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Epidemiology of Infections Caused by ESBL-Producing Enterobacteriaceae and Antibiotic Resistance Profile of Strains Isolated at Meknes-Based Moulay Ismail Military Hospital: A Retrospective Study from January 2018 to December 2020

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Abstract **Original Research Article**

Introduction: Infections caused by ESBL-producing Enterobacteriaceae (ESBL-PE) pose a major public health challenge. In addition to their widespread presence and growing resistance to several categories of antibiotics, the medical management of these bacteria becomes intricate, potentially resulting in a therapeutic impasse. Our study's goal is to examine the regional epidemiological characteristics of ESBL-PE infections and present a current assessment of their antibiotic resistance. ***Methods***: The retrospective investigation undertaken at the bacteriology laboratory of the Meknes-based Moulay Ismail Military Hospital, covering a period of three years (January 2018 to March 2021), specifically examines the isolates of ESBL-PE. ***Results***: Among the 2596 strains of *Enterobacteriaceae* described, 16.4% were found to produce ESBL, with *E. coli* being accountable for 63.6% of these strains. 85.1% of these ESBL-PE were isolated from urine samples. Surgical services were the largest source of these ESBL-PE (54.3%), followed by the emergency department (22%), medical services (14.5%), and intensive care unit (9.2%). The antibiotic resistance of these ESBL-PE has been studied and found to be high for gentamicin (63%), tobramycin (66%), cotrimoxazole (85%), and ciprofloxacin (91%). Only 7% exhibited good sensitivity to amikacin, 4% to imipenem, and 5% to fosfomycin. ***Conclusion***: The advent of ESBL-PE in our institution is a big challenge. To limit the use of carbapenems and prevent the spread of strains causing carbapenemases, other kinds of antibiotics can be utilized. The partnership between clinicians and the bacteriology laboratory is vital for efficiently preventing and monitoring the spread of these multidrug-resistant bacteria.

Keywords: Epidemiology, ESBL-PE, Resistance profile, Moulay Ismail Military Hospital.

INTRODUCTION

Enterobacteriaceae is an extensive group of Gram-negative bacteria ubiquitously present in the gastrointestinal tract. Various pathogenic processes can make these bacteria responsible for diseases of varied degrees of severity [1].

Since the 1960s, species within this family have been subjected to excessive exposure to various antibiotics, mainly in hospital settings. As a result, resistance to these medications has emerged. This very alarming public health issue poses a threat to the future due to its influence on morbidity and mortality, as well as the increasingly limited therapy possibilities that lead to failures and rising treatment costs [2].

Among the mechanisms of resistance of enterobacteria to antibiotics is enzymatic inactivation through the formation of extended-spectrum β-lactamases (ESBL). These are enzymes acquired through a plasmid, allowing these bacteria to hydrolyze the β-lactam core and resist β-lactams except for carbapenems and cephamycins. Extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBL-PE) are now the prevalent multidrug-resistant bacteria (MDR). So far, more than 230 variations of ESBL-PE have been described worldwide [3].

Although managing the proliferation of these ESBL-PE is a priority, there is little updated data available to quantify the prevalence of this occurrence in our region. In this context, our investigation aims to establish the epidemiological profile of ESBL-PE in the Moulay Ismail Military Hospital of Meknes and evaluate the resistance profile of the isolated ESBL-PE strains to several antibiotics.

METHODS

This is a descriptive, retrospective study covering three years (from January 2018 to December 2020), done at the bacteriology laboratory of the Moulay Ismail Military Hospital of Meknes.

All bacteriological samples for diagnostic purposes gathered at the laboratory from patients admitted in various departments or consulting externally were included in our investigation. The strains isolated from the same patient, which demonstrated an identical antibiotic sensitivity profile, were regarded as duplicates and consequently constituted the criteria for non-inclusion.

The algorithm of the analytical phase for any bacteriological examination was followed, specifically the macroscopic examination (organoleptic characteristics), the microscopic examination in the fresh state, and after Gram staining, the culture and isolation, followed by identification and the antibiogram.

The culture mediums employed were bromocresol purple (BCP) lactose agar, boiled blood agar, and blood agar. The seeding changes according to the nature of the material, and then the incubation was carried out at 37 °C in an aerobic environment and/or under 5 to 10% CO_2 for 24 to 48 hours.

Bacterial identification was carried out using API® 20E galleries (BioMérieux SA, France) and on chromogenic medium of the UriSelect™ 4 type (BioRad, United States).

The study of antibiotic susceptibility in isolates was conducted using disk diffusion on Mueller-Hinton agar, which relies on the use of impregnated disks in accordance with the recommendations of the Antibiogram Committee of the French Society of Microbiology (CA-SFM) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019 version.

The detection of the ESBL character was carried out using the synergy test between ceftriaxone and/or cefotaxime and/or ceftazidime and a protected penicillin. This test was subsequently verified by a fast chromatographic test of the CTX-M type.

The examination of the collected data was undertaken using LibreOffice Calc version 7.5 from the bacteriology laboratory. The findings were provided in percentages.

RESULTS

During the study period, 2596 enterobacteria were isolated. *E. coli* is the prevalent strain with a rate of 63.6%, followed by *K. oxytoca* at 16.9%, *K. pneumoniae* at 9.6%, and *E. cloacae* at 5.7%. The remainder of the other enterobacteria accounted for 4.2% (Table 1).

Table 1: Global distribution of isolated Enterobacteriaceae according to bacterial species

Bacteria	Number	Percentage
Escherichia coli	1652	63.6%
Klebsiella oxytoca	439	16.9%
Klebsiella pneumonia	248	9.6%
Enterobacter cloacae	147	5.7%
Enterobacter aerogenes	50	1.9%
Morganella morganii	26	1.0%
Citrobacter freundii	24	0.9%
Pantoea agglomerans	10	0.4%
Total	**2596**	**100%**

69.6% of these enterobacteria were identified from outpatients, compared to 30.4% from hospitalized patients. Of these 30.4% of hospitalized patients, 38.9% of the isolates originated from surgical services, 30.3% from the emergency department, 22.9% from medical services, and 7.9% from critical care services.

According to the type of sample, 84.5% of the identified enterobacteria originated from the cytobacteriological study of urine, 8% from pus samples, 2% from vaginal samples, and 1.1% from blood cultures. The remaining 4.4% is split among the various deductions (Table 2).

Table 2: Distribution of enterobacteria according to the nature of the samples

Specimen collection		Number of isolates	Percentage
Urogenital	*Cytobacteriological study of urine*	2193	84.5%
	Urethral	9	0.3%
	Urinary catheter	4	0.2
	Sperm culture	15	0.6%
Puncture specimen and suppurations	*Pus*	208	8.0%
	Joint aspiration	1	0.0%
	Ascitic puncture	6	0.2%
	Pleural puncture	3	0.1%
Gynecological	*Vulvar*	2	0.1%
	Vaginal	52	2.0%
Digestif	*Stool culture*	20	0.8%
Respiratory	*Protected distal sampling*	20	0.8%
	Sputum/Expectoration	18	0.7%
	Bronchial aspiration	9	0.3%
Blood	*Blood culture*	28	1.1%
Unidentified		8	0.3%
Total		**2596**	**100%**

Out of the 2596 identified enterobacteria, 426 strains were ESBL-PE, which equals 16.4%. 59.4% of these ESBL-PE came from outpatients, whereas 40.6% came from hospitalized patients.

Male patients accounted for 66.4% of ESBL-PE isolates compared to 33.6% of female patients, resulting in a male-to-female sex ratio of 1.97.

Like the isolated enterobacteria, the ESBL-PE predominantly came from surgical services with 54.3%, the emergency department with 22%, medical services with 14.5%, and intensive care unit with 9.2% (Table 3).

Table 3: Distribution of ESBL-PE according to hospital departments

Hospital departments	Number	Percentage
Emergency	38	22%
Medical services	25	14,5%
Surgical services	94	54.3%
Intensive care unit	16	9.2%
Total	**173**	**100%**

Within the context of surgical services, the ESBL-PE was distributed as follows: 74.1% originated from the urology department, 14.6% from the visceral surgery department, 4.6% from the ENT department, and 3.4% from the plastic surgery department. The residual 3.3% is distributed across the departments of gynecology, vascular surgery, and trauma (Table 4).

Table 4: Distribution of ESBL-PE according to surgical services

Surgical services	Number	Percentage
Urology	70	74.1%
Visceral surgery	14	14.6%
ENT	4	4.6%
Plastic surgery	3	3.4%
Vascular surgery	1	1.10%
Traumatology	1	1.10%
Gynecology	1	1.10%
Total	**94**	**100%**

The distribution of ESBL-PE based on sample type reveals that 85.1% of the samples are from cytobacteriological study of urine, 10,1% from fluid punctures, 2.4% from blood cultures, and 0.7% from gynecological samples (Table 5).

Table 5: Distribution of ESBL-PE according to the nature of the samples

Sample collection		Number	Percentage
Urogenital	*Cytobacteriological study of urine*	359	85.1%
	Urethral	1	0.2%
	Urinary catheter	1	0.2%
Puncture specimen and suppurations	*Pus*	41	9.7%
	Joint aspiration	1	0.2%
	Pleural puncture	1	0.2%
Gynecological	*Vaginal*	3	0.7%
Respiratory	*Protected distal sampling*	4	0.9%
	Bronchial aspiration	1	0.2%
Blood	*Blood culture*	10	2.4%
Total		**422**	**100%**

E. coli was the predominant bacterial species in these ESBL-PE, accounting for 63.6% of cases. *Klebsiella spp*. followed at 30.7% including *K. oxytoca* at 19.2%, *K. pneumoniae* at 11.5%, and *E. cloacae* at 4.7%. The remaining bacterial strains account about 0.9%. Refer to Table 6.

Table 6: Global distribution of isolated ESBL-PE according to bacterial species

Bacteria	Number	Percentage
Escherichia coli	271	63.6%
Klebsiella oxytoca	82	19.2%
Klebsiella pneumonia	49	11.5%
Enterobacter cloacae	20	4.7%
Enterobacter aerogenes	2	0.5%
Other	2	0.4%
Total	**426**	**100%**

Antibiotic resistance analysis of the ESBL-PE revealed significant resistance to third-generation cephalosporins, with resistance rates of 96% to ceftriaxone, 87% to ceftazidime, and 81% to cefepime. Furthermore, resistance rates are substantial for aztreonam (87%), cotrimoxazole (85%), and ciprofloxacin (91%). It is moderate for gentamicin (63%) and tobramycin (66%). For amikacin, fosfomycin, imipenem, and ertapenem, the ESBL-PE retained good sensitivity with resistance rates of 7%, 5%, 4%, and 6%, respectively (Figure 1).

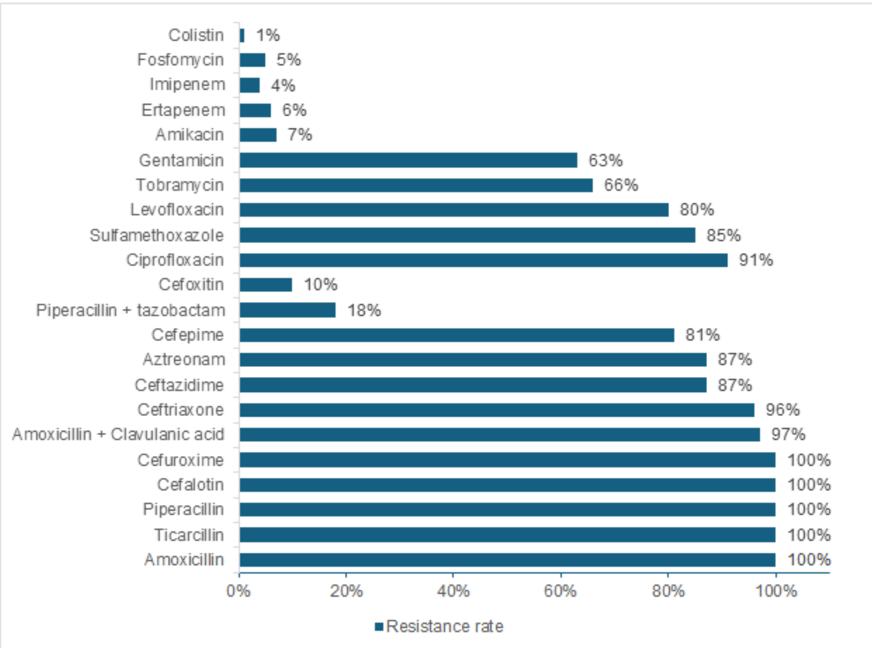

Figure 1: Resistance/sensitivity rates of the ESBL-PE to various antibiotics

DISCUSSION

Over the three-year period from January 1, 2018, to December 31, 2020, a total of 2,596 strains of enterobacteria were identified. *E. coli* remained the most frequent bacterial species with an isolation rate of 63.6%, followed by *K. oxytoca* at 16.9% and *K. pneumoniae* at 9.6%. Most national investigations demonstrate that *E. coli* is the most isolated bacteria among all enterobacteria, with rates close to ours: 59.1% in Rabat in 2020 [4], 63.5% in 2019 [5], and 74% in Meknes in 2015 [6]. *K. pneumoniae* ranked second in Rabat, with a rate of 23% and 25%, respectively, in 2020 [4] and 2013 [7]. However, some studies show that *K. pneumoniae* ranks first. This was the case in Marrakech in 2019, with a rate of 29%, followed by *E. coli* with a rate of 18% [8] (Table 7).

Table 7: Comparison of the distribution of enterobacteria relative to the germs

	Marrakech 2019 [1]	**Rabat 2009 [2]**	**Rabat 2013 [3]**	**Rabat 2020 [4]**	**Meknes 2015 [5]**	**Algeria 2022 [6]**	**Russia 2010 [7]**	**Our study**
E. coli	18%	63.52%	52%	59.1%	74%	30%	80%	63.6%
K. oxytoca	–	17.58%	3%		16.7%	4%	–	16.9%
K. pneumoniae	29%	–	25%	23.1%		9%	14%	9.6%
E. cloacae	31%	11.91%	–	7,8%	6.1%	7%	4%	5.6%
E. aerogenes			–	–		–		1.9%
P. agglomerans	–	–	–	–	–	–	–	0.4%
M. morganii	–	0.38%	1%	1%	–	2%	–	1.0%
C. freundii	–	–	1%	0.3%	–	–	–	0.92%

In our investigation, the ESBL-PE rate was 16.4%. This rate is close to that seen in various studies, including the one conducted in Rabat in 2013 (18%) [6], in Marrakech in 2019 (20%) [4], in Meknes in 2015 (14%) [8], and in Rabat in 2020 (13.65%) [7]. Compared to other countries like Japan in 2011 (6.4%) [11], our rate is bigger. It is lower than the one recorded in Ivory Coast in 2019 (58.8%) [12] (Table 8). These discovered variations are related to regional variances, socio-economic levels, and the way antibiotics are utilized according to their type.

Table 8: A comparison of the isolation frequency of ESBL-PE

	Marrakech 2019 [1]	**Rabat 2009 [2]**	**Rabat 2013 [3]**	**Rabat 2020 [4]**	**Meknes 2015 [6]**	**Japan 2011 [11]**	**Ivory Coast 2019 [8]**	**Our study**
ESBL-PE rate	20%	7.5%	18%	13.65%	14%	6%	59%	63.6%

E. coli is the most frequent ESBL-PE in our isolate (63.6%), followed by *K. oxytoca* (19.24%), *K. pneumoniae* (11.50%), and *E. cloacae* (4.69%). Many investigations have demonstrated that *K. pneumoniae*, *K. oxytoca*, *P. aeruginosa*, and *P. mirabilis* are the dominating species [12, 13]. According to the results of our analysis, 94% of the recorded ESBL-PE were strains of *E. coli*, *K. oxytoca*, and *K. pneumoniae*, which matches with the literature.

ESBL-PE are more frequently observed in men compared to women, with a male-to-female sex ratio of 1.97. This ratio stays the same as that observed in the study done in Meknes in 2015 [8]. This masculine predominance remains controversial. While some investigations have verified it [12-14], others have revealed a masculine predominance [15]. This can be explained by geographical disparities in the practice of antibiotic prescribing according to gender. (example: treatment of cystitis in women). This can also be attributed to a selection bias, such as the inclusion of persons who have undergone prostate surgery [16]. Regarding us, the male predominance is attributable to the predominantly male military patients that comes to consult at the Military Hospital.

Our data reveals that the isolated ESBL-PE primarily came from outpatients. This is not the case for multiple research that revealed the opposite, particularly the study conducted in Marrakech in 2019 (89.88% of outpatients) [8], Rabat in 2009 (54.05%) [5], Rabat in 2013 (93.41%) [7], Meknes in 2015 (92.3%) [6], and Rabat in 2020 (64.71%) [4]. This increase in the frequency of outpatient patients compared to hospitalized patients can be explained firstly by the spread of the isolated ESBL-PE, not only at the hospital level but also in the community, by the laboratory receiving a high number of external samples compared to hospital samples, and by the improvement in asepsis and hospital hygiene.

We found that 54.3% of isolated ESBL-PE primarily come from surgical services, with the urology department leading the list at 38.9%. The intensive care unit comes in last with a rate of 9.2%. Normally, patients hospitalized in intensive care units are at a higher risk of contracting an ESBL- PE due to the generally long duration of hospitalization, the severity of the illness, the use of several invasive medical devices (such as probes, catheters, intubation, etc.), and the use of many antibiotics, particularly broad-spectrum cephalosporins [12]. Fortunately, our results reveal a low prevalence of

ESBL-PE in the intensive care unit, a finding that supports the excellent management of aseptic and hospital hygiene protocols in this department. However, the increase in ESBL-PE in surgical services is explained by invasive operations coupled with the selection of resistant variants following antibiotic treatments.

Urine samples were the predominant source of isolated ESBL-PE (84.7%). This finding confirms others published previous studies, especially the one from Rabat in 2020 (61.2%) [4] and from France in 2012 (70%) [12]. However, our percentages are greater than those reported by those from Marrakech in 2019 (15%) [8], in Qatar (24.4%) [13], and in Senegal in 2015 (19%) [14]. Indeed, the main risk factors for infections are functional dependency and, above all, the installation of a urinary catheter, which should only be placed with a specific indication and then withdrawn as soon as practical. Adherence to these guidelines, together with the implementation of sanitary measures, has led to a 52% reduction in the incidence of ESBL-PE infections [15].

The antibiotic resistance investigation of ESBL-PE isolates demonstrated substantial resistance rates to major cephalosporins. Furthermore, ceftazidime and cefepime demonstrate a lower resistance rate (87% and 81%, respectively) compared to ceftriaxone (96%). Regarding resistance to aminoglycosides, the rates we detected remain close to those reported in Meknes in 2015 [6] and in Qatar in 2016 [21]. However, these rates remain lower than those reported in Algeria in 2015 [9], in Marrakech in 2019 [8], and in Rabat in 2020 [4]. For fluoroquinolones, a resistance rate of 91% was recorded, which is consistent with the rates obtained in other studies: 91% in Marrakech in 2019 [8], 84% in Meknes in 2015 [6], 88% in Rabat in 2009 [5], and 87% in 2020 [4], as well as 89% in Algeria in 2015 [12]. This significant resistance to fluoroquinolones can be explained by its massive usage as a first-line treatment for urine infections without previous verification, due to their broad bacterial spectrum and good urinary distribution. Regarding fosfomycin, the low resistance rate we obtained (5%) is close to the study conducted in Rabat in 2020 [4] and in Meknes in 2015 [6]. However, it remains quite low compared to the rate found in Marrakech in 2019 (74%) [8], in Rabat in 2013 (90%), and in 2009 (27.52%) [7, 5]. This great sensitivity revealed in comparison to other compounds is explained by their very rare utilization due to stock shortages at pharmaceutical laboratories. For sensitivity to imipenem (4%) and colistin (1%), our findings are consistent with those obtained in studies conducted in Marrakech [8], Rabat [7, 5], Meknes [6], France in 2012 [13], Algeria in 2015 [12], and Qatar [21] (Table 9).

Table 9: Comparison of the antibiotic resistance of ESBL-PE

Antibiotics	Marrakech 2019 [8]	Meknes 2015 [6]	Rabat 2013 [7]	Rabat 2009 [5]	Rabat 2020 [4]	Qatar 2016 [21]	France 2012 [9]	Algeria 2015 [10]	Our study
AML	–	100%	–	–	–	–	–	–	100%
AMC	–	100%	100%	–	88%	–	–	–	97%
FOX	–	55%	–	–	27%	–	–	–	10%
CRO	–	98%	100%	–	100%	–	–	–	96%
CTX	–	98%	99.66%	–	100%	–	–	–	96%
CAZ	–	91%	99.68%	–	100%	–	–	–	87%
ATM	–	90%	98.73%	–	100%	–	–	–	87%
FEP	–	86%	95.45%	–	92%	–	–	–	81%
CT	0%	1%	–	–	–	0%	–	0%	1%
ETP	–	18%	3.44%	–	24%	–	–	–	6%
IMP	7%	6%	3.44%	0%	16%	0,5%	0%	0%	4%
GN	85%	61%	75%	79%	54%	67%	46%	90%	63%
TOB	88%	64%	76.12%	–	84%	–	84%	100%	66%
FOS	74%	6%	27.52%	90%	8%	–	–	–	5%
CIP	80%	91%	75.55%	88%	87%	67%	70%	90%	91%
STX	90%	84%	76.71%	82%	77%	–	–	89%	85%
NA	5%	–	15.52%	13%	7%	–	15%	56%	7%

AML: amoxicillin, **AMC**: amoxicillin+clavulanic acide, **FOX**: cefoxitin, **CRO**: ceftriaxone, **CTX**: cefotaxime, **CAZ** : ceftazidime, **ATM**: aztreonam, **FEP**: cefepime, **CT**: colistin, **ETP**: ertapenem, **IMP**: imipenem, **GN**: gentamicin, **TOB**: tobramycin, **FOS**: fosfomycin, **CIP**: ciprofloxacin, **STX**: co-trimoxazole, **NA** : nalidixic acid

CONCLUSION

The ESBL-PE takes on a progressively significant place among MDR bacteria. This has been confirmed by the outcomes of our inquiry and the data from the literature. Considering this delicate situation and given the increased risk of therapeutic failure caused by these strains, whether in hospital or community settings, the bacteriology laboratory plays a crucial role in the isolation and detection of these germs, alerting clinicians, and in surveillance and prevention. The main goal is to minimize the spread of antimicrobial-resistant bacteria, as well as morbidity and mortality. Our analysis indicated that we have very few therapeutic possibilities left to treat the ESBL-PE. The development of new medications aimed at sustaining carbapenems would be particularly beneficial. Given the socio-economic ramifications of these diseases, this work, despite its limitations, serves as a warning signal calling on different health stakeholders for quick joint action to reduce morbidity and mortality and control the spread of MDR bacteria.

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