



Efficacy and safety of tigecycline for complicated urinary tract infection: a systematic review

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Background: Facing the global threat of emerging resistance to antibiotics, tigecycline, a novel glycycline antibiotic, is developed to against multidrug-resistant pathogens, but not recommended for the treatment of complicated urinary tract infection (cUTI). We performed a summary of the literatures to characterize and evaluate the efficacy and safety of tigecycline in patients with cUTI.

Methods: We searched PubMed, EMBASE, Cochrane and Clinical Trials using appropriate syntax to retrieve potential articles up to Jan 2020. General information, pathogen, medication regimen, comorbidities of patients from eligible literatures were recorded. Univariate logistic regression analysis was used to detect the potential factors associated with clinical cure.

Results: Nineteen articles comprising 31 cases were included. The subpopulation with transplantation (25.8% of the patients) was the most common comorbidity, and cUTIs were mainly caused by *Klebsiella pneumoniae* (*K. pneumoniae*) (48.28%) in our research. Tigecycline 100 mg per day as monotherapy was most common. Clinical cure was reported as majority (77.4%), and microbiological eradication cases accounted for the most (65.2%) among the clinical cure cases. Univariate analysis showed that *K. pneumoniae* caused cUTI and tigecycline as a single treatment have significant meaning to clinical outcomes (P=0.044 and P=0.034, respectively).

Conclusions: Clinical and microbiological outcomes of tigecycline treatment revealed high rate of successful response. Tigecycline monotherapy may have a role in the treatment of cUTI except that caused by the pathogen *K. pneumoniae*. Further randomized controlled trials was still needed to evaluate tigecycline monotherapy for cUTI.

Keywords: Tigecycline; antibiotics; complicated urinary tract infection (cUTI); *Klebsiella pneumoniae* (*K. pneumoniae*); systematic review

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Introduction

It is well known that tigecycline, a novel glycolcycline antibiotic with potent antibacterial activity against most multidrug-resistant pathogens such as extended spectrum β -lactamase (ESBL) positive organisms, carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), has been approved for the treatment of skin infections, intra-abdominal infections and community-acquired bacterial pneumonia by the United States Food and Drug Administration (FDA), European Medicine Agency (EMA) and National Medical Products Administration (NMPA) (1-3).

With increasing bacterial resistance, antibiotic options for treatment of complicated urinary tract infection (cUTI) caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms are often limited for clinicians. Colistin and aminoglycosides are potential therapeutic options for untreatable gram-negative infections, however, both of those drugs are highly nephrotoxic agents, and acute kidney injury occurs frequently with conventional doses, especially in severe cUTI patients (4).

Although tigecycline is not considered as a valid option for cUTI because of its low serum concentration and limited excretion into urine (33% of the total dose is excreted as unchanged tigecycline in urine) (5), several successful cases for the treatment of multidrug-resistant cUTI by tigecycline has been reported in recent years representing tigecycline, as the last-resort drug, become the less toxic option for patients with renal disease (6,7). However, the outcomes of these reports have not been completely consistent. Results of a retrospective cohort study showed no statistically significant differences in microbiologic clearance rates between tigecycline group and untreated group (8). It is hard to demonstrate that tigecycline is as effective in cUTI as in other infections. We therefore summarized and analyzed articles of cUTI patients who were treated with tigecycline to evaluate the efficacy and safety of tigecycline therapy. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-959>).

Methods

This systematic review was established according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement.

Literature search

Relevant studies were identified through PubMed, EMBASE, Cochrane and Clinical Trials, all the studies were manually searched from inception to Jan 2020 using the following search syntax: "(tigecycline OR TGC OR tygacil) AND (complicated urinary tract infection OR cUTI OR Urinary infection OR urinary system infection)". Items were searched both in Medical Subject Headings (MeSH) and free text. Language was restricted to English. The reference lists of all articles were reviewed for further identification of potential relevance.

Study selection

Any study reporting the clinical outcomes of patients with cUTI and receiving tigecycline treatment was considered eligible for inclusion in our study. Two authors (YX Liu and KJ Le) independently reviewed each title and abstract, and assessed full texts of retrieved studies, with any disagreements being resolved via consultation with a third author (H Zhong).

Data extraction

The following data were extracted from each study: (I) main characteristics of the study (author name, year of publication, and location); (II) main characteristics of the patient (age, gender, sex, comorbidities, type of infection, sepsis or not, and causative pathogen); (III) antibiotic treatment (dose, duration, prior antibiotic therapy, monotherapy or combination therapy); (IV) clinical outcomes (clinical response, microbiological response, recurrence, and total follow-up time). Data were collected by two independent reviewers (YX Liu and KJ Le).

Definition of clinical and microbiological outcomes

Clinical response was defined as cure (partial or complete improvement of cUTI), failure (no improvement or deterioration of cUTI). Microbiological response was defined as positive (sterile culture results during or at the end of antibiotic therapy), negative (failure to eradicate the organism during or at the end of antibiotic therapy), or not documented.

Statistical analysis

SPSS 24.0 statistical package (SPSS, Chicago, IL, USA)

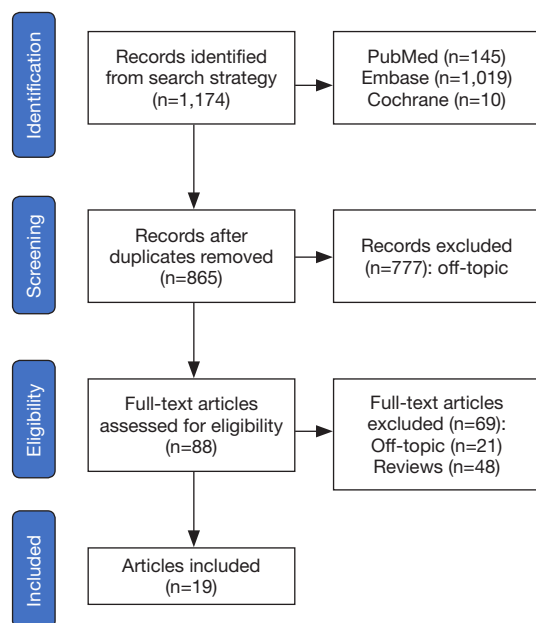


Figure 1 Flow diagram of articles selection. Articles published in PubMed, Embase, Cochrane and Clinical Trials were searched and selected.

was used for data processing and statistical analysis. Student *t*-test was used to evaluate continuous variables and Chi-square test was used to analyze categorical variables. Univariate logistic regression analysis was carried out to detect potential factors related to clinical outcomes. $P < 0.05$ was considered statistically significant.

Results

Study identification and selection

The electronic search strategy yielded 1,174 records, of which 777 were excluded either due to duplication or off-topic after screening title and abstract. Further 69 articles were excluded because they were reviews or had no outcomes of interest. Nineteen eligible studies (2,9-26) were included and the details are summarized in Table S1. The flow gram of identification of the eligible studies is presented in Figure 1.

Characteristic of patients

Baseline demographics of patients with tigecycline treatment are showed in Table 1. A total of 19 studies involving 31 patients reported cUTI treated with tigecycline. Median age of patients was 61.5 years

Table 1 Baseline characteristics of the included patients

Variables	Number	Values
Age (years)	28	61.5 (IQR: 51.5–68.5)
Gender, n (%)	24	
Male		12 (50)
Female		12 (50)
Region, n (%)	31	
North America		13 (41.94)
Europe		11 (35.48)
Asia		5 (16.12)
South America		2 (6.45)
Comorbidities, n (%)	31	
Transplantation		8 (25.80)
Diabetes mellitus		7 (22.58)
Urinary catheter		6 (19.35)
ESRD		4 (12.90)
Prostatitis and kidney stones		4 (12.90)
Surgery and trauma		3 (9.68)
Pulmonary disease		2 (6.45)
Sepsis, n (%)	23	13 (56.52)
Causative pathogen, n (%)	29	
<i>K. pneumoniae</i>		14 (48.28)
Acinetobacter		7 (24.14)
ESBL <i>E. coli</i>		6 (20.69)
<i>Myroides odoratimimus</i>		2 (6.90)
VRE		1 (3.45)
MDR <i>E.aerogenes</i>		1 (3.45)
Prior antibiotic therapy, n (%)	15	
None		4 (26.67)
β -lactam antibiotics		10 (66.67)
Polymyxin B + tigecycline		1 (6.67)

IQR, interquartile range; ESRD, end-stage renal disease; ESBL, extended-spectrum beta-lactamase; VRE, vancomycin resistant Enterococcus; MDR, multiple drug resistance.

[interquartile range (IQR) 51.5–68.5] and the percentage of female was equal to male. Of the 31 cases identified, 25.8% of patients had comorbidities of transplantation and 22.58% had diabetes mellitus. Sepsis (56.52%, $n=13$) was featured

Table 2 Treatments of tigecycline

Variables	Number	Values
Dose of tigecycline treatment, n (%)	23	
Standard (100 mg/d)		15 (65.22)
Higher than standard dose (200 mg/d)		7 (30.43)
Lower than standard dose (50 mg/d)		1 (4.35)
Duration of tigecycline treatment (days)	28	14, IQR (11 to 17)
≤7		3 (10.71)
7–14		16 (57.14)
15–21		3 (10.17)
>21		5 (17.86)
Concomitant antibiotics, n (%)	28	
None		18 (64.29)
Carbapenems		4 (14.29)
Colistin		3 (10.71)
Piperacillin/tazobactam		2 (7.14)
Fluconazole		1 (3.57)
Total duration of follow-up (days)	18	34, IQR (21 to 120)

IQR, interquartile range.

prominently amongst the cases with detailed description of sepsis. The information of pathogens was obtained in 29 cases. Common causative pathogens including *Klebsiella pneumoniae* (*K. pneumoniae*) (48.28%), *Acinetobacter spp.* (24.14%) and ESBL positive *Escherichia coli* (20.69%) were frequently observed and other pathogens such as *Myroides odoratimimus* were extremely rare. In 15 cases provided the information of prior antibiotic therapy, a significant group of patients were treated with β -lactam antibiotics previously (66.67%, n=10) or without prior antibiotic therapy (26.67%, n=4).

Treatment

Details of tigecycline treatments are shown in *Table 2*. Dosage of tigecycline were available in 23 cases, the vast majority of cases used tigecycline 100 mg/d as a standard dose (65.22%, n=15), and high-dose tigecycline (200 mg/d) or

low-dose tigecycline (50 mg/d) was also reported in a few cases. Duration and detailed antibiotic agent of tigecycline treatment were clear in 28 cases, the median duration was 14 days (IQR 11–17) and the duration between 7–14 days was found in most patients (57.14%), a majority of cases used tigecycline as monotherapy for cUTI (64.29%, n=18), while carbapenems (14.29%), colistin (10.71%), piperacillin/tazobactam (7.14%) and fluconazole (3.17%) were used as a concomitant therapy with tigecycline in other reports. Median follow-up of all patients was 34 days (IQR 21–129) among the 18 available cases.

Outcomes

In terms of detailed outcomes, 24 cases were defined clinical cure account for 77.42% (n=24) as a majority in all 31 cases. Recurrence of cUTI was reported in some patients (36.36%, n=4) among the 11 cases with detailed outcomes of follow-up. Among the clinical cure cases, patients defined microbiological positive accounted for the vast majority (65.2%), only a few cases reserved pathogenic bacteria (8.33%) (*Figure 2*). Two cases reported as clinical failure but showed microbiological positive result, because both patients died but the death were not related to tigecycline treatment and their urinary tract pathogen culture were defined as microbiological positive.

Factors predicting clinical outcome

The correlation between clinical cure and influence factors such as age, gender and others were analyzed by univariate logistic regression analysis. Univariate analysis showed that pathogen *K. pneumoniae* might be the risk factor of clinical failure, and tigecycline monotherapy was related to clinical cure ($P<0.1$). The details of factors analyses were described in *Table 3*.

Discussion

Major findings and interpretations

Our findings drew the detailed information for the effectiveness and safety of tigecycline treatment for cUTI based on 31 cases in 19 articles. The results demonstrated tigecycline has a favorable clinical response in cUTI, and in the patients who was confirmed clinical cure, vast majority observed bacteria eradication in urine culture with no recurrence. Univariate logistical analysis suggested that

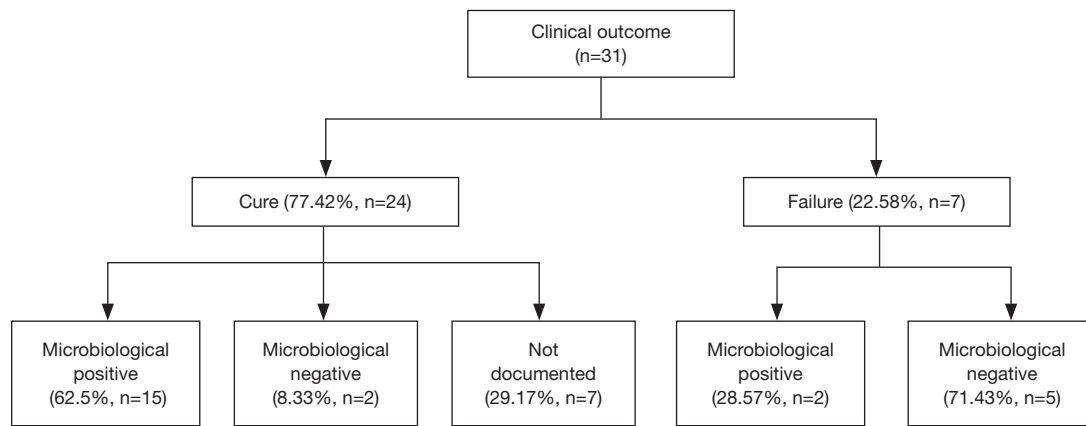


Figure 2 Flow diagram of outcome. The clinical and microbiological outcome of 31 cases in 19 articles.

Table 3 Univariate logistic regression analysis of clinical outcomes

Variables	Univariate analysis	
	P value	OR (95% CI)
Age	0.12	0.94 (0.87–1.02)
Gender	0.62	1.67 (0.23–12.35)
Risk factors/etiology		
Transplantation	0.42	0.48 (0.08–2.92)
Diabetes mellitus	0.91	0.89 (0.13–6.16)
Urinary catheter	0.69	0.67 (0.09–4.81)
ESRD	0.93	1.13 (0.10–13.04)
Sepsis	0.25	0.25 (0.02–2.70)
Causative pathogen		
<i>K. pneumoniae</i>	0.04	0.95 (0.01–0.94)
Acinetobacter	0.49	2.25 (0.22–22.80)
Dose of tigecycline		
Standard (100 mg/d)	0.65	0.57 (0.05–6.61)
High (200 mg/d)	0.80	1.39 (0.12–16.23)
Duration of tigecycline	0.54	1.04 (0.93–1.16)
Concomitant antibiotics		
None	0.03	8.00 (1.17–54.72)
Carbapenems	0.23	0.26 (0.03–2.24)
Colistin	0.73	0.63 (0.05–8.25)

OR, odds ratio; ESRD, end-stage renal disease.

tigecycline failed in treatment of *K. pneumoniae* caused cUTI even with increased dose, and tigecycline monotherapy achieved better clinical results. It was especially remarkable given the fact that tigecycline was not recommend for

K. pneumoniae caused cUTI. Despite these concerns, tigecycline monotherapy was still considered alternative for treating cUTI when other options are limited.

Comparison with previous studies

Tigecycline is a derivative of minocycline which attracted clinicians attention because of its excellent *in vitro* activity against most gram-negative pathogens and relatively mild adverse effects (2). Numerous studies have suggested tigecycline in the treatment of infections caused by MDR organisms, especially *Acinetobacter baumannii* and carbapenemase producing *Enterobacteriaceae* (5). However, although tigecycline has high rates of *in vitro* susceptibility to MDR, the package insert of tigecycline states that 33% of a dose is excreted in urine, and tigecycline has a much greater volume of distribution than most other antimicrobials which can achieve 7–10 L/kg (20). These findings generally doubted that tigecycline is a viable option for cUTI because tigecycline has limited excretion into lower urinary system (27). Meanwhile, the previous studies published have demonstrated inconsistent results. In a study by Satlin *et al.*, tigecycline achieved microbiological clearance and better clinical outcomes in patients with cUTI (8). In addition, high-dose tigecycline regimen of 200 mg was administered to patients with UTI caused by *K. pneumoniae* in several reports (6), and the microbiological clearances were achieved. However, most studies were case reports that positive results observed may attributed to publication bias and has not been validated in a systematically evaluated study.

Our study evaluated tigecycline for cUTI from a number

of heterogeneous patients and the results suggested that tigecycline may be a viable therapeutic option for cUTI. In our study, tigecycline had a higher success rate in clinical and microbiological outcomes and dosage was not a factor affecting the outcomes through logistic regression analysis.

Potential mechanism

A possible explanation of success in cUTI treatment of tigecycline could be that pathogens causing cUTI were various and tigecycline had a broad antimicrobial spectrum covering both gram-positive and gram-negative bacteria. Furthermore, as a relatively new glycolcycine, highly resistant gram-negative bacteria (including ESBL or CRE) might be sensitive to tigecycline even at low concentration. Above speculation provide a possible explanation of successful use of tigecycline for cUTI. The results by univariate analyses showed that the rate of pathogen *K. pneumoniae* was significantly high in the failure group. Although tigecycline showed high antimicrobial activity against a broad spectrum of pathogens among which most pathogens were resistant to other antibiotics, the clinical efficacy of tigecycline was most closely related to AUC/MIC ratio. In a study by Nicasio *et al.* (28), the free AUC₂₄/MIC ratio against strains of *K. pneumoniae* needed to achieve adequate bacterial killing was between 1.3 and 1.8 which can be achieved in serum with standard dose. However, this effective concentration was not reached with excreted 33% of a dose in urine.

Clinical consideration

Urinary tract is a common site of infection and cUTI can involve any age group, especially in patients with functional or structural abnormality of the urinary tract (6). With increasing bacterial resistance and the slower pace of antimicrobial development, the regimens for cUTI is gradually decreasing, and there is very little published literature on cUTI due to MDR organisms and other rare pathogens (29). The finding is important for clinical practice because our study added to the accumulating data that tigecycline regimen demonstrated a relatively good clinical response on cUTI and provided a possible option for limited clinical treatment for cUTI. Adverse events possibly associated with tigecycline were not observed in most cases, but there still might be a risk of tigecycline such as diarrhea, neutrophil engraftment delay (7). Therefore, tigecycline must be administered according to results of

pathogen culture and adverse effects should be monitored adequately during tigecycline treatment process.

Limitations

There are inherent limitations in this study. Firstly, the small sample size limited the availability of epidemiologic data and outpatient could not be adequately evaluated with this design. Secondly, although our article described that tigecycline treatment for cUTI had a better clinical outcome, there was a potential publication bias as authors may not reported cUTI that were treated with tigecycline with unsuccessful treatment outcome. In addition, some valid cases might be excluded because the language restrictions. And this meta-summary was a retrospective design of case report to evaluate the presented management strategy, which required more data from large real-world registries or randomized control trials.

Conclusions

Based on our study, the use of tigecycline in cUTI achieved favored clinical and microbiological outcomes. However, if the cUTI was caused by *K. pneumoniae*, tigecycline might not be a good choice. In addition, a majority of data from our review showed no clear adverse effects caused by tigecycline. Thus, tigecycline can be considered when target pathogen and well-established safety monitoring system are available.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tau-20-959>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-959>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethical approval and consent are not required because no patient-level data is involved for this systematic review.

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