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Role of tigecycline in the treatment of urinary tract infections: a systematic review of published case reports

Reema Charles[1], Shreya Das Adhikari[2], Ankit Mittal[3], Souvik Chaudhuri[4], Mukund Gupta[5], Wasim Khot[6], Marco Schito[1], Nitin Gupta[7]

[1]CURE Drug Repurposing Collaboratory (CDRC), Critical Path Institute, Tucson, AZ, USA;
[2]Department of Anaesthesiology, Kasturba Medical College and Hospital, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India;
[3]Department of Medicine, All India Institute of Medical Sciences, New Delhi, Delhi, India;
[4]Department of Critical Care, Kasturba Medical College and Hospital, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India;
[5]Department of Community Medicine and Family Medicine, All India Institute of Medical Sciences, Jodhpur, India;
[6]Infectious Disease, Global Hospitals, Mumbai, India;
[7]Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

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SUMMARY

Introduction: The emergence of multi-drug resistance has forced clinicians to occasionally use drugs that are not approved to treat urinary tract infections (UTIs). This systematic review aimed to evaluate the utility of tigecycline in patients with UTIs.
Methodology: A systematic review of case studies was used to retrieve articles between 1.1.1999 to 1.1.2021 from two databases, PubMed and Embase. The title-abstract screening was done for 198 articles, out of which 69 articles were included for full-text screening. A total of 18 articles with 27 cases were included for final analysis.
Results: Of the 27 cases, there were 13 cases with complicated UTI and five had catheter-associated UTI. The most common organisms were *Klebsiella pneumoniae* (n=11), *Acinetobacter baumannii* (n=9), and *Escherichia coli* (n=6). Tigecycline was used as monotherapy in 19 patients and as a combination therapy in 8 patients. The median duration of tigecycline was 13 (10-15) days. A favourable clinical or microbiological response at varying intervals was seen in 24/27 (88.9%). Within three months of a favourable response, recurrence of symptoms was seen in four patients.
Conclusion: In a small analysis of published case reports, tigecycline appeared to be a relatively effective treatment in patients with UTIs, caused by multidrug-resistant organisms. Where tigecycline is the only susceptible drug, it can be used for treatment. Further research, such as randomized controlled trials, is needed to fully assess the drug's efficacy in this context.

Keywords: UTI, prostatitis, catheter-associated UTI, AMR.

INTRODUCTION

The emergence of multi-drug resistance in urinary tract infections (UTIs) poses a significant therapeutic challenge. This is especially true for developing countries where indiscriminate usage of antibiotics is common [1]. The choice of antimicrobials for UTIs is dependent not only on the organisms and their minimum inhibitory concentrations (MICs), but also on the ability of antimicrobials to achieve adequate concentration in the urine [2]. Drugs such as beta-lactams, aminoglycosides, nitrofurantoin and fluoroquinolones have traditionally been the mainstay of treatment [3]. However, with increasing rates

Corresponding author
Nitin Gupta
E-mail: nityanitingupta@gmail.com

of drug resistance, clinicians have been forced to look for alternatives such as newer beta-lactam/beta-lactam inhibitors (BL-BLI) combinations, as well as other antibiotics, such as fosfomycin and colistin [1]. In cases where clinical conditions, adverse effect profile, cost and availability preclude using these second-line drugs, rescue drugs such as tigecycline are the only available option. Tigecycline is approved for routine use in intra-abdominal infections and skin-soft tissue infections. Since tigecycline was thought to have poor urinary concentration, its use in UTIs has never been encouraged [4]. Therefore, in this systematic review, we aimed to summarize the available literature on the use of tigecycline for UTIs.

MATERIALS AND METHODS

A systematic review of case studies was conducted to ascertain the anecdotal efficacy of intravenous tigecycline in patients with urinary tract infections to achieve clinical and microbiological cure. All study types where the authors deemed the individual cases in question to be having a UTI were considered for the review. For the purpose of this review, UTI was defined broadly as infectious involvement of the urinary tract as evidenced by clinical or radiological evaluation and culture positivity [1]. *In vitro* or animal studies were excluded. The studies where individual details of the patients, details of identified organisms or evidence of clinical or microbiological cure were not present were also excluded.

The following search string was used to retrieve articles between 1.1.1999 to 1.1.2021 from two databases, PubMed and Embase*:* Tigecycline AND (Urinary Tract Infections OR bacteriuria OR pyuria OR prostatitis OR pyelonephritis OR cystitis OR UTI). For Embase, the search was restricted to title and abstract only. A total of 93 articles were retrieved from PubMed, and 157 articles were retrieved from Embase. A total of 6 papers were added from additional sources (references of included articles). After removing 58 duplicates, the title-abstract screening (done by two independent authors) was done for 198 articles. A total of 69 articles were included for full-text screening. Fifty-one articles were excluded either because they did not meet the inclusion/exclusion criteria (n=50), or because full text was unavailable (n=1).

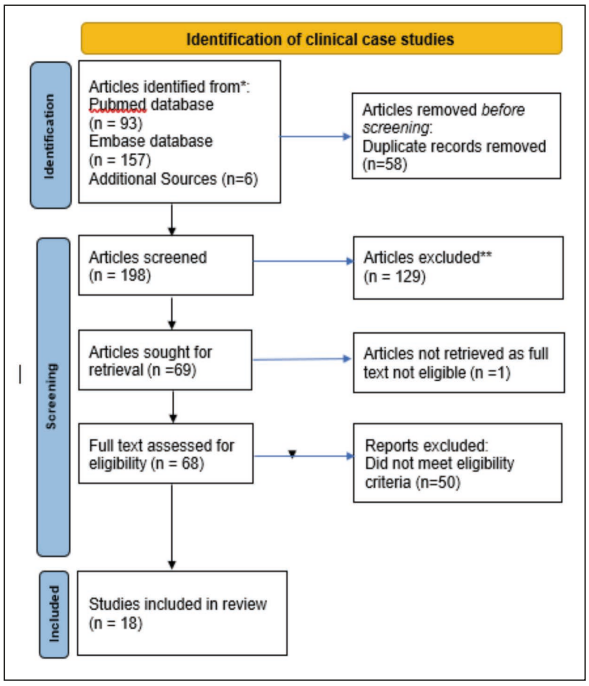

Figure 1 - PRISMA chart showing the inclusion process of articles where tigecycline was used for treating patients with urinary tract infections.

A total of 18 articles with 27 cases were included in the final analysis (4-21) (Figure 1).

The included articles were analyzed using the JBI checklist to critically appraise case reports (Table 1) (22). Of the eight questions on the checklist, only one article had all eight positive responses. Six articles had a total of seven positive responses to the checklist question. All of these six articles had a negative response to the identifying adverse event question. It should, however, be noted that adverse event identification was not an objective of the study. The rest of the articles had four or more positive responses.

The following demographic and clinical data were collected from each case: age, gender, country of origin, year of presentation, co-morbidities, presenting features, treatment details and outcome. Those patients with urinary symptoms accompanied by fever, kidney or prostate involvement on radiology or blood culture positivity with the same organism were classified as complicated UTI. Those patients with a history of at least three UTIs in the last year were classified as recurrent UTIs. Those patients with a significant

improvement in clinical symptoms after initiating tigecycline were said to have a positive clinical outcome. Those patients where culture negativity was established any time after initial culture positivity and initiation of tigecycline therapy were said to have a positive microbiological outcome. Those patients with either positive clinical or positive microbiological outcomes were classified as an overall positive outcome. All three outcomes were evaluated separately.

Table 1 - JBI checklist for critical appraisal of case reports where tigecycline was used for urinary tract infections

References of included articles	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*(12)*	*(13)*	*(14)*	*(15)*	*(16)*	*(17)*	*(18)*	*(19)*	*(20)*	*(21)*
Were patient's demographic characteristics clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Was the intervention or treatment procedure clearly described?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Were adverse events (harms) or unanticipated events identified and described?	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The data were entered into an excel workbook, and the analysis was done using SPSS v26. For categorical variables, the frequencies were expressed as a percentage. Mean (± Standard deviation) or Median (with interquartile range) were calculated for quantitative variables.

RESULTS

The majority of the cases were from Europe (n=12) and the United States of America (n=13) and were reported between 2005 and 2018. The mean age of the included cases was 58.4±14.9 years. Of the 24 cases where gender was specified, there were 13 females (Table 2). There were 13 cases with complicated UTI (including two with prostatitis) and five with catheter-associated UTI (CAUTI). A total of five patients had a history of recurrent UTIs (Table 2). The most common co-morbidities were diabetes (DM) (n=5), chronic kidney disease (CKD) (n=6), history of surgery (n=6) and transplants (n=4). The most common organisms were *Klebsiella pneumoniae* (n=11), *Acinetobacter baumannii* (n=9), and *Escherichia coli* (n=6) (Table 2). Of the cases where susceptibility results were available, the organism was resistant to carbapenems in 86% (18/21) patients and resistant to colistin in 47% (8/17) patients. The

Table 2 - Clinical features, and microbiological details in cases with urinary tract infections treated with tigecycline.

Sn	*Author and year*	*Age (in years)*	*Gender*	*Presentation*	*Comorbidity*	*Organism*	*Carbapenem susceptibility*	*Colistin susceptibility*	*Tigecycline susceptibility*	*Susceptibility method for tigecycline*
1	Bhatt et al. [4]	25	Female	CAUTI	Disseminated TB	*K. pneumoniae*	Resistant	Resistant	Sensitive	
2	Tsai et al. [5]	70	Female	Recurrent complicated UTI	Chronic lung disease	*E. coli*	Resistant		Sensitive	Disc diffusion method
3	Geerlings et al. [6]	44	Male	Recurrent UTI	DM, CKD, Malignancy	*E. coli*				
4	Geerlings et a. [6]	66	Female	Recurrent UTI	CKD	*E. coli*				
5	Reid et al. [7]	53	Female	CAUTI	CKD, Chronic liver disease, SOT	*A. baumannii*	Resistant	Sensitive	Sensitive	
6	Aykota et al. [8]	64	Female	Complicated UTI	CKD, Chronic liver disease, SOT	*A. baumannii*	Resistant	Sensitive	Sensitive	
7	Anthony et al. [9]	54	Female	UTI	DM	*A. baumannii*			Sensitive	E-test
8	Anthony et al. [9]	64	Male	UTI	DM	*K. pneumoniae*			Sensitive	E-test
9	Drekonja et al. [10]	63	Male	Recurrent prostatitis		*E. coli*	Sensitive	Sensitive	Sensitive	E-test
10	Gallagher et al. [11]	63	Not specified	UTI		*A. baumannii*	Resistant	Resistant		
11	Gallagher et al. [11]	49	Not specified	UTI		*A. baumannii*	Resistant	Resistant		
12	Gallagher et al. [11]	63	Not specified	UTI		*A. baumannii*	Resistant	Resistant		
13	Cunha et al. [12]		Male	CAUTI		*K. pneumoniae, Enterobacter aerogenes*	Resistant	Resistant	Sensitive	E-test

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Sn	*Author and year*	*Age (in years)*	*Gender*	*Presentation*	*Comorbidity*	*Organism*	*Carbapenem susceptibility*	*Colistin susceptibility*	*Tigecycline susceptibility*	*Susceptibility method for tigecycline*
14	Krueger et al. [13]	25	Female	Recurrent Complicated UTI		*E. coli*	Sensitive			
15	Kuo et al. [14]	76	Male	UTI		*A. baumannii*	Resistant			
16	Brust et al. [15]	53	Female	Complicated UTI	DM, CKD	*K. pneumoniae*	Resistant		Sensitive	E-test
17	Elemam et al. [16]	70	Female	UTI		*K. pneumoniae*		Resistant	Sensitive	
18	Balfousias et al. [17]	72	Male	Complicated UTI	Trauma, surgery	*A. baumannii*				
19	Moreno et al. [18]	65	Female	Complicated UTI	BMT	*K. pneumoniae*	Resistant	Sensitive	Sensitive	E-test
20	Moreno et al. [18]	60	Female	Complicated UTI	Surgery	*K. pneumoniae*	Resistant	Sensitive	Sensitive	E-test
21	Moreno et al. [18]	34	Male	Complicated UTI		*K. pneumoniae*	Resistant	Sensitive	Sensitive	E-test
22	Moreno et al. [18]	80	Male	Complicated UTI	Surgery	*K. pneumoniae*	Resistant	Sensitive	Sensitive	E-test
23	Moreno et al. [18]	54	Male	Complicated UTI	Malignancy	*K. pneumoniae*	Resistant	Sensitive	Sensitive	E-test
24	Alexander et al. [19]	42	Female	Complicated UTI		*K. pneumonia, A. baumannii*	Resistant		Sensitive	E-test
25	Priore et al. [20]	79	Male	Prostatitis	CKD, Surgery	*E. coli*	Sensitive	Sensitive	Sensitive	E-test
26	Licker et al. [21]	59	Female	CAUTI	DM, Surgery	*Myroides odoratimimus*	Resistant	Resistant		
27	Licker et al. [21]	72	Male	CAUTI	Surgery	*Myroides odoratimimus*	Resistant	Resistant		

**Abbreviations:* Sn- Serial number, Age- Age in years, UTI- Urinary tract infection, CAUTI- Catheter-associated urinary tract infection, DM- Diabetes mellitus, CKD- Chronic Kidney Disease, SOT- Solid Organ Transplantation, BMT- Bone Marrow Transplantation, TB- Tuberculosis, *E. coli- Escherichia coli, K. pneumoniae- Klebsiella pneumoniae, A. baumannii- Acinetobacter baumannii.*

organism was sensitive to tigecycline in all the 17 tested patients. Barring one patient, E-test was used to determine the susceptibility of tigecycline in all the patients (Table 2).

Tigecycline was used as monotherapy in 19 patients, as a combination therapy with two drugs in 5 patients and as a combination of three drugs in 3 patients (Table 3). Carbapenems (n=3) and colistin (n=2) were most frequently used as combination therapy. Tigecycline was used in the following maintenance dosages: 50 mg BD (n=13), 100 mg BD (n=6), 200 mg OD (n=1) and 100 mg OD (n=1) (Table 2). The median duration of tigecycline use was 13 (10.25-14.75) days. The outcomes were assessed at varying time points: while on treatment (n=10), at treatment completion (n=9), and after a variable period of follow-up was completed (n=8). A microbiological response was seen in 15/19 patients (78.9%), and a clinical response was seen in 21/24 (87.5%) patients. Overall positive response was seen in 24/27 (88.9%) patients (Table 3). Within three months of a favourable response, recurrence of symptoms was seen in four (15%) patients.

Table 3 - Treatment details and response in cases with urinary tract infections treated with tigecycline.

Sn	*Author and year*	*Tigecycline dose*	*Tigecycline duration (in days)*	*Combination*	*Duration of follow-up (days)*	*Microbiological response*	*Clinical response*	*Overall response*	*Recurrence of symptoms (within 3 months)*
1	Bhatt et al. [4]	100 mg BD	7		365	Yes	Yes	Yes	Unknown
2	Tsai et al. [5]	100 mg OD	7		14	Unknown	Yes	Yes	Yes
3	Geerlings et al. [6]		42		120	Unknown	Yes	Yes	Unknown
4	Geerlings et al. [6]		42		150	Unknown	Yes	Yes	Unknown
5	Reid et al. [7]	50 mg BD	14		14	Yes	Yes	Yes	Yes
6	Aykota et al. [8]	50 mg BD	14	Imipenem, fosfomycin	14	Yes	Yes	Yes	Unknown
7	Anthony et al. [9]	50 mg BD	17		17	Yes	Yes	Yes	Unknown
8	Anthony et al. [9]	50 mg BD	11		11	Yes	No	Yes	Unknown
9	Drekonja et al. [10]	50 mg BD	14		150	Yes	Yes	Yes	Yes
10	Gallagher et al. [11]	50 mg BD	4		4	Yes	Yes	Yes	Unknown
11	Gallagher et al. [11]	50 mg BD	13		13	Yes	Yes	Yes	Unknown
12	Gallagher et al. [11]	50 mg BD	12	Colistin	12	Yes	Yes	Yes	Unknown
13	Cunha et al. [12]	200 mg OD	14		14	Yes	Yes	Yes	Unknown
14	Krueger et al. [13]		13		13	Unknown	Yes	Yes	Unknown
15	Kuo et al. [14]	50 mg BD	12		12	No	No	No	Unknown
16	Brust et al. [15]	100 mg BD	17		17	Yes	Yes	Yes	Yes
17	Elemam et al. [16]		10	Rifampicin	10	No	No	No	Unknown
18	Balfousias et al. [17]	5 0mg BD	14	Rifampicin, vancomycin	14	Yes	Yes	Yes	Unknown
19	Moreno et al. [18]	100 mg BD	11	Piperacillin-tazobactam	11	Yes	Unknown	Yes	Unknown
20	Moreno et al. [18]	100 mg BD	6	Imipenem	6	Unknown	Yes	Yes	Unknown
21	Moreno et al. [18]	100 mg BD	8		8	Unknown	Yes	Yes	Unknown
22	Moreno et al. [18]	100 mg BD	9		9	No	Unknown	No	Unknown
23	Moreno et al. [18]	50 mg BD	15	Meropenem	15	Yes	Unknown	Yes	Unknown

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Sn	*Author and year*	*Tigecycline dose*	*Tigecycline duration (in days)*	*Combination*	*Duration of follow-up (days)*	*Microbiological response*	*Clinical response*	*Overall response*	*Recurrence of symptoms (within 3 months)*
24	Alexander et al. [19]	50 mg BD	11	Doxycycline, colistin	11	No	Yes	Yes	Unknown
25	Priore et al. [20]	50 mg BD	28		210	Yes	Yes	Yes	Unknown
26	Licker et al. [21]					Unknown	Yes	Yes	Unknown
27	Licker et al. [21]					Unknown	Yes	Yes	Unknown

**Abbreviations:* Sn- Serial number, OD- Once daily, BD- Twice daily.

DISCUSSION

Tigecycline is a glycylcycline antibiotic derived from minocycline that inhibits bacterial protein synthesis and is effective against a wide range of organisms, including multi-drug resistant Gram-negative bacilli (MDR GNB), *Vancomycin-Resistant Enterococcus (VRE)* and *Methicillin-Resistant Staphylococcus aureus (MRSA)*. It should be noted that *Morganella morganii*, *Proteus mirabilis* and *Pseudomonas aeruginosa* are intrinsically resistant to tigecycline. Acquired resistance is rare with tigecycline and is most likely due to over-expression of the efflux pumps. Tigecycline exhibits complicated linear and non-linear pharmacokinetics at different dosing schedules with highly variable elimination half-lives. Moreover, the protein binding of the drug is also pH-dependent. Most of the drug (59%) is excreted unchanged in faeces, whereas only 10-15% of the drug is excreted unchanged in the urine.

Since Enterobacteriaceae like *Klebsiella pneumoniae* and *Escherichia coli* are most commonly associated with urinary tract infections, it is understandable that most included cases in the review were from the Enterobacteriaceae family. However, this review also had nine cases of *Acinetobacter spp*., which is not a common cause of UTI. Since *Acinetobacter spp*. is multi-drug resistant with limited therapeutic options, there are more reported cases where tigecycline was used as salvage therapy. In the cases where details of UTI associated with *Acinetobacter spp*. were reported, it was commonly seen that UTI was descending and a part of multi-system disease [7, 8, 14]. A total of 86% of the isolates were carbapenem-resistant and 47% were resistant to colistin in this review. In some cases, especially for colistin, susceptibility was done by unsuitable methods [23]. All of the tested isolates were sensitive to tigecycline in the included studies. Tigecycline susceptibility was determined by E-test in most cases. Data on the susceptibility of newer BL-BLI were not available in the included studies.

Based on the available PK-PD data, standard tigecycline dosing may not be ideal for UTIs [24, 25]. Higher doses of tigecycline have been successfully utilized in patients with ventilator-associated pneumonia. Given the urgent need for an effective drug against MDR/XDR organisms and a favourable susceptibility profile, there has been some interest in high-dose tigecycline as a treatment for UTIs caused by highly resistant organisms. Although recent studies have discussed the pharmacokinetics of high-dose tigecycline in nosocomial pneumonia, soft tissue infections and intra-abdominal infections, literature on UTIs is still scarce [26-28]. Recent systematic reviews have concluded that high dose tigecycline is associated with lower all-cause mortalities, higher clinical cure and microbiological eradication [29, 30]. In our review, 7 cases were treated with high doses. While 100 mg twice daily was the most common dosing schedule, Cunha et al. used 200 mg once daily for their patient. When compared to monotherapy, the role of combination therapy needs special mention with tigecycline. Since tigecycline is not approved for the treatment of UTIs, many patients inevitably receive combination therapy with other drugs. In our review, eight patients were on variable combination therapy with either one or two drugs. Although the majority of pa-

tients on combination therapy responded in our review, it is difficult to ascertain whether the addition of the partner drug had any impact on the outcome. In practice, use of tigecycline as a monotherapy may be ill-advised in the context of high drug resistance. Strategic combination therapies should be studied more robustly to reduce the likelihood of development of further resistance.

Our review supplements the systematic review conducted by Brust et al. on the role of tigecycline in the treatment of MDR GNB related UTIs. Similar to our findings, their review of 14 cases of UTIs noted favourable clinical (78.6%) and microbiological (85.7%) outcomes with a similar mean duration of antibiotic therapy [32]. In the study by Van Duin et al. on UTIs due to carbapenem-resistant *Klebsiella pneumoniae*, 30 patients were treated with tigecycline monotherapy, and 36 were treated with tigecycline-based combination therapy [31]. The microbiological cure rate in those with a definitive outcome was 3/17 (17.6%) for monotherapy patients and 5/18 (27.8%) for combination therapy patients. Tigecycline therapy was independently associated with poor microbiological outcomes. However, this study considered a microbiological failure as any culture positivity after seven days from the index culture positivity. This duration of therapy was possibly inadequate as the median duration of therapy in our analysis was 13 days. Also, most of the patients were labelled with indeterminate outcomes in their study, making the analysis difficult. The drug dosage used and the final duration of therapy was also not mentioned, thereby severely limiting the conclusions of that study. In another study by Satlin et al. (2011), of 21 patients with carbapenem-resistant *Klebsiella pneumoniae* treated with tigecycline, microbiological cure rates were achieved in 9/21 (43%) patients [33]. Compared to aminoglycosides and colistin, the microbiological clearance rates were significantly worse with tigecycline. However, it should be noted that the standard dosing of tigecycline was used in this series (50 mg twice daily). Also, the median duration of tigecycline before a follow-up culture was taken was only six days. Similar to the study by Van Duin et al., this study also included patients who could have had asymptomatic colonization, leading to persistently positive cultures [31].

Our review is mainly plagued by publication bias, where positive outcomes are more likely to be reported than negative outcomes. Also, the method of susceptibility testing, reporting of outcome and follow-up for recurrence was non-uniform. Hence, it would be premature to draw conclusions about the efficacy of tigecycline in UTIs without an adequately conducted randomized controlled trial. However, it can be reasonably concluded that in UTI cases, due to multidrug-resistant organisms, where tigecycline is the only susceptible drug, it can be used as a rescue drug, preferably at a higher dose and longer duration of treatment.

Conflict of interest
None

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None

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