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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.

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