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ORIGINAL RESEARCH

High-Dose versus Standard-Dose Tigecycline Treatment of Secondary Bloodstream Infections Caused by Extensively Drug-Resistant *Acinetobacter baumannii*: An Observational Cohort Study

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Background: Extensively drug-resistant *Acinetobacter baumannii* (XDR-AB) infections have become difficult to treat and are associated with a high mortality rate. Tigecycline is one of the most effective agents used to treat XDR-AB infections, but data from treating bloodstream infection (BSI) in standard dose do not look promising, because of its low plasma concentration. Secondary BSI with primary infection source may indicate tigecycline treatment with a higher dose. Currently, little is known about the application of high-dose tigecycline among patients with secondary BSI caused by XDR-AB. We aimed to investigate the outcomes for high-dose (HD) tigecycline treatment versus standard-dose (SD) treatment of these patients.

Methods: An observational cohort study was conducted at four university affiliated hospitals in mainland China. Adult inpatients who were confirmed as having secondary BSI caused by XDR-AB and received definitive tigecycline treatment were consecutively included. Patients who were treated with 50 mg every 12 h were defined as the SD group, and a twice dose was defined as the HD group.

Results: Of the enrolled patients, 63 received SD and 88 received HD tigecycline treatment. Patients in the two groups had similar with regard to baseline clinical conditions. The 30-day survival was affected by the source of the primary infection. Survival was significantly better in patients with non-pulmonary-infection-related BSI than in patients with pulmonary-infection-related BSI. Multivariate Cox regression confirmed that HD had a protective effect only observed in patients with non-pneumonia-related BSI.

Conclusion: A tigecycline dose that is twice its standard dose is better for the treatment of XDR-AB infection only in BSI associated with non-pulmonary infection.

Keywords: *Acinetobacter baumannii*, bloodstream infection, extensively drug-resistant, tigecycline, high-dose

Introduction

The bacterium *Acinetobacter baumannii* (AB) is as an important causative pathogen of bloodstream infection (BSI) among in-hospital patients worldwide, and it has also been gaining drug resistance. In fact, the incidence of extensively drug-resistant *A. baumannii* (XDR-AB) infections in hospital settings has been increasing; as a result, these infections have become difficult to treat and are associated with a very high mortality rate.[1,2]

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Tigecycline, an analog of minocycline, is currently one of the most effective agents used to treat XDR-AB infections, especially in developing countries. However, data from patients with BSI do not look promising, as treatment with the standard dose (50 mg every 12 h) of tigecycline was associated with a significantly higher mortality rate than treatment with other antibiotics.[3–5] As the antimicrobial activity of tigecycline is determined by the ratio of area under the plasma concentration versus time to minimal inhibitory concentration (MIC),[6] a high-dose (HD) regimen of tigecycline was proposed and resulted in better clinical outcomes in patients with different infection sites, including ventilator-associated pneumonia,[7,8] skin and soft tissue infections, complicated intra-abdominal infections,[9,10] and spondylodiscitis.[11] Secondary BSIs with the above sites as primary sources may also benefit from HD tigecycline. Currently, there are very few clinical reports on the application of HD tigecycline among patients with secondary *A. baumannii* BSI (ABBSI).

In the past decade in mainland China, tigecycline has been the only agent in use for the treatment of XDR-AB infections that was resistant to other antimicrobial agents in most Chinese hospitals where polymyxin was not available. In this study, we performed this analysis of patients with secondary BSI who received tigecycline treatment for microbiologically confirmed tigecycline-susceptible XDR-AB infections. The aim of this study was to determine the efficacy of tigecycline administered at doses higher than the standard doses.

Methods

Patients

This was an observational cohort study conducted at four university affiliated hospitals in mainland China (Qilu Hospital of Shandong University, Second Hospital of Shandong University, Qingdao Branch of Qilu Hospital of Shandong University, and Liaocheng People's Hospital affiliated with Shandong First Medical University) from January 2016 to December 2018. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Qilu Hospital of Shandong University (KYLL-2015KS-170).

Adult inpatients who were confirmed as having secondary BSI caused by tigecycline-susceptible XDR-AB and received definitive tigecycline treatment were prospectively and consecutively included. Secondary BSI was defined as BSI occurring in patients with a recognized source of BSI. The sources of BSI were assessed by study investigators according to clinical symptoms, signs, imaging data, surgical findings, and microbiological evidence. Microbiological evidence refers to the isolation from the source of the same organism (tigecycline-susceptible XDR-AB) that was isolated in blood culture.[12] Patients were excluded if they received inappropriate treatment for tigecycline, including initiation of treatment more than 24 h after antibiogram was obtained, treatment for fewer than 3 days, and the absence of a loading dose.

Blood cultures were processed at the participating hospitals by the Bactec system (Becton Dickinson, Franklin Lakes, NJ, USA) or BacT/ALERT 3D system (bioMérieux, Marcy-l'Étoile, France). The blood culture bottles were incubated in the above two blood culture systems until a positive alert was gotten or for a maximum of 5 days. Two or three drops of positive blood culture broth were

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streaked onto the 5% sheep blood agar plate and MacConkey agar plate, respectively, and all the plates were incubated at 5% CO_2 and 35°C. AB isolates were Gram-negative, non-fermentative and oxidase-negative coccobacillus using the Gram stain and manual biochemical tests, and they were identified using the VITEK-2 compact system with GN identification card (bioMérieux, Marcy-l'Étoile, France) according to the manufacturer's manual. The antibiotic susceptibility testing (AST) of AB isolates was performed on the VITEK-2 compact system with AST-GN16 card. The strains of *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality controls to ensure the credibility of identification and AST results of AB isolates. Susceptibility tests of antimicrobials were performed by determining minimal inhibitory concentrations (MICs) and were interpreted according to the recommendations of the Clinical and Laboratory Standards Institute.[13] MICs of tigecycline were interpreted according to the recommendation of the US Food and Drug Administration, and MICs of ≤2, 4, and ≥8 μg/mL were respectively interpreted as susceptible, intermediate, and resistant.[14] XDR was defined according to internationally accepted criteria.[15] Patients treated with 50 mg of tigecycline every 12 h after a 100-mg loading dose were classified as the standard-dose (SD) group and 100 mg every 12 h after a 200-mg loading dose were classified as the HD group.

We collected the following information based on chart review: demographic and microbiological data, comorbidities, precipitating factors, laboratory test results, concurrent BSIs caused by other pathogens, antibacterial agent treatment, and outcome. The data were recorded on standardized case report forms.

Diagnosis and Treatment of ABBSI

At the onset of ABBSI (within 24 h after collection of the first *A. baumannii*-positive blood sample), we calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II score to evaluate the severity of the initial presentation of ABBSI. The primary outcome was all-cause 30-day mortality after onset of BSI. Patients discharged from the hospital were followed up by the medical electronic system or by telephone to determine their survival status. Adequate source control was defined as removal of any preexisting devices thought to be the source of BSI, or documented interventions using appropriate decompression, debridement, drainage, and other surgical procedures to control the source of infection within 48 h of its onset,[16] and was assessed independently by a multidisciplinary panel of experts composing of an infectious disease specialist, an intensivist, and a surgeon (all of whom had more than 10 years of experience). The empirical antimicrobial regimen was defined as appropriate when it included ≥1 antimicrobial agent that exhibited activity against the AB isolate in the first 24 h from the onset of the bacteremia with an approved route and dosage. The classifications of concomitant antibiotics include beta-lactam/betalactamase inhibitors (piperacillin/tazobactam, ticarcillin/clavulanic acid, cefoperazone/sulbactam), carbapenem (imipenem, meropenem and biapenem), fluoroquinolone (ciprofloxacin, levofloxacin and moxifloxacin) and others.

Statistical Analysis

SPSS 16.0 (SPSS Inc., IL, USA) and R v3.6 used for Kaplan–Meier curves were used to visually compare survival associated with the various doses of tigecycline. Prespecified subgroup analysis was used to assess the consistency of HD tigecycline treatment in terms of its effects on survival in intention-to-treat populations. The Cox proportional-hazards model with Efron's method of handling ties was used to assess the difference in the magnitude of HD tigecycline treatment between groups. Cox proportional hazards regression included significant variables ($P < 0.10$) that were identified in the univariate analysis, and the results were expressed as estimated hazard ratios (HRs) and 95% confidence intervals (CIs). $P < 0.05$ was considered as statistical significance.

Results

Clinical Characteristics of the Patients

Initially, 180 patients who received tigecycline treatment were identified, but 29 patients were excluded because they received inappropriate tigecycline treatment. Of the remaining 151 patients, 63 received the standard dose of tigecycline and 88 received HD tigecycline treatment. The mean age of the enrolled participants (n = 151) was 57.2 ± 17.5 years, and 68.2% were male. The overall 30-day mortality was 45.7%. The three primary sources of infection were the lung (56.3%), abdomen and pelvis (19.9%), and skin and soft tissue (10.6%). The mean duration of tigecycline treatment was 12.0 ± 4.7 days, and 51.0%, 27.2%, and 12.6% were treated with beta-lactam/beta-lactamase inhibitors, carbapenem, and fluoroquinolone, respectively (Table 1).

Table 1 Clinical Characteristics of Patients with Extensively Drug-Resistant *Acinetobacter baumannii* Bloodstream Infection

Characteristics	Total (n = 151)	HD Tigecycline Group (n = 88)	SD Tigecycline Group (n = 63)	*P* value
Baseline				
Age (years), mean (SD)	57.2 (17.5)	56.9 (18.9)	58.0 (17.5)	0. 837
Male sex	103 (68.2%)	60 (68.2%)	43 (68.3%)	0.993
Charlson index, mean (SD)	2.6 (1.5)	2.6 (1.5)	2.4 (1.4)	0.441
Comorbidities				
Cardiovascular disease	24 (15.9%)	13 (14.8%)	11 (17.5%)	0.656
Type II diabetes mellitus	33 (21.9%)	19 (21.6%)	14 (22.2%)	0.926
Solid tumor	19 (12.6%)	12 (13.6%)	7 (11.1%)	0.645
Hematologic malignancy	5 (3.3%)	3 (3.4%)	2 (3.2%)	0.703
Chronic renal insufficiency	17 (11.3%)	10 (11.4%)	7 (11.1%)	0.961
Characteristics of ABBSI				
Tigecycline MIC 1–2 mg/mL	82 (54.3%)	54 (61.4%)	28 (44.4%)	0.040
Polymicrobial bloodstream infection	36 (23.8%)	22 (25.0%)	14 (22.2%)	0.693
Acquired in the intensive care unit	114 (75.5%)	68 (77.3%)	46 (73.0%)	0.549
Source of bloodstream infection				
Lung	85 (56.3%)	51 (58.0%)	34 (54.0%)	0.626
Intra-abdomen	30 (19.9%)	16 (18.2%)	14 (22.2%)	0.539
Skin and soft tissue	16 (10.6%)	9 (10.2%)	7 (11.1%)	0.862
Catheter-related	10 (6.6%)	6 (6.8%)	4 (6.3%)	0.828
Mediastinal and pleural	8 (5.3%)	4 (4.5%)	4 (6.3%)	0.626
Others*	2 (1.3%)	1 (1.1%)	1 (1.6%)	0.629
Fever	97 (64.2%)	57 (63.5%)	40 (64.8%)	0.871
Febrile neutropenia	5 (3.3%)	2 (2.3%)	3 (4.8%)	0.703
Acuity score at initial presentation				
APACHE II score, mean (SD)	18.6 (6.7)	18.7 (7.1)	18.3 (6.2)	0.742
Treatment and support				
Use of invasive ventilation	102 (67.5%)	60 (68.2%)	42 (66.7%)	0.845
Use of renal replacement therapy	42 (27.8%)	25 (28.4%)	17 (27.0%)	0.847
Inadequate source control	34 (22.5%)	19 (21.6%)	15 (23.8%)	0.748
Appropriate empiric therapy	17 (11.3%)	9 (10.2%)	8 (12.7%)	0.832
Duration of tigecycline treatment (days), mean (SD)	12.0 (4.7)	11.8 (6.6)	10.9 (3.7)	0.567
Concomitant use of other antibiotics				
None	10 (6.6%)	6 (6.8%)	4 (6.3%)	0.828
Beta-lactam/beta-lactamase inhibitor	77 (51.0%)	44 (50.0%)	33 (52.4%)	0.773
Carbapenem	41 (27.2%)	25 (28.4%)	16 (25.4%)	0.682
Fluoroquinolone	19 (12.6%)	10 (11.4%)	6 (9.5%)	0.717
Others	7 (4.6%)	3 (3.4%)	4 (6.3%)	0.649
Outcome				
Length of stay (days), mean (SD)	22.2 (7.5)	23.1 (7.8)	21.0 (6.9)	0.089
30-day mortality	69 (45.7%)	39 (44.3%)	30 (47.6%)	0.688

Notes: Data are presented as n (%). *Other sources included the endocardium in one case and the urinary tract in another case.

Abbreviations: XDR, extensively drug resistant; ABBSI, *Acinetobacter baumannii* bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation; HD, high-dose; SD, standard-dose.

Treatment Outcomes According to Tigecycline Dose

Patients treated with SD or HD tigecycline had similar with regard to baseline clinical conditions, fever and febrile neutropenia, principal comorbidities, infection source, disease severity, and concomitant use of other active antibiotics (Table 1). AB isolates with tigecycline MIC values of 1–2 mg/mL were more often observed in patients treated with HD tigecycline than in SD tigecycline. The incidence of adverse events did not differ between the SD and HD groups (Table 2), in terms of blood urea nitrogen increase, impaired renal function, hepatopancreatic function and hematological function. Tigecycline dosage, course, and concomitant use of other antibiotics were not risk factors for 30-day mortality in the univariate model (Table 3). Additionally, no significant difference in survival was found between the HD and SD tigecycline patients ($P = 0.622$, Figure 1A).

In the prespecified subgroup analysis, survival did not differ between the HD and SD tigecycline patients in all subgroups, with the exception of the non-lung infection-related BSI subgroup (Figure 2). Among patients with non-lung-infection-related BSI, the number of survival days was significantly higher in the HD tigecycline-treated patients than in the SD patients ($P = 0.006$, Figure 1B), but there was no significant dose-dependent difference among patients with lung infection-related BSI ($P = 0.148$, Figure 1C).

Factors Associated with 30-Day Mortality in Pneumonia and Non-Pneumonia ABBSI Cases

Potential risk factors associated with 30-day survival in patients with pneumonia- and non-pneumonia-related ABBSI were identified in the univariate analysis (Tables 4 and 5). Multivariate Cox regression with the identified factors confirmed that HD tigecycline treatment was an independent factor associated with 30-day mortality and had a protective effect. However, this effect was only observed in patients with non-pneumonia-related ABBSI (Table 5), and it was not observed in patients with pneumonia-related ABBSI (Table 4). Besides, inadequate source control and APACHE II score are also independent factors associated with 30-day mortality in patients with non-pneumonia-related ABBSI. While in patients with pneumonia-related ABBSI, APACHE II score is the only risk factor of 30-day mortality in our study.

Discussion

In this study, we investigated the efficacy of tigecycline administered at higher-than-standard doses for treating secondary BSI caused by XDR-AB. The findings did not indicate any differences in the 30-day survival between HD and SD tigecycline treatment in the study population. However, subgroup analysis indicated that the 30-day survival differed according to the source of the primary infection: that is, survival was significantly better with HD tigecycline when the secondary BSI was associated with non-pulmonary infection than when it was associated with pulmonary infection.

Considering the pharmacokinetic/pharmacodynamic features of tigecycline, increasing its dose may lead to a higher tigecycline concentration and a longer time above MIC.[17] In the present study, the survival benefits of HD tigecycline observed in ABBSI patients with a primary non-pulmonary infection could be attributed to the higher concentration of tigecycline both in tissue and in the bloodstream. Secondary BSI occurs when pathogens have entered the body at another site; therefore, eliminating the pathogens at the site of entry is very important.

Table 2 Comparison of Adverse Events in the SD Tigecycline Group and HD Tigecycline Group

Adverse Events	Total (n = 151)	HD Tigecycline Group (n = 88)	SD Tigecycline Group (n = 63)	*P* value
Blood urea nitrogen increase	16 (10.6%)	9 (10.2%)	7 (11.1%)	0.862
Impaired renal function	22 (14.6%)	13 (14.8%)	9 (14.3%)	0.933
Impaired hepatopancreatic function	25 (16.6%)	15 (17.0%)	10 (15.9%)	0.848
Impaired hematological function	13 (8.6%)	8 (9.1%)	5 (7.9%)	0.803

Note: Data are presented as n (%).
Abbreviations: HD, high-dose; SD, standard-dose.

Table 3 Univariate Analysis of the Association Between Different Variables and 30-Day Mortality

Characteristics	Non-Survivors (n = 69)	Survivors (n = 82)	HR (95% CI)	*P* value
Baseline				
Age (years), mean (SD)	60.0 (17.3)	54.8 (17.4)	1.10 (0.99–1.03)	0.067
Male sex	47 (66.7%)	56 (68.3%)	0.99 (0.61–1.60)	0.967
Charlson index, mean (SD)	3.0 (1.7)	2.2 (1.1)	1.23 (1.06–1.42)	0.005
Characteristics of ABBSI				
Tigecycline MIC 1–2 mg/mL	41 (59.4%)	41 (50.0%)	1.32 (0.82–2.14)	0.255
Acquired in the intensive care unit	51 (73.9%)	63 (76.8%)	1.08 (0.63–1.85)	0.778
Polymicrobial bloodstream infection	16 (23.2%)	20 (24.4%)	1.11 (0.63–1.94)	0.720
Source of bloodstream infection				
Lung	44 (63.8%)	41 (50.0%)	1.61 (0.99–2.64)	0.056
Intra-abdomen	13 (18.8%)	17 (20.7%)	1.01 (0.55–1.85)	0.969
Skin and soft tissue	6 (8.7%)	10 (12.2%)	0.62 (0.27–1.42)	0.257
Mediastinal and pleural	2 (2.9%)	6 (7.3%)	0.44 (0.11–1.80)	0.255
Catheter-related	3 (4.3%)	7 (8.5%)	0.45 (1.11–1.82)	0.259
Others	1 (1.4%)	1 (1.2%)	1.10 (0.15–7.89)	0.928
Fever	45 (65.2%)	52 (63.4%)	1.00 (0.61–1.64)	0.996
Febrile neutropenia	2 (2.9%)	3 (3.7%)	0.82 (0.26–2.61)	0.738
Acuity score at initial presentation				
APACHE II score, mean (SD)	19.9 (7.3)	17.2 (6.1)	1.03 (1.01–1.07)	0.048
Treatment and support				
Use of invasive ventilation	47 (68.1%)	54 (65.9%)	1.28 (0.79–2.10)	0.310
Use of renal replacement therapy	21 (30.7%)	21 (25.6%)	1.12 (0.67–1.88)	0.652
Inadequate source control	20 (29.0%)	14 (17.1%)	1.76 (1.05–2.94)	0.031
Appropriate empirical therapy	7 (10.1%)	10 (12.2%)	0.86 (0.39–1.88)	0.703
HD tigecycline	30 (43.5%)	33 (40.2%)	1.15 (0.71–1.84)	0.577
Duration of tigecycline treatment (days), mean (SD)	11.5 (4.7)	12.4 (4.6)	0.96 (0.90–1.01)	0.102
Concomitant use of other active antibiotics				
None	3 (4.3%)	7 (8.5%)	0.59 (0.19–1.88)	0.374
Beta-lactam/beta-lactamase inhibitor	34 (49.3%)	43 (52.4%)	0.84 (0.53–1.35)	0.475
Carbapenem	19 (27.5%)	22 (26.8%)	1.07 (0.63–1.81)	0.813
Fluoroquinolone	8 (11.5%)	7 (8.5%)	1.69 (0.80–3.54)	0.163

Note: Data are presented as n (%) or mean (SD).
Abbreviations: HR, hazard ratio; CI, confidence interval; ABBSI, *Acinetobacter baumannii* bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation; MIC, minimum inhibitory concentration.

A higher tigecycline dose may be associated with a higher concentration in intra-abdominal, mediastinal, and pleural tissue, as well as skin and soft tissue. Previous reports have demonstrated the effects of HD tigecycline on decreasing the mortality associated with skin and soft tissue infections and complicated intraabdominal infections,[9,10] spondylodiscitis,[11] and urinary tract infections.[18] Therefore, all of these findings indicate that HD treatment with tigecycline can provide improved therapeutic effects through increased bloodstream and tissue concentrations.

In the present study, pneumonia-associated AB bacteremia had a higher mortality rate and was difficult to treat. Similar to these findings, another study has reported that patients with hospital-acquired pneumonia-related AB bacteremia had a significantly higher incidence of antibiotic resistance, higher frequency of ICU treatment, longer hospital stay, and higher mortality rate than those who did not have pneumonia.[19] Additionally, another study has also shown ABBSI with a primary respiratory source was associated with an increased risk of 30-day mortality.[20] A meta-analysis showed that in

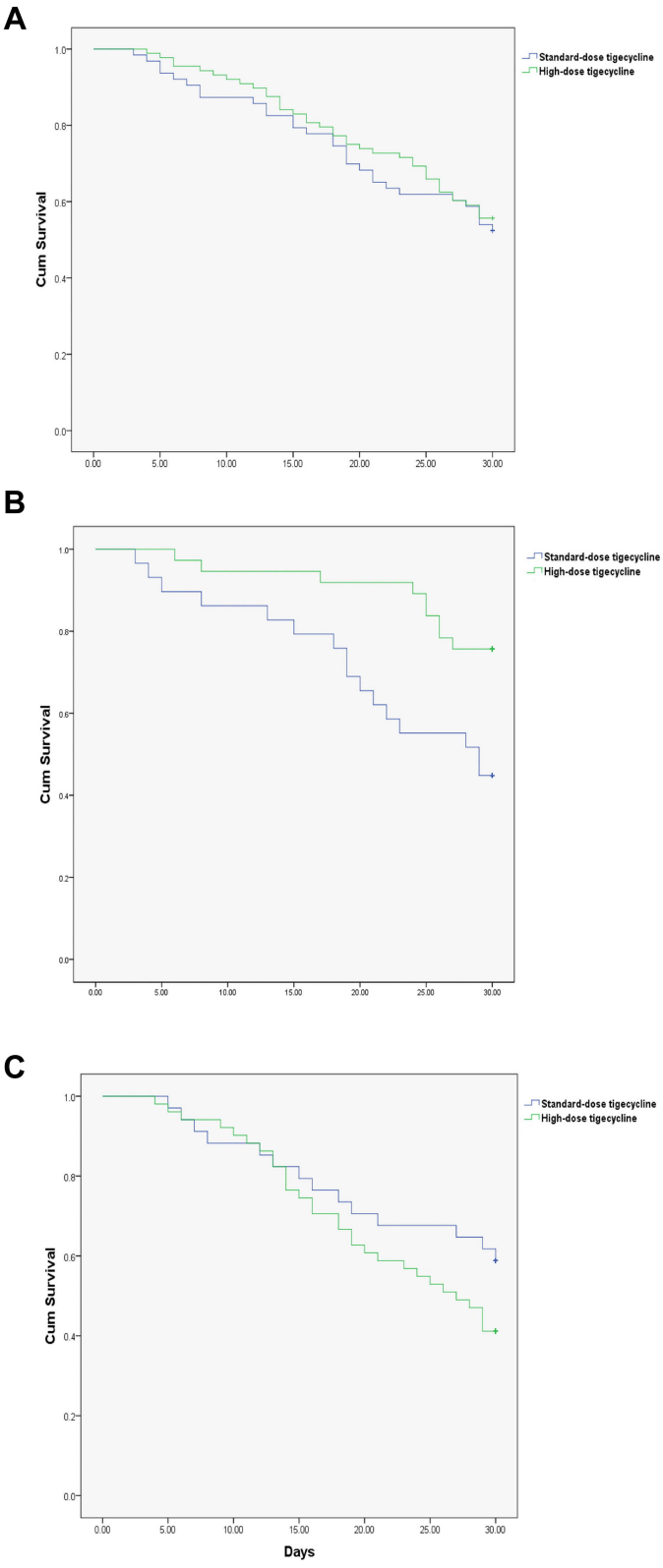

Figure 1 Kaplan–Meier survival analysis stratified by high-dose tigecycline treatment and standard-dose tigecycline treatment. The 30-day survival rate was calculated. (**A**) Kaplan–Meier analysis of survival in all patients with extensively drug-resistant (XDR) *Acinetobacter baumannii* bloodstream infection (ABBSI). (**B**) Kaplan-Meier analysis of survival in the non-pulmonary-infection-related ABBSI subgroup. (**C**) Kaplan–Meier analysis of survival in the pulmonary-infection-related ABBSI subgroup.

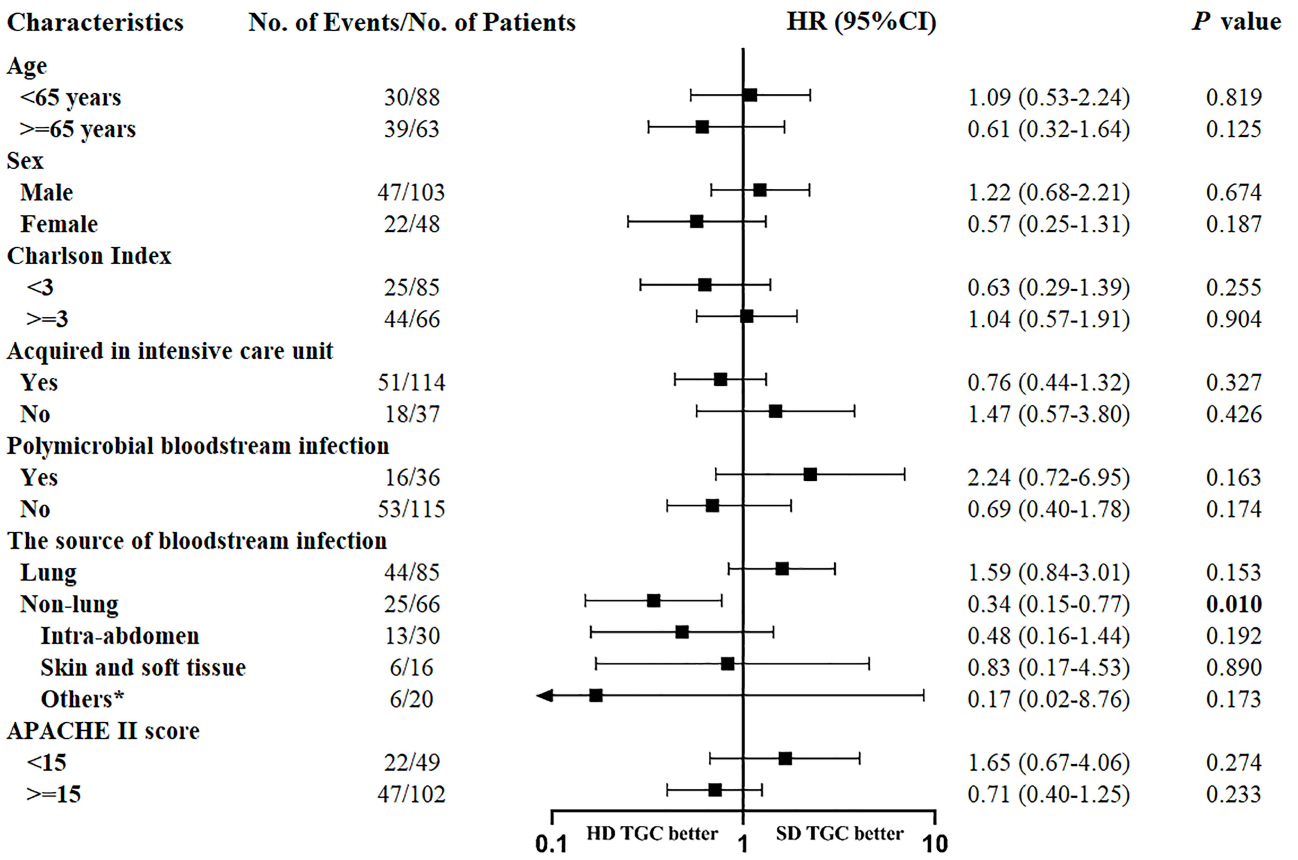

Figure 2 Subgroup analysis of the impact of high-dose tigecycline on 30-day survival in the intention-to-treat population. Hazard ratios (HRs) for 30-day survival are compared between the high-dose tigecycline and standard-dose tigecycline groups.
Abbreviations: HG, high-dose; SD, standard-dose; TGC, tigecycline.

treatment of pneumonia caused by multidrug-resistant *A. baumannii* (MDR-AB), SD tigecycline was associated with lower microbiological eradication rate and did not affect the clinical cure rate and mortality.[21] However, the impact of HD tigecycline treatment with regard to pneumonia-associated mortality is controversial.[7,8] In studies that did not distinguish between AB and other pathogens, HD tigecycline was associated with better clinical prognosis.[7,8] In previous studies in patients with ventilator-associated pneumonia and BSI caused by MDR bacteria, HD tigecycline was also associated with higher clinical effective rate and better microbiological eradication, and was relatively safe, though did not improve 28-day mortality.[22,23] However, in patients with pneumonia who had MDR-AB infection, HD tigecycline was related with a higher microbial eradication rate, but it was not related with lower crude mortality.[24] This finding may be explained by the low concentration of tigecycline in the epithelial lining fluid[25] and difficulties in microbial eradication in airways. Microbial colonization may still exist in the airway even after tigecycline treatment. Our previous study demonstrated that consistent colonization of XDR-AB in the upper airway is associated with more consequent XDR-AB infections and lower overall survival of critically ill patients.[26]

Notably, in our study, inadequate source control was identified as an independent factor associated with 30-day mortality in non-pneumonia-related ABBSI. Source control aims to eliminate infectious foci, the methods of which include removal of any preexisting devices thought to be the source of BSI, or documented interventions using appropriate decompression, debridement, drainage, and other surgical procedures to control the source of infection.[27] The results of our study special addressed the importance of adequate source control in non-pneumonia-related infections, including intra-abdomen, skin and soft tissue, mediastinal and pleural, and catheter-related bloodstream infections. The impact of source control in those infectious diseases has been

Table 4 Univariate and Multivariate Analysis of 30-Day Mortality in Pneumonia-Related *Acinetobacter baumannii* Bloodstream Infection

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline				
Age (years)	1.02 (0.99–1.04)	0.092	1.01 (0.99–1.03)	0.314
Male sex	0.83 (0.46–1.52)	0.544		
Charlson index	1.20 (1.02–1.40)	0.027	1.04 (0.85–1.27)	0.697
Characteristics of ABBSI				
Tigecycline MIC 1–2 mg/mL	1.11 (0.61–2.00)	0.738		
Polymicrobial bloodstream infection	1.00 (0.48–2.09)	0.991		
Acquired in the intensive care unit	1.28 (0.63–2.60)	0.488		
Fever	0.85 (0.45–1.61)	0.623		
Febrile neutropenia	0.97 (0.30–3.12)	0.953		
Acuity score at initial presentation				
APACHE II score	1.05 (1.01–1.10)	0.028	1.05 (1.01–1.10)	0.048
Treatment and support				
Use of invasive ventilation	0.91 (0.47–1.76)	0.777		
Use of renal replacement therapy	1.41 (0.74–2.71)	0.298		
Appropriate empiric therapy	0.67 (0.24–1.87)	0.441		
HD tigecycline	1.59 (0.84–2.99)	0.156	1.44 (0.68–3.05)	0.335
Duration of tigecycline treatment (days)	0.98 (0.91–1.05)	0.540		
Concomitant use of other active antibiotics				
None	0.52 (0.13–2.14)	0.363		
Beta-lactam/beta-lactamase inhibitor	0.98 (0.54–1.77)	0.937		
Carbapenem	0.70 (0.45–1.17)	0.092	0.62 (0.31–1.26)	0.186
Fluoroquinolone	1.82 (0.71–4.63)	0.211		
Inadequate source control	1.63 (0.86–3.07)	0.133		

Abbreviations: HR, hazard ratio; CI, confidence interval; ABBSI, *Acinetobacter baumannii* bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation; MIC, minimum inhibitory concentration.

demonstrated in previous studies.[28–31] Foci of infection are readily amenable to source control in the above non-pneumonia-related infections,[32] instead of pneumonia-related infections. Furthermore, clinical experience suggests that, without adequate source control, some more severe presentations will not stabilize or improve despite rapid resuscitation and provision of appropriate antimicrobials.[28,32,33] In patients with severe sepsis and septic shock, source control for abdominal, urinary, and soft-tissue infections within 12 hours was reported to reduce mortality in hospital.[28] Thus, adequate source control is a key measure in systematic infection management. And whether the beneficial effects are time dependent or more significant in specific sources of bacteremia still needs more clinical evidence.

We need to mention some of the limitations of this study. First, the study is limited by the observational nature of the data. Second, further research is needed regarding the effectiveness and potential toxicity of HD tigecycline, as the findings reported so far for the HD tigecycline regimen are contradictory.

Conclusions

In conclusion, a tigecycline dose that is twice its standard dose is better for the treatment of XDR-AB only in BSI associated with non-pulmonary infection. Our findings indicate that the HD tigecycline regimen is not beneficial for the treatment of BSI associated with pulmonary infection.

Table 5 Univariate and Multivariate Analysis of 30-Day Mortality in Non-Pneumonia-Related *Acinetobacter baumannii* Bloodstream Infection

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline				
Age (years)	1.02 (0.99–1.26)	0.093	1.01 (0.71–1.44)	0.663
Male sex	2.75 (0.82–9.20)	0.097	3.34 (0.92–12.16)	0.067
Charlson index	1.52 (1.15–1.99)	0.003	1.01 (0.71–1.44)	0.970
Characteristics of ABBSI				
Tigecycline MIC 1–2 mg/mL	1.20 (0.86–4.64)	0.107		
Polymicrobial bloodstream infection	0.98 (0.41–2.34)	0.959		
Acquired in the intensive care unit	0.62 (0.27–1.44)	0.264		
Source of bloodstream infection				
Intra-abdomen	1.61 (0.73–3.53)	0.235		
Skin and soft tissue	0.81 (0.32–2.04)	0.658		
Mediastinal and pleural	0.58 (0.14–2.47)	0.461		
Catheter-related	0.72 (0.22–2.40)	0.592		
Others	1.11 (0.26–4.73)	0.885		
Fever	1.01 (0.46–2.22)	0.985		
Febrile neutropenia	NA	NA		
Acuity score at initial presentation				
APACHE II score	1.10 (1.03–1.17)	0.006	1.12 (1.15–1.20)	0.001
Treatment and support				
Use of invasive ventilation	1.03 (0.46–2.30)	0.938		
Use of renal replacement therapy	0.98 (0.42–2.26)	0.953		
Appropriate empiric therapy	1.24 (0.37–4.13)	0.730		
HD tigecycline	0.35 (0.15–0.79)	0.012	0.16 (0.05–0.54)	0.003
Duration of tigecycline treatment (days)	0.90 (0.80–1.16)	0.108		
Concomitant use of other active antibiotics				
None	0.61 (0.08–4.51)	0.628		
Beta-lactam/beta-lactamase inhibitor	0.73 (0.33–1.59)	0.423		
Carbapenem	1.77 (0.78–4.01)	0.172		
Fluoroquinolone	1.58 (0.47–5.30)	0.456		
Inadequate source control	2.27 (0.97–5.28)	0.058	4.27 (1.16–15.8)	0.029

Abbreviations: HR, hazard ratio; CI, confidence interval; ABBSI, *Acinetobacter baumannii* bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation; MIC, minimum inhibitory concentration.

Abbreviations

AB, *Acinetobacter baumannii*; ABBSI, *Acinetobacter baumannii* bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CI, confidence interval; HD, high-dose; HR, hazard ratio; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; SD, standard-dose; XDR, extensively drug-resistant.

Data Sharing Statement

The raw data supporting the conclusions of this article are available from the corresponding authors on reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Qilu Hospital of Shandong University (KYLL-2015KS-170). Informed consent was obtained for each participant.

Author Contributions

Hui Han and Weidong Qin contributed to data analysis and manuscript preparation. Yue Zheng contributed to manuscript preparing. Dongming Cao, Haining Lu and Lu Zhang

contributed to information acquisition and data analysis. Yi Cui and Yuanyuan Hu participated in data analysis. Wei Li, Haipeng Guo and Dawei Wu helped information collection. Hao Wang and Yuguo Chen contributed to study design and manuscript preparation. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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