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ORIGINAL RESEARCH

Evaluation of Tigecycline Utilization and Trends in Antibacterial Resistance from 2018 to 2021 in a Comprehensive Teaching Hospital in China

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Purpose: Tigecycline, the first glycylcycline antibiotic, which was widely used for off-label indications because of its broad-spectrum antibacterial activity. This study evaluated the indications for clinical use of tigecycline, clinical and microbiological effectiveness, factors associated with in hospital mortality, and bacterial resistance.

Methods: This retrospective study evaluated all inpatients who received tigecycline treatment for >72 hours between January 2018 and December 2021 in a comprehensive teaching hospital in China. The evaluation included indications, administration regimen, etiology, efficacy and so on. Univariate and multivariate analyses were used to evaluate the risk factors for all-cause mortality.

Results: There were 203 patients treated with tigecycline. Tigecycline was commonly prescribed for off-label indications (83.25%, 169/203), and hospital-acquired pneumonia ranked first (79.29%, 134/169). The most common pathogen was *Acinetobacter baumannii*. Clinical and microbiological success was 57.14% (116/203) and 32.28% (41/127), respectively. Fifty-four patients died and all-cause mortality was 26.60%. Univariate and multivariate analyses showed no significant difference in age, gender, off-label indication, duration of treatment, combination with other drugs, multidrug-resistant or extensively drug-resistant infections and tigecycline application scoring with respect to mortality.

Conclusion: Although detection of *A. baumannii* has decreased in the past 4 years in our hospital, resistance to tigecycline has increased. For clinical application, physicians attach importance to detection of pathogenic microorganisms, but there is still empirical medication without bacterial culture reports. Therefore, an antibiotic stewardship program oriented toward tigecycline should be strengthened to curb bacterial resistance.

Keywords: off-label indication, antimicrobial resistance, rationality of medication, clinical prognosis

Introduction

With the emergence of multidrug-resistant and super-resistant bacteria, the problem of bacterial resistance has become a major challenge in global public health, and a concern for governments and society.[1–3] In 2020, the National Health Commission of the People's Republic of China published the theme on continuous management of the clinical application of antibiotics.[4]

Tigecycline, also known as GAR-936 or Tygacil, is a chemically modified minocycline (9-tbutylglycylamido derivative of minocycline).[5] The main mechanism of action of tigecycline is causing protein synthesis inhibition by interaction with the bacterial 30S ribosome subunit.[6] Tigecycline was approved by the US Food and Drug Administration (FDA) to treat complicated skin and soft tissue infections (cSSTIs), complicated intra-abdominal infections (cIAIs), and community-acquired pneumonia

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(CAP).[7] The recommended standard dosing regimen for all indications is a 100 mg loading dose followed by 50 mg every 12 h.[8] The recommended duration of treatment with tigecycline for cSSTI or cIAI and CAP is 5–14 and 7–14 days, respectively.[9] Tigecycline has broad-spectrum antibacterial activity, especially against Gram-negative bacteria resistant to other antibiotics. Therefore, it has been widely used off-label for ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), and bloodstream infections (BSIs) caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens, especially carbapenem-resistant bacteria.[8] Consumption of tigecycline has increased as a result of its widespread off-label application in clinical practice and the clinical effectiveness varied between different indications.[5] However, resistance to tigecycline has emerged since its approval.[10] Related literature about the occurrence of tigecycline resistance to *Klebsiella pneumonia* and *Stenotrophomonas maltophilia* have been reported in China.[11] Tigecycline was first introduced to the Chinese pharmaceutical market in 2012, but our hospital officially included it into the hospital antibacterial drug list in 2018. In the same year, rules for clinical application of tigecycline were published by the National Health Commission of the People's Republic of China, which formulated the indications, administration regimen, etiology, efficacy evaluation, and consultation about and prescription of antibiotics for special use.[12] According to the China Antimicrobial Surveillance Network (CHINET), which covered 1371 hospitals in China, the national average resistance rates of two commonly treated bacteria with tigecycline, *A. baumannii* and *K. pneumoniae* to carbapenems were 53.7% and 10.9%, respectively in 2020.[13] Bacteriological monitoring reports in our hospital have shown an upward trend in drug resistance.The aim of this study was to evaluate the indications for clinical use of tigecycline, clinical and microbiological effectiveness, factors associated with in hospital mortality, and bacterial resistance in a comprehensive teaching hospital in China.

Materials and Methods

Setting and Study Design

This single center retrospective observational study was conducted in Beijing Chaoyang Hospital affiliated to Capital Medical University. The hospital is a Level III A hospital integrating medical, teaching, scientific research and prevention under direct leadership of Beijing Municipal Administration of Hospitals, is the third clinical medical college of Capital Medical University, and is also the designated Category A medical institution for Beijing Municipal medical insurance. The study included inpatients who received tigecycline for >72 hours between January 1, 2018 and December 31, 2021, excluding those for whom detailed evaluation data were not available. The protocol was approved by the Drug and Therapeutics Committee and the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (Approval number: 2022-9-19-1).

Data Collection

The demographic information, diagnosis, medication details, biochemical and bacteriological test results of patients were collected from the electronic medical records system. Bacteriological surveillance data from 2018 to 2021 were provided by the Department of Infectious Diseases and Clinical Microbiology, and obtained through the Clinical Microbiology Laboratory Management System. The following data were collected: (1) gender and age; (2) diagnosis, including infection sites and treatment indications; (3) comorbidity, such as diabetes, heart disease, hypertension, hepatic dysfunction, and renal insufficiency; (4) medication details, such as dose, duration of treatment, and concomitant antibiotics; (5) biochemical test results, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, and creatinine; (6) microbiology laboratory results, such as specimen type, culture results, and drug sensitivity; and (7) indicators of infection, such as C-reactive protein, procalcitonin, white blood cell count, and erythrocyte sedimentation rate. A quality management plan for the research was developed before the study conducted. The data was collected by two-person and re-checked.

Tigecycline Application Scoring

The rationale for the use of tigecycline was evaluated based on the rules for clinical application of tigecycline, which was constructed and published by the National Health Commission of the People's Republic of China (Table 1).[14] Evaluation included indications, administration regimen, etiology, efficacy, prescription and consultation. There were 100 points in the evaluation form, and points were deducted if the evaluation criteria were not met.

Table 1 Rules for Evaluation of Clinical Application of Tigecycline

Evaluation Rules	Score
Part one: indications	100 points deducted for noncompliance
(1) Complicated IAI, cSSTI, critically ill patients with CAP. (2) MRAB and CRE infection (central nervous system and urinary tract infections not included).	
Part two: treatment strategy	Violation results in 15-point deductions for each item
(1) Tigecycline should not be used alone for the treatment of extensively drug-resistant Gram-negative infection. (2) Initial dose 100 mg, followed by 50 mg every 12 hours. Children 8–11 years: 1.2 mg/kg every 12 hours, maximum dose 50 mg every 12 hours; 12–17 years: 50 mg every 12 hours. (3) No dose adjustment is warranted in patients with mild to moderate hepatic impairment (Child–Pugh A and B). Patients with severe hepatic insufficiency (Child–Pugh C): initial dose 100 mg, followed by 25 mg every 12 hours. (4) For treatment of HAP, VAP, and severe infections caused by CRE or CRAB, maintenance dose can be increased to 100 mg every 12 hours.	
Part 3: pathogenic microbiology and evaluation of efficacy.	20 points deducted for noncompliance
(1) Bacterial culture of pathogenic microorganisms should be performed before the drug is used. (2) Dynamic laboratory tests, such as blood tests, procalcitonin, and bacterial cultures, should be monitored to evaluate treatment efficacy.	
Part 4: management and consultation on the use of special category drugs	10 points deducted for noncompliance
(1) Prescriptions should be issued by senior physicians. (2) Specialist consultation records are required. (3) The overstep use[a] needs to be explained in the case, and evidence should be submitted within 24 hours. (4) Special registration is required for patients treated with tigecycline. (5) Physicians need to participate in regularly organized training and assessment.	

Notes: [a]A junior doctor in an emergency prescribed tigecycline. Data translated from National Health and Family Planning Commission. Open Access.[14]
Abbreviations: CAP, community-acquired pneumonia; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; cSSTI, complicated skin and soft tissue infection; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; MRAB, Multidrug-resistant *A. baumannii*; VAP, ventilator-associated pneumonia.

Evaluation of Clinical Outcomes

The "Technical Guidelines for Clinical Trials of Antibacterial Drugs" was used for clinical efficacy evaluation.[15] According to the symptoms, signs, laboratory and etiological examinations, the therapeutic effect was divided into four grades: cured, effective, improved and ineffective. Cured referred to the disappearance or return to normal of clinical symptoms, signs, laboratory tests, and/or bacteriological eradication. Effective meant that the condition was significantly improved, but one of the above indicators had not completely returned to normal. Improved was defined as improvement of clinical symptoms and signs relative to the condition before treatment, but not significant relative to cured and effective. In clinical prognostic evaluation, cured, effective and improved were considered to be clinical success. Ineffective referred to unchanged or worsened symptoms and signs, and switching to other anti-infective treatment, which represented clinical failure.

Evaluation of Microbiological Outcomes

Based on microbiological results and drug susceptibility testing, the microbiological efficacy was divided into eradication, no eradication and not available. Eradication was defined as the absence of the original pathogens in culture of specimens collected from the original site, which was identified with microbiological success. No eradication meant the persistence of original pathogens in follow-up cultures from the original infection site after treatment, which was identified with microbiological failure. Not available referred to specimen that was not available for estimation of eradication. In microbiological outcome evaluation, the not available cases were excluded.[16]

Mortality

The primary outcome of the study was in hospital mortality, which was defined as the status at the time of hospital discharge in survivors and non-survivors.[17]

Antimicrobial Susceptibility Test

Bacterial identification was performed according to standard microbiological procedures. Antibiotic susceptibility was performed using the VITEK-2 Compact and the disc diffusion method. All microbiological methods were acted in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines of the corresponding year and the CLSI breakpoints of the corresponding year was used to identify the antimicrobial susceptibility. A 15-μg disc of tigecycline (Oxoid Ltd, Cambridge, UK) was used to determine susceptibility, and the breakpoints suggested by the FDA for *Enterobacteriaceae* (susceptible ≥19 mm; intermediate 15–18 mm, and resistant ≤14 mm), and gram-positive microorganisms (susceptible ≥19 mm) were used.[18] Tigecycline clinical breakpoints using the disc-diffusion method against *A. baumannii* have not been established by both the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Our laboratory applied the clinical breakpoints recommended by the expert consensus of operating procedures for tigecycline in vitro sensitivity test published in 2013 (susceptible ≥16 mm, intermediate 13–15 mm, and resistant ≤12 mm).[19]

Statistical Analysis

The data were analyzed using SPSS version 26.0 (SPSS, Inc, Chicago, IL, USA). The numerical variables were represented by mean ± standard deviation. The categorical variables were expressed by number and percentage. Univariate analysis was used to evaluate the effects of gender, age, course of treatment, off-label drug use, and combined drug use on mortality. Chi-square tests were used for univariate analysis of categorical variables. $P<0.05$ was considered to indicate statistical significance. Multivariate logistic regression was used to assess all-cause mortality. Results were presented as odds ratio (OR) and 95% confidence interval (CI).

Results

Between January 1, 2018 and December 31, 2021, 274 hospitalized patients were treated with tigecycline. We excluded 56 patients whose treatment course was ≤3 days, and 15 for whom basic information was missing, which left 203 patients for inclusion in the study.

Demographics and Epidemiology

The utilization rate of antibiotics in inpatients from 2018 to 2021 was 33.77%, 31.16%, 41.03% and 35.51%, respectively. At the same time, the utilization rate of tigecycline was 1.394‰, 2.196‰, 2.912‰ and 2.745‰. There were 203 patients, 154 male and 49 female, aged 17–97 years (median 62±14.65 years). All demographic and clinical characteristics are shown in Table 2. Over half the patients (105/203, 51.72%) were older than 65 years. Heart diseases were the main underlying conditions (102/203, 50.25%). Followed by liver-related diseases (93/203, 45.81%). According to Child-Pugh Score (CPS) classification, there were seven cases with CPSc, five with CPS_B, and nine with CPS_A.[20] Pulmonary diseases (80/203, 39.41%) ranked the third. The rate of admission to intensive care unit was 73.89% (150/203).

Diagnosis and Strategy of Treatment

Most infections were pulmonary or abdominal, and most cases were complicated with multiple infections (As shown in Table 3). Patients with indications for FDA-approved use of tigecycline included 18 with CAP, 14 with cIAIs, and two with cSSTIs. Off-label indications included 134 patients with HAP, 24 with BSI, nine with sepsis, and one each with VAP or urinary tract infection (UTI). We found that only 34 (16.75%) patients were treated with tigecycline for an indication approved by the FDA or European Medicines Agency. Conversely, the number of off-label indications was at a significantly high rate of 83.25% (169 patients). Tigecycline was combined with other antibiotics in 186 (91.62%) cases. Tigecycline was most frequently combined with cefoperazone–sulbactam (52/186, 27.96%) followed by

Table 2 Demographics and Epidemiology of Patients Treated with Tigecycline

Characteristics	Values
Demographic parameters	
Age, mean±SD, years	62±14.65
Male/female	154/49
Comorbidities	
Heart disease	102
Hepatic dysfunction	93
Pulmonary disease	80
Hypertension	69
Renal insufficiency	62
Diabetes	42
Malignancy	36
Immunocompromise	6
Organ transplantation	4
Patient's ward distribution	
ICU	150
Non-ICU	53

Table 3 Indications, Duration and Treatment Strategy in Patients Receiving Tigecycline

Tigecycline Treatment	Case	Tigecycline Treatment	Case
FDA-approved indications	34	Monotherapy	17
CAP	18	Combination therapy	186
cIAI	14	Cefoperazone–sulbactam	52
cSSTI	2	Carbapenem	29
Off-label	169	Amikacin	11
HAP	134	Piperacillin–tazobactam	10
BSI	24	Quinolones	9
Sepsis	9	Glycopeptide	6
UTI	1	Others[a]	69
VAP	1	Duration of TGC therapy regardless the indication, mean ± SD, days	11 ± 5.86
		≤7 days	52
		7–14 days	99
		≥14 days	52

Notes: [a]Included tigecycline combined with, eg, amphotericin B, metronidazole, ceftazidime, avibactam, sulfamethoxazole, and linezolid.
Abbreviations: CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; cSSTI, complicated skin and soft tissue infection; FDA, US Food and Drug Administration; HAP, hospital-acquired pneumonia; BSI, bloodstream infection; UTI, urinary tract infection; VAP ventilator-associated pneumonia.

carbapenems (29/186, 15.59%) and amikacin (11/186, 5.91%). The duration of treatment with tigecycline was 3–41 days; 52 patients were treated within 7 days, 52 for >14 days, and 99 within 7–14 days. The median length of hospital stay was 41±33.07 days, and the mean length of tigecycline treatment was 11±5.86 days.

Bacterial Isolates and Drug Susceptibility

All the 203 patients were sent for etiology test, and the positive proportion of pathogen culture results was 97.54% (198/203). The main sources of bacteria were sputum, bronchoalveolar lavage fluid, ascites, and venous whole blood; among

Table 4 Distribution of Top 10 Detected Bacteria and Drug Sensitivity

Name of Pathogens	Sputum	Blood	BALF	Drainage Fluid	Wound Fluid	Tissue and Body Fluids[a]	Urine	Catheter Tip	Strains	MDR	PDR
A.baumannii	88	8	62	9	1	1	5	1	110	101	5
K. pneumoniae	54	22	14	9	5	2	12	1	86	64	–
P. aeruginosa	22	1	8	4	–	1	1	1	35	4	–
Efm	–	9	–	11	1	2	6	1	27	23	–
S. maltophilia	14	1	6	2	–	–	–	1	21	–	–
S. epidermidis	–	12	–	4	–	2	–	1	18	13	–
E. coli	4	6	–	5	1	1	2	2	18	14	–
E. cloacae	4	2	1	3	1	–	4	–	14	9	–
S. aureus	8	–	1	1	2	–	–	–	11	8	–
SE (Hominine)	–	6	–	2	–	1	–	–	9	–	–
Total	194	67	92	50	11	10	31	8	355 [b]	236 [b]	5

Notes: [a]Tissue and body fluids contain cerebrospinal fluid and bile. [b]Number of cases more than 203 because multiple pathogenic bacteria may have been detected at the same time. The antibiotics tested in drug sensitivity tests include: Gentamicin, Tobramycin, Amikacin, Piperacillin-tazobactam, Imipenem, Meropenem, Cefazolin, Cefuroxime, Ceftriaxone, Ceftazidime, Cefoxitin, Ciprofloxacin, Trimethoprim-sulphamethoxazole, Tigecycline, Aztreonam, Ampicillin, Amoxicillin-clavulanic acid, Ampicillin-sulbactam, Chloramphenicol, Colistin.

Abbreviations: BALF, Bronchoalveolar lavage fluid; MDR, Multidrug-resistant; PDR, Pan-drug resistant; *A.baumannii*, *Acinetobacter baumannii*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *Efm*, *Enterococcus faecium*; *S. maltophilia, Stenotrophomonas maltophilia; S. epidermidis, Staphylococcus epidermidis; E. coli, Escherichia coli; E. cloacae*, *Enterobacter cloacae*; *S. aureus*, *Staphylococcus aureus*; SE (hominine), *Staphylococcus epidermidis* (hominine).

which, sputum specimens accounted for 43.60% (194/445). A total of 55 bacteria were isolated. The top 10 were *A. baumannii* (n=110), *Klebsiella pneumoniae* (n=86), *Pseudomonas aeruginosa* (n=35), *Enterococcus faecium* (n=27), *Stenotrophomonas maltophilia* (n=21), *Staphylococcus epidermidis* (n=18), *Escherichia coli* (n=18), *Enterobacter cloacae* (n=14), *Staphylococcus aureus* (n=11), and *Staphylococcus hominis* subspecies *hominis* (n=9). We detected 236 drug-resistant bacteria among the above-mentioned strains (detected as different secretions from patients). Among them, MDR *A. baumannii* was the most commonly detected strain, followed by MDR *K. pneumoniae* (Table 4).

Trends in Microbiology and Antibacterial Resistance

In the past 4 years, the top five most frequently isolated Gram-negative bacilli in our hospital were *E. coli, P. aeruginosa, K. pneumoniae, A. baumannii* and *E. cloacae. E. coli* was always listed as the most common isolate from 2018 to 2021. The percentage of *K. pneumoniae* isolates showed a decreasing trend from 17.98% in 2018 to 17.18% in 2020, and then increasing to 20.09% in 2021. *A. baumannii* decreased from 12.52% in 2018 to 7.24% in 2021 (Figure 1). These two types of bacteria were also the most common bacteria among patients treated with tigecycline.

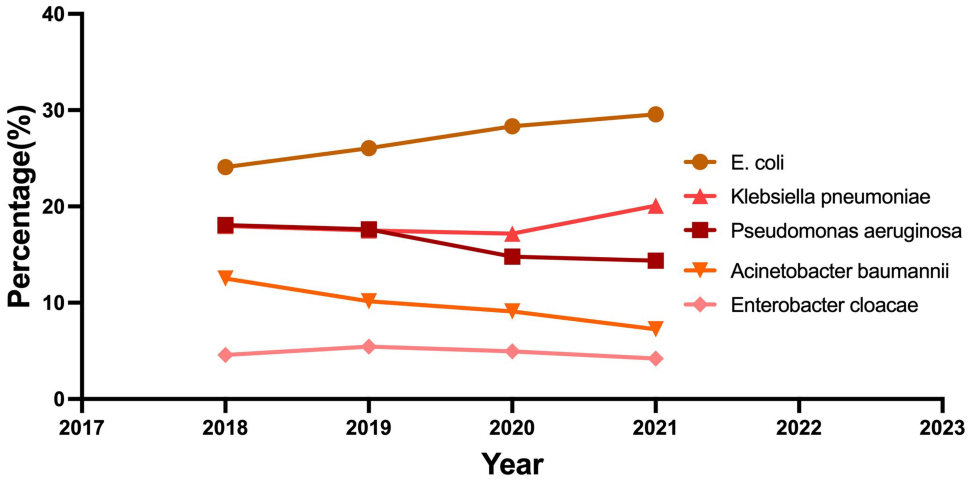

Figure 1 Top five Gram-negative bacilli isolated from 2018 to 2021.

A. baumannii had a high rate of resistance against six commonly used antibiotics. The resistance rates of *A. baumannii* to cefoperazone sulbactam, piperacillin-tazobactam, imipenem, meropenem, amikacin and tigecycline was 60.60%, 64.54%, 63.56%, 63.12%, 62.54% and 32.71%, respectively. The resistance rates of *K. pneumoniae* against those six commonly used antibiotics was 25.62%, 19.32%, 15.05%, 14.36%, 11.00% and 24.04%, respectively. The year by year trends were shown in Figures 2–3.

Rationale for Tigecycline Use and Outcome

The rationale for tigecycline prescription was judged according to its evaluation for clinical application. The result was shown in Table 5. Among the 203 cases, one hundred and sixty-three (80.30%) scored 100 points, which fully met the evaluation criteria of four aspects in Table 1. Eight cases (3.94%) were 90 points, and the deduction reason was lack of specialist consultation records. Thirty-two (15.76%) cases were 0 points because of without indications listed in Table 1, such as UTI.

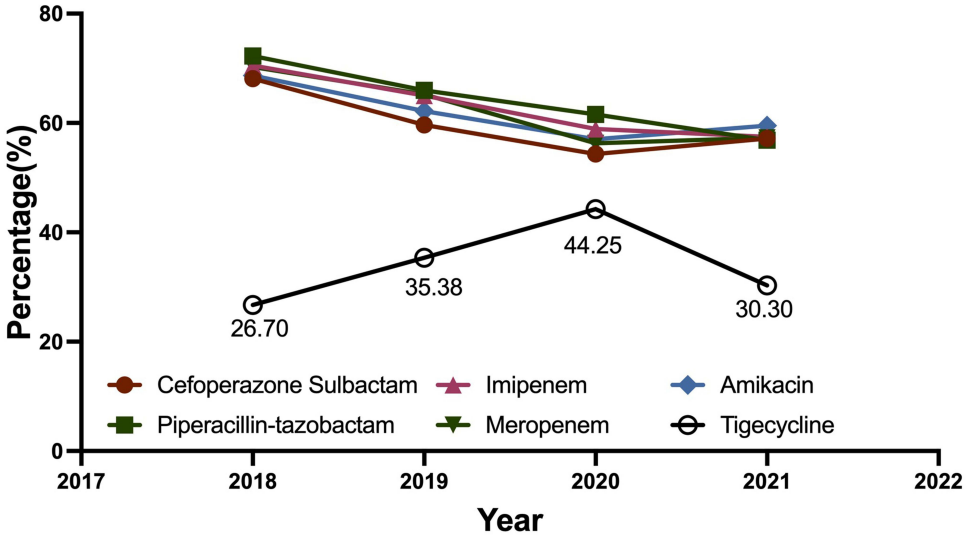

Figure 2 Resistance profile of *Acinetobacter baumannii* species for six commonly used antimicrobials from 2018 to 2021.

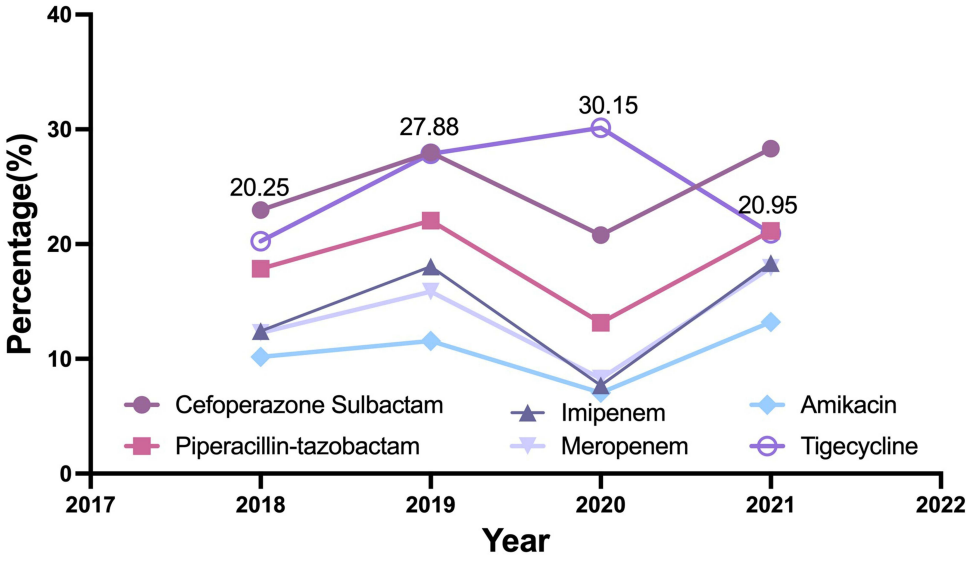

Figure 3 Resistance profile of *Klebsiella pneumoniae* species for six commonly used antimicrobials from 2018 to 2021.

Table 5 Rationale for Tigecycline Use and Outcome

Medication Evaluation (score)	Case/percentage
100	163/80.30%
90	8/3.94%
0	32/15.76%
Clinical outcome	
Success	116/57.14%
Failure	87/42.86%
Deaths	54/26.60%
Microbiological outcome	
Success	41/32.28%
Failure	86/67.72%
Not available[a]	71/35.86%

Notes: 100 points = compliance with the guidelines for tigecycline use; 90 points = lack of consultation records; 0 points = non-compliance with guidelines for tigecycline use . [a]Not available referred to specimen that was not available for estimation of eradication. The not available cases were excluded when calculated microbiological success rate.

Microbiological evaluation was based on the 198 patients whose pathogen culture was positive. The microbiological success rate was 32.28% (41/127). According to the efficacy evaluation in "Technical Guidelines for Antimicrobial Clinical Trials", among the 203 patients who received tigecycline, 116 (57.14%) achieved clinical success and 87 (42.86%) were judged as clinical failure. This included 54 patients who died, which resulted in an all-cause mortality rate of 26.60%. Univariate and multivariate analyses showed that there was no significant difference in age, gender, off-label indication, duration of treatment, combination with other drugs, MDR or XDR infections and tigecycline application scoring. With respect to comorbidities, patients with cardiovascular disease had a higher mortality rate than those without cardiovascular disease by univariate analysis (P=0.012) and multivariate analysis (OR=2.111, 95% CI 1.006–4.179, P=0.032) (Table 6). The univariate analysis (P=0.001) and multivariate analysis (OR=4.554, 95% CI 1.667–12.441, P=0.003) showed a significant difference in the mortality in the patients admission to ICU.

Table 6 Analysis of Risk Factors Associated with Mortality

Risk Factor (n)	Survivors	Nonsurvivors	Univariate Analysis,	Multivariate Logistic Regression Analysis
			P Value	P Value (95% CI)
Age ≥65 years (104)	72	32	0.168	
Male (154)	111	43	0.414	
Comorbidities				
Hypertension (69)	53	16	0.385	
Hepatic dysfunction (93)	71	22	0.330	
Diabetes (42)	28	14	0.296	
Renal insufficiency (62)	45	17	0.922	
Heart disease (102)	67	35	0.012	P=0.032, (OR=2.111, 95% CI 1.066–4.179)
Pulmonary disease (80)	63	17	0.164	P=0.178, (OR=1.898, 95% CI 0.748–4.816)
Tumor (36)	25	11	0.592	
Immunocompromise (6)	3	3	0.197	
Organ transplantation (4)	2	2	0.294	
FDA approved indications (34)	25	9	0.985	
Duration of therapy				

(*Continued*)

Table 6 (Continued).

Risk Factor (n)	Survivors	Nonsurvivors	Univariate Analysis, P Value	Multivariate Logistic Regression Analysis P Value (95% CI)
≤7 days (53)	40	13	0.842	
7–14 days (113)	76	37	0.091	
>14 days (37)	27	10	0.470	
Combination medication (186)	136	53	0.148	P=0.131, (OR=0.574, 95% CI 0.280–1.180)
ICUs	116	43	0.001	P=0.003, (OR=4.554, 95% CI 1.667–12.441)
XDR[b]	75	28	0.849	
MDR[c]	46	14	0.495	
Score 100[a]	116	43	0.768	

Notes: [a]Cases with a score of 100 points according to the score of rationality of drug use (Table 1). [b]XDR: non-susceptible to ≥1 agent in all but ≥2 categories.[8] cMDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.[8]
Abbreviations: CI, confidence interval; OR, odds ratio; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Discussion

Tigecycline was first approved by the FDA in 2005 for treatment of cIAIs and cSSTIs in adults.[21] In 2009, the FDA added CAP in adults to the list of approved indications. Tigecycline has demonstrated promising in vitro activity against extended spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and extensively drug-resistant *A. baumannii*.[22–25] Because of the lack of other treatment options, tigecycline was prescribed for off-label indications such as HAP, VAP, UTI, sepsis, bacteremia, and febrile neutropenia.[26,27] In an Chinese consensus statement, tigecycline was recommended for the treatment of XDR-Enterobacteriaceae and XDR-*A. baumannii*.[28] Among the 203 cases included in this study, there were more off-label indications (83.25% 169/203) than FDA-approved indications (16.75%, 34/203). It was accordance with previous studies.[27] HAP (79.29%, 134/169) was the most common indication for off-label use. However, the application of off-label indications remains controversial. The 2016 guidelines for the diagnosis and treatment of HAP jointly formulated by the Infectious Disease Society of America and American Thoracic Society clearly oppose the use of tigecycline for treatment of HAP caused by *A. baumannii*. These recommendations place a higher value on avoiding potential adverse effects of combination therapy with rifampicin and colistin, than on achieving increased microbial eradication rate, because eradication rate was not associated with improved clinical outcome.[29] Although strongly recommended, the quality of the evidence is low. The etiology and bacterial resistance in China differ from those in the USA; therefore, more clinicians agree that the existing evidence is far from denying the value of tigecycline for treatment of *A. baumannii*-induced HAP. At present, tigecycline-based combination therapy is an indispensable and important option for HAP caused by *A. baumannii* in China.[30]

According to the regulation of antibiotics grading management in China, tigecycline belongs to the special use class of antibiotics. This means that it can be used only after consultation with a clinician or clinical pharmacist specialized in infection. In special cases, it can be used for 24 hours and recorded in the medical records. In our study, eight patients (3.94%) lacked consultation records; therefore, the rationale evaluation was 90 points. In the rules for evaluation in Table 1, the indications for tigecycline have been extended from CAP, cIAI and cSSTI to MRAB and CRE infections (central nervous system infections and UTIs not included). We had 32 patients (15.76%) which did not meet the above indications; one of whom received tigecycline for treatment of UTI. Tigecycline has good tissue penetration and distribution in bone, liver, spleen and kidney, but only 33% of the total dose is excreted unchanged in urine.[31] A meta-analysis of 19 studies showed that clinical cure was 77.4% and microbiological eradication accounted for 65.2% of these cases.[32] However, only 31 patients were included in that study, and considering the pharmacokinetic characteristics of tigecycline, it is still not recommended for UTI treatment.

A. baumannii is a cause of serious healthcare-associated infections worldwide.[33] Mortality associated with invasive *A. baumannii* infection is high, especially for carbapenem-resistant cases. Crude mortality for carbapenem-resistant *A. baumannii* infections ranges from 16% to 76%, as opposed to 5–53% for carbapenem-susceptible infections.[34] In our study, the total mortality was 26.6%. Univariate and multivariate analyses showed that patient with cardiovascular disease and patients admitted to ICU had significant effect on all-cause mortality. In September 2013, the FDA approved a new box warning about an

increased risk of death with tigecycline, and updated the warnings and precautions and adverse reactions sections. Therefore, tigecycline should be reserved for use in situations in which alternative treatments are not suitable.[35]

This study had some limitations. First, it was a single center retrospective analysis and the sample size was limited. There was potential for inclusion bias because some basic information was missing. The observed microbiological success rate was subject to surveillance bias because some cases did not have follow-up cultures. Nevertheless, we believe this was a meaningful comparative clinical study in which we analyzed the rationale for tigecycline use, clinical efficacy, and risk factors for all-cause mortality. In the future, a prospective multicenter study should be conducted to determine the efficacy and safety of tigecycline.

Conclusion

We found that tigecycline is commonly used in off-label indications, among which, HAP ranked first. From the bacteriological perspective, tigecycline is mostly used for treatment of *A. baumannii* infection. Although the detection rate of *A. baumannii* has decreased in the past 4 years, resistance to tigecycline has increased in our hospital. In clinical applications, physicians attach importance to detection of pathogenic microorganisms, but there is still empirical medication without bacterial culture reports. Therefore, antibiotic stewardship programs oriented toward tigecycline should be strengthened to curb bacterial resistance.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University and was conducted in accordance with the principles of the Declaration of Helsinki. Patient information collected in the case system did not contain name, address or other personal information, so the patient's written informed consent was exempt.

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Disclosure

The authors report no conflicts of interest in this work.

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