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Impact of Tigecycline's MIC in the Outcome of Critically Ill Patients with Carbapenemase-Producing *Klebsiella pneumoniae* Bacteraemia Treated with Tigecycline Monotherapy—Validation of 2019's EUCAST Proposed Breakpoint Changes

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Abstract: Background: Tigecycline is a therapeutic option for carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp). Our aim was to evaluate the impact of the tigecycline's minimum inhibitory concentration (MIC) in the outcome of patients with CP-Kp bacteraemia treated with tigecycline monotherapy. Methods: Patients with monomicrobial bacteraemia due to CP-Kp that received appropriate targeted monotherapy or no appropriate treatment were included. Primary outcome was 30-day mortality. MICs of meropenem, tigecycline, and ceftazidime/avibactam were determined by Etest, whereas for colistin, the broth microdilution method was applied. PCR for bla_{KPC}, bla_{VIM}, bla_{NDM}, and bla_{OXA} genes was applied. Results: Among 302 CP-Kp bacteraemias, 32 isolates (10.6%) showed MICs of tigecycline ≤ 0.5 mg/L, whereas 177 (58.6%) showed MICs that were 0.75–2 mg/L. Colistin and aminoglycoside susceptibility was observed in 43.0% and 23.8% of isolates, respectively. The majority of isolates carried bla_{KPC} (249; 82.5%), followed by bla_{VIM} (26; 8.6%), both bla_{KPC} and bla_{VIM} (16; 5.3%), and bla_{NDM} (11; 3.6%). Fifteen patients with tigecycline MIC ≤ 0.5 mg/L and 55 with MIC 0.75–2 mg/L were treated with tigecycline monotherapy; 30-day mortality was 20.0% and 50.9%, respectively ($p = 0.042$). Mortality of 150 patients that received other antimicrobials was 24.7%; among 82 patients that received no appropriate treatment, mortality was 39.0%. No difference in 30-day mortality was observed between patients that received tigecycline (MIC ≤ 0.5 mg/L) or other antimicrobials. Conclusion: Tigecycline monotherapy was as efficacious as other antimicrobials in the treatment of bloodstream infections due to CP-Kp isolates with a tigecycline's MIC ≤ 0.5 mg/L.

Keywords: tigecycline; bloodstream infection; carbapenemase; carbapenem-resistance; ceftazidime/avibactam; colistin; mortality

1. Introduction

Carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) has become a significant global public health challenge [1]. The arrival of novel beta-lactam/beta-lactamase inhibitor combinations, such as ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, the siderophore cephalosporin, cefiderocol, and a next-generation aminoglycoside, plazomicin, has increased the available treating options in our arsenal, improving the outcome of such infections [2]. Previously, the available antimicrobial treatment options were colistin, tigecycline, aminoglycosides, fosfomycin, and carbapenems [3,4]. Combination therapy has been proposed as the best choice, but there are no clear data showing which combination therapy is superior [5].

Tigecycline is the first member of the glycylcycline class, has a broad spectrum of antibacterial activity, and achieves adequate levels into different tissues [6]. It has been approved for community-acquired pneumonia, skin and soft-tissue, and intraabdominal infections [6]. The use of tigecycline in bacteremia is controversial because of its low serum levels with standard dosing [7]. Despite such limitation, tigecycline is a useful alternative for the treatment of infections due to CP-Kp and has been shown to be an effective and safe drug for the treatment of severe CP-Kp infections [8,9]. In observational studies, tigecycline was equally effective to other options (colistin, aminoglycosides, carbapenems) even when used as monotherapy [8,9].

In 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) revised the minimum inhibitory concentration (MIC) breakpoints for tigecycline [10]; prior to 2019, an isolate was considered susceptible if the MIC was ≤ 1 mg/L and resistant if MIC was > 2 mg/L [11]; since 2019, an isolate with MIC > 0.5 mg/L has been considered resistant [10]. This revision rendered most of the isolates that were previously considered as susceptible to be considered resistant [12].

The aim of the present study was to evaluate the impact of the tigecycline's MIC in the outcome of critically ill patients with CP-Kp bacteraemia treated with tigecycline monotherapy.

2. Results

In total, 302 episodes of monomicrobial bloodstream infections (BSIs) due to CP-Kp were included. Most BSIs were primary (131; 43.4%) and catheter-related (111; 36.8%); the remaining bacteraemias were associated with ventilator-associated pneumonia (24; 7.9%), abdominal infection (22; 7.3%), meningitis (7; 2.3%), urinary tract infection (6; 2.0%) and deep surgical site infection (1; 0.3%). The majority carried bla_{KPC} (249; 82.5%), followed by bla_{VIM} (26; 8.6%), both bla_{KPC} and bla_{VIM} (16; 5.3%), and bla_{NDM} (11; 3.6%) (Supplementary Materials).

Two isolates (0.7%) had MIC ≤ 8 mg/L to tested carbapenem (imipenem, meropenem). Concerning tigecycline, 32 isolates (10.6%) showed MIC ≤ 0.5 mg/L and 177 (58.6%) MICs ranging from 0.75 to 2 mg/L (Table 1). Susceptibility rates for aztreonam, sulfamethoxazole-trimethoprim, and ciprofloxacin were 2.3%, 4.3%, and 0.7%, respectively. Colistin and aminoglycoside susceptibility was observed in 43.0% and 23.8% of isolates, respectively. Fosfomycin and ceftazidime/avibactam were tested in 58 and 24 isolates, respectively; among them, 29 (50.0%) and 21 (87.5%) were susceptible.

Table 1. Minimum inhibitory concentration (MIC) distribution and susceptibility of 302 carbapenemase-producing *Klebsiella pneumoniae* isolates to different antimicrobials according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

	MIC (mg/L)														EUCAST	
	0.125	**0.25**	**0.38**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**32**	**S (%)**	**R (%)**
Tigecycline	1	3	6	22	**20**	**52**	**52**	**53**	**18**	**47**	**6**	**12**	**3**	**7**	32 (10.6)	270 (89.4)

Resistant isolates according to EUCAST appear in bold. S: susceptible; R: resistant.

Group A (tigecycline monotherapy; MIC of tigecycline ≤ 0.5 mg/L) and B (tigecycline monotherapy; MIC of tigecycline 0.75–2 mg/L) included 15 and 55 patients, respectively; the 30-day mortality was 20.0% and 50.9%, respectively. Group C (appropriate targeted monotherapy other than tigecycline) included 150 patients and had a 30-day mortality of 24.7%; the repartition of antimicrobials received was 111 colistin, 29 aminoglycoside, 8 ceftazidime/avibactam, and 2 carbapenems (MIC of imipenem and meropenem ≤ 4 mg/L). Group D (no appropriate targeted therapy) included 82 patients and had a 30-day mortality of 39.0%. The univariate analyses comparing different groups are shown in Table 2. Compared with Group A, Group B showed a statistically higher mortality ($p = 0.042$), while no difference in types of infections or septic shock occurrence or comorbidities was observed. No difference in 30-day mortality was observed among patients in Groups A and C. In addition, patients receiving appropriate monotherapy (Group A and C) had significantly lower 30-day mortality ($p < 0.001$) as compared to those that did not (Group B and D).

Univariate and multivariate analyses among Group A and Group B patients of predictors of 30-day mortality are shown in Table 3. Multivariate analysis revealed septic shock ($p = 0.001$; Odds Ratio 7.834, 95% Confidence Interval 2.343–26.198) as the sole independent predictors of mortality.

Table 2. Univariate analyses of characteristics of patients depending on received antibiotic treatment among patients with carbapenemase-producing *K. pneumoniae* (CP-Kp) bloodstream infection (BSI) during intensive care unit (ICU) hospitalization.

Characteristics	Group A (*N* = 15) Tigecycline Monotherapy (MIC ≤ 0.5 Mg/L)	Group B (*N* = 55) Tigecycline Monotherapy (MIC 0.75–2 Mg/L)	*p* [a]	Group C (*N* = 150) [b] Monotherapy Other Than Tigecycline	*p* [c]	Group D (*N* = 82) No Appropriate Treatment	*p* [d]
Age (years)	47.3 ± 18.2	58.4 ± 17.9	0.063	55.1 ± 17.5	0.110	55.7 ± 17.1	0.310
Male gender	10 (66.7%)	38 (69.1%)	1.000	110 (73.3%)	0.556	57 (69.5%)	0.526
Charlson Comorbidity Index	2.3 ± 3.1	3.6 ± 3.7	0.095	3.5 ± 3.5	0.132	2.9 ± 3.2	0.734
Obesity	3 (20.0%)	18 (32.7%)	0.527	40 (26.7%)	0.716	25 (30.5%)	0.370
Infection data							
Days at risk	39.0 ± 69.1	26.5 ± 25.9	0.726	19.6 ± 27.0	0.134	28.5 ± 36.9	0.027
Type of bacteraemia							
Primary	6 (40.0%)	28 (50.9%)	0.564 [e]	60 (40.0%)	1.000 [e]	37 (45.1%)	0.202 [e]
Catheter-related	4 (26.7%)	15 (27.3%)		65 (43.3%)		27 (32.9%)	
Other [f]	5 (33.3%)	12 (21.8%)		25 (16.7%)		18 (22.0%)	
Septic shock	7 (46.7%)	34 (61.8%)	0.378	62 (41.3%)	0.786	32 (39.0%)	0.296
SAPS II upon onset of infection	39.5 ± 11.3	41.4 ± 13.1	0.784	39.9 ± 11.4	0.849	41.3 ± 13.2	0.626
SOFA score upon onset of infection	7.3 ± 4.0	8.4 ± 3.6	0.192	7.2 ± 3.3	0.823	7.4 ± 3.5	0.149
Hemofiltration	1 (6.7%)	4 (7.3%)	1.000	11 (7.3%)	1.000	8 (9.8%)	0.673
Outcome							
30-day mortality	3 (20.0%)	28 (50.9%)	0.042	37 (24.7%)	0.767	32 (39.0%)	<0.001

Data are number (%) of patients or mean ± standard deviation. SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment. [a] Comparison between Group A and B. [b] 111 colistin, 29 aminoglycoside, 8 ceftazidime/avibactam, and 2 carbapenems. [c] Comparison between Group A and C. [d] Comparison between Groups A and C against Groups B and D. [e] Comparison of primary BSIs against secondary ones. [f] 24 ventilator-associated pneumonias, 22 abdominal infections, 7 meningitis, 6 urinary tract infections, and 1 deep surgical site infection.

Table 3. Univariate and multivariate analyses of predictors of 30-day mortality among Groups A and B patients with carbapenemase-producing *K. pneumoniae* (CP-Kp) bloodstream infection (BSI) during intensive care unit (ICU) hospitalization.

	Univariate Analysis			Multivariate Analysis	
Characteristics	**Survivors (*N* = 39)**	**Non-Survivors (*N* = 31)**	***p***	***p***	**OR (95% CI)**
Age (years)	53.4 ± 17.5	61.6 ± 16.3	0.001		
Male gender	27 (69.2%)	21 (67.7%)	1.000		
Charlson Comorbidity Index	2.9 ± 3.4	4.5 ± 3.4	0.016	0.227	1.100 (0.942–1.283)
Obesity	10 (25.6%)	11 (35.5%)	0.436		
Infection data					
Days at risk	25.0 ± 35.4	22.1 ± 25.5	0.636		
Type of bacteraemia					
Primary	20 (51.3%)	14 (45.2%)			
Catheter-related	14 (35.9%)	5 (16.1%)	0.104 [a]		
Other [b]	5 (13.7%)	12 (38.2%)			
Septic shock	15 (38.5%)	26 (83.9%)	<0.001	0.001	7.834 (2.343–26.198)
SAPS II upon onset of infection	37.4 ± 9.9	51.4 ± 13.0	0.001		
SOFA score upon onset of infection	6.4 ± 2.8	10.7 ± 3.4	<0.001		
Hemofiltration	2 (5.1%)	3 (9.7%)	1.000		
Tigecycline MIC ≤ 0.5 mg/L	12 (30.8%)	3 (9.7%)	0.042	0.069	0.242 (0.052–1.118)

Data are number (%) of patients or mean ± standard deviation. OR: odds ratio; CI: confidence interval; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment. [a] Comparison between catheter-related bacteraemia and all other types of infection. [b] Seven ventilator-associated pneumonias, five abdominal infections, three meningitis, one urinary tract infection, and one deep surgical site infection.

3. Discussion

In the last decades, there has been an important paucity of agents for adequately treating patients with CP-Kp bacteraemia [4]. Before the revision of tigecycline's breakpoints, resistance rates to tigecycline were lower than other treatment options, such as colistin or aminoglycosides, leading to its wide use [3,12,13]. In 2019, the revision of tigecycline's breakpoints resulted in a significant change of its susceptibility rates; in the present study, 89.4% of isolates were resistant according to 2019's EUCAST breakpoints, whereas if the previous breakpoints were used, the resistance rate would drop to 30.8%. The latter rate represented the resistance rate reported in other studies conducted before the change of breakpoints [13,14].

The benefit of combination treatment over monotherapy remains a matter of debate when treating such infections, with some studies favoring the use of combination treatment, especially in critically ill patients [9,13,14]. Concerning monotherapy, tigecycline was considered as efficacious as other options for the treatment of CP-Kp infections [8,9,15]. Moreover, in a meta-analysis, in the subgroup of 398 KPC-producing *K. pneumoniae* bacteraemias, tigecycline was better than the other options [9].

Our data validate the change proposed by EUCAST in 2019, since the outcome of bacteraemias treated with tigecycline with MICs between 0.75 and 2 mg/L was worse than that of with MICs ≤ 0.5 mg/L, and comparable to those receiving no appropriate targeted treatment [10]. If the isolate's MIC was ≤0.5 mg/L, tigecycline monotherapy was as efficacious as monotherapy with other treatment options (colistin, aminoglycoside, ceftazidime/avibactam, or carbapenems).

A main concern regarding the use of tigecycline to treat CP-Kp bacteraemias is the suboptimal concentrations, which could be overcome by increasing the dose, leading to better outcomes. [7] While this can be true for some types of infections, such as intra-abdominal or lower respiratory tract infections, bacteraemias represent difficult-to-treat infections, especially in critically ill patients. In an in vitro model, the standard tigecycline dose (100 mg/day) could be sufficient to treat bacteraemias by isolates with MICs < 0.06 mg/L, while a double dose (200 mg/day) was necessary for isolates with MICs of 0.125 to 0.25 mg/L [16]. Thus, the doses administered would not be sufficient to treat the majority of patients with CP-Kp bacteraemia [3,13,14].

This study has several limitations. It is a retrospective study in a Greek ICU with a moderate number of patients. The number of patients that received tigecycline for bacteraemia due to a CP-Kp isolate with tigecycline's MIC ≤ 0.5 mg/L was small. While tigecycline was compared to other antimicrobials

combined, no analysis was performed separately, since most of the patients in Group C received colistin and the other options (aminoglycoside, ceftazidime/avibactam, carbapenems) were underrepresented.

4. Materials and Methods

This retrospective study was carried out in the intensive care unit (ICU) of the University General Hospital of Patras (UGHP), Greece, during a ten-year period (2010–2019). The Ethical Committee of the UGHP approved the study (No 858).

Patients with a monomicrobial bacteraemia due to CP-Kp that received appropriate targeted monotherapy or no appropriate targeted treatment were included in the study. Those who received two or more appropriate antimicrobials were excluded. Groups A and B comprised of patients treated with tigecycline monotherapy, of which the infecting isolate had MICs of tigecycline ≤ 0.5 mg/L and 0.75–2 mg/L, respectively. Group C included patients treated with appropriate targeted monotherapy of colistin, aminoglycoside, ceftazidime/avibactam, or carbapenem, while Group D included patients that did not receive appropriate targeted therapy. Multiple episodes of bacteraemia from the same patient were included if a duration of at least two months occurred between two episodes.

Primary outcome was 30-day mortality. Data (epidemiological, comorbidities, antimicrobial administration, types of infection, and outcome) were obtained from patients' chart reviews and the ICU computerized database (Criticus^{TM}, University of Patras, Patras, Greece). Primary or secondary BSI was determined in accordance to the Centers for Disease Control and Prevention definition [17]. Infection was categorized as sepsis or septic shock according to new sepsis definition [18]. The date of collection of the first positive blood culture was defined as infection onset.

K. pneumoniae isolates from clinical specimens of patients hospitalized in UGHP were identified by the Vitek 2 Advanced Expert System (bioMérieux, Marcy-l'Étoile, France). Antimicrobial susceptibility testing was performed by the agar disk diffusion method against imipenem, meropenem, aztreonam, amikacin, gentamicin, sulfamethoxazole-trimethoprim, and ciprofloxacin. Minimum inhibitory concentrations (MICs) of imipenem, meropenem, tigecycline, fosfomycin, and ceftazidime/avibactam were determined by Etest (bioMérieux, Marcy-l'Étoile, France), whereas the MIC of colistin was determined by the broth microdilution method according to EUCAST methodology. EUCAST criteria were applied to interpret susceptibility result [10]. bla_{VIM}, bla_{IMP}, bla_{KPC}, bla_{NDM}, and bla_{OXA} were detected by PCR [19,20].

Data analysis was performed with SPSS version 23.0 (SPSS, Chicago, IL, USA). Fisher exact test or the chi^2 test was used for categorical variables and Mann–Whitney *U*-test for continuous ones. Multiple logistic regression analysis was used to identify independent predictors of 30-day mortality. A p value < 0.05 was considered significant.

5. Conclusions

Tigecycline was as efficacious as other antimicrobials for the treatment of bacteraemia due to CP-Kp isolate with an MIC for tigecycline ≤ 0.5 mg/L. When tigecycline's MIC ranged from 0.75 to 2 mg/L, patients' clinical outcome was comparable to patients that received no appropriate antimicrobial treatment, thus affirming the proposed changes from EUCAST. Tigecycline can be used as monotherapy only if tigecycline's MIC is ≤0.5 mg/L.

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