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Brief Communication

Impact of reduced tigecycline susceptibility on clinical outcomes of *Acinetobacter* bacteremia

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Abstract The higher 14-day mortality rate for patients with *Acinetobacter* bacteremia receiving tigecycline appropriately compared to other appropriate antibiotics (36.4% *versus* 14.2%, $P = 0.028$) was due to the poor effect of tigecycline for isolates with a minimum inhibitory concentration of 2 μg/mL (63.6% of 11 *versus* 14.2% of 127, $P = 0.001$).

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Tigecycline has exhibited good *in vitro* activity against multidrug-resistant pathogens, including the *Acinetobacter calcoaceticus—Acinetobacter baumannii* (Acb) complex.[1] However, *in vivo*, low serum concentrations of tigecycline have been a major concern. While the constant plasma concentration of tigecycline has rarely exceeded 2 μg/mL,[2] most studies have adopted 2 μg/mL as the breakpoint for the Acb complex as suggested by the U.S. Food And Drug Administration (FDA).[3–5] In contrast, the breakpoints for Enterobacteriaceae in the CLSI and the EUCAST are 1 μg/mL and 0.5 μg/mL for *Staphylococcus* spp.[6,7] These breakpoint discrepancies may account for the better clinical outcomes in the treatment of Enterobacteriaceae compared to Acb complex.[3–5,8] Therefore, the aim of this retrospective, multicenter study was to determine the clinical outcomes of bacteremic patients who received tigecycline for treatment of the Acb complex with a minimum inhibitory concentration (MIC) of 2 μg/mL (high MIC) or with a MIC < 2 μg/mL (low MIC).

This retrospective study was conducted from January 2009 to December 2015 at four medical centers in Taiwan. The charts of non-repetitive patients with sepsis and a positive blood culture for the Acb complex were reviewed. Only the Acb complex from the first set of positive blood cultures was collected. Patients who received appropriate intravenous antibiotics were included in this study. The antimicrobial therapy to which the Acb complex was susceptible and was administered at an appropriate dose within one day of the onset of bacteremia was defined as appropriate. The onset of bacteremia was defined as the day when the blood culture that eventually yielded *Acinetobacter* was drawn. We excluded the patients with an acute physiology and chronic health evaluation II (APACHE II) score <10 or those without signs of sepsis to minimize the possibility of including patients with contaminated blood culture. The MIC for the antibiotics administered was determined according to the Vitek 2 (BioMerieux) automated system. The results were subsequently interpreted according to CLSI standards,[6] except for the tigecycline breakpoint which was defined according to the U.S. FDA guidelines (susceptibility, ≤ 2 μg/mL).[9] The 14-day mortality rate was compared using Fisher's exact test. Statistical significance was set at $P < 0.05$.

A total of 149 patients received appropriate antibiotic treatment for *Acinetobacter* infections within one day of bacteremia onset. All 22 patients in the tigecycline group

Table 1 Clinical characteristics in the tigecycline and comparison groups.[a]

Characteristic	Tigecycline group (n = 22)	Comparison group (n = 127)	*P* value
Demographic data			
Age, year (median, IQR)	78 (51—83)	72 (58—80)	0.921
Male	18 (81.8)	73 (57.5)	0.034
Polymicrobial blood culture	6 (27.3)	42 (33.1)	0.805
APACHE II score within 48 h of bacteremia onset (median, IQR)	21 (15—27)	19 (15—26)	0.357
APACHE II score ≧20	12 (54.5)	61 (48.0)	0.647
Comorbid condition			
Type 2 diabetes mellitus	7 (31.8)	43 (33.9)	>0.999
Chronic pulmonary disease	5 (22.7)	19 (15.0)	0.355
Coronary artery disease	1 (4.5)	14 (11.0)	0.699
Congestive heart failure	4 (18.2)	22 (17.3)	>0.999
Renal impairment (CCr < 50 mL/min)	5 (22.7)	25 (19.7)	0.775
End stage renal disease	0 (0.0)	13 (10.2)	0.217
Cerebrovascular accident	3 (13.6)	28 (22.0)	0.570
Collagen vascular disease	0 (0.0)	2 (1.6)	>0.999
Solid tumor	5 (22.7)	61 (48.0)	0.036
Hematologic malignancy	1 (4.5)	13 (10.2)	0.694
Hospital duration prior to bacteremia, days (median, IQR)	25 (11—57)	13 (5—28)	0.130
Mechanical ventilator use at bacteremia onset	16 (72.7)	39 (30.7)	<0.001
Acquired in intensive care unit	7 (31.8)	31 (24.4)	0.440
Infection source			
Respiratory tract	10 (45.5)	34 (26.8)	0.083
Urinary tract	2 (9.1)	3 (2.4)	0.158
Catheter related	1 (4.5)	21 (16.5)	0.200
Intra-abdominal	1 (4.5)	6 (4.7)	>0.999
Skin and soft tissue	1 (4.5)	3 (2.4)	0.476
Central nervous system	1 (4.5)	0 (0.0)	0.148
Primary bacteremia	6 (27.3)	60 (47.2)	0.105
Dual appropriate antimicrobial agents[b]	7 (31.8)	4 (3.1)	<0.001
14-day mortality rate	8 (36.4)	18 (14.2)	0.028

[a] Data are presented as number of cases (%) for categorical variables.
[b] Dual appropriate antimicrobial agents was defined as ≧2 intravenous antibiotics, to which the bacterium was susceptible.
APACHE II = Acute Physiology and Chronic Health Evaluation II; IQR = interquartile range; CCr = creatinine clearance.

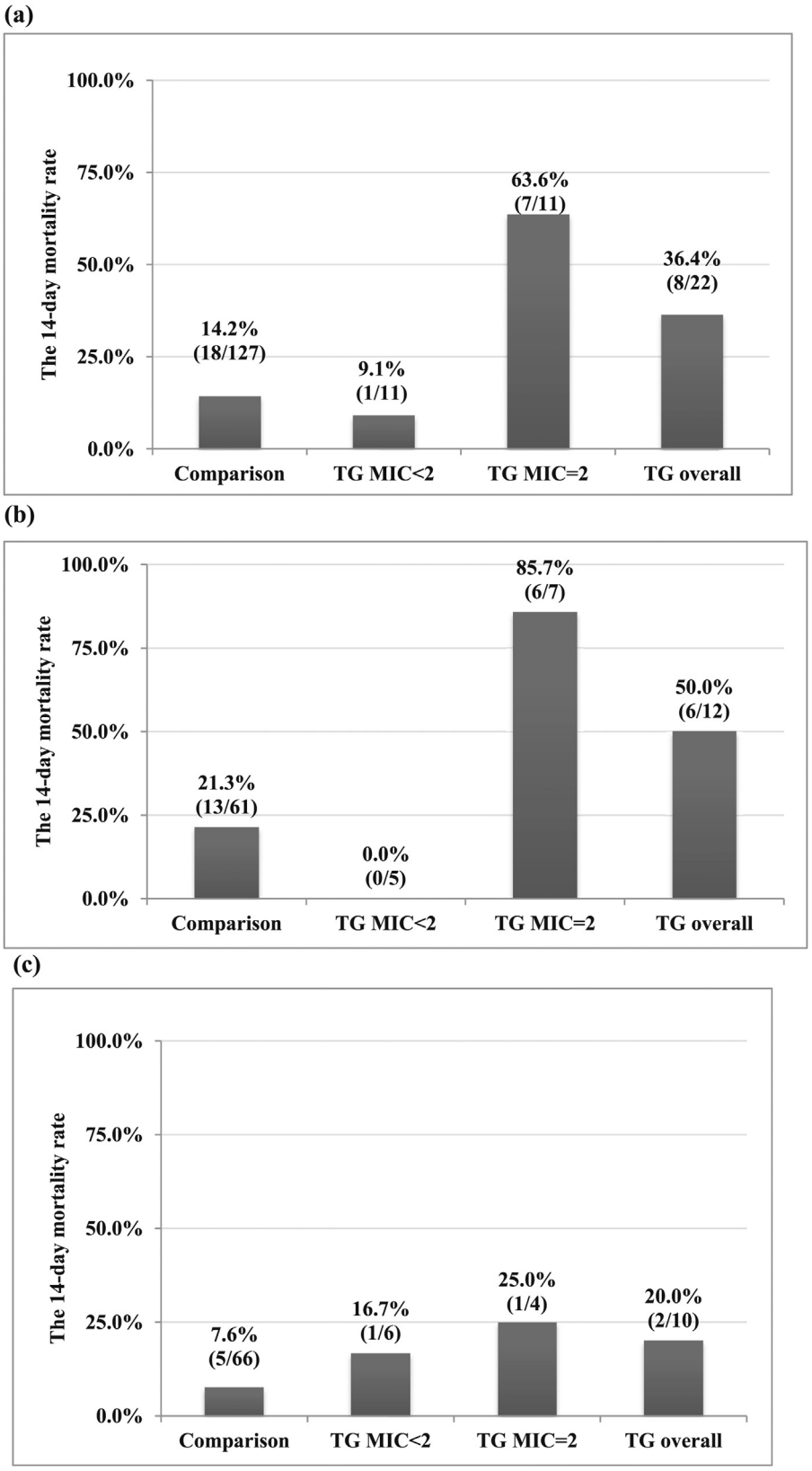

Figure 1. The 14-day mortality rates associated with the use of appropriate antibiotics with and without tigecycline for the treatment of *Acinetobacter* infections within one day of the onset of bacteremia in all patients (a), patients with an APACHE II score $\geq$ 20 (b), or patients with an APACHE II score $<$ 20 (c). TG, tigecycline; MIC, minimum inhibitory concentration (μg/mL).

received a standard dose of 50 mg every 12 h, and the main dual appropriate antimicrobial regimens is colistin ($n = 5$). The median duration of tigecycline therapy was 9 days (interquartile range 6–14). In the comparison group, 127 patients received 131 appropriate antibiotics other than tigecycline and the most common appropriate antimicrobial regimens is piperacillin/tazobactam ($n = 32/131$, 24.4%), followed by carbapenems including imipenem and meropenem ($n = 26$, 19.8%), colistin ($n = 20$, 15.3%), and sulbactam-based regimen ($n = 19$, 14.5%) (Table 1). The demographic characteristics, comorbid conditions, and infection sources were mostly similar between groups (Table 1).

The tigecycline group had a higher overall 14-day mortality rate (8/22, 36.4%) compared to the comparison group (18/127, 14.2%, $P = 0.028$) (Fig. 1a). In the tigecycline group, the 14-day mortality rate for the treatment for isolates with a high MIC was 63.6% (7/11), higher than the comparison group (14.2%, $P = 0.001$) and that for a low MIC group was 9.1% (1/11), similar to the comparison group (14.2%, $P > 0.99$). The 14-day mortality rates were stratified based on the clinical characteristics that differed in Table 1. The trend of higher mortality in the tigecycline group, especially isolates with a high MIC, remained in the subgroup analyses (Supplementary Table 1).

When the 14-day mortality rates were further stratified according to disease severity (Fig. 1b and c), a higher mortality rate was observed for the isolates with a high MIC in the tigecycline group compared with the comparison group, especially for the patients that had an APACHE II score ≥ 20 (85.7% [6/7] vs. 21.3% [13/61], $P = 0.001$); a higher mortality trend was also observed for the patients with an APACHE II score < 20 (25.0% [1/4] vs. 7.6% [5/66], $P = 0.307$). In contrast, tigecycline had a comparable effect on the isolates with a low MIC compared to other appropriate therapies, regardless of disease severity of patients with APACHE II score ≥ 20 (0% [0/5] vs. 21.3% [13/61], $P = 0.574$) or APACHE II score < 20 (16.7% [1/6] vs. 7.6% [5/66], $P = 0.418$).

As new microbiologic, pharmacodynamic, and clinical data are reported, antimicrobial susceptibility breakpoints may need to be reconsidered. A previous pharmacodynamics study of tigecycline showed that a concentration of 2 μg/mL was difficult to achieve under the current dosing regimen (50 mg every 12 h).[2] In addition, the clinical data of the present study reveal that tigecycline exhibited a poor effect for isolates with a MIC of 2 μg/mL. The latter observation is consistent with the finding that 20% of *Acinetobacter* spp. were found to have a MIC of 2 μg/mL between 2011 and 2014,[10] and the poor efficacy previously reported for tigecycline.[3–5] In contrast, the efficacy of tigecycline for the treatment of isolates with a low MIC was comparable to the other appropriate antibiotic therapies applied in this study, and to the treatment of other susceptible bacteria in previous studies.[8]

The major strength of the present study was the inclusion of patients from multiple centers, the stringent inclusion criteria that was applied for the selection of bacteremic patients, and the avoidance of immortality bias by excluding patients who received appropriate therapy one day after the onset of bacteremia. Inclusion of patients with appropriate therapy for prolonged time may preferentially select for patients with longer survival time or better outcome. In addition, the impact of disease severity on the outcomes of antimicrobial therapy was considered. After the patients were stratified according to disease severity, similar results remained. The poor outcomes described in previous studies[3–5] have deterred the use of tigecycline for the treatment of Acb complex infections in clinical practice, especially for bacteremia. These previous results have also prohibited the initiation of a prospective study due to the ethical considerations. Consequently, the present study was limited by a small number of cases and its retrospective design. One may argue the higher rate of patients with pneumonia in tigecycline group may be the reason of higher mortality. After excluding the patients with pneumonia, the 14-day mortality rate is still higher in tigecycline group (41.7% [5/12] vs. 11.8% [11/93], $P = 0.018$). Tigecycline is commonly combined with other antibiotics because of association with better clinical outcomes[11] and avoidance of resistance. However, tigecycline–colistin combination against Acb complex was associated with worse clinical outcome.[12] Whether the higher rate of dual appropriate therapy in tigecycline group may hamper our conclusion was unknown and requires further study.

In conclusion, the results of the present study demonstrated that tigecycline exhibited good efficacy for the treatment of bacteremia caused by the Acb complex with a MIC <2 μg/mL. For those with a MIC of 2 μg/mL, tigecycline should be considered after other reasonable therapeutic options have been exhausted.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.08.024.

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