

Evaluation of *Tigecycline* Susceptibility in Multidrug-Resistant Bacteria at the University Hospital of Marrakech (Morocco)

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Abstract: The phenomenon of bacterial resistance to antibiotics is a major public health problem. The prevalence of multidrug-resistant bacteria is rapidly increasing with heavy consequences in terms of morbidity and mortality and health care costs. *Tigecycline* is a new active glycylycylcline on this type of germ and could be a therapeutic alternative for the management of these infections. The aim of this work is to evaluate the in vitro activity of *Tigecycline* against multidrug-resistant organisms isolated at Mohammed VI hospital in Marrakech. It is a descriptive prospective study of a series of 171 multidrug-resistant bacteria including 102 clinical isolates of extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL) and 85 clinical isolates of multidrug-resistant *Acinetobacter baumannii*. The in vitro activity of *Tigecycline* was measured by the determination of the minimum inhibitory concentration (MIC) by diffusion method on agar medium using the strips "E-test" according to the recommendations of the CASFM. 71% of *Acinetobacter baumannii* isolates were sensitive to *Tigecycline* of with MIC ≤ 1 mg / l, while 17.6% of tested strains had intermediate sensitivity to *Tigecycline* with a MIC between 1 and 2 mg / l, 11,4% were resistant with a MIC > 2 mg / l. ESBL enterobacterial strains were mostly (77,5%) with a MIC ≤ 1 mg / l. Intermediate sensitivity was found in 15.6% of the isolates with a MIC between 1 and 2 mg / l, however, resistance to *Tigecycline* was found in 6.8% of enterobacterial isolates with a MIC > 2 mg / l. *Tigecycline* is an interesting therapeutic option and may have an important role in the treatment of multidrug-resistant infections. Detection of the sensitivity status of *Tigecycline* is necessary to optimize its use and preserve this molecule in our therapeutic arsenal.

Keywords: Tigecycline, Multidrug-Resistant Bacteria, In Vitro Activity

1. Introduction

The phenomenon of bacterial resistance to antibiotics is a major public health problem on a global scale. For years, there has been a significant and steady increase in resistance to antibiotics used in the treatment of community and hospital infections [1]. The prevalence of multidrug-resistant bacteria is rapidly increasing with serious consequences in terms of morbidity and mortality and costs of care.

Tigecycline is a new glycylycylcline synthetic analogue of tetracyclines. This antibiotic inhibits bacterial protein synthesis by blocking the 30S ribosome subunit by

attachment to the tRNA binding site. It has been designed that its activity escapes the two main mechanisms of tetracycline resistance that are efflux and ribosomal protection.

In this work, the in vitro activity of *Tigecycline* is routinely tested against clinically significant isolates of third-generation cephalosporin-resistant enterobacteria by the production of extended-spectrum β -lactamases and *Acinetobacter baumannii*.

The aim of this work is to evaluate the in vitro activity of *Tigecycline* against multidrug-resistant germs isolated at the Mohammed VI hospital in Marrakech for a possible

therapeutic use.

2. Patients and Methods

2.1. Collection of Clinical Strains

It's a prospective study on a series of 171 multidrug-resistant bacteria, including 102 clinical isolates of extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL) and 85 multidrug-resistant clinical isolates of *Acinetobacter baumannii*, isolated from diagnostic specimens from hospitalized patients presenting with a documented and clinically significant infection in the various hospital departments of the Mohammed VI University Hospital in Marrakech. Inclusion is independent of medical history, previous antibiotic therapy, age and sex. All sampling sites were included.

2.2. Phenotypic Identification and Determination of Antibiotic Sensitivity

Enterobacteriaceae and *Acinetobacter baumannii* were identified according to morphological, cultural and biochemical characters using the BD Phoenix® automaton and / or API 20E, API 20NE (bioMérieux®) galleries according to the methodologies defined by the manufacturer with controls integrated quality. Antibiotic bacterial susceptibility of isolated strains was evaluated using the BD Phoenix® and / or Mueller-Hinton agar (BioRAD®). The distinction between ESBL and high-level cephalosporinase was carried out by the synergy test between third-generation cephalosporin disks and an amoxicillin / clavulanic acid disc according to the recommendations of the Committee of the antibiogram of the French Society of microbiology.

The in vitro activity of Tigecycline was measured by the determination of the minimum inhibitory concentration by diffusion method on agar medium using the strips "E-test"

according to the recommendations of the CASFM.

3. Results

3.1. Epidemiology of the Strains Collected

Susceptibility to *Tigecycline* was tested on 102 enterobacterial strains including 56 strains of *Klebsiella pneumoniae* (55%), 30 strains of *Enterobacter cloacae* (29.4%), and 16 strains of *Escherichia coli* (15.6%). These strains were isolated mainly from blood cultures (39.2%), urinary samples (30.4%), various suppured samples (22.5%) and respiratory samples (7.7%). The majority of these strains were isolated from intensive care units (47%), 29.4% from surgical departments, 19.6% from medical services and 4% of the strains were isolated in emergency services.

The 85 multidrug-resistant strains of *Acinetobacter baumannii* were isolated from blood cultures (33%), respiratory samples (20%) from urinary samples (14%) and various suppured samples (33%). 7% of the patients were hospitalized in medical services, 81% in intensive care units, and 12% in surgical services.

3.2. Tigecycline Susceptibility of C3G Resistant Enterobacteriaceae

The results of multidrug-resistant enterobacterial isolates showed that the majority of strains, 77.5%, were considered sensitive with a MIC of ≤ 1 mg / l. In the different species, *Escherichia coli* was the most frequently susceptible species in the enterobacteriaceae group with 100% sensitivity. For *Enterobacter cloacae*, the percentage of susceptible strains was lower (86.7%). This sensitivity was more reduced in *Klebsiella pneumoniae* isolates where a sensitivity of 69.8% was observed. Resistant or intermediate susceptibility strains were isolated mainly in intensive care units (60%). (Table 1)

Table 1. Sensitivity profile of ESBL Enterobacteriaceae to Tigecycline by Infectious Site and by Service.

Sensitivity of EBs to TGC	No. of isolates	%	Bacterial species (% of Sensitivity within the species)	Hospitalization services	Collection sites
Sensitive MIC ≤ 1 mg/L	79	77,5%	16 <i>E. coli</i> (100% sensitivity) 37 <i>K. pneumoniae</i> (66% sensitivity) 26 <i>E. cloacae</i> (86,7% sensitivity)	ICU: 34 isolates (43%) surg: 26 isolates (32,9%) Med: 16 isolates (20,3%) Emerg: 3 isolates (3,8%)	Blood culture: 33 isolates (41,7%) Pus: 17 isolates (21,5%) Respiratory: 6 isolates (7,7%) Urinary: 23 isolates (29,1%)
Intermediate 1 mg/L \leq MIC \leq 2 mg/L	16	15,7%	12 <i>K. pneumoniae</i> (21,4% intermediate sensitivity) 4 <i>E. cloacae</i> (13,3% intermediate sensitivity)	ICU: 9 isolates (56,3%) Surg: 3 isolates (18,7%) Med: 3 isolates (18,7%) Emerg: 1 isolat (6,3%)	Blood culture: 4 isolates (25%) Pus: 5 isolates (31,2%) Respiratory: 1 isolates (6,3%) Urinary: 6 isolates (37,5%)
Resistant MIC ≤ 2 mg / L	7	6,8%	7 <i>K. pneumoniae</i> (12,6% resistance)	ICU: 5 isolates (71,4%) Surg: 1 isolate (14,3%) Med: 1 isolate (14,3%)	Blood culture: 3 isolates (42,8%) Pus: 1 isolat (14,3%) Respiratory: 1 isolate (14,3%) Urinary: 2 isolates (28,6%)

EB: enterobacteriaceae; TGC: Tigecycline; E. coli: Escherichia coli; K. pneumoniae: Klebsiella pneumoniae; E. cloacae: Enterobacter cloacae; ICU: intensive care unit; Surg: Surgery; Med: Medicine; Emerg: Emergency

3.3. Tigecycline Sensitivity of Multidrug-Resistant Acinetobacter Baumannii Strains

This study included 85 strains of *Acinetobacter baumannii*; Sensitivity to *Tigecycline* was found in 71% of

Acinetobacter baumannii isolates with MIC ≤ 1 mg / l. 17.6% of the strains tested had an intermediate sensitivity to *Tigecycline* with a MIC between 1 and 2 mg / l. 11.4% of isolates were resistant with a MIC > 2 mg / l. *Tigecycline*-

resistant and intermediate susceptibility strains were isolated mainly from burns, bacteremia, and acquired pneumonia

under mechanical ventilation in the intensive care unit (Table 2).

Table 2. Profile of the susceptibility of *Acinetobacter baumannii* strains to *Tigecycline* by infectious site and by service.

Sensitivity to TGC	Number of AB isolates	%	Hospitalization services	Collection sites
Sensitive MIC ≤ 1 mg/L	60	71%	ICU: 48 isolates (80%) Surgery: 7 isolates (11,7%) Medicine: 5 isolates (8,3%)	Blood culture: 21 isolates (35%) Pus: 23 isolates (38,3%) Respiratory: 10 isolates (16,7%) Urinary: 6 isolates (10%)
Intermediate 1 mg/L ≤ MIC ≤ 2 mg L	15	17,6%	ICU: 12 isolates (80%) Surgery: 2 isolates (13,3%) Medicine: 1 isolates (6,7%)	Blood culture: 4 isolates (26,7%) Pus: 3 isolates (20%) Respiratory: 3 isolates (20%) Urinary: 5 isolates (33,3%)
Resistant MIC > 2 mg / L	10	11,4%	ICU: 9 isolates (90%) Surgery: 1 isolates (10%)	Blood culture: 3 isolates (30%) Pus: 2 isolates (20%) Respiratory: 4 isolates (40%) Urinary: 1 isolates (10%)

TGC: Tigecycline; AB: *Acinetobacter baumannii*; ICU: intensive care unit

4. Discussion

Increasing bacterial resistance to antibiotics continues to grow and can lead to therapeutic impasses. This phenomenon sometimes seriously limits the number of anti-infective agents available in the therapeutic arsenal and can be particularly problematic in severe infections and in high-risk patients [2].

Tigecycline is a recent antibiotic, a semi-synthetic derivative of minocycline belonging to the glycylglycyl class, with a large spectrum of activity against difficult-to-treat pathogens, such as *Acinetobacter baumannii* and Gram-negative bacterial strains producing extended spectrum β -lactamases. Its advantage lies in its high power of action and in its escape to the two main mechanisms of resistance to tetracyclines, the protection of ribosomes and efflux. Minimal organic toxicity and lack of dosage adjustment in most patients are important considerations for the use of *Tigecycline*. It has been shown to be as effective and safe as standard antimicrobial therapy for the treatment of complicated intra-abdominal infections of adults, complex skin conditions and skin structure infections, and bacterial pneumonia acquired in the community. [3]. *Tigecycline* resistance mechanisms are mainly associated with RND (resistance-nodulation-division) transporters: the AdeABC, AdeFGH and AdeIJK efflux pumps, but other resistance mechanisms have also been implicated. [4, 5]

ESBL-producing enterobacteriaceae, since their first description in the 1980s, have caused numerous epidemics at the local, regional and international levels, frequently having as origin the resuscitation services. The commensal nature of these bacteria and the plasmid genetic support of the mechanism of resistance have allowed their spread on a very large scale. The infections caused by these strains present an increased risk of therapeutic failure and are associated to prolonged hospitalizations and additional costs related to care. *Tigecycline* is a therapeutic alternative to eradicate these multiresistant strains. This study confirms a good activity of *Tigecycline* on ESBL enterobacteriaceae with a sensitivity reaching 77.5% on all strains tested. The most effective

efficacy is observed in isolates of *Escherichia coli* with 100% sensitivity, this sensitivity decreases in *Enterobacter* and *Klebsiella* (respectively 86.7% and 66% sensitivity) which is consistent with data from the literature [6-8]

Acinetobacter baumannii is a pathogen of increasing concern, usually causing epidemics in hospitals. It has many resistance mechanisms and may be involved in therapeutic impasse situations. In this study, the *Acinetobacter baumannii* strains have a sensitivity of 71% to *Tigecycline*. This sensitivity could be interesting in therapeutics because of the increase in the frequency of antibiotic-resistant *Acinetobacter baumannii* infections [9]. However, the high frequency of intermediate sensitivity *Acinetobacter baumannii* strains or resistant ones to *Tigecycline* (17.6% and 11.4% respectively) can be explained by the non-rational use of antibiotics, especially in intensive care unit. [10].

Although the use of *Tigecycline* in case of multidrug-resistant infection is an attractive choice, the prescription should be made with caution as therapeutic failures have been reported mainly in strains of *Acinetobacter baumannii* [11]. Dual antibiotic therapy with *Tigecycline* has become an attractive option for clinicians. Combination antibiotic therapy suggestions are being studied in vitro with moderate synergistic results that may suppress *Tigecycline* resistance, which should be confirmed in animal models and clinical trials [12, 13].

5. Conclusion

This study reports the emergence of *Tigecycline* resistance in isolates of *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Acinetobacter baumannii* in our context. The treatment of multidrug-resistant infections is a real challenge for the clinician, and the therapeutic experience with these germs is limited. *Tigecycline* is an interesting therapeutic option and may have an important place in the treatment of these infections. Accurate detection of *Tigecycline*-sensitive status and surveillance of resistant organisms in hospitals is necessary to optimize its prescription and preserve this molecule in our therapeutic arsenal. However, its use would

require clarification of the sensitivity threshold and better knowledge of the correlation between in vitro and in vivo activity.

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