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Original article

Antimicrobial resistance of multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii* isolates to colistin in a Moroccan hospital

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ABSTRACT

Background: The challenge of treating infections caused by multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii* has significantly increased for medical professionals due to their resistance to conventional antibiotics. In such cases, colistin is employed as a final line of defense. This study was aimed to determine the in-vitro efficacy of colistin against multidrug-resistant gram-negative bacteria. **Methods**: The research was carried out in the bacteriology department of the Mohammed V Military Teaching Hospital in Rabat, Morocco. 321 isolates of multi-resistant *Enterobacterales* and *Acinetobacter baumannii* from various clinical samples were identified by standard microbiological protocols, and the Colistin minimum inhibitory concentrations value was determined using the microdilution method. **Results**: Of the 321 isolates included in the study, 76.3% were *Enterobacterales* and 23.6% were *Acinetobacter baumannii*. The minimum inhibitory analysis showed that 96.3% of the isolates were sensitive, while 3.7% were identified as resistant. The prevalence of resistance to colistin among multi-resistant *Enterobacterales* was 4.1%, and the MIC50 and MIC90 were 0.5 µg/ml and 1µg/ml respectively. Among the collected *Acinetobacter baumannii* isolates, the prevalence of colistin resistance was 2.6%, with the MIC50 and MIC90 of 0.5 µg/ml. **Conclusion**: The research indicates that colistin could be a viable treatment option for infections caused by multi-resistant *Enterobacterales* and *Acinetobacter baumannii*.

Introduction

The emergence of multidrug-resistant (MDR) bacteria characterized by their resistance to multiple classes of antibiotics, has become a pervasive issue, causing increased morbidity and mortality worldwide. The World Health Organization (WHO) has identified antimicrobial resistance as one of the top 10 public health threats facing humanity[1]. In 2019, AMR was directly attributed to an estimated 1.27 million deaths worldwide, with nearly 5 million more deaths associated indirectly [2].

Despite the escalating threat posed by MDR bacteria, the development of new antibiotics has stagnated in last decades[3]. The lengthy and

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costly process of antibiotic discovery, compounded by a lack of economic incentives for pharmaceutical companies, has led to a profound scarcity of novel antimicrobial agents. The development of new antimicrobial drugs is currently stagnant, in 2019 WHO identified 32 antibiotics in clinical development that address the list of priority pathogens, of which only six were classified as innovative[1]. Furthermore, the pervasive challenge of access to high-quality antimicrobials exacerbates the problem, Antibiotic shortages are affecting countries of all levels of development and especially in health- care systems[1]. This scarcity of new drugs has left clinicians with limited treatment options, often resorting to older, more toxic antibiotics such as colistin. This antibiotic was discovered in the 1950s but fell out of favor due to its nephrotoxicity and neurotoxicity[4,5]. However, the relentless advance of MDR pathogens has compelled a resurgence of interest in colistin as a last-resort treatment[1]. In recent years, colistin has been deployed as a crucial defense against MDR *Enterobacterales* and *Acinetobacter baumannii* infections when no other viable options remain [6-9].

Contrarily of the use of colistin for human, colistin has been widely used in veterinary medicine for both prevention and treatment purposes for years[10,11]. However, the extensive use of colistin, in livestock has led to the spread of bacteria that're resistant to colistin[12].

Until the year 2015, instances of colistin resistance were primarily known to associated with chromosomal genes, specifically *pho*PQ, *pmr*AB, and *mgr*B[13,14]. In 2015, a plasmid-mediated *mcr*-1 gene has been reported in China[15]. Since that pivotal discovery, over 27 distinct bacterial species carrying the *mcr* 1 gene have been recorded worldwide[16]. Furthermore, plasmids harboring the mcr-1 gene have been detected within multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii* isolates[17,18].

This study aims to determine the in vitro efficacy of colistin against multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii* clinical isolates. These findings will contribute to our understanding of colistin's role in combating MDR organisms and inform strategies for managing these challenging infections.

Materials and Methods

Bacterial Strains and microbiology methods

This study was carried out at the Bacteriology Department of the Mohammed V Military Teaching Hospital in Rabat, Morocco through February 2018 to April 2019.The various clinical samples (urine, pus, blood, respiratory samples, and body fluid aspirates) collected from inpatients and outpatients were incubated at 37°C under aerobic conditions for a period ranging from 18 to 24 hours on CLED agar (Oxoid Ltd., Basingstoke, Hampshire, England) for urinary samples and blood agar (Oxoid Ltd., Basingstoke, Hampshire, England) for the other samples types according to "Bactériologie médicale: techniques usuelles" [19].

The identification of bacteria was performed by standard bacteriological and biochemical methods using API-20E for *Enterobacterales* and API-20E for *Acinetobacter baumannii* (bioMérieux SA, Marcy-l'Étoile/France) ready-to-use strips.

Antibiotic Susceptibility Testing

Testing *Enterobacterales* and *Acinetobacter baumannii* isolates for Antimicrobial susceptibility was done using disk diffusion method against different antimicrobial agents (Oxoid, Basingstoke, UK) as recommended by EUCAST [20]. *Escherichia coli* ATCC 25922 had been used as standard quality control strain. Isolated gram negative bacilli were further preserved on tryptic soy broth with 20% glycerol and frozen at -80°C[21]

Inclusion and exclusion Criteria:

In this study, we included *Enterobacterales* and *Acinetobacter baumannii* isolates resistant to third-generation cephalosporins and/or carbapenems. MDR isolates from the same patient with similar antibiotic susceptibility profiles were excluded.

Colistin susceptibility testing

The minimum inhibitory concentrations (MICs) of colistin were determined using the microdilution (BMD) method, following the guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI)[22]. We prepared a concentration of 8 µg/mL of colistin (Sigma-Aldrich, France), then diluted it twice to reach a concentration of 0.125µg/mL. These dilutions were made in Mueller Hinton broth (CA-MHB). In each well of a 96 well microdilution plate we introduced the isolates at a concentration of 5 ×

10^5UFC. The microdilution plates were then incubated at 37°C for 18 hours. MICs interpretation was based on the cut-off values recommended by the EUCAST which are provided in brackets for the BMD method performed in CA-MHB. Specifically we defined colistin susceptibility as an MIC of ≤2 µg/mL while colistin resistance was defined as an MIC exceeding 2 µg/mL[20].

Statistical Analysis

We analyzed the data with IBM SPSS Statistics, Version 25.0 (IBM Corp, New York, NY, USA, 2017). We utilized numbers and percentages to present qualitative data. We used a p-value of ≤0.05 to determine statistical significance.

Results

Clinical characteristics

A total of 321 cases of multi-resistants *Enterobacterales* and *Acinetobacter baumannii* isolates that met the inclusion criteria were included, comprising 245 (76.3%) *Enterobacterales* and 76(23.6%) *Acinetobacter baumannii*. Among the multidrug-resistant *Enterobacterales, Klebsiella pneumoniae* is the most common pathogen, accounting for 56.7% of cases, followed by *Escherichia coli* with 40% and *Enterobacter cloacae* with 3.3%.

Regarding the 321 isolates, 208 were isolated from urinary tract infection, 47 from fluid samples, 33 from respiratory tract infections, 21 from bloodstream infections, and 13 from other samples (Table 1). Approximately 53.6% of the isolates originated from inpatients, whereas 46.4% were obtained from outpatient.

Antimicrobial susceptibility of isolates

Based on the results obtained from the disc diffusion assay, the majority of *Enterobacterales* isolates displayed notable levels of co-resistance to the antibiotics used in our study. In general, a remarkable 98% of these isolates exhibited resistance to ceftriaxone, while 91% displayed resistance to amoxicillin–clavulanic acid. Additionally, a significant 86% and 85% of the isolates demonstrated resistance to norfloxacin and cotrimoxazole, respectively, while 37% exhibited resistance to ertapenem (Figure1).

When considering the resistance patterns among *Acinetobacter baumannii* isolates, it became apparent that the resistance rates surpassed 90% for most of the antibiotics tested, including imipenem, ciprofloxacin, and gentamicin. Notably, tobramycin displayed the lowest resistance rate at 67%, while netilmicin exhibited a slightly higher resistance rate of 71% (Figure 2).

The minimum inhibitory concentration

The results, presented in Table 2, show the MIC values obtained for 321 isolates tested against colistin.The majority of isolates had MIC values ranging from 0.25 to 0.5*mg/l*.

Bacterial strains that showed resistance when exposed to concentrations above 2 mg/l were classified as resistant. Out of the isolates, 96.3% (n=309) were determined to be sensitive, while 3.7% (n=12) were designated as resistant.Out of the 12 resistant isolates, 10 belonged to the Enterobacteriaceae family (Figure 3).

The colistin MIC50 was determined to be 0.5 µg/ml and 0.25µg/ml for *Enterobacteriacae* and *Acinetobacter baumannii* respectively, while the colistin MIC90 was determined to be 1 µg/ml for Enterobacterale. For *Acinetobacter baumannii* the colistin MIC90 were equal to MIC50 (0.5 µg/ml).K. pneumoniae were found to have the higher MIC90 with a concentration of 2 mg/l. The colistin MIC50 and MIC90 for our isolates were found to be sensitive (Table 3)

Table 1. Prevalence of multidrug-resistant bacteria isolated from various clinical specimens.

Sample Type	Effective	Percent
Urinary tract infection	208	64.8%
Fluid samples	47	14.6%
Respiratory tract infections	33	10.3%
Bloodstream infections	21	6.5%
Other samples	12	3.7%

Table 2. Distribution of minimum inhibitory concentration values obtained for isolates

MIC in mg/l	*Acinetobacter baumannii*	Enterobacterales	*K. pneumoniae*	*E. coli*	*E. cloacae*	Total
0.125	(2) 22.2%	(7) 77.8%	(4) 44.4%	(3) 33.3%	0.0%	(9) 100%
0.25	(39) 33.1%	(79) 66.9%	(32) 27.1%	(43) 36.4%	(4) 3.4%	(118) 100%
0.5	(32) 26%	(91) 74%	(38) 30.9%	(50) 40.7%	(3) 2.4%	(123) 100%
1	(0) 0%	(47) 100%	(45) 95.7%	(1) 2.1%	(1) 2.1%	(47) 100%
2	(1) 8.3%	(11) 91.7%	(11) 91.7%	(0) 0%	0.0%	(12) 100%
4	(0) 0%	(2) 100%	(1) 50%	(1) 50%	0.0%	(2) 100%
8	(2) 20%	(8) 80%	(8) 80%	(0) 0%	0.0%	(10) 100%

Table 3. Distribution of cumulative percentage of minimum inhibitory concentration.

MIC in mg/l	*A. baumannii* (%)	Enterobacterale (%)	*K. pneumoniae* (%)	*E. coli* (%)	*E. cloacae* (%)	Total (%)
0.125	2.6	2.9	4.9	3.1	0.0	2.8
0.25	53.9	35.1	27.5	46.9	50.0	39.6
0.5	96.1	72.2	54.2	98.0	87.5	77.9
1	96.1	91.4	85.9	99.0	100.0	92.5
2	97.4	95.9	93.7	99.0	100.0	96.3
4	97.4	96.7	94.4	100.0	100.0	96.9
8	100.0	100.0	100.0	100.0	100.0	100.0

Figure 1. Antibiotic resistance profile of multidrug-resistant Enterobacterales (n=245)

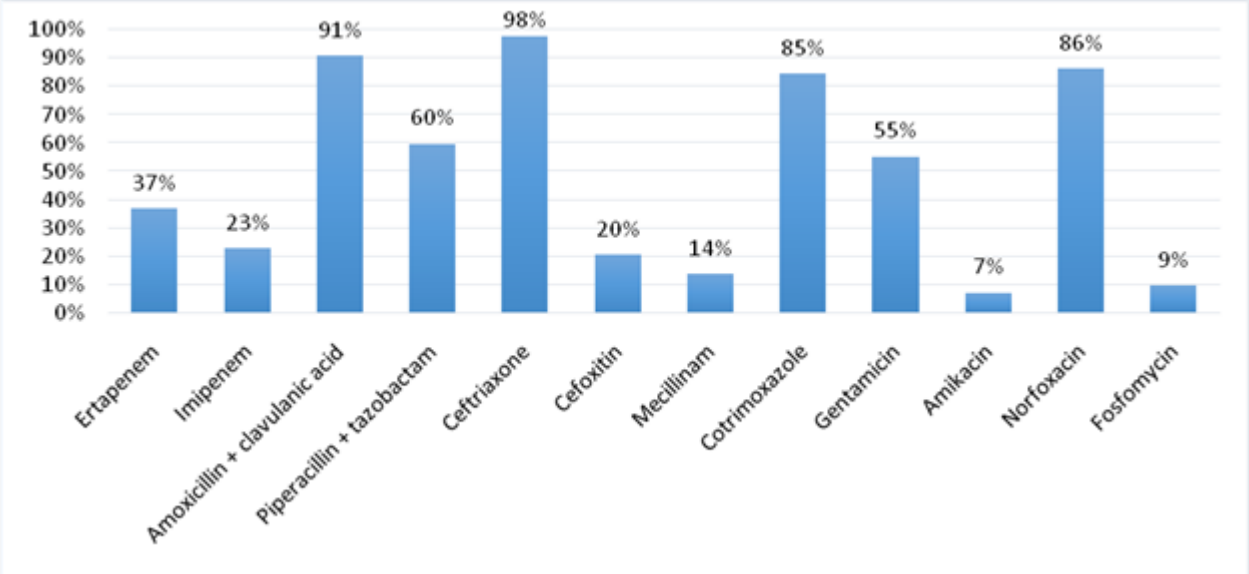
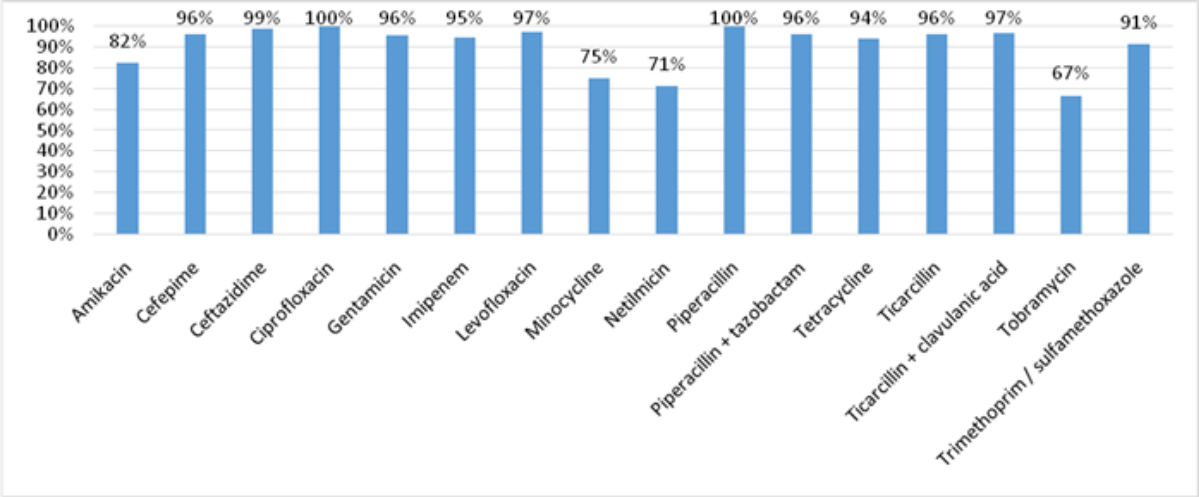


Figure 2. Antibiotic resistance profile of multidrug-resistant Acinetobacter baumannii isolates (n=76)



Discussion

The rise of resistance has emerged as a worldwide issue in public health, and a wide range of categories have proven to be ineffective in combating gram-negative bacteria [23]. Colistin, a type of antimicrobial peptide, continues to be a crucial medication in our arsenal that is still effective against bacterial infections caused by multidrug-resistant gram-negative pathogens. These include carbapenem-resistant bacteria, such as *Acinetobacter*, *Pseudomonas*, and *Enterobacteriaceae* [24]. The rise in colistin usage has resulted in the development of colistin resistance in numerous countries globally [25]. Based on the availability and utilization of these antibiotic, a variable prevalence of the emergence resistance across worldwide regions has been reported [26]. Therefore, this study was designed to determine the colistin susceptibility pattern in multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii* clinical isolates derived from clinical samples.

This research focused on 321 cases of multi-resistant *Enterobacterales* and *Acinetobacter baumannii*, with a minimum inhibitory analysis of 96.3% of the sensitive bacteria. In a related study by Pawar et al., a colistin resistance rate of 9.98% among 3596 gram-negative bacteria isolates was determined [27].

In the study carried out in Japan by Kawamoto et al., it was found that 7.7% of multi-resistant *Enterobacterales* were resistant to colistin [28]. However, in the current study, the resistance to colistin among multi-resistant *Enterobacterales* was lower (4.1%). Despite this, the rate is high when compared to two other studies conducted in Bangalore[29] and in India [25], where 100% bacteria were sensitive to colistin

In the global surveillance program, 19,719 *Enterobacterales* isolates were gathered from 180 locations across 39 countries[30]. The MIC50 for colistin in multi-resistant *Enterobacterales* was found to be ≤0.12 µg/ml. In our study, the MIC50 and MIC90 for colistin among multi-resistant *Enterobacterales* in the present study were higher suggesting a potential increase in resistance in the near future. These differences can be due the different type of resistance. Indeed, MIC50 was 0.25 µg/ml for *Enterobacterales* producing extended-spectrum beta-lactamases, and 4 µg/ml for those producing carbapenemases.

In a meta-analysis study conducted by Pormohammad et al., which encompassed researches from 41 distinct nations, it was found that the prevalence of colistin resistance in *Acinetobacter baumannii* isolates was 3%. The study had also revealed that Germany had the lowest prevalence of colistin resistance at 2%, while Lebanon exhibited the highest rate at 17.5%[31].In the *Acinetobacter baumannii* isolates collected, the prevalence of colistin resistance was found to be 2.6%, a figure that aligns closely with the rates reported in Germany, and the MIC50 and MIC90 in our research were both 0.5 µg/ml. In a study conducted in Egypt by Amer, *Acinetobacter* spp. revealed that *Acinetobacter* spp. were entirely susceptible to colistin, with MIC50 and MIC90 values of 0.5 µg/ml and 1 µg/ml, respectively[32]. On the other hand, Chinnappan et al. reported a 5% prevalence of *Acinetobacter* spp. resistance to

colistin, with MIC50 and MIC90 values of 0.75 µg/ml and 1.5 µg/ml, respectively[25].

The ATLAS global surveillance program reported the MIC50 and MIC90 for colistin in *Acinetobacter baumannii* isolates as 0.25 mg/L and 1 mg/L, respectively. In 2021, it was found that 7.4% of *Acinetobacter baumannii* isolates in Europe were resistant to colistin, with the MIC50 and MIC90 values being 0.5 mg/L and 2 mg/L, respectively[33]. The values obtained in these studies reinforce the observation that resistance of *Acinetobacter baumannii* to colistin is significantly lower in the current research.

Conclusion

Investigating the antibiotic susceptibility patterns of MDR bacteria is a critical step in determining suitable antimicrobial treatments and limiting the emergence of antibiotic resistance. However, based on our results, it can be deduced that colistin may be a viable choice treatment for infections caused by multidrug-resistant *Enterobacterales* and *Acinetobacter baumannii*. Given the widespread use of colistin in animal production and its importance in controlling multiresistant gram-negative nosocomial infections in humans, it is strongly recommended to conduct both national and international surveillance studies to establish guidelines for the administration and dosage adjustment of colistin.

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Conflict of interest

The authors declare no competing interest

Availability of data and material

The data for the current study are available from the corresponding author on reasonable request.

Ethical considerations

In accordance with Moroccan legislation, retrospective studies that utilize anonymous laboratory data are not obligated to obtain ethical approval. The research was carried out using unidentified biological samples and did not involve any personal information that could be used to directly or indirectly identify an individual.

Authors' contributions

Every author has made significant contributions to this work. The study was conceptualized and designed by NE, EB, and EM, they also drafted the manuscript and analyzed and interpreted the data. The experimental work was carried out by NE and EB. AM and EB offered their expertise, critically evaluated the manuscript for its content and english language usage. All authors have reviewed and given their approval for the final version of the manuscript.

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