbapenem-resistant *K. pneumoniae* and *E. coli* BSIs.[19] Moreover, subsequent meta-analyses suggested that tigecycline might be at least as effective as other comparators in BSI treatment, particularly when combined with other antimicrobial agents.[11] Although previous studies have compared tigecycline with other treatments for BSI, our study adds a critical dimension to this discourse by showing a higher rate of clinical failure in patients with BSI treated with tigecycline. In conjunction with the rapid tissue distribution of tigecycline, its relatively low serum concentration,[20] and higher MIC against gram-negative bacilli, this

may account for the increased clinical failures observed in BSI.[15] Although these observations do not necessarily preclude the use of tigecycline in BSI treatment, they highlight the need for careful consideration and monitoring when administering tigecycline in clinical settings.

The strategy of increasing tigecycline dosage to enhance the clinical response has garnered attention in recent research. Pascale's single-center study in 2014 highlighted that high-dose tigecycline therapy (loading dose of 200 mg and maintenance dose of 100 mg every 12 h) was an independent predictor of clinical cure in MDRO-related ventilator-associated pneumonia, as opposed to standard-dose therapy (loading of 100 mg and maintenance dose of 50 mg every 12 h).[21] Furthermore, two meta-analyses indicated the potential benefits of high-dose tigecycline in reducing mortality, showing higher clinical response and microbiological eradication rates than standard doses.[22,23] Specifically, in subgroup analyses, the all-cause mortality rate was significantly reduced in patients with ventilator-associated pneumonia and intra-abdominal infections. The Infectious Diseases Society of America guidelines recommend high-dose tigecycline therapy for complicated intra-abdominal infections,[2] while the Infectious Disease Society of Taiwan guidelines acknowledge the possible role of high-dose therapy in critically ill patients with carbapenem-resistant Enterobacterales infections.[3] Our study did not demonstrate an association between administering a higher dose of tigecycline and favorable outcomes. This might be partly attributed to the lack of significant differences in mortality rates between high-dose and standard-dose therapies in BSI subgroup analyses,[22,24] combined with the fact that approximately 30% of patients in our cohort had BSIs. Given its high volume of distribution, even high-dose tigecycline achieves a relatively modest steady-state maximum concentration of only 0.34 mg/L in critically ill patients.[25] This is despite the fact that a 100 mg intravenous infusion of tigecycline can reach a peak concentration as high as 1.94 mg/L, as shown in pharmacokinetic studies.[26] Such concentrations may be insufficient to effectively target gram-negative bacilli at high MICs. Additionally, our inability to establish a direct association between high-dose tigecycline and better clinical outcomes may have been influenced by confounding factors. Therefore, clinicians may prefer high-dose therapy in critically ill patients. In our study, patients receiving high-dose tigecycline had higher Pitt bacteremia scores than those receiving lower doses (1.4 vs 1.0; $P = 0.05$, rank-sum test), which adds complexity to the assessment of drug efficacy.

Observational studies have indicated that combination therapy involving tigecycline may reduce all-cause mortality in cases of nosocomial pneumonia caused by carbapenem-resistant gram-negative bacteria and could potentially decrease mortality rates in *K. pneumoniae* carbapenemase-producing *K. pneumoniae* bacteremia.[27,28] Combined antibiotic therapies may exhibit synergistic effects.[29] However, combination therapy may not necessarily improve outcomes.[30] In our study, using tigecycline in combination with aminoglycosides did not result in a significant difference in outcomes between the groups with favorable outcomes and those with clinical failure. In contrast, combining tigecycline with *P. aeruginosa*-active fluoroquinolones and carbapenems emerged as predictive factors for clinical failure. The observed association between the use of combination therapies and poor outcomes may have been influenced by confounding factors. The concurrent use of *P. aeruginosa*-active fluoroquinolones and carbapenems could be a marker for unobserved underlying factors contributing to clinical failure. Our data showed that patients receiving *P. aeruginosa*-active carbapenem in combination with other treatments had a higher incidence of BSI compared with those who did not receive this combination (29.6% vs 22.1%, $P = 0.17$). Similarly, using *P. aeruginosa*-active fluoroquinolone combinations was associated with a higher proportion of BSIs than in those not receiving such combinations (37.7% vs 19.9%, $P = 0.003$). Additionally, the possibility of antagonism between these drug combinations cannot be discounted.[31]

Our study has several limitations. First, the retrospective cohort design inherently carries the risk of imbalanced baseline conditions among participants. While we conducted a multivariable analysis to mitigate this issue, unobserved biases still have the potential to affect the outcomes. Second, the study was conducted at a single tertiary medical center, meaning that the treatment choices and outcomes observed might be specific to this setting and may not necessarily be generalizable to other contexts. Third, due to the retrospective nature of this study and the design of the NTUH database, it was challenging to definitively identify the causative pathogens responsible for infections, and the database does not enable clear attribution of specific pathogens to clinical outcomes. As a result, pathogen-specific factors may have been underrepresented in our analysis. Although clinicians are likely to prescribe antibiotics based on in vitro susceptibility, and the study focuses on the influence of clinical characteristics on outcomes, the impact of these pathogens on treatment outcomes may not have been fully captured. Fourth, critical factors that can influence clinical outcomes, such as

tigecycline dosage and its use in combination therapies, are confounded by other risk factors. This complexity suggests that the impact of high-dose tigecycline or its use in combination treatments on effectiveness warrants additional study.

Conclusion

In our study, patients with multiple comorbidities, as quantified by the Charlson comorbidity index, and greater infection severity, as measured by the Pitt bacteremia score, were more likely to experience clinical failure when treated with tigecycline. Additionally, patients with BSI at the primary site exhibited a higher likelihood of clinical failure. Therefore, clinicians should exercise caution when considering the potential for clinical failure. In the presence of risk factors, judicious evaluation of alternative therapies is warranted. However, close monitoring of the treatment responses in these patients is imperative.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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