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Epidemiology of Multi-Resistant Gram Negative Bacteria in Central Morocco

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Abstract **Original Research Article**

Introduction: Antibiotic resistance is a major global public health problem, constituting one of the most serious threats to global health. A bacteria is said to be multi-resistant when it is resistant to at least one antibiotic molecule belonging to more than three different classes normally active against these bacteria. These infections are responsible for an increase in therapeutic impasse situations, hospital costs and the number of deaths. ***Material and Method:*** This is a retrospective and descriptive study covering the results of antibiograms carried out in the bacteriology laboratory of the Moulay Ismail military hospital in Meknes spread over a period of 12 months (from June 2022 to May 2023). ***Results and Discussion:*** During this study period, 1217 bacterial strains were identified, 338 of which were multi-resistant gram-negative bacteria (MR BGN), representing a prevalence of 28%. The main MR BGN isolated were extended spectrum beta lactamase producing Enterobacteriaceae (ESBL-E) at 43% Imipenem-resistant Acinetobacter baumannii (IRAB) 16.1% and Carbapenemase-Producing Enterobacteriaceae (CPE) 15.9% (with a predominance of the species K.pneumoniae at 44.4%). ***Conclusion:*** The rationalization of the prescription of antibiotics and the rigorous application of hygiene and prevention rules will make it possible to limit the emergence of these multi- and highly resistant bacteria in our healthcare structures, a better knowledge of bacterial ecology and levels of resistance to different antibiotics will allow better care adapted to each hospital environment.

Keywords: Multi-Resistant Bacteria, Epidemiology, Antibiogram, Therapeutic Failure, Resistance.

INTRODUCTION

Antimicrobial resistance is one of the most serious threats to threats to global health. Over the past decades of antibiotic (ATB) use, most pathogenic bacteria have pathogenic bacteria have developed worrying levels of resistance to many ATBS. The discovery of the first ATB, penicillin, by Alexander Fleming in 1928, was considered a major breakthrough in the medical field. However, this prospect soon came to an end due to the extensive and sometimes inappropriate which led to the emergence of antibiotic resistance antimicrobial resistance, favoring the spread of multi-resistant bacteria [1]. Antimicrobials act against bacteria through bacteria by a variety of mechanisms, and many species have risen to the challenge by developing resistance through a variety of equivalent mechanisms [2]. Bacterial resistance remains significantly more prevalent in hospitals than in the community, in line with the selection pressure exerted by the massive use of ATBs and the bacterial plasmid bacterial plasmid support, which favors the rapid and widespread diffusion of resistance. Multi-resistant gram-negative bacteria (MR BGN) are bacteria that have bacteria that have developed resistance to several types of antibiotic. This increased resistance to antibiotics makes the treatment of infections infections caused by these bacteria much more difficult, and in some to a state of therapeutic impasse. The economic consequences are no less important, with longer hospital stays and higher healthcare costs. and higher healthcare costs, against a backdrop of resistance to first-line and resistance to first- and second-line antibiotics antibiotic alternatives are often more toxic, less are often more toxic, less effective, more costly and require longer treatment times [3]. According to data the World Health Organization (WHO), antibiotic resistance has reached reached alarming levels in many parts of the world [4]. The Center for Disease Control and Prevention's Antibiotic Threat Report 2019 from the Centers for Disease Control

and Prevention (CDC) states that further action is needed to protect the public. Every year, there are more than 2.8 million antibiotic-resistant infections and over 35,000 deaths due to antibiotic resistance [5]. In addition it is estimated that this resistance will be responsible for a dramatic increase these figures, and could cause more deaths than cancer, 10 million a year deaths per year, and become the world's leading cause of death by 2050 in the absence of intervention [6]. In Morocco, there are no national reports available concerning these MR BGN and their consequences, but numerous studies have been studies have been carried out in several university hospitals. In 2021, as part of the national strategy to combat antimicrobial resistance (AMR), Morocco has drawn up an integrated national plan, in alliance with the WHO, covering human, veterinary and environmental health, veterinary and environmental health. Within this framework, the proposed study is to identify MR BGN isolated in the bacteriology laboratory of the Moulay Ismail Moulay Ismail de Meknes Military Hospital (HMMI), over a 12-month period months. The aim of this work is to describe the epidemiological profile of MR BGN isolated in our hospital structure, as well as the resistance profile of these of these bacteria to the various ATBs, and to guide clinicians in the adjustment of therapeutic regimens and prescribing practices in the event of infections, whether community-acquired or healthcare-associated infections.

MATERIALS AND METHODS

This is a retrospective descriptive study spanning one year (June 2022 to May 2023), carried out at the HMMI medical bacteriology laboratory. Our study covered all bacteriological samples received at the HMMI bacteriology laboratory for diagnostic purposes, from patients hospitalized in our facility or consulting on an outpatient basis. Strains were isolated from the following specimens: Cytobacteriological examinations of urine (ECBU), pus, catheters (KT), blood cultures (HC), genital samples (sperm culture, vaginal and urethral swabs ....), respiratory samples (cytobacteriological examination of sputum (ECBC), protected distal sampling (PDP) and bronchial aspiration), and puncture fluids (ascites puncture, pleural puncture (PP)....).

*** Phenotypic Tests Used to Detect Multi-Resistant Bacteria**

Extended-spectrum Betalactamase-producing Enterobacteriaceae (EBLSE) are identified using the positive synergy test, which consists of a synergy test between the clavulanic acid present on the CoAmoxiclave (AMC) disc and Ceftriaxone (CRO) or Cefotaxime (CTX). When EBLSE is present, this test produces a characteristic image resembling a “champagne cork”. This method is used routinely to detect the presence of extended-spectrum betalactam-resistant bacteria [7]. (Figure 1), this identification can also be carried out by immunochromatographic testing, which is a qualitative immunological test used for the rapid detection of the five main CTX-M-type enzyme groups of extended-spectrum beta-lactamases (ESBLs) produced by Enterobacteriaceae. The test is performed on a bacterial colony. Rapid tests detect enzymes belonging to CTX-M groups 1, 2, 8, 9 and 25, as well as their clinically relevant variants. All this information is obtained in the same cassette in less than 15 minutes from the bacterial colony, enabling rapid identification of CTX-M ESBL-producing bacterial strains.

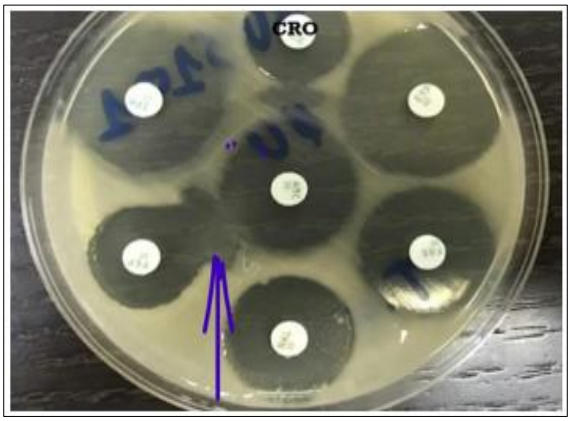

Figure 1: Positive synergy test: characteristic champagne cork appearance between the 2 ATB disks.

Carbapenemase-producing Enterobacteriaceae (EPC) are identified by immunochromatographic testing, which confirms the presence of four of the most widespread carbapenemases in Enterobacteriaceae: Oxacillinas48 (OXA48), New Delhi metallo-betalactamase (NDM), Klebsiella Pneumoniae carbapenemase (KPC) and Verona Integronencoded metallo B-lactamase (VIM). This test, performed directly on the laboratory bench using a small number of colonies, is simpler and more affordable than molecular tests. Results are available in 15 minutes. Identification of methicillin-resistant Staphylococcus aureus (MRSA) was carried out using a cefoxitin disk (FOX) under standard antibiogram conditions. Strains with a zone of inhibition diameter equal to or greater than 27 mm were considered sensitive to methicillin. On the other hand,

strains with a zone of inhibition diameter of less than 25 mm were considered resistant to methicillin, meaning that they were also resistant to all beta-lactam antibiotics. These methicillin-resistant strains are often characterized by resistance to several families of antibiotics, making them difficult to treat. (Figure 2)

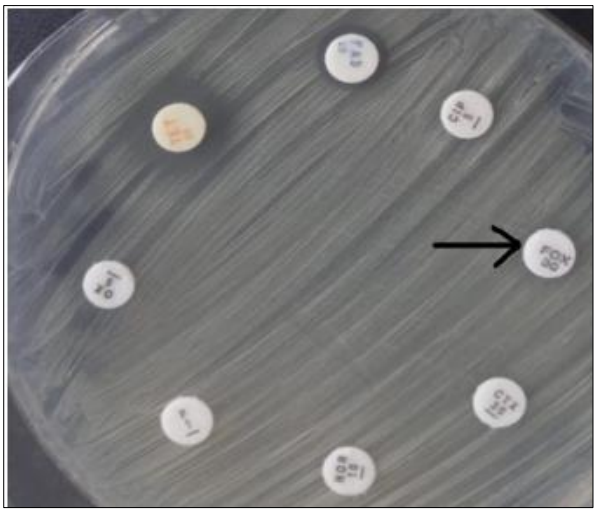

Figure 2: Antibiogram of MRSA on Mueller-Hinton agar medium

Identification of multi-resistant Pseudomonas aeruginosa (P.aeruginosa mulltirésistant) and Imipenem-resistant Acinetobacter baumannii (ABRI): for these bacteria, antibiotic resistance was directly detected using Mueller-Hinton agar against the antibiotic tested in our study. This resistance is observed when the inhibition diameters for Ceftazidime (CAZ) or Imipenem (IPM) are less than the small diameter, or the minimum inhibitory concentrations (MICs) of Ceftazidime and/or Imipenem are greater than the high critical concentrations in the case of standardized antibiotic susceptibility testing, in accordance with the recommendations established by CASFM/EUCAST (Figure 3).

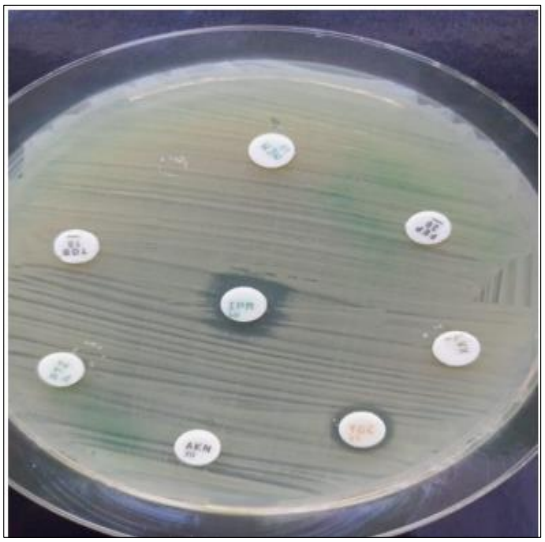

Figure 3: Antibiogram on ABRI Mueller-Hinton agar medium

RESULTS

After analyzing the samples we received during our 12-month study, and isolating and identifying various bacterial strains, we found that out of a total of 1217 strains, 338 were multi-resistant, corresponding to 28%, while 879 were more sensitive (not meeting BMR criteria), thus representing 72% of all strains isolated. Of the 338 multi-resistant bacteria isolated, EBLSEs largely dominate the BMRs isolated, with ABRI occupying an important place in this distribution, while multi-resistant P.aeruginosa is the least isolated species, while highly resistant bacteria (HRB) are represented by EPCs with a significant number (15.9%). The number of BMR we counted was 338 out of a total of 1,217 bacterial strains isolated. Within each bacterial species, we identified the bacteria that were multi-resistant. Among the Enterobacteriaceae (n=811), 17.9% were EBLSE (n=145), while 6.7% were EPC (n=54). Among Staphylococci (n=171). Among A.baumannii (n=57),

96.5% were ABRI (n=55). Among P.aeruginosa (n=60), 20% were PARC (n=12) and 6.7% were PARI (n=4) .The distribution of EBLSE by bacterial species showed a predominance of Escherichia coli (E.coli), accounting for 58% of the total, followed by Klebsiella spp at 27%, while Enterobacter cloacae (E.cloacae) represented 7% of the total. Other Enterobacteriaceae accounted for 8% of the total. (Figure 4)

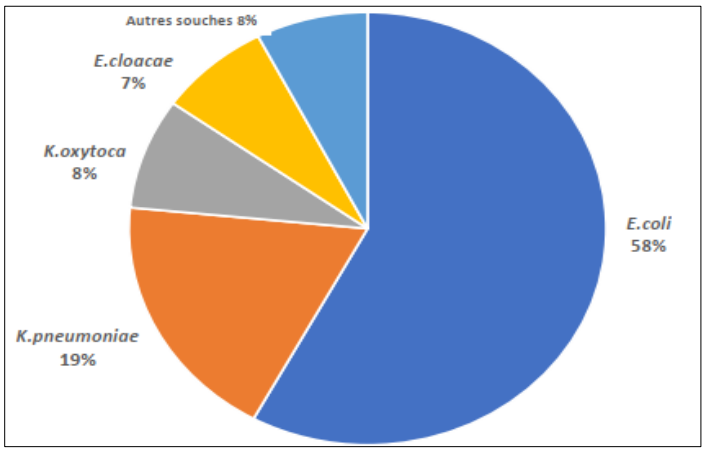

Figure 4: Distribution of EBLSE by bacterial species (N=145)

The distribution of EPCs by bacterial species showed a predominance of K.pneumoniae at 44.4%, followed by E.coli at 31%, K.oxytoca at 18.6%, while E.cloacae represented 6% of the total. Carbapenemases were not detected in the other enterobacteria. (Table I)

Table I: EPC distribution by bacterial species

Souche bactérienne	Nombre	Pourcentage
K.pneumoniae	24	44.4%
E.coli	17	31%
K.oxytoca	10	18,6%
E.cloacae	3	6%

Among the 54 EPCs isolated, we noted a predominance of the NDM enzyme type at 50%, represented by 12 K.pneumoniae, 6 K.oxytoca and 4 E.coli. In 2nd position was the OXA 48 type at 32%, represented by 8 E.coli and 6 K.pneumoniae. An OXA48+NDM association was also observed at 18%, represented by 6 K.pneumoniae and 2 K.oxytoca. For the remaining 10 EPCs, the enzyme type was not determined by immunochromatographictesting (Figure 5).

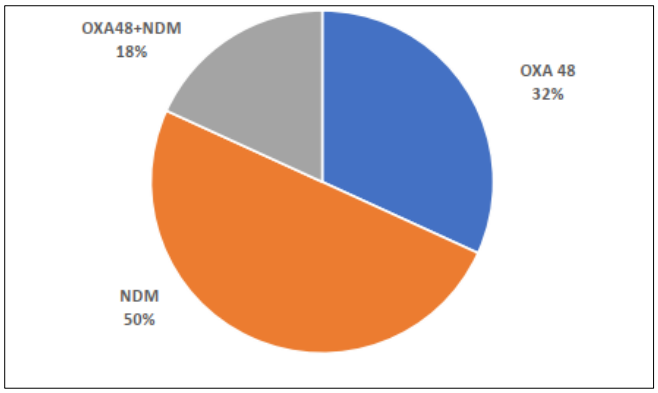

Figure 5: Distribution of different enzyme types in isolated EPCs

The total distribution of BMRs by type of sample showed the presence of these bacteria mainly in urine (ECBU at 54%), pus samples (16%) and respiratory samples divided between bronchial aspirates (7.8%), ECBCs (6%) and PDPs (1.2%). Next came blood cultures (HC) at 9%, followed by puncture fluids (2.7%). Other samples (KT, coproculture, genital...) account for 3.3%. In terms of BMR distribution by species and type of sample, we note that EBLSE and EPC were mainly found in ECBU (72.4% and 50% respectively) and pus

(12.4% and 20% respectively). ABRI was found mainly in respiratory samples (58%). PARC was more or less evenly distributed between ECBU (4 strains out of a total of 12), blood cultures and pus (3 strains each) and respiratory samples (2 strains). IRAP was mainly isolated from ECBU.

The EBLSE resistance study revealed a high rate of resistance to cephalosporins: ceftriaxone 96%, ceftazidime 87% and cefepime 81%. Resistance to aztreonam was 87%. For other TBAs, our study showed significant resistance to ciprofloxacin (93%) and cotrimoxazole (85%), and resistance to gentamicin (63%). On the other hand, these EBLSE strains retain good sensitivity to amikacin (5% resistance) and fosfomycin (7% resistance), and to ertapenem and imipenem, with resistance rates of 6% and 4% respectively. There were 2 colistin-resistant strains, representing 1% resistance. Of the 54 EPC strains isolated, 96% were resistant to imipenem, cotrimoxazole and gentamicin, 92% to tobramycin, 78% to fosfomycin and 70% to ciprofloxacin. In addition, 57% of isolates were resistant to amikacin. All strains were resistant to ceftazidime. All strains were sensitive to colistin. Of the 68 MRSA strains isolated, 100% were resistant to penicillin G, oxacillin and cefoxitin. 50% to gentamycin and ciprofloxacin, 47% to erythromycin and 41% to clindamycin. 35% to fusidic acid, 25% to levofloxacin and 15% to fosfomycin. All isolates were sensitive to vancomycin and teicoplanin. Of the 55 ABRI isolates, 100% were resistant to ertapenem, imipenem, ceftazidime and cefepime. 94% were resistant to ciprofloxacin. 90% of strains were resistant to gentamycin. Resistance to other TBAs such as amikacin and cotrimoxazole reached 82%. However, all strains were sensitive to colistin. In the course of our study, we isolated 12 PARC and 4 PARI, constituting 16 multidrug-resistant Pseudomonas aeruginosa. These Pseudomonas strains were 75% resistant to ceftazidime, 60% to gentamycin, 43% to levofloxacin and ciprofloxacin, 33% to imipenem and 13% to amikacin. All strains retained sensitivity to colistin.

DISCUSSION

In the early 2000s, there was a lack of consensus and harmonization in the definition of multidrug-resistant bacteria (MDRB) in studies. A common definition involved the accumulation of multiple acquired resistance mechanisms to at least three different antibiotic classes. In 2011, a consensus of experts convened by the US CDC and ECDC established precise definitions for MDRB, highly resistant bacteria (HRB) and pan-resistant bacteria (PRB) [8]. According to these definitions, MRB are bacteria resistant to at least one antibiotic molecule belonging to more than three different classes of antibiotics normally active against these bacteria. Examples of MRB include methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase-producing Enterobacteriaceae (EBLSE) and non-fermenting Gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter baumannii, which are multi-resistant to antibiotics. BHR bacteria are resistant to at least one antibiotic molecule in all but two or fewer classes, while PDR bacteria are resistant to all molecules in all antibiotic classes normally active against the species in question. In 2013, the Haut Conseil de la Santé Publique introduced a sub-category called “BHRe” for emerging BHR, which are species of commensal bacteria of the digestive tract and emerging in France in the form of sporadic cases or limited clustered cases. This category includes carbapenemase-producing Enterobacteriaceae (EPC) and glycopeptide-resistant Enterococci (GRE) [9]. It is important to note that the definition of BHRe takes into account the ecological characteristics of the species, their emergence and the management measures required to control their spread. Various hospital establishments report an increase in the prevalence of BMR in the hospital environment, affecting all bacterial species, although the degree of this increase varies according to city and department [10, 11]. In our study, we identified 338 BMRs between June 2022 and May 2023, out of a total of 1217 bacteria isolated, corresponding to a prevalence of 28%. Nationally, there has been a significant increase in BMR prevalence over the years, rising from 11.8% in Fez in 2012 [12], to 16% in Marrakech in 2016 [13], to 24% in Oujda in 2018 [14], arriving at 32% in Marrakech in 2019 [15]. The Tunisian study in 2020 [16], is similar to ours, with a rate of 26.4% [16]. Studies from various countries, including China in 2012 [17], and Italy in 2020 [18], show particularly high rates of overall prevalence of BMRs, at 33.4% and 35% respectively (Table II).

Table II: Comparison of the overall distribution of BMRs with literature data

	Fès 2012(60)	Marrakech 2016(61)	Oujda 2018(62)	Marrakech 2019(63)	Monastir 2020(64)	Chine 2012 (65)	Italie 2020 (66)	Notre étude (Meknès 2023)
Prévalence globale des BMR	11,8%	16%	24%	32%	26,4%	33,4%	35%	28%

Geographical differences, socio-economic status, and the way in which ATBs are used also play a role in the prevalence of BMRs in different countries, and even regions. But there is one overriding observation: the prevalence of these microbial pathogens is increasing in different regions of the world, which is a wake-up call and prompts us to take initiatives to address this phenomenon. Among all BMR isolated during our study, totaling 338 cases, we objectified a clear predominance of EBLSE representing 43% of all BMR, followed by MRSA representing 20%, ABRI 16.1%, EPC 15.9%, finally PARC presented 4% of the total and PARI 1%. All these national and international studies report that EBLSE are the most frequent among all BMR isolated with different prevalences. 63% in Marrakech 2016 [13], and Rabat 2012 [19], 59.5% in Monastir 2020 [16], 45% in China 2012 [17], and 43% in our series. ABRI occupies an important place in the majority of studies, 39% in Fez 2012 [12], 26% Marrakech 2016 [13], 23% in China 2012 [17], and 16% in our series. The only study to report a low prevalence of ABRI was Italy 2020 at 2.4% [18]. For EPCs, there has been a clear evolution in their frequency, with an evolution at national level from 2.3% in Marrakech 2016 [13], to 16% in Marrakech in 2019 [15], and 15.9% in our study. Even internationally, there has been a high frequency of these strains in recent years 10.5% in Monastir in 2020 [16], and 26% in Italy 2020 [18]. MRSA generally presents low figures in the majority of studies, 2% in Rabat 2012[19], 7% in Marrakech 2016 [13], and 8% in Monastir 2020. Our study and that of Italy 2020 [18], show rates of 20% and 31% respectively. Generally speaking, this strain does not pose a problem in our hospitals. Rates of multi-resistant Pseudomonas aeruginosa have remained more or less stable over the years, always occupying last place in terms of BMR distribution. After this comparison, we can deduce that EBLSE and ABRI represent a real public health problem at national and international level. The rate of EPC is also increasing significantly in recent studies, which prompts us to be more vigilant in view of the seriousness of these strains, which limit therapeutic options and are sometimes resistant even to colistin [20]. In our study, E.coli accounted for 58% of all EBLSE isolated, followed by K.pneumoniae at 19% and K.oxytoca at 8%, while E.cloacae represented 7% of the total. Most national studies report that E.coli is the most isolated bacterium among all EBLSE with rates close to our study: 49% in Fez in 2012 [12], 44.2% in Marrakech in 2016 [13]. However, in the Marrakech study in 2019 [15], Klebsiella spp ranked 1st with a rate of 42.5%, followed by E.coli at 22.5%. The Rabat study in 2020 [21], shows an almost identical rate of E.coli and Klebsiella spp (42%). Even international studies report a predominance of E.coli in the distribution of EBLSE and in 2nd place Klebsiella spp. 41% followed by 39% in the Monastir study [16], 71.7% followed by 28.3% in the China study [17]. Factors that explain the predominance of E.coli among EBLSE are: the naturally high frequency of E.coli in the digestive tract, its capacity for transmission via the fecal-oral route, E. The distribution of EPCs by bacterial species showed a predominance of Klebsiella spp, accounting for 63%, followed by E.coli at 31%, while E.cloacae accounted for 6% of the total. The predominance of Klebsiella spp in the distribution of EPCs is reported in all these national and international studies. In most studies, E.coli is the second most represented species, whether in our study, in Switzerland 2014 [22], or in France 2018 [23]. Some studies have shown that E.coli occupies 3rd place, in Marrakech in 2019 [15], it's the other BGNs that follow Klebsiella spp, on the other hand in Tunisia in 2016 [24], it's E.cloacae that takes second place. The predominance of Klebsiella in the distribution of EPCs is explained by the fact that these strains have a high carbapenemase production capacity and genetic adaptation by exchanging resistance genes. In addition, these Klebsiella strains are characterized by a high level of transmission in hospital environments, particularly among immunocompromised patients. a male predominance has been noted among patients from whom a BMR has been isolated. In fact, the percentage of BMRs isolated from men was 79%, compared with 21% from women, giving a sex ratio of 3.82. In all the studies, the sex ratio is greater than 1, so there is a predominance of males. However, in our study, the sex ratio is much higher than in the other studies, and the studies that come closest to ours are: that of the Hôpital Militaire d'Instruction in Rabat, at 2.57 [19], and that of the Hôpital Militaire Avicenne in Marrakech, at 1.96 [13]. All three hospitals are military establishments that mainly admit male patients. This variability in the sex ratio can be explained by regional differences in antibiotic prescription (as in the treatment of cystitis in women...).

CONCLUSION

Antibiotic resistance is one of the most serious threats to global health today. It is responsible for longer hospital stays, higher healthcare costs and increased morbidity and mortality. A thorough understanding of local bacterial ecology will enable us to implement evidence-based strategies. Our study provided an epidemiological and resistance profile of multi-resistant bacteria identified at the Moulay Ismail military hospital in Meknes over a 12-month period. The current challenge of multidrug resistance is posed mainly by EBLSE, ABRI and EPC isolated mainly in intensive care and surgical units. This study also revealed that we are left with a limited choice regarding the treatment of these BMR (notably fosfomycin, amikacin, colistin and the new molecules), given the multi-resistance of the latter to the various antibiotics. The spread of BMR and the absence of new antibiotics mean that the risk of therapeutic impasse is becoming ever more frequent. To deal with this situation, the emphasis must be on preserving the efficacy of existing antibiotics for as long as possible, rather than trying to prevent the emergence of these bacteria, as they will always develop new

adaptation mechanisms. This calls for careful, targeted and reasoned use of ATBs. It is also crucial to develop and keep up to date local and national surveillance programs for bacterial resistance to antibiotics, including the role of CLINs in both prevention and treatment. This would make it possible to adapt therapeutic and prophylactic protocols for these bacteria in a dynamic and targeted way.

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