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(RESEARCH ARTICLE)

Tigecycline susceptibility among multi-drug resistant bacteria: A 7-year retrospective study

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Abstract

The emergence and spread of multidrug-resistant bacteria (MDR) are major public health issues worldwide. The objective of this study is to evaluate the microbiological efficacy of tigecycline against multi-drug-resistant bacteria and to explore its potential place in clinical practice. A retrospective study was carried out over 7 years, from January 2015 to December 2021, at the Avicenne Military Hospital. Were collected all bacteriological samples received for diagnostic purposes at the microbiology laboratory. Tigecycline susceptibility was tested among 846 isolates among the 4293 isolates during the study period. The overall frequency of MDR bacteria was of 14,3%. 60% of the MDR bacteria isolated were susceptible, 35% were declared resistant and 5% were declared intermediate. Co-resistance levels in MDR bacteria are high. Tigecycline remained active in vitro on most of the MDR bacteria tested. The susceptibility rates for tigecycline found were respectively 76%, 57%, and 34%, for the ESBL Enterobacteriaceae strains, the CPEs, and the multi-drug resistant *Acinetobacter baumanii* strains. In this study, the MDR bacteria isolated showed overall satisfying susceptibility rates to tigecycline.

Keywords: MDR bacteria; Tigecycline; Susceptibility testing; Antibiotics resistance

1. Introduction

Multi-Drug-Resistant Bacteria (MDR) are bacteria combining several mechanisms of resistance to different families of antibiotics, thereby limiting the therapeutic possibilities in the event of infection [1].

Antibiotic resistance is a serious problem worldwide, leading to increased morbidity, mortality, and healthcare costs. Multi-resistant and highly resistant bacteria have emerged over time under the pressure of excessive use of antibiotics. This multi-resistance can eventually lead to pan-resistance affecting all families of antibiotics and thus causing major therapeutic impasses [2].

It is, therefore, necessary to develop new anti-microbial agents to deal with multi-resistant bacteria; to meet this need, the FDA in 2005 approved the use of tigecycline: a glycylcycline-based antibiotic with a broad microbiological spectrum for intravenous use [3].

The objective of this study is to evaluate the microbiological efficacy of tigecycline against multi-drug resistant bacteria and to explore its potential place in clinical practice.

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2. Material and methods

2.1. Collection of isolates

A retrospective study was carried out over 7 years, from January 2015 to December 2021, at the Avicenne Military Hospital. The investigation covered all bacteriological samples received for diagnostic purposes at the microbiology laboratory. All bacterial strains isolated from samples for ecological purposes and duplicates were therefore excluded. Data were collected and processed retrospectively with Microsoft Office Excel® software.

2.2. Identification of isolates and susceptibility testing

The identification of the bacterial strains was based on the study of their morphological, cultural, and biochemical characteristics on the BD Phoenix™ i200 Automated System, which also allows susceptibility testing. Detection of resistance phenotypes was completed by the conventional agar disc diffusion method. The interpretation was based on CA-SFM/EUCAST guidelines. (http://www.sfm-microbiologie.org/).

2.2.1. Inclusion criteria:

The study concerned the following MDR bacteria:

- Enterobacteriaceae resistant to 3rd generation cephalosporins by secretion of extended-spectrum beta-lactamase (ESBL),
- Acinetobacter baumannii resistant to ceftazidime and/or imipenem
- Enterobacteriaceae resistant to carbapenems.

2.2.2. Exclusion criteria

Methicillin-resistant *Staphylococcus aureus*, and multi-drug resistant *Pseudomonas aeruginosa*. The susceptibility of these bacteria will not be discussed in this study.

2.2.3. Antibiogram and phenotypic identification

Strains of Enterobacteriaceae producing an extended-spectrum β-lactamase detected by the automaton were confirmed by a double-disk synergy test between a third-generation cephalosporin and clavulanate. For strains categorized as intermediate sensitivity or resistant to cefotaxime and/or ceftazidime and/or aztreonam, in the absence of synergy between the molecules and clavulanic acid, a cloxacillin test carried out on Mueller Hinton (MH) supplemented with 250 mg/L of cloxacillin (cephalosporinase inhibitor) made it possible to highlight an ESBL possibly masked by a cephalosporinase.

Any Enterobacteriaceae strain with decreased susceptibility to ertapenem (MIC ≥0.5 mg/L or inhibition diameter < 25 mm; 10 µg discs) by agar diffusion test was considered suspicious for Carbapenemase-producing Enterobacteriaceae (CPE) (CASFM/EUCAST). To improve the detection sensitivity of carbapenemase production, both imipenem and ertapenem were tested.

3. Results and discussion

Over 7 years, 615 MDR bacteria were collected among 4293 bacterial strains isolated at the Avicenne Military Hospital of Marrakesh. The overall frequency was 14, 3%.

The distribution of these MDR bacteria shows a large predominance of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (54,1%, n=333) followed by *Acinetobacter baumannii* resistant to ceftazidime and/or imipenem (28,1%, n=173), methicillin-resistant *Staphylococcus aureus* (9,3%, n=57), then Enterobacteriaceae resistant to carbapenems (5,2%, n=32), and finally *Pseudomonas aeruginosa* resistant to ceftazidime and/or imipenem (3.3%, n=20). No strains of *Enterococcus faecium* resistant to glycopeptides were isolated.

ESBL-producing strains accounted for 10% of Enterobacteriaceae isolated (total number of Enterobacteriaceae = 3486). *K pneumoniae* and *E. coli* were most predominant (48% and 32% respectively). The percentage of multiresistant *A. baumannii* (total number of *A. baumannii*=216) in the specie was 80%.

The departments most affected by these MDR bacteria are respectively intensive care (48%), urology (21%), general surgery (12%), and traumatology (8%).

MDR bacteria were mainly isolated from urinary tract infections (42%), bacteremia (27%), pneumopathy (19%), surgical site infections (11%), and meningitis (1%).

The epidemiological characteristics of patients infected with MDR bacteria showed a male predominance (overall sex ratio of 1.4) with extreme ages ranging from 17 to 87 years.

Concerning the evolution of the frequency of the MDR bacteria, a gradual was noted, especially during the last two years of the study, as shown in figure 1. (Figure 1).

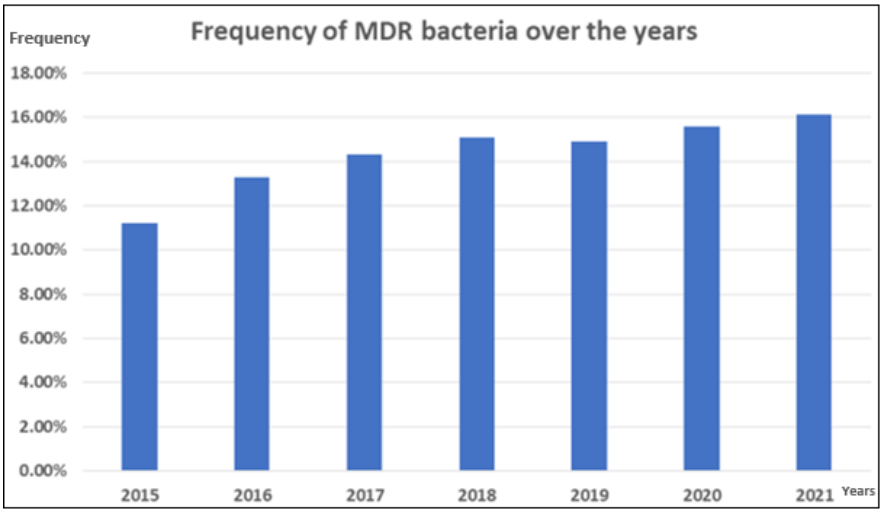

Figure 1 Frequency of MDR bacteria reported over 7 years

Tigecycline was tested on 846 isolates among the 4293 isolates during the study period. 60% (n=507) of the MDR bacteria isolated were susceptible, 35% (n=296) were declared resistant and 5% (n=43) were declared intermediate.

Regarding the co-resistance rates found in ESBL bacteria, we found a resistance rate of 15% to imipenem, 26% to fosfomycin, 32% to nitrofurantoin, 43% to amikacin, and 86% to ciprofloxacin. Concerning tigecycline, the sensitivity rate in ESBL bacteria was 76%. Among the ESBL Enterobacteriaceae isolated, *Escherichia coli* was the most sensitive to tigecycline with a sensitivity rate of 80%, followed by *Klebsiella pneumoniae* with a sensitivity rate of 64%.

Concerning carbapenemase-producing Enterobacteriaceae, 57% of isolates were sensitive to tigecycline in this study.

Of the 173 multi-resistant *Acinetobacter baumanii* strains isolated, 87% were resistant to ciprofloxacin, 80% to gentamicin, 73% to co-trimoxazole, and 71% to amikacin. Tigecycline encountered the lowest resistance rate which was 66%.

4. Discussion

Are to be considered as "MDR" bacteria resistant to at least one antibiotic molecule belonging to more than three different classes among the classes usually active on this bacterium. The following species are currently listed as "MDR": methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-EB), ceftazidime-resistant and/or imipenem, and multidrug-resistant *Acinetobacter baumannii*, Carbapenemase-producing Enterobacteriaceae (EPC), and Vancomycin-resistant enterococci (VRE) [4].

Tigecycline is a new bacteriostatic semi-synthetic minocycline antibiotic belonging to the glycylcyclines family. The glycylcyclines are derivatives of tetracycline antibiotics. Tigecycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit with an affinity five times greater than that of cyclins. Tigecycline is a bacteriostatic antibiotic in vitro [5]. It has a very broad spectrum including all Gram-positive cocci, as well as a large proportion of Gram-negative bacilli and anaerobes. Some species, however, are inconstantly sensitive. As for *Pseudomonas æruginosa*, it has a natural

resistance to tigecycline [6]. The prevalence of acquired resistance may vary geographically and over time for some species; it is, therefore, useful to have information on the prevalence of local resistance, especially for the treatment of severe infections [7].

Regarding the ESBL Enterobacteriaceae strains isolated, 76% were sensitive to tigecycline. The results found are comparable to those of a multicenter study conducted in Europe that assessed the susceptibility to tigecycline among Gram-Negative and Gram-Positive isolates in 226 different centers [8]. The results in the European countries varied from a level of 98,9% susceptibility to 78.1% for the ESBL Enterobacteriaceae strains [8]. A study conducted in Madrid, Spain, found a sensitivity rate of 97.5% of ESBL Enterobacteriaceae to tigecycline [9]. Studies carried out in Greece have shown that the use of tigecycline has proved to be of some benefit, alone or in combination [10].

In this study, 57% of the carbapenemase-producing strains were sensitive to tigecycline. The rates found are close to those reported by a study conducted in Reunion Island, a French territory in the Southwest Indian Ocean, which found a susceptibility rate of 67% to tigecycline of CPE strains [11]. A study conducted in Tunisia in a major burns unit found that for CPE, the lowest resistance rates were recorded for tigecycline (43%) and fosfomycin (33%). An American study on the efficacy of tigecycline against carbapenemase-producing *Klebsiella pneumoniae* (CRKP) in urine found a microbiological clearance rate of 43% in the group of patients treated with tigecycline ($p < 0.001$; $n = 21$). [12]

A. baumannii is a pathogen that causes nosocomial infections, particularly in intensive care units. The increase of carbapenem-resistant A. baumanni presents a serious treatment challenge. Among the rare therapeutic options in these situations; are Colistin, a relatively old polymyxin drug, and the newer molecule tigecycline, used in combination with other antibiotics [13]. A resistance rate of 66% for tigecycline was observed in this study. The results found are similar to those found by an Israeli study, which also reported a resistance rate of 66% [14]. A study conducted in Turkey noted better results when tigecycline was combined with aminoglycosides for the treatment of multidrug-resistant *A. baumanii* infections [13].

5. Conclusion

Bacterial resistance to antimicrobial agents and the emergence of different strains of MDR bacteria is a major public health problem, responsible for high morbidity and mortality and an additional cost of care. The main objective of this study was to assess the frequency of MDR bacteria and to evaluate the in-vitro efficacy of tigecycline against these bacteria. In this study, 60% of the MDR bacteria isolated were susceptible to tigecycline. The susceptibility rates found were respectively 76%, 57%, and 34%, for the ESBL Enterobacteriaceae strains, the CPEs, and the multiresistant *Acinetobacter baumanii* strains.

Currently, the indications for tigecycline according to the Marketing Authorization and the FDA remain limited to complicated skin and soft tissue infections and intra-abdominal infections, excluding foot infections in diabetic patients [3, 15]. To limit the emergence of resistant bacteria and to maintain the effectiveness of tigecycline and other antibacterial agents, tigecycline should be used only against infections caused by bacteria known or strongly assumed to be susceptible. When cultures or antibiograms have been performed, their results should guide the choice or adaptation of antibiotic treatment. In the absence of such results, epidemiological data and local susceptibility profiles could facilitate the empirical choice of treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All the data has been collected anonymously following patient confidentiality.

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