In Vitro Susceptibility Of Tigecycline Among *Acinetobacter Baumanii* Clinical Isolates From a Hospital in Indonesia

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Abstract

Acinetobacter baumanii (*A. baumanii*) has arisen as the most important cause of nosocomial infection, typically in severely ill patients with many comorbidities and medical supportive devices. Tigecycline is a therapeutic option for treating this infection because of its potential ability against wide spectrum of bacterias, including multi-drug resistance *A. baumannii* (MDRAB). Our study determine the in vitro susceptibility of tigecycline against *A. baumanii* isolates and the emergence of MDRAB. The frequency of isolates that were not inhibited at MIC ≤ 0.5 µg/ml was 50.46%, at MIC = 1µg/ml was 2.38%, and at MIC = 2 µg/ml was 19.07%. The susceptibility rate of tigecycline against *A. baumanii* was 68.27% in 2015, 79.58% in 2016, and 67.87% in 2017. In vitro result demonstrated that tigecycline had good value of MIC against *A. baumanii* at the range of 0.5 to 2 µg/ml.

Keywords: **multi-drug resistance *A. baumannii* (MDRAB), tigecycline, susceptibility**

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Introduction

A. baumanii is a pleomorphic Gram negative bacilli, that accounts for approximately 17.44% of reported nosocomial infections in Indonesia.[1] This organism typically affects immunocompromised patients with medical devices, with high incidences and difficult-to-treat infection due to the resistance of the bacteria. In the past decades, the rise of severe infection by this bacteria was related to the lower proportion of susceptible *A. baumanii* isolates which induced high mortality.[2,3]

Over the past few decades, clinicians have noticed a significant increase in the rate of multi-drug resistance *A. baumannii* (MDRAB). The emergence of this multi-drug resistant organism has impacted on the choice of antibiotic therapy which becoming limited, and subsequently to prolonged length-of-stay along with inflated general costs of hospitalization.
The new molecule tigecycline is one of the few therapeutic options against MDRAB.[2-5]

Tigecycline, a newer derivate minocycline, is a glycylcyclines that strongly counter a broad range of both Gram negative and positive bacterial activity, including *Acinetobacter spp* and multiple isolates.[4,6] The addition of a 9-t-butyl-glycylamido side chain affects the bacterial ribosomes with high affinity and active drug efflux, therefore inhibits the primary resistance mechanisms of tetracycline.[4,6-7]

Information regarding this organism and their antibiotic susceptibility profiles among hospitalized patients in Indonesia is scarce. In our hospital, the multi-drug resistant organisms was prevalent across both Gram positive and negative bacterial genera due to excessive antibiotic use. Thus, the objective of the present study was to appraise in vitro susceptibility of tigecycline against *A. baumanii* isolates and the emergence of MDRAB.

Materials and Methods

This study involved 692 clinical isolates of *A. baumanii* from patients in a hospital located in Tangerang, Indonesia from January 2015 to December 2017. This was a retrospective descriptive study on microbiology laboratory data with one isolate for each patient. *Acinetobacter baumanii* identification and antibiotic susceptibility testing was evaluated by colony morphological features, Gram-staining and the VITEX-2 Compact® (Biomérieux, France) system.

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All isolates were testing for susceptibility to β-lactams (ampicillin/sulbactam, piperacillin/tazobactam, cefazolin,ceftazidime, ceftriaxone, and meropenem); aminoglycosides (amikacin, gentamicin); fluoroquinolones (ciprofloxacin,levofloxacin);trimethoprim/sulfa methoxazole; and tigecycline.

The recommendation for MIC and susceptibility breakpoint based on Clinical and Laboratory Standard Institute (CLSI) guideline.

The breakpoints for agents against *Enterobacteriaceae* were used to interpret tigecycline susceptibility against *Acinetobacter spp*. isolates (susceptible ≤ 2 μg/ml; intermediate 4 μg/ml; and resistant ≥ 8 μg/ml).[6,8-9] *Escherichia coli* ATCC® 25922 and *A. baumanii* ATCC® 19606 were provided as quality control isolates.[4,9-10]

Results

All *A. baumanii* isolates involved in this study were identified from patients hospitalised in intensive care and ward shown in **Table 1**. The clinical materials were sputum (500 samples), pus (67 samples), urine (61 samples), bronchial and pleural fluid (40 sample), blood (21 samples), cerebrospinal fluid (2 samples), and feces (1 sample). From all isolates, 78% came from lower respiratory tract, 9.86% from wound exudate (pus) and 8.82% from urine.

Table 1. General features of *A. baumanii* isolates from clinical specimen (n total = 692)

Characteristics	N	%
Specimen source		
Blood	21	3.03
Bronchial fluid	34	4.91
Cerebrospinal fluid	2	0.29
Feces	1	0.15
Pleural fluid	6	0.87
Pus	67	9.68
Sputum	500	72.25
Urine	61	8.82
Gender		
Female	264	38.15
Male	428	61.85
Ward		
Intensive care	250	36.13
Inpatient	320	46.24
Outpatient	38	5.49
Paediatric	19	2.75
Refferal from another hospital	65	9.39

The frequency of *A. baumanii* was higher in year 2016. As the number of isolates of *A. baumanii* decreased from January – June 2016 period to July – December 2017, the tigecycline sensitivity against it increased for the same period (**Figure 1**).

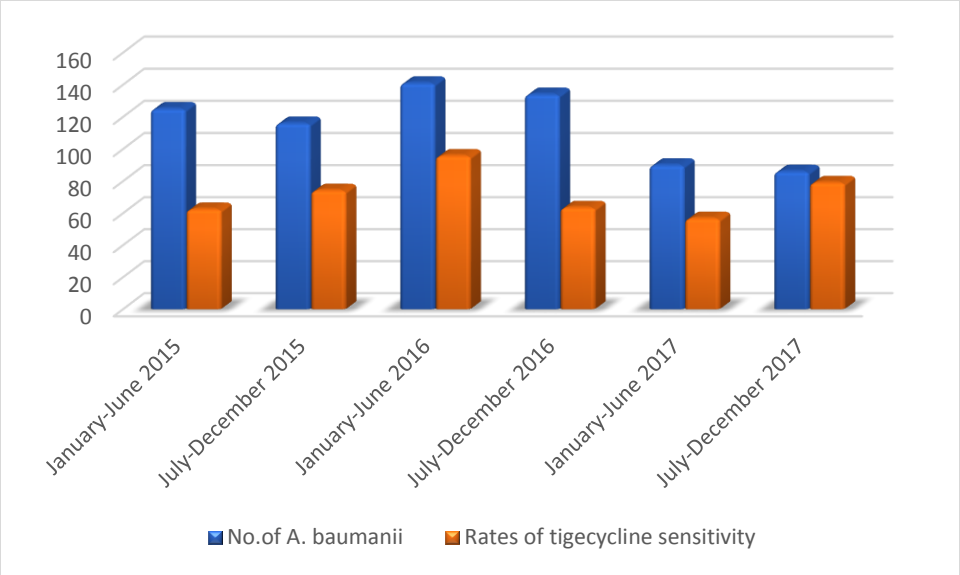

Figure 1. Number of isolates and tigecycline sensitivity against *A. Baumanii* from January 2015 – December 2017

From a total of 692 *A. baumanii* isolates, tigecycline MIC ranged from ≤ 0.5 to ≥ 8 µg/ml (Table 2.). Most of *A. baumanii* isolated in the study were multi-drug resistant with good susceptibility to tigecycline. Detailed result the activity of tigecycline were shown in Table 2, as well as Figure 1. This study identified 50.46% isolates had MIC ≤ 0.5 µg/ml, 2.38% with MIC = 1 µg/ml, and 19.07% with MIC = 2 µg/ml. The susceptibility rate for *A. baumanii* (MIC ≤ 2 µg/ml) were 68.27% in 2015, 79.58% in 2016, and 67.87% in 2017.

Table 2. In vitro activity of tigecycline against *A. baumanii* isolates

	No. of isolates (%)					
	January-June 2015	July-December 2015	January-June 2016	July-December 2016	January-June 2017	July-December 2017
MIC range (µg/ml)						
≤ 0.5	36,80	42,24	95,74	43,28	28,89	55,81
1	3,20	2,59	0,00	1,49	0,00	6,98
2	22,40	29,31	0,00	18,66	27,78	16,28
4	30,40	24,14	0,00	28,36	23,33	13,95
≥ 8	7,20	1,72	4,26	8,20	20,00	6,98
Susceptibility						
Susceptible*	62,40	74,14	95,74	63,43	56,67	79,07
Intermediate**	30,40	24,13	0,00	28,36	23,33	13,95
Resistant***	7,20	1,72	4,26	8,21	20,00	6,99

Discussion

A. baumanii has emerged especially in hospital evironment as one of the leading cause of nosocomial infection in immunocompromised patients. Resistance of this bacteria to numerous antibacterial agents, such as cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems is an increasing problem globally.[7,9-10]

During the past decades, the incidence of multi-drug resistance *A. baumanii* particularly carbapenem-resistant has accounted for approximately 93% of reported infection in hospital setting.[11] Therefore, therapeutic options available for infected patients are limited, as the strain frequently exhibit high resistance to most existing antibiotics.[4,7,11-12]

Several studies from different geographical regions found that the prevalence of MDRAB infection/colonization varied from 17.2% to 92.89%.[1,10-14,] Thus, tigecycline is considered as the last option in the management of clinical infection caused by MDRAB.

Tigecycline MIC for *A. baumanii* in this study varied from ≤ 0.5 to ≥ 8 μg/ml, that was comparable with a study by Talaga K, et al. which found that ESBL-producing *A. baumanii*, likewise isolates non-carbapenemases, had the highest MIC level of 8.0 μg/ml; for AmpC-producing *A. baumanii* the highest MIC level was 6.0 μg/ml; and for MBL-producing isolates the MIC level was 2.0 μg/ml.[2] Since there was no reference MIC value for in vitro tigecycline susceptibility against *A. baumanii*, a suitable congruence of various tigecycline MIC value sensitivity test by Pieewngam and Kiratisin was used, with sensitive at MIC ≤ 0,5 and resistant at MIC > 2 μg/ml.[2,15] These values were different with EUCAST reference which MIC ≥ 1 μg/ml was regarded as resistant as these resistant strains do not have mutation that enables them to acquire resistance.[2]

The present study noted that tigecycline had a good in vitro activity against all isolates tested. This result is in contrast with a study from European country, where tigecycline showed activity of 50% or lower against MDRAB isolates.[6-7,16]

On the other side, previous studies conducted in other province in Indonesia and India revealed high susceptibility of tigecycline (75% and 82 - 88% respectively), although a sharp decline in the recent years has been marked.[1,10,12,17] Previous study by Chen et al detect a decreased susceptibility rate for *A. baumanii* (55.3% in 2009 and 73.4% in 2010).[17]

Almost all *A. baumanii* were obtained from respiratory tract of inpatients ward (78.03%). A study in other province in Indonesia demonstrated similar results, as 59.94% of *A. baumanii* were obtained in sputum, 0.9% in pleural fluid, and 0.3% in broncho alveolar lavage (BAL).[1] These results were in contrast with other studies such as a study by Dolma et al isolated 18.9% from sputum, a study by Villers et al isolated 24.8% from tracheo-bronchial specimens, and Suri et al isolated 45.6%.[1,18-19]

Conclusion

As tigecycline demonstrated good value of MIC in this study, ranging between ≤ 0,5 to ≤ 2 μg/ml, it could be considered an effective antibiotic against *A. baumanii*, especially MDRAB. Due to the absence of bactericidal activity of tigecycline, these result must be interpreted cautiously before using tigecycline for infection due to MDR organisms, particularly MDRAB. The susceptibility rate of tigecycline against MDR isolates is alarming, thus wise consumption is warranted to prevent further increase of MDR organism.

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