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Research Article

Epidemiology and Sensitivity to Antibiotics of Enterobacteriaceae Producing Extended-Spectrum Beta-Lactamases (ESBL) in the Region of Nouakchott (Mauritania)

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Abstract

Introduction : Extended-spectrum beta-lactamases (ESBL) are a large heterogeneous family of bacterial enzymes discovered in 1980. They are induced either by plasmids or by mutation of the natural genome in the bacterium. Both mechanisms give affected bacteria the ability to hydrolyze a very wide variety of beta-lactams. (ESBL)-producing bacteria represent a major concern due to their epidemic spread and their multiresistance to antibiotics

The purpose of this study was to: determine their frequency of ESBL, know their distribution according to sex, hospital department, assess their levels of resistance to antibiotics and educate clinicians on the rational prescription of antibiotics.

Materials and Methods : This is a retrospective study which was carried out within the central laboratory of the National Hospital Center of Nouakchott (CHN) over two years. The antibiogram was carried out by the method of diffusion in agar medium or on the Vitek-2 automaton (Biomérieux®)

The production of ESBLs has been demonstrated by looking for a synergy between clavulanic acid and third-generation cephalosporins according to the usual techniques.

Results: Out of 650 species of Enterobacteriaceae, 18.46% produced ESBL, including 58% in hospitalized patients and 42% in outpatients. The ESBL resistance rate was high to quinolones, aminoglycosides (except amikacin) and cotrimoxazole, fosfomycin and carbapenems retain good activity.

Discussion : ESBLs are increasingly incriminated in both community-acquired and nosocomial infections and represent a real public health problem. In fact, 42% of ESBL isolated during our study came from outpatient consultations. This dissemination of ESBL in the community is alarming and could be explained, in part, by the anarchic use of antibiotics, it has also been mentioned by several studies.

Fosfomycin retains excellent efficacy against ESBL in our study with 90% sensitivity. The resistance of Enterobacteriaceae to carbapenems remained marginal with sensitivity rates of 98 to 100% , making them the best treatment against ESBL-producing Enterobacteriaceae. However, the misuse of these molecules has led to the emergence of resistance to these antibiotics, especially in certain enterobacteriaceae.

Conclusion : Considering the results of our study and the data from the literature, it clearly appears that ESBLs are taking an increasingly important place among multiresistant bacteria. The increase in resistance should be compared with the increase in antibiotic consumption.

These trends are problematic because they promote not only the emergence and spread of ESBL enterobacteriaceae, but also those of carbapenemase-producing enterobacteriaceae (CPE).

Faced with this worrying situation and given the increased risk of therapeutic impasse caused by these multi-resistant strains; very early detection of ESBL germ infections, isolation of patients carrying a transmissible infection and rational use of antibiotics should be carried out.

Kew Words: enterobacteriaceae; extended-spectrum betalcatamase; antibiogram; nouakchott; mauritania

Introduction

In the early 1960s, we witnessed an increase in the number of bacteria resistant to antibiotics, especially in hospitals, and the emergence of new resistances.

This is a major public health problem of great concern, affecting many countries, although resistant strains are often different from country to country [1].

The bacterium thus develops several strategies to resist the action of antibiotics:

The modification of the target of the antibiotic, the impermeability of the antibiotic, the enzymatic inactivation of the antibiotic…etc. The latter is done by the secretion of enzymes such as broad-spectrum beta-lactamases secreted by a number of bacteria and which inhibit almost the majority of beta-lactams which represent the largest family of antibiotics. [2].

Enterobacteriaceae are the most frequent cause of community and nosocomial infections.

Generally treated with beta-lactams, over the last few decades there has been an emergence of a very significant resistance of enterobacteriaceae to these antibiotics. [3].

Extended-spectrum beta-lactamases (ESBL) are a large heterogeneous family of bacterial enzymes discovered in 1980 in France and Germany. They are induced either by plasmids or by mutation of the natural genome in the bacterium. Both mechanisms give affected bacteria the ability to hydrolyze a very wide variety of beta-lactams.

The genetic mutations at the origin of (ESBL) broaden the spectrum of these enzymes and affect third-generation cephalosporins (ceftazidime and cefotaxime, etc.) and monobactams (aztreonam). ESBL-inducing bacteria do not hydrolyze cephamycins (cefoxitin) or carbapenems (imipenem) and they are inhibited by clavulanic acid, tazobactam and sulbactam representing classical beta-lactamase inhibitors [3,4].

Thus, we conducted a study on enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLE) isolated in the central laboratory of the National Hospital Center for 2 years from January 1, 2019 to December 31, 2020.

With the following objectives:

- Determine their frequency.
- To know their distribution according to several parameters such as gender, patient department
- Assess their levels of antibiotic resistance
- Educate clinicians on the rational prescription of antibiotics

MATERIAL AND METHODS

This is a retrospective study that was conducted within the central laboratory of the National Hospital Center of Nouakchott (CHN) over 2 years, from January 1, 2019 to December 31, 2020 on all bacteriological samples for diagnostic purposes received. at the central laboratory of Nouakchott Hospital Center (CHN) from hospitalized patients or outpatients.

The antibiogram was carried out by the agar diffusion method according to the recommendations of the EUCAST-CA-SFM of the current year, or on the Vitek-2 automaton (Biomérieux®)

The production of ESBLs has been demonstrated by looking for a synergy between clavulanic acid and third-generation cephalosporins according to the usual techniques.

RESULTS

1. Breakdown by species of all Enterobacteriaceae isolates
2. The distribution by species of all Enterobacteriaceae isolates is shown in Table I.

Strains	Number	Percentages
Escherichia coli	400	61.54%
Klebsiella pneumoniae	120	18.46%
Enterobacter cloacae	80	12.31%
Proteus mirabilis	30	4.62%
Salmonella enterica	15	2.31%
Enterobacter aerogenes	4	0.62%
Proteus peneri	1	0.15%
Total	650	100

Table 1: Percentage and number of species of Enterobacteriaceae isolates

2 Distribution of ESBL-producing Enterobacteriaceae

The distribution of ESBL-producing strains is shown in Table 2

species	Effective	Percentage
Escherichia coli	**30**	**25%**
Klebsiella pneumoniae	**50**	**41.7%**
Enterobacter cloacae	**15**	**12.5%**
Proteus mirabilis	**10**	**8.3%**
Salmonella enterica	**8**	**6.7%**
Enterobacter aerogenes	**5**	**4.15**
Proteus peneri	**2**	**1.65**
Total	**120**	**100%**

Table 2: Distribution of ESBL-producing strains

3. Frequency of ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae (ESBL) during our study represents **18.46%.**

4. Distribution of ESBLs according to patient gender:

ESBL-producing enterobacteria (ESBL) were predominant in males (58%) against 42% in females in our series.

5. Distribution of ESBLE strains by department:

The distribution of EBLSE according to the services is represented in table 3

Service	Number	Percentage
Internal Medicine	16	13.3%
Urology	20	16.7%
Nephrology	12	10.0%
General surgery	10	8.3%
Outpatient consultation	50	41.7%
Intensive care	8	6.7%
Pediatrics	4	3.3%
Total	120	100%

Table 3: Distribution of ESBLs by department

6. ESBL sensitivity to antibiotics: The resistance profile of ESBL-producing strains to common antibiotics is shown in Table 4

Antibiotic	Resistance		Sensitivity	
	Number	Percentage	Number	Percentage
Amoxicillin	120	100%	0	0%
Amoxicillin + clavulanic acid	12	10%	108	90%
Ticarcillin	120	100%	0	0%
Piperacillin	120	100%	0	0%
Cefalotin	120	100%	0	0%
Cefoxitin	0	0%	120	100%
Cefotaxime	120	100%	0	0 %
Cefixime	120	100 %	0	0%
Acide nalidixique	100	83,3 %	20	16,7 %
Ofloxacine	99	83 %	21	17 %
Ciprofloxacine	95	79 %	25	21 %
Amikacine	16	13 %	104	87 %
Gentamicine	95	79 %	25	21 %
Tobramycine	97	81%	23	19%
Sulfamethoxazole-trimethoprim	90	75%	30	25%
Colistin	12	5%	114	90%
Fosfomycin	12	10%	108	90%
Imipenem	4	3%	116	97%

NB: -The percentage of resistance to colistin corresponds to the percentage of *Proteus:* natural resistance
- We have kept the old nomenclature of Enterobacteriaceae

Table 4: Resistance profile of ESBL-producing strains to antibiotics.

DISCUSSION

Enterobacteriaceae producing broad-spectrum beta-lactams are diversely distributed according to continents, and within the same continent according to geographical areas [5,6].
(ESBL)-producing bacteria represent a major concern in the hospital environment because of their epidemic spread and their multidrug resistance to antibiotics.
The (ESBL) are obtained from a large proportion of gram-negative bacilli, but enterobacteriaceae are the most incriminated germs.
They are increasingly implicated in both community-acquired and nosocomial infections and represent a real public health problem.

Data collected by the National Hospital Center laboratory between 2019 and 2020 confirms that E coli is the species most encountered by all enterobacteriaceae as shown by many authors in Meknes [6], El Jadida [7], and Rabat [8].
Klebsiella pneumoniae is the most common ESBL-secreting Enterobacteriaceae, representing 58.33% of ESBL-secreting Enterobacteriaceae, followed by Escherichia coli representing 25% and then Enterobacter cloacae with 8.33%.
These rates remain close to those found in Rabat with 45%, 26%, 15% respectively [9], and in France with 59.2%, 20.2% and 11.8% respectively [10].

According to our study, the overall frequency of isolation of ESBL-producing Enterobacteriaceae is 18.46%. A Moroccan series showed a rate of 18.53% in Rabat [9]. Lower rates were reported in Europe: 2.6 and 2% [11,12].
Infections with extended-spectrum beta-lactam-producing enterobacteriaceae (ESBL) are more common in males than females.
This male predominance remains controversial, while studies have confirmed it [13,14], others have found a female predominance [15,16].
These differences may reflect regional disparities in gender-related antibiotic prescribing practices (Example: antibiotic therapy for cystitis in women).
Other authors report that male sex and transfer from a long-stay hospital are two major risk factors associated with ESBL carriage [17].

According to our study, patients over the age of 55 constituted the majority age group representing almost 75% of our sample. BMR) including EBLSE, figure an advanced age, generally over 65 years.
Forty-two percent (42%) of the ESBLs isolated during our study, come from outpatient consultations, this dissemination of ESBLs in the community is alarming and could be explained, in part, by the anarchic use of antibiotics, it has been mentioned by several studies [18].
In hospitals, a high frequency of ESBLs was noted in urology departments in our series (17%), probably related to the use of invasive devices (urinary catheter, etc.) and the use of multiple antibiotic therapy.
The ESBL rate in the surgery department (8%) is not negligible and could be related to the accumulation of surgical antibiotic prophylaxis and postoperative antibiotic therapy.
There is a consensus to try to eradicate urinary colonization in patients before undergoing urological surgery, or invasive explorations of the urinary tract.
It is a rule to also propose it during the placement of an osteo-articular, endo-vascular or heart valve prosthesis [19].
The distribution of (ESBL) according to the infectious sites, 60% of isolated ESBL-producing Enterobacteriaceae come from urinary tract infections. This rate remains high compared to other studies which report a predominance of ESBL from urinary tract infections [20].
Urinary tract infections are common conditions in daily practice. The essential causative agent is Escherichia coli since it is responsible for 50–80% of UTIs [21].

Resistance to Gram-negative bacteria has gained prominence lately.
years. Indeed, the Infectious Diseases Society of America (IDSA) recently identified six bacteria grouped under the name "ESKAPE" including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species which are responsible for two-thirds of hospital-acquired infections, two-thirds of which are Gram-negative bacteria.
ESBLs are the most important threats by their frequency.
As a result, the WHO identifies this phenomenon as a major public health threat.
Beta-lactam resistance in BGNs can be caused by several
mechanisms, hydrolysis of the betalactam nucleus by the action of a betalactamase is the most frequent mechanism.
Over the past 70 years, the use of beta-lactams, including
new beta-lactams such as C3Gs and carbapenems, with a spectrum
increasingly broad action against BGNs, has selected betalactamase-type enzymes, each more powerful than the previous one.

Since 1983, transferable resistance to 3rd generation cephalosporins and monobactams in ESBLs has been disseminated in the majority of French hospitals [22].
These ESBLs derive for the majority of the enzymes TEM-1, TEM-2 and SHV by substitution of one or more amino acids; many types have been reported [23].
ESBL genes are usually carried by large transferable plasmids on which they are often associated with genes coding for resistance to aminoglycosides, chloramphenicol, sulfonamides, trimethoprim, cyclins and also fluoroquinolones [24].
In our study as in others, amikacin is less affected than gentamicin and tobramycin, but the rate of resistance to this molecule continues to increase due to its wide prescription [25].
The trimethoprim-sulfamethoxazole association has low activity on ESBL-producing enterobacteriaceae, with 25% sensitivity, this rate is 23% in Morocco and 25% in Iran [9,26]. A recent study in Benin found a resistance rate of 100%.
The ciprofloxacin resistance rate reported in our study is 79%. This rate is close to those reported by studies in Rabat, and in Switzerland with respective rates of 75% and 93% [9,27].
The massive use of fluoroquinolones for first-line treatment of urinary tract infections without prior documentation due to their broad bacterial spectrum and their good urinary diffusion could be responsible for this high rate of resistance.
Fosfomycin retains excellent efficacy against ESBL in our study, with 90% sensitivity.

The resistance of Enterobacteriaceae to carbapenems remained marginal with sensitivity rates of 98–100% [28], making carbapenems the best treatment for ESBL-producing Enterobacteriaceae [9]. Unfortunately, the misuse of these molecules has led to the emergence of resistance to these antibiotics, especially in Klebsiella pneumoniae [29].
In our study, the rate of resistance to imipenem is alarming, reaching 3% of isolates, so it is important to insist on the rational use of carbapenems in our country.
Similar resistance rates have been reported in Benin and Rabat with respective rates of 3.40% and 3.44% [26.30].
This decrease in sensitivity could be the result of a change in porins, associated with the production of ESBL-type beta-lactamases, therefore decreasing the permeability of the outer membrane [31], or even more alarmingly, the production of carbapenemases [32], making the treatment of ESBL infections very difficult and limiting treatment options [29].
Currently, there are no randomized and controlled studies for the treatment of ESBL infections.
Treatments with carbapenems (imipenem, meropenem, ertapenem) are burdened with the lowest mortality.
But the use of carbapenems, in the presence of ESBL, also promotes the emergence of other enzymes, the metallo-beta-lactamases which hydrolyze the carbapenems and render them ineffective. [33].
It should be noted that the carbapenems are not interchangeable and that there are ertapenem-resistant and imipenem-sensitive strains.

Today, it is appropriate to initiate a reflection on the molecules which could be used in the management of ESBL E infections, knowing already that none of the proposals can be ideal.
These are not recommendations or therapeutic strategies that have been validated today, but lines of research that could constitute avenues for study [34]:

- Fosfomycin-trometamol and nitrofurantoin (molecules reserved for mild infections, particularly uncomplicated acute cystitis in women), longer administration schedules of fosfomycin-trometamol would be likely to provide better eradication rates. However, the Increasing resistance to fosfomycin parallel to increasing consumption has been described in some countries.
- New beta-lactams with or without beta-lactamase inhibitors are now available. The oldest is temocillin, of which in vitro studies show more than 90% of ESBL enterobacteriaceae sensitive to temocillin, and the two most recent are the combinations ceftolozane–tazobactam and cefatzidime–avibactam respectively. Like all beta-lactams, the activity of these 3 molecules depends on their minimum inhibitory concentration necessary for each of the species of ESBL-producing enterobacteriaceae. French

epidemiological data suggest better activity with respect to ESBL E. coli than the species K. pneumoniae, E. cloacae or E. aerogenes [35].

- Cephamycins (cefoxitin), a risk of resistance by "impermeability" was described very early in certain ESBL enterobacteriaceae
- Cephalosporin + beta-lactamase inhibitor combinations: These combinations are of potential interest. The most effective beta-lactamase inhibitor is clavulanic acid.
- Tigercycline: it is active in vitro against these strains, although it has obtained Marketing Authorization in the treatment of complicated intra-abdominal infections, no Marketing Authorization has been granted in the treatment of urinary tract infections.
- Colimycin: The use of colimycin should preferentially be reserved for the treatment of infections caused by multi-resistant Gram-negative bacteria (in particular carbapenemase-secreting bacteria) which are only sensitive to colimycin.

The fight against the emergence of ESBLs is therefore a public health duty.
In a hospital environment, the diagnosis of colonization by ESBL is made by a smear from the perineum, inguinal or anal, given the probable digestive reservoir of this germ. In the community setting, there is no indication to perform screening smears.
In the presence of a patient colonized by an ESBL-producing germ, it is recommended to set up isolation measures, such as contact and individual room, in order to avoid nosocomial transmissions.
It is also recommended to limit the movements of carrier patients as much as possible in order to limit the risk of transmission to other patients [36].
The best prevention for this type of germ remains the rational prescription of broad-spectrum antibiotics aimed at reducing the selection pressure that can promote the emergence of ESBL-producing bacteria [37].

CONCLUSION

Our study made it possible to carry out a description of the epidemiological profile and the resistance of ESBL-producing enterobacteriaceae in the central laboratory of the National Hospital Center of Nouakchott between January 2019 and December 2020.
Considering the results of our study and the data from the literature, it clearly appears that ESBLs are taking an increasingly important place among multiresistant bacteria.
Indeed, almost three decades after their discovery, ESBLs initially confined in the years 1985 to the species K. pneumoniae during nosocomial infections in hospital intensive care units are now easily identified on a global scale.
Their involvement in nosocomial and community-acquired infections requires clinical, microbiological and therapeutic vigilance given their particular antibiotic resistance profile.
The increase in resistance should be compared with the increase in antibiotic consumption.
These trends are problematic because they promote not only the emergence and spread of ESBL enterobacteriaceae, but also those of carbapenemase-producing enterobacteriaceae (CPE).
Faced with this worrying situation and given the increased risk of therapeutic impasse caused by these multi-resistant strains; it is necessary to proceed to:

- Very early detection of ESBL germ infections
- Isolation of patients with a transmissible infection
- Controls of reservoirs and transmission routes by geographic and technical isolation of colonized or infected patients
- Rational use of antibiotics
- Collective awareness, cooperation between services and in-depth training of healthcare teams in order to reduce the risk of cross-transmission as much as possible.

State of current knowledge on the subject

• E-ESBLs are multi-resistant bacteria with cross-resistance with other families other than beta-lactams
• The therapeutic management of ESBL-E infections poses a serious public health problem.

Contribution of our study to knowledge

• Our study is the first in Mauritania reserved for the prevalence of ESBL-E and their resistance to other common antibiotics
• It allowed us to highlight this high prevalence (18.46 %) of all enterobacteriaceae isolates over two years.
• It has demonstrated significant resistance to other families of antibiotics
• Carbapenems, fosfomycin, colistin and amikacin still retain good activity on these strains.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the conduct of this work.
All authors declare to have read and approved the final version of the manuscript.

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