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REVIEW

Effectiveness and Safety of High Dose Tigecycline for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Studies assessing the effect of high dose tigecycline on severe infections are limited and remain controversial.
Objectives: To assess systematically the effectiveness and safety of high dose tigecycline in the treatment of severe infections.

Methods: Pubmed, Web of Science, Embase, MEDLINE, Cochrane Library and ClinicalTrials were searched up to February 20, 2019 for studies that compared the effectiveness and safety of high dose tigecycline with standard dose tigecycline or other non-tigecycline-containing regimens in the treatment of severe infections. Rates for all-cause mortality, clinical cure, microbiological eradication and adverse events were analysed.
Results: Ten studies with 593 patients were included. The results indicated that using high dose tigecycline resulted in better outcomes compared with controls with lower all-cause mortality (OR 0.44, 95% CI 0.30–0.66, $p < 0.0001$), higher clinical cure (OR 3.43, 95% CI 2.09–5.63, $p < 0.00001$), higher microbiological eradication (OR 2.25, 95% CI 1.44–3.50, $p = 0.0003$), and without increasing adverse events rates. Subgroup analysis showed that high dose tigecycline reduced all-cause mortality in nosocomial acquired pneumonia (OR 0.39, 95% CI 0.22–0.70, $p = 0.002$), bloodstream infections (OR 0.19, 95% CI 0.06–0.58, $p = 0.004$) and mixed infections (OR 0.20, 95% CI 0.07–0.59, $p = 0.003$), with no statistical differences in complicated intra-abdominal infections (OR 2.04, 95% CI 0.80–5.23, $p = 0.14$). In carbapenem-resistant pathogens, the microbiological eradication rate in those given high dose tigecycline did not differ from controls (OR 1.07, 95% CI 0.44–2.60, $p = 0.87$), although mortality was reduced (OR 0.20, 95% CI 0.09–0.45, $p = 0.0001$). The main limitation of

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the review is that most of the included studies are observational studies with small sample sizes and high risks of bias.
Conclusions: High dose tigecycline treatment is effective and safe for severe infections owing to its lower all-cause mortality, higher clinical cure, microbiological eradication and comparable adverse events. However, as a result of the high risks of bias of the included studies, well-designed randomised clinical trials are warranted to establish the effectiveness and safety of high dose tigecycline compared with standard dose tigecycline and other commonly used antibiotics.

Keywords: Carbapenem resistance; Gram-negative bacteria; Infectious disease; Multidrug resistance; Tigecycline

Key Summary Points

Why carry out this study?

Resistance to carbapenems has been steadily increasing in many bacteria causing nosocomial infections. Therefore, antibiotics like tigecycline and colistin are considered as the last resort against some of those multidrug-resistant bacteria.

However, some studies have indicated that using the standard dose of tigecycline might result in worse clinical outcomes compared with other antibiotics. As a result, applying the higher dose of tigecycline has been a common clinical practice. Despite such widespread practice, studies assessing the effect of high dose tigecycline on severe infections are still limited and remain controversial.

What was learned from the study?

High dose tigecycline (200 mg loading dose, 100 mg q12h) had better outcomes (lower all-cause mortality, higher clinical cure and microbiology eradication rate) and comparable adverse events compared with standard dose tigecycline (100 mg loading dose, 50 mg q12h) and other antibiotics.

High dose tigecycline is recommended if a tigecycline-containing regimen is the clinical choice for severe infections, especially those with multidrug-resistant bacterial infections.

Well-designed randomised controlled trials with larger sample size are warranted to confirm the effectiveness and safety of high dose tigecycline in the treatment of severe infections.

INTRODUCTION

Severe infections, especially those caused by multidrug-resistant (MDR) bacteria, are associated with increased mortality, length of hospital stay and cost [1–3]. MDR Gram-negative bacterial infections are responsible for more than 30% of hospital-acquired infections, with even higher rates in critically ill, cancer and immunosuppressed patients [4, 5]. Resistance to carbapenems, initially considered potent broad-spectrum antibiotics used to treat these infections [6], has increased significantly within the last decade because of the prevalence of carbapenemases among these pathogens [7–10]. Moreover, infections caused by extensively drug-resistant (XDR) or pandrug-resistant (PDR) organisms have emerged and spread all over the world [11–14]. Under such situations, older drugs like colistin, tigecycline, fosfomycin, clindamycin and cotrimoxazole are being deployed as the last resort in clinical practice for infections caused by MDR bacteria [15, 16].

Tigecycline was the first glycylcycline approved by the US Food and Drug Administration (FDA) to treat complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), and community-acquired pneumonia [17–19]. Owing to its broad spectrum antibacterial activity, particularly against Gram-negative bacteria which are resistant to other antibiotics, it has been widely used off-label in ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP) and bloodstream infections (BSI) caused by MDR

pathogens, especially carbapenem-resistant (CR) bacteria [20–22].

The efficacy of standard dose tigecycline (SDT) (100 mg initial dose, followed by 50 mg twice per day) in the clinic is controversial. Previous studies had indicated that tigecycline was not better than other antimicrobial agents and might be associated with increased mortality [23–25]. Pharmacokinetic and pharmacodynamic research suggested that this lack of efficacy may be due to its suboptimal concentrations in both serum and pulmonary epithelial lining fluid [26]. Therefore, a regimen of high dose tigecycline (HDT) (200 mg initial dose, followed by 100 mg twice per day) has been used in clinical practice. A systematic review in 2014 attempted to evaluate the effectiveness of HDT for the treatment of severe infections, but it could not draw conclusions regarding the efficacy of HDT because of limited clinical evidence [27]. With the accumulation of new studies, we aimed to reassess the effectiveness and safety of HDT for the treatment of severe infections.

METHODS

Protocol and Guideline

The full protocol of the systematic review and meta-analysis was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) as CRD42019129283. The systematic review adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Literature Search

We performed an extensive search of PubMed, Web of Science, Embase, MEDLINE and the Cochrane Library using the terms “tigecycline”, “dose” and “dosage” up to February 20, 2019. In order to identify completed but unpublished or ongoing studies, ClinicalTrials.gov was also searched. The reference lists of identified reports were hand-searched for relevant studies. No language restrictions were applied.

Study Selection

The relevant studies were examined by two reviewers (L.Z. and L.P.) independently. Eligible studies compared the efficacy of HDT with SDT or other non-tigecycline antibiotic regimens in the treatment of severe infections regardless of pathogens. Single-arm studies, repetitive studies, case report, reviews, studies with limited or uncertain information and those using tigecycline in other dosage (i.e. not the defined high dose) were excluded, as were animal, pharmacokinetic/pharmacodynamic and in vitro studies. No restrictions were placed on the characteristics of participants, lengths of follow-up, antibiotics used in combination with HDT, and antibiotic regimens in the control group. Any disagreements were resolved through discussion with a third assessor (J.G.).

Data Extraction

Two reviewers working independently extracted the following information from each study: first author’s name and year of publication, study design, patient characteristics (age, infection sites and score of the severity of diseases), type of microorganism, concomitant antibiotics and antimicrobial agents used in the control groups, outcomes (all-cause mortality, clinical cure and microbiology eradication rate) and reported clinical adverse events.

Quality Assessment

The quality of the included non-randomised studies was evaluated using the modified Newcastle–Ottawa scale (NOS) [29]. Studies with NOS scores below 3 were considered as poor quality and excluded from this review. The risk of bias of included non-randomised studies was assessed using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies of Interventions) [30]. The risk of bias of the single randomised

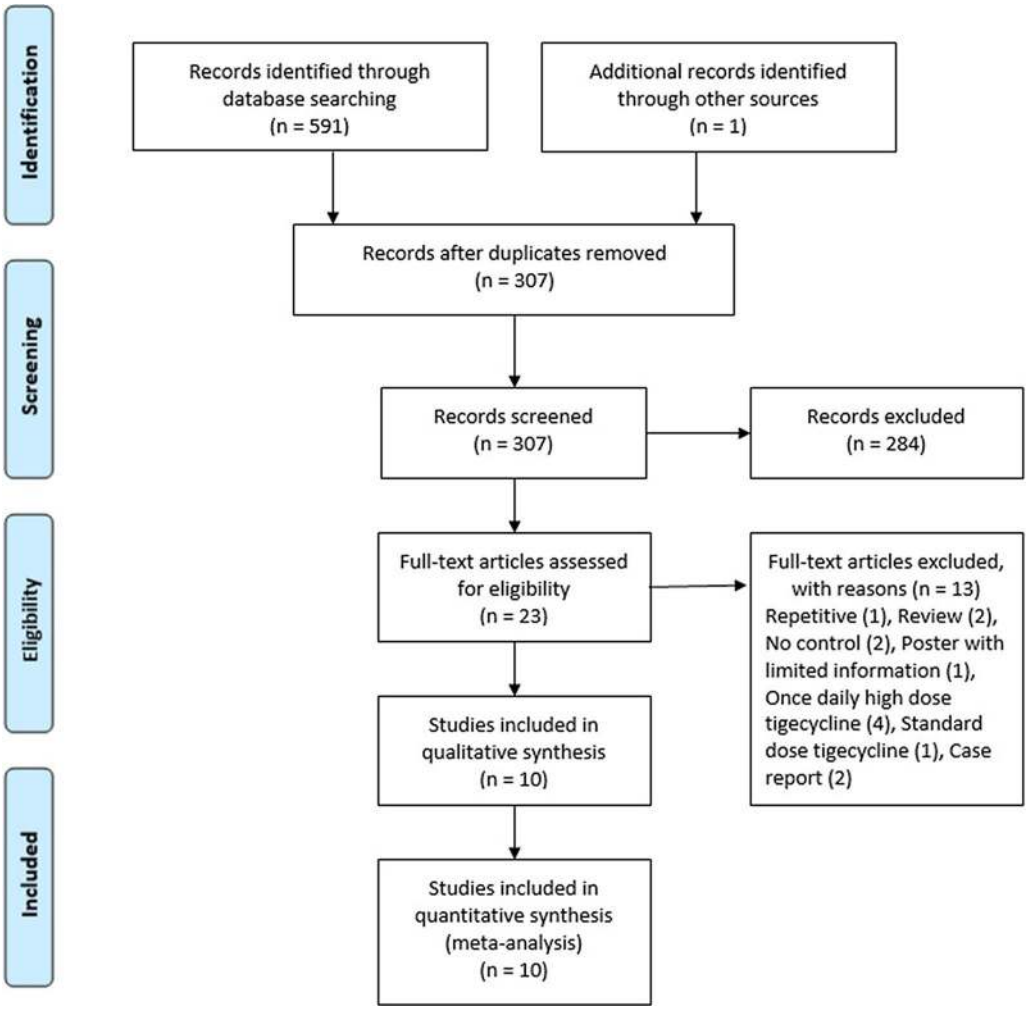

Fig. 1 Flow chart indicating the process of literature search and review for effectiveness and safety of high dose tigecycline for the treatment of severe infections based on eligible criteria

controlled trial (RCT) included in this review was assessed with the Cochrane Collaboration's tool for assessing the risk of bias [31].

Definitions and Outcomes

The outcome of primary interest of the review is all-cause mortality. Secondary outcomes include the clinical cure rate, microbiological eradication rate and adverse events (diarrhoea, nausea, vomiting, renal impact, hepatic injury and haematological injury). Clinical cure was defined as complete resolution or improvement from the symptoms and signs of infection. Microbiological eradication was defined as sterile culture or absence of the original pathogen in sequential culture after antibiotics treatment. As a result of the lack of standard definitions of adverse events, the criteria as reported in each study were used. HDT was defined as using tigecycline 100 mg twice per day after a 200 mg loading dose, whereas SDT was defined as using 50 mg twice per day after a 100 mg loading dose. HAP, VAP, BSI, cIAI and cSSTI were defined using criteria reported in each study. Mixed infection was defined as the presence of at least two types of infection in patients (i.e. patients diagnosed as cIAI, BSI and HAP were all included in one study).

Table 1 Characteristics of included studies in the systematic review and meta-analysis

Reference	Study design, period, country	Population characteristics HDT/control (mean ± standard deviation)	Type of infection	Causative pathogens	Mortality assessed	Sample size (HDT/SDT)	Concomitant antibiotics in HDT group	Antibiotics used in control group	Sensitivity to TGC
Chen et al. [35]	SC, retrospective, 2013–2015, China	NCU patients APACHE II 18.38 ± 4.73/19.59 ± 5.77, age 58.26 ± 17.5/64.59 ± 19.7	VAP	MDR-AB, MDR-KP, other GNB	28 days	69/54	Cefoperazone–sulbactam/piperacillin–tazobactam/imipenem/meropenem	SDT + cefoperazone-sulbactam/piperacillin–tazobactam/imipenem/meropenem	NR
De Pascale et al. [36]	SC, retrospective, 2009–2012, Italy	ICU patients, SOFA 7.4 ± 2.7/7.8 ± 3.2, age 60.7 ± 12.5/64.5 ± 16.9	VAP	GNB (AB, KP), CR (94%)	ICU	33/30	87.9% used combination of antibiotics	SDT + 80% concomitant antibiotics	All MIC ≤ 2 mg/ml
Di Carlo et al. [42]	SC, prospective, 2011–2012, Italy	ICU patients, APACHE II 23.4 ± 1.7, age 56.6 ± 15	BSI	CRKP	ICU	12/18	Colistin	SDT + colistin	100% susceptible
Geng et al. [37]	SC, retrospective, 2014–2016, China	ICU patients, APACHE II 20.7 ± 9.4/20.2 ± 6.0, SOFA 4.7 ± 3.3/5.4 ± 2.9, age 65.1 ± 14.3/61.8 ± 13.9	BSI	CRKP	In-hospital	23/17	Carbapenems or β-lactamase inhibitors or aminoglycosides	SDT + carbapenems or β-lactamase inhibitors or aminoglycosides	79.5% susceptible
Ibrahim et al. [38]	SC, retrospective, 2013–2014, Egypt	ICU patients, SOFA 9.5, age 57.5	cSSTI, cIAI, CAP	AB, KP, *E. coli*, *Enterobacter*, *Enterococcus*, *Staphylococcus*, *Streptococcus*	ICU	35/33	No	SDT	100% susceptible
Maseda et al. [39]	MC, retrospective, 2012–2013, Spain	SICU patients, SOFA 7.0 ± 3.3/5.5 ± 3.7, age 65.7 ± 7.3/65.7 ± 16.3	cIAI	Polymicrobial (*Enterococcus* as major)	28 days	54/67	Piperacillin–tazobactam/antifungals	Carbapenems	NR
Moreno et al. [34]	SC, retrospective, 2009–2011, Spain	ICU patients, APACHE II 19.7 ± 8.2/21.8 ± 3.1, age 56.4 ± 15.8/51.5 ± 7.5	Pneumonia (5), UTI (5), cIAI (3), BSI (2), meningitis (1)	CRKP	30 days	10/6	Colistin/carbapenems/ciprofloxacin/piperacillin–tazobactam	SDT + colistin/carbapenems/ciprofloxacin/amikacin	100% susceptible

Table 1 continued

Reference	Study design, period, country	Population characteristics HDT/control (mean ± standard deviation)	Type of infection	Causative pathogens	Mortality assessed	Sample size (HDT/SDT)	Concomitant antibiotics in HDT group	Antibiotics used in control group	Sensitivity to TGC
Ramirez et al. [43]	MC, RCT, DB, 2008–2011, 75 sites	APACHE II, 74.3% ≤ 15/ 67.7% ≤ 15, age 61.5 ± 16.1/64.9 ± 15.3	HAP (VAP 40.6%)	GNB, *Staphylococcus aureus*, *Streptococcus* spp.	21 days	35/34	Ceftazidime and tobramycin or amikacin	Imipenem/cilastain + vancomycin and tobramycin or amikacin	NR
Vardakas et al. [40]	SC, retrospective, Greece	ICU patients APACHE II 16.3 ± 7 age 65.8 ± 13.5	Bacteremia (22), LRTI (3), UTI (1), cIAI (3), cSSTI (3)	CRKP	In-hospital	26/6	Colistin/aminoglycoside/ carbapenem	SDT + colistin/ aminoglycoside/ carbapenem	96.8% (31) susceptible
Wu et al. [41]	SC, retrospective, 2013–2015, China	RICU patients APACHE II 15–19 (IQR), SOFA 3.5 ± 1.1, age 74.6 ± 9.4	HAP (VAP)	CR-GNB (CRAB, CRKP)	ICU	20/11	Cefoperazone–sulbactam/ piperacillin–tazobactam/ carbapenem	SDT + cefoperazone–sulbactam/piperacillin–tazobactam/carbapenem	All susceptible except 1 AB intermediate

SC single centre, *MC* multiple centres, *NCU* neurological care unit, *RICU* respiratory intensive care unit, *ICU* intensive care unit, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia, *CAP* community-acquired pneumonia, *UTI* urinary tract infection, *cIAIc* complicated intra-abdominal infections, *BSI* bloodstream infection, *LRTI* lower respiratory tract infection, *cSSTIc* complicated skin and soft tissue infections, *MDR* multidrug resistant, *AB Acinetobacter baumannii, KP Klebsiella pneumoniae, CR* carbapenem resistant, *CRKP* carbapenem-resistant *Klebsiella pneumoniae, CRAB* carbapenem-resistant *Acinetobacter baumannii, GNB* Gram-negative bacteria, *NR* not report, *SDT* standard dose tigecycline, *HDT* high dose tigecycline, *MIC* minimum inhibitory concentration, *IQR* interquartile range, *TGC* tigecycline

Table 2 Assessment of the risk of bias for included non-randomised studies

	Confounding	Selection bias	Classification bias of interventions	Deviations from intended interventions	Bias due to missing data	Measurement bias	Report bias	Overall
Chen et al. [35]	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Serious
De Pascale et al. [36]	Serious	Serious	Serious	NI	Low	Low	Moderate	Serious
Di Carlo et al. [42]	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Serious
Geng et al. [37]	Serious	Serious	Serious	NI	Low	Low	Moderate	Serious
Ibrahim et al. [38]	Serious	Serious	Serious	NI	Low	Low	Moderate	Serious
Maseda et al. [39]	Critical	Critical	Serious	Serious	Low	Low	Moderate	Critical
Moreno et al. [34]	Serious	Serious	Serious	Serious	Low	Low	Moderate	Serious
Vardakas et al. [40]	NI	NI	Serious	NI	Low	Low	Moderate	NI
Wu et al. [41]	Serious	Serious	Serious	Serious	Low	Low	Moderate	Serious

Statistical Analysis

The review was performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Statistical heterogeneity was assessed by the I^2 test, and $I^2 > 50\%$ was defined as substantial heterogeneity [32]. In the presence of substantial heterogeneity, a random-effects model was used. Otherwise, a fixed-effects model was calculated. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using the Mantel–Haenszel method. The sequential monitoring boundary and required information size (RIS) were constructed and calculated with the software Trial Sequential Analysis (http://www.ctu.dk/tsa/) [33]. Publication bias was

evaluated with funnel plots and the Egger regression-based test implemented in Stata version 14 (StataCorp, College Station, Texas). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Included Studies and Characteristics

Overall, 591 studies were identified from five databases, and one was identified through reference lists. After application of eligibility criteria, ten studies were included in the systematic review and meta-analysis (Fig. 1). Among the included studies, eight were retrospective observational studies [34–41], one was a prospective observational study [42], and one was an RCT [43]. A total of 593 patients were enrolled, with the majority (88.4%) being admitted to intensive care with severe infections (these patients had an Acute Physiology and Chronic Health Evaluation II [APACHE II] score more than 15).

The main pathogens were CR-Gram-negative bacteria, especially CR-*Klebsiella pneumoniae*. The indications for using tigecycline were nosocomial pneumonia (HAP and VAP), BSI, cIAI and cSSTI. Seven studies [34, 36–38, 40–42] evaluated the sensitivity of pathogens to tigecycline, and the susceptibility rate ranged from 79.5% to 100%. The most commonly used antibiotics in the control group was SDT; only two studies [39, 43] assessed non-tigecycline treatments. The characteristics of the studies included in this review are shown in Table 1.

Assessment of Bias

Most of the included non-randomised studies had serious or critical risks of bias due to the nature of the design of observational studies (Table 2). When studies with critical risk or no information were excluded, the all-cause mortality in the HDT group was still lower than that in the control group without obvious heterogeneity (OR 0.32, 95% CI 0.20–0.50, $I^2 = 0\%$, $p < 0.00001$). The included RCT was assessed as unclear risk of bias because of unclear information in the selection bias domain, although other domains were at low risk.

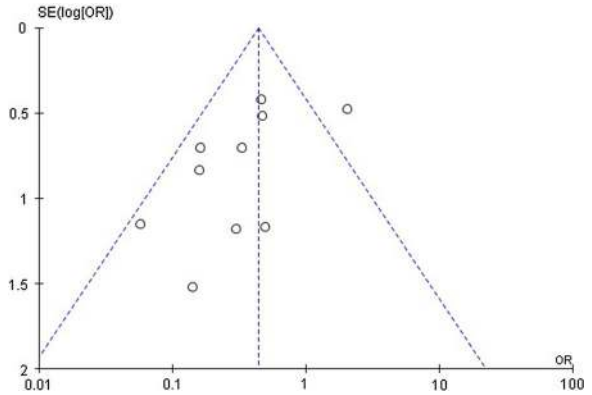

Fig. 2 Funnel plot of all-cause mortality in high dose tigecycline (HDT) regimens compared with controls

The funnel plot of all-cause mortality of the included studies is shown in Fig. 2. The Egger regression-based test gave $p = 0.303$, which means no obvious publication bias was detected.

All-Cause Mortality

The pooled all-cause mortality was 31.4%. Compared with the control group, mortality in the HDT group was statistically lower (OR 0.44, 95% CI 0.30–0.66, $I^2 = 49\%$, $p < 0.0001$). Further analysis indicated that the major pathogens were *Enterococcus faecium* and *Enterococcus faecalis* in Maseda et al.'s study [39], whereas in other studies, the main pathogens were Gram-negative bacteria. When Maseda et al.'s study was excluded, statistical heterogeneity was eliminated (OR 0.30, 95% CI 0.19–0.48, $I^2 = 0\%$, $p < 0.00001$).

All subgroups (HAP (VAP) [35, 36, 41, 43], BSI [37, 42], and mixed infections [34, 38, 40]) except cIAI [39] showed a favourable outcome in the HDT group. In cIAI no statistical differences between HDT and control were seen (OR 2.04, 95% CI 0.80–5.23, $p = 0.14$). The impact of carbapenem resistance on mortality showed that HDT-containing regimens reduced mortality in CR-bacterial infections (OR 0.20, 95% CI

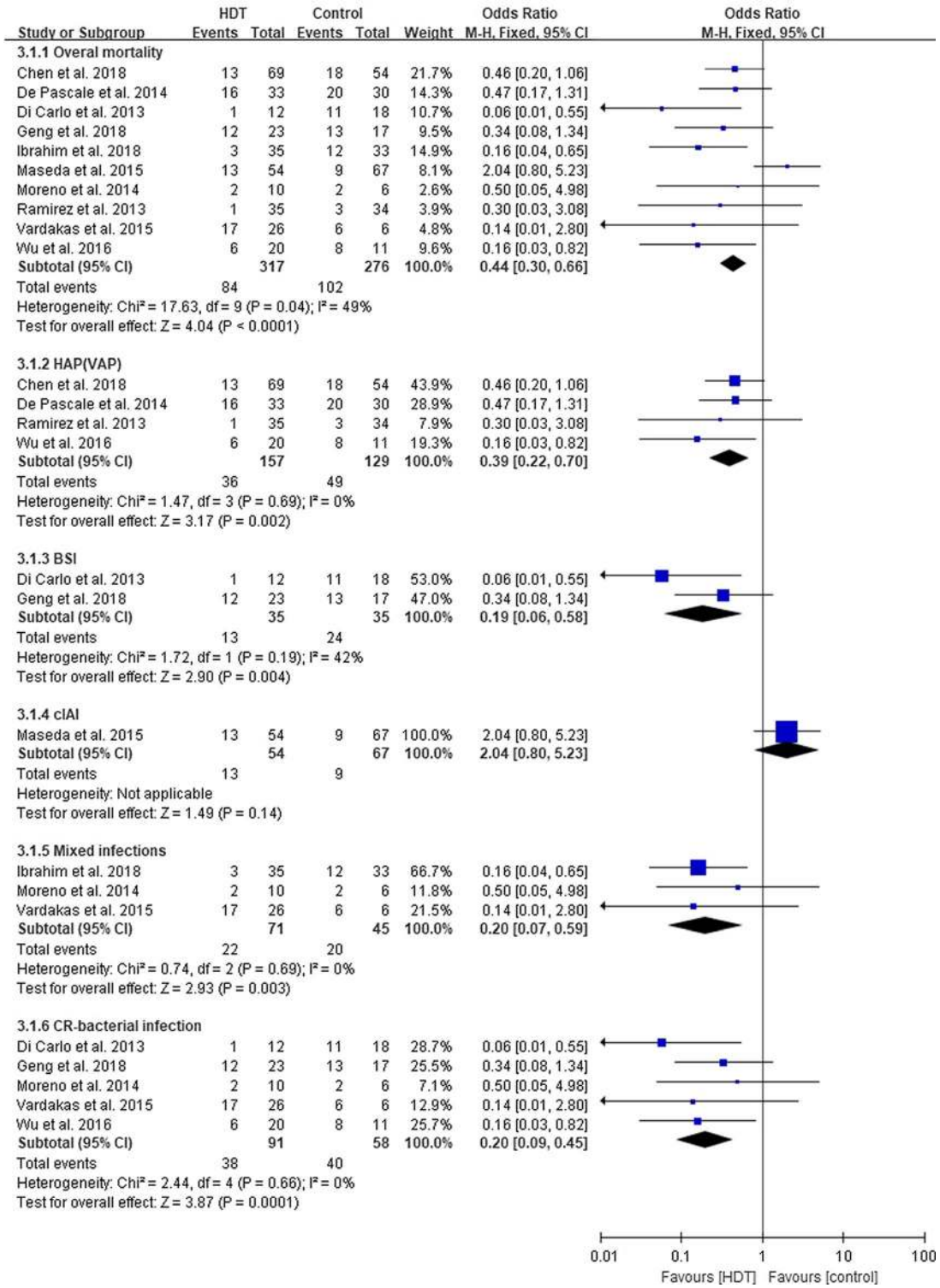

Fig. 3 All-cause mortality of the high dose tigecycline (HDT) regimens compared with controls. HAP hospital-acquired pneumonia, VAP ventilator-associated pneumonia, BSI bloodstream infection, cIAI complicated intra-abdominal infections, CR carbapenem resistant

0.09–0.45, I^2 = 0%, p = 0.0001) (Fig. 3) [34, 37, 40–42].

Clinical Cure and Microbiological Eradication Rate

Four studies [35, 36, 41, 43] with 286 patients evaluated the clinical cure rate. Patients given HDT had a higher clinical cure rate compared to controls (OR 3.43, 95% CI 2.09–5.63, I^2 = 0%, $p < 0.00001$). In the seven studies [34–38, 41, 43] and 344 patients assessing the microbiological eradication rate, a pooled result favouring the HDT group was found (OR 2.25, 95% CI 1.44–3.50, I^2 = 30%, p = 0.0003) (Fig. 4). However, the pooled result of the microbiological eradication rate did not reach statistical significance when bacteria were resistant to carbapenem (OR 1.07, 95% CI 0.44–2.60, I^2 = 32%, p = 0.87) (Fig. 4) [34, 37, 41].

Adverse Events

Five studies [35–38, 43] documented 197 adverse events, including diarrhoea (n = 36), nausea (n = 18), vomiting (n = 14), renal injury (n = 21), hepatic injury (n = 66), and haematological injury (n = 42). There were no statistical differences in the distributions of adverse events in the two groups (Fig. 5).

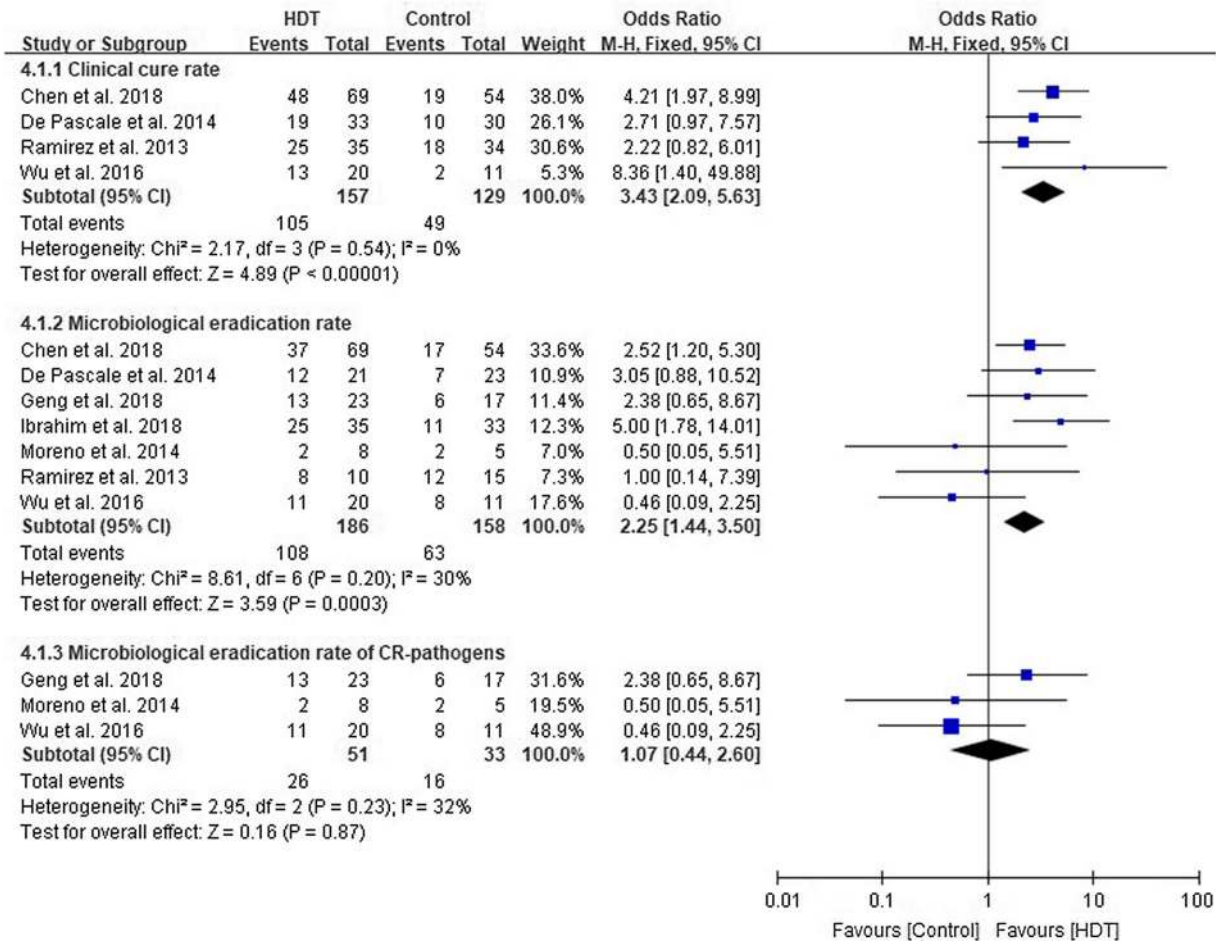

Fig. 4 Clinical cure rate and microbiological eradication rate of high dose tigecycline (HDT) regimens compared with controls. CR carbapenem resistant

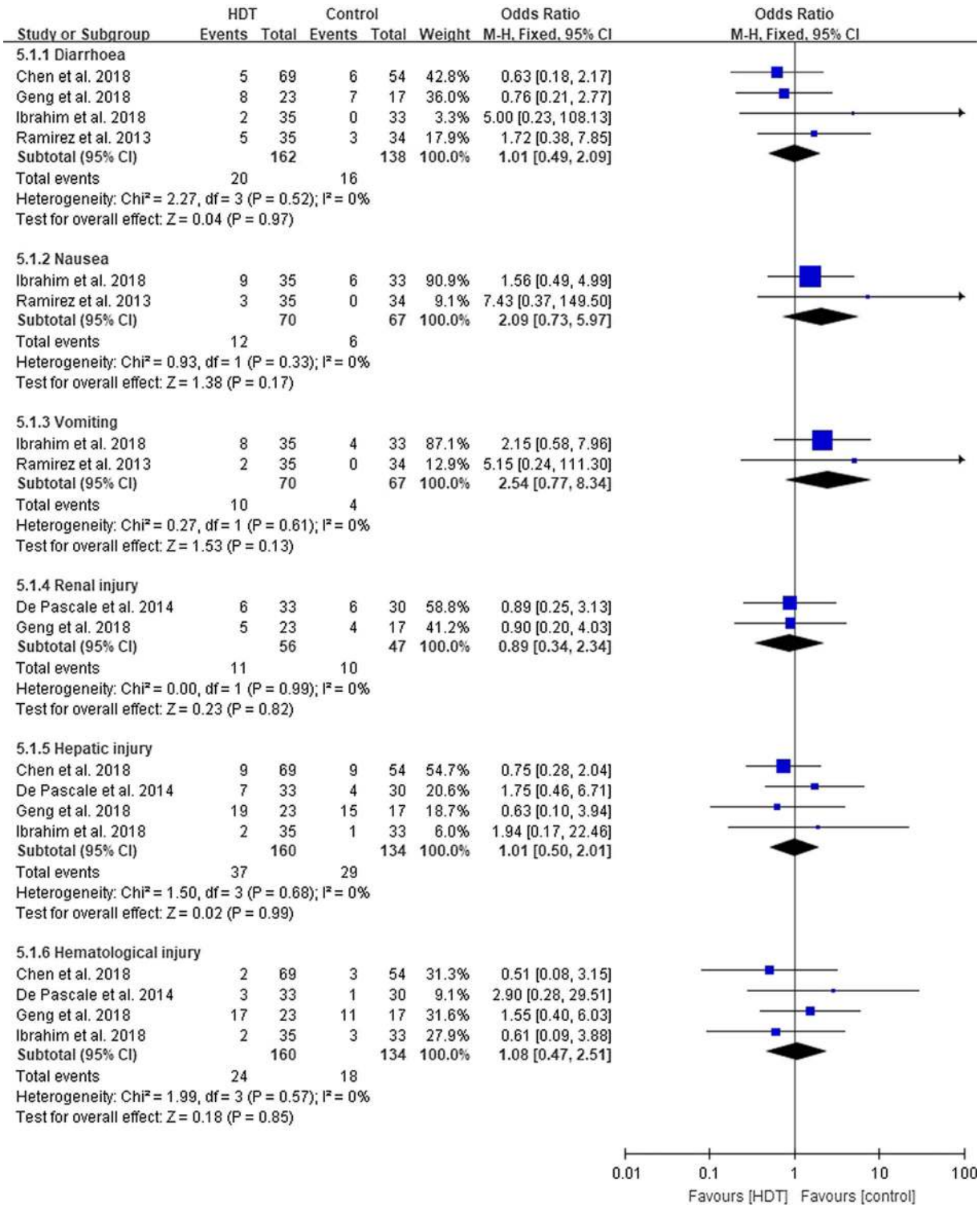

Fig. 5 Adverse events of the high dose tigecycline (HDT) regimens compared with controls

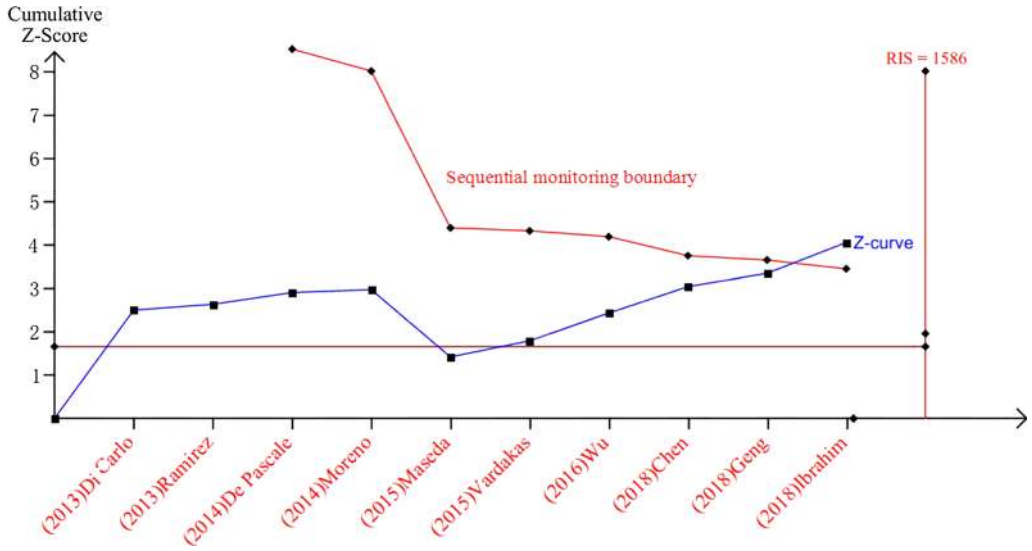

Fig. 6 Cumulative meta-analysis assessing the effect of high dose tigecycline on all-cause mortality of severe infections. The sequential monitoring boundary, which assumes a 42% control event rate and a 12% relative risk reduction with 80% power and two-sided α of 5%, has been crossed, indicating that the cumulative evidence is conclusive

Reliability and Conclusiveness of the Primary Outcome

To determine the RIS for overall mortality, the control event rate was assumed to be 42% (calculated in this meta-analysis), the relative risk reduction was defined as 12% (estimated from this meta-analysis) with 80% power and a two-sided α error of 5%. At least 1586 patients were required to get a reliable treatment effect analysis. In this review, there were 593 patients enrolled for the analysis of all-cause mortality. Although the pooled sample size was less than the RIS, the cumulative curve (Z-curve) crossed the sequential monitoring boundary indicating that the result in our meta-analysis is reliable and conclusive (Fig. 6).

DISCUSSION

Tigecycline is widely used for difficult-to-treat infections because of its broad spectrum of antimicrobial ability and low rate of resistance. Studies illustrated that tigecycline had good activity against MDR pathogens, included methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, vancomycin-resistant *Enterococcus*, *Clostridium difficile* and other *Enterobacteriaceae* [6, 18, 44, 45]. However, studies evaluating the efficacy of SDT in the treatment of severe infections raised concern about its effectiveness. A meta-analysis of 14 RCTs of around 7400 patients showed that tigecycline treatment is no better than the control antibiotics [23]. Two other studies concluded that tigecycline increased mortality and adverse events [24, 46]. Ni et al. [47] reported that in terms of CR-*Enterobacteriaceae* infections, SDT had similar overall mortality, clinical response and microbiological eradication rates when compared with other antibiotics, but that the HDT group decreased the mortality rate compared with the SDT regimen (OR 0.08, 95% CI 0.013–0.080, $p = 0.006$).

In our meta-analysis, 10 studies with 593 patients indicated that treatment with HDT decreased overall mortality while improving both the clinical cure and microbiological eradication rates. Subgroup analysis of the type of infection illustrated that all subgroups except cIAI showed favourable results under HDT. In the cIAI group, the lack of effect of HDT could

be explained by the severity of infection in patients enrolled in the HDT group compared to the control group (i.e. patients had significantly higher Sequential Organ Failure Assessment [SOFA] and Simplified Acute Physiology Score II [SAPS II], and a higher percentage of patients required mechanical ventilation, renal replacement therapy and presented septic shock) [39]. Since there are no other studies focusing on cIAI included in our meta-analysis, the true effect of HDT in cIAI cannot be concluded with certainty.

In the subgroup analysis of infections caused by CR-pathogens, the microbiological eradication rate did not show any statistical significance in the HDT group compared with SDT treatment. Epidemiological studies have shown that CR-Gram-negative bacteria usually present resistance against other antibiotics [8, 10, 48]. In our meta-analysis, all the included pathogens for CR-subgroup analysis were MDR *K. pneumoniae* and MDR *A. baumannii*, and the antibiotics used were those with high resistant rates in CR-*K. pneumoniae* and CR-*A. baumannii*. As tigecycline is a tetracycline-derived bacteriostatic agent, without the synergistic effect of other active bactericides, the clearance of those pathogens would be slow [18]. The combination of these reasons may explain the lack of difference in the microbiological eradication rate between HDT and the control group in the CR-subgroup.

Our analysis of the impact of carbapenem resistance on mortality showed that the HDT group experienced better outcomes. Previous studies reported that CR-infections had higher mortality rates because the proportion of inappropriate antibiotics therapy was higher [49–51]. In our meta-analysis, the patients in almost all studies (excepting Geng et al. [37]) showed around 100% susceptibility to tigecycline. Therefore, although the microbiological eradication rate did not show any statistical differences, the mortality rate is still lower in the HDT group of the CR-infections subgroup.

Previous studies reported higher rates of adverse events in the SDT group when compared with non-tigecycline regimens [24]. In our meta-analysis, eight out of ten studies used SDT as controls. The lack of any statistically significant differences in our results suggests that HDT is tolerable and as safe as SDT, although it has higher adverse events rate when compared with non-tigecycline regimens reported in one included study [43].

The adverse events analysis of our review failed to assess the rate of development of tigecycline resistance in the HDT and SDT group because of limited information of the included studies. However, the results in this review showed that the microbiological eradication rate was lower in the SDT group compared with the HDT group. The lower microbiological eradication rate suggests that there were more pathogens exposed to a suboptimal concentration of tigecycline and hence would possibly select for more antimicrobial resistant bacteria. A similar result was also found in a recently published review paper, which illustrated that the microbiological eradication rate was lower in the SDT group compared with other non-tigecycline antibiotics in the treatments of pneumonia caused by MDR *A. baumannii* [52]. Therefore, the selection of SDT-containing regimens as the clinical choice should be reconsidered because it might increase the probability of emergence of XDR or PDR pathogens. Nevertheless, the real effect of tigecycline dose on the selection of antimicrobial resistance should be further studied.

There are several limitations in our study. First, all the included studies are limited to observational studies of small sample sizes and one RCT. Although the accumulated sample size crossed the sequential monitoring boundary, the real efficacy of HDT would only be concluded through a well-designed, properly powered RCT because of the nature of unavoidable confounders and bias in observational studies. Second, apart from the only RCT and one observational study, all the other studies included in the review had the control group utilizing SDT regimens, which limited the conclusion to comparisons between HDT and SDT, rather than comparisons between HDT and other commonly used non-tigecycline antibiotics. Third, although the calculated heterogeneity values between studies are low, the variations of interventions (concomitant antibiotics, time to start therapy, inappropriate

antibiotics therapy rate), outcomes measurement (time to assess mortality, definition of clinical response, time to evaluate microbiological eradication rate, etc.) may affect the interpretation of the results.

CONCLUSIONS

This systematic review and meta-analysis suggests that HDT treatment has better outcomes in the treatment of severe infections when compared with SDT and other non-tigecycline-containing regimens. The HDT regimen is associated with lower mortality rate, higher clinical cure and microbiological eradication rate, while having similar adverse events rates compared with controls. We recommend using HDT if a tigecycline-containing regimen is the clinical choice for severe infections, especially those infected with MDR bacteria. However, as a result of the high risks of bias of the included studies, well-designed, properly powered RCTs are warranted to confirm the effectiveness and safety of HDT compared with SDT and other commonly used antibiotics.

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Data Availability. All data generated or analysed during our study are included in this published article.

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