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Evaluation of the ratio of the estimated area under the concentration-time curve to minimum inhibitory concentration (estimated AUIC) as a predictor of the outcome for tigecycline treatment for pneumonia due to multidrug-resistant bacteria in an intensive care unit

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ABSTRACT

Objectives: Based on pharmacokinetics/pharmacodynamics (PK/PD) and the minimum inhibitory concentration (MIC) of tigecycline (TGC), dose increases have been advocated to maximize the efficacy against pneumonia that is suspected to be due to multidrug-resistant (MDR) bacteria in an intensive care unit. This practice-based study explored the relationship between the predicted PK parameter, the ratio of the area under the concentration-time curve to the 24 h of dosing/minimum inhibitory concentration (AUC_{0-24}/MIC or AUIC), and the clinical and microbiological outcomes in critically ill patients with pneumonia due to MDR bacteria.

Methods: We conducted a prospective cohort study of the treatment of pneumonia due to MDR bacteria in an intensive care unit. The study patients were recruited and assigned to either TGC standard dose (SD, 50 mg q12 h) or high dose (HD, 100 mg q12 h) for the treatment of pneumonia due to MDR bacteria depending on the doctors' decisions. The relationships between the PK/PD parameters and outcomes were examined.

Results: Over the study period, 105 patients were included in the study. Whereas C1/2, Cmin, MIC and AUC were dramatically higher in the HD group than in the SD group (all $P < 0.05$), the Cmax and AUIC had no difference in both groups (all $P > 0.05$). The patients in the HD group had a higher clinical cure rate than those in the SD group ($P = 0.029$), but the bacterial eradication rate and survival rate of the patients in the HD group were not better than those in SD group ($P = 0.279$ and 0.416, respectively). The Cmax, C1/2, Cmin and AUC in the cured group were higher than those in failure group (all $P < 0.05$). The MICs were dramatically higher in the failure group than those in cure group ($P = 0.0001$), which led to significantly lower AUICs ($P = 0.0001$). In the ROC analysis, the areas of Cmax, C1/2, Cmin, AUC, negative-MIC and AUIC under the ROC curve were 0.64, 0.69, 0.67, 0.66, 0.73 and 0.82, respectively. The sensitivity was ascertained to be 75% and the specificity was 89% when the AUIC cut-off value was considered to be 10.12. Moreover, the sensitivity was ascertained to be 63% and the specificity was 80% when the MIC cut-off value was considered to be 1.75 mg/L.

Conclusions: The AUIC and MIC are associated with tigecycline treatment outcomes in pneumonia due to MDR bacteria, and aiming to achieve an individualized AUIC $\geq$ 10.12 when MIC < 1.75 mg/L could improve outcomes.

Introduction

The rapid growth of antimicrobial resistance among gram-negative bacteria has been becoming a worldwide problem in recent years (Solomon and Oliver, 2014). There has been a steady

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increase in rates of extended-spectrum β-lactamase-producing *Enterobacteriaceae, carbapenemresistant Enterobacteriaceae* and *Acinetobacter baumannii*, especially among critically ill patients with intraabdominal infections, ventilator-associated pneumonia and bacteremia (Kaye and Pogue, 2015). The rapid spread of resistance mechanisms of gram-negative bacteria and limited drug options may be the most probable causes. Tigecycline (TGC), the first glycylcycline of the tetracycline antibiotic class, is approved for the treatment of complicated skin and skin-structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) in the US (FDA, 2013) and Europe (EMA, 2013). It may be a new option in cases of widespread resistance of gram-negative bacteria infections, but a recent Food and Drug Administration (FDA) alert announced an increase in TGC-attributable mortality (Food and Drug Administration, 2013), and thus it is not approved for hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP). However, due to the scarcity of other effective antimicrobials, the use of TGC is frequently extended to the treatment for multidrug-resistant (MDR) bacterial infections (Cai et al., 2012; Frampton and Curran, 2005).

TGC was approved for standard administration at a loading dose of 100 mg followed by 50 mg twice daily (Frampton and Curran, 2005). However, high percentages of treatment failure and higher mortality among patients treated with the standard dose of TGC were documented (Cai et al., 2011; Vardakas et al., 2012; Prasad et al., 2012; Tasina et al., 2011; Yahav et al., 2011). In the past few years, numerous studies have demonstrated an association of tigecycline pharmacokinetic (PK) and pharmacodynamic (PD) indices with antimicrobial activity and clinical outcomes (Falagas et al., 2009; Sogaard et al., 2005; Meagher et al., 2007). An AUC_{0-24}/MIC, a correlation between the 24-h area under the inhibitory curve for 24 h of dosing (AUC) and minimum inhibitory concentration (MIC), has been described for TGC efficacy (Xie et al., 2014). However, it is likely that the standard doses of tigecycline do not achieve the desired PK/PD targets in critically ill patients (Roberts and Lipman, 2009). This made us suspect that the ineffectiveness and increased TGC-attributable mortality is due to underdosage. So far, however, very little information exists regarding the appropriate PK/PD target or the dose of TGC for ICU patients with MDR bacterial pneumonia.

On this basis, the AUIC value and clinical efficacy of various doses of TGC in the treatment of MDR bacterial pneumonia were compared in this study to investigate how the AUIC value and dose of TGC affect the outcomes of critically ill patients with MDR pneumonia.

Methods

Study design and patients

A prospective cohort, open-labeled study was conducted in the 45-bed adult ICU of Drum Tower Hospital affiliated with the Medical School of Nanjing University (Nanjing, Jiangsu, China) between 1 April 2015 and 31 January 2017. This study was approved by the Ethical Committee of Drum Tower Hospital affiliated with the Medical School of Nanjing University, and written informed consent was obtained from all patients or responsible caregivers.

The study patients were recruited and assigned to either the standard-dose (SD) or high-dose (HD) TGC groups for the treatment of MDR bacterial pneumonia depending on the doctors' decisions. The standard-dose (SD) patients were treated with TGC 50 mg every 12 h after a 100-mg loading dose. The high-dose (HD) subjects received 100 mg every 12 h after a 150-mg loading dose. The TGC was administered as an intermittent infusion over approximately 1 h. The duration of TGC treatment was ≥7 days. A total of 105 patients completed the study.

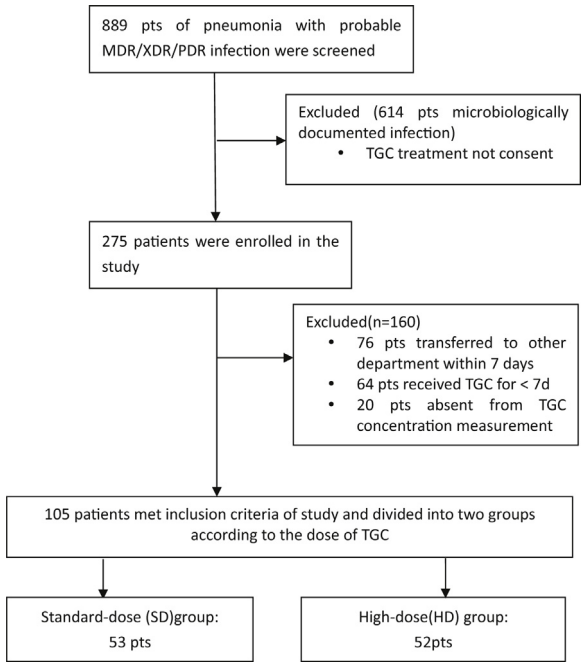

Figure 1. Flow chart of study inclusion process.
MDR, Multidrug-resistance; XDR, extensive drug resistance; PDR, pandrug-resistance; TGC, tigecycline.

The diagnosis of pneumonia was based on the clinical signs and symptoms (e.g., cough, sputum color or airway secretions) plus the presence of a new, persistent or progressive radiographic lung infiltrate. All patients were confirmed to have infections caused by an MDR pathogen which was susceptible, moderately susceptible or resistant to TGC. The pathogens that were resistant to TGC were defined as pandrug-resistant (PDR) pathogens, which were non-susceptible to all agents in all antimicrobial categories.

Data collection

The data collection was performed by trained staff and entered into a case report form. The demographic and clinical data for the patients, which included sex, gender, weight, height, underlying diseases, concomitant drugs, and habitual history, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the sequential organ failure assessment (SOFA) score, the presence of extracorporeal circuits (for example, renal replacement therapy), and the clinical outcome of the infection were recorded. Laboratory parameters including blood cell counts, procalcitonin (PCT), C-reactive protein (CRP), clinical pulmonary infection score (CPIS), serum creatinine (Scr), TB (total bilirubin), and albumin were monitored periodically. In addition, the antibiotic dosing (dose and frequency, time of dosing and sampling, days of antibiotic therapy), concomitant use of other antibiotics and infection data (including known pathogens and pathogen MIC) were collected.

The AUIC ratio is the main PK/PD variable for TGC. Clinical cure was defined as the complete resolution of all signs and symptoms of the infection by the end of TGC therapy. Microbiological eradication was defined as the absence of the original pathogens from the culture of sputum subsequently collected from the patients. Finally, mortality at 28 days was recorded.

Sample collection and analysis

From each patient, at least three blood samples were taken after at least six doses: blood sample A (Cmax) was collected 30 min

Table 1
Clinical characteristics of patients with MDR/PDR/XDR infection.

Characteristic (mean ± S.D.)	Total patients (N = 105)	SD group (N = 53)	HD group (N = 52)	P-value
Age, years	60.00 ± 17.07	65.11 ± 14.72	54.19 ± 17.84	0.002
Sex male, n (%)	81 (77.1%)	42 (79.2%)	39 (75.0%)	0.388
APACHE II score	18.97 ± 6.26	18.45 ± 6.59	19.61 ± 5.88	0.446
SOFA score	8.03 ± 4.13	8.58 ± 4.61	7.38 ± 3.50	0.398
T (°C)	38.24 ± 0.88	38.16 ± 0.85	38.34 ± 0.92	0.390
Leukocyte ($^{*}10^{9}$/L)	11.08 ± 6.42	11.18 ± 7.24	10.982 ± 5.50	0.894
PCT (ug/L)	2.64 ± 9.13	2.16 ± 12.41	2.79 ± 6.16	0.201
CRP (mg/L)	97.78 ± 48.15	105.45 ± 56.10	89.62 ± 37.10	0.199
CPIS score	7.16 ± 1.19	7.08 ± 1.21	7.25 ± 1.17	0.453
TB (umol/L)	36.87 ± 55.47	32.58 ± 36.14	41.55 ± 71.18	0.506
Albumin (g/L)	31.56 + 3.79	31.39 ± 3.59	31.73 ± 4.05	0.716
Scr (mmol/L)	122.71 ± 95.96	146.08 ± 111.77	96.81 ± 67.10	0.023
Septic shock, n (%)	26 (24.72%)	14 (26.42%)	12 (23.08%)	0.548
Comorbidities, n (%)				
Malignancies	28 (26.67%)	15 (28.30%)	13 (24.53%)	0.436
Diabetes	30 (28.57%)	20 (37.74%)	10 (19.23%)	0.029
Cardiovascular disease	24 (22.86%)	14 (26.42%)	10 (19.23%)	0.260
Respiratory disease	36 (34.29%)	14 (26.42%)	22 (42.30%)	0.065
Chronic kidney disease	12 (11.43%)	6 (11.32%)	6 (11.54%)	0.606
Chronic liver disease	4 (3.81%)	1 (1.87%)	3 (5.77%)	0.302
Immunosuppressive status	12 (11.43%)	5 (9.43%)	7 (13.46%)	0.367
Responsible pathogens, n (%)				
Acinetobacter baumannii MDR/XDR/PDR	80 (76.19%)	36 (67.92%)	44 (84.62%)	0.037
Klebsiella neumoniae MDR/XDR/PDR	18 (17.14%)	4 (7.54%)	14 (26.92%)	0.008
Escerichia coli MDR/XDR/PDR	7 (6.67%)	4 (7.55%)	3 (5.77%)	0.367
MIC (mcg/mL), median [IQR]	2.0 (1.0–4.0)	1.0 (1.0–4.0)	4.0 (1.0–4.0)	0.015
Therapeuti aspects				
CRRT (%)	20 (38.46%)	9 (16.98%)	11 (21.15%)	0.384
Concomitant use of other antibiotics, n (%)	90 (85.75%)	42 (79.24%)	48 (92.31%)	0.383
Duration of TGC treatment, days	14.00 ± 5.00	14.75 ± 5.31	12.53 ± 4.79	0.547

MIC, minimum inhibitory concentration; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment; PCT, procalcitonin; CRP, C-reactive protein; CPIS, clinical pulmonary infection score, TB, total bilirubin; Scr, serum creatinine; MDR, multidrug resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant bacteria; CRRT, continuous renal replacement treatment.

after completion of intravenous infusion of TGC for the determination of the peak concentration, blood sample B (C1/2) was a mid-dose blood sample taken 50% of the way through a dosing interval, and blood sample C (Cmin) was a pre-dose concentration taken at the end of a dosing interval (within 30 minutes of the next dose). The serum was separated and stored at −70°C until assay.

The TGC serum concentrations were measured using a validated HPLC assay method (Mullangi et al., 2012). The calibration curve range of the assay was 0.03–30 mg/L. The mean accuracy (%bias) and precision [%coefficient of variation (%CV)] for the serum QC samples were ≤4.7% and ≤5.8%, respectively. The limit of quantification for tigecycline was 0.03 mg/L.

The estimated AUC from 0 to 24 h (AUC_{0-24}) was calculated as double the AUC_{0-12}, assuming steady state (after at least 4–5 doses) when TGC was administered every 12 h. The estimated area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) was calculated using the linear trapezoidal approximation.

Microbiological studies

The Clinical and Laboratory Standards Institute (CLSI) criteria were used to interpret the results. The TGC minimum inhibitory concentrations (MICs) were identified with the Sensititre broth microdilution method (Trek Diagnostic Systems, Cleveland, OH, USA). The isolates were considered susceptible if the MIC was ≤2 mg/L, intermediate if the MIC was 2 −8 mg/L and resistant if the MIC was≥8 mg/L (Sader et al., 2011). Multidrug-resistance (MDR) was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories, extensive drug resistance (XDR) was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories and pandrug-resistance (PDR) was defined as nonsusceptibility to all agents in all antimicrobial categories (Magiorakos et al., 2012).

Statistical analyses

Continuous variables were expressed as mean [standard deviation] while categorical variables were expressed as number (%). MICs and AUICs as non-continuous variables were expressed by median (interquartile range, IQR). Continuous variables were compared using a Chi-squared testing while non-continuous variables were compared using Mann-Whitney U test, and categorical variables were compared using Wilcoxon test. The sensitivity and specificity of the AUIC in the determination of outcomes were determined using ROC curve analysis. Statistical significance was defined as $P < 0.05$. SPSS version 18.0 (SPSS Inc., Chicago, IL) was used for all statistical calculations.

Results

Demographics and clinical characteristics in the overall Population

During the study period, 889 patients with probable MDR/PDR/XDR infections who were admitted to our ICU were screened. Of these, 275 patients met the inclusion criterion of pneumonia and were considered for the prospective analysis. Sputum cultures for MDR/PDR/XDR bacteria were performed on all of these patients at the Drum Tower Hospital during the study period. Of these, 76 patients were transferred to another department within 7 days and 20 received TGC for < 7d (18 patients died within 7d and 20 were

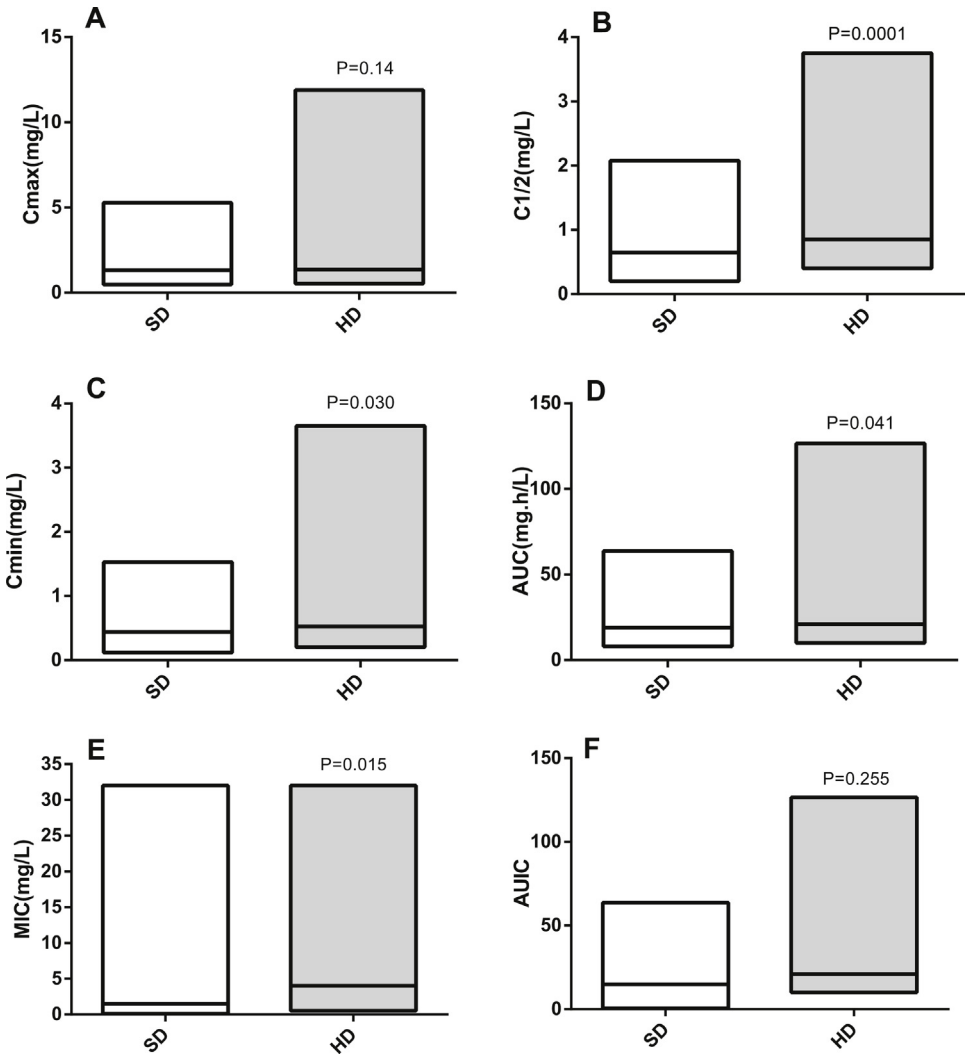

Figure 2. The PK/PD parameters in SD and HD group. A shows the Cmax in the two groups, B shows the C1/2 in the two groups, C shows the Cmin in the two groups, D shows the AUC in the two groups, and F shows the AUIC in the two groups.
Cmax, peak serum concentration of TGC; C1/2, serum concentration in the middle of a dosing interval; Cmin, trough serum concentration of TGC; AUC, the concentration-time curve over a 24-h period; MIC, minimum inhibitory concentration; AUIC, the ratio of the area under the concentration-time curve over a 24-h period divided by the minimum inhibitory concentration of the drug for the bacteria; SD, standard-dose; HD, high-dose.

Table 2
Clinical efficacy indexes of patients in the SD and HD groups.

Characteristic (median, IQR)	SD group (N = 53)	HD group (N = 52)	P-value
ΔT (°C)	0.5 (−0.3-0.9)	0.5 (0.25-0.68)	0.545
Δ leukocyte ($\times 10^9$/L)	0.8 (−1.56-0.6)	1.3 (−2.5-6.0)	0.784
ΔPCT (μg/L)	3.0 (0-3)	3 (0-3)	0.604
ΔCRP (mg/L)	20 (−0.15-27.03)	19.2 (−6.1-21.65)	0.469
ΔCPIS score	1 (0-1	0.5 (0-1)	0.887

PCT, procalcitonin; CRP, C-reactive protein; CPIS, clinical pulmonary infection score.
Δ refers to the difference between the baseline value and the value after 7 days of tigecycline treatment.

switched to other antibiotics in 7d). A final total of 105 patients were included in the study. The enrolled patients were divided into standard-dose (SD) and high-dose (HD) groups according to the dose of TGC (Figure 1, Table 1).

The median (IQR) age was 60 (26–97)years, and 77.1% were male. The age and Scr of the subjects in the SD group were higher than those of the HD group ($P < 0.05$).

Respiratory disease was the most common underlying disease (34.29%), followed by diabetes (28.57%), malignancies (26.67%) and cardiovascular disease (22.86%). There were no statistically significant differences between the two groups for the other demographic, clinical and laboratory characteristics (Table 1).

In all of the patients, the causative organisms were Gram-negative, most often *Acinetobacter baumannii* (n = 80). Of the remaining 25 bacteria, *Klebsiella pneumoniae* (n = 18) and *Escherichia coli* (n = 7) were isolated. Carbapenem resistance was detected in all isolated organisms (Table 1).

The great majority of patients received tigecycline as a combination therapy (85.75%). Furthermore, 100% of patients in the MIC ≥ 8 group (100% of those infected with PDR bacteria) received combination therapy. Most of the patients who were treated with combination regimens received carbapenem or cefoperazone/sulbactam in addition to tigecycline. The median duration of the treatment for pneumonia was 14 days (range 7–28) (Table 1).

The PK/PD parameters in SD and HD group

As shown in Figure 2, the Cmax tended to be higher in the high-dose group than that in standard-dose group, but there was no

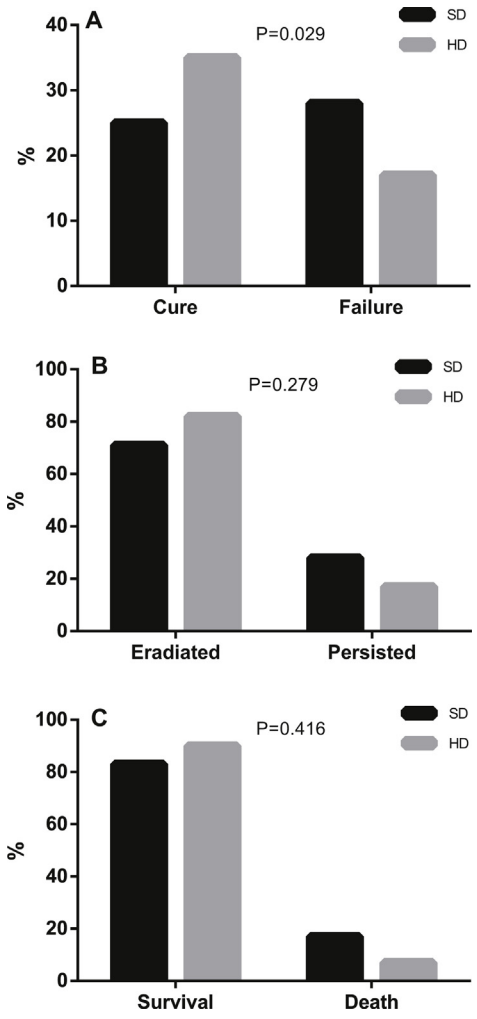

Figure 3. The prognostic indicators in SD and HD group. A shows the cure and failure rates in the two groups, B shows the bacterial eradication and persistence rates in the two groups, and C shows the survival and death rates in the two groups. SD, standard-dose; HD, high-dose.

significant difference between the SD and HD groups [median (IQR) 1.32 mg/L (0.95–1.84 mg/L) vs. 1.37 mg/L (1.14–2.03 mg/L), P = 0.14)]. However, the median (IQR) of C1/2, Cmin and AUC were dramatically higher in the HD group than in the SD group [0.85 mg/L (0.62–1.08 mg/L) vs. 0.65 mg/L (0.44–0.80 mg/L), 0.53 mg/L (0.36–0.76 mg/L) vs. 0.44 mg/L (0.33–0.61 mg/L), 20.96 mg.h/L (16.78–28.06 mg.h/L) vs. 19.08 mg.h/L (12.57–22.49 mg.h/L), respectively, all P < 0.05]. The median (IQR) MIC in HD group was 4.0 (1.0–4.0) mg/L, higher than that in SD group [median (IQR) 1.0 (1.0–4.0 m) g/L, P = 0.015]. In general, the AUIC was not significantly different in HD and SD groups [median (IQR) 7.87(3.63–16.43) vs. 10.8(5.57–18.94), P = 0.255].

Impact of different doses of TGC on patient outcomes

The patient outcomes were evaluated in the SD and HD groups, as shown in Table 2 and Figure 3. There were no statistically significant differences between ΔT, Δleukocyte, ΔPCT, ΔCRP and ΔCPIS in the two groups. Δ refers to the difference between the baseline value and the value after 7 days of TGC treatment. The patients in HD group had a higher clinical cure rate than those in the SD group (P = 0.029), but the bacterial eradication rate and survival rate in the HD group were not better than those in the SD group (P = 0.279 and 0.416, respectively).

The clinical efficacy index and PK/PD parameters of TGC in the cure and failure groups

The clinical efficacy index and the PK/PD parameters of TGC in the cure and failure groups are shown in Table 3. The Cmax, C1/2 and Cmin in the cure group were higher than those in the failure group (P = 0.016, 0.001, 0.07, respectively). The AUCs in the cure group tended to be higher than those in the failure group (P = 0.008). However, the MICs were dramatically higher in the failure group than those in the cure group [median 4.0(2.0–8.0) vs. 1.0(1.0–4.0), P = 0.0001]. Thus, the AUICs in the cure group were significantly greater than those in the failure group [median 15.72 (9.93–20.00) vs. 4.65(2.24–8.30), P = 0.0001].

The sensitivity and specificity of PK/PD parameters in the determination of cure were assessed according to the ROC curve shown in Figure 4. Upon obtaining the ROC curve, the areas for Cmax, C1/2, Cmin, AUC, MIC and AUIC under the ROC curves were 0.64, 0.69, 0.67, 0.66, 0.73 and 0.82, respectively. The sensitivity was ascertained to be 75% and the specificity was 89% when the cut-off value for AUIC of 10.12 was used. Moreover, the sensitivity was ascertained to be 63% and the specificity was 80% when the cut-off value for MIC of 1.75 mg/L was used.

Discussion

This study suggested that the AUIC is a predictor for tigecycline treatment outcomes in pneumonia due to MDR/PDR/XDR bacteria, and an AUIC ≥ 10.12 was identified as a significant breakpoint for clinical cure. This is consistent with previous clinical studies that also found an association between the AUIC and clinical and/or microbiological outcomes in CAP (Rubino et al., 2012; Ramirez et al., 2013; Docobo-Perez et al., 2012). For instance, an AUIC > 12.8 was associated with a faster time to fever resolution in patients with CAP (Rubino et al., 2012). However, in fact, the exact cut-off values differed in the various studies and different infection sites. AUIC > 17.9 (Meagher et al., 2007) and AUIC > 6.96 (Passarell et al., 2008) were the PK/PD targets of tigecycline identified by

Table 3
PK/PD parameters of Tigecycline for treatment of MDR/PDR/XDR pneumonia in cure and failure groups.

PK/PD parameters (median, IQR)	Total patients (N = 105)	Cure group (n = 60)	Failure group (n = 45)	P-value
Cmax (mg/L)	1.33 (1.09–1.86)	1.42 (1.19–2.08)	1.25 (0.77–1.83)	0.016
C1/2 (mg/L)	0.74 (0.54–0.89)	0.8 (062–1.08)	0.65 (0.42–0.81)	0.001
Cmin (mg/L)	0.48 (0.35–0.67)	0.54 (0.38–0.77)	0.42 (0.32–0.56)	0.07
AUC (mg.h/L)	19.16 (14.78–25.64)	20.43 (16.82–29.66)	18.6 (11.53–22.49)	0.008
MIC (mg/L)	2.0 (1.0–4.0)	1.0 (1.0–4.0)	4.0 (2.0–8.0)	0.0001
AUIC	9.84 (4.24–18.49)	15.72 (9.93–20.00)	4.65 (2.24–8.30)	0.0001

MDR, multidrug resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant bacteria; Cmax, peak serum concentration of TGC; C1/2, a middle serum concentration through a dosing interval; Cmin, trough serum concentration of TGC; AUC, the concentration-time curve over a 24-h period; MIC, minimum inhibitory concentration; AUIC, the ratio of the area under the concentration-time curve over a 24-h period divided by the minimum inhibitory concentration of the drug for the bacteria.

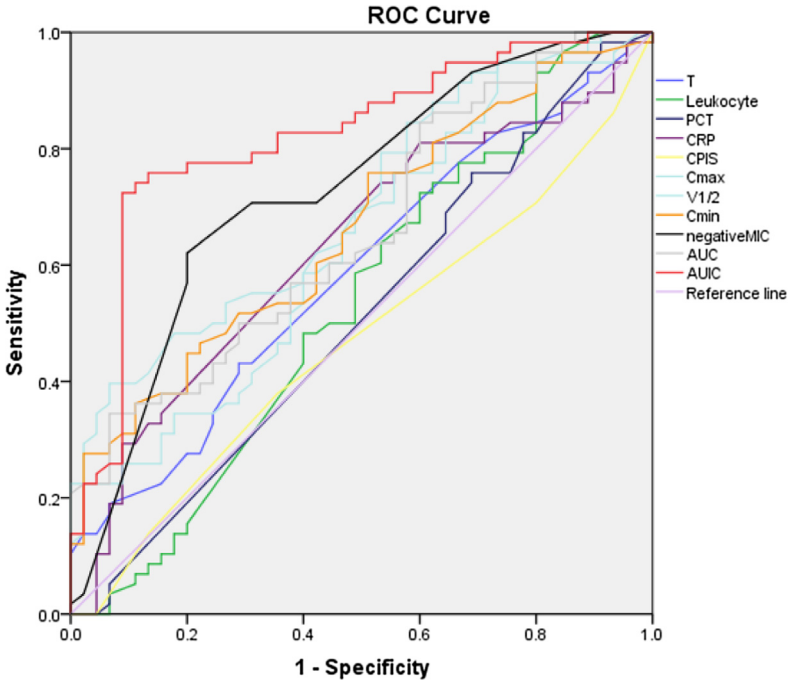

Figure 4. ROC curve analysis of clinical characteristics on admission, PK/PD parameters and MIC of TGC to assess the cure prognosis.
T, temperature, PCT, procalcitonin; CRP, C-reactive protein; CPIS, clinical pulmonary infection score; Cmax, peak serum concentration of TGC; C1/2, the serum concentration in the middle of a dosing interval; Cmin, trough serum concentration of TGC; AUC, the concentration-time curve over a 24-h period; MIC, minimum inhibitory concentration; AUIC, the ratio of the area under the concentration-time curve over a 24-h period divided by the minimum inhibitory concentration of the drug for the bacteria.

classification and regression tree (CART) analysis for the treatment of cSSSI and cIAI.

Some studies have shown that the high-dose regimen is associated with better outcomes in critically ill patients with severe infections. For instance, a high-dose TGC regimen was successfully used in combination with other active antimicrobials in patients with K. pneumonia Carbapenemase-producing (KPC) pneumonia infections. In addition, a recent phase 2 study in HAP and VAP investigated the use of two high-dose TGC regimens (200 mg initial and then 100 mg twice daily or 150 mg initial and then 75 mg twice daily), which showed higher cure rates compared to the standard-dose regimen or imipenem/cilastatin. Similarly, another study showed no differences in terms of ICU mortality between the standard and high-dose TGC regimens but a numerically higher clinical cure rate and microbiological eradication in the high-dose group. One possibility is that high doses of tigecycline can improve the pharmacokinetic characteristics and the concentration of the drug in the lung tissue to improve clinical symptoms. In our study, the subjects in the HD group had significantly higher AUCs than those in SD groups. However, there was no statistical difference in AUICs in both groups due to the MIC differences. Therefore, we assumed that if MIC were similar in both groups, high dose could achieve higher AUICs and improve the prognosis.

The AUIC value is related to the AUC and MIC. The AUC is clearly a factor that should be considered to be affected by doses, frequency and administration methods of drugs. Nevertheless, the MIC value had a greater effect on the AUIC in our study. As shown in Table 2, the MIC values in the failure groups were much higher than those in the cure groups for both the high and standard dose. This suggests that increasing the doses might not be an efficient way to attain ideal PK/PD parameters in those patients (Sbrana et al., 2013; Ramirez et al., 2013; Lee et al., 2013). Therefore, we should pay equal attention to the effects of the MIC and AUIC on the outcomes. Similarly, a previous study by Anthony et al. suggested that the TGC MIC values in *A. baumannii* isolates may predict the clinical outcome. This affects the necessity for high doses when the MIC of the pathogen exceeds 0.5 mg/L (Anthony et al., 2008). Another study demonstrated that the excess mortality in the TGC-treated group might be related to the higher MIC of TGC (≥2 mg/L) (Chuang et al., 2014). Thus, the TGC MIC was considered to be fully as important as the AUIC on the outcomes for MDR-pneumonia patients.

Our data fail to support the use of either high-dose or standard-dose TGC treatment in treating MDR/XDR/PDR pneumonia when the MIC was >1.75 mg/L. Another study also showed that the excess mortality due to tigecycline-based treatment for MDR-AB pneumonia may be related to a higher MIC of tigecycline (>2 mg/L) (Chuang et al., 2014). Since increasing the dose is not a reliable method to treat less-susceptible bacteria, combination therapy is often used, although it is controversial whether this therapy can improve the efficiency of TGC treatment for MDR infection in critically ill patients. Schafer JJ et al. showed that the combination of TGC with carbapenem resulted in a better outcome than TGC monotherapy for ventilator-associated pneumonia and bacteremia caused by MDR-AB (Schafer et al., 2007). However, in a recent review of the use of TGC against MDR-AB infections, in comparison with tigecycline monotherapy, combination therapy did not affect the mortality, the clinical response or the microbiological response (Ni et al., 2016). Thus, further well-designed prospective studies with large sample sizes are warranted to determine the effectiveness and safety of combination therapy compared to tigecycline monotherapy.

This study had several limitations. First, this is a single-center prospective analysis with a relatively small number of patients and more than 50% of enrolled patients had dropped out. Since it is not a randomized controlled study, although the AUCs in the HD group were significantly higher than those in SD group, due to a significant difference in MIC between the two groups resulted in no difference in AUICs in both groups and it was impossible to compare the efficacy of the two groups. Second, patients who received TGC for <7d were excluded. As a result, early treatment

outcomes could not be assessed. Third, we did not monitor the tissue concentrations, which could have confirmed our clinical observations. Last, we did not analyze the impact on outcome by age, Scr and diabetes rate, which were statistical differences in clinical characteristics. Despite these limitations, to the best of our knowledge, this is the largest comparative clinical study for which the clinical TGC MIC and AUC have been described, and this is one of only a few studies that have examined the AUIC as a predictor of tigecycline treatment outcomes in ICU patients with MDR/XDR/PDR pneumonia.

In conclusion, AUIC and MIC are associated with tigecycline treatment outcomes in pneumonia due to MDR bacteria, and aiming to achieve an individualized AUIC $\geq$ 10.12 with high-dose TGC when the MIC < 1.75 mg/L may improve the outcomes.

Conflict of interest statement

All work has been approved by all co-authors. Ying Xu and Qin Gu made substantial contributions to the conception and design; the acquisition of data was performed Ying Xu; the analysis and interpretation of data were performed by Ying Xu and Lu Jin; Ying Xu and Qin Gu wrote the draft of the article and revised it critically for intellectual content. The final version was approved by all authors. All individuals who accept direct responsibility for the manuscript are identified. No conflicts of interest exist in the submission of this manuscript, and the manuscript was approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Ethical approval

This study was approved by the Ethical Committee of Drum Tower Hospital affiliated with the Medical School of Nanjing University.

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