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ARTICLE

Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections

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Abstract Tigecycline (TG) has been shown to be active in vitro against *Acinetobacter baumannii*, although data on the clinical efficacy of TG alone or in combination for the treatment of infections due to multidrug-resistant *A. baumannii* (MDRAB) remain limited. The purpose of this study was to investigate the clinical outcomes of patients with healthcare-associated infections (HAIs) caused by MDRAB who were treated with imipenem/cilastatin and sulbactam, and TG alone or in combination with other antibiotics. A total of 386 patients with HAIs caused by MDRAB were retrospectively analyzed and grouped into TG and non-TG groups, depending on whether they received TG treatment. Of the 266 patients in the TG group, 108 were treated with TG alone and 158 were treated with TG in combination with ceftazidime, ceftriaxone, piperacillin/tazobactam, or a carbapenem. All 120 patients in the non-TG group were treated with imipenem/cilastatin and sulbactam. The primary outcome measure was 30-day mortality after TG treatment and the secondary outcome was clinical outcome. There were no significant differences in survival rates between the two groups. However, the rate of unfavorable outcome was significantly lower ($p<0.05$) among patients in the TG group than among patients in the non-TG group. The most significant predictor of unfavorable outcome was sepsis, whereas TG treatment and microbial eradication were the most significant predictors of favorable outcomes. Our study represents the largest study of patients with MDRAB infection treated with TG and expands our understanding of the role of TG therapy alone or in combination with other agents for the treatment of HAI caused by MDRAB.

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Introduction

Healthcare-associated infection (HAI), an important cause of morbidity and mortality in the hospital setting, has a negative impact on the cost of healthcare worldwide [1, 2]. The rapid increase in the occurrence of HAI, especially in intensive care units (ICUs) is due, in part, to the emergence of multidrug resistance [3]. Although the epidemiology of multidrug-resistant (MDR) organisms is complex, it is accepted that the excessive use of broad-spectrum antibiotics has contributed to this increasing problem [4]. Multidrug-resistant *Acinetobacter baumannii* (MDRAB) has emerged as one of the major challenges in the healthcare setting, and is known to cause nosocomial pneumonia, bacteremia, meningitis, urinary tract infections, and wound infections [5, 6]. Infection with MDRAB has been linked with poor clinical outcomes [7], increased morbidity, and prolonged duration of hospital stay [8].

Tigecycline (TG), part of a new class of antibiotics called glycylcyclines, has been shown to bind efficiently to bacterial ribosomes [9]. TG has been recently licensed to treat skin and soft tissue as well as intra-abdominal infections [10, 11] and is

active against a broad spectrum of bacteria in vivo, including resistant aerobic and fermentative Gram-positive and Gram-negative bacteria and anaerobes [12–14]. Resistance to TG is not common, although TG has limited activity against *Pseudomonas aeruginosa* and *Proteus* species [15].

Data from a limited number of patients suggest that TG is effective for the treatment of infections caused by MDR *Enterobacteriaceae* [16]. TG has also been shown to be active in vitro against *A. baumannii*, although data on the clinical efficacy remains limited [14, 17]. However, the effect of TG on ventilator-associated pneumonia or bacteremia and bloodstream infection remains inconclusive [6, 18, 19]. In addition, studies on the effects of TG are often clouded by the effects of combination antibiotic therapy [18, 19].

In this study, our primary objective was to investigate the role of TG on the outcomes of patients treated with TG for serious HAIs caused by MDRAB. The secondary objective was to investigate the clinical outcomes of these patients.

Materials and methods

Patient recruitment

We retrospectively reviewed the records of patients admitted to the Chung Shan Medical University Hospital, Taiwan, from January 2007 to June 2011. All patients admitted to the hospital for more than 48 h were monitored for HAI, which was diagnosed based on the Centers for Disease Control and Prevention (CDC) definition of nosocomial infections [20, 21]. Study participants diagnosed with HAIs caused by MDRAB were divided into two treatment groups: (1) patients in the TG group were treated with TG alone (100 mg intravenous TG initially, followed by 50-mg doses intravenously administered twice daily, for at least 5 days) or TG plus a carbapenem or a third-generation cephalosporin (ceftazidime or ceftriaxone) or piperacillin/tazobactam; (2) patients in the non-TG group were treated with a carbapenem and sulbactam (imipenem/cilastatin 500 mg and sulbactam 1-g doses intravenously administered every 6 h daily, for at least 5 days). The study protocols were approved by the Institutional Review Board (IRB) of the Chung Shan Medical University Hospital and a waiver of informed consent was obtained from the IRB for this retrospective study (no. CS1105).

Inclusion criteria were: (1) age >20 years; (2) a confirmed diagnosis of HAI caused by MDRAB; (3) receipt of empirical treatment or concordant therapy with TG after microbiologic data had been obtained for cultures susceptible to TG in vitro; and (4) receipt of empirical treatment or concordant therapy with imipenem/cilastatin and sulbactam after microbiologic data had been identified for MDRAB isolates. Exclusion criteria were: (1) the presence of HAI caused by non-Gram-negative bacteria; (2) severe liver failure; (3) the presence of community-associated infections; or (4) the presence of HAI caused by Gram-negative bacteria which was not treated with TG or imipenem/cilastatin and sulbactam. In addition to data on patient characteristics, we also obtained laboratory data, Glasgow Coma Scale (GCS) scores [22], Acute Physiology and Chronic Health Evaluation (APACHE) II scores [23], and Sequential Organ Failure Assessment (SOFA) scores [24] prior to receiving TG. Other risk factors such as recent comorbidities in the 6 months prior to this infection during this hospital admission (underlying illness), sepsis [25], duration of hospitalization, duration of ICU stay, history of recent invasive procedures in the 6 months prior to this infection during this hospital admission, the presence of invasive devices, prior antimicrobial therapy, immunosuppressive drug use, and the presence of bacteremia due to MDRAB, or co-infection with fungus or *Pseudomonas*, were also collected from patient records.

Bacteriological identification and antimicrobial susceptibility testing

A. baumannii was identified using standard biochemistry testing [26] and confirmed using the Vitek 2 system (bioMérieux Inc., La Balme les Grottes, France) and API 20 E strips (bioMérieux). Antimicrobial susceptibility testing of *A. baumannii* isolates to antimicrobial agents, including TG, was performed using the Kirby–Bauer disk diffusion method and interpreted as recommended by the Clinical and Laboratory Standards Institute (CLSI) [27–29]. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains. Susceptibility to colistin is not routinely evaluated in our clinical microbiology laboratory. MDRAB was defined as an *A. baumannii* isolate resistant to all currently available systemic antimicrobial agents, with the exception of colistin and TG, including cephalosporins (cefotaxime and ceftazidime), penicillins, piperacillin/tazobactam, aztreonam, carbapenems (imipenem and meropenem), aminoglycosides (gentamicin and amikacin), fluoroquinolones (ciprofloxacin and levofloxacin), and sulbactam [26].

Microbiological data collection

All microbiological data were collected from medical records. Clinical specimens evaluated included blood, sputum, urine, pleural effusion, ascites, synovial joint fluid, pus, and cerebral spinal fluid. All specimens were subjected to standard microbiological procedures in our hospital. Samples of sputum, bronchoalveolar lavage (BAL) fluid, and tracheal aspirate fluid were cultured and subjected to Gram staining to evaluate the presence of white blood cells (WBCs) and microorganisms. The causative pathogen was defined as: (1) a single microorganism with a bacterial

density $>10^4$ colony-forming units (CFU)/mL in tracheal aspirates or BAL; (2) more than 25 polymorphonuclear cells and fewer than 10 epithelial cells per low-power field in sputum smears; (3) a single microorganism with a bacterial density $>10^5$ CFU/mL in wound cultures; or (4) a single microorganism with a bacterial density $>10^5$ CFU/mL and pyuria (>10 white blood cells/μL) in urine cultures. The definitions of complicated skin and soft tissue infections (cSSTIs) are based on CDC guidelines [21].

Primary bacteremia was defined as bacteremia associated with intravenous catheters, while secondary bacteremia was defined as bacteremia secondary to concomitant infections associated with urinary tract infection (UTI), cSSTI, complicated intra-abdominal infection (cIAI), or pneumonia [21]. Ventilator-associated pneumonia was diagnosed as healthcare-associated pneumonia based on CDC guidelines [21].

The primary outcome measure in this study was 30-day mortality after TG treatment. Differences in primary outcome were evaluated in patients with MDRAB-positive and in patients with negative blood cultures. The secondary outcome measure in this study was assessed as favorable and unfavorable responses. Favorable responses included: (1) a cure; (2) eradication of the causative pathogen; or (3) partial or complete improvement in clinical signs and symptoms. Unfavorable responses included a plateauing or deterioration in clinical signs and symptoms requiring a switch to other antimicrobials. Data on in-hospital mortality, 60-day mortality, and >60-day mortality were also collected.

Microbial eradication was defined as the absence of growth of the primary pathogen in 14-day surveillance cultures from the primary site of infection. Superinfections with bacteremia or fungemia were assessed during the period of or after TG treatment.

Statistical analysis

Continuous data are presented by the median and interquartile range (IQR), and categorical data are presented as count and percentage. Differences between the non-TG and TG groups in continuous data and categorical data were tested with the Mann–Whitney test and the Fisher's exact test, respectively. We used Kaplan–Meier survival curves to show the cumulative survival rate of patients and the log-rank test to compare the survival rates of patients in the two groups. To further investigate the differences in 30-day mortality rate as well as clinical outcomes between the TG and non-TG groups while controlling for other clinical characteristics, the comparisons between the two groups were stratified by sepsis (no vs. yes), GCS (>9 vs. ≤9), SOFA (≤7 vs. >7), and APACHE II scores (≤21 vs. >21), respectively. Logistic regression analyses were performed to evaluate factors independently influencing unfavorable clinical outcomes (stationary or deterioration). Variables with a significant impact in the univariate logistic regression analyses and without severe multicollinearity were entered into a multivariate logistic regression model to identify factors independently influencing unfavorable clinical outcomes. The statistical hypothesis tests were two-sided and set at a significance level of 0.05. All statistical analyses were performed using the statistical software package SPSS (Version 15.0, SPSS Inc., Chicago, IL, USA).

Results

Patients

During the study period, a total of 496 patients with a diagnosis of HAI were recruited. Of these, 110 patients were excluded for the following reasons: one patient was younger than 18 years, 29 patients had non-Gram-negative bacteria infections, and 80 patients with infections not caused by MDRAB [including *K. pneumoniae* (n=19), *Escherichia coli* (n=17), extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* (n=14), *Pseudomonas aeruginosa* (n=13), ESBL-producing *E. coli* (n=2), *Enterobacter aerogenes* (n=6), *Stenotrophomonas maltophilia* (n=4), *Proteus mirabilis* (n=3), and *Sphingomonas paucimobilis* (n=2)] and were not treated with TG or imipenem/cilastatin and sulbactam. A total of 386 patients with HAIs due to MDRAB met the inclusion criteria and were included in the final analysis. These patients were stratified into two treatment groups (TG and non-TG), based on whether they received TG treatment. The TG group comprised 266 patients (108 were treated with TG alone and 158 were treated with TG in combination with ceftazidime, ceftriaxone, piperacillin/tazobactam, or a carbapenem). The non-TG group comprised 120 patients (all were treated with imipenem/cilastatin and sulbactam).

Clinical characteristics

There were no significant differences in age or gender between the non-TG and TG groups. Compared with the non-TG group, the TG group had a significantly higher rate of prior exposure to antibiotics (99.2 % vs. 93.3 %, p=0.002) and a significantly lower incidence of Foley catheter insertion (64.7 % vs. 87.5 %, p<0.001). The percentage of patients who required treatment in the ICU was significantly lower in the TG group (71.8 %) than in the non-TG group (87.5 %) (p<0.001). In addition, the percentage of patients with fever was significantly lower in the TG group (16.5 %) than in the non-TG group (26.7 %) p=0.027). Patients in the TG group also had significantly lower serum creatinine levels than patients in the non-TG group (1.4 mg/dL vs.

1.7 mg/dL, $p=0.02$). Also, the TG group had a significantly lower percentage of patients with sepsis (42.5 % vs. 66.7 %, $p<0.001$) and a significantly higher number of patients with heart disease (45.1 % vs. 33.3 %, $p=0.034$) than the non-TG group. However, there were no significant differences in other laboratory data or disease severity measurements between the two groups (Table 1).

Microbiological analyses showed that the rate of concurrent infection was significantly higher in the TG group than in the non-TG group (13.2 % vs. 4.2 %, $p=0.006$), but the rate of concurrent MDRAB infection and *Candida* infection was significantly lower in the TG group than in the non-TG group (65.4 % vs. 81.7 %, $p<0.001$). We also found that the two groups differed significantly in the distribution of organisms isolated from the primary site of infection (Table 2). In addition, secondary bacteremia occurred in 40.8 % of patients who did not receive TG and in 19.5 % of patients who received TG ($p<0.001$) (Table 2).

Table 1 Summary of baseline characteristics of patients with multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection in the tigecycline (TG) and non-TG treatment groups

Characteristic	Total ($n=386$)	Group		p-Value[a]
		Non-TG ($n=120$)	TG ($n=266$)	
Age (years) [b]	71.5 (59.0, 79.0)	73.0 (58.5, 80.0)	71.0 (60.0, 79.0)	0.525
Gender[c]				
Male	267 (69.2 %)	83 (69.2 %)	184 (69.2 %)	1.000
Female	119 (30.8 %)	37 (30.8 %)	82 (30.8 %)	
Comorbidity				
Heart disease[c]	160 (41.5 %)	40 (33.3 %)	120 (45.1 %)	**0.034**
Diabetes mellitus[c]	159 (41.2 %)	54 (45.0 %)	105 (39.5 %)	0.317
Chronic liver disease[c]	54 (14.0 %)	20 (16.7 %)	34 (12.8 %)	0.342
Chronic lung disease[c]	177 (45.9 %)	57 (47.5 %)	120 (45.1 %)	0.741
Chronic kidney disease[c]	130 (33.7 %)	39 (32.5 %)	91 (34.2 %)	0.816
Malignancy[c]	87 (22.5 %)	30 (25.0 %)	57 (21.4 %)	0.433
Corticosteroid therapy[c]	32 (8.3 %)	10 (8.3 %)	22 (8.3 %)	1.000
Immunocompromised status[c]	57 (14.8 %)	22 (18.3 %)	35 (13.2 %)	0.215
ICU stay[c]	296 (76.7 %)	105 (87.5 %)	191 (71.8 %)	**0.001**
Risk factors				
Prior antibiotic exposure[c]	376 (97.4 %)	112 (93.3 %)	264 (99.2 %)	**0.002**
Surgery[c]	295 (76.4 %)	92 (76.7 %)	203 (76.3 %)	1.000
Wound or bed sore[c]	323 (83.7 %)	104 (86.7 %)	219 (82.3 %)	0.303
Mechanical ventilation use[c]	325 (84.2 %)	103 (85.8 %)	222 (83.5 %)	0.652
Foley catheter use[c]	277 (71.8 %)	105 (87.5 %)	172 (64.7 %)	**<0.001**
Central venous catheter use[c]	317 (82.1 %)	103 (85.8 %)	214 (80.5 %)	0.251
Fever (>38.5 °C) [c]	76 (19.7 %)	32 (26.7 %)	44 (16.5 %)	**0.027**
Laboratory data				
White blood cell count[b] (10^3/mL)	11.7 (8.2, 15.6)	12.1 (8.6, 15.1)	11.6 (7.9, 15.7)	0.726
C-reactive protein[b] (mg/dL)	9.2 (4.2, 14.5)	10.5 (4.3, 15.7)	8.6 (4.0, 14.3)	0.097
Serum albumin[b] (mg/dL)	2.6 (2.2, 2.9)	2.5 (2.2, 2.9)	2.6 (2.2, 2.9)	0.708
Blood urea nitrogen[b] (mg/dL)	42.0 (21.0, 79.0)	42.5 (23.4, 90.5)	41.8 (20.9, 76.0)	0.136
Serum creatinine[b] (mg/dL)	1.5 (0.8, 3.3)	1.7 (0.9, 4.4)	1.4 (0.8, 3.0)	**0.020**
Severity of illness				
Sepsis[c]	193 (50.0 %)	80 (66.7 %)	113 (42.5 %)	**<0.001**
GCS score[b]	9.0 (6.0, 11.0)	8.0 (6.0, 11.0)	9.0 (7.0, 12.0)	0.057
SOFA score[b]	7.0 (5.0, 10.0)	7.0 (5.0, 10.5)	7.0 (5.0, 9.0)	0.088
APACHE II score[b]	21.0 (15.0, 26.0)	22.0 (15.5, 28.0)	20.5 (15.0, 25.0)	0.072

[a] p-Values marked in **bold** indicate statistical significance (≤0.05)

[b] Data are presented as median with inter-quartile range

[c] Data are presented as number (%) of patients

Table 2 Summary of microbiological data among patients with MDRAB infection in the TG and non-TG groups

Characteristic	No. (%) of patients			*p*-Value [a]
	Total (*n*=386)	Group		
		Non-TG (*n*=120)	TG (*n*=266)	
Concurrent infection with	40 (10.4 %)	5 (4.2 %)	35 (13.2 %)	**0.006**
Pseudomonas aeruginosa	209 (60.4 %)	61 (53.0 %)	148 (64.1 %)	0.062
Candida species	245 (70.8 %)	94 (81.7 %)	151 (65.4 %)	**0.002**
Site of primary infection				
Blood	100 (25.9 %)	52 (43.3 %)	48 (18.0 %)	**<0.001**
Urine	54 (14.0 %)	22 (18.3 %)	32 (12.0 %)	
Respiratory specimens[b]	210 (54.4 %)	38 (31.7 %)	172 (64.7 %)	
Other[c]	22 (5.7 %)	8 (6.7 %)	14 (5.3 %)	
Bacteremia				
No	251 (65.0 %)	65 (54.2 %)	186 (69.9 %)	**<0.001**
Primary, catheter-related infection	34 (8.8 %)	6 (5.0 %)	28 (10.5 %)	
Secondary bacteremia	101 (26.2 %)	49 (40.8 %)	52 (19.5 %)	

[a] *p*-Values marked in **bold** indicate statistical significance (≤0.05)

[b] Includes sputum, bronchoalveolar lavage fluid, and tracheal aspirate fluid

[c] Includes pus, synovial joint fluid, and cerebral spinal fluid

Patients in the TG group had a significantly shorter duration of antimicrobial use than patients in the non-TG group (8.0 days vs. 12.0 days, $p<0.001$). Also, the percentage of patients in the TG group that switched to other antibiotics was significantly higher than that of patients in the non-TG group (53.8 % vs. 29.2 %, $p<0.001$). Interestingly, the percentage of patients who showed evidence of microbial eradication was significantly lower in the TG group than in the non-TG group (1.1 % vs. 11.7 %, $p<0.001$) (Table 3).

Evaluation of clinical outcomes

The percentage of patients with unfavorable outcome (stationary or deterioration) was significantly lower in the TG group than in the non-TG group (30.8 % vs. 50.0 %, $p<0.001$). However, there were no significant differences in the number of infection-related deaths, length of hospital stay, or length of ICU stay between the two groups (Table 3). In addition, there were no significant differences in the survival rates between the TG and non-TG groups. In the TG group,

Table 3 Summary of treatments and outcomes among patients with MDRAB in the TG and non-TG treatment groups

	Total (*n*=386)	Group		*p*-Value[a]
		Non-TG (*n*=120)	TG (*n*=266)	
Treatment				
Duration of antibiotic use[b] (days)	10.0 (7.0, 14.0)	12.0 (9.0, 18.5)	8.0 (6.0, 13.0)	**<0.001**
Switch to other antibiotics[c]	178 (46.1 %)	35 (29.2 %)	143 (53.8 %)	**<0.001**
Death				
No[c]	211 (54.7 %)	64 (53.3 %)	147 (55.3 %)	0.930
Death related to MDRAB infection[c]	142 (36.8 %)	46 (38.3 %)	96 (36.1 %)	
Death not related to MDRAB infection[c]	33 (8.5 %)	10 (8.3 %)	23 (8.6 %)	
Length of hospital stay[b] (days)	40.0 (26.0, 62.0)	37.5 (25.5, 62.0)	43.0 (26.0, 62.0)	0.526
Length of ICU stay[b] (days)	21.0 (10.0, 41.0)	23.5 (10.0, 46.0)	20.0 (10.0, 40.0)	0.338
Microbiological and clinical outcomes				
Microbiological eradication[c]	17 (4.4 %)	14 (11.7 %)	3 (1.1 %)	**<0.001**
Favorable (cure or improvement) [c]	244 (63.2 %)	60 (50.0 %)	184 (69.2 %)	**<0.001**
Unfavorable (stationary or deterioration) [c]	142 (36.8 %)	60 (50.0 %)	82 (30.8 %)	

[a] *p*-Values marked in **bold** indicate statistical significance (≤0.05)

[b] Data are presented as median with inter-quartile range

[c] Data are presented as number (%) of patients

Table 4 Univariate and multivariate analysis to identify risk factors influencing unfavorable clinical outcomes (stationary or deterioration) among patients with MDRAB infection

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95 % confidence interval)	*p*-Value[a]	Odds ratio (95 % confidence interval)	*p*-Value[a]
Age (years)	1.001 (0.987, 1.015)	0.894		
Gender (female vs. male)	1.012 (0.647, 1.583)	0.959		
Comorbidity				
Heart disease	0.837 (0.549, 1.276)	0.408		
Diabetes mellitus	0.851 (0.558, 1.298)	0.454		
Chronic liver disease	1.584 (0.887, 2.830)	0.120		
Chronic lung disease	0.794 (0.523, 1.205)	0.279		
Chronic kidney disease	1.009 (0.651, 1.563)	0.969		
Malignancy	1.546 (0.952, 2.512)	0.078		
Corticosteroid therapy	1.373 (0.661, 2.853)	0.395		
Immunocompromised status	1.540 (0.873, 2.718)	0.136		
ICU stay	1.072 (0.656, 1.753)	0.782		
Invasive procedures or devices				
Surgery	0.968 (0.595, 1.575)	0.896		
Wound or bed sore	0.863 (0.496, 1.501)	0.603		
Mechanical ventilation use	1.038 (0.587, 1.833)	0.899		
Foley catheter use	0.809 (0.513, 1.275)	0.361		
Central venous catheter use	1.202 (0.694, 2.083)	0.512		
Fever (>38.5 °C)	1.620 (0.974, 2.692)	0.063		
Laboratory data				
White blood cell count (10^3/mL)	1.005 (0.976, 1.035)	0.718		
C-reactive protein (mg/dL)	1.029 (1.001, 1.058)	**0.042**	1.014 (0.984, 1.044)	0.374
Serum albumin (mg/dL)	1.000 (0.999, 1.001)	0.901		
Blood urea nitrogen (mg/dL)	1.005 (1.000, 1.010)	**0.039**	1.001 (0.996, 1.006)	0.622
Serum creatinine (mg/dL)	1.086 (0.986, 1.195)	0.094		
Severity of illness				
Sepsis	2.369 (1.548, 3.626)	**<0.001**	1.737 (1.078, 2.798)	**0.023**
GCS score	0.921 (0.871, 0.973)	**0.004**	1.037 (0.942, 1.142)	0.454
SOFA score	1.055 (0.986, 1.129)	0.119		
APACHE II score	1.063 (1.031, 1.095)	**<0.001**	1.040 (0.986, 1.098)	0.152
Concurrent infection	1.836 (0.951, 3.545)	0.070		
With *Pseudomonas aeruginosa*	1.259 (0.798, 1.984)	0.322		
With *Candida* species	1.176 (0.720, 1.920)	0.518		
Site of primary infection				
Blood	1.182 (0.463, 3.016)	0.727		
Urine	0.850 (0.308, 2.341)	0.753		
Respiratory	0.692 (0.282, 1.697)	0.421		
Other	Reference			
Bacteremia				
No	Reference			
Primary, catheter-related	1.988 (0.966, 4.091)	0.062		
Secondary bacteremia	1.359 (0.844, 2.186)	0.207		
Treatment				
	Reference		Reference	
TG alone	0.385 (0.221, 0.668)	**0.001**	0.470 (0.256, 0.863)	**0.015**

Table 4 (continued)

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*p*-Value[a]	Odds ratio (95% confidence interval)	*p*-Value[a]
TG in combination	0.491 (0.301, 0.799)	**0.004**	0.553 (0.322, 0.950)	**0.032**
Switch to other antibiotics	0.407 (0.264, 0.626)	**<0.001**	0.468 (0.294, 0.746)	**0.001**
Microbiological eradication	0.218 (0.049, 0.968)	**0.045**	0.155 (0.032, 0.747)	**0.020**

[a] *p*-Values marked in **bold** indicate statistical significance (≤0.05)

Logistic regression analyses were performed to evaluate the clinical outcome. A total of 244 patients in both groups who had prior antibiotic exposure had favorable clinical outcomes, while 142 patients had unfavorable clinical outcomes. The odds ratio was not available due to zero count

the 3-month survival rate was 50.8 %, the 6-month survival rate was 45.9 %, and the 1-year survival rate was 42.4 %; the corresponding survival rates in the non-TG group were 47.3 %, 44.9 %, and 38.1 %, respectively.

Evaluation of factors influencing unfavorable clinical outcomes

The results of the univariate analysis showed that age, gender, comorbidities, fever, and infection sources did not have a significant impact on clinical outcome. However, the clinical outcome was significantly influenced by eight variables, including laboratory values of C-reactive protein and blood urea nitrogen, severity of sepsis, GCS and APACHE II scores, TG therapy, a switch to other antibiotics, and microbial eradication. These variables had no serious collinearity, and were used in our multivariate logistic regression model to determine factors independently influencing unfavorable clinical outcome. The results from the multivariate analysis showed that patients with sepsis were more likely to have unfavorable outcomes [odds ratio (OR) of 1.737] and that patients treated with TG were less likely to have unfavorable outcomes (ORs of 0.470 and 0.553 for patients treated with TG alone and TG plus other antibiotics, respectively). In addition, patients who switched to other antibiotics or had microbial eradication were less likely to have unfavorable outcomes (ORs of 0.468 and 0.155, respectively) (Table 4). We used logistic regression analyses to evaluate prior exposure to antibiotics as a risk factor for clinical outcome. We showed that 244 patients with prior antibiotic exposure in both groups had a favorable clinical outcome, while 142 patients had an unfavorable clinical outcome.

Patients with sepsis in the TG group were less likely to have unfavorable outcomes than patients with sepsis in the non-TG group (38.9 % vs. 57.5 %, $p=0.013$). Patients in the TG group with a GCS score≤9 were less likely to have unfavorable outcomes than patients with similar scores in the non-TG group (31.9 % vs. 56.2 %, $p=0.001$). Also, patients in the TG group with a SOFA score >7 were less likely to have unfavorable outcomes than patients with similar SOFA scores in the non-TG group (33.9 % vs. 60.7 %, $p=0.002$). Patients in the TG group with an APACHE II score >21 were also less likely to have unfavorable outcomes than patients with similar scores in the non-TG group (37.2 % vs. 59.7 %, $p=0.007$).

Discussion

In this retrospective study, we evaluated the efficacy of TG (alone or in combination with other antimicrobial drugs) in patients with MDRAB HAIs. We showed that the TG and non-TG groups did not differ significantly in the number of infection-related deaths, length of hospital stay, or length of ICU stay. There were also no significant differences in the survival rates between the two groups. However, the percentage of patients with an unfavorable outcome was significantly lower in the TG group than in the non-TG group.

Different drug sensitivities in HAIs and community-acquired infections are dictated by differences in the genotypes and phenotypes of the pathogens involved [30]. Managing MDR pathogens is a growing challenge in the ICU setting, because of the especially vulnerable patient population and the high use of invasive procedures. The recent emergence of antimicrobial resistance in *Acinetobacter* spp. is an important problem in the ICU, because of its ability to survive in a hospital setting for prolonged periods of time. *A. baumannii* is thought to acquire antimicrobial resistance via a number of mechanisms, including the presence of antimicrobial-inactivating enzymes, reduced access to bacterial targets, and mutations altering bacterial targets [31], resulting in challenges in infection control as well as treatment. In this study, we determined the optimal treatment for patients with infections due to MDRAB, the efficacy of TG for treating MDRAB infections, and the efficacy of TG for treating seriously ill patients.

Glycylcyclines like TG are structurally similar to tetracyclines and inhibit the bacterial translation machinery [32]. There has been a recent focus on the use of TG for the treatment of HAI [33–36]. In this study, we demonstrated

that the TG group had a significantly lower percentage of patients with unfavorable outcomes compared to the non-TG group (30.8 % vs. 50.0 %, $p<0.001$). Previous studies have shown that, although TG alone is not superior to imipenem, TG in combination with ceftazidime is effective for patients with hospital-acquired pneumonia [37, 38]. TG monotherapy was also previously shown to be clinically ineffective for patients with MDRAB infections, although the rate of microbial eradication was high [39]. However, a larger case series study recently demonstrated a favorable clinical as well as microbiological response (73 % and 78 %, respectively) in patients with HAIs [33]. Our findings are consistent with those in this study, namely, that patients who received TG monotherapy and patients who received TG combination therapy had a significantly better clinical outcome than patients who did not receive TG treatment. It is important to note that our study enrolled a significantly higher proportion of seriously ill patients in the TG group who required ICU care prior to receiving TG treatment (71.8 %). In the present study, seriously ill patients with sepsis, high APACHE II scores, and high SOFA scores in the TG group were less likely to have unfavorable outcomes compared to patients in the non-TG group. Our findings are consistent with a previous study showing that seriously ill patients with APACHE II scores >21 who received TG for HAIs had a good clinical success rate (73 %) [33].

We found no significant difference in the survival rate between the two groups, possibly because the study participants in both groups were seriously ill patients with sepsis, high APACHE II scores, and high SOFA scores. In contrast, data from a previous meta-analyses study showed that TG treatment was associated with increased mortality [40]. These data suggest that it is important for clinicians to carefully consider when to administer TG to seriously ill patients with difficult-to-treat, resistant pathogens that are susceptible to TG in vitro [41].

Our multivariate analysis showed that sepsis and high APACHE II scores were risk factors for unfavorable outcome. However, patients in the TG group with sepsis, SOFA score >7, GCS score <9, and APACHE II score >21 were less likely to have unfavorable outcomes compared to patients with similar scores in the non-TG group. We suggest that this could be attributed to the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of TG. The lipophilic properties of TG play a role in the PK of TG, enabling rapid and extensive penetration into body tissue, and a high volume distribution (Vd) of approximately 7–10 L/kg [42]. Theoretically, plasma TG concentrations are unlikely to change when patients have increased Vd in a serious illness. In contrast, carbapenems are hydrophilic antibiotics with a low intracellular penetration, which would increase the Vd and decrease plasma concentrations in seriously ill patients [42]. Furthermore, the PD profile of TG has been shown to exhibit time-dependent bactericidal activity with a prolonged post-antibiotic effect that is likely to be correlated with its efficacy [42]. However, there is little information to support the concept of potentially altered PK/PD of TG in seriously ill patients.

Our data showed favorable microbiologic outcomes in the non-TG group compared to the TG group, and are consistent with a previous study that showed a poor correlation between microbiological clearance and clinical outcome in patients with MDRAB treated with TG [6]. Our data can be explained by the clinical characteristics of our study patients who presented with a higher proportion of pulmonary (64.7 %), bloodstream (18.0 %), and urinary tract (12.0 %) infections. Patients who are colonized or infected with *A. baumannii* can become a reservoir of infection. In fact, it has been shown that *A. baumannii* can colonize multiple body sites in hospitalized patients and can be isolated after more than 4 months from the patient's respiratory tract [43]. The clinical use of TG for bloodstream infection remains controversial, since its rapid distribution from the bloodstream into tissues could result in TG serum concentrations which are sub-optimal for maximal antibacterial activity. Low concentrations of TG in urine also render it unsuitable to treat urinary tract infections [13, 14]. TG has been shown to be bacteriostatic against MDRAB, while imipenem has bactericidal activity against *A. baumannii* isolates [44]. However, the correlation between the microbiological clearance and in vitro antibacterial activity remains unclear with the limited amount of clinical data available.

In summary, we suggest that our data can be explained by: (1) the significantly shorter duration of antimicrobial use by patients in the TG group compared to patients in the non-TG group; (2) the high number of patients with pneumonia; and (3) the significantly higher percentage of patients in the TG group who switched to other antibiotics compared to the non-TG group.

While sulbactams and carbapenems continue to be the most widely used therapeutic options for patients with HAIs, tetracyclines, aminoglycosides, and polymyxins are also used either alone or in combination to combat *A. baumannii* infection [45]. A regimen of carbapenems plus sulbactam has previously demonstrated in vitro and in vivo activity against MDRAB and been used to treat MDRAB isolates [46, 47]. However, the increased use of carbapenem is associated with a risk of developing antimicrobial resistance in MDRAB and non-fermenters [48]. To the best of our knowledge, our study represents the largest study of patients with MDRAB infection treated with TG and imipenem plus sulbactam.

Our study design has a few important limitations. The retrospective nature of the study limited our ability to collect complete information on adverse events. A second limitation is that it is a single-center study. A third limitation of this study is that it was an observational study, thereby,

precluding our ability to control the type of antimicrobial used prior to TG administration or the duration of TG treatment. However, our data have important clinical implications because of the limited number of therapeutic options for MDRAB isolates at present and the preliminary nature of evidence for the clinical use of these regimens [18, 33, 47, 49]. Although the overall clinical response rates in these previous reports appear favorable, the results are not conclusive because of the small sample sizes [13, 18, 19, 39, 47, 49]. Additionally, in vitro susceptibility to TG is often taken as in vivo efficacy in patients with MDRAB infections where TG is used off-label [18].

Treatment for MDRAB remains controversial. In spite of challenges with colistin, such as pharmacokinetics, renal toxicity, emergence of drug resistance, and a low concentration in the lungs, in vitro susceptibility data suggest that the only two drugs which can be used for MDRAB treatment are colistin (polymyxin B) and TG (this study). Other than clinical studies of TG conducted before entering the market, we believe that, among all the post-marketing surveillance studies, this study is the only controlled study with a large cohort. Based on our data, clinicians may still choose to use TG off-label for the treatment of MDRAB in critically ill patients who are in the ICU.

In conclusion, our data expand our understanding of the role of TG therapy in HAI. Since the treatment for *A. baumannii* has not been optimized, the treatment of HAIs caused by MDRAB is determined by in vitro susceptibility testing and by the susceptibility patterns of the MDRAB strains present in a given region. However, there is an imperative need for future studies to focus on large, well-controlled clinical trials for MDRAB infections, development of new antimicrobials regimens, and prevention of healthcare-associated MDRAB infections. MDRAB strains remain generally susceptible to polymyxins (colistin and polymyxin B), and there has been a recent focus on combination therapy to treat MDRAB infections [50, 51]. It will be interesting to review our data in the context of other novel antimicrobials against *A. baumannii* that are in the pipeline or in the experimental phase [52].

Conflict of interest The authors declare that they have no conflict of interest.

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