

SUSCEPTIBILITY TO TIGECYCLINE OF MULTIRESTANT BACTERIA AT IBN ROCHD UNIVERSITY HOSPITAL-CASABLANCA

Assiya El Kettani^{1,2*}, Soufiane Arji^{1,2}, Fakhreddine Maaloum^{1,2}, Khalid Katfy^{1,2}, Khalid Zerouali^{1,2},
Houria Belabbes^{1,2}, Naima Elmdaghri^{1,2}

¹.Dep^t of Microbiology, Faculty of Medicine and Pharmacy, Hassan II^d University of Casablanca, Morocco.

².Bacteriology-Virology & Hospital Hygiene Laboratory, Ibn Rochd University Hospital, Casablanca, Morocco.

ABSTRACT

A descriptive prospective study was conducted between 2015 and 2017 at the Microbiology laboratory of the Casablanca University Hospital Center to study the Tigecycline susceptibility of isolated multi drug resistant bacteria (MDRB): Imipenem-resistant *Acinetobacter baumannii* (IRAB), ESBL+/- Carbapenemase -producing enterobacteria (ESBLE), Meticillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant Enterococci (VRE). Antibiotic sensitivity tests were performed by diffusion method and those for Tigecycline by E-test strips according to EUCAST / CA-SFM. Breakpoints of interpretation of Tigecycline sensitivity were according to the FDA. A total of 692 MDRB strains were studied. The Tigecycline resistance rate was 33.9% (25.3% I, 8.6% R). For IRAB, it was 46% (30.5% I, 15.5% R), for ESBLE 27.9% (100% I), for MRSA 10% (100% R) and no VRE was resistant to Tigecycline. However, as EUCAST has not determined breakpoints for the in vitro thresholds of *A.baumannii* concerning Tigecycline, conclusions should not be formally established as to its sensibility.

Keywords: Multi-resistant bacteria; Sensibility; Tigecycline.

Corresponding Author:

Assiya El Kettani,

Address: Dep^t of Microbiology, Faculty of Medicine & Pharmacy, Hassan II^d University, Casablanca, Morocco.

E-mail: assiyaelkettani@gmail.com

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INTRODUCTION

According to the WHO, bacterial resistance is a major upsurge and represents a public health problem. Although the evaluation of older antimicrobial agents is important, there is a real need to develop new agents and to monitor the development and spread of bacterial resistance mechanisms [1]. Tigecycline is a glycy cycline derivative of tetracyclines which obtained its marketing authorization (MA) in France in 2006 [2]. Tigecycline is a molecule that is active on multi-resistant bacteria (MDRB). However, some authors have revealed the emergence of resistant strains to this antibiotic.

Therefore, the aim of this work was to study the Tigecycline susceptibility profile of isolated MDRB in the Microbiology laboratory of Ibn Rochd University Hospital in Casablanca.

PATIENTS AND METHODS

A prospective descriptive study has been conducted over 2 years (between September 2015 and August 2017). Data from the study were stored in the computerized database of the Microbiology laboratory of Ibn Rochd University Hospital-Casablanca.

The strains studied were: Imipenem-resistant *Acinetobacter baumannii* (IRAB), Extended-spectrum β -lactamase producing enterobacteria (ESBLE) +/- Carbapenemase, Meticillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant Enterococci (VRE). The strains were isolated from laboratory-derived diagnostic specimens for IRABs, EBLSEs and MRSA, and rectal carriage for VRE. Duplicates have been excluded. The isolates were identified according to standard bacteriological techniques. The identification of *S. aureus* was performed by an agglutination or coagulase test. API 20 E and API 20

NE (Biomérieux, Marcy l'Etoile) were used to identify Gram-negative bacilli and API STREP (Biomérieux, Marcy l'Etoile) to identify Enterococci.

The study of antibiotic susceptibility was carried out by diffusion method in agar and the study of the sensitivity to Tigecycline was carried out by E-test strips (Biomérieux, Marcy l'Etoile) according to the recommendations of EUCAST / CA-SFM.

Methicillin-resistant staphylococci were detected by the search for resistance to cefoxitin. Extended-spectrum beta-lactamase producing strains (ESBL) were detected by the synergy test between central amoxicillin + clavulanic acid disc and the

cefotaxime and ceftazidime disks. The carbapenemase search was performed by the Hodge test.

E. coli strain ATCC 25922 was used as the reference strain. The interpretation breakpoints of Tigecycline were based on EUCAST 2015 recommendations. The interpretation criteria for MICs for *A. baumannii* were based on FDA recommendations [3, 4] according to the modalities:

- Sensible ≤ 2 mg / l
- Intermediate = 4 mg / l
- Resistant > 4 mg / l

RESULTS

A total of 692 MDRB strains were studied. Results were reported in **Table I**.

Table I: Distribution and percentage of tested strains on Tigecycline.

Strains	Number	
IRAB	353 (52%)	
<i>K.pneumoniae</i>	146(21%)	Total ESBL : 240 (34%)
<i>E.Coli</i>	53(7%)	
<i>E.Cloacae</i>	41(6%)	
MRSA	50(7%)	
VRE	49(7%)	
Total	692	

IRAB: Imipenem-resistant *Acinetobacter baumannii*; ESBL: Extended spectrum beta-lactamases

The strains of IRAB, ESBL, and MRSA were isolated from bronchial samples (28%), blood cultures (23%), pus samples (22%), cutaneous and mucosal samples (15%), medical devices (8%) and body fluids (4%). Sixty five percent of these samples came from patients hospitalized in intensive care

units. Furthermore, all of the VRE strains came from the rectal carriage samples of intensive care patients.

The MICs found for Tigecycline for IRAB, ESBL and MRSA ranged from 0.5 to 8 mg / l (**Fig.1**).

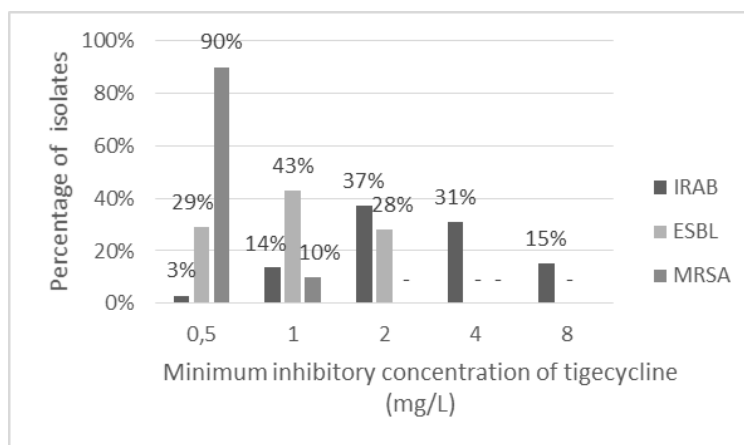


Fig.1 In vitro activities of Tigecycline against the different MDR strains

The Tigecycline resistance rate was 33.9% (25.3% I, 8.6% R). The IRAB resistance rate was 46% (31% I

and 15% R). The sensitivity of ESBL, MRSA and ERV were 72%, 90%, and 100% respectively.

DISCUSSION

The results of this study highlight the interesting activity of this antibiotic against MDR bacteria with a total sensitivity of 66%. These results were broadly comparable to those in the literature (**Table II**).

Table II: Comparison of our results with existing studies [5-9]

Studies	Our study (2015-2017)	Asia 2015 [5]	Montpellier 2008-2011 [6]	Angers 2006-2009 [7]	Spain 2004-2014 [8]	Poland 2008-2013 [9]
Strains						
IRAB	54% MIC \leq 2 MIC90=8mg/l	- MIC90=2mg/l	47% MIC \leq 2 MIC90=8mg/l	- MIC90=1mg/l	-	40% MIC \leq 2 MIC90=8
<i>K.pneumoniae</i>		86.7%	76.7%	97%	80.5%	-
ESBL						
<i>E.coli</i> ESBL	72%	100%	98%	100%	98.9%	-
<i>E.cloacae</i>		96.1%	75.6%	92%	92.6%	-
ESBL						
MRSA	90%	100%	-	100%	100%	-
VRE	100%	100%	-	100%	99.5%	-

IRAB: Imipenem resistant *A.baumannii*, ESBL: Extended-spectrum β -lactamase, MRSA: Meticillin resistant *S.aureus*, VRE: Vancomycin resistant enterococcus

Breakpoints of interpretation concerning *A.baumannii* are subject to controversy. Indeed, sensitivity thresholds vary from 0.5 to 2 mg / l according to some studies [6, 9].

Some authors have defined the MIC90 as the lowest concentration capable of inhibiting 90% of strains of the species studied in order to overcome the disagreement over the interpretation thresholds to *A.baumannii*.

Our MIC50 and MIC90 (2 and 8 mg / l respectively) were higher than those described by some authors [5, 7] and comparable to others [6, 9]. These high MICs can be explained by the dissemination of resistant clones.

Tigecycline thus, represents a potential alternative in the therapeutic management of MDR infections. However, as EUCAST did not determine breakpoints for the in vitro sensitivity thresholds of Tigecycline in *A.baumannii*, conclusions should not be formally established regarding its sensitivity.

Some limitations to the use of tigecycline persist, including its documented inefficiency in urinary sites, its ineffectiveness against certain enterobacteria that are naturally resistant (*Morganella* spp, *Proteus* sp, and *Providencia* spp) and against *P.aeruginosa* as well as in children under 8 years old. [11]

A rationalization of its prescription is thus essential, it should be limited to the infections labeled with

MDRB in order to avoid the emergence of resistant mutants.

CONCLUSION

The MDR bacteria resistance rate for Tigecycline remains relatively low in our context and shows that it may be a therapeutic alternative. However, there is still no consensus on sensitivity thresholds of *A.baumannii* to Tigecycline.

It is imperative to institute a rigorous MDR surveillance policy and to insist on the rationalization of the prescription of antibiotics including Tigecycline in order to avoid the spread of resistant strains.

ABBREVIATIONS:

- IRAB: Imipenem resistant *A.baumannii*,
- ESBL: Extended-spectrum β -lactamase
- MRSA: Meticillin resistant *S.aureus*,
- VRE: Vancomycin resistant enterococcus
- EUCAST: European committee on antimicrobial susceptibility testing
- CA-SFM: comité de l'antibiogramme- société française de microbiologie
- FDA: Food and drug administration
- MIC: minimum inhibitory concentration

CONFLICTS OF INTEREST: None

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