Efficacy and safety of high-dose tigecycline for the treatment of infectious diseases

A meta-analysis

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Abstract

Background: High-dose (HD) tigecycline regimen is increasingly used in infectious diseases, however its efficacy and safety versus low-dose (LD) is still unclear.

Methods: A systematic review and meta-analysis was performed; PubMed, Embase, Cochrane Library, ScienceDirect, Web of Science, clinicalTrials.gov, Wanfang, VIP, and China National Knowledge Infrastructure (CNKI), were searched using terms "tigecycline" AND "dose" up to October 31, 2018. Eligible studies were randomized trials or cohort studies comparing mortality, clinical response, microbiological eradication and safety of different tigecycline dose regimens for any bacterial infection. The primary outcome was mortality, and the secondary outcomes were clinical response rate, microbiological eradiation rate and adverse events (AEs). Meta-analysis was done with random-effects model, with risk ratios (RR) and 95% confidence intervals (CI) calculated for all outcomes.

Results: Of 951 publications retrieved, 17 studies (n = 1041) were pooled in our meta-analysis. The primary outcome was available in 11 studies, and the RR for mortality was 0.67 (95% *Cl* 0.53–0.84, P < .001). Clinical response (*RR* 1.46, 95% *Cl* 1.30–1.65, P < .001) and microbiological eradication rate (*RR* 1.61, 95% *Cl* 1.35–1.93, P < .001) were both higher in HD than in LD tigecycline regimen. However, non-Chinese study subgroup presented no statistical significance between HD and LD regimen, RR for mortality, clinical response and microbiological eradication were 0.79 (95% *Cl* 0.56–1.14, P = .21), 1.35 (95% *Cl* 0.96–1.92, P = .26), 1.00 (95% *Cl* 0.22–4.43, P = 1.00), respectively. AEs did not differ between HD and LD tigecycline (*RR* 1.00, 95% *Cl* 0.80–1.26, P = .97).

Conclusion: HD tigecycline regimen reduced mortality meanwhile improved clinical efficacy and should be considered in serious infections caused by multidrug-resistant and extensively drug-resistant (MDR/XDR) bacteria.

Abbreviations: AEs = adverse events, CI = confidence intervals, HAP = hospital-acquired pneumonia, HD = high-dose, LD = low-dose, MDR = Multidrug-resistant, PK/PD = pharmacokinetic and pharmacodynamic, RR = risk ratios, VAP = ventilator-associated pneumonia, XDR = extensively drug-resistant.

Keywords: clinical response, high dose, meta-analysis, mortality, tigecycline

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1. Introduction

Multidrug-resistant (MDR) to current available antibiotics is increasing. Resistant pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacter species, Enterococcus faecium and *Staphylococcus aureus* account for the majority of nosocomial infections which challenged the prognostic of infection diseases. Infections with resistant pathogens are associated with increased mortality, morbidity, and length and cost of hospital stay. Classic agents used to treat these pathogens have become powerless and new antibiotics available might have already become targets for bacterial mechanisms of resistance.^[1,2] Therefore, development of new antibiotics with high potency, stability against the mechanisms of resistance, and favorable pharmacokinetic and pharmacodynamic (PK/PD) characteristics has become an urgent priority.

Medicine

Tigecycline is a glycylcycline antibiotic with broad-spectrum activity against nearly all Gram-positive, Gram-negative (except Proteus sp. and *Pseudomonas aeruginosa*), atypical, anaerobic, as well as MDR pathogens.^[3,4] Tigecycline was first approved by the FDA in 2005. Its FDA approved uses include complicated skin/skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia.^[4]

Due to its low potential for resistance and broad spectrum activity, tigecycline is increasingly used for treatment of MDR infections.^[5] However, several studies have reported on the treatment failures of standard dose tigecycline therapy (100 (IV) $\times 1$ followed by 50 mg (IV) q12 h), for example, in a phase 3 study, the cure rates for patients with hospital-acquired pneumonia (HAP) treated with tigecycline at the approved dose were lower than those seen with patients treated with imipenem/ cilastatin (47.9% vs 70.1%, respectively).^[6] A meta-analysis of Phase 3 and 4 clinical trials also demonstrated an increase in allcause mortality in standard dose tigecycline treated patients especially with ventilator-associated pneumonia (VAP) compared to controls.^[7] From the point of its PK/PD characteristics, tigecycline is initially concluded to display linear pharmacokinetics,^[8] however, closer evaluation supports non-linear pharmacokinetics, which may be further utilized to optimize the therapeutic dosing regimen.^[9] A higher dose tigecycline was proposed for serious infections caused by MDR pathogens,^[10,11] and some centers have implemented clinically but with unequal outcome.^[12-14] To date there has not been a meta-analysis performed on studies investigating high-dose (HD) vs low-dose (LD) tigecycline, whether HD regimen is beneficial still remains obscure.

Therefore, we performed a systematic review and metaanalysis to compare the efficacy and safety of HD with LD tigecycline regimens in treating serious infections.

2. Methods

2.1. Data source and searches

An extensive search of PubMed, Embase, Cochrane Library, ScienceDirect, Web of Science, clinicalTrials.gov, as well as Wanfang, VIP, and China National Knowledge Infrastructure (CNKI) up to October 31, 2018 were performed. The search terms applied to all databases was as follows: "tigecycline" AND "dose". The reference lists of the all relevant articles were manually searched to find further potentially eligible studies. No language restrictions were imposed.

2.2. Study selection

Studies that compared HD tigecycline vs LD tigecycline for the treatment of any bacterial infections were considered eligible for inclusion in the meta-analysis. Studies published as both conference abstracts/posters and full-text articles were included. Studies including overlapped patient populations, the latest published studies were included. Cohort studies only reporting on the outcomes of patients receiving HD tigecycline without comparing with LD regimen were excluded. Case reports, clinical studies reporting on PK/PD outcomes as well as studies reporting none of the following outcomes were also excluded: mortality, clinical response rate (as defined in individual studies), microbiological eradication rate and adverse events (AEs).

2.3. Data extraction and outcomes

Two reviewers (JHG and ZQS) independently did the search, applied predefined inclusion & exclusion criteria and extracted the data. For all outcomes, data were extracted for the available largest patient population evaluated. The

following data were extracted from every study: name of the first author, year of publication, study design and period, country, number of patients, site of infection, causative pathogen, dosing regimen of tigecycline, concomitant antibiotic treatment administered. In addition, outcomes such as mortality, clinical response rate, microbiological eradication rate and AEs according to different tigecycline doses were recorded. The primary outcome was all-cause mortality, secondary outcomes including treatment response, microbiological eradication and AEs.

2.4. Statistical analyses

The meta-analysis was done with random-effects models in Review Manager (RevMan) [Computer program] (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Mantel-Haenszel model with random effects was used because of the obvious heterogeneity across the studies included in the meta-analysis (e.g., different site or severity of infections, concomitant antibiotic treatment, and time to test of cure visit).^[15] For all outcomes, pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated according to the Mantel-Haenszel method. Heterogeneity in the results of the studies was assessed using the χ^2 test for heterogeneity and the I^2 measure of inconsistency.^[16] For outcomes of mortality and AEs, RR <1 favors HD-regimen of tigecycline, and for clinical response rate and microbiological eradication rate, RR >1 favors HD-regimen. Subgroup analyses were done by country, type of infection and, for the outcome of AEs, by systems/manifestation. All subgroup and sensitivity analyses were pre-specified, with the exception of 1 sensitivity analysis excluding 2 studies with different HD or LD regimen.

This is a meta-analysis, which does not need to be approved by the institutional review board or Ethics committee.

3. Results

3.1. Characteristics of included studies

Figure 1 presents the overall search protocol. 951 potential articles were identified, 26 studies met the inclusion & exclusion criteria according to information in the title and abstract were assessed for eligibility, of which 9 were excluded.^[13,17–24] Seventeen studies^[12,14,25–39] with a total of 1041 patients were included in the meta-analysis: 16 single-center study and one multi-center study.^[12] 3 random controlled trial,^[12,34,36] among which one was a phase 2 double-blind study,^[12] one described the randomization method,^[34] while the other without any detail illustration,^[36] 3 prospective cohort study^[25,28,32] and 11 retrospective cohort study. Studies covered several different countries, including Italy (2 studies^[25,26]), Spain (2 studies^[27,39]), Brazil (1 study^[28]), China (11studies, 3 published in English,^[14,31,35] and 8 in Chinese) and one international multicenter.^[12]

The HD and LD regimen in most studies were 100 mg every 12 hours and 50 mg every 12 hours respectively, except $one^{[12]}$ compared 100 mg every 12 hours vs 75 mg every 12 hours and $one^{[33]}$ compared 75 mg every 12 hours vs 50 mg every 12 hours. At least 1 concomitant systemic antibiotic was applied in 14 trials, 2 trials^[32,36] without concomitant antibiotic treatment and $one^{[39]}$ did not refer to concomitant antibiotics (Table 1).



3.2. All-cause mortality

Eleven studies^[12,14,25-28,31-33,35,39] reporting mortality were included for analysis. All-cause mortality for patients treated with HD tigecycline was significantly lower than LD (RR 0.67, 95% CI 0.53-0.84, 11 studies, 629 patients) without significant heterogeneity (P = .30, $I^2 = 15\%$). Subgroup analyses by country showed similar result in Chinese study (RR 0.56, 95% CI 0.41-0.75), while studies in other countries presented no significant difference (RR 0.79, 95% CI 0.56-1.14) (Fig. 2A). Compared with LD regimen, all-cause mortality significantly decreased in HD regimen for subgroup of VAP (*RR* 0.61, 95% *CI* 0.45–0.83), nosocomial pneumonia (RR 0.42, 95% CI 0.22-0.81) and intraabdominal infection (RR 0.14, 95% CI 0.02-0.92), while bloodstream infection subgroup showed no statistical significance (RR 0.68, 95% CI 0.43-1.09) (Fig. 2B). Sensitivity analysis excluding two different dose regimen studies^[12,33] was consistent (RR 0.68, 95% CI 0.53-0.87).

3.3. Clinical response rate

Twelve studies^[12,26,29–38] reporting clinical response rate were included for analysis. Clinical response rate of HD regimen was

significantly higher than LD (RR 1.46, 95% CI 1.30–1.65, 12 studies, 755 patients) without significant heterogeneity (P=.37, I^2 =8%). Subgroup analyses by country showed similar result in Chinese study (*RR* 1.49, 95% CI 1.30–1.70), while studies in other countries presented a negative result (*RR* 1.35, 95% CI 0.96–1.92) (Fig. 3A). Clinical response rate of HD regimen in subgroup of VAP (*RR* 1.55, 95% CI 1.32–1.82) and nosocomial pneumonia (*RR* 1.40, 95% CI 1.19–1.64) increased significantly than LD regimen (Fig. 3B). Sensitivity analysis excluding 2 different dose regimen studies^[12,33] was consistent (*RR* 1.53%, 95% CI 1.34–1.76).

3.4. Microbiological eradication rate

Ten studies^[14,26,27,30,31,33–36,38] reported microbiological eradication rate were included for analysis. Microbiological eradication rate of HD regimen was significantly higher than LD (*RR* 1.61, 95% *CI* 1.35–1.93, 10 studies, 580 patients) without significant heterogeneity (P=.86, I^2 =0%). Subgroup analyses by country showed similar result in Chinese study (*RR* 1.63, 95% *CI* 1.35–1.97), while studies in other countries presented a negative result (*RR* 1.00, 95% *CI* 0.22–4.43) (Fig. 4A). HD tigecycline

Table 1

Main characteristics of the studies included in the meta-analysis.

First author, year	Study design, period, country	No. of pts	Type of infection & causative pathogens	i.v. Tigecycline dose- regimen/pts	Concomitant antibiotic treatment	Outcomes
Ramirez 2013 ^[12]	MC, DB-RCT 2008.11–2011.6 Europe, Asia, America, Australia	71	nosocomial pneumonia; AC, Enterobacteria- ceaeb, Haemophilus spp., Streptococcus spp., MSSA, MRSA	HD: 35 pts, 200 mg × 1+ 100 mg q12h LD: 36 pts, 150 mg × 1 + 75 mg q12h	Yes (ceftazidime + tobramycin, amikacin + i.v. vancomycin)	1, 2, 4 VAP-Sub:2
Di Carlo 2013 ^[25]	SC-PC 2011.8.1–2012.8.31 Italy	30	Severe IAI; CPKP	HD: 12 pts, 200 mg × 1+ 100 mg q12h LD: 18 pts, 100mg × 1+ 50 mg q12h	Yes (colistin)	1, 4
De Pascale 2014 ^[26]	SC-RC 2009.6.1–2012.5.31 Italy	100 VAP-sub: 63	Severe infections (VAP, IAI, BSI and cSSTI); CR-GN (mainly AB, KP)	HD: 46 pts, VAP-sub 33 pts: 200 mg × 1+ 100 mg q12h LD: 54 pts, VAP-sub 30 pts: 100 mg × 1+ 50 mg q12h	Yes, NS	Total:4 VAP-sub:1, 2, 3,
Balandin Moreno 2014 ^[27]	SC-RC 2009.9–2011.9 Spain	15	Serious infections (Pneumonia, UTI, peri- tonitis, CRB, meningi- tis); CPKP	HD: 9 pts, 100 mg q12 h LD: 6 pts, 50 mg q12 h	Yes (Colistin; Carbapenems, Ciprofloxacin, Piperacillin-tazo- bactam, amikacin)	1, 3, 4
De Maio Carrilho 2016 ^[28]	SC-PC 2011.3–2012.12 Brazil	115	CRE infections, eg. Pneumonia, UTI, etc.	HD: 46 pts, 100 mg q12h LD: 69 pts, 50 mg q12h	Yes, NS	1
Lv 2016 ^[29]	SC-RC 2011.6–2014.3 China	79	VAP, mainly AB, PA and KP	HD: 28 pts, 100 mg q12h LD: 51 pts, 50 mg q12h	Yes, NS	2
Fei 2016 ^[30]	2012.2–2015.12 China	71	VAP; AB, KP, Serratia marcescens, E.coli, S. aureus	HD: 40 pts, 200 mg × 1+ 100 mg q12h LD: 31 pts, 100mg × 1+ 50 mg q12h	Yes (Penicillins, third generation cephalosporin, carbapenems, aminoglycosides, fluoroquino- lones, phosphonomycin)	2, 3
Wu 2016 ^[31]	SC-RC 2013.1.1–2015.12.31 China	31	nosocomial pneumonia; CR-GNB (AB, KP, <i>E.</i> <i>coli</i> , SM, <i>etc.</i>)	HD: 20 pts, 200 mg × 1+ 100 mg q12h LD: 11 pts, 100 mg × 1+ 50	Yes (cefoperazone-sulbactam, piperacillin-tazobactam, carba- penem)	1, 2, 3
Zhao 2016 ^[32]	SC-PC 2014.2–2016.5 China	63	VAP	mg q12h HD: 36 pts, 200 mg × 1+100 mg q12h LD: 27 pts, 100 mg × 1+ 50	None	1, 2, 4
Zhao 2017 ^[33]	SC-RC 2015.4–2016.4 China	57	pneumonia; MDR-AB	mg q12h HD: 29 pts, 100 mg × 1+ 75 mg q12h LD: 28 pts,100 mg × 1+ 50	Yes (cefoperazone-sulbactam)	1, 2, 3, 4
Wu 2017 ^[34]	SC-RCT 2015.8–2017.7 China	52	Pneumonia; XDR-AB	mg q12h HD: 26 pts, 100 mg q12h LD: 26 pts, 100 mg × 1+ 50 mg q12h	Yes (cefoperazone-sulbactam)	2, 3, 4
Chen 2018 ^[35]	SC-RC 2013.1–2015.12 China	123	VAP; MDR pathogens (mainly AB, KP)	HD: 69 pts, 100 mg q12h LD: 54 pts, 100 mg × 1+ 50 mg q12h	Yes (cefoperazone-sulbactam, piperacillin-tazobactam, carba- penem)	1, 2, 3, 4
Cui 2018 ^[36]	SC-RCT 2013.5–2016.5 China	100	HAP	HD: 50 pts, 200 mg × 1+100 mg q12h LD: 50 pts, 100 mg × 1+ 50 mg q12h	None	2, 3, 4
Geng 2018 ^[14]	SC-RC 2014.1–2016.12 China	40	Nosocomial BSI; CRKP	HD: 23 pts, 200 mg × 1+ 100 mg q12h LD: 17 pts, 100 mg × 1+ 50	Yes (Carbapenems, beta-lacta- mase inhibitors, aminoglyco- sides)	1, 3
Xia 2018 ^[37]	SC-RC 2015.8–2018.1 China	27	Carbapenems failure blood diseases coinfec- tion; KP, <i>Enterobacter</i> <i>cloacae</i> , AB, PA)	mg q12h HD: 11 pts, 100mg q12h LD: 16 pts, 100 mg × 1+ 50 mg q12h	Yes (imipenem-cilastin, mero- penem, cefoperazone sodium/ sulbactam sodium, piperacillin sodium/tazobactam sodium, amikacin, linezolid)	2, 4
Li 2018 ^[38]	SC-RC 2016.2–2017.8 China	46	pneumonia; CR-AB	HD: 22 pts, 100 mg q12h LD: 24 pts, 100 mg × 1+ 50 mg q12h	Yes (cefoperazone-sulbactam)	2, 3, 4
Caballero Requejo 2018 ^[39]	SC-RC 2017.1–2017.3 Spain	21	Infections due to MDR- AB	HD: 9 pts, 200 mg × 1+ 100 mg q12h LD: 12 pts, 100 mg × 1+ 50 mg q12h	NR	1

1 = mortality, 2 = Clinical response rate, 3 = microbiological eradication rate, 4 = AEs, AB = *Acinetobacter baumannii*, AC = *Acinetobacter calcoaceticus*, BSI = bloodstream infection, CAP = community-acquired pneumonia, CPKP = carbapenemase producing *Klebsiella pneumoniae*, CR = carbapenem resistant, CRB = catheter-related bacteraemia, CRE = carbapenem-resistant enterobacteriaceae, cSSSI = complicated skin and skin-structure infection, DB = double-blind, *E.coli* = *Escherichia coli*, GNB = Gram-negative bacteria, HAP = hospital-acquired pneumonia, HD = high-dose regimen, IAI = intra-abdominal infection, KP = *Klebsiella pneumoniae*, LD = low-dose regimen, MC = multi-center, MDR = Multidrug-resistant, MRSA = methicillin-resistant *staphylococcus aureus*, MSSA = methicillin-sensitive *staphylococcus aureus*, NR = not reported, NS = not specified, PA = *Pseudomonas aeruginosa*, PC = prospective cohort study, pts = number of patients, RC = retrospective cohort study, RCT = random controlled trial, SC = single-center, SM = *stenotrophomonas maltophilia*, sub = subgroup, UTI = urinary tract infection, VAP = ventilator-associated pneumonia, XDR = extensively drug-resistant.



B Test for subaroup differences: Chi² = 3.71. df = 3 (P = 0.29). l² = 19.1%

Figure 2. A. All-cause mortality. The analysis is subcategorized by country. RR < 1.0 suggests decreased mortality with HD tigecycline treatment. B. All-cause mortality. The analysis is subcategorized by infection type. RR < 1.0 suggests decreased mortality with HD tigecycline treatment. BSI=bloodstream infection, HD=high-dose, IAI=intra-abdominal infection, LD=low-dose, RR=risk ratio, VAP=ventilator-associated pneumonia.

had a higher microbiological eradication efficiency in subgroup of VAP (RR 1.68, 95% CI 1.28–2.21) and nosocomial pneumonia (*RR* 1.62, 95% CI 1.25–2.09), but bloodstream infection subgroup showed no statistical significance (*RR* 1.60, 95% CI 0.77–3.35) (Fig. 4B). Sensitivity analysis excluding one different dose regimen study^[33] was consistent (*RR* 1.63% 95%*CI* 1.35–1.99). There existed a high heterogeneity in non-Chinese subgroup analysis (P=.06, I^2 =71%), which might be induced by the opposite clinical result of the 2 included studies.^[26,27]

	HD		LD			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I	M-H, Random, 95% Cl	
1.2.1 Non-Chinese st	tudy								
De Pascale 2014	19	33	10	30	4.0%	1.73 [0.96, 3.10]			
Ramirez 2013	17	20	16	23	11.8%	1.22 [0.88, 1.69]			
Subtotal (95% CI)		53		53	15.8%	1.35 [0.96, 1.92]		•	
Total events	36		26			0.0175 A.C. 200 State			
Heterogeneity: Tau ² =		= 1.29		P = 0.2	6): I= 239	8			
Test for overall effect	100 Per 10 Per 1								
1.2.2 Chinese study									
Chen 2018	48	69	19	54	8.4%	1.98 [1.33, 2.93]			
Cui 2018	42	50	31	50		1.35 [1.06, 1.74]			
Fei 2016	24	40	10	31	4.2%	1.86 [1.05, 3.29]			
Li 2018	20	22	15	24	11.2%	1.45 [1.04, 2.04]			
Lu 2016	20	28	24	51	9.3%	1.52 [1.04, 2.21]			
Wu 2016	13	20	2	11	0.8%	3.58 [0.98, 13.04]			
wu 2017	20	26	12	26	6.2%	1.67 [1.05, 2.65]			
Xia 2018	7	11	11	16	4.4%	0.93 [0.53, 1.61]			
Zhao 2016	26	36	11	27	5.4%	1.77 [1.08, 2.92]			
Zhao 2017	26	29	19	28	15.2%	1.32 [1.00, 1.75]		-	
Subtotal (95% CI)		331		318	84.2%	1.49 [1.30, 1.70]		•	
Total events	246		154			The state of the state of the second		1.0	
Heterogeneity: Tau ² =		= 10.1	11. df = 9	(P = 0)	34); I ² = 11	1%			
Test for overall effect	and the second se		and the second second						
Total (95% CI)		384		371	100.0%	1.46 [1.30, 1.65]		•	
	202		180					00	
Total events	282								
Total events Heterogeneity: Tau ² =	282 = 0.00: Chi	² =11.9		1 (P = 1	0.37): I ² = 8	3%	t t		
Heterogeneity: Tau ² =	= 0.00; Chi		95, df = 1	1 (P = 1	0.37); l² = 8	3%	0.01 0.1	1 10	10
Heterogeneity: Tau ² = Test for overall effect:	= 0.00; Chi Z = 6.24 (P < 0.0	95, df = 1 10001)					1 10 vours LD Favours HD	10
Heterogeneity: Tau ² =	= 0.00; Chi : Z = 6.24 (ferences: (P < 0.0	95, df = 1 10001) 0.25. df =			0%		vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subaroup dif	= 0.00; Chi : Z = 6.24 (ferences: (HD	P < 0.0 Chi² = (95, df = 1 10001) 0.25. df = LD	1 (P =	0.62), I² =	0% Risk Ratio	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif Study or Subgroup	= 0.00; Chi : Z = 6.24 (ferences: (HD	P < 0.0 Chi² = (95, df = 1 10001) 0.25. df = LD	1 (P =	0.62), I² =	0%	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif <u>Study or Subgroup</u> 2.2.1 VAP	= 0.00; Chi : Z = 6.24 (ferences: (HD Events	P < 0.0 Chi ² = (Total	95, df = 1 10001) 0.25. df = LD Events	1 (P =	0.62), I ^z = Weight	0% Risk Ratio M-H. Random, 95% CI	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif Study or Subgroup 2.2.1 VAP Chen 2018	= 0.00; Chi : Z = 6.24 (ferences: (HD Events 48	P < 0.0 Chi ^z = (<u>Total</u> 69	95, df = 1 10001) 0.25. df = LD Events 19	1 (P = <u>Total</u> 54	0.62), I ^z = <u>Weight</u> 16.4%	0% Risk Ratio <u>M-H. Random, 95% CI</u> 1.98 (1.33, 2.93)	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif Study or Subgroup 2.2.1 VAP Chen 2018 De Pascale 2014	= 0.00; Chi : Z = 6.24 (ferences: (HD <u>Events</u> 48 19	P < 0.0 Chi ^z = (<u>Total</u> 69 33	95, df = 1 10001) 0.25. df = LD Events 19 10	1 (P = <u>Total</u> 54 30	0.62). ² = <u>Weight</u> 16.4% 7.4%	0% Risk Ratio <u>M-H. Random, 95% Cl</u> 1.98 (1.33, 2.93) 1.73 (0.96, 3.10)	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif Study or Subgroup 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016	= 0.00; Chi : Z = 6.24 (ferences: (HD Events 48 19 24	P < 0.0 Chi ² = (<u>Total</u> 69 33 40	95, df = 1 10001) 0.25. df = LD Events 19 10 10	1 (P = <u>Total</u> 54 30 31	0.62). ² = <u>Weight</u> 16.4% 7.4% 7.8%	0% Risk Ratio <u>M-H. Random, 95% Cl</u> 1.98 (1.33, 2.93) 1.73 (0.96, 3.10) 1.86 (1.05, 3.29)	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif Study or Subgroup 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016	= 0.00; Chi : Z = 6.24 (ferences: (<u>HD</u> <u>Events</u> 48 19 24 20	P < 0.0 Chi ² = (<u>Total</u> 69 33 40 28	95, df = 1 10001) 0.25. df = LD Events 19 10 10 24	1 (P = <u>Total</u> 54 30 31 51	0.62). ² = <u>Weight</u> 16.4% 7.4% 7.8% 18.2%	0% Risk Ratio <u>M-H. Random, 95% Cl</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21]	Fa	vours LD Favours HD	10
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Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016 Ramirez 2013 Zhao 2016 Zhao 2017 Subtotal (95% CI) Total events	= 0.00; Chi : Z = 6.24 (ferences: (HD Events 48 19 24 20 6 26 26 26 169	P < 0.0 Chi ² = (69 33 40 28 7 36 29 242	95, df = 1 10001) 0.25, df = LD Events 19 10 10 24 5 11 19 98	1 (P = <u>Total</u> 54 30 31 51 7 27 28 228	0.62). I ² = <u>Weight</u> 16.4% 7.4% 7.8% 18.2% 8.2% 0.3% 31.7% 100.0%	0% Risk Ratio <u>M-H. Random. 95% CI</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21] 1.20 [0.69, 2.10] 1.77 [1.08, 2.92] 1.32 [1.00, 1.75] 1.55 [1.32, 1.82]	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016 Ramirez 2013 Zhao 2016 Zhao 2017 Subtotal (95% CI)	= 0.00; Chi : Z = 6.24 (ferences: (HD Events 48 19 24 20 6 26 26 26 169 = 0.00; Chi	P < 0.0 Chi ² = (7 36 29 242 2 = 4.9	95, df = 1 10001) 0.25. df = LD Events 19 10 10 24 5 11 19 98 98, df = 6 (0	1 (P = <u>Total</u> 54 30 31 51 7 27 28 228	0.62). I ² = <u>Weight</u> 16.4% 7.4% 7.8% 18.2% 8.2% 0.3% 31.7% 100.0%	0% Risk Ratio <u>M-H. Random. 95% CI</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21] 1.20 [0.69, 2.10] 1.77 [1.08, 2.92] 1.32 [1.00, 1.75] 1.55 [1.32, 1.82]	Fa	vours LD Favours HD	10
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Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016 Ramirez 2013 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2.2.2 nosocomial pm Cui 2018 Li 2018 Ramirez 2013 Wu 2016	= 0.00; Chi : Z = 6.24 (Terences: (HD Events 48 19 24 20 6 26 26 169 = 0.00; Chi : Z = 5.39 (eumoniae 42 20 17 13	P < 0.0 Chi ² = (Total 69 33 40 28 7 36 29 242 242 242 242 242 242 50 222 20 20	95, df = 1 10001) 0.25, df = LD Events 19 10 10 24 5 11 19 98 9, df = 6 (1 10001) 31 15 16 2	1 (P = <u>Total</u> 54 30 31 51 7 27 28 228 228 P = 0.5 50 24 23 11	0.62). I ² = <u>Weight</u> 16.4% 7.4% 7.8% 18.2% 8.2% 10.3% 100.0% 4); I ² = 0% 40.9% 22.3% 23.6% 1.5%	0% Risk Ratio <u>M-H, Random, 95% CI</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21] 1.20 [0.69, 2.10] 1.77 [1.08, 2.92] 1.32 [1.00, 1.75] 1.55 [1.32, 1.82] 1.35 [1.06, 1.74] 1.45 [1.04, 2.04] 1.22 [0.88, 1.69] 3.58 [0.98, 13.04]	Fa	vours LD Favours HD	10
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Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016 Ramirez 2013 Zhao 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 2.2.2 nosocomial pn Cui 2018 Li 2018 Ramirez 2013 Wu 2016 Wu 2017 Subtotal (95% Cl) Total events	= 0.00; Chi : Z = 6.24 (ferences: (Events 48 19 24 20 6 26 26 26 26 26 26 26 26 26 26 26 26 2	P < 0.0 Chi ² = (Total 69 33 40 28 7 36 29 242 29 242 29 242 20 20 20 20 20 20 20 20 20 21 8 = 1.38	95, df = 1 10001) 0.25, df = LD Events 19 10 10 24 5 11 19 98 9, df = 6 (10001) 31 15 16 2 12 76 8, df = 4 (0)	1 (P = <u>Total</u> 54 30 31 51 7 28 228 P = 0.5 50 24 23 11 11 26 134	0.62). P= Weight 16.4% 7.4% 7.8% 18.2% 8.2% 10.3% 31.7% 100.0% 4); P= 0% 40.9% 22.3% 1.5% 1.5% 1.7% 100.0%	0% Risk Ratio <u>M-H, Random, 95% CI</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21] 1.20 [0.69, 2.10] 1.77 [1.08, 2.92] 1.32 [1.00, 1.75] 1.55 [1.32, 1.82] 1.35 [1.06, 1.74] 1.45 [1.04, 2.04] 1.22 [0.88, 1.69] 3.58 [0.98, 1.304] 1.67 [1.05, 2.65] 1.40 [1.19, 1.64]	Fa	vours LD Favours HD	10
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup dif 2.2.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Lu 2016 Ramirez 2013 Zhao 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2.2.2 nosocomial pn Cui 2018 Li 2018 Ramirez 2013 Wu 2016 Wu 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	= 0.00; Chi : Z = 6.24 (ferences: (Events 48 19 24 20 6 26 26 26 26 26 26 26 26 26 26 26 26 2	P < 0.0 Chi ² = (Total 69 33 40 28 7 36 29 242 29 242 29 242 20 20 20 20 20 20 20 20 20 21 8 = 1.38	95, df = 1 10001) 0.25, df = LD Events 19 10 10 24 5 11 19 98 9, df = 6 (10001) 31 15 16 2 12 76 8, df = 4 (0)	1 (P = <u>Total</u> 54 30 31 51 7 28 228 P = 0.5 50 24 23 11 11 26 134	0.62). P= Weight 16.4% 7.4% 7.8% 18.2% 8.2% 10.3% 31.7% 100.0% 4); P= 0% 40.9% 22.3% 1.5% 1.5% 1.7% 100.0%	0% Risk Ratio <u>M-H, Random, 95% CI</u> 1.98 [1.33, 2.93] 1.73 [0.96, 3.10] 1.86 [1.05, 3.29] 1.52 [1.04, 2.21] 1.20 [0.69, 2.10] 1.77 [1.08, 2.92] 1.32 [1.00, 1.75] 1.55 [1.32, 1.82] 1.35 [1.06, 1.74] 1.45 [1.04, 2.04] 1.22 [0.88, 1.69] 3.58 [0.98, 1.304] 1.67 [1.05, 2.65] 1.40 [1.19, 1.64]	Fa	vours LD Favours HD	10

B Test for subaroup differences: Chi² = 0.83. df = 1 (P = 0.36). I² = 0%

Figure 3. A. Clinical response. The analysis is subcategorized by country. RR > 1.0 suggests increased clinical response with HD tigecycline treatment. B. Clinical response. The analysis is subcategorized by infection type. RR > 1.0 suggests increased clinical response with HD tigecycline treatment. HD = high-dose, LD = lowdose, RR=risk ratio, VAP=ventilator-associated pneumonia.

3.5. AEs

Twelve studies^[12,25-27,30,32-38] reported AEs were included for analysis. Averse events between HD and LD regimen was similar (RR 1.00, 95% CI 0.80-1.26, 12 studies, 710 patients) without significant heterogeneity (P = .86, $I^2 = 0\%$). Subgroup analyses by country showed similar result in both Chinese study (RR 1.00, 95% CI 0.70-1.44) and non-Chinese study (RR 1.01, 95% CI 0.75–1.35) (Fig. 5A). Sensitivity analysis excluding 2 different dose regimen studies^[12,33] was consistent (*RR* 1.03, 95% *CI* 0.80–1.32). Further analysis showed that there was no difference between HD and LD in allergy, diarrhea, nausea/vomiting, hepatopancreatic, and hematological toxicity (Fig. 5B).

	HD		LD			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total \	Neight M-	H, Random, 95% CI Y	ear	M-H, Random, 95% Cl	
1.3.1 Non-Chinese study									
De Pascale 2014	12	21	7	23	6.2%	1.88 [0.91, 3.86] 20			
Balandin Moreno 2014	2	10	3	6	1.5%	0.40 [0.09, 1.75] 20	014		
Subtotal (95% CI)		31		29	7.7%	1.00 [0.22, 4.43]			
Fotal events	14		10						
Heterogeneity: Tau ² = 0.85	5; Chi² = 3	3.42, df=	= 1 (P = 0	.06); 🖻	= 71%				
Fest for overall effect: Z =	0.01 (P=	1.00)							
1.3.2 Chinese study								100000	
ei 2016	20	40	8	31	7.1%	1.94 [0.99, 3.80] 20	016		
Vu 2016	9	20	3	11	2.8%	1.65 [0.56, 4.86] 20	016		
Zhao 2017	20	29	13	28	14.8%	1.49 [0.93, 2.37] 20	017		
vu 2017	17	26	9	26	9.0%	1.89 [1.04, 3.43] 20	017		
Cui 2018	34	50	23	50	25.5%	1.48 [1.04, 2.11] 20	018		
i 2018	16	22	10	24	11.1%	1.75 [1.02, 2.99] 20	018		
Chen 2018	37	69	17	54	15.9%	1.70 [1.09, 2.67] 20			
Geng 2018	13	23	6	17	5.9%	1.60 [0.77, 3.35] 20	018		
Subtotal (95% CI)		279		241	92.3%	1.63 [1.35, 1.97]		•	
Fotal events	166		89						
Heterogeneity: Tau ² = 0.00	0; Chi ² = 1	.05, df=	= 7 (P = 0	.99); 12:	= 0%				
Fest for overall effect: Z =									
Total (95% CI)		310		270 1	100.0%	1.61 [1.35, 1.93]		•	
Fotal events	180		99						
Heterogeneity: Tau ² = 0.00	at the State	1.65, df=	And the second	.86); 12:	= 0%				
Test for overall effect: Z = 1							0.01	0.1 1 10	10
Test for subaroup differen	and the second second			= 0.52)	$I^{2} = 0.96$			Favours LD Favours HD	
	ieee. em	- 0.41.	ui - i u	- 0.027					
	HD		LD			Risk Ratio		Risk Ratio	
Study or Subgroup					Weight	M-H, Random, 95% (M-H, Random, 95% CI	
		10101	LIGHTO	10101	TTO IGHT	in the real of the objection		in the number of the	
2.3.1 VAP	27	60	17	54	26.10	1 70 11 00 0.6	71	_	
2.3.1 VAP Chen 2018	37	69	17	54		1.70 [1.09, 2.6]			
2.3.1 VAP Chen 2018 De Pascale 2014	12	21	7	23	14.1%	1.88 [0.91, 3.86	6]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016	12 20	21 40	7	23 31	14.1% 16.2%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8)	6] D]	-	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017	12	21 40 29	7	23 31 28	14.1% 16.2% 33.6%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8) 1.49 (0.93, 2.3)	6] D] 7]	*	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016	12 20 20	21 40	7 8 13	23 31 28	14.1% 16.2%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8)	6] D] 7]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017	12 20	21 40 29	7	23 31 28	14.1% 16.2% 33.6%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8) 1.49 (0.93, 2.3)	6] D] 7]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	12 20 20 89 0.00; Ch	21 40 29 159	7 8 13 45 5, df = 3	23 31 28 136	14.1% 16.2% 33.6% 100.0%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8) 1.49 (0.93, 2.3) 1.68 (1.28, 2.2)	6] D] 7]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events	12 20 20 89 0.00; Ch	21 40 29 159	7 8 13 45 5, df = 3	23 31 28 136	14.1% 16.2% 33.6% 100.0%	1.88 (0.91, 3.8) 1.94 (0.99, 3.8) 1.49 (0.93, 2.3) 1.68 (1.28, 2.2)	6] D] 7]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne	12 20 20 0.00; Ch Z = 3.77	21 40 29 159 1 ² = 0.5 (P = 0.0	7 8 13 45 5, df = 3 002)	23 31 28 1 36 (P = 0.9	14.1% 16.2% 33.6% 100.0%	1.88 (0.91, 3.80 1.94 (0.99, 3.80 1.49 (0.93, 2.3 1.68 (1.28, 2.21	6] D] 7] 1]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne Cui 2018	12 20 20 0.00; Ch Z = 3.77 sumoniae 34	21 40 29 159 P = 0.55 (P = 0.0	7 8 13 45 5, df = 3 002) 23	23 31 28 136 (P = 0.9	14.1% 16.2% 33.6% 100.0% 31); I ² = 0% 52.7%	1.88 (0.91, 3.80 1.94 (0.99, 3.80 1.49 (0.93, 2.3 1.68 (1.28, 2.21	6] D] 7] 1]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne	12 20 20 0.00; Ch Z = 3.77 sumoniae 34 16	21 40 29 159 (P = 0.55 (P = 0.0 50 22	7 8 13 45 5, df = 3 002)	23 31 28 136 (P = 0.9	14.1% 16.2% 33.6% 100.0% 31); I ² = 0% 52.7%	1.88 (0.91, 3.80 1.94 (0.99, 3.80 1.49 (0.93, 2.3 1.68 (1.28, 2.21	6] D] 7] 1]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne Cui 2018	12 20 20 0.00; Ch Z = 3.77 sumoniae 34	21 40 29 159 P = 0.55 (P = 0.0	7 8 13 45 5, df = 3 002) 23	23 31 28 136 (P = 0.9	14.1% 16.2% 33.6% 100.0% 31); I ² = 0% 52.7%	1.88 (0.91, 3.80 1.94 (0.99, 3.80 1.49 (0.93, 2.3 1.68 (1.28, 2.21	6] 0] 7] 1] 1]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.3.2 nosocomial pne Cui 2018 Li 2018	12 20 20 0.00; Ch Z = 3.77 sumoniae 34 16	21 40 29 159 (P = 0.55 (P = 0.0 50 22	7 8 13 45 5, df = 3 002) 23 10	23 31 28 136 (P = 0.9 50 24	14.1% 16.2% 33.6% 100.0% 31); I ² = 0% 52.7% 23.0% 5.7%	1.88 (0.91, 3.80 1.94 (0.99, 3.80 1.49 (0.93, 2.3 1.68 (1.28, 2.21 1.48 (1.04, 2.1 1.75 (1.02, 2.9)	6] 7] 1] 1] 9] 6]	*	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect : 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016	12 20 20 0.00; Ch Z = 3.77 eumoniae 34 16 9	21 40 29 159 i ² = 0.5% (P = 0.0 50 22 20	7 8 13 45 5, df = 3 002) 23 10 3	23 31 28 136 (P = 0.9 50 24 11 26	14.1% 16.2% 33.6% 100.0% 31); I ² = 0% 52.7% 23.0% 5.7%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.33 1.68 [1.28, 2.24 1.68 [1.04, 2.14 1.75 [1.02, 2.99 1.65 [0.56, 4.80	6] 0] 7] 1] 9] 6] 3]	•	
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 wu 2017	12 20 20 0.00; Ch Z = 3.77 eumoniae 34 16 9 17	21 40 29 159 i ² = 0.55 (P = 0.0 50 22 20 26	7 8 13 45 5, df = 3 002) 23 10 3 9	23 31 28 136 (P = 0.9 50 24 11 26	14.1% 16.2% 33.6% 100.0% 91); I² = 0% 52.7% 23.0% 5.7% 18.6%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.33 1.68 [1.28, 2.21 4.68 [1.04, 2.11 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.43	6] 0] 7] 1] 9] 6] 3]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2017 Subtotal (95% CI) Total events	12 20 20 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76	21 40 29 159 (P = 0.0 (P = 0.0 20 26 118	7 8 13 45 5, df = 3 002) 23 10 3 9 45	23 31 28 136 (P = 0.9 50 24 11 26 111	14.1% 16.2% 33.6% 100.0% 31); I* = 0% 52.7% 23.0% 5.7% 18.6% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.33 1.68 [1.28, 2.21 6 1.48 [1.04, 2.11 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.43 1.62 [1.25, 2.09	6] 0] 7] 1] 9] 6] 3]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 wu 2017 Subtotal (95% Cl)	12 20 20 89 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch	21 40 29 159 (P = 0.0 (P = 0.0 20 26 118 i ² = 0.55	7 8 13 45 5, df = 3 002) 23 10 3 9 9 45 3, df = 3	23 31 28 136 (P = 0.9 50 24 11 26 111	14.1% 16.2% 33.6% 100.0% 31); I* = 0% 52.7% 23.0% 5.7% 18.6% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.33 1.68 [1.28, 2.21 6 1.48 [1.04, 2.11 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.43 1.62 [1.25, 2.09	6] 0] 7] 1] 9] 6] 3]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect : 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² =	12 20 20 89 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch	21 40 29 159 (P = 0.0 (P = 0.0 20 26 118 i ² = 0.55	7 8 13 45 5, df = 3 002) 23 10 3 9 9 45 3, df = 3	23 31 28 136 (P = 0.9 50 24 11 26 111	14.1% 16.2% 33.6% 100.0% 31); I* = 0% 52.7% 23.0% 5.7% 18.6% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.33 1.68 [1.28, 2.21 6 1.48 [1.04, 2.11 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.43 1.62 [1.25, 2.09	6] 0] 7] 1] 9] 6] 3]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2016 Wu 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.3.3 BSI	12 20 20 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch Z = 3.65	21 40 29 159 1 ² = 0.55 (P = 0.0 50 22 20 26 118 1 ² = 0.55 (P = 0.0 (P = 0.0	7 8 13 45 5, df = 3 002) 23 10 3 9 45 3, df = 3 003)	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.3] 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.68 [1.04, 2.1] 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.4] 1.62 [1.25, 2.09	6] 0] 7] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 wu 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.3 BSI Geng 2018	12 20 20 89 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch	21 40 29 159 159 159 159 20 26 118 17 = 0.55 (P = 0.0 22 20 26 118 17 = 0.55 22 20 26 118	7 8 13 45 5, df = 3 002) 23 10 3 9 9 45 3, df = 3	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0% 30); * = 0% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.37 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.65 [0.56, 4.80 1.89 [1.04, 3.47 1.62 [1.25, 2.09 1.60 [0.77, 3.37	6] 0] 7] 1] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 wu 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.3.3 BSI Geng 2018 Subtotal (95% Cl)	12 20 20 89 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch Z = 3.65	21 40 29 159 1 ² = 0.55 (P = 0.0 50 22 20 26 118 1 ² = 0.55 (P = 0.0 (P = 0.0	7 8 13 45 5, df = 3 002) 23 10 3 9 45 3, df = 3 003) 6	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.3] 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.68 [1.04, 2.1] 1.75 [1.02, 2.99 1.65 [0.56, 4.80 1.89 [1.04, 3.4] 1.62 [1.25, 2.09	6] 0] 7] 1] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 wu 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: . 2.3.3 BSI Geng 2018 Subtotal (95% Cl) Total events	12 20 20 89 0.00; Ch Z = 3.77 eumoniae 34 16 9 17 76 0.00; Ch Z = 3.65 13 13	21 40 29 159 159 159 159 20 26 118 17 = 0.55 (P = 0.0 22 20 26 118 17 = 0.55 22 20 26 118	7 8 13 45 5, df = 3 002) 23 10 3 9 45 3, df = 3 003)	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0% 30); * = 0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.37 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.65 [0.56, 4.80 1.89 [1.04, 3.47 1.62 [1.25, 2.09 1.60 [0.77, 3.37	6] 0] 7] 1] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.3 BSI Geng 2018 Subtotal (95% CI) Total events Heterogeneity: Not ap	12 20 20 89 0.00; Ch Z = 3.77 sumoniae 34 16 9 17 76 0.00; Ch Z = 3.65 13 13 plicable	21 40 29 159 (P = 0.05) (P = 0.0 20 26 118 (P = 0.0 (P = 0.0 23 23	7 8 13 45 5, df = 3 002) 23 10 3 9 45 9, df = 3 003) 6 6	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0% 30); * = 0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.37 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.65 [0.56, 4.80 1.89 [1.04, 3.47 1.62 [1.25, 2.09 1.60 [0.77, 3.37	6] 0] 7] 1] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2016 Wu 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.3.3 BSI Geng 2018 Subtotal (95% Cl) Total events	12 20 20 89 0.00; Ch Z = 3.77 sumoniae 34 16 9 17 76 0.00; Ch Z = 3.65 13 13 plicable	21 40 29 159 (P = 0.05) (P = 0.0 20 26 118 (P = 0.0 (P = 0.0 23 23	7 8 13 45 5, df = 3 002) 23 10 3 9 45 9, df = 3 003) 6 6	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0% 30); * = 0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.37 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.65 [0.56, 4.80 1.89 [1.04, 3.47 1.62 [1.25, 2.09 1.60 [0.77, 3.37	6] 0] 7] 1] 1] 9] 6] 3] 9]		
2.3.1 VAP Chen 2018 De Pascale 2014 Fei 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.2 nosocomial pne Cui 2018 Li 2018 Wu 2016 Wu 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect . 2.3.3 BSI Geng 2018 Subtotal (95% CI) Total events Heterogeneity: Not ap	12 20 20 89 0.00; Ch Z = 3.77 sumoniae 34 16 9 17 76 0.00; Ch Z = 3.65 13 13 plicable	21 40 29 159 (P = 0.05) (P = 0.0 20 26 118 (P = 0.0 (P = 0.0 23 23	7 8 13 45 5, df = 3 002) 23 10 3 9 45 9, df = 3 003) 6 6	23 31 28 136 (P = 0.9 50 24 11 26 111 (P = 0.9 17	14.1% 16.2% 33.6% 100.0% 31); * = 0% 52.7% 23.0% 5.7% 18.6% 100.0% 30); * = 0%	1.88 [0.91, 3.80 1.94 [0.99, 3.80 1.49 [0.93, 2.37 1.68 [1.28, 2.21 1.68 [1.28, 2.21 1.65 [0.56, 4.80 1.89 [1.04, 3.47 1.62 [1.25, 2.09 1.60 [0.77, 3.37	6] 0] 7] 1] 1] 9] 6] 3] 9]		1

B Test for subaroup differences: Chi² = 0.05. df = 2 (P = 0.98). l² = 0%

Figure 4. A. Microbiological eradication. The analysis is subcategorized by country. RR > 1.0 suggests increased microbiological eradication with HD tigecycline treatment. B. Microbiological eradication. The analysis is subcategorized by infection type. RR > 1.0 suggests increased microbiological eradication with HD tigecycline treatment. BSI=bloodstream infection, HD=high-dose, LD=low-dose, RR=risk ratio, VAP=ventilator-associated pneumonia.

4. Discussion

Recently, the increasing risk of MDR/XDR organisms propelled the use of tigecycline either in approved indications or off-label uses and high-dose regimen was resorted to be an approach for serious infections. We conducted a meta-analysis of all available studies comparing high and low dose tigecycline regimen. The pre-defined primary outcome was all-cause mortality. We found a statistically significant decrease in all-cause mortality with HD tigecycline. The RR for mortality was 0.67, denoting a 33% decrease in mortality, the 95% *CI* ranging between a 16% and 47% increase, different infection type presented no discrepancy.

Study or Subgroup	H Events		L Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H. Random, 95% CI
1.4.1 Non-chinese stu							
Balandin Moreno 2014		3	9 () (6	Not estimable	1
De Pascale 2014	21	3 4	6 3	5	49.8%	1.06 [0.77, 1.47]	
Di Carlo 2013		3 1	2 1	0 1	3	Not estimable	
Ramirez 2013		3					
Subtotal (95% CI)		8		9			•
Total events	3	7	4				
Heterogeneity: Tau ² = 0					F= 0%		
Test for overall effect Z							
and the state of the							
1.4.2 Chinese study							
Chen 2018	11	6 6	9 1	3 5	16.2%	0.70 [0.39, 1.23]	
Cui 2018							
Fei 2016		4		3		Not estimable	
LI 2018				4 2			
wu 2017				2			
Xia 2018		3 1		3 1			
Zhao 2016		3 3		2			
Zhao 2017		3 2					
Subtotal (95% CI)		28		25	5 40.2%	1.00 [0.70, 1.44]	T
Total events	41		4		G		
Heterogeneity: Tau ² = (= 0.75)	; l ² = 0%		
Test for overall effect Z	= 0.01 (P	= 0.99)				
Total (95% CI)		36			5 100.0%	1.00 [0.80, 1.26]	•
Total events	85		81				
Heterogeneity: Tau ² = 0				= 0.86)	; l ² = 0%		0.01 0.1 1 10 100
Test for overall effect: Z							Favours HD Favours LD
Test for subaroup diffe	rences: Cl	hi² = 0.1	00. df = 1	(P = 0.	99). F= 0	%	arvere the Payous LU
	HD		LD			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
2.5.1 Diarrhoea	a service stress						
Chen 2018	5	69	6	54	35.5%	0.65 [0.21, 2.02]	
Cui 2018	2	50	1	50	8.1%	2.00 [0.19, 21.36]	
Li 2018	2	22	2	24	13.0%	1.09 [0.17, 7.10]	
Ramirez 2013	5	35	1	36	10.4%	5.14 [0.63, 41.83]	
wu 2017	2	26	2	26	12.8%		
Xia 2018		11	1	16	4.7%	1.00 [0.15, 6.57]	
	0					0.47 [0.02, 10.63]	
Zhao 2017	3	29	2	28	15.5%	1.45 [0.26, 8.02]	
Subtotal (95% CI)		242		234	100.0%	1.11 [0.57, 2.19]	
Total events	19		15				
Heterogeneity: Tau ² =	0.00; Chi ²	= 3.58	, df = 6 (F	= 0.7	3); 2 = 0%	6	
Test for overall effect 1							
			12				
2.5.2 Nausea & Vomit	ing						
Cui 2018	3	50	2	50	17.6%	1.50 [0.26, 8.60]	
Li 2018	1	22	2	24	9.9%	0.55 [0.05, 5.60]	
Ramirez 2013	5	35	2	36	21.7%		
						2.57 [0.53, 12.39]	
wu 2017	2	26	2	26	15.1%	1.00 [0.15, 6.57]	
Xia 2018	1	11	1	16	7.6%	1.45 [0.10, 20.87]	
Zhao 2016	2	36	1	27	9.7%	1.50 [0.14, 15.70]	
Zhao 2017	2	29	3	28	18.3%	0.64 [0.12, 3.57]	
Subtotal (95% CI)		209		207	100.0%	1.23 [0.59, 2.55]	-
Total events	16		13				
Heterogeneity: Tau ² = Test for overall effect: 3				P = 0.9	2); l ² = 0%		
2.5.3 Impaired hepato	pancreat	ic fund	ction				2.85
Chen 2018	9	69	9	54	38.7%	0.78 [0.33, 1.84]	
Cui 2018	2	50	1	50	5.0%	2.00 [0.19, 21.36]	
De Pascale 2014	9	46	9	54	40.3%	1.17 [0.51, 2.71]	
wu 2017	2	26	2	26	7.9%	1.00 [0.15, 6.57]	
Xia 2018	0	11	1	16	2.9%	0.47 [0.02, 10.63]	
	2	29	1	28	5.1%	1.93 [0.19, 20.12]	
		231	1		5.1%	1.02 [0.60, 1.73]	•
Zhao 2017	2			220	100.0%	1.02 [0.00, 1.13]	
Zhao 2017 Subtotal (95% CI)		231					
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	24 0.00; Chi ^a	= 1.31		e = 0.9	3); I² = 0%		
Zhao 2017 Subtotal (95% CI) Total events	24 0.00; Chi ^a	= 1.31	, df = 5 (F	^o = 0.9	3); I² = 0%		
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect :	24 0.00; Chi ^a Z = 0.06 (F	= 1.31 P = 0.9	, df = 5 (f 5)	^o = 0.9	3); I² = 0%	0	
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	24 0.00; Chi ^a Z = 0.06 (F	= 1.31 = 0.9	, df = 5 (f 5)	^o = 0.9			
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect :	24 0.00; Chi ^a Z = 0.06 (F	= 1.31 P = 0.9	, df = 5 (f 5)	54	36.5%	0.52 (0.09, 3.01)	-
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.5 Impaired hemat	24 0.00; Chi ^a Z = 0.06 (F ological fi	= 1.31 = 0.9	, df = 5 (f 5) n	54			-
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.5 Impaired hemat Chen 2018	24 0.00; Chi ^a Z = 0.06 (F ological fr 2	= 1.31 = 0.9 unction 69	, df = 5 (f 5) n 3	54 54	36.5%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22]	-
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.5 Impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI)	24 0.00; Chi ^a Z = 0.06 (F ological fr 2	= 1.31 = 0.9 unction 69 46	, df = 5 (f 5) n 3	54 54	36.5% 63.5%	0.52 (0.09, 3.01)	*
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Testfor overall effect : 2.5.5 impaired hemat Chen 2018 De Pascale 2014	24 0.00; Chi ^a z = 0.06 (F ological fi 2 3 5 0.00; Chi ^a	e = 1.31 e = 0.9 unction 69 46 115 e = 0.01	, df = 5 (f 5) n 3 6 9 1, df = 1 (f	54 54 108	36.5% 63.5% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62]	
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect : 2.5.5 impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau [®] =	24 0.00; Chi ^a z = 0.06 (F ological fi 2 3 5 0.00; Chi ^a	e = 1.31 e = 0.9 unction 69 46 115 e = 0.01	, df = 5 (f 5) n 3 6 9 1, df = 1 (f	54 54 108	36.5% 63.5% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62]	ŧ
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect : 2.5.5 impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau [®] =	24 0.00; Chi ^a z = 0.06 (F ological fi 2 3 5 0.00; Chi ^a	e = 1.31 e = 0.9 unction 69 46 115 e = 0.01	, df = 5 (f 5) n 3 6 9 1, df = 1 (f	54 54 108	36.5% 63.5% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62]	*
Zhao 2017 Subtotal (05% Cl) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.5 Impaired hemat Chen 2018 De Pascale 2014 Subtotal (05% Cl) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.7 Allergy	24 0.00; Chi ^a z = 0.06 (F ological fi 2 3 5 0.00; Chi ^a	e = 1.31 e = 0.9 unction 69 46 115 e = 0.01	, df = 5 (f 5) n 3 6 9 1, df = 1 (f 9)	54 54 108 P = 0.9	36.5% 63.5% 100.0% 2); I ² = 0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62]	ŧ
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect : 2.5.5 Impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect : 2.5.7 Allergy U 2018	24 0.00; Chi ^a Z = 0.06 (f ological fi 2 3 5 0.00; Chi ^a Z = 1.07 (f	2 = 1.31 P = 0.9 unction 69 46 115 P = 0.01 P = 0.2 22	, df = 5 (f 5) n 3 6 9 1, df = 1 (f	54 54 108 P = 0.9	36.5% 63.5% 100.0% 2); I ² = 0% 23.1%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10]	*
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity, Tau*= Test for overall effect: 2 2.5.5 impaired hemat Chen 2018 Subtotal (95% CI) Total events Heterogeneity, Tau*= Test for overall effect: 2 2.5.7 Allergy Li 2018 wu 2017	24 0.00; Chi ⁴ Z = 0.06 (f ological fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1	2 = 1.31 2 = 0.9 46 115 2 = 0.01 2 = 0.2 22 26	, df = 5 (f 5) n 3 6 9 1, df = 1 (f 9) 0 0	54 54 108 9 = 0.9 24 26	36.5% 63.5% 100.0% 2); I ² = 0% 23.1% 23.0%	0.52 (0.09, 3.01) 0.59 (0.16, 2.22) 0.56 (0.19, 1.62) 3.26 (0.14, 76.10) 3.00 (0.13, 70.42)	*
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ²² = Test for overall effect: 2 2.5.5 Impaired hermat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : 2.5.7 Altergy Li 2018 Wu 2017 Zhao 2016	24 0.00; Chi ² Z = 0.06 (f ological fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1	2 = 1.31 2 = 0.9 46 115 2 = 0.01 2 = 0.2 22 26 36	(, df = 5 (f 5)	54 54 108 2 = 0.9 24 26 27	36.5% 63.5% 100.0% 2); I ² = 0% 23.1% 23.0% 22.9%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66]	*
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect: 2 2.5.5 impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau [®] = Test for overall effect: 2 2.5.7 Allergy U 2018 wu 2017 Zhao 2016 Zhao 2017	24 0.00; Chi ⁴ Z = 0.06 (f ological fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1	2 = 1.31 2 = 0.9 46 115 2 = 0.01 2 = 0.2 22 26 36 29	, df = 5 (f 5) n 3 6 9 1, df = 1 (f 9) 0 0	54 54 108 2 = 0.9 24 26 27 28	36.5% 63.5% 100.0% 2); P = 0% 23.1% 23.0% 22.9% 30.9%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66] 0.97 [0.06, 14.70]	*
Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau [®] =: Test for overall effect 2.5.5 Impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau [®] =: Test for overall effect .: 2.5.7 Allergy Li 2018 wu 2017 Zhao 2016 Zhao 2017 Subtotal (95% CI)	24 0.00; Chi ² Z = 0.06 (f ological fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1	2 = 1.31 2 = 0.9 46 115 2 = 0.01 2 = 0.2 22 26 36	I, df = 5 (f 5) 1 3 6 9 1, df = 1 (f 9) 0 0 0 1	54 54 108 2 = 0.9 24 26 27 28	36.5% 63.5% 100.0% 2); I ² = 0% 23.1% 23.0% 22.9%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66]	*
Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau [*] = Test for overall effect: 2.5.5 Impaired hematil the Pascale 2014 De Pascale 2014 De Pascale 2014 Subtotal (95% Cl) Total events Heterogeneity: Tau [*] = Test for overall effect: 2.5.7 Allergy Li 2018 Wu 2017 Zhao 2016 Zhao 2016 Zhao 2016 Zhao 2017 Subtotal (95% Cl) Total events	24 0.00; Chi ^a Z = 0.06 (f ological fi 2 3 5 0.00; Chi ^a Z = 1.07 (f 1 1 1 1 1	2 = 1.31 2 = 0.9 46 115 2 = 0.01 2 = 0.2 22 26 36 29 113	, df = 5 (f 5) , df = 1 (f 9) 0 0 0 1 1	54 54 108 2 = 0.9 24 26 27 28 105	36.5% 63.5% 100.0% 2); F = 0% 23.1% 23.0% 22.9% 30.9% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66] 0.97 [0.06, 14.70] 2.02 [0.44, 9.19]	*
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Zhao 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau [*] = Test for overall effect: 2.5.5 Impaired hematil the Pascale 2014 De Pascale 2014 De Pascale 2014 Subtotal (95% Cl) Total events Heterogeneity: Tau [*] = Test for overall effect: 2.5.7 Allergy Li 2018 Wu 2017 Zhao 2016 Zhao 2016 Zhao 2016 Zhao 2017 Subtotal (95% Cl) Total events	24 0.00; Chi ² Z = 0.06 (f 0logical fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1 1 1 1 4 0.00; Chi ²	2 = 1.31 2 = 0.9 69 46 115 2 = 0.01 22 26 36 29 113 2 = 0.44	, df = 5 (f 5)	54 54 108 2 = 0.9 24 26 27 28 105	36.5% 63.5% 100.0% 2); F = 0% 23.1% 23.0% 22.9% 30.9% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66] 0.97 [0.06, 14.70] 2.02 [0.44, 9.19]	*
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Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau"= Test for overall effect: 2 2.5.5 impaired hemat Chen 2018 De Pascale 2014 Subtotal (95% CI) Total events Heterogeneity: Tau"= Test for overall effect: 2 2.5.7 Allergy U 2018 wu 2017 Zhao 2016 Zhao 2017 Subtotal (95% CI) Total events Heterogeneity: Tau"=	24 0.00; Chi ² Z = 0.06 (f 0logical fi 2 3 5 0.00; Chi ² Z = 1.07 (f 1 1 1 1 1 4 0.00; Chi ²	2 = 1.31 2 = 0.9 69 46 115 2 = 0.01 22 26 36 29 113 2 = 0.44	, df = 5 (f 5)	54 54 108 2 = 0.9 24 26 27 28 105	36.5% 63.5% 100.0% 2); F = 0% 23.1% 23.0% 22.9% 30.9% 100.0%	0.52 [0.09, 3.01] 0.59 [0.16, 2.22] 0.56 [0.19, 1.62] 3.26 [0.14, 76.10] 3.00 [0.13, 70.42] 2.27 [0.10, 53.66] 0.97 [0.06, 14.70] 2.02 [0.44, 9.19]	

Figure 5. A. Adverse events. The analysis is subcategorized by country. RR > 1.0 suggests more adverse events with HD tigecycline treatment. B. Adverse events. The analysis is subcategorized by manifestation. RR > 1.0 suggests more adverse events with HD tigecycline treatment. HD = high-dose, LD = low-dose, RR = risk ratio.

Pooled analysis of non-Chinese study also showed a mortality decrease by 21% but without significant difference.

We found a statistically significant increase of clinical response and microbiological eradication efficiency with HD

vs LD tigecycline. Although no significant difference was observed in non-Chinese subgroup, the trend of improved efficacy (RR >1) was consistent. We speculated that the non-significant advantage of HD regimen might due to the different

situation of bacterial resistance between Chinese and non-Chinese countries.

FDA stated a "black box" warning^[40] of higher mortality with tigecycline than comparators based on data from one meta-analysis.^[7] Recent meta-analyses also suggested increased risk of death in patients receiving tigecycline compared with other antibiotics, particularly in patients with VAP.^[41,42] Further interpretation considered the increased death probably was ascribed to decreased clinical and microbiological efficacy.^[7] Knowledge on PK/PD of tigecycline has been questioned and updated during recent years^[21,43-45] Many studies and experts suggested dose adjustment of tigecycline based on the indication, pathogens and their susceptibility, PK targets and etc.^[46,47] A higher dose regimen might be a solution to treat infections caused by pathogens for which therapeutic options are currently lacking.^[48] PK/PD relationships for efficacy evaluation suggested treatment failure of tigecycline for HAP was related to a low $f_{AUC0-24}$: MIC.^[49] A double-blind randomized study of patients with HAP/VAP compared 2 different doses of tigecycline. Numerically higher efficacy values were observed with the high dose regimen.^[12] Other case series studies reported the use of HD tigecycline in infections caused by carbapenemase-producing K. pneumoniae with a favorable result.^[50] The results observed in our metaanalysis are consistent with the above findings.

In our meta-analysis, HD tigecycline did not elevated the risk of AEs, however a minor increase was seen in non-Chinese subgroup analysis (RR >1) with no statistical significance. Other systematic analysis indicated more AEs with HD tigecycline.^[51] Nausea, vomiting, diarrhea are still the most common AEs,^[40,52] nevertheless, reports on tigecycline related coagulopathy and hypofibrinogenemia are increasing;^[53–55] Tigecycline could change series of coagulation parameters, including prolonged prothrombin time, activated partial thromboplastin time, thrombin time, and decreased fibrinogen, especially obvious in patients receiving higher dose.^[56–59] Tigecycline induced coagulation disorders usually could be reversed after promptly discontinuation. Routine strict monitoring of coagulation parameters in patients receiving tigecycline, particularly when given at high dose and/or will last for a longer duration.

Limitations of our analysis include missing data of a negative results study,^[24] we tried to obtain detail data by contacting with the author for several times but failed. Only one high-quality RCT study and 3 prospective cohort studies were available, others were all retrospective cohort studies. Most available studies were from European and China, with the latter predominating. Additionally, in most included studies, tigecycline was used in combination with other systematic antibiotics, and concomitant antibiotics were various.

5. Conclusions

HD tigecycline regimen was safe and effective in patients with serious infections caused by MDR/XDR pathogens. It should be a choice for serious infections with closely monitoring of AEs. Furthermore, well-designed studies especially RCTs from more different countries are required to establish the effectiveness and safety of HD tigecycline.

Author contributions

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References

- Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamaseproducing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Pseudomonas aeruginosa. Mayo Clinic Proc 2011;86:250–9.
- [2] Eckmann C, Dryden M. Treatment of complicated skin and soft-tissue infections caused by resistant bacteria: value of linezolid, tigecycline, daptomycin and vancomycin. Eur J Med Res 2010;15:554–63.
- [3] Zhanel GG, Homenuik K, Nichol K, et al. The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004;64:63–88.
- [4] Stein GE, Babinchak T. Tigecycline: an update. Diagn Microbiol Infect Dis 2013;75:331–6.
- [5] Ni WT, Han YL, Liu J, et al. Tigecycline treatment for carbapenemresistant enterobacteriaceae infections: A systematic review and metaanalysis. Medicine (Baltimore) 2016;95:e3126.
- [6] Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68:140–51.
- [7] Yahav D, Lador A, Paul M, et al. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66:1963–71.
- [8] Meagher AK, Ambrose PG, Grasela TH, et al. The pharmacokinetic and pharmacodynamic profile of tigecycline. Clin Infect Dis 2005;41(Suppl 5):S333–40.
- [9] Barbour A, Schmidt S, Ma B, et al. Clinical pharmacokinetics and pharmacodynamics of tigecycline. Clin Pharmacokinet 2009;48:575–84.
- [10] Bassetti M, Peghin M, Pecori D. The management of multidrug-resistant enterobacteriaceae. Curr Opin Infect Dis 2016;29:583–94.
- [11] Poulakou G, Bassetti M, Righi E, et al. Current and future treatment options for infections caused by multidrug-resistant Gram-negative pathogens. Future Microbiol 2014;9:1053–69.
- [12] Ramirez J, Dartois N, Gandjini H, et al. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. Antimicrob Agents Chemother 2013;57:1756–62.
- [13] De Pascale G, Montini L, Spanu T, et al. High-dose tigecycline use in severe infections [abstract P80]. In: 33rd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium. Crit Care 2013;17(Suppl 2):S29.
- [14] Geng TT, Xu X, Huang M. High-dose tigecycline for the treatment of nosocomial carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Medicine (Baltimore) 2018;97:e9961.
- [15] Barza M, Trikalinos TA, Lau J. Statistical considerations in metaanalysis. Infect Dis Clin North Am 2009;23:195–210.
- [16] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed) 2003;327:557–60.
- [17] Gandjini H, McGovern PC, Yan JL, et al. Clinical efficacy of two high tigecycline dosage regimens vs. imipenem/cilastatin in hospital-acquired pneumonia: Results of a randomised phase II clinical trial. Clin Microbiol Infec 2012;18(Suppl 3):64.
- [18] Lou Y, Shi XY. Clinical study of high dose tigecycline on ventilatorassociated pneumonia caused by multi-drug resistant gram-negative bacilli. Chin J Emerg Med 2015;24:1267–71.
- [19] Balandin Moreno B, Fernandez Simon I, Romera Ortega MA, et al. Clinical experience with tigecycline in intensive care unit [abstract]. In: 24th Annual Congress of the European Society of Intensive Care Medicine (ESICM), Berlin, Germany. Intens Care Med 2011;37(Suppl 1):S266.
- [20] De Pascale G, Montini L, Bernini V, et al. Tigecycline use in critically ill patients. Do we need higher doses? [abstract]. In: 25th Annual Congress of the European Society of Intensive Care Medicine (ESICM), Lisbon, Portugal. Intens Care Med 2012;38(Suppl 1):S82.

- [21] Baron J, Cai S, Klein N, et al. Once daily high dose tigecycline is optimal: Tigecycline PK/PD parameters predict clinical effectiveness. J Clin Med 2018;7:e49.
- [22] Gao HH, Yao ZL, Li Y, et al. Safety and effectiveness of high dose tigecycline for treating patients with acute leukemia after ineffctiveness of carbapenems chemotherapy combinating with febrile neutropenia: retrospective study. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2018;26:684–90.
- [23] Zang HL, Wang SC, Cheng H. Clinical effect of high dose tigecycline on ventilator-associated pneumonia caused by multi-drug resistant bacteria. Zhongguo Yi Yao 2018;13:380–2.
- [24] Jesus R, Pablo PH, Esther V, et al. Analysis of treatment failure with standard and high dose of tigecycline in critically ill patients with multidrug-resistant bacteria. Eur J Clin Pharm 2017;19:93–9.
- [25] Di Carlo P, Gulotta G, Casuccio A, et al. KPC 3 Klebsiella pneumoniae ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: Analysis of a case series of 30 patients. BMC Anesthesiol 2013;13:13.
- [26] De Pascale G, Montini L, Pennisi MA, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. Crit Care 2014;18:R90.
- [27] 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.
- [28] de Maio Carrilho CMD, de Oliveira LM, Gaudereto J, et al. A prospective study of treatment of carbapenem-resistant Enterobacteriaceae infections and risk factors associated with outcome. BMC Infect Dis 2016;16:629.
- [29] LV XC, Cai GL, Xu QH. Observation of the clinical efficacy of tigecycline for treatment of ventilator-associated pneumonia in critically ill elderly patients. Zhonghua Yi Xue Za Zhi 2016;96:535–8.
- [30] Fei M, Zhang M, Cai W. Efficacy and safety of high dose tigecycline in treatment of patients with ventilator-associated pneumonia. Chin J Clin Infect Dis 2016;9:416–21.
- [31] Wu XM, Zhu YF, Chen QY, et al. Tigecycline therapy for nosocomial pneumonia due to carbapenem-resistant gram-negative bacteria in critically ill patients who received inappropriate initial antibiotic treatment: a retrospective case study. Biomed Res Int 2016;2016.
- [32] Zhao GY. Clinical study on tigecycline for the treatment of ventilatorassociated pneumonia in critically ill elderly patients. Zhongguo Ji Xu Yi Xue Jiao Yu 2016;8:119–21.
- [33] Zhao ZH, Wang XL, Ma ZQ. Clinical study on off-label use of tigecycline combined with cefoperazone and sulbactam in the treatment of pneumonia caused by multidrug-resistant acinetobacter baumannii. J China Pharm 2017;28:201–4.
- [34] Wu YH, Yang YY, Gao XH. The clinical analysis of different doses of tigecycliue in the treatment of severe pneumonia caused by extensivelydrug resistant acinetobacter baumannii. Zhongguo Wei Sheng Biao Zhun Guan Li 2017;8:104–7.
- [35] Chen ZH, Shi XY. Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. Medicine (Baltimore) 2018;97:e12467.
- [36] Cui N, Yang LZ, Yu ZB, et al. Comparative effects among different doses of tigecycline and imipenem cilastatin in treating hospital acquired pneumonia. Zhongguo Yao Ye 2018;27:62–4.
- [37] Xia L, Bao J, Xia RX. Efficacy and safety of salvage tigecycline in severe infection with haematological disorders. Anhui Yi Xue 2018;39:1109– 11.
- [38] Li ZH, Zhang H, Gao YQ. Study on tigecycline in the treatment of pneumonia patients with carbapenems-resistant acinetobacter baumannii. Zhongguo shi yong yi kan 2018;45:99–101.
- [39] Caballero Requejo C, Gil Candel M, Gallego Munoz C, et al. High dosage of tigecycline in multidrug resistant acinetobacter baumannii: Use

analysis during an outbreak. Eur J Hosp Pharm Sci Pract 2018;25(Suppl 1):A179–80.

- [40] Inc. WP. TYGACIL (tigecycline) for injection for intravenous use (highlights of prescribing information). Available at: http://labelingpfi zercom/ShowLabelingaspx?id=491 [Accessed Oct 31, 2018].
- [41] Prasad P, Sun J, Danner RL, et al. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54:1699–709.
- [42] Cai Y, Wang R, Liang BB, et al. Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. Antimicrob Agents Chemother 2011;55:1162–72.
- [43] Xie J, Wang TT, Sun JY, et al. Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation. Int J Infect Dis 2014;18:62–7.
- [44] Cunha BA, Baron J, Cunha CB. Once daily high dose tigecycline pharmacokinetic/pharmacodynamic based dosing for optimal clinical effectiveness: dosing matters, revisited. Expert Rev Anti Infect Ther 2017;15:257–67.
- [45] Deitchman AN, Singh RSP, Derendorf H. Nonlinear protein binding: not what you think. J Pharm Sci 2018;107:1754–60.
- [46] Giamarellou H, Poulakou G. Pharmacokinetic and pharmacodynamic evaluation of tigecycline. Expert Opin Drug Metab Toxicol 2011;7:1459–70.
- [47] Borsuk-De Moor A, Rypulak E, Potrec B, et al. Population pharmacokinetics of high-dose tigecycline in patients with sepsis or septic shock. Antimicrob Agents Chemother 2018;62:e02273–2317.
- [48] Xie J, Roberts JA, Alobaid AS, et al. Population pharmacokinetics of tigecycline in critically ill patients with severe infections. Antimicrob Agents Chemother 2017;61:e00345–417.
- [49] Bhavnani SM, Rubino CM, Hammel JP, et al. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. Antimicrob Agents Chemother 2012;56:1065–72.
- [50] Sbrana F, Malacarne P, Viaggi B, et al. Carbapenem-sparing antibiotic regimens for infections caused by Klebsiella pneumoniae carbapenemaseproducing K. pneumoniae in intensive care unit. Clin Infect Dis 2013;56:697–700.
- [51] Xu L, Wang YL, Du S, et al. Efficacy and safety of tigecycline for patients with hospital-acquired pneumonia. Chemotherapy 2016;61:323–30.
- [52] Rello J. Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. J Chemother 2005;17(Suppl 1):12–22.
- [53] Sabanis N, Paschou E, Gavriilaki E, et al. Hypofibrinogenemia induced by tigecycline: a potentially life-threatening coagulation disorder. Infect Dis (Lond) 2015;47:743–6.
- [54] Bourneau-Martin D, Crochette N, Drablier G, et al. Hypofibrinogenemia complicated by hemorrhagic shock following prolonged administration of high doses of tigecycline [Abstract]. In: 20th Annual Meeting of French Society of Pharmacology and Therapeutics, 37th Pharmacovigilance Meeting, 17th APNET Seminar, 14th CHU CIC Meeting. France Fundam Clin Pharmacol 2016;30(Suppl 1):29.
- [55] Yilmaz Duran F, Yildirim H, Sen EM. A lesser known side effect of tigecycline: hypofibrinogenemia. Turk J Haematol 2018;35:83–4.
- [56] Pieringer H, Schmekal B, Biesenbach G, et al. Severe coagulation disorder with hypofibrinogenemia associated with the use of tigecycline. Ann Hematol 2010;89:1063–4.
- [57] Zhang Q, Zhou SM, Zhou J. Tigecycline treatment causes a decrease in fibrinogen levels. Antimicrob Agents Chemother 2015;59:1650–5.
- [58] Routsi C, Kokkoris S, Douka E, et al. High-dose tigecycline-associated alterations in coagulation parameters in critically ill patients with severe infections. Int J Antimicrob Agents 2015;45:90–3.
- [59] Wu XQ, Zhao P, Dong L, et al. A case report of patient with severe acute cholangitis with tigecycline treatment causing coagulopathy and hypofibrinogenemia. Medicine (Baltimore) 2017;96:e9124.