Original Article

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

Yang-Xi Liu[1#], Ke-Jia Le[1#], Hong-Yao Shi[2#], Zai-Li Zhang[1], Min Cui[1], Han Zhong[1], Yue-Tian Yu[3], Zhi-Chun Gu[1]

[1]Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; [2]Department of Laboratory Medicine, Shanghai Pubin Children's Hospital, Shanghai, China; [3]Department of Critical Care Medicine, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Contributions: (I) Conception and design: YX Liu, KJ Le; (II) Administrative support: ZC Gu, YT Yu, H Zhong; (III) Provision of study materials or patients: YX Liu, KJ Le; (IV) Collection and assembly of data: YX Liu, KJ Le; (V) Data analysis and interpretation: YX Liu, KJ Le, HY Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Han Zhong. Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China. Email: zhonghan@renji.com; Yue-Tian Yu. Department of Critical Care Medicine, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China. Email: fishyyt@sina.com; Zhi-Chun Gu. Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China. Email: guzhichun213@163.com.

Background: Facing the global threat of emerging resistance to antibiotics, tigecycline, a novel glycylcycline 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

Submitted May 30, 2020. Accepted for publication Oct 30, 2020.
doi: 10.21037/tau-20-959
View this article at: http://dx.doi.org/10.21037/tau-20-959

Introduction

It is well known that tigecycline, a novel glycylcycline 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)

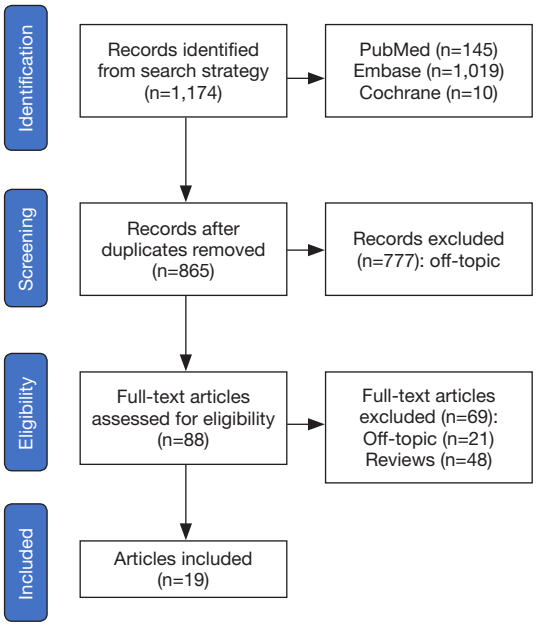

Figure 1 Flow diagram of articles selection. Articles published in PubMed, Embase, Cochrane and Clinical Trials were searched and selected.

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 [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 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	
K. pneumoniae		14 (48.28)
Acinetobacter		7 (24.14)
ESBL E. coli		6 (20.69)
Myroides odoratimimus		2 (6.90)
VRE		1 (3.45)
MDR *E.aerogenes*		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.

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

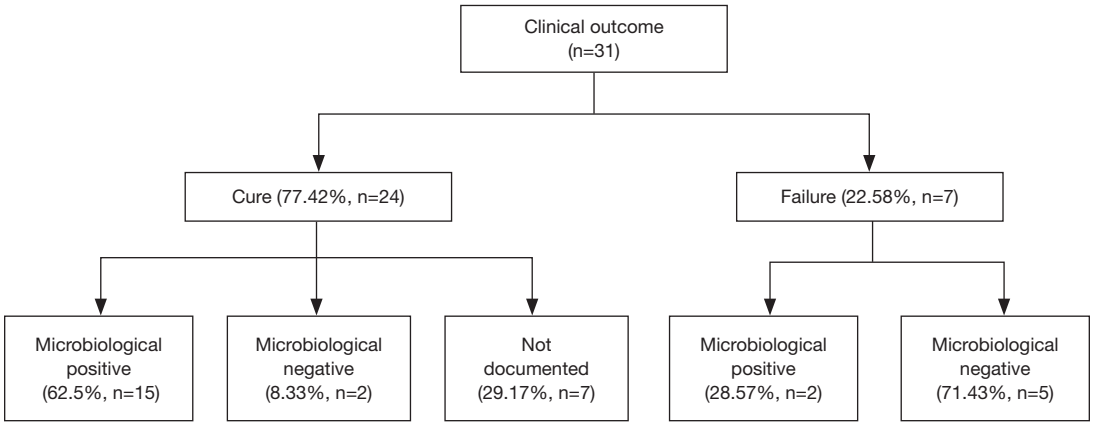

Figure 2 Flow diagram of outcome. The clinical and microbiological outcome of 31 cases in 19 articles.

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		
K. pneumoniae	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 heterogenous 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 glycylcycine, 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 AUC_{24}/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 administrated 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.

Acknowledgments

Funding: This study was funded by Clinical Pharmacy Innovation Research Institute of Shanghai Jiao Tong University School of Medicine (CXYJY2019ZD001, CXYJY2019QN004), Research Funds of Shanghai Health and Family Planning commission (20184Y0022, 20194Y0007), WU JIEPING medical foundation (320.6750.2020-04-31), Cultivation fund of clinical research of Renji hospital (PY2018-III-06), and Program for Key but Weak Disciplines of Shanghai Municipal Commission of Health and Family Planning (2016ZB0304).

Footnote

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

Peer Review File: Available at http://dx.doi.org/10.21037/tau-20-959

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.

References

1. Rodrigues dos Santos BG, Amaral ES, Fernandes PFCBC, et al. Urinary Tract Infections and Surgical Site Infections due to Carbapenem-Resistant Enterobacteriaceae in Renal Transplant. Transplant Proc 2016;48:2050-5.
2. Brust K, Evans A, Plemmons R. Tigecycline in treatment of multidrug-resistant Gram-negative bacillus urinary tract infections: A systematic review. J Antimicrob Chemother 2014;69:2606-10.
3. Tasina E, Haidich AB, Kokkali S, et al. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis 2011;11:834-44.
4. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39:10-39.
5. Meagher AK, Ambrose PG, Grasela TH, et al. The pharmacokinetic and pharmacodynamic profile of tigecycline. Clin Infect Dis 2005;41 Suppl 5:S333-40.
6. Wu G, Abraham T, Saad N. Role of tigecycline for the treatment of urinary tract infections. J Pharm Technol 2014;30:87-92.
7. Temocin F, Tülek NE, Hekimoğlu Ş, et al. Five-years tigecycline experience an analysis of real-life data. Haseki Tip Bulteni 2018;56:125-30.
8. Satlin MJ, Kubin CJ, Blumenthal JS, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant Klebsiella pneumoniae from urine. Antimicrob Agents Chemother 2011;55:5893-9.
9. Cunha BA, McDermott B, Nausheen S. Single daily high-dose tigecycline therapy of a multidrug-resistant (MDR) Klebsiella pneumoniae and Enterobacter aerogenes nosocomial urinary tract infection. J Chemother 2007;19:753-4.
10. Reid GE, Grim SA, Aldeza CA, et al. Rapid development of Acinetobacter baumannii resistance to tigecycline. Pharmacotherapy 2007;27:1198-201.
11. Anthony KB, Fishman NO, Linkin DR, et al. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. Clin Infect Dis 2008;46:567-70.
12. Gallagher JC, Rouse HM. Tigecycline for the treatment of Acinetobacter infections: A case series. Ann Pharmacother 2008;42:1188-94.
13. Krueger WA, Kempf VA, Peiffer M, et al. Treatment with tigecycline of recurrent urosepsis caused by extended-spectrum-beta-lactamase-producing Escherichia coli. J Clin Microbiol 2008;46:817-20.
14. Elemam A, Rahimian J, Mandell W. Infection with panresistant Klebsiella pneumoniae: a report of 2 cases and a brief review of the literature. Clin Infect Dis 2009;49:271-4.
15. Weisenberg SA, Morgan DJ, Espinal-Witter R, et al. Clinical outcomes of patients with Klebsiella pneumoniae carbapenemase-producing K. pneumoniae after treatment with imipenem or meropenem. Diagn Microbiol Infect Dis 2009;64:233-5.
16. Geerlings SE, van Donselaarvan der Pant KAMI, Keur I. Successful treatment with tigecycline of two patients with complicated urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. J Antimicrob Chemother 2010;65:2048-9.
17. Drekonja DM, Johnson JR. Tigecycline treatment for

urinary tract infections: Case report and literature review. J Chemother 2011;23:168-70.
18. Kuo SC, Wang FD, Fung CP, et al. Clinical experience with tigecycline as treatment for serious infections in elderly and critically ill patients. J Microbiol Immunol Infect 2011;44:45-51.
19. Solak Y, Atalay H, Turkmen K, et al. Community-acquired carbapenem-resistant Acinetobacter baumannii urinary tract infection just after marriage in a renal transplant recipient. Transpl Infect Dis 2011;13:638-40.
20. Bates D, Parkins M, Hellweg R, et al. Tigecycline treatment of urinary tract infection and prostatitis: Case report and literature review. Can J Hosp Pharm 2012;65:209-15.
21. Tsai HY, Liao CH, Cheng A, et al. Emergence of tigecycline-resistant Klebsiella pneumoniae after tigecycline therapy for complicated urinary tract infection caused by carbapenem-resistant Escherichia coli. J Infect 2012;65:584-6.
22. Cicora F, Mos F, Paz M, et al. Infections with blaKPC-2-producing Klebsiella pneumoniae in renal transplant patients: A retrospective study. Transplant Proc 2013;45:3389-93.
23. Balandin Moreno B, Fernandez Simon I, Pintado Garcia V, et al. Tigecycline therapy for infections due to carbapenemase-producing Klebsiella pneumoniae in critically ill patients. Scand J Infect Dis 2014;46:175-80.
24. Mouloudi E, Massa E, Piperidou M, et al. Tigecycline for treatment of carbapenem-resistant klebsiella pneumoniae infections after liver transplantation in the intensive care unit: A 3-year study. Transplant Proc 2014;46:3219-21.
25. Lee CT, Chu HM, Chang CL. Is tigecycline prescribed to treat carbapenem-resistant acinetobacter baumannii complicated urinary tract infections. J Microbiol Immunol Infect 2015;48:S137.
26. Licker M, Sorescu T, Rus M, et al. Extensively drug-resistant Myroides odoratimimus - A case series of urinary tract infections in immunocompromised patients. Infect Drug Resist 2018;11:743-9.
27. Castanheira M, Sader HS, Jones RN. Antimicrobial susceptibility patterns of KPC-producing or CTX-M-producing Enterobacteriaceae. Microb Drug Resist 2010;16:61-5.
28. Nicasio AM, Crandon JL, Nicolau DP. In vivo pharmacodynamic profile of tigecycline against phenotypically diverse Escherichia coli and Klebsiella pneumoniae isolates. Antimicrob Agents Chemother 2009;53:2756-61.
29. Alexander BT, Marschall J, Tibbetts RJ, et al. Treatment and Clinical Outcomes of Urinary Tract Infections Caused by KPC-Producing Enterobacteriaceae in a Retrospective Cohort. Clin Ther 2012;34:1314-23.

Cite this article as: Liu YX, Le KJ, Shi HY, Zhang ZL, Cui M, Zhong H, Yu YT, Gu ZC. Efficacy and safety of tigecycline for complicated urinary tract infection: a systematic review. Transl Androl Urol 2021;10(1):292-299. doi: 10.21037/tau-20-959

Supplementary

Table S1 Details of 31 patients treated with tigecycline in 19 literature for cUTI

Patient No.	Age, years	Sex	Risk factors	Sepsis	Causative pathogen	Prior antibiotic therapy	Tigecycline regimen			Response		Relapse	Follow-up
							Dose	Duration	Concomitant	Clinical	Microbiologic		
1 (2)	54	F	DM	NS	MDR AB	NS	100 mg q12h	17 days	None	Cure	Positive	NS	6 weeks
	64	M	DM	NS	ESBL *K. pneumoniae*	NS	100 mg q12h	11 days	None	Failure	Positive	Died	6 weeks
2 (9)	NS	M	Urinary catheter	NS	MDR *K. pneumoniae* E. aerogenes	NS	200 mg q24h	12 days	None	Cure	Positive	NS	12 days
3 (10)	53	F	Kidney and liver transplantation, urinary catheter	NS	MDR AB and VRE	LVX, P/T, VAN	100 mg q12h	14 days	None	Cure	Positive	Yes	3 months
4 (11)	25	F	chronic urinary reflux, lumbar meningomyelocele and paraparesis below the second lumbar segment	Yes	ESBL *E. coli*	LVX, P/T, CTX, AMK, MEM, LNZ, voriconazole	NS	13 days	None	Cure	Positive	NS	38 days
5 (12)	63	NS	NS	NS	NS	NS	100 mg q12h	4 days	None	Cure	Positive	NS	30 days (range, 3–89)
	49	NS	NS	NS	NS	NS	100 mg q12h	13 days	None	Cure	Positive	NS	30 days (range, 3–89)
	63	NS	NS	NS	Acinetobacter	NS	100 mg q12h	12 days	Col	Cure	Positive	NS	30 days (range, 3–89)
6 (13)	70	F	Pneumonia, urinary catheter	NS	PDR *K. pneumoniae*	Tigecycline, PMB	NS	10 days	Rifampin	Failure	Negative	Yes	1 year
7 (14)	39	F	Stem cell transplant	Yes	*K. pneumoniae*	IMI	100 mg q12h	14 days	None	Cure	NS	NS	3 weeks
8 (15)	67	M	Polyneuropathy	Yes	*K. pneumoniae*	IMI	100 mg q12h	7 days	None	Failure	Negative	NS	3 weeks
	44	M	Renal transplant, DM, chronic prostatitis	NS	ESBL *E. coli*	MEM	NS	42 days	None	Cure	Positive	NO	18 weeks, 5 months
9 (16)	66	F	ESRD	NS	ESBL *E. coli*	NS	NS	42 days	None	Cure	Positive	NO	6 weeks, 4 months
	63	M	Prostatitis	Yes	ESBL *E. coli*	CIP, DOX, CTX, NTF, MOX, ETP	100 mg q12h	14 days	None	Cure	Positive	NO	4 months
10 (17)	27	F	Renal transplant	Yes	MDR AB	IMI	50 mg/d	NS	None	Cure	Positive	NS	NS
11 (18)	76	M	Spinal stenosis, lumbar osteomyelitis with epidural abscess, CKD	Yes	MDR AB	NS	100 mg q12h	12 days	P/T, IMI, sulbactam	Failure	Negative	NS	19 days
12 (19)	70	F	Polymyositis, interstitial lung disease	NO	ESBL *E. coli*	CEL, CFM, LVX	100 mg/d	14 days, 7 days	None	Cure	Positive	NS	3 weeks
13 (20)	86	M	CKD, DM, HTN, prostatic hypertrophy	Yes	ESBL *E. coli*	CTX, P/T, MEM, ETP	100 mg q12h	25 days, 42 days	Fluconazole	Cure	Negative	NO	157 days
14 (21)	71	NS	Renal transplant, DM, urinary catheter	Yes	blaKPC-2-Producing *K. pneumoniae*	None	NS	21 days, 16 days	CST	Failure	Negative	Yes	NS
	50	NS	Renal transplant	None	blaKPC-2-Producing *K. pneumoniae*	None	NS	26 days, 21 days	MEM	Failure	Negative	Yes	NS
15 (22)	65	F	Bone marrow transplantation	Yes	CRKP	NS	200 mg/d	11 days	P/T	Failure	Positive	NS	NS
	60	F	Cardiac surgery	Yes	CRKP	NS	200 mg/d	6 days	IMI	Cure	NS	NS	NS
	34	M	Multiple trauma	Yes	CRKP	NS	200 mg/d	8 days	None	Cure	NS	NS	NS
	80	M	Ulcerative colitis, abdominal surgery	Yes	CRKP	NS	200 mg/d	9 days	None	Cure	Negative	NS	NS
	54	M	Non-Hodgkin lymphoma	Yes	CRKP	NS	100 mg/d	15 days	MEM	Cure	Positive	NS	NS
16 (23)	53	F	DM, stage 3 CKD, nephrolithiasis, right double-J ureteral stent	None	CRKP	VAN, P/T	200 mg, 100 mg q12h, then 200 mg q24h, then 100 mg q12h	17 days		Cure	Positive	None	14
17 (24)	54	M	Heart disease, alcoholic hepatitis, liver transplant	None	CRKP	NS	100 mg q12h	26 days	CST	Cure	Positive	None	NS
18 (25)	NS	NS	NS	None	CRAB	NS	50 mg q12h	14 days	NS	Cure	NS	NS	NS
	NS	NS	NS	None	CRAB	NS	100 mg q12h	14 days	NS	Cure	NS	NS	NS
19 (26)	59	F	DM, PAD, HTN, Urethro-vesical catheterization	None	Myroides odoratimimus	None	NS	NS	None	Cure	NS	NS	NS
	72	M	BPH, COPD	None	Myroides odoratimimus	None	NS	NS	None	Cure	NS	NS	NS

F, female; M, male; NS, not stated; DM, diabetes mellitus; ESRD, end stage renal disease; CKD, chronic kidney disease; HTN, hypertension; PAD, peripheral arterial disorder; BPH, benign prostate hyperplasia; COPD, chronic obstructive pulmonary disease; MDR, multidrug resistance; ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant enterococci; PDR, pandrug resistant; AB, *Acinetobacter baumanmii*; CRKP, *Carbapenem Resistant Klebsiella Pneumoniae*; CRAB, *Carbapenem Resistant Acinetobacter baumanmii*; KPC, *Klebsiella pneumoniae carbapenemase*; LVX, levofloxacin; VAN, vancomycin; P/T, piperacilin/tazobactam. AMK, amikacin; CTX, cefotaxime; MEM, meropenem. LNZ, linezolid; PMB, polymyxin B; IMI, imipenem; CIP, ciprofloxacin; DOX, doxycycline; CTX, ceftriaxone; NTF, nitrofurantoin; MOX, moxifloxacin; ETP, ertapenem; CEL, cephalexin; CFM, cefixime; CST, colistin.

http://dx.doi.org/10.21037/tau-20-959