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Surveillance of Resistance to Imipenem and Meropenem in Broad-spectrum Beta-lactamase-producing *E. coli* Strains Isolated from Urine Samples in Njombe, Cameroon

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Abstract: The emergence and spread of carbapenems resistance *Enterobacteriaceae* remain a major public health, a real threat as well as a silent tsunami. This phenomenon leading to reduce the therapeutic option and increase the additional cost. The general objective of this study was to determine the frequency of *Escherichia coli* strains producing broad-spectrum beta lactamases and resistant to carbapenems. We carried out a descriptive, cross sectional and prospective study between August and November 2020 at the Hospital Saint Jean de Malte in Njombe, on a consecutive sample of 249 patients received at the bacteriology unit. Our study population consisted of all patients who came for inpatient or outpatient consultations, were prescribed an cytobacterioligical urine exam, and in whom an *E. coli* strain was isolated. The identification of *E. coli* strains was confirmed using the Api 20E mini gallery. Resistance to carbapenems (Meropenem and Imipenem) was defined by determining the Minimal Inhibitory Concentration (MIC) by the microdilution plate method. Of the 249 cytobacterioligical urine exam samples received during our study period, 131 presented a pathogenic germ and *E. coli* strains were identified in 85 of them. The age of the patients in whom the *E. coli* strains were identified ranged from 70 to 85 years and the male sex dominated with a frequency of 38.2%. Of these identified *E. coli* strains, we detected 08 (9.41%) BLSE-producing strains. The resistance rate of the isolated *E. coli* strains producing BLSE was 75% and 50% for Meropenem and Imipenem respectively. The results of this study underline the urgent need for a regular surveillance system for broad-spectrum antibiotics in our context.

Keywords: Resistance, Imipenem, Meropenem, *E. coli*, Broad-spectrum Beta-lactamases

1. Introduction

Urinary tract infection is a major public health problem [1]. According to the World Health Organization (WHO), *Escherichia coli* (*E. coli*) urinary tract infections are by far the most common infection in hospitals and communities [2, 3]. In the last decade, the epidemiology of urinary tract infections had changed in a worrying way due to the major dissemination of Cefotaximase M (CTX-M) type enzymes within extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4–6]. In addition, these plasmids carrying the ESBL gene also harbor other resistance genes that confer resistance to other families of antibiotics to the vast majority of ESBL *Enterobacteriaceae*, including cotrimoxazole, fluoroquinolones and aminoglycosides [7–9]. This multi-resistance of the *Enterobacteriaceae* ESBL has led to the clinical prescription of carbapenems. Unfortunately, the use of carbapenems has favored the emergence of carbapenemases inactivating these antibiotics, the last molecules in the therapeutic arsenal to combat *Enterobacteriaceae* [4]. The

emergence of resistance to these molecules therefore represents a major threat to the health of populations.

In developing countries, poverty, malnutrition, poor sanitation, inadequate access to medicines, lack of efficient health care systems, governmental crises, civil wars, and frequent population displacement are factors contributing to the emergence and spread of carbapenem resistance in these regions of the world [10]. Carbapenem resistance has not spared developed countries, particularly affecting the most frequently isolated pathogens [11, 12]. This bacterial resistance to antibiotics poses the problem of choice of antibiotic therapy.

In sub-Saharan Africa, and particularly in Cameroon, *E. coli* urinary tract infections are a priority in the field of antibiotic resistance surveillance and study, given the majority of patients do not have access to a laboratory and the management of infectious syndromes is probabilistic. The effectiveness of this approach lies in the knowledge of the resistance of bacteria to anti-microbial agents at the local level. Some studies conducted in Cameroon in urban areas have shown the presence of ESBL-producing *Enterobacteriaceae* resistant to carbapenems [13, 14]. However, in rural areas, there are very few studies on the resistance of *E. coli* strains to carbapenems. The aim of this study was to collect information in rural areas necessary for a better therapeutic management of bacterial infections.

In this paper, we provide an update on the imipenem and meropenem resistance of ESBL-producing *E. coli* strains to redefine their uses in the probabilistic treatment of bacterial infections.

2. Methods

2.1. Study Site

This study was conducted in Njombe, village of Cameroon located in the Moungo department, Littoral region; more precisely at the Saint Jean de Malte Hospital. During the 2005 national census, the locality had 31 792 inhabitants with an estimated density of 121.4 inhabitants per km² [15]. Saint Jean de Malte Hospital is located by the banana plantation, in the middle of the population of Njombe, consequently, it receives a very large number of patients spread over the many villages of the region. The population is affected by malaria, HIV/AIDS, urinary tract infections and other diseases. The microbiology unit of the Saint Jean de Malte Hospital of Njombe laboratory has a technical platform (apparatus and equipment) appropriate to the types of analyses that we have carried out in this study.

2.2. Type and Period of Study

This study is a cross-sectional and prospective study conducted at the Microbiology Unit of the Saint Jean de Malte Hospital of Njombe in Cameroon between August and November 2020.

2.3. Study Population

All persons who came to the Saint Jean de Malte Hospital for consultation and who were prescribed a urine cytobacteriological examination were included in the study. Exclusion criteria were as follows: (1) uncooperative patients who refused to give consent or participate in the study; (2) Urine sample containing an isolated strain of the *Enterobacteriaceae* family other than *E. coli.*

2.4. Sampling Technique

A consecutive, nonprobability sampling technique was used to recruit all of the patients who were part of the study.

2.5. Sample Collection

Fifty milliliters of a mid-stream jet urine sample were collected in a sterile container. Twenty milliliters were used in this study. The semi-quantitative technique to determine significant bacteriuria was employed by using 0.01 ml calibrated wire loop to inoculate cystine lactose electrolyte deficient agar (CLED) and Eosine-Methylene Blue agar (EMB) with uncentrifuged urine. Culture plates were incubated at 37°C for 18–24 h. After inoculation of media, the remaining sample was centrifuged at 2000 rpm for 5 minutes and sediment used for microscopy. A specimen was considered positive if a single organism was isolated at a concentration of greater than 10^5 CFU/mL and associated with microscopy findings of greater than 10 leucocytes per high power field. Bacteria were identified by Gram's stain and standard biochemical procedures. Identity of enterobacteriaceae was confirmed using the API 20E kit.

2.6. Test for the Production of Extended Spectrum Beta-lactamases

We performed a synergy test between a disc of Amoxicillin + Clavulanic Acid and 3rd generation cephalosporins or Aztreonam, on Muller Hinton agar to check if our identified *E. coli* strain is a producer of extended spectrum beta-lactamases. The revelation of the champagne cork synergy between the different discs related that this enterobacterium is a beta-lactamase producer [16].

2.7. Antibiogramme

All *E. coli* strains were isolated and cultured according to routine procedures [17]. Microdilution of the bacterial inoculum was performed according to Clinical and Laboratory Standards Institute 30th edition guidelines [18] and the concentrations of Imipenem and Meropenem were measured at 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16, 32 and 64 µg/mL. The microplates, in order to avoid drying out, were stacked on top of each other. For regular heating, not more than five microplates were stacked at a time. Microplates were incubated at 34-37°C in ambient air for 18±2h in a humid chamber protected from light. Readings were taken using the positive growth controls. Susceptibility was defined by an MIC $\leq$ 2 µg/mL. Isolates with an MIC $\geq$ 4 µg/mL were considered resistant.

2.8. Data Analysis

The data was entered into the Excel 2016 spreadsheet and

analyzed from IBM SPSS version 28.0 software. The results were presented in tabular and graphical form.

2.9. Ethical Approval

A written informed consent was obtained from the study subjects prior to enrollment. Permission to conduct the study was obtained from the Director of the Saint Jean de Malte Hospital; while ethical clearance was obtained from the institutional ethics committee of the School of Health Sciences, Catholic University of Central Africa (N°2019/020358/CEIRSH/ESS/MIM).

3. Results

3.1. Characteristics of Study Population

As shown in Table 1, out of a total of 249 clinical samples received at the bacteriology department of the Saint Jean de Malte Hospital for cytobacterioligical urine exam during the study period, 131 presented a pathogenic germ and *E. coli* strains were identified in 85 of them, i.e. a percentage of 34.13%. Patients ranged in age from 1 to 85 years (mean 28.1 ± 23.7 years) and 119 (47.8%) were in the age range 1-24 years. Female patients were more represented compared to male patients, 160/249 (64.3%) females versus 89/249 (35.7%) males respectively. The age of the patients in whom the *E. coli* strains were identified ranged from 70 to 85 years and the male sex dominated with a frequency of 38.2%. The observed difference in the percentages of *E. coli* strains isolated was significant between classes. The majority of examinations were requested by the Gynecological-Obstetrics and Medicine departments: 70/249 (26.11%) and 71/249 (28.51%) respectively. Inpatients were the most represented, 206/249 (82.7%) and 140/249 (56.2%) of the samples were collected using urine pots.

Table 1. *Sociodemographic characteristics of study subjects and correlations with isolated E. coli strains.*

Characteristics	Frequency (%) N=249	Number of strains *E. coli* isolated (%) n=85	ESBL-producing *E. coli* strains n=8 (%)
Age groups (years)			
[1 – 24]	119 (47.8)	39 (32.8)	6 (75.0)
[24 – 47]	69 (27.7)	16 (23.2)	1 (12.5)
[47 – 70]	42 (16.9)	16 (38.1)	0 (0.0)
[70 - 85]	19 (7.6)	14 (73.7)	1 (12.5)
Gender			
Male	89 (35.7)	34 (38.2)	6 (75.0)
Female	160 (64.3)	51 (31.9)	2 (25.0)
Services			
Maternity	19 (7.6)	4 (21.1)	0 (0.0)
Medicine	70 (28.1)	33 (47.1)	3 (37.5)
Obstetrics gynecologist	71 (28.5)	19 (26.8)	3 (37.5)
Pediatrics	42 (16.9)	19 (45.2)	2 (25.0)
Surgery	47 (18.9)	10 (21.3)	0 (0.0)
Clinical status			
External	43 (17.3)	20 (46.5)	1 (12.5)
Internal	206 (82.7)	65 (31.6)	7 (87.5)
Means of collection			
Urinary catheter	25 (10.1)	8 (32)	0 (0.0)
Urine bag	84 (33.7)	25 (29.8)	5 (62.5)
urine pots	140 (56.2)	52 (37.1)	3 (37.5)

3.2. Frequencies of Beta-lactamase-producing E. coli Strains

As shown in Figure 1, out of a total of 85 *E. coli* strains isolated, 8 strains (9.41%) were found to be beta-lactamase producers.

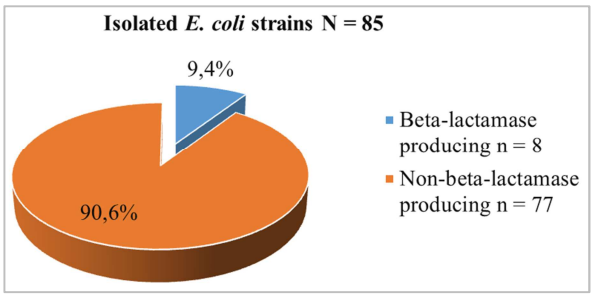

Figure 1. *Frequency of beta-lactamase-producing E. coli strains.*

3.3. Resistance Profile of Beta-lactamase-producing E. coli Strains to Carbapenems

Table 2. *Resistance profile of beta-lactamase-producing E. coli strains to carbapenems.*

MIC (mg/L)	Antibiotics	
	Imipenem (%) n=8	Meropeneme (%) n=8
≤2 (Sensitive)	50%	25%
≥4 (Resistant)	50%	75%

MIC: Minimum Inhibitory Concentrations.

As shown in Table 2, of a total of 8 beta-lactamase producing strains isolated, 4 (50%) were resistant to Imipenem. The percentage of strains resistant to Meropenem was 75%.

4. Discussion

Enterobacteriaceae are a group of bacteria frequently

isolated in bacteriology laboratories, *E. coli* being the most common species with a very alarming rate of antibiotic resistance [19–21]. In this study, *E. coli* strains were isolated from urine samples collected at the microbiology laboratory of the Hospital Saint Jean de Malte in Njombe. Out of 249 urine samples analyzed, 85 strains of *E. coli* were isolated or 34.13%. Although this result is similar to previous studies [21, 22], *E. coli* was isolated more in men (38.2%) than in women (31.9%), although the observed difference was not significant. This predominance of male positivity could be explained by the fact that the request for cytobacterioligical urine exam is more systematic in men, given their greater risk factors and complications [23]. The mean age of the patients was 28.1±23.7 years. The majority of the patients from whom *E. coli* was isolated were in the age group 70-85 years. This result corroborates with the statements made by De Wazieres [24] according to which, Urinary tract infection is one of the most frequent infectious problems in geriatrics, whether in urban or rural areas. Indeed, these populations have an increased risk of dependence for the acts of daily life and a greater frequency of general pathologies (diabetes, neoplasia, etc.). All this contributes to increase the risk of urinary tract infection in these patients [25, 26]. The majority of patients from whom *E. coli* was isolated were from the medicine ward (47.1%). This result is different from that reported by Kalambry *et al*. (2019), in Mali who reported 63.5% in medicine [27]. This can be explained by the different distribution of services: the presence of an endocrinology department at the Mali Hospital, with frequent urinary infections in patients with metabolic diseases, versus the absence of a urology department at Hospital Saint Jean de Malte.

A study conducted in France in 2011 reported an ESBL-producing *E. coli* strain carriage frequency of 6% [25]. Compared to a similar study conducted in 2006, the porting rate increased by a factor of 10 [28]. In this study, we reported a ESBL-producing *E. coli* strain frequency of 9.4%. In contrast, in the northern region of Cameroon, Djim-Adjim-Ngana *et al*. (2020), reported a frequency of 55% [29]. In fact, this frequency varies from one country to another and from one center to another. In general, southern European countries recorded frequencies in excess of 10%, while northern countries recorded less than 5% [30].

The study also revealed the presence of ESBL-producing *E. coli* strains resistant to meropenem at 75% and 50% for imipenem. Ten years ago, these molecules were the most active on resistant *Enterobacteria* strains in Cameroon [31]. This high level of resistance found in our study is probably due to inappropriate use of antibiotics, both in medical prescription and self-medication. In fact, in Cameroon, antibiotics are sold over the counter in pharmacies and are used for self-medication in various pathological situations such as colds, coughs, diarrhea. In medical prescriptions, imipenem and meropenem are the most widely prescribed antibiotics for any suspected urinary tract infection, documented or not. This massive use of antibiotics does not spare developed countries. According to Lafaurie Met *et al*. (2013), the proportion of antibiotic therapy prescribed in France to treat urinary tract infections represents 12% of antibiotic prescriptions [32]. According to Sekhsokh *et al*. (2008), the massive prescription and often abusive use of broad-spectrum ATBs in both hospital and community settings is responsible for the selection pressure of resistance genes [33]. The evolution of *E. coli* resistance to carbapenems at Hospital Saint Jean de Malte at Njombe exposes a problem of difficulty in the therapeutic management of infections related to this pathogen and requires the implementation of surveillance systems.

5. Conclusion

At the end of our work, the objective of which was to determine the frequency of strains of *E. coli* producing ESBL and resistant to carbapenems. It appears that:

1. 85 *E. coli* strains were isolated from the 249 cytobacterioligical urine exam samples received.
2. 9.41% of *E. coli* strains produced ESBL, of which 50% and 75% were resistant to Imipenem and Meropenem respectively.

The presence of ESBL-producing *E. coli* strains resistant to Meropenem and Imipenem in the Njombe locality is an obstacle to the therapeutic management of urinary tract infections. Raising awareness among the population of this locality on the dangers of self-medication and the uncontrolled use of antibiotics has proven to be essential.

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