

Original Article

In Vitro Activity of Tigecycline and Colistin against clinical isolates of *Acinetobacter baumannii* in Hospitals in Tehran and Bandar-Abbas, Iran

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Abstract:

Background: The *Acinetobacter* species, particularly *A. baumannii*, has emerged as one of the main causes of nosocomial infections in recent years. The high prevalence of drug resistance in *A. baumannii* limits the therapeutic options for treating infections caused by these bacteria. The objective of this study was to determine the *in vitro* activity of Tigecycline and Colistin against clinical isolates of *A. baumannii* in Tehran and Bandar Abbas, Iran.

Methods: This study was conducted from March 2009 to November 2010 at three hospitals in Tehran and Bandar Abbas, Iran, using 165 *Acinetobacter* species isolated from clinical specimens. All isolates were subjected to PCR to detect *bla*_{OXA-51}-like genes that are unique to *Acinetobacter baumannii*. Isolates that gave a band for the *bla*_{OXA-51}-like genes were identified as *A. baumannii*. Anti-microbial susceptibility tests were performed for Tigecycline, Colistin, and other antibiotics.

Results: Sensitivity rates to Colistin and Polymyxin-B were 100%. Resistance rates for Tigecycline were 4.2% in Tehran and 8.8% in Bandar-Abbas according to Jones criteria, whereas, according to U.S. FDA criteria, the resistance rates were 20.8% and 17.6%, respectively.

Conclusions: New alternative drugs are needed for the treatment of drug resistant *A. baumannii*. Although Colistin appears to be a good choice, adverse reactions have limited its usage. Tigecycline is effective against *A. baumannii* isolates, and it shows promise for solving the problem.

Keywords: *Acinetobacter baumannii*; Polymyxin-B, Colistin; Tigecycline

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i.e., $S \geq 19$ mm; $I = 15-18$ mm; $R \leq 14$ mm) (Tygacil package insert [June, 2005], Wyeth Pharmaceuticals, Inc., Philadelphia, PA) (13).

2.4. Susceptibility to antibiotics other than Tigecycline and Colistin

We collected the data of the antibiogram pattern of the *A. baumannii* isolates to commonly-used antibiotics, e.g., Imipenem, Ciprofloxacin, Amikacin, Cefepime, Ceftazidime, and Polymyxin-B. The susceptibility testing of these antibiotics was performed by the disk diffusion method on Mueller-Hinton agar plates. The disks were obtained from Mast Pharmaceutical, Inc. U.K.

3. Results

This study included 165 *Acinetobacter* isolates that were collected from hospitals in Tehran and Bandar-Abbas. One hundred and fifty-seven isolates (95.15%) that gave a band for *bla*_{OXA-51}-like identified as *A. baumannii*, Figure (1). Thirty-four isolates were from Bandar-Abbas, and 123 were from Tehran. Nine of the isolates were from sputum (5.7%), 25 were from pus (15.1%), 12 were from urine (7.64%), four were from cerebrospinal fluid (2.54%), two were from ascites (1.27%), two were from ears (1.27%), three were from catheters (1.9%), 24 were from burn wounds (15.28%), and 84 were from pleural effusion (53.5%). The quantities of isolates related to wards were as follows: Among the isolates 114(72.6%) were from intensive care unit, 26 (16.56%) were from internal ward, 9 (5.73%) were from surgical ward, 3 (1.9%) from neurosurgery ward, 2 (1.27%) from pediatric ward, 7 (4.45%) from emergency unit, 1 (1.9%) from coronary care unit, and 2 (2.27%) from ear, nose, and throat ward. For the two cities, Table 1 shows the results of susceptibility to Tigecycline and compares the susceptibility rates of the isolates to eight antibiotics.

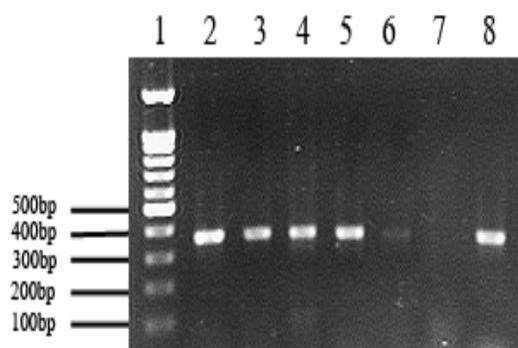


Figure 1. Polymerase chain reaction *bla*_{OXA-51} like gene (353 bp), line1:100-bp ladder, line 8: positive control, line 7: negative control and lines 2-6 subjects

Table 1. Susceptibility rates of *A. baumannii* isolates (n = 157) for eight anti-microbials in two cities in Iran

antibiotics	City Tehran n = 120			Bandar-Abbas n = 34		
	S	I	R	S	I	R
Colistin	120 (100%)	0	0	34 (100%)	0	0
Polymyxin B	120 (100%)	0	0	34 (100%)	0	0
imipenem	31 (25.8%)	25 (20.8%)	64 (53.3%)	11 (32.3%)	11 (32.3%)	12 (35.3%)
Ciprofloxacin	5 (4.2%)	0	115 (95.8%)	3 (8.8%)	0	31 (91.2%)
Amikacin	51 (42.5%)	8 (6.7%)	61 (50.8%)	17 (50%)	1 (2.9%)	16 (47%)
cefepime	7 (5.8%)	16 (13.3%)	97 (80.8%)	3 (8.8%)	4 (11.8%)	27 (79.4%)
ceftazidime	6 (5%)	0	114 (95%)	2 (5.9%)	1 (2.9%)	31 (91.2%)
Tygecycline Jones criteria	80 (66.7%)	35 (29.2%)	5 (4.2%)	26 (76.5%)	5 (14.8%)	3 (8.8%)
Tygecycline FDA criteria	29 (24.2%)	66 (55%)	25 (20.8%)	8 (23.5%)	20 (58.8%)	6 (17.6%)

4. Discussion

A high prevalence of multi-drug resistance by *A. baumannii* limits the therapeutic options for the treatment of infections caused by these bacteria. It is clear that new drugs are needed for the treatment of MDR *A. baumannii*. In some studies, Tigecycline has been found to be active in about 87 to 93% in of *Acinetobacter* species (3). In our study, according to the Jones criteria, the susceptibility rate to Tigecycline in the hospital in Tehran was 66.7%, and it was 76.5% in the hospital Bandar-Abbas. However, based on the FDA criteria, the rates were 24.2% in Tehran and 23.5% in Bandar-Abbas. All isolates (100%) were susceptible to Colistin and polymyxin B. Several studies have reported the susceptibility to Colistin as 98 to 100% (3). There are two problems in evaluating the effectiveness of Tigecycline against *Acinetobacter baumannii*. First, the U.S. Food and Drug Administration (FDA) has not assigned Tigecycline breakpoints for *Acinetobacter* species, and no interpretive criteria are currently available (7). The U.S. FDA-approved breakpoints of Tigecycline were defined against *Enterobacteriaceae*, and the diameter of the inhibition zone is ≥ 19 mm and MIC ≤ 2 mg/L (14). The second problem, identified by Surapee in Thailand, is that the U.S. FDA-approved breakpoint of Tigecycline against *Enterobacteriaceae* was not applicable to Tigecycline against *A. baumannii*. The breakpoint for an inhibition zone diameter of ≥ 13 mm was more accurate in predicting the susceptibility of *A. baumannii* to Tigecycline with a sensitivity of 99% and a specificity of 100% (15). In Bouchillon's study, Tigecycline was the most active drug against all species of *Acinetobacter* (7). The Tigecycline MIC₉₀ of 2 µg/ml was 16-fold and 64-fold more potent than the β -lactams and Carbapenems, respectively, against all tested strains. Tigecycline was 8-fold and 16-fold more potent against *Acinetobacter* species than Levofloxacin and Doxycycline, respectively (7). A Taiwanese study showed that the overall susceptibility rate of *A. baumannii* to Tigecycline was 80.9%. The susceptibility rates determined in various hospitals to Tigecycline were 37-100%. The rates of susceptible, intermediate, and resistant isolates by the disk diffusion method, using the criteria of Jones et al., were 88.3, 9.9, and 1.8%, whereas they were 44.0, 51.7, and 4.3% by the U.S. FDA's criteria. By comparison with their previous report on Tigecycline activity against *A. baumannii* isolates in Taiwan, they observed a seven-fold increase (from 3% in 2003 to 20% in 2007) in the number of *A. baumannii* isolates that are not susceptible to Tigecycline (13). Since the most probable resistance mechanism for Tigecycline in *A. baumannii* is the presence of an efflux pump mechanism, exposure to sub-therapeutic levels of Tigecycline for even short periods of time may promote the rapid emergence of Tigecycline resistance and cause therapeutic failure. In our study, a possible explanation for increased Tigecycline resistance was the exposure to multiple antibiotics in our hospitals in which the efflux systems of these strains already are highly active. The disk diffusion method is the most commonly used (> 90%) susceptibility method in our hospitals, since automated susceptibility test systems are not available in most microbiology laboratories. This situation also exists in other countries (16). Therefore, selection of appropriate criteria for the disk diffusion method is crucial. There was no resistance to Colistin in our study. It appeared to be a good option in the treatment of MDR *A. baumannii*, but adverse reactions limit its extensive use. However, Colistin resistance is rare worldwide at the current time, which likely reflects its very limited use. Colistin-resistant isolates have recently been identified in several Gram-negative species, such as *A. baumannii*, *Klebsiella pneumoniae*, and *P. aeruginosa* (4). Only sporadic cases of Colistin resistance have been reported in the literature in clinical isolates of patients admitted to the ICUs of an Argentinian University Hospital. Colistin hetero-resistance was observed in 4% of these isolates (17).

5. Conclusions

The findings of this study showed that Colistin and Polymyxin-B still show the highest potency against *A. baumannii* in our hospitals. However, the resistance of *A. baumannii* to Tigecycline may limit their use in the future. The broad-spectrum *in vitro* activity of Tigecycline and Colistin may make them a suitable candidate for use in the empirical treatment of serious infections. However, it should be noted that *in vitro* data do not equate to clinical efficacy, and resistance rates should be monitored continuously. Finding cases of resistance to Tigecycline suggests an efflux-based mechanism, and further work is ongoing to elucidate this mechanism.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All of authors contributed to this project and article equally. All authors read and approved the final manuscript.

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