Infection and Drug Resistance Dovepress

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Optimizing Treatment Strategies for Carbapenem-Resistant Acinetobacter Baumannii-Associated Pneumonia: A Multicenter Study in Chinese Hospitals

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Purpose: To evaluate the clinical outcomes and safety of tigecycline (TGC) plus cefoperazone/sulbactam (CPS) or TGC monotherapy in patients with hospital-acquired pneumonia (HAP) caused by Carbapenem-Resistant *Acinetobacter baumannii* (CRAB).

Methods: This was a retrospective analysis of multicenter data from 62 Chinese hospitals with CRAB HAP. Risk factors for receiving TGC with CPS therapy and predictors of mortality were assessed using multivariate logistic and Cox regression analyses, respectively. Propensity score matching (PSM) evaluated the efficacy and safety of antimicrobial regimens.

Results: A total of the 180 patients were included, with 95 receiving TGC monotherapy and 85 receiving combination therapy. Multivariate logistic regression analysis revealed that older age ($P = 0.011$), and intensive care unit (ICU) admission ($P = 0.007$) were significant risk factors for combination therapy. Multivariate Cox regression demonstrated that combination therapy was associated with a significantly higher risk of 90-day mortality ($P = 0.031$). Patients in the standard-dose TGC (SDT) plus CPS subgroup had significantly higher rates of SOFA scores ≥ 7 ($P = 0.009$) and MV used ($P = 0.028$), as well as higher 30-/90-day mortality compared to high-dose TGC (HDT) plus CPS group. TGC plus CPS significantly reduced CRP levels ($P = 0.009$), while the variations in ALT, TBIL, Cr, Hb, and PLT levels did not differ between different antimicrobial regimens after PSM.

Conclusion: HDT and CPS combination therapy was more effective in patients with advanced age and more severe condition. Safety profiles of different antimicrobial regimens were similar with liver, kidneys, and coagulation functions.

Keywords: carbapenem-resistant *Acinetobacter baumannii*, hospital acquired pneumonia, tigecycline, cefoperazone/sulbactam, risk factors

Introduction

The gram-negative bacilli (GNB)[1] were the primary pathogens of HAP in our country, with AB[2] being the most common, accounting for 25.6%. The treatment of AB is limited by the availability of antimicrobial agents due to its increasing resistance to various antibiotics, particularly carbapenems. Additionally, AB can survive long-term in vitro, making it widespread in the hospital environments. Patients with AB infections tend to have severe conditions, leading to longer lengths of hospital stay (LOS), higher medical costs, and worse prognosis.[3] In this circumstance, AB has been classified by the World Health Organization (WHO) as a priority on the global priority list for research and development of new antibiotics.[4] AB infections have thus become a major global public health issue, posing significant challenges to the safety of medical and healthcare systems worldwide. Strengthening surveillance and control efforts to prevent the spread of AB is crucial.

Received: 7 June 2024
Accepted: 2 October 2024
Published: 13 October 2024

In 2020, Chen et al[5] conducted a study on the in vitro activity of various antimicrobials against AB in the Asia-Pacific region, including novel β-lactam combination agents, TGC, and colistin. The study revealed that drug-resistant AB strains in China exceeded 70.0%, ranking third after South Korea and India. According to the China Antimicrobial Surveillance Network (CHINET) in 2021,[6] the rate of CRAB among clinical isolates had risen to 71.5%. While CRAB shows greater than 88.0% susceptibility to polymyxin B and tigecycline,[7] currently considered last resource antibiotics, the optimal treatment for CRAB infection remains controversial. For severe CRAB infections, TGC monotherapy may result in higher mortality, particularly in cases of bacteremia or pneumonia.[8] The Infectious Diseases Society of America (IDSA), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), and the 2023 IDSA Guidelines for the treatment of drug-resistant gram-negative bacterial infections recommend that patients with severe CRAB infections should receive a combination of at least two in vitro active drugs.[9–11] Moreover, it also mentioned that ampicillin-sulbactam combined with TGC or cefiderocol was the preferred treatment for CRAB-associated pneumonia. Similarly, the Chinese Expert Consensus on Diagnosis, Treatment, Prevention, and Control of AB Infections also proposed that the two-drug combination therapy, primarily sulbactam-based compounds, with CPS being the most commonly used in China,[12] followed by polymyxin E and TGC. However, colistin, when alone or in combination with antibacterial agents is associated with carried a higher risk of nephrotoxicity.[13] Current literature does not provide sufficient evidence to support a preference between colistin-based and tigecycline-based regimens for treating CRAB infections.

However, there are currently only well-controlled, unsampled clinical case studies or case reports regarding the treatment of AB pneumonia with TGC, which had low quality of evidence as monotherapy or combination therapy,[9,10,14,15] and there remains a need for further validation concerning the clinical efficacy and safety of regimens. Therefore, it is essential and of significant clinical value to explore CRAB-infected patients with HAP based on different doses of TGC, either as monotherapy or in combination with CPS.

Materials and Methods

Study Design and Patients Population

We performed a multicenter retrospective study of 62 hospitals in China between October 2019 and June 2021. A total of 180 hospitalized adult patients with CRAB pneumonia were included, all of whom received either TGC monotherapy or combination with CPS.

The inclusion criteria were as follows: (1) patients diagnosed with CRAB HAP, and (2) patients who received either TGC monotherapy or combination therapy with CPS. The exclusion criteria were as follows: (1) the presence of pathogenic bacteria other than CRAB, (2) samples not derived from sputum or bronchoalveolar lavage fluid (BALF), and (3) treatment duration of fewer than two days[16] (Figure 1).

Data Collection and Analysis

The collected data included demographic characteristics (sex, age, BMI), history of chronic illness (Charlson comorbidity index (CCI) score, severity of the condition Sequential Organ Failure Assessment (SOFA) score, comorbid conditions (septic shock), intensive care unit (ICU) admission, Mechanical Ventilation (MV), Continuous Renal Replacement Therapy (CRRT)), laboratory findings, and follow-up information.

The primary clinical outcome was all-cause 30/90-day mortality.

The secondary outcomes included length of hospital stay (LOS) and variations in white blood cell (WBC), C-reactive protein (CRP), and procalcitonin (PCT) levels (maximum minus minimum) within one week of antibiotic treatment.

To assess the incidence of adverse events, we calculated the variation in alanine aminotransferase (ALT), total bilirubin (TBIL), creatinine (Cr), platelet (PLT) count, and hemoglobin (Hb) levels (maximum minus minimum) within one week of antibiotic use.

Definitions

Pneumonia caused by CRAB was defined as clinical evidence of HAP with a qualified sample testing positive for CRAB.[17]

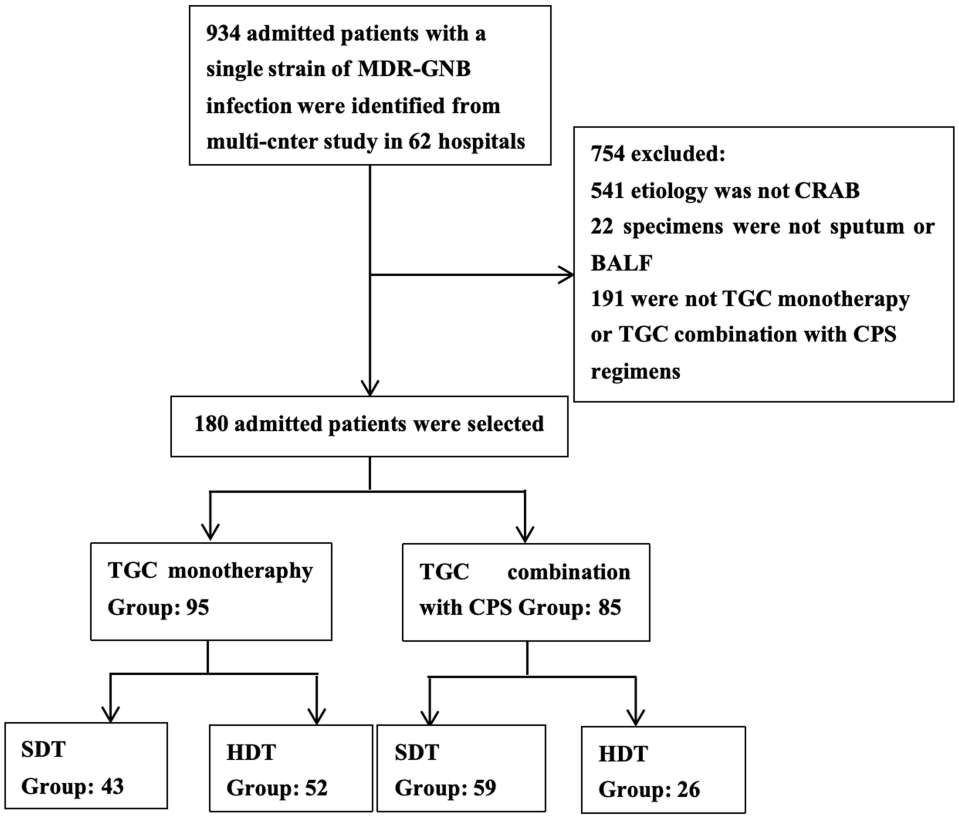

Figure 1 Flow chart of TGC monotherapy or TGC combination with CPS regimen for treatment of CRAB HAP.
Abbreviations: MDR-GNB, Multidrug-Resistant Gram-Negative Bacteria; CRAB, Carbapenem-Resistant Acinetobacter *baumannii*; HAP, hospital-acquired pneumonia; BALF, bronchoalveolar lavage fluid; TGC, tigecycline; CPS, cefoperazone/sulbactam; SDT, standard-dose-TGC; HDT, High-Dose-TGC.

Patients were treated with a standard-dose-TGC (SDT) regimen, consisting of an intravenous dose of 100 mg, followed by a maintenance dose of 50 mg every 12 hours. The High-Dose-TGC (HDT) regimen involved an initial dose of 200 mg, followed by 100 mg every 12 hours. Cefoperazone/sulbactam (cefoperazone 0.5g with sulbactam 0.5g or cefoperazone 1.0g with sulbactam 0.5g) was administered intravenously at a total daily dose of 6–9g.

Statistical Analyses

All statistical analyses were performed using SPSS software (version 26.0). Continuous variables were assessed for normality using the Shapiro–Wilk test. Data that conformed to a normal distribution are presented as the mean and standard deviation (SD) and were analyzed using a *t*-test. Otherwise, data are presented as median and interquartile range (IQR) using the Mann–Whitney *U*-test. Categorical Data are presented as numbers and proportions (%). The chi-square test or Fisher's exact test was used to compare categorical variables between the groups. The relative efficacy and adverse effects of different antimicrobial regimens were assessed using propensity score matching (PSM). Multi-logistic regression analysis and ROC curves were used to predict the independent risk factors for different antibiotic regimens. The Kaplan-Meier product-limit method was used to estimate the survival distribution function. The predictors of 30-day and 90-day mortality for CRAB Pneumonia were identified using Cox regression analysis. *P* values less than 0.05 were considered statistically significant.

Results

We collected data from 180 patients with CRAB HAP and analyzed their characteristics, with 95 receiving TGC monotherapy and 85 receiving TGC combined with CPS therapy.

Patients receiving TGC monotherapy were classified as the control group, while those receiving TGC combined with CPS were classified as the observation group. Age (73 (63,85) vs 65 (56.5,76), $P = 0.009$), BMI (23.0 (21.3,24.8) vs 21.6 (20.1,24.4), $P = 0.049$), CCI score (2(1,4) vs 1(0,2), $P = 0.002$), and SOFA scores (9(6,11) vs 5(4,9), $P = 0.000$) were significantly higher in the observation group. Further analysis revealed that patients receiving the TGC plus CPS combination had a significantly higher proportion with SOFA scores ≥7 (72.9% vs 35.8%, $P = 0.000$) and those aged ≥65 years (68.2% vs 52.6%, $P = 0.033$), compared to those receiving TGC monotherapy. However, there were no significant differences in the BMI subgroup ($P > 0.05$). Additionally, the rates of ICU admission, MV use, and CRRT were also higher in the TGC with CPS compared to the TGC monotherapy group (91.8% vs 56.8%, 87.1% vs 45.3%, and 25.9% vs 5.3%, respectively, $P = 0.000$). A similar difference was observed in the incidence of shock (57.6% vs 34.7%, $P = 0.002$) (Table 1).

Table 1 Characteristics of Patients with CRAB HAP Receiving TGC Monotherapy and TGC Combined with CPS Therapy

Characteristics	TGC n = 95	TGC plus CPS n = 85	*P* value
Gender, male, n (%)	65 (68.4)	63 (74.1)	0.400
Age/years (IQR)	65 (56.5,76)	73 (63,85)	0.009**
Age/years, n (%)			
<65	45 (47.4)	27 (31.8)	0.033*
≧65	50 (52.6)	58 (68.2)	
BMI (M±SD)	21.6 (20.1,24.4)	23.0 (21.3,24.8)	0.049*
BMI, n (%)			
<24	69 (72.6)	55 (64.7)	0.433
[24,27.9]	21 (22.1)	26 (30.6)	
≧28	5 (5.3)	4 (4.7)	
CCI score (IQR)	1 (0,2)	2 (1,4)	0.002**
CCI score, n (%)			
<2	50 (52.6)	33 (38.8)	0.064
≧2	45 (47.4)	52 (61.2)	
SOFA score (IQR)	5 (4,9)	9 (6,11)	0.000**
SOFA score, n (%)			
<7	61 (64.2)	23 (27.1)	0.000**
≧7	34 (35.8)	34 (62,72.9)	
ICU admission, n (%)	54 (56.8)	78 (91.8)	0.000**
MV, n (%)	43 (45.3)	74 (87.1)	0.000**
CRRT, n (%)	5 (5.3)	22 (25.9)	0.000**
Shock, n (%)	33 (34.7)	49 (57.6)	0.002**

Notes: Data are the number (%) of patients, median (interquartile range, IQR), or mean ± standard (M±SD) deviation.* $P < 0.05$, ** $P < 0.01$.

Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; HAP, hospital-acquired pneumonia; TGC, tigecycline; CPS, cefoperazone/sulbactam; BMI, Body Mass Index; CCI, Charlson comorbidity index; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; MV, Mechanical Ventilation; CRRT, Continuous Renal Replacement Therapy.

There was a significant difference in the primary outcomes of all-cause 30-day mortality between the TGC monotherapy and TGC combined with CPS therapy groups (6.3% vs 16.5%, $P = 0.03$). Additionally, the all-cause 90-day mortality rate was also higher in the TGC plus CPS group, but no statistical difference was observed (25.9% vs 15.8%, $P = 0.094$). Despite these findings, LOS was similar in both groups (26 (21,41) vs 30 (20,42), $P = 0.627$). PSM was performed to adjust for age, BMI, CCI, SOFA, WBC, PCT, ALT, TBIL, Hb, and PLT levels. The analysis demonstrated that TGC plus CPS therapy was superior to TGC monotherapy in reducing CRP levels (88.2 (36.2,152) vs 22.6 (9.5,71), $P = 0.009$). Moreover, the incidence of adverse effects did not differ from between TGC plus CPS and TGC monotherapy groups ($P > 0.05$) (Table 2).

Multivariate logistic regression analysis revealed that the independent risk factors associated with TGC plus CPS therapy included age [$P = 0.011$; odds ratio, OR (95% CI), 1.083 (1.018–1.152]), ICU admission ($P = 0.007$; OR (95% CI): 12.801 (1.980–82.747)), WBC count ($P = 0.023$; OR (95% CI): 0.877 (0.784–0.982)), and Hb level ($P = 0.047$; OR (95% CI): 0.951 (0.904–0.999)) (Table 3). The model demonstrated an area under the AUC of 0.931 with 95%

Table 2 The Clinical Outcome and Adverse Effect of TGC Monotherapy and TGC Combined with CPS Regimens

Variable	Before PSM		*P* value	After PSM		*P* value
	TGC n = 95	TGC Plus CPS n = 85		TGC n = 35	TGC Plus CPS n = 35	
Baseline (IQR/M±SD)						
WBC, $\times 10^9$/L	26.8 (22,35)	18.7 (16,22.4)	0.000**	20.4±6.4	20.5±7.5	0.975
CRP, mg/dL	70.9 (45.9,120)	139 (93,198)	0.127	68 (26,214.8)	139 (86.5,245.9)	0.097
PCT, ng/mL	4.97 (3.9,11.4)	3.4 (0.6,18.8)	0.004**	5.4 (2.2,11.0)	3 (0.6,20.9)	0.452
ALT, U/L	8.9 (7.9,12)	18.4 (9,32)	0.017**	11 (7.6,35)	16 (9,28)	0.851
TBIL, μmol/L	1.3 (1.2,2.5)	4.3 (1.8,7.2)	0.000**	2.5 (1.2,11.8)	2.2 (1.7,5.4)	0.991
Cr, μmol/L	64 (54,67.4)	48 (38,71)	0.146	55 (42.5,66.2)	45 (38.2,73.5)	0.551
Hb, g/L	96 (90,106)	116 (101,127)	0.007**	116.5±25.2	121.2±24.1	0.435
PLT, $\times 10^9$/L	301 (144,345)	323 (266,410)	0.045*	326.6±152.5	296.3±126.9	0.370
Variation (IQR)						
WBC, $\times 10^9$/L	9 (3.7,11.6)	7.5 (4.1,9.9)	0.726	7.3 (4.6,10.0)	7.8 (5.5,12.3)	0.466
CRP, mg/dL	46 (14,70)	85 (16,127.2)	0.003**	22.6 (9.5,71)	88.2 (36.2,152)	0.009**
PCT, ng/mL	2.8 (1.7,7)	2.4 (0.8,7.0)	0.009**	1.95 (1.02,6.62)	2.44 (0.42,14.3)	0.934
ALT, U/L	25.8 (12.1,38.1)	27.3 (8.7,52)	0.851	35 (23.5,61.7)	20 (6,37.5)	0.114
TBIL, μmol/L	0.2 (0.14)	2.4 (0.8,7.0)	0.000**	1.18 (0.18,8.4)	1 (0.3,3.5)	0.643
Cr, μmol/L	96 (42,125)	25.1 (12,59)	0.001**	52 (31.5,111)	132 (68.5,223)	0.366
Hb, g/L	16 (12,21)	16 (7,26)	0.472	16 (9.5,25)	18 (7,26)	0.533
PLT, $\times 10^9$/L	80 (75,110)	132 (55,220)	0.004**	84 (72,110)	132 (68.5,223)	0.175
LOS, days (IQR)	26 (21,41)	30 (20,42)	0.627	31 (20.5,50.5)	35 (23,44.5)	0.869
Thirty, Mortality, n(%)	(6,6.3)	(14,16.5)	0.03*	(2,5.7)	(7,20)	0.153
Ninety, Mortality, n(%)	(15,15.8)	(22,25.9)	0.094	(6,17.1)	(10,28.6)	0.255

Notes: Data are the number (%) of patients, median (interquartile range, IQR), or mean ± standard (M±SD) deviation. * $P < 0.05$, ** $P < 0.01$.
Abbreviations: TGC, tigecycline; CPS, cefoperazone/sulbactam; PSM, propensity score matching; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; TBIL, total bilirubin; Cr, creatinine; Hb, hemoglobin; PLT, procalcitonin; LOS, length of hospital stay.

Table 3 Risk Factors for Patients with TGC Plus CPS Therapy

Variable	Multivariable Analysis	
	OR (95% CI)	***P* value**
Age	1.083 (1.018–1.152)	0.011*
BMI	1.225 (0.951–1.578)	0.117
CCI score	1.009 (0.595–1.713)	0.972
SOFA score	1.123 (0.843–1.496)	0.427
ICU admission	12.801 (1.980–82.747)	0.007**
MV	1.340 (0.145–12.358)	0.796
CRRT	14.404 (0.498–416.385)	0.120
Shock	1.051 (0.241–4.581)	0.947
WBC	0.877 (0.784–0.982)	0.023*
CRP	1.004 (0.997–1.011)	0.255
PCT	1.013 (0.983–1.044)	0.399
ALT	1.027 (0.989–1.066)	0.167
TBIL	0.913 (0.821–1.014)	0.089
Cr	0.998 (0.979–1.018)	0.871
Hb	0.951 (0.904–0.999)	0.047*
PLT	1.001 (0.996–1.007)	0.679

Notes: * *P*< 0.05, ** *P*< 0.01.
Abbreviations: TGC, tigecycline; CPS, cefoperazone/sulbactam; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; MV, Mechanical Ventilation; CRRT, Continuous Renal Replacement Therapy; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; TBIL, total bilirubin; Cr, creatinine; Hb, hemoglobin; PLT, procalcitonin.

confidence interval of 0.887–0.975, indicating excellent prediction ability. The validation of this risk model showed a the cut-off value of 0.3, with the sensitivity of 100% and specificity of 75.4% (Supplementary Figure 1).

A significant increase in all-cause 30-day mortality ($P = 0.04$) was observed in patients with CRAB HAP receiving TGC with CPS, as shown by the Kaplan-Meier survival curve (Figure 2). The 90-day mortality rate was also higher in receiving TGC with CPS group compared to TGC monotherapy group; however, the difference was not statistically significant (Figure 3).

Multivariate Cox regression analysis showed that shock and PLT were independent predictors of 30-day and 90-day mortality ($P < 0.05$). After adjusting for confounding factors, TGC with CPS therapy was found to be an independent predictor of 90-day mortality[$P = 0.031$, HR 2.934 (95% CI), (1.104–7.802)]. The results are presented in Table 4.

We included data from 43 patients who received SDT and 52 patients who received HDT monotherapy. Baseline characteristics, such as sex, age, BMI, CCI score, SOFA score, ICU stay, MV, CRRT, and shock, were similar between the groups ($P > 0.05$) (Supplementary Table 1). There was no significant difference in primary and secondary outcomes between the groups ($P > 0.05$). Additionally, the variations in ALT, TBIl, Cr, Hb, and PLT levels were not statistically significant when comparing the SDT and HDT groups ($P > 0.05$). (Supplementary Table 2).

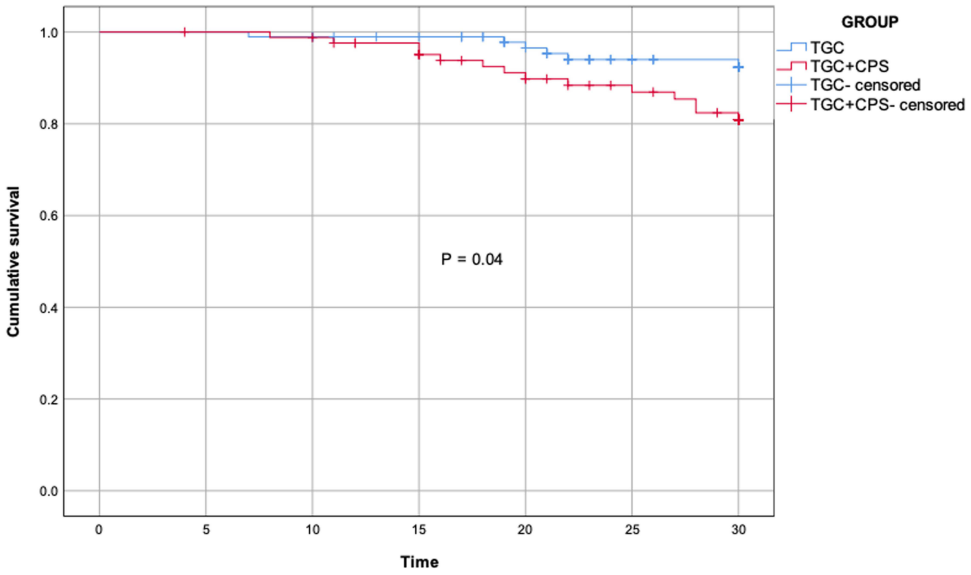

Figure 2 30-Day Survival Curve of Patients with CRAB HAP Treated with Different Antibiotical Therapy Regiments.
Abbreviations: CRAB, Carbapenem-Resistant Acinetobacter *baumannii*; HAP, hospital-acquired pneumonia; TGC, tigecycline; CPS, cefoperazone/sulbactam.

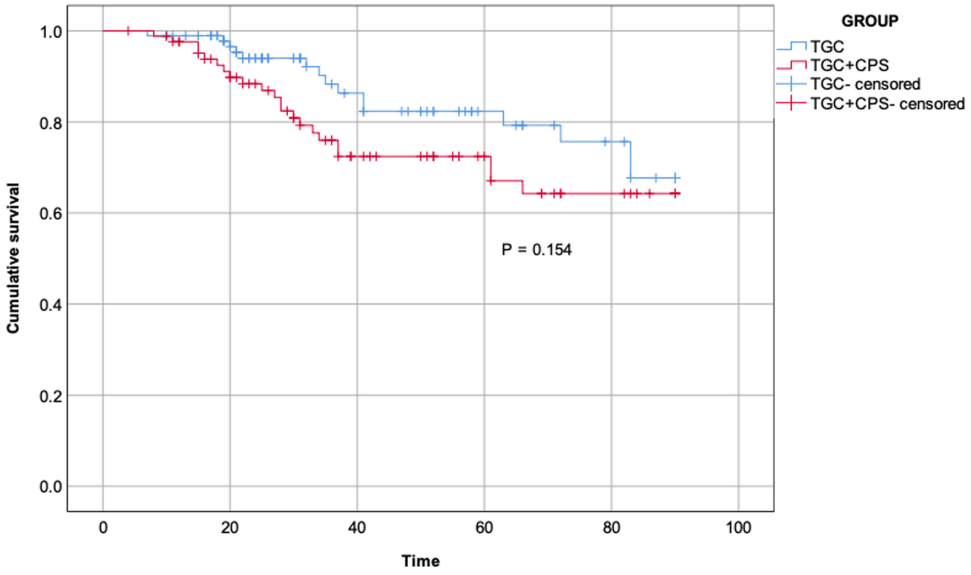

Figure 3 90-Day Survival Curve of Patients with CRAB HAP Treated with Different Antibiotical Therapy Regimens.
Abbreviations: CRAB, Carbapenem-Resistant Acinetobacter *baumannii*; HAP, hospital-acquired pneumonia; TGC, tigecycline; CPS, cefoperazone/sulbactam.

We included data from 59 patients who received SDT with CPS, and 26 patients who received HDT with CPS. Some baseline characteristics, such as sex, age, BMI, CCI score, SOFA score, ICU stay, CRRT, and shock, were similar between the groups ($P > 0.05$). However, the MV used was higher in the SDT plus CPS group (93.2% vs 73.1%, $P = 0.028$). In subsequent analysis, the proportion of patients with a BMI ≧28 were significantly lower in the SDT plus CPS group (0% vs 15.4%, $P = 0.006$). However, the SOFA score ≥ 7 for patients in the SDT combined with CPS was higher than that for those in the HDT combined with CPS (81.4% vs 53.8%, $P = 0.009$). (Supplementary Table 3) No significant difference was found between the SDT and HDT combined with CPS groups in primary and secondary outcomes ($P > 0.05$). Similarly, variations in ALT, TBIl, Cr, Hb, and PLT were not statistically significant in terms of adverse events ($P > 0.05$). (Supplementary Table 4).

Table 4 Analysis of the Risk Factors for 30-Day and 90-Day Mortality in Patients with CRAB HAP

Variable	30-Day Mortality Cox Regression				90-Day Mortality Cox Regression			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender, male, n (%)	1.356 (0.541–3.399)	0.516			0.968 (0.478–1.961)	0.927		
Age, years	1.023 (0.992–1.054)	0.144	–	0.521	1.025 (1.002–1.049)	0.030	–	0.151
BMI	0.93 (0.821–1.052)	0.249			0.962 (0.884–1.046)	0.365		
CCI score	1.208 (1.022–1.429)	0.027	–	0.271	1.186 (1.038–1.356)	0.012	–	0.268
SOFA score	1.290 (1.144–1.454)	0.000	–	0.470	1.270 (1.158–1.393)	0.000	–	0.156
ICU admission	33.216 (0.515–2144.2)	0.099	–	0.110	2.882 (1.020–8.138)	0.046	–	0.194
MV	37.902 (0.742–1936.0)	0.070	–	0.157	7.186 (1.725–29.933)	0.007	–	0.086
CRRT	6.398 (1.874–21.847)	0.003	–	0.979	2.963 (1.482–5.926)	0.002	–	0.550
Shock	2.388 (0.918–6.217)	0.074	18.845 (2.484–142.935)	0.005**	5.704 (2.378–13.682)	0.000	15.690 (3.672–67.053)	0.000**
WBC	0.941 (0.882–1.003)	0.061	–	0.568	0.960 (0.917–1.005)	0.081	–	0.834
CRP	1.0 (0.994–1.006)	0.980	–		1.002 (0.998–1.007)	0.270		
PCT	0.997 (0.983–1.011)	0.655	–		0.998 (0.991–1.005)	0.599		
ALT	0.982 (0.944–1.021)	0.362	–		0.982 (0.956–1.008)	0.178		
TBIL	1.008 (0.999–1.018)	0.090	–	0.923	1.008 (1.002–1.015)	0.014	–	0.472
Cr	1.005 (0.996–1.014)	0.255	–		1.003 (0.995–1.010)	0.476		
Hb	0.990 (0.946–1.035)	0.647	–		0.986 (0.954–1.019)	0.394		
PLT	0.995 (0.991–0.999)	0.014	0.995 (0.991–0.999)	0.017**	0.994 (0.991–0.997)	0.000	0.994 (0.991–0.997)	0.000**
TGC+CPS	2.615 (1.004–6.808)	0.049	–	0.114	1.603 (0.831–3.090)	0.159	2.934 (1.104–7.802)	0.031*

Notes: * $P < 0.05$, ** $P < 0.01$.

Abbreviations: CRAB, Carbapenem-Resistant *Acinetobacter baumannii*; HAP, hospital-acquired pneumonia; BMI, Body Mass Index; CCI, Charlson comorbidity index; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; MV, Mechanical Ventilation; CRRT, Continuous Renal Replacement Therapy; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; TBIL, total bilirubin; Cr, creatinine; Hb, hemoglobin; PLT, procalcitonin; TGC, Tigecycline; CPS, Cefoperazone/Sulbactam.

Discussion

CRAB HAP has become a challenging clinical dilemma worldwide, owing to its high antimicrobial resistance, limited availability of regimens, and high mortality.[18] While both TGC and colistin are considered first-line treatment options for severe CRAB infections, it is notable that colistin exhibits insufficient permeability to the lungs,[19] whereas TGC can achieve higher drug concentrations in the lungs.[12] Few clinical studies have explored the comparative treatment outcomes of colistin and TGC in CRAB HAP infections. Kimberly Ku et al[20] reported that patients with CRAB and (or) CRE infection receiving polymyxin E alone or in combination with TGC had higher mortality rates [33/90 (37%) vs 0/16, $P = 0.002$] and longer LOS [29.5 (37.7±30.3) vs 23.3 (23.5±14.0), $P = 0.004$] compared to those receiving TGC alone. No statistically significant differences were found in a meta-analysis by Abushanab D et al[21] regarding clinical efficacy or mortality between tigecycline-based and polymyxin E-based combination therapy regimens for MDR/PDR-GNB infections. Notably, tigecycline had a lower incidence of nephrotoxicity compared to polymyxin E, whether used as monotherapy or in combination therapy. In contrast, Chang K et al[22] demonstrated that the 28-day all-cause mortality rate was significantly lower in the polymyxin B-based combination therapy group compared to tigecycline-based combination therapy group [28.3% (28/99) vs 39.3% (68/173)] and the polymyxin B combined with tigecycline group [28.3% (28/99) vs 48.9% (45/92)], in patients with HAP caused by carbapenem-resistant organisms (CRO).

In fact, experts have not yet reached a consensus on the optimal treatment for CRAB infections due to the limited number of antibiotics and multiplicity of host factors. Thus, more clinical research is needed to clarify the best treatment regimens for CRAB HAP infections. To our knowledge, no study has investigated the priority between TGC monotherapy and TGC combination with CPS regimens in CRAB HAP infections. In this study, we summarized the clinical features, treatment effectiveness, and safety of various TGC doses, either as monotherapy or in combination with CPS for CRAB pneumonia. Moreover, we evaluated the independent predictors of all-cause 30-/90-day mortality and risk factors associated with different antibiotic regimens in CRAB pneumonia. The primary findings of this study are as follows.

We observed a significant increase in all-cause 30/90-day mortality in patients receiving TGC plus CPS therapy, which remained an independent predictor of all-cause 90-day mortality after adjusting for compound factors. In addition, shock was found to be significantly associated with both 30-day and 90-day mortality. Notably, patients receiving TGC with CPS therapy were significantly superior to those receiving TGC monotherapy in reducing CRP levels. And similar safety was shown in different antimicrobial regimens, including liver, kidney, and coagulation outcomes. Subgroup analysis revealed that HDT combined with CPS therapy was a prior treatment option for patients with CRAB HAP who were older and admitted to the ICU. Furthermore, the primary and secondary outcomes were similar in the SDT and HDT monotherapy groups, as well as between combination with CPS therapy groups. This study is the first to demonstrate the difference between TGC monotherapy and TGC combined with CPS, using large-scale, real-world data, to provide valuable insights into optimal drug regimens for CRAB HAP in the clinic.

Our research revealed TGC combined with CPS treatment had different clinical features than TGC monotherapy for CRAB HAP. Patients receiving TGC plus CPS therapy had significantly higher rates of ICU admission, MV, and CRRT, compared to those receiving TGC monotherapy. Additionally, the multivariate logistic regression analysis identified advanced age and ICU admission as independent risk factors for receiving TGC plus CPS therapy for CRAB HAP. ICU patients are usually critically ill and immunocompromised, with many undergoing invasive operations, which increase the risk of CRAB. However, invasive surgery was not found to be an independent risk factor for TGC combined with CPS therapy in our study. This might be attributed to the fact that almost all patients in the ICU underwent invasive procedures, with some having multiple invasive devices simultaneously. As a result, these factors can interfere with and influence each other.

Although the food and drug administration (FDA)-approved indications are limited to complicated intra-abdominal infections (cIAI), complicated skin and skin structure infections (cSSSI), and and community-acquired pneumonia (CAP), not HAP, due to increased multidrug-resistant infections, TGC has been widely used for non-approved indications, with studies on CRAB HAP accounting for one-third.[8] A previous meta-analysis of five trials[23] analyzed the prognosis of patients with CRAB HAP receiving TGC monotherapy compared to those receiving TGC combination therapy, no significant difference was found between the two prospective cohort studies (OR = 2.22, 95% CI 0.79–6.20, $P = 0.13$). In addition to in-hospital mortality, Li et al[24] found that regimens containing TGC-CPS combination therapy in

patients with CRAB HAP were not superior to TGC monotherapy in terms of clinical and microbiological efficacy. Therefore, the efficacy of TGC monotherapy or combination regimens in patients with CRAB HAP remains controversial.

In our study, we observed an increase in all-cause 30/90 mortality (16.5% vs 6.3%, $P = 0.03$; 25.9% vs 15.8%, $P = 0.094$, respectively) in patients receiving TGC-CPS combination therapy compared to those receiving TGC monotherapy; however, the difference in 90-day mortality was not significant. Further multivariate Cox regression analysis demonstrated that shock and TGC-CPS combination treatment were independent predictors of 30/90- and 90-day mortality, respectively. Owing to older age (73 vs 65 years, $P = 0.009$) and more comorbidities among patients treated with TGC-CPS therapy, which made them more vulnerable to multiple organ failure and septic shock following severe infections. These patients also had significantly higher SOFA scores (9 (6, 11) vs 5 (4, 9), $P = 0.000$) and mortality, indicating a worse clinical condition. In terms of laboratory findings, we observed that patients receiving TGC plus CPS therapy showed a greater decline in CRP levels compared to those on TGC monotherapy, which indicated better outcomes in reducing the inflammatory response, consistent with previous results.[25] The treatment regimen for patients in the combination therapy group was based on established guidelines and expert consensus recommendations,[9–11] with TGC plus CPS therapy being the preferred option for treating severe CRAB infections.

In addition, the mortality and efficacy of various doses of TGC monotherapy remains unclear.[26,27] A previous systematic review and meta-analysis reported[28] that while the microbiological eradication rate in patients receiving HDT did not differ from those on SDT monotherapy for CR pathogens (OR 1.07, 95% CI 0.44–2.60, $P = 0.87$), mortality was reduced (OR 0.20, 95% CI 0.09–0.45, $P = 0.0001$). Shields RK et al[29] also found that HDT combined with in vitro active antibiotics was superior to SDT in improving prognosis. Accordingly, we hypothesized that the high mortality rate in patients with severe infection might be related to the tigecycline dose. In our study, subgroup analysis showed no statistically significant difference in mortality or laboratory findings between SDT and HDT monotherapy or combination therapy, although there was a lack of microbiological data. We also found that patients receiving SDT with CPS had higher SOFA scores (≧7) and more frequent use of MV compared to those receiving HDT with CPS, which suggested that more severe infection occurred in the SDT combined with CPS group. TGC, as a bacteriostatic agent, inevitably may lead to delayed bacterial clearance and increased mortality in case of severe infection, if the drug concentration in the tissues are low and bacteriostatic activity is reduced. Notably, while the 30-/90-day mortality rates were higher in the SDT plus CPS group, it showed equivalent primary mortality outcomes in treating CRAB HAP when compared to HDT plus CPS group, possibly due to the limited sample size. There is an urgent need for well-designed studies to evaluate the efficacy of different doses of TGC in monotherapy compared to combination therapies.

However, safety must be considered when prescribing TGC or CPS. Both TGC[30,31] and CPS[31–33] have been associated with coagulation disorders, raising concerns about their safety. In addition, severe infection can lead to increased consumption of coagulation factors and PLTs, resulting in bleeding events. Notably, there is controversy regarding whether TGC-CPS combination treatment increases the risk of bleeding events.[34–36] Despite the absence of coagulation data, we found no difference in PLT or HGB levels between the TGC monotherapy and TGC-CPS combination therapy groups, and no bleeding events occurred in our retrospective study. This suggests that TGC-CPS treatment did not increase the risk of bleeding compared to TGC monotherapy. TGC is primarily eliminated through biliary excretion (59%) and urine (22%), contributing to a lower prevalence of abnormal liver or kidney function.[37] Our results showed that the variation in ALT, TBIL, and Cr did not differ between the TGC monotherapy and TGC combined with CPS therapy groups, indicating combination therapy does not increase the risk of liver or kidney adverse events. In general, TGC plus CPS therapy significantly reduced inflammation in patients with CRAB HAP infection without increasing adverse effects.

The limitations of this study are as follows. First, it was a retrospective study with a small sample size and high risk of bias. Second, subcenters did not provide complete details, such as subjective symptoms, pulmonary signs, imaging, microbiological, and coagulation data, which affected our ability to fully assess treatment efficacy. These missing data points were not included in our analysis.

Conclusions

Mortality associated with severity of patient condition in CRAB HAP. Although there was no significant difference in primary mortality outcome between the SDT and HDT plus CPS combination therapy groups for treating CRAB HAP, the SDT plus CPS therapy group had higher mortality rates. The TGC plus CPS combination group showed significantly reduced inflammation levels, with similar safety across different antimicrobial regimens concerning liver, kidney, and coagulation. Therefore, HDT combined with CPS therapy appears more effective for patients who are advanced age and have more severe conditions. This is the first study to compare the clinical outcomes and safety of TGC monotherapy versus TGC in combination with CPS therapy for CRAB infections. Considering the high mortality rates and the limited effective treatment options for CRAB infection, there is an emerging need for further researches through prospective studies with larger sample sizes to confirm these findings.

Abbreviations

TGC, Tigecycline; CPS, Cefoperazone/Sulbactam; HAP, Hospital-acquired pneumonia; PSM, Propensity score matching; MDR-GNB, Multidrug-Resistant Gram-Negative Bacteria; CRAB, carbapenem-resistant *Acinetobacter baumannii*; PDR-GNB, Pan-Drug Resistant Gram-Negative Bacteria; CRO, carbapenem-resistant organisms; BMI, Body Mass Index; CCI, Charlson comorbidity index; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; MV, Mechanical Ventilation; CRRT, Continuous Renal Replacement Therapy; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; TBIL, total bilirubin; Cr, creatinine; Hb, hemoglobin; PLT, procalcitonin; LOS, length of hospital stay; cIAI, complicated intra-abdominal infections; cSSSI, complicated skin and skin structure infections; CAP, community-acquired pneumonia.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College (Protocol No. JS-3029B), and was performed in accordance with the ethical standards of the "Declaration of Helsinki 1964" and its later amendments or comparable ethical standards. Our multicenter study used only one ethics committee and the content and procedures were based on multicenter research. This study met requirements for consent waived by the Ethics Committee. This study was a retrospective study, where researchers only conducted retrospective analysis on the medical records and data from laboratory examinations, not involving personal privacy or commercial interests. All the clinical samples were part of the routine hospital laboratory procedure and there was no additional burden on patients. Meanwhile, Strict confidentiality was maintained for all patient information, and no any intervention was performed on patients. Hence, the patient consent was waived by the Ethics Committee.

Consent for Publication

All authors approved the final manuscript and the submission to this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by grants from the Beijing Medical Award Foundation (grant number: 2019-1002 and grant number: YXJL-2021-0385) and the National High Level Hospital Clinical Research Funding (grant number 2022-PUMCH-B-043).

Disclosure

The authors declare that they have no competing interests.

This paper has been uploaded as, "The Clinical Outcomes and Safety of Tigecycline in Monotherapy or Combination with Cefoperazone/sulbactam for Carbapenem-Resistant Acinetobacter baumannii-Associated Pneumonia: A Multicenter Retrospective Study" to Research Square as a preprint: https://www.researchsquare.com/article/rs-4176720/v1.

References

1. Yin K, Liu L, Fan G. Classification and drug resistance analysis of pathogenic bacteria in patients with bacterial pneumonia in emergency intensive care unit. *Contrast Media Mol Imaging*. 2022;30(9):6980091.
2. Yin Y, Zhao C, Li H, et al. Clinical and microbiological characteristics of adults with hospital-acquired pneumonia: a 10-year prospective observational study in China. *Eur J Clin Microbiol Infect Dis*. 2021;40(4):683–690. doi:10.1007/s10096-020-04046-9
3. Kanj SS, Bassetti M, Kiratisin P, et al. Clinical data from studies involving novel antibiotics to treat multidrug-resistant Gram-negative bacterial infections. *Int J Antimicrob Agents*. 2022;60(3):106633. doi:10.1016/j.ijantimicag.2022.106633
4. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327. doi:10.1016/S1473-3099(17)30753-3
5. Chen CH, Wu PH, Lu MC, et al. Geographic patterns of carbapenem-resistant, multi-drug-resistant and difficult-to-treat Acinetobacter baumannii in the Asia-Pacific region: results from the Antimicrobial Testing Leadership and Surveillance (ATLAS) program, 2020. *Int J Antimicrob Agents*. 2023;61(2):106707. doi:10.1016/j.ijantimicag.2022.106707
6. Ding L, Chen BY, Li M, et al. Expert consensus on antimicrobial synergy testing and reporting of carbapenem resistant Gram-negative bacteria. *Chin J Infect Chemother*. 2023;23(1):80–90.
7. Chen YB, Ji JR, Liu ZY, et al. BRICS report of 2021: the distribution and antimicrobial resistance profile of clinical bacterial isolates from blood stream infections in China. *Chin J Clin Infect Dis*. 2023;16(1):33–47.
8. Yaghoubi S, Zekiy AO, Krutova M, et al. Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review. *Eur J Clin Microbiol Infect Dis*. 2022;41(7):1003–1022. doi:10.1007/s10096-020-04121-1
9. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America guidance on the treatment of AmpC beta-lactamase-producing Enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. *Clin Infect Dis*. 2022;74(12):2089–2114.
10. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect*. 2022;28(4):521–547. doi:10.1016/j.cmi.2021.11.025
11. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clin Infect Dis*. 2023:ciad428. doi:10.1093/cid/ciad428
12. Zeng M, Xia J, Zong Z, et al.; Society of Bacterial Infection and Resistance of Chinese Medical Association; Expert Committee on Clinical Use of Antimicrobial Agents and Evaluation of Antimicrobial Resistance of the National Health Commission; Infectious Diseases Society of Chinese Medical Education Association. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. *J Microbiol Immunol Infect*. 2023;56(4):653–671. doi:10.1016/j.jmii.2023.01.017
13. Liu J, Shu Y, Zhu F, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: a systematic review and network meta-analysis. *J Glob Antimicrob Resist*. 2021;24(3):136–147.
14. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis*. 2022;75(2):187–212. doi:10.1093/cid/ciac268
15. Sy CL, Chen PY, Cheng CW, et al. Recommendations and guidelines for the treatment of infections due to multidrug resistant organisms. *J Microbiol Immunol Infect*. 2022;55(3):359–386. doi:10.1016/j.jmii.2022.02.001
16. Wang SH, Yang KY, Sheu CC, et al. Efficacies of colistin-carbapenem versus colistin-tigecycline in critically Ill patients with CR-GNB-Associated pneumonia: a multicenter observational study. *Antibiotics*. 2021;10(9):1081. doi:10.3390/antibiotics10091081
17. Infectology Group of Respiratory Diseases Branch of Chinese Medical Association (CMA). Chinese guidelines for the diagnosis and treatment of hospital-acquired pneumonia and ventilator-associated pneumonia in Chinese adult hospitals (2018 edition). *Chin J Tuberc Respir Dis*. 2018;41:255–280.
18. Du X, Xu X, Yao J, et al. Predictors of mortality in patients infected with carbapenem-resistant Acinetobacter baumannii: a systematic review and meta-analysis. *Am J Infect Control*. 2019;47(9):1140–1145. doi:10.1016/j.ajic.2019.03.003
19. Abdul-Mutakabbir JC, Griffith NC, Shields RK, et al. Contemporary perspective on the treatment of Acinetobacter baumannii infections: insights from the society of infectious diseases pharmacists. *Infect Dis Ther*. 2021;10(4):2177–2202. doi:10.1007/s40121-021-00541-4
20. Ku K, Pogue JM, Moshos J, et al. Retrospective evaluation of colistin versus tigecycline for the treatment of Acinetobacter baumannii and/or carbapenem-resistant Enterobacteriaceae infections. *Am J Infect Control*. 2012;40(10):983–987. doi:10.1016/j.ajic.2011.12.014

21. Abushanab D, Nasr ZG, Al-Badriyeh D. Efficacy and safety of colistin versus tigecycline for multi-drug-resistant and extensively drug-resistant gram-negative pathogens-a meta-analysis. *Antibiotics*. 2022;11(11):1630. doi:10.3390/antibiotics11111630
22. Chang K, Wang H, Zhao J, et al. Polymyxin B/Tigecy-cline combination vs. polymyxin b or tigecycline alone for the treatment of hospital-acquired pneumonia caused by carbapenem-resistant Enterobacteria ceae or carbapenem-resistant Acinetobacter baumannii. *Front Med*. 2022;9:772372. doi:10.3389/fmed.2022.772372
23. Bai XR, Liu JM, Jiang DC, et al. Efficacy and safety of tigecycline monotherapy versus combination therapy for the treatment of hospital-acquired pneumonia (HAP): a meta-analysis of cohort studies. *J Chemother*. 2018;30(3):172–178. doi:10.1080/1120009X.2018.1425279
24. Li Y, Xie J, Chen L, et al. Treatment efficacy of tigecycline in comparison to cefoperazone/sulbactam alone or in combination therapy for carbapenem-resistant Acinetobacter baumannii infections. *Pak J Pharm Sci*. 2020;33(1):161–168.
25. Duan WW, Qin C. Clinical effect of cefoperazone sulbactam combined with tigecycline in the treatment of pan-drug-resistant Acinetobacter baumannii pulmonary infection. *Qingdao Med*. 2023;55(2):123–125.
26. Yao F, Wang XP, Wang YF, et al. The clinical efficacy of high-dose tigecycline in ICU patients with pulmonary infections. *Pharm Today*. 2021;31(6):449–453.
27. Han H, Qin W, Zheng Y, et al. High-dose versus standard-dose tigecycline treatment of secondary bloodstream infections caused by extensively drug-resistant Acinetobacter baumannii: an observational cohort study. *Infect Drug Resist*. 2021;14(9):3837–3848. doi:10.2147/IDR.S322803
28. Liu J, Yan Y, Zhang F. Risk factors for tigecycline-associated hypofibrinogenemia. *Ther Clin Risk Manag*. 2021;17(4):325–332. doi:10.2147/TCRM.S302850
29. Shields RK, Paterson DL, Tamma PD. Navigating available treatment options for carbapenem-resistant Acinetobacter baumannii-calcoaceticus complex infections. *Clin Infect Dis*. 2023;76(5):S179–S193. doi:10.1093/cid/ciad094
30. Lei H, Liu X, Li Z, et al. Analysis of the clinical characteristics of tigecycline-induced hypofibrinogenemia. *J Chemother*. 2023;35(4):292–297.
31. Wang W, Liu Y, Yu C, et al. Cefoperazone-sulbactam and risk of coagulation disorders or bleeding: a retrospective cohort study. *Expert Opin Drug Saf*. 2020;19(3):339–347. doi:10.1080/14740338.2020.1713090
32. Guclu E, Kaya G, Ogutlu A, et al. The effect of cefoperazone sulbactam and piperacillin tazobactam on mortality in Gram-negative nosocomial infections. *J Chemother*. 2020;32(3):118–123. doi:10.1080/1120009X.2020.1730087
33. Lin C, Tan M, Wang D, et al. Safety of tigecycline in patients on antithrombotic therapy: a single-center retrospective study. *Pharmacology*. 2023;108(6):540–549. doi:10.1159/000532001
34. Zhang L, Cai X, Peng F, et al. Comparison of bleeding risk and hypofibrinogenemia-associated risk factors between tigecycline with cefoperazone/sulbactam therapy and other tigecycline-based combination therapies. *Front Pharmacol*. 2023;14(6):1182644. doi:10.3389/fphar.2023.1182644
35. Miao W, Guo J, Cheng H, et al. Risk factors for cefoperazone/sulbactam-induced coagulation disorder. *Infect Drug Resist*. 2023;16(9):6277–6284. doi:10.2147/IDR.S429706
36. LaPlante KL, Dhand A, Wright K, et al. Re-establishing the utility of tetracycline-class antibiotics for current challenges with antibiotic resistance. *Ann Med*. 2022;54(1):1686–1700. doi:10.1080/07853890.2022.2085881
37. Zha L, Pan L, Guo J, et al. Effectiveness and safety of high dose tigecycline for the treatment of severe infections: a systematic review and meta-analysis. *Adv Ther*. 2020;37(3):1049–1064. doi:10.1007/s12325-020-01235-y