Systematic Review and Meta-Analysis

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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% *CI* 0.53–0.84, $P < .001$). Clinical response (*RR* 1.46, 95% *CI* 1.30–1.65, $P < .001$) and microbiological eradication rate (*RR* 1.61, 95% *CI* 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% *CI* 0.56–1.14, $P = .21$), 1.35 (95% *CI* 0.96–1.92, $P = .26$), 1.00 (95% *CI* 0.22–4.43, $P = 1.00$), respectively. AEs did not differ between HD and LD tigecycline (*RR* 1.00, 95% *CI* 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

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.

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]

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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) ×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 all-cause 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 meta-analysis 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).

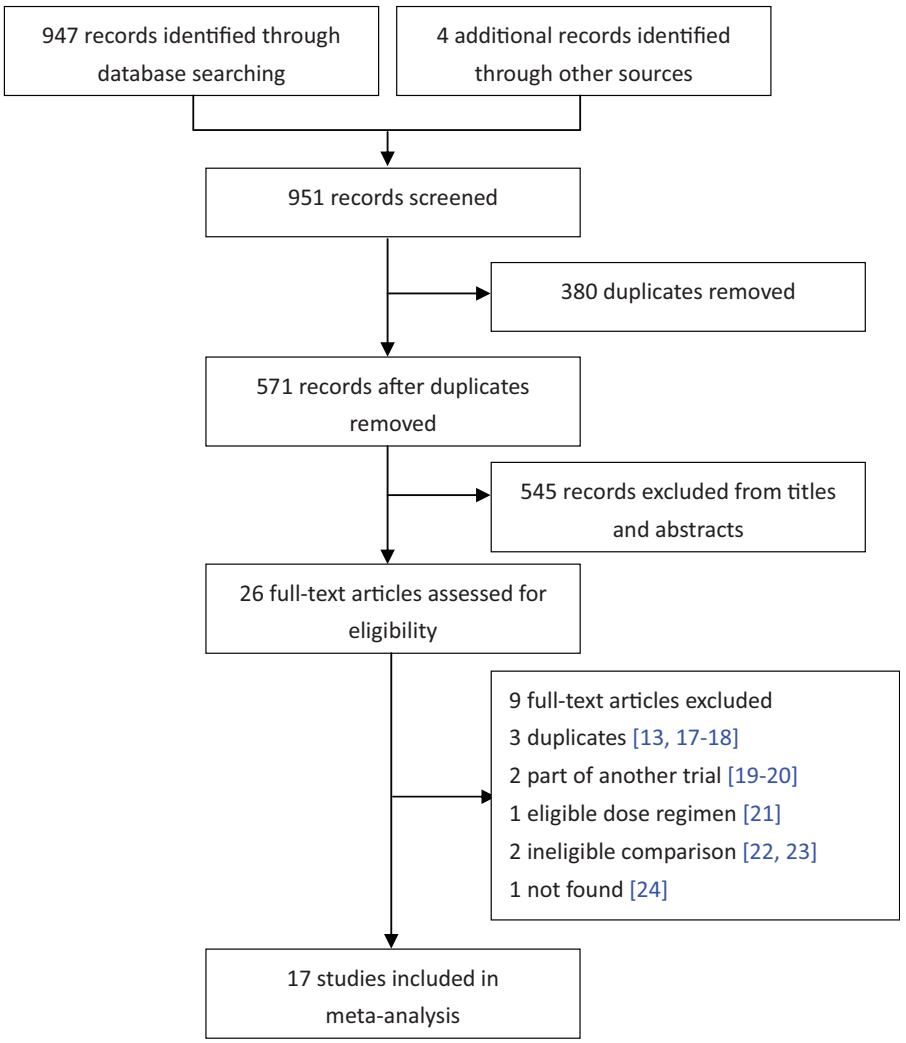

Figure 1. Flow diagram of study selection.

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 intra-abdominal 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, 4
Balandin Moreno 2014[27]	SC-RC 2009.9–2011.9 Spain	15	Serious infections (Pneumonia, UTI, peritonitis, CRB, meningitis); CPKP	HD: 9 pts, 100 mg q12 h LD: 6 pts, 50 mg q12 h	Yes (Colistin; Carbapenems, Ciprofloxacin, Piperacillin-tazobactam, 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]	SC-RC 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, fluoroquinolones, phosphonomycin)	2, 3
Wu 2016[31]	SC-RC 2013.1.1–2015.12.31 China	31	nosocomial pneumonia; CR-GNB (AB, KP, *E. coli*, SM, *etc.*)	HD: 20 pts, 200 mg × 1+ 100 mg q12h LD: 11 pts, 100 mg × 1+ 50 mg q12h	Yes (cefoperazone-sulbactam, piperacillin-tazobactam, carbapenem)	1, 2, 3
Zhao 2016[32]	SC-PC 2014.2–2016.5 China	63	VAP	HD: 36 pts, 200 mg × 1+100 mg q12h LD: 27 pts, 100 mg × 1+ 50 mg q12h	None	1, 2, 4
Zhao 2017[33]	SC-RC 2015.4–2016.4 China	57	pneumonia; MDR-AB	HD: 29 pts, 100 mg × 1+ 75 mg q12h LD: 28 pts,100 mg × 1+ 50 mg q12h	Yes (cefoperazone-sulbactam)	1, 2, 3, 4
Wu 2017[34]	SC-RCT 2015.8–2017.7 China	52	Pneumonia; XDR-AB	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, carbapenem)	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 mg q12h	Yes (Carbapenems, beta-lactamase inhibitors, aminoglycosides)	1, 3
Xia 2018[37]	SC-RC 2015.8–2018.1 China	27	Carbapenems failure blood diseases coinfection; KP, *Enterobacter cloacae*, AB, PA)	HD: 11 pts, 100 mg q12h LD: 16 pts, 100 mg × 1+ 50 mg q12h	Yes (imipenem-cilastin, meropenem, 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 *staphycoccus 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.

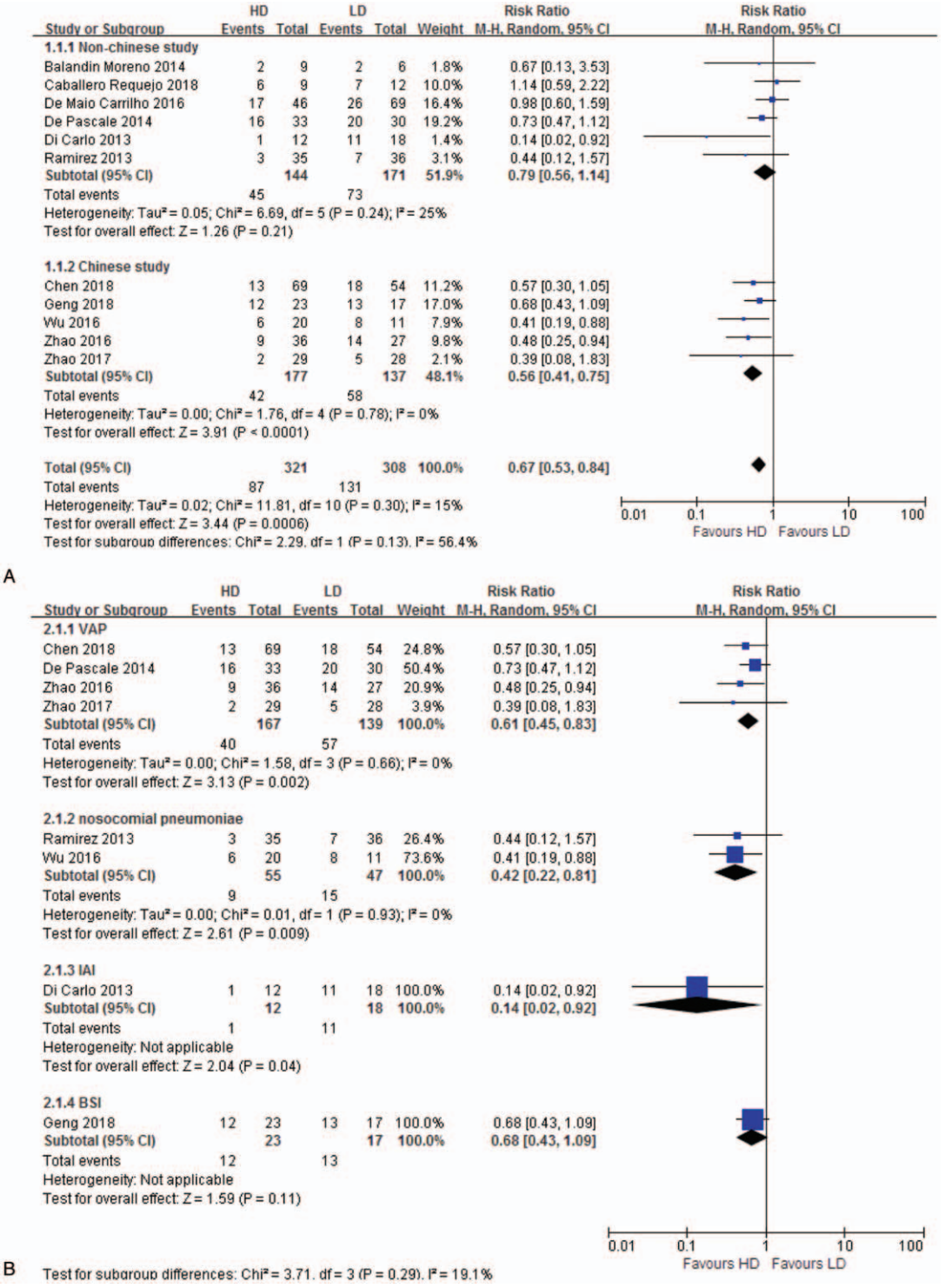

Figure 2. A. All-cause mortality. The analysis is subcategorized by country. RR < 1.0 suggests decreased mortality with HD tigecycline treatment. B. All-cause mortality. The analysis is subcategorized by infection type. RR < 1.0 suggests decreased mortality with HD tigecycline treatment. BSI = bloodstream 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]

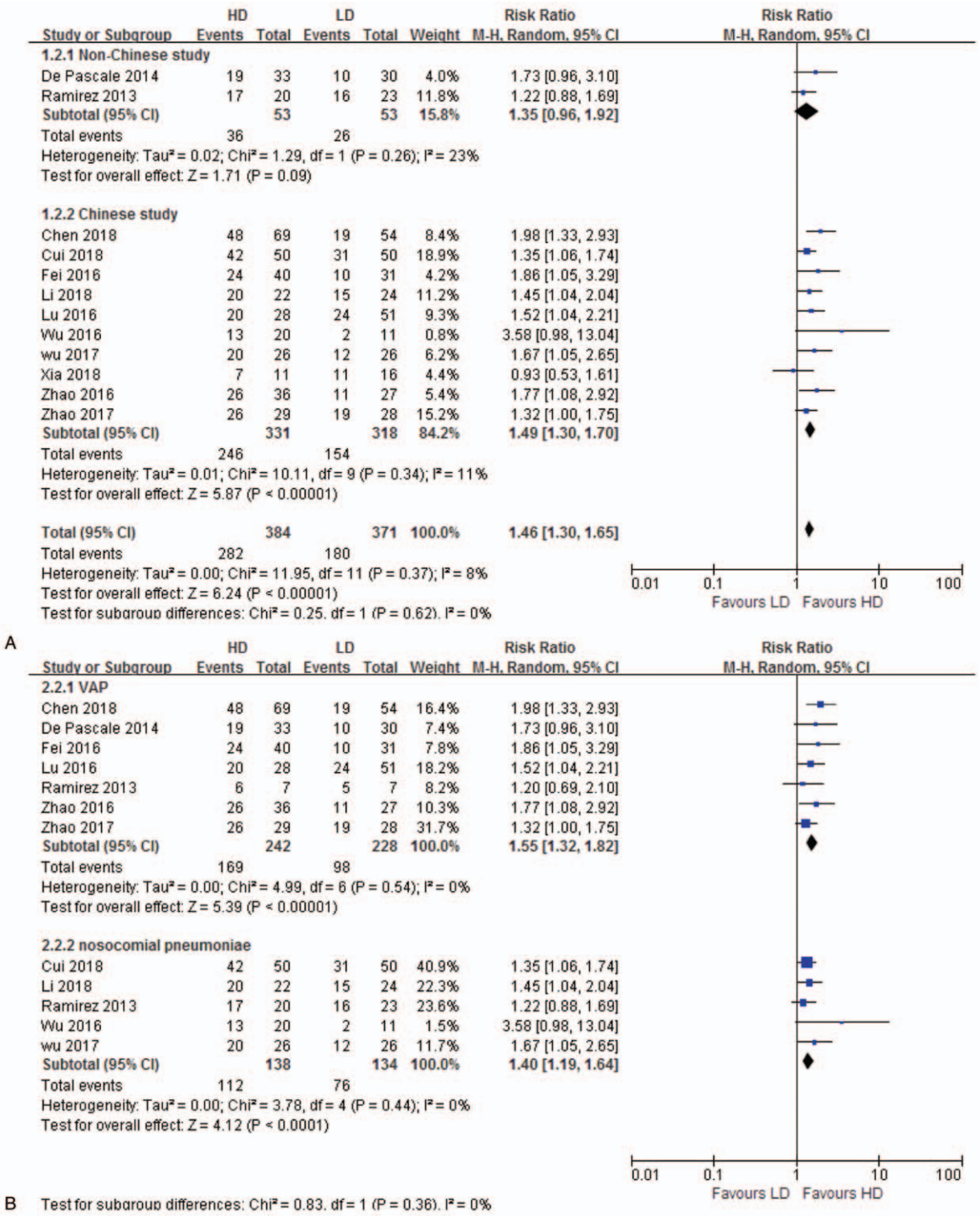

Figure 3. A. Clinical response. The analysis is subcategorized by country. RR > 1.0 suggests increased clinical response with HD tigecycline treatment. B. Clinical response. The analysis is subcategorized by infection type. RR > 1.0 suggests increased clinical response with HD tigecycline treatment. HD = high-dose, LD = low-dose, 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).

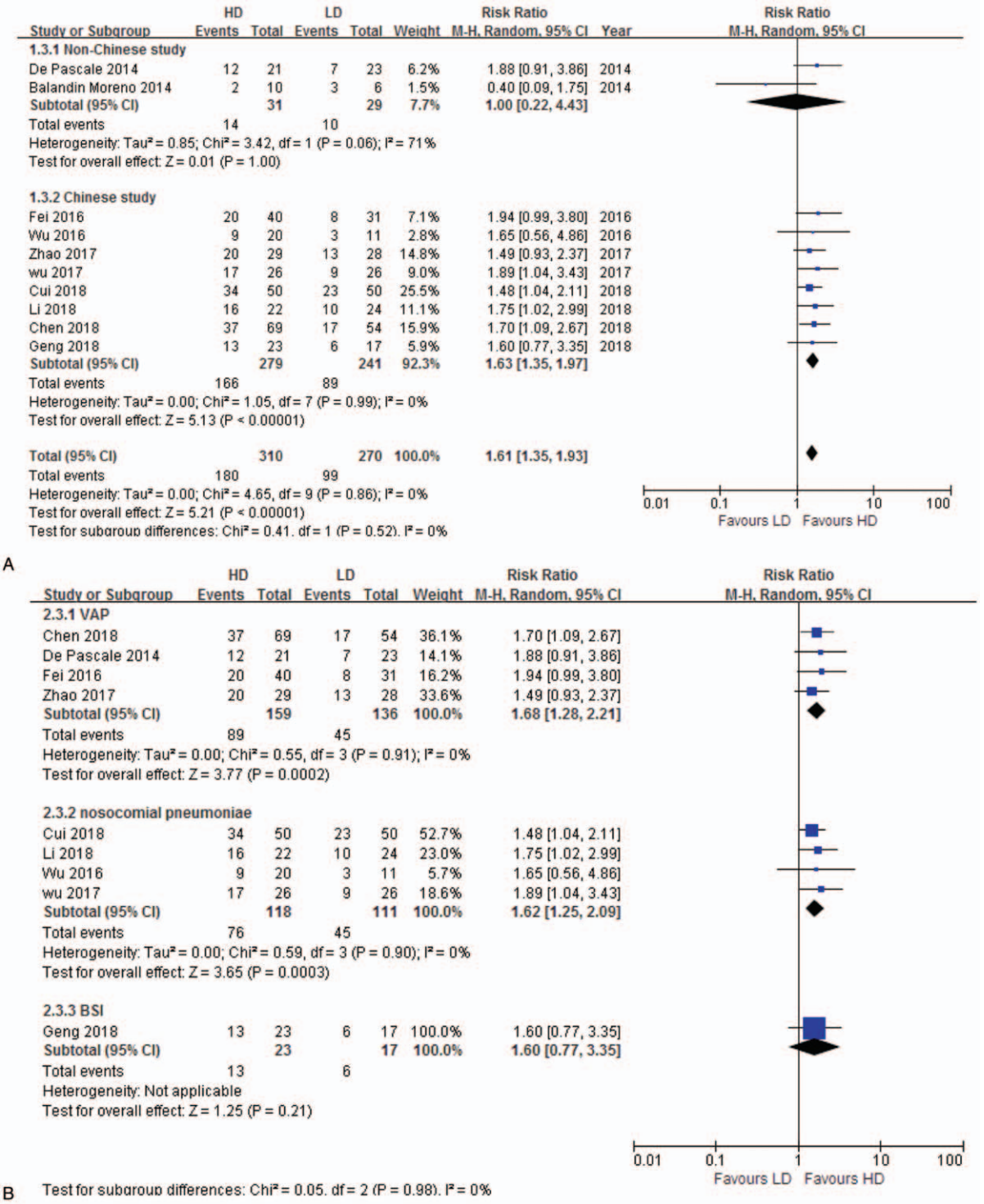

Figure 4. A. Microbiological eradication. The analysis is subcategorized by country. RR > 1.0 suggests increased microbiological eradication with HD tigecycline treatment. B. Microbiological eradication. The analysis is subcategorized by infection type. RR > 1.0 suggests increased microbiological eradication 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.

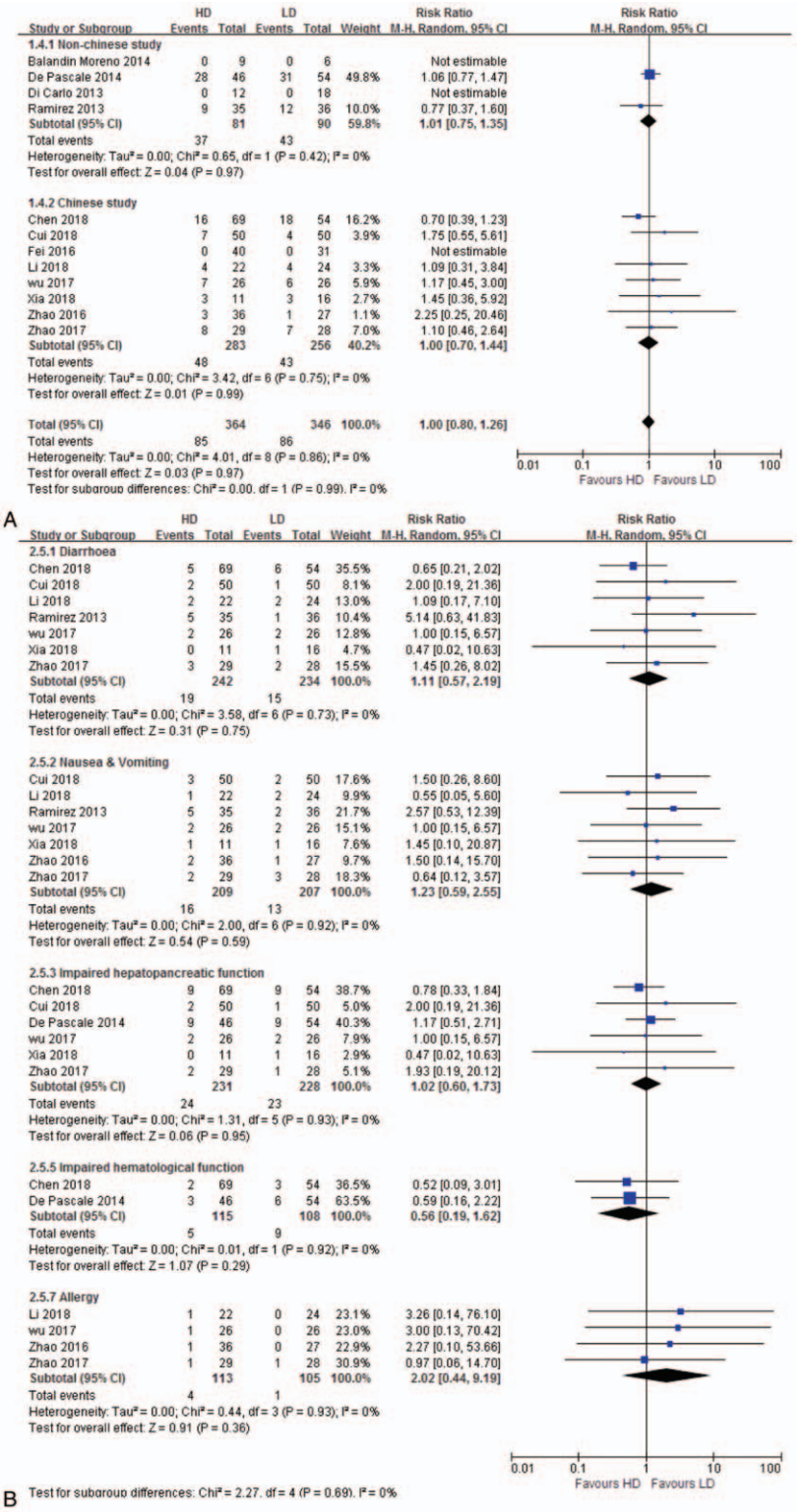

Figure 5. A. Adverse events. The analysis is subcategorized by country. RR > 1.0 suggests more adverse events with HD tigecycline treatment. B. Adverse events. The analysis is subcategorized by manifestation. RR > 1.0 suggests more adverse events with HD tigecycline treatment. HD = high-dose, LD = low-dose,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

Conceptualization: Hai Yu, Zhiqiang Sun, Guangjun Liu.
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Writing – original draft: Jinhong Gong.
Writing – review & editing: Hai Yu, Zhiqiang Sun.

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