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Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens

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Abstract

The off-label uses of tigecycline (TGC) to treat ventilator-associated pneumonia (VAP) have aroused worldwide concerns. The efficacy about TGC has been recently reported. However, the adverse events (AEs) remain controversial. Our study aims to analyze the safety of the high-dose (HD) regimens in the treatment of VAP due to multidrug-resistant (MDR) pathogens.

The clinical data of 134 patients who were diagnosed with VAP from January 2013 to December 2015 in the NeuroScience Care Unit (NCU) were analyzed retrospectively. The incidence and the occurrence time of AEs, 28-day mortality, and the factors of clinical effectiveness were explored.

A total of 54 patients received the standard dose group (SD), 69 in the HD, and 11 in the nonstandard HD group (NHD). Acinetobacter baumannii were the main pathogenic bacteria. There was no statistic difference in the incidence of AEs and the 28-day mortality among the 3 groups ($P > .05$). Total bilirubin (TBIL) increased significantly after SD of TGC treatment ($P = .004$). Liver dysfunction occurred the latest (10.83 ± 7.08), not in the duration of HD group (9.63 ± 3.92), whereas in the SD group (13.00 ± 7.57) and NHD group (12.64 ± 3.70). Patients with septic shock, MODS, and higher APACHE II score were of high risk in mortality. The HD group was associated with higher clinical effective rate and bacteria clearance rate.

HD TGC was relatively safe and tolerable in ICU patients. The risk of side effects was related to the TGC duration, although not increased as the dosage rose. Full course of the HD regimen was associated with better outcomes for the treatment of VAP patients, especially for the MDR gram-negative bacilli infection. Inappropriate antimicrobial treatment might lead to clinical treatment failure.

Abbreviations: AE = adverse events, ALT = alanine aminotransferase, APACHE = the Acute Physiology and Chronic Health Evaluation, ARDS = acute respiratory distress syndrome, AUC = area under the plasma concentration versus time, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CRRT = continuous renal replacement therapy, DHHS-CTCAE = Department of Health and Human Services—common terminology criteria for adverse events, ELF = epithelial lining fluid, ESBLs = extended-spectrum β-lactamase, FDA = Food and Drug Administration, HAP = hospital-acquired pneumonia, HD = high-dose, ICU = intensive care units, IIAT = inappropriate antimicrobial treatment, MDR = multidrug resistance, MIC = minimal inhibitory concentration, MODS = multiple organ dysfunction syndrome, MRSA = Methicillin-resistant *Staphylococcus aureus*, MV = mechanical ventilation, NHD = nonstandard dose group, NICU = neurological intensive care unit, PCT = procalcitonin, PDR = pandrug resistance, SD = standard dose, TBIL = total bilirubin, TGC = tigecycline, T_{max} = the body temperature peak, VAP = ventilator-associated pneumonia, VRE = vancomycin-resistant enterococci, WBC = white blood cell count, XDR = extensively drug resistance.

Keywords: Acinetobacter baumannii, adverse events, high-dose tigecycline, multidrug-resistant, ventilator-associated pneumonia

1. Introduction

Ventilator-associated pneumonia (VAP) is one of the most common complications in the process of mechanical ventilation (MV), which seriously affects the prognosis of critically ill patients. The scarcity of new antibiotics for VAP infections with drug-resistant strains is a highly complicated issue. Tigecycline (TGC), the last-resort antibiotic, was intended to alleviate this stress.

TGC, with broad antibiotic spectrum and better permeability to lung tissue, might be an alternative worth considering for VAP due to multidrug-resistant (MDR) gram-negative bacteria.[1–3] TGC is currently approved by the US Food and Drug Administration (FDA) for complicated skin and skin structure infections, complicated intraabdominal infections, and community-acquired pneumonia at a dose of 50 mg twice daily after a 100 mg loading dose. Nevertheless, it is not approved for hospital acquired pneumonia (HAP), including VAP.[4] A recent FDA black-boxed warning announced an increased TGC-attributable mortality in the treatment of HAP, especially in VAP.[5] However, a recent meta-analysis showed that there was no significant difference in mortality when TGC treated for HAP.[6] Some researchers also found that as the dosage increased, TGC showed good pharmacokinetic characteristics and better clinical outcomes.[7] Similar safety profile of the higher dosage was also identified.[8] The clinical data of VAP patients, who had no choice

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but to use TGC for the treatment of MDR, were retrospectively analyzed to further explore the safety and efficacy of high-dose (HD) TGC.

2. Materials and methods

2.1. Study design and population

All patients who received TGC for VAP consecutively admitted to our NeuroScience Care Unit (NCU) between January 2013 and December 2015 were included in the Second Affiliated Hospital of Zhejiang University School of Medicine, a 2000-bed tertiary care teaching hospital in the People's Republic of China. According to the different dosages of TGC, the dosage groups were divided into standard dose group (SD; 50 mg every 12 hours after a 100 mg loading dose intravenous infusion), HD group (100 mg every 12 hours intravenous infusion of full course), and nonstandard dose group (NHD; 100 mg for 3–5 days at first, followed by 50 mg every 12 hours intravenous infusion). All patients were treated with combined administration on the basis of TGC, including cefoperazone/sulbactam, piperacillin/tazobactam, imipenem, and meropenem. TGC treatment lasting <3 days was not included in the study.

2.2. Data collection

Data were extracted retrospectively from patients' electronic medical record, including sex, age, pathogenic strains, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, albumin level, basic diseases, septic shock, continuous renal replacement therapy (CRRT), multiple organ dysfunction syndrome (MODS), chronic organ insufficiencies, previous surgery, concomitant infection, combined therapies, duration of hospitalization before NCU, and length of mechanical ventilation (MV) before NCU. Safety was assessed with the incidence of adverse events (AEs) and 28-day mortality in 3 TGC groups. The clinical effective rate, microbiological eradication rate, and hospitalization time were evaluated for the efficacy. White blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT) were detected in different TGC dosage regimens by extracting 5 mL of venous blood before and 3 to 5 days after TGC treatment.

2.3. Definitions

The diagnosis of VAP was defined as "a new or progressive pulmonary infiltration occurring >48 hours after receiving invasive MV or within 48 hours after extubation, plus at least 2 of the following: temperature >38.0 or <36.0°C; leukocytosis or leukopenia; and purulent tracheal secretions or sputum," as recommended by the ATS/IDSA 2016 criteria.[9]

Septic shock is consistent with the "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016." Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.[10]

The body temperature peak (T_{max}) drop time is defined as the days when the maximum value of the body temperature drops for the first time during the treatment of TGC, and the body temperature starts to drop daily.

The initial antibiotic treatment (that used before bacterial culture and sensitivity test come out) is inappropriate (IIAT) when it did not include any sensitive agents or not cover pathogenic bacteria spectrum, and used within 24 hours after a clinical diagnosis of VAP.

2.4. Microbiology analysis

TGC susceptibility test results follow the "Tigecycline Susceptibility Test in Vitro Procedures: Expert Consensus." Isolates of Acinetobacter baumannii and Enterobacteria bacteria were considered susceptible if the MIC was ≤2 mg/L and resistant if the MIC was ≥8 mg/L and intermediary if the MIC was 4 mg/L.[11] MDR was defined as nonsusceptibility to 3 common agent or more antimicrobial categories. Extensive drug resistance (XDR) was defined as susceptibility to only 1 agent or 2 antimicrobial categories and pandrug resistance (PDR) was defined as nonsusceptibility to all agents in all antimicrobial categories.[12]

2.5. Clinical efficacy

Clinical effective: chest radiographs improved or no progress, whereas the clinical symptoms and signs improved significantly. *Clinical ineffective*: chest radiographs progress, whereas symptoms and signs intensified.

2.6. Microbiological efficacy

Microbiological eradication: pathogenic bacteria were not cultured in sputum or bronchoalveolar lavage fluid at the end of TGC treatment. *Microbiological not eradication*: pathogenic bacteria were still cultured or new drug-resistant bacteria were cultured out at the end of TGC treatment.

2.7. Statistical analysis

For continuous variables, the one Sample Kolmogorov–Smirnov test was used to value the variables distribution. The data with a non-normal distribution were assessed with Kruskal–Walis *H* test and the median and interquartile range (IQR) were given. The data with a normal distribution were expressed as the mean ± standard deviation ($\bar{x} \pm s$) and assessed with Student *t* test or one-way ANOVA, as appropriate, whereas pairwise comparisons among groups with post hoc multiple comparisons (LSD or Scheffe method). Paired samples test was used for comparing the clinical variables before and after TGC treatment in each group. Categorical variables were presented as proportions and were analyzed with the use of the χ^2 test or Fisher exact test, when appropriate. A $P < .05$ was considered statistically significant, and adjusted for pairwise comparisons. The crude odds ratio (OR) and 95% CI were calculated for each variable. We included all variables in the multivariable logistic regression if they achieved a *P* value of less than or equal to .2 at the univariate analysis. The backward conditional stepwise logistic regression method was used to select variables for inclusion in the final model. The Hosmer–Lemeshow goodness-of-fit test and the receiver-operating characteristic (ROC) curve analysis were used to assess the goodness of the logistic final model. All data were entered into a database and analyzed using SPSS 13.0 software package (SPSS Inc.,Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 134 patients altogether diagnosed with VAP due to MDR gram-negative bacilli-received TGC treatment. Eighty-one

percent (n = 109) of the protopathy was related to Nervous System Disease (cerebral hemorrhage [n = 43]; brain trauma [n = 38]; cerebral infarction [n = 13]; brain tumor [n = 9]; viral encephalitis [n = 3]; epilepsy [n = 2]; acute transverse myelitis [n = 1]). Eight percent of cases (n = 11) was related to respiratory system problem (severe pneumonia [n = 5]; chronic obstructive pulmonary disease [COPD] [n = 4]; lung cancer [n = 1]; obstructive sleep apnea syndrome [n = 1]), whereas 4% of cases (n = 5) was related to the coronary atherosclerotic heart disease. Of the remaining 7% patients (n = 9), 2 (colon cancer [n = 1]; adhesive intestinal obstruction ([= 1]) were postoperative and 7 the remaining (multiple injuries [n = 2]; drowning [n = 1]; organophosphorus poisoning [n = 1]; allergic purpura [n = 1]; renal failure [n = 1]; septic shock [n = 1]). A total of 99 patients were male and 35 female, aged 15 to 94 years, with an average of (60.80 ± 18.10) years. Duration of TGC treatment was 4 to 53 days, the average (11.39 ± 6.27). A total of 54 patients received the SD of TGC, 69 the HD, and 11 the NHD. Acinetobacter baumannii was isolated in 104 and Klebsiella pneumoniae in 40, both of them in 32.

3.2. Drug safety

The 3 groups of VAP patients treated with TGC were similar in their basic disease, complications, severity of disease, and combination regimens (Table 1). Safety and AEs are determined by biochemical abnormalities recorded in medical records and the classification of commonly used terms for AEs (DHHS-CTCAE V.3.0). The severity of AEs is classified from 1 to 5 grade.[13]

A total of 35 patients have suffered side effects, 34.3% (12 of 35) diarrhea, 51.4% (18 of 35) hepatic injury, and 14.3% (5 of 35) of coagulation disorders. The research showed that liver damage and gastrointestinal symptoms were the most common adverse reactions. The incidence of AEs was similar with the 3 groups ($P > .05$) (Table 2). Furthermore, the classification of impaired liver function was further compared between alanine aminotransferase (ALT) and total bilirubin (TBIL). By analyzing the occurrence time of AEs, it was found that liver dysfunction occurred the latest (10.28 ± 6.25), not in the duration of HD group (9.63 ± 3.92), whereas in the SD group (13.31 ± 8.21) and NHD group (12.64 ± 3.70).

Table 1

Clinical characteristics of the 134 patients with VAP in 3 tigecyline groups.

Variable	SD TGC group (n = 54)	HD TGC group (n = 69)	NHD TGC group (n = 11)	*P*
Age, y, $\bar{x} \pm s$	64.59 ± 19.70	58.26 ± 17.50	58.09 ± 9.31	.137
Male, n (%)	38 (70.4)	52 (75.4)	9 (81.8)	.759
APACHE II score, $\bar{x} \pm s$	19.59 ± 5.77	18.38 ± 4.73	17.45 ± 4.06	.288
Albumin, g/L	31.96 ± 5.44	30.03 ± 5.54	31.36 ± 5.29	.150
Septic shock, n (%)	13 (24.1)	14 (20.3)	1 (9.1)	.618
CRRT, n (%)	13 (24.1)	8 (11.6)	0 (0)	.071
Aspiration pneumonia, n (%)	13 (24.1)	15 (21.7)	0 (0)	.205
Hernia, n (%)	12 (22.2)	13 (18.8)	3 (27.3)	.729
MODS, n (%)	9 (16.7)	11 (15.9)	0 (0)	.439
Length of stay before NICU, d, median (IQR)	4.5 (0.25, 16)	4 (1, 13)	7 (5, 11)	.721
Length of MV before NICU, d, median (IQR)	1 (0, 9)	1 (0, 6)	7 (5, 11)	.070
VAP onset time, d, $\bar{x} \pm s$	7.26 ± 2.62	8.46 ± 3.82	9.18 ± 2.68	.089
Comorbidities, n (%)				
COPD	7 (13.0)	2 (2.9)	0 (0)	.086
Diabetes mellitus	12 (22.2)	10 (14.5)	1 (9.1)	.469
Cardiac insufficiency	9 (16.7)	11 (15.9)	0 (0)	.439
Renal insufficiency	17 (31.5)	11 (15.9)	1(9.1)	.073
Malignancies	7 (13.0)	3 (4.3)	0(0)	0.155
long-term glucocorticoid treatment of large dosage	7 (13.0)	2 (2.9)	1(9.1)	0.091
Combination regimen, n (%)				
Cefoperazone/sulbactam	21 (38.9)	20 (29.0)	3(27.3)	.465
Piperacillin/tazobactam	1 (1.9)	3 (4.3)	2(18.2)	.094
Meropenem	12 (22.2)	15 (21.7)	3(27.3)	.903
Imipenem	6 (11.1)	4 (5.8)	1 (9.1)	.486
Invasive operation, n (%)				
Craniotomy	22 (40.7)	31 (44.9)	8 (72.7)	.165
Ventricular/lumbar cistern drainage	10 (18.5)	14 (20.3)	1 (9.1)	.840
Other operations	5(9.3)	7 (10.1)	0 (0)	.812
Microbiology, n (%)				
Acinetobacter baumannii	42 (77.8)	52 (75.4)	10 (90.9)	.603
Klebsiella pneumoniae	23 (42.6)	21 (30.4)	4 (36.4)	.352
Other bacteria	8 (14.8)	14 (20.3)	0 (0)	.254
Concomitant infection, n (%)				
Bloodstream infection	19 (35.2)	17 (24.6)	2 (18.2)	.369
Urinary tract infection	4 (7.4)	3(4.3)	0 (0)	.837
Intestinal infection	3 (5.6)	5(7.2)	2 (18.2)	.338
Initial antibiotic therapy, n (%)				
Appropriate	36 (66.7)	51 (73.9)	8 (72.7)	.651
Inappropriate	18 (33.3)	18 (26.1)	3 (27.3)	

APACHE = the Acute Physiology and Chronic Health Evaluation, COPD = chronic obstructive pulmonary disease, CRRT = continuous renal replacement therapy, HD = high-dose, MODS = multiple organ dysfunction syndrome, MV = mechanical ventilation, NHD = nonstandard dose group, NICU = neurological intensive care unit, SD = standard dose, VAP = ventilator-associated pneumonia.

Table 2

Comparison the cases and the occurrence time of adverse events (AEs) in 3 tigecycline groups.

Adverse events	Total	SD group (n = 54)	HD group (n = 69)	NHD group (n = 11)	*P*
Diarrhea, n (%)	12 (9.0)	6 (11.1)	5 (7.2)	1 (9.1)	.731
Hepatic injury, n (%)	18 (13.4)	9 (16.7)	9 (13.0)	0 (0)	.406
ALT increased, n (%)	8 (6.0)	4 (7.4)	4 (5.8)	0 (0)	.866
TBIL increased, n (%)	10 (7.5)	5 (9.3)	5 (7.2)	0 (0)	.789
Coagulation disorders, n (%)	5 (3.1)	3 (5.6)	2 (2.9)	0 (0)	.775
Diarrhea, d, $\overline{x} \pm s$	5.83 ± 3.16	5.33 ± 3.88	5.40 ± 1.14	11.00	.249
Hepatic injury, d, $\overline{x} \pm s$	10.28 ± 6.25	11.89 ± 6.19	8.67 ± 6.23		.287
ALT increased, d, $\overline{x} \pm s$	10.00 ± 7.98	10.25 ± 7.32	9.75 ± 9.74		.937
TBIL increased, d, $\overline{x} \pm s$	10.50 ± 4.91	13.2 ± 5.63	7.8 ± 2.05		.079
Coagulation disorders, d, $\overline{x} \pm s$	7.00 ± 3.08	6.67 ± 4.04	7.50 ± 2.12		.812

ALT = alanine aminotransferase, HD = high-dose, NHD = nonstandard dose group, SD = standard dose, TBIL = total bilirubin.

Table 3

Comparison the changes of ALT and TBIL in each group, $\overline{x} \pm s$.

Groups	Laboratory indicators	Before treatment	After treatment	*P*
SD group	ALT (U/L)	68.00 ± 64.88	395.75 ± 451.97	.243
	TBIL (mmo/L)	18.20 ± 17.67	58.36 ± 13.48	.004
HD group	ALT (U/L)	69.75 ± 81.37	128.75 ± 106.52	.064
	TBIL (mmo/L)	17.66 ± 4.61	47.7 ± 24.84	.079

ALT = alanine aminotransferase, HD = high-dose, SD = standard dose, TBIL = total bilirubin.

It should be noted that TBIL increased significantly after SD of TGC treatment ($P = .004$), instead of no numerical difference in HD regimens ($P > .05$) (Table 3). Moreover, no difference was observed between the 2 groups in the changes of ALT and TBIL before and after TGC treatment ($P > .05$) (Table 4), namely, that the use of high-dose TGC might not deteriorate the incidence of liver damage.

In addition, 5 patients altogether with abnormal coagulation were observed in this study, of which 3 patients combined with cefoperazone/sulbactam. It was reported that fibrinogen decline and vitamin K deficiency might be the cause of the abnormal coagulation function.[14,15] As the subjects were mostly sedation, the clinical common nausea and vomiting were not observed in this study. No other adverse reactions such as pancreatitis and hypoglycemia were found, either.[16]

Further multivariate logistics regression analysis showed that factors such as sepsis shock, hypoproteinemia, and APACHE II score had no significant difference in the incidence of side effects, indicating those were not the risk factors for AEs ($P > .05$) (Annex 1, http://links.lww.com/MD/C502).

3.3. Clinical efficacy

The results showed that the clinical effective rate in the HD group (48/69, 69.6%) was higher than that in the SD group (19/54, 35.2%) and the NHD group (5/11, 45.5%) ($\chi^2 = 14.73$, $P = .001$); HD group manifested higher total bacterial clearance rate (37/69, 53.6%) than the SD group (17/54, 31.5%) and the NHD group (4/11, 36.4%) ($\chi^2 = 5.78$, $P = .04$). Moreover, the clearance of Acinetobacter baumannii (27/69, 51.9%) and Klebsiella pneumoniae (14/69, 66.7%) in HD group was both statistically significant ($P < .05$). It can also be seen that high dosage for the clearance of Klebsiella pneumoniae was superior to the Acinetobacter baumannii (66.7% vs 51.9%). The duration of HD regimen (9.63 days, $P = .004$), length of stay in NICU (28.97 days, $P = .011$), and MV time (16.79 days, $P = .011$) were numerically shorter than the other groups. Therefore, the results showed that higher dosage in whole duration was associated with better efficacy (Table 5).

Table 4

The changes of ALT and TBIL between the HD group and the SD group, $\overline{x} \pm s$.

Laboratory indicators		SD group	HD group	*P*
Before	ALT (U/L)	68.00 ± 64.88	69.75 ± 81.37	.974
	TBIL (mmo/L)	18.20 ± 17.67	17.66 ± 4.61	.949
After	ALT (U/L)	395.75 ± 451.97	128.75 ± 106.52	.294
	TBIL (mmo/L)	58.36 ± 13.48	47.7 ± 24.84	.423

ALT = alanine aminotransferase, HD = high-dose, SD = standard dose, TBIL = total bilirubin.

3.4. Comparison and analysis inflammatory indicators

The changes of inflammatory indicators were conducted in WBC, CRP, and PCT in ICU patients in each group, which was similar in the 3 groups before TGC usage (Annex 2, http://links.lww.com/MD/C502). It should be noted that CRP changes showed an obviously statistical significance only in the HD group ($P < .01$). The time required for CRP decreased by 50% (3.93 ± 1.93) in the HD group was shorter than that in the control groups, and the differences were numerically significant ($P < .01$). However, there was no significant difference among the 3 groups in the time required for the inflammatory markers to back to normal (Table 6).

3.5. Predictors of 28-day mortality in patients with VAP

There was no difference in the 28-day mortality rate between these groups ($P > .05$) (Table 5). Potential prognostic factors for 28-day mortality were evaluated by means of univariate analysis (Annex 3, http://links.lww.com/MD/C502). The logistics regression analysis showed that patients with septic shock (OR = 0.33, 95% CI, 0.12–0.92), MODS (OR = 0.26, 95% CI, 0.08–0.83), and higher APACHE II score (OR = 0.89, 95% CI, 0.80–0.98) were of high risk in mortality, which is consistent with related report that the HD of TGC did not increase clinical mortality[17] (Table 7).

3.6. Predictors of clinical effectiveness in patients with VAP

According to the clinical efficacy, 134 cases of VAP patients were divided into 2 groups, namely, clinical effective (72 cases) and

Table 5

Comparison of clinical efficacy in 3 tigecyline groups.

Clinical efficacy	SD group (n = 54)	HD group (n = 69)	NHD group (n = 11)	P
28-d mortality rate, n (%)	18 (33.3)	13 (18.8)	2 (18.2)	.179
Clinical effective rate, n (%)	19 (35.2)^{AB}	48 (69.6)^{A}	5 (45.5)^{A}	.001
Microbiological eradication rate, n (%)	17 (31.5)^{ab}	37 (53.6)^{a}	4 (36.4)^{a}	.041
Acinetobacter baumannii, n (%)	11 (26.2)^{ab}	27 (51.9)^{a}	4 (40.0)^{b}	.038
Klebsiella pneumoniae, n (%)	7 (30.4)^{ab}	14 (66.7)^{a}	2 (50.0)^{b}	.040
TGC duration, d, $\overline{x} \pm s$	13.31 ± 8.21^{A}	9.63 ± 3.92^{B}	12.64 ± 3.70^{AB}	.004
Tmax drop time, d, $\overline{x} \pm s$	3.25 ± 2.63^{Aa}	1.16 ± 0.53^{Bb}	1.55 ± 1.21^{Bb}	<.001
Temperature normal time, d, $\overline{x} \pm s$	8.56 ± 6.18^{A}	5.61 ± 2.99^{B}	8.18 ± 3.68^{AB}	.005
Hospitalization time, d, $\overline{x} \pm s$	62.80 ± 57.41^{a}	40.02 ± 20.44^{b}	51.60 ± 23.72^{ab}	.012
NICU hospital stay, d, $\overline{x} \pm s$	44.06 ± 37.00^{a}	28.97 ± 14.61^{b}	42.80 ± 26.42^{ab}	.011
MV time, d, $\overline{x} \pm s$	26.63 ± 23.66^{a}	16.79 ± 7.65^{b}	23.50 ± 10.06^{ab}	.011

The 3 groups conduct multiple comparisons. The same column with different capital letters showed significant difference between groups ($P < .01$); those with different lower case letters indicated significant difference between groups ($P < .05$); those with the same lower case letters indicated that there was no significant difference between groups ($P > .05$).
HD = high-dose, MV = mechanical ventilation, NHD = nonstandard dose group, NICU = neurological intensive care unit, SD = standard dose, TGC = tigecycline, T_{max} = the body temperature peak.

Table 6

Comparison of inflammatory index among the 3 groups, $\overline{x} \pm s$.

Inflammatory index		SD group	HD group	NHD group	P
Before	WBC ($\times 10^9$/L), $\overline{x} \pm s$	10.75 ± 6.24	11.32 ± 6.59	9.91 ± 3.96	.745
	CRP (mg/L), $\overline{x} \pm s$	88.81 ± 69.89	101.88 ± 70.14	98.45 ± 76.74	.990
	PCT (ng/mL), $\overline{x} \pm s$	0.32(0.19, 1.43)	0.26(0.15, 0.81)	0.24(0.16, 0.53)	.344
After	WBC ($\times 10^9$/L), $\overline{x} \pm s$	10.25 ± 4.30	10.22 ± 5.40	11.06 ± 4.50	.865
	CRP (mg/L), $\overline{x} \pm s$	81.11 ± 73.87^{a}	58.02 ± 40.84^{ab}	73.46 ± 68.39^{a}	.001
	PCT (ng/mL), $\overline{x} \pm s$	0.42(0.21, 1.03)	0.36(0.15, 0.80)	0.34(0.15, 0.58)	.501
WBC decreased by 50%, d, $\overline{x} \pm s$		4.48 ± 3.12	4.27 ± 2.55	4.75 ± 3.06	.895
CRP decreased by 50%, d, $\overline{x} \pm s$		6.46 ± 5.42^{a}	3.93 ± 1.93^{ab}	4.00 ± 2.29^{a}	.012
PCT decreased by 50%, d, $\overline{x} \pm s$		5.63 ± 7.01	2.56 ± 1.70	3.00 ± 1.58	.078
WBC back to normal, d, $\overline{x} \pm s$		8.06 ± 2.49	8.76 ± 4.00	8.00 ± 3.52	.784
CRP back to normal, d, $\overline{x} \pm s$		10.35 ± 6.01	8.61 ± 3.36	9.83 ± 3.19	.360
PCT back to normal, d, $\overline{x} \pm s$		6.64 ± 2.71	6.00 ± 3.41	8.00 ± 3.46	.570

The 3 groups conduct multiple comparisons. The same column with different capital letters showed significant difference between groups ($P < .01$); those with different lower case letters indicated significant difference between groups ($P < .05$); those with the same lower case letters indicated that there was no significant difference between groups ($P > .05$).
CRP = C-reactive protein, HD = high-dose, NHD = nonstandard dose group, PCT = procalcitonin, SD = standard dose, WBC = white blood cell count.

clinical ineffective group (62 cases). The univariate analysis of the 134 patients with VAP showed that individuals with clinical ineffectiveness were older, higher APACHE II score, CRRT treatment, and bloodstream infection than the clinical effective patients, whereas the HD of TGC treatment ($P < .001$) and the initial right antibiotics ($P < .001$) were beneficial for patients with VAP. No specific invasive operation or antibiotic combination was associated with a better outcome (Annex 4, http://links.lww.com/MD/C502). The logistic regression analysis indicated that APACHE II score was the sole independent predictor of clinical failure (OR = 0.78, 95% CI, 0.70–0.88), whereas the HD regimen (OR = 5.07, 95% CI, 2.04–12.57) and initial appropriate antibiotic treatment (OR = 6.49, 95% CI, 2.28–18.5) were significantly associated with clinical effectiveness (Table 7).

4. Discussion

In the study, most of the 134 VAP patients were with carbapenem resistance to Acinetobacter baumannii or Klebsiella pneumoniae. TGC has been specifically developed to overcome the 2 major

Table 7

Logistic regression analysis of factors associated with 28-day mortality and clinical cure in 134 patients with VAP.

	28-d Mortality multivariate analysis			
Variable	B	Odds ratio	95% CI	P
Septic shock	−1.11	0.33	0.12–0.92	.035
MODS	−1.36	0.26	0.08–0.83	.024
APACHE II score	−0.12	0.89	0.80–0.98	.024
	Clinical effectiveness multivariate analysis			
Variable	B	Odds ratio	95% CI	P
APACHE II score	−0.25	0.78	0.70–0.88	<.001
HD of TGC	1.62	5.07	2.04–12.57	<.001
Initial appropriate treatment	1.87	6.49	2.28–18.5	<.001

APACHE = the Acute Physiology and Chronic Health Evaluation, HD = high-dose, MODS = multiple organ dysfunction syndrome, TGC = tigecycline

mechanisms of tetracycline resistance (ribosomal protection and efflux),[18–20] with high sensitivity to the MDR pathogens, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) and producing extended-spectrum β-lactamase (ESBLs) Enterobacteriaceae bacteria. Still, *Pseudomonas aeruginosa*, *Proteus* spp., and *Providencia* spp. are intrinsically resistant to it.[21–26] Thus TGC usage in clinical practice have good prospects for drug resistance bacteria.

The main concern of the TGC usage was the reported safety problems.[27,28] An RCT conducted by Ramirez et al had documented that the incidence of gastrointestinal AEs in higher TGC dosage was higher than that in the conventional dose group, but the difference was not significant.[8] However, De Pascale et al concluded that higher dose of TGC did not develop serious AEs and proved good tolerability for critically ill patients with MDR.[29] Our results showed that the incidence of AEs and the 28-day mortality were similar with the 3 groups, whereas the hepatic dysfunction in the SD group might deteriorate. High-dose TGC was well tolerated and had similar safety profiles in ICU patients. The incidence of liver damage might not be associated with the usage of high-dose TGC, but was increased as the duration extended. Thus, clinicians should be alert to the development of hepatic function on TBIL by the long administration of SD regimen and NHD treatment, especially on the 10th day. Although diarrhea and impaired liver function were the major AEs during TGC treatment, they could all be relieved after symptomatic treatment. Therefore, the high TGC regimens seem safe and acceptable for patients with VAP.

In addition, studies have shown that the incidence of sepsis-related liver injury was association with the evolution of the sepsis.[30] However, our study showed that at baseline, the 3 groups of VAP patients treated with TGC did not differ in their basic disease, septic shock, or severity of disease. The logistic regression analysis indicated that sepsis shock might not affect the incidence of liver dysfunction. All the side events in this study were recorded during TGC usage and reduced quickly after TGC withdrawal, implying TGC treatment was the main factor.

The results of the recent study suggest that the high mortality in patients with VAP may have been related to suboptimal TGC doses. Ramirez et al reported that clinical cure with TGC 100 mg (17/20, 85.0%) was significantly higher than with TGC 75 mg (16/23, 69.6%) and imipenem/cilastatin group (18/24, 75.0%), which was consistent with the result De Pascale had reported.[8,29] Burkardt et al had observed that the steady-state AC concentrations of TGC were much greater than those of plasma and ELF. Although TGC concentrations determined in ICU patients were comparable to healthy volunteers, the current dosage of 50 mg twice daily was probably insufficient for the treatment of pneumonia caused by MDR pathogens.[18,31,32] Specifically, exposure to relatively low antibiotic concentrations might also promote the development of drug resistance.[24] Therefore, TGC should not be imprudently abandoned without further evaluation.

The management of the severe infections due to MDR gram-negative Acinetobacter bacteria mainly adopts combination with the base of other antibiotics such as TGC, polymyxins, and carbapenems.[33,34] Polymyxins also have good antibacterial activity compared with TGC. However, due to the drug screening, the resistance of gram-negative bacteria to polymyxins is attracting increasing attention. A latest study found that the transferability of the mcr-1 gene could be detected in various bacteria, even from animal to healthy people, thus might be one of the reasons that caused rapid prevalence of colistin resistance.[35,36] Moreover, polymyxin has not yet been officially on Chinese market and if we ignore the application of TGC, polymyxin resistance may even be a wide range of outbreaks, let alone its potential nephrotoxicity when used to treat MDR Acinetobacter.[37–41] Given that, the presence of TGC may buffer the colistin-resistant pressure and reduce the enormous threatens.

At present, the clinical usage of TGC for VAP may confront with the dual problems of overdose and off-label uses, even in combination with other antibiotics, it also required higher dose.[8,29,42] Hence, we suggested the use of TGC in combination with other effective antibiotics to timely control the VAP infections due to MDR. Of course, do not rule out the possibility that monotherapy can cure if the occurrence of infection caused by mild strains with high sensitivity.

Our study has several limitations. First, this is a single-center retrospective analysis with a relatively small number of patients. Second, in almost all of the patients, TGC was used in combination with other antibiotics, therefore we cannot draw any conclusion regarding the efficacy of HD TGC as monotherapy. Finally, we did not monitor the plasmatic and tissue concentrations. We believe that further studies will be confirmed by rigorously designed animal trials and multicenter prospective clinical trials.

5. Conclusions

The risk of AEs and mortality might not increase as the dose of TGC rose, whereas side effects were related to the TGC duration. Full course of HD regimen of TGC (100 mg, q12 hours) is more efficient and associated with a better clinical prognosis. Further evidence derived from well-designed animal experiments and multicenter prospective clinical trial on HD TGC is desirable to confirm the results in the study.

Author contributions

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