Rational use of tigecycline and tigecycline blood concentration monitoring in patients with severe infection

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Abstract. Tigecycline, a tetracycline antibiotic, is widely used against antimicrobial resistance; therefore, medical staff should use tigecycline rationally to improve clinical efficacy and reduce resistance to this drug. The present study aimed to enhance the rate of rational tigecycline usage. The patients were divided into a low-dose (50 mg tigecycline twice daily, every 12 h) and a high-dose group (100 mg twice daily, every 12 h). The blood concentrations of tigecycline were examined and the area under the curve $(AUC)_{0\text{-}12\ h}$ values of the two groups were calculated. Prescriptions of tigecycline for 40 intensive care unit (ICU) cases were reviewed to evaluate the rationality of tigecycline usage. The peak plasma concentrations (the 7th administration after 1 h) of tigecycline were significantly higher in the high-dose group (2.46±0.43 μg/ml) compared with those in the low-dose group (1.25±0.16 μg/ml). The $AUC_{0\text{-}12\ h}$ was 16.35±3.09 h μg/ml in the high-dose group and 9.83±1.23 h μg/ml in the low-dose group (P<0.001). There were 29 irrational prescriptions identified, involving: i) Lack of consultation records (n=20); ii) inappropriate usage or dosage (n=17); iii) inappropriate drug selection (n=2); or iv) lack of dynamic laboratory tests to evaluate the efficacy (n=4). The irrational use of tigecycline in ICU patients is common. The rate of rational tigecycline usage can be improved by strengthening the management, training and participation of clinical pharmacists.

Introduction

Antimicrobial resistance has become a global public health concern, endangering both human health and quality of life. The issue of antimicrobial resistance in China is becoming increasingly severe (1-3). The results of the China Bacterial Surveillance Network in 2021 showed that carbapenem-resistant *Klebsiella pneumoniae* is only sensitive to certain antibiotics, such as tigecycline (92.7%), colistin (94.7%), polymyxin (94.1%), ceftazidime and avibactam (89.9%) (4). Carbapenem-resistant *Acinetobacter baumannii* also shows sensitivity to tigecycline (97.5%), colistin (98.4%) and polymyxin (99.3%). The resistance rates of *A. baumannii* to imipenem and meropenem are as high as 72.3 and 71.5%, respectively (4). The detection of multidrug-resistant and pan-drug-resistant *A. baumannii* and carbapenem-resistant *Enterobacter* is one of the main reasons for the significant increase in the use of tigecycline in recent years (5-7).

Tigecycline was the first new-generation, broad-spectrum, glycyl tetracycline antibiotic approved by the US Food and Drug administration in 2005, which exerted good antibacterial activity against common pathogenic bacteria and multidrug-resistant bacteria, such as multidrug-resistant *Acinetobacter baumannii,* carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Acinetobacter baumannii* (8,9). At present, it is mainly used clinically for the treatment of complicated intra-abdominal infections, severe community-acquired pneumonia, multidrug-resistant *A. baumannii* infections and infections caused by carbapenem-resistant Enterobacteriaceae (8-11). With the wide application of tigecycline in clinical practice, its irrational use has attracted the attention of the Chinese Health Commission. It is required that medical institutions document the prescription of tigecycline in a special file, invite experts on infectious diseases for consultation before prescription, and promptly review, analyse and summarise prescriptions (12). Feedback on numerous problems (inappropriate drug selection, inappropriate dosage and usage, lack of consultation record and lack of dynamic laboratory tests to evaluate efficacy) to the clinical frontline is also required to improve clinical efficacy, and reduce adverse drug reactions and drug resistance.

The present study intended to investigate the rational use of tigecycline in the intensive care unit (ICU) of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) through prescription review. Currently, there are two regimens used by clinicians for maintenance administration

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of tigecycline to treat pulmonary infection caused by carbapenem-resistant *A. baumannii*: i) 50 mg twice daily (every 12 h); and ii) 100 mg every 12 h. The blood drug concentrations of the two doses were monitored and the association with clinical prognosis was analysed. This provided a basis for the empirical treatment of carbapenem-resistant *A. baumannii* pulmonary infection. The present study may provide a reference for the rational use and management of tigecycline in hospitals.

Patients and methods

Patients. The inclusion criterion for blood concentration monitoring consisted of pulmonary infection cases caused by multidrug-resistant and pan-drug-resistant *A. baumannii* between September 2019 and March 2022 from The First Affiliated Hospital of Bengbu Medical College (Bengbu, China). The patients were divided into two groups according to the 'Evaluation Criteria for Clinical Application of Tigecycline' (Table I) formulated by Chinese experts and previous reports (8,13-15): i) The low-dose group (first loading dose of 100 mg or no loading dose, followed by 50 mg of maintenance dose), 9 patients (8 male and 1 female; age range, 42-84 years); and ii) the high-dose group (first loading dose of 200 mg, followed by 100 mg of maintenance dose), 9 patients (5 male and 4 female; age range, 31-71 years). The exclusion criterion was the use of tigecycline for <72 h.

The inclusion criterion for the tigecycline prescription review consisted of 40 patients (24 male and 16 female; age range, 29-85 years) treated with tigecycline at the ICU of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) between September 2019 and March 2022. Prescriptions were randomly selected from 100 prescriptions for review. The exclusion criterion was the use of tigecycline for <72 h. The present study was approved by the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) and written informed consent was obtained from each patient.

Observation indicators. The observation indicators were as follows: i) Observation indicators of tigecycline blood concentration monitoring: Use of tigecycline, white blood cell count, neutrophil count, C-reactive protein (CRP) level, and body temperature before and after treatment; and ii) observation indicators of prescription review: Patient's admission number, sex, age, diagnosis, doctor's advice regarding the administration of tigecycline alone or a combination therapy, and bacterial culture results before and after medication. The indications, dosing schedule, aetiology and efficacy were analysed according to the 'Evaluation Criteria for Clinical Application of Tigecycline' (Table I), previous publications (15-18) and the instruction manual for tigecycline. Prescription reviews were conducted based on four factors: i) Indication; ii) dosing schedule; iii) aetiology and efficacy evaluation; and iv) prescription and consultation on the special use grade of antibiotics.

Blood drug concentration monitoring. The blood concentrations of tigecycline were monitored at five time-points: 0 h at the 7th administration, and 30 min, 1, 6 and 12 h after the 7th administration. From each patient, 1-2 ml blood was collected, and following centrifugation (22,000 x g, 5 min, 25˚C), the supernatants were subjected to high-performance liquid chromatography. An Agilent 1200 high-performance liquid chromatography instrument (Agilent Technologies Co., Ltd.) with a Kromasil C18 chromatographic column (4.6x150 mm, 5 μm; Agilent Technologies Co., Ltd.) was used to check the blood concentrations of tigecycline. The mobile phase was acetonitrile -0.023 mmol/l phosphate buffer (24:76, *v/v*, pH=3.0), the flow velocity was 1.0 ml/min, the temperature of the column was 25˚C and the injection volume was 50 μl. Tigecycline standard (Beijing Bei Ao Lai Bo Technology Co., Ltd.) was diluted with distilled water to 1.00 mg/ml stock solution, then the above stock solution was diluted successively with PBS (pH=3.0, 0.1 mmol/l) to a series of standard solutions with concentrations of 25,000, 10,000, 5,000, 2,500, 1,250 and 0.500 μg/ml and the quality control solutions were 15,000, 5,000, 0,125 μg/ml. The internal standard solution of minocycline (1.00 mg/ml; Sigma-Aldrich; Merck KGaA) was prepared in distilled water, then diluted in phosphate buffer (pH=3.0, 0.1 mmol/l) to obtain a 100 μg/ml concentration. Phoenix WinNonlin software 6.4 (Pharsight Corporation) was used for non-compartmental analysis and for fitting pharmacokinetic parameters. The area under the curve $(AUC)_{0\text{-}12\,h}$ was calculated using the statistical moment method.

$$AUC_{0-12} = \sum_{i=1}^{N} \frac{C_i + C_{i-1}}{2}(t_i - t_{i-1})$$

(i=0, 0.5, 1, 6, 12)

Evaluation of the clinical efficacy of tigecycline. Efficacy evaluation was performed based on the 'Technical Guidelines for Clinical Trials of Antibacterial Drugs' published by Chinese experts (12). Evaluation parameters included: i) Clinical symptoms (cough, expectoration, dyspnoea, chest distress and elevated body temperature); ii) signs (lung auscultation with thickened respiratory sounds and rales); iii) laboratory test results (hematology and CRP); and iv) bacteriological test results. The definitions of efficacy were as follows: i) 'Cure' was defined when the patients showed absence or negative results for all four aforementioned parameters; ii) 'significant improvement' was defined as the patient having a positive result for three of the four parameters; iii) 'effective' was defined as a positive result for two of the aforementioned parameters; and iv) 'ineffective' was defined as the patient's condition worsening or no obvious improvement after 72 h of treatment. The overall effective rate was calculated as: Overall effective rate (%)=(cure + significant improvement + effective cases)/total number of patients x100%.

Statistical analysis. SPSS 22.0 (IBM Corp.) was used for statistical analysis. Continuous data were presented as the mean ± SD. A paired or an independent sample Student's t-test was used for inter-group comparisons of data that conformed to a normal distribution, whereas the Mann-Whitney U-test or the Wilcoxon signed-rank test was used for non-normally distributed data. Count data are presented as n (%) and Fisher's exact test was used for inter-group comparisons. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Evaluation criteria for the clinical application of tigecycline.

Category	Parameters
Indication	i) Severe cases of complicated intra-abdominal infection, complicated skin and soft tissue infection, and community-acquired pneumonia.
	ii) Multidrug-resistant *A. baumannii* infections (excluding CNS and UT infections).
	iii) Carbapenem-resistant Enterobacteriaceae infections (excluding CNS and UT infections). For multidrug or carbapenem resistance, the use is considered rational even if the infection site is not specified, provided that it is not a CNS or UT infection.
Regimen	i) Monotherapy is not appropriate for treating extensively drug-resistant gram-negative bacterial infections.
	ii) The first loading dose is 100 mg, and the maintenance dose is 50 mg every 12 h; for children aged 8-11 years old, 1.2 mg/kg every 12 h, and the maximum dose is 50 mg every 12 h; for children aged 12-17 years, 50 mg every 12 h.
	iii) Hepatic insufficiency: No dose adjustment is required for patients with mild to moderate hepatic insufficiency (Child Pugh class A and B); for patients with severe hepatic impairment (Child Pugh class C), the first dose should be adjusted to 100 mg, followed by 25 mg every 12 h.
	iv) When treating hospital-acquired pneumonia or ventilator-associated pneumonia, the dose can be increased. The maintenance dose can be up to 100 mg every 12 h; for severe infections caused by carbapenem-resistant Enterobacterales or carbapenem-resistant *A. baumannii*, the dose can be doubled.
Aetiology and efficacy evaluation	i) Aetiological testing should be applied before the use of antibacterial drugs, such as bacterial culture, including effective aetiological evidence from other hospitals.
	ii) During treatment, dynamic laboratory tests should be performed to evaluate the efficacy, such as routine blood tests, procalcitonin level tests and bacterial culture.
Prescription and consultation of the 'special use class' of antibiotics	i) Prescription is issued by a senior physician and supported by the information management system.
	ii) Timely consultation with in-hospital or out-of-hospital experts specialized in the 'special use class' of antibacterial drugs, with appropriate consultation records.
	iii) Prescribing bypassing a senior consultant is limited to within 24 h after tigecycline is administered, and there is a record of the corresponding disease course.
	iv) Special file registration is carried out in accordance with the 'National Health Office (2017) no. 10' document.
	v) Physicians who are authorised to prescribe and consult on the 'special use class' of antibiotics require regular training and assessment and should have the corresponding records.

A. baumannii, Acinetobacter baumannii; CNS, central nervous system; UT, urinary tract.

Results

Pharmacodynamic profile and clinical efficacy of tigecycline. A total of 18 ICU patients with pulmonary infection caused by multidrug-resistant or pan-drug-resistant *A. baumannii* were included in the blood concentration monitoring study. The patients were divided into two groups: i) The low-dose group; and ii) the high-dose group, with 9 cases in each group. There were 7 cases of carbapenem-resistant *A. baumannii* pulmonary infection in each of the two groups. Blood drug concentrations at five different time points (0 h, 30 min, 1, 6 and 12 h after the 7th administration) were detected. The results showed that the blood drug concentrations in the high-dose group were significantly higher compared with those in the low-dose group (Fig. 1). The maximum concentration (C_{max}) in the high-dose group was 2.46±0.43 μg/ml, which was significantly higher compared with the C_{max} of 1.25±0.16 μg/ml in the low-dose group (P<0.001). $AUC_{0\text{-}12\ h}$ was 16.35±3.09 h·μg/ml in the high-dose group and only 9.83±1.23 h·μg/ml in the low-dose group (Table II), and there was a significant difference between the two groups (P<0.001). The overall rates of efficacy in the high-dose and low-dose groups were 77.78 and 55.56%, respectively. In addition, the concentration of tigecycline was positively associated with the efficacy (Fig. 2). These results suggested that for multidrug-resistant or pan-drug-resistant *A. baumannii*, especially carbapenem-resistant *A. baumannii* pulmonary infection, the regimen of 200 mg for the first loading dose plus 100 mg every 12 h for the maintenance dose is the most effective.

Inflammatory factors before and after tigecycline treatment. After tigecycline treatment, the body temperature, white blood cell and neutrophil counts, and CRP level in both the low-dose and high-dose groups were lower than the corresponding pre-treatment values. The body temperature and CRP level were significantly decreased (P<0.05) compared with the pre-treatment values in the high-dose group, whereas only

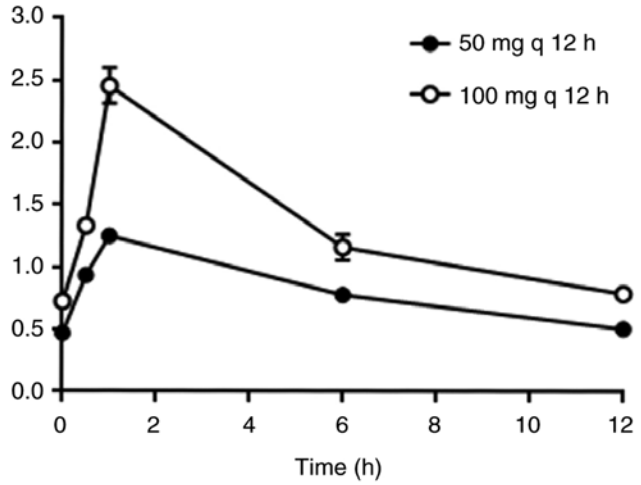

Figure 1. Blood drug concentrations at 0 h of the 7th administration and 30 min, 1, 6 and 12 h after the 7th administration in the low-dose and high-dose groups. *P<0.001 vs. 100 mg dose. q 12 h, every 12 h.

body temperature showed a significant decrease (P<0.05) compared with pre-treatment in the low-dose group, the white blood cell and neutrophil counts, and the CRP level did not show a significant difference in the low-dose group (Table III).

Infection sites and infecting pathogens for tigecycline prescriptions. A total of 40 tigecycline prescriptions were analysed. Pulmonary infections accounted for the largest proportion (n=29, 72.5%), followed by multi-site infections (n=8, 20%) and abdominal infections (n=3, 7.5%) (Table IV). All 40 cases (100%) received an aetiological test before tigecycline treatment. In total, 42 pathogen strains were isolated from the 40 cases, with *A. baumannii* accounting for the largest proportion (n=28, 66.67%), followed by *Klebsiella pneumoniae* (n=4, 9.52%) (Table V).

Tigecycline prescription review. A total of 40 prescriptions of tigecycline were reviewed following the predefined standards. In total, 11 prescriptions were considered rational and the remaining 29 prescriptions were considered irrational. In both rational and irrational groups, tigecycline was used with other antibiotics, especially carbapenems, which accounted for the largest proportion (Table VI). The infections in the rational and irrational groups are shown in Table VII. Both groups had severe infection (90.9% in the rational and 79.3% in the irrational group), including carbapenem-resistant *A. baumannii* (rational group) and carbapenem-resistant *Klebsiella pneumoniae* (irrational group), which caused lung and other serious infections, such as abdominal infection, septic shock and sepsis (P=0.65; Table VII). No significant differences were observed in the body temperature, white blood cell count, neutrophil count and CRP between both groups before treatment with tigecycline (Table VIII).

In the irrational group with 29 cases, 20 prescriptions (20/40, 50%) lacked consultation records. The first doses stated on 17 prescriptions were not the recommended loading administration, thereby resulting in inappropriate usage and dosage of tigecycline. Drug selection was inappropriate in two prescriptions, and four prescriptions lacked dynamic laboratory tests for the evaluation of efficacy (Table IX).

Table II. Comparison of the pharmacokinetic parameters and efficacy between the two groups.

Parameter	Low-dose group (n=9)	High-dose group (n=9)	P-value
C_{max}, μg/ml	1.25±0.16	2.46±0.43	0.001
$AUC_{0\text{-}12\,h}$, h·μg/ml	9.83±1.23	16.35±3.09	0.001
Effective rate, n (%)	5 (55.56)	7 (77.78)	0.317

Values are expressed as the mean ± SD or n (%). AUC, area under the curve; C_{max}, maximum concentration.

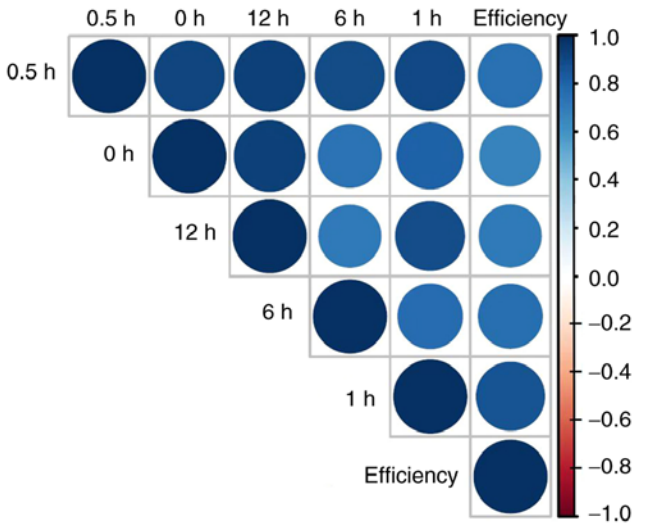

Figure 2. Concentration of tigecycline is positively associated with its efficacy. The size of the circles indicates the magnitude of the correlation between the concentration of tigecycline and the efficacy.

Discussion

By conducting a prescription review, the present study showed that the major problems in tigecycline usage in the ICU of The First Affiliated Hospital of Bengbu Medical College included: i) Inappropriate usage and dosage (the first dose was not the recommended loading administration); ii) inappropriate drug selection; iii) lack of consultation before administration; and iv) lack of dynamic laboratory tests to assess treatment efficacy. Blood drug concentration monitoring of 18 patients showed that the blood drug concentration in the high-dose group was significantly higher compared with that in the low-dose group, and the rate of clinical efficacy in the high-dose group was also higher compared with that in the low-dose group.

Based on blood concentration monitoring and prescription review analysis, the results of the present study suggested that, for the rational use of tigecycline, the first dose should be administered with loading (double

Table III. Changes in inflammatory factors in the two groups before and after treatment.

Group	Time-point	Temperature, ˚C	White blood cell count, x10^9/l	Neutrophil count, x10^9/l	CRP, mg/l
Low-dose	Pre-treatment	38.31±0.89	12.02±4.73	10.41±4.21	81.71±57.89
	Post-treatment	36.93±0.91[a]	10.47±5.49	8.49±5.40	72.64±68.52
High-dose	Pre-treatment	38.19±1.24	15.18±5.28	13.35±4.69	113.37±80.07
	Post-treatment	36.61±0.59[a]	12.76±5.70	10.52±5.98	44.10±28.81[a]

[a]P<0.05 compared with pre-treatment. Values are expressed as the mean ± SD. CRP, C-reactive protein.

Table IV. Infection site distribution among the 40 cases.

Site	Cases
Lung	29 (72.5)
Abdominal cavity	3 (7.5)
Multiple sites	8 (20.0)

Values are expressed as n (%).

Table V. Distribution of the 42 pathogenic strains isolated from the 40 patients.

Pathogen	Strain cases
Acinetobacter baumannii	28 (66.67)
Staphylococcus aureus	3 (7.14)
Stenotrophomonas maltophilia	1 (2.38)
Enterococcus faecium	2 (4.76)
Klebsiella pneumoniae	4 (9.52)
Pseudomonas aeruginosa	2 (4.76)
Escherichia coli	2 (4.76)

Values are expressed as n (%).

Table VI. Tigecycline combined with various antimicrobials in the rational use and irrational use groups.

Antimicrobial	Rational use group (n=15)	Irrational use group (n=37)
Carbapenems	10 (66.7)	19 (51.4)
β-Lactamase	1 (6.7)	11 (29.7)
Quinolones	1 (6.7)	2 (5.4)
Aminoglycosides	1 (6.7)	1 (2.7)
Polypeptides	1 (6.7)	3 (8.1)
Polyphosphates	1 (6.7)	0 (0.0)
Nitroimidazoles	0 (0.0)	1 (2.7)

Values are expressed as n (%).

dose), so that the steady-state trough concentration can be reached quicker (19). This approach may improve efficacy and reduce the chance of drug resistance. Tigecycline is not recommended for severe infections caused by *Pseudomonas aeruginosa*, since tigecycline shows low antibacterial activity against this pathogen (20,21). Hospitals should strengthen the management and consultation systems for tigecycline usage. The present study highlighted that for severe pulmonary infections caused by carbapenem-resistant *A. baumannii*, 200 mg of the first loading dose and 100 mg of the maintenance dose would be recommended for initial treatment. The recommendation of the present study is in line with previous studies indicating that high doses of tigecycline should be used to treat infections involving carbapenem-resistant *A. baumannii* (5,22,23). The current study confirms that the recommended regimen has a higher $AUC_{0\text{-}12\ h}$ and higher efficacy compared with the regimen using 50 mg of the maintenance dose.

Certain measures can be taken into consideration to improve the rational use of tigecycline in The First Affiliated Hospital of Bengbu Medical College. Firstly, the hospital management can organise a hospital prescription review team to conduct special prescription reviewing for tigecycline in the ICU. Secondly, based on the review results, the hospital should aim to correct major problems and formulate rewards and penalties, to ensure the rational use of tigecycline in the ICU. Thirdly, the drug susceptibility test kit can be updated. The currently used kit cannot show the minimum inhibitory concentration (MIC) values of gram-negative bacteria. It has been reported that the dosage of tigecycline can be empirically prescribed based on the MIC (24,25). At MIC <0.5, the regimen of 100 mg of the loading dose and 50 mg every 12 h of the maintenance dose should be used; however, at MIC >1.0, the regimen of 200 mg of the loading dose and 100 mg of the maintenance dose is recommended. The aforementioned dosage schedule is also suitable for hospital-acquired pneumonia, ventilator-associated pneumonia or carbapenem-resistant Enterobacterales, as well as other severe infections caused by carbapenem-resistant *A. baumannii* (21,22). The current kit does not provide the MIC of tigecycline, but rather a positive/negative result; therefore, it is difficult for clinicians to formulate an initial treatment plan. The drug susceptibility test kit should therefore be replaced. Fourthly, the role of clinical pharmacists can be enhanced. Clinical pharmacists may give feedback to medical staff in the form of lectures based on the results of prescription reviews. The latest research on tigecycline can be summarized and

Table VII. Infections in the rational/irrational groups.

Variable	Rational use group	Irrational use group	P-value
Infections caused by carbapenem-resistant bacteria or other infections (abdominal infection, septic shock, sepsis)	10 (90.9)	23 (79.3)	0.65
Infections caused by multidrug-resistant or pan-drug-resistant bacteria	1 (9.1)	6 (20.7)	

Values are expressed as n (%).

Table VIII. Inflammatory factors in the two groups.

Group	Temperature, ˚C	White blood cell count, x10^9/l	Neutrophil count, x10^9/l	CRP, mg/l
Rational use	38.17±0.93	12.58±5.55	10.98±5.05	79.35±52.98
Irrational use	37.91±0.98	14.16±10.48	11.93±10.12	83.61±55.24
P-value	0.448	0.716	0.868	0.891

Values are expressed as the mean ± SD. CRP, C-reactive protein.

Table IX. Irrational use of tigecycline (n=40).

Type	Cases
Inappropriate dosage and usage	17 (42)
Inappropriate drug selection	2 (5)
Lack of consultation record	20 (50)
Lack of dynamic laboratory tests to evaluate efficacy	4 (10)

Values are expressed as n (%).

taught to improve awareness of the rational use of tigecycline among medical staff. In addition, clinical pharmacists can conduct large sample pharmacokinetics/pharmacodynamics studies to guide clinical medication. Lastly, hospitals may formulate measures to regularly conduct random inspections of the use of tigecycline, carbapenems and colistin, to increase their rational use and ensure pre-administration consultation.

In summary, irrational use of tigecycline exists in the ICU of The First Affiliated Hospital of Bengbu Medical College where the present study was conducted. The major problems include irrational usage and dosage, inappropriate drug selection, lack of consultation and lack of dynamic laboratory tests to evaluate the efficacy of treatment. The dose of 50 mg q12 h tigecycline used to treat pulmonary infections caused by *A. baumannii* is relatively low in the hospital. Hospitals may improve the rational use of tigecycline through special prescription reviews, regular spot checks, training and relevant research.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MY and XD designed the study and interpreted the data. MY drafted the manuscript. BQ and XW evaluated the cases treated with tigecyclin and collected the blood samples. SW analysed the data and constructed the graphs. XD revised the manuscript. All authors have read and approved the final manuscript. MY and XD confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethics approval (approval no. 2022KY012) was obtained from the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) and written informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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