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Carbapenem Resistance and Metallo-β-Lactamase Production in Enterobacteriaceae Isolated from Urogenital Tract Infections in Brazzaville

Nicole Prisca Makaya Dangui Nieko[1,2*], Tarcisse Baloki Ngoulou[1,3], Doria Moïse Kaya-Ongoto[1,3], Faly Armel Soloka Mabika[1,3], Vikène Juste Babela Koumou[2], Etienne Nguimbi[3]

[1]Laboratoire National de Santé Publique, République du Congo
[2]Laboratoire de Microbiologie, Infectiologie et Immunologie, École Normale Supérieure, Université Marien Ngouabi, Brazzaville, République du Congo
[3]Laboratoire de Biologie Cellulaire et Moléculaire, Faculté des Sciences et Techniques, Université Marien NGOUABI, Brazzaville, République du Congo
Email: *nicolemakaya@gmail.com

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Abstract

The emergence and spread of antibiotic-resistant bacteria constitute a major global public health threat, compromising treatment efficacy and increasing morbidity and mortality associated with infections. In response to this concerning situation, carbapenems are considered last-resort antibiotics. However, Enterobacteriaceae exhibit high resistance rates to these drugs. The aim of this study was to determine carbapenem resistance profiles and the prevalence of Metallo-β-Lactamase (MBL) production among Enterobacteriaceae isolated from urogenital tract infections. Enterobacteriaceae strains were isolated on selective media from urine and vaginal swab samples and identified using the API 20 E system. Antibiotic susceptibility testing was performed using the Mueller-Hinton disk diffusion method. MBL production was assessed using the combined carbapenem/carbapenem + EDTA disk test. A total of 123 Enterobacteriaceae were isolated from 325 samples, of which 81.6% were from urine and 17.4% from vaginal swabs. Identification revealed 12 species distributed across five genera: *Escherichia*, *Enterobacter*, *Citrobacter*, *Klebsiella*, and *Proteus*. Susceptibility testing showed the highest sensitivity to ertapenem (79.67%) followed by meropenem (69.92%), whereas doripenem showed the lowest sensitivity (33.33%). Resistance patterns varied between species for different antibiotics. Chi-square analysis revealed a significant difference in bacterial resistance among the different strains for all tested antibiotics. MBL pro-

duction testing revealed that 100% of strains produced MBLs in the presence of imipenem. Only *E. coli* and *Enterobacter aerogenes* were MBL producers in the presence of meropenem. Despite the high resistance rates and the capacity of these strains to produce carbapenem-hydrolyzing enzymes, meropenem and ertapenem, due to their lower resistance rates, may still be considered first-line treatment options for urogenital tract infections caused by these bacterial genera.

Keywords

Resistance, Metallo-Betalactamases, Enterobacteriaceae, Brazzaville

1. Introduction

Urogenital Tract Infections (UTIs) are currently among the most common reasons for medical consultation and represent a major global public health issue, both in community and hospital settings [1]. Enterobacteriaceae are ubiquitous Gram-negative bacilli and opportunistic pathogens frequently implicated in UTIs [2]. Due to their wide distribution and ability to acquire virulence factors and antibiotic resistance mechanisms, they are isolated in both community and healthcare settings [3]. The emergence and dissemination of antibiotic-resistant Enterobacteriaceae represent a major global public health threat, compromising treatment efficacy and increasing infection-associated morbidity and mortality [4]. Over the past decades, the emergence and spread of Enterobacteriaceae resistant to last-resort antibiotics such as carbapenems have posed a growing challenge to treatment efficacy [3]. Carbapenems, as broad-spectrum β-lactams, are often considered essential agents for the treatment of severe infections caused by multidrug-resistant bacteria [4]. However, the appearance of resistance mechanisms, mainly through carbapenemase production, poses a significant therapeutic challenge, limiting effective treatment options and increasing the risk of therapeutic failure and resistance dissemination via genetic transfer to other bacterial species. Carbapenem-resistant Enterobacteriaceae often produce enzymes that hydrolyze carbapenems, known as carbapenemases [5]. Among these enzymes, Metallo-β-Lactamases (MBLs) are particularly important due to their ability to inactivate a wide range of β-lactams, including carbapenems, and their resistance to clinically available β-lactamase inhibitors, except for avibactam, which does not inhibit MBLs [6]. In Africa, several studies have investigated carbapenem resistance in Enterobacteriaceae, including work by Habibou *et al.* [7] in Senegal, Ramkisson *et al.* [8] in South Africa, Garba *et al.* [9] in Burkina Faso, Ragueh *et al.* [10] in Djibouti, Dos *et al.* [11] in Gabon, and more recently by Hamidou *et al.* [12] in Niger and Benin. In the Republic of Congo, bacterial infectious diseases remain a major concern, further compounded by the absence of national surveillance on antibiotic resistance. The literature review revealed several studies on β-lactamase production in bacteria iso-

lated from wound infections and on the transmission of β-lactam resistance among Enterobacteriaceae from mothers to children in Brazzaville [13] [14]. Mpelle *et al.* [15] reported the first detection of *TEM*, *CTX-M*, *SHV*, and *OXA-48* β-lactamases in *Escherichia coli* in the Republic of Congo. Although Makaya *et al.* [16] (2022) studied MBL- and ESBL-producing Enterobacteriaceae in Brazzaville, epidemiological data specific to carbapenem resistance in Enterobacteriaceae from urinary infections remain insufficient. Therefore, it is crucial to improve understanding of carbapenem resistance profiles and MBL production prevalence among Enterobacteriaceae isolated from urogenital tract infections. This work contributes to strengthening strategies for surveillance, prevention, and management of urinary tract infections.

2. Materials and Methods

2.1. Study Materials

This prospective study was conducted over three months, from July 1 to September 30, 2022, at the Bacteriology Department of the National Public Health Laboratory in Brazzaville. Biological materials analyzed included bacterial isolates from urine and vaginal swab samples collected from patients of all ages and both sexes submitted for routine laboratory analysis. Any urine or vaginal swab sample submitted for routine biological analysis at the National Public Health Laboratory was included in the study. No ethical approval was obtained. This institution also has a mandate for research and scientific production. After the results were returned to patients, bacterial strains were used for the research component. The samples were received regularly during the study period and were included in this study, including any vaginal and urinary specimens intended for bacteriological analysis. After the results were given to the patients, a code was assigned to each sample based on the type of collection.

2.2. Methods

2.2.1. Isolation and Identification

Bacterial isolation was performed by culturing samples on Eosin Methylene Blue (EMB) agar. Plates were incubated for 18 - 24 hours at 37˚C. Isolates were identified using the API 20 E system (BioMérieux, France) according to the manufacturer's instructions.

2.2.2. Quality Control

Quality control of antibiotic disks was performed using *Klebsiella pneumoniae* ATCC 700603, following CASFM recommendations [17].

2.2.3. Carbapenem Susceptibility Testing

The following antibiotics were tested: imipenem 10 µg, meropenem 10 µg, doripenem 10 µg, and ertapenem 10 µg. Resistance profiles were determined using the Kirby-Bauer disk diffusion method [18] [19]. Inocula were prepared by suspending a well-isolated colony from a 24-hour pure culture in 5 ml of 0.9% NaCl.

Turbidity was adjusted to 0.5 McFarland using a Vitek Densichek. Mueller-Hinton agar plates were inoculated with a sterile swab as recommended by CLSI [20] [21]. Disks were placed on inoculated plates, which were incubated at 37˚C for 18 - 24 hours. Inhibition zone diameters were measured, and susceptibility was interpreted according to CASFM breakpoints [17]. Strains were classified as susceptible, intermediate, or resistant. Strains were declared susceptible to doripenem, imipenem and meropenem when the critical diameter was ≥ 23 mm and ≥ 25 mm for ertapenem.

2.2.4. Detection of Metallo-*β*-Lactamase-Producing Strains: Combined Carbapenem/Carbapenem + EDTA Disk Test

This technique detects MBL production by pre-identified bacterial strains. *In vitro* activity of carbapenems (imipenem or meropenem) alone and combined with EDTA, an MBL inhibitor, was tested. Bacterial inocula were adjusted to 0.5 McFarland in 2 ml of 0.9% saline and seeded on Mueller-Hinton agar. Two disks of the same carbapenem were placed 3 cm apart. One disk was supplemented with 4 µL of 0.5 M EDTA (pH 8). After 18 - 24 hours of incubation at 37˚C, inhibition zones were measured. Strains were considered MBL producers if the inhibition zone around the carbapenem + EDTA disk was ≥7 mm larger than the carbapenem-only disk [16] [22], indicating restored carbapenem activity via MBL inhibition.

2.2.5. Statistical Analyses

Data were processed using Excel 2016 (Microsoft Corporation, USA). Percentages were calculated from measured inhibition diameters. Resistance rates were compared using the Chi-square test, with significance set at $p < 0.05$ and a 95% confidence interval, using GraphPad Prism 2008.

3. Results

3.1. Sample Collection

A total of 325 samples were collected: 185 urine samples (57%) and 140 vaginal swabs (43%).

3.2. Isolation and Identification of Strains

3.2.1. Isolation

Out of 325 samples, 123 were positive, giving a prevalence of 37.85%. Among positive samples, 100 were from urine (81.6%) and 23 (17.4%) from vaginal swabs (**Figure 1**).

3.2.2. Identification

Five genera, *Escherichia*, *Enterobacter*, *Citrobacter*, *Klebsiella*, and *Proteus* were identified and distributed among twelve (12) bacterial species. Among these, *Escherichia coli* was the predominant species, accounting for 35%, followed by *Klebsiella oxytoca* at 11%. In contrast, *Klebsiella ozaenae* and *Klebsiella pneumoniae* were the least represented, each with a frequency of 3% (**Figure 2**).

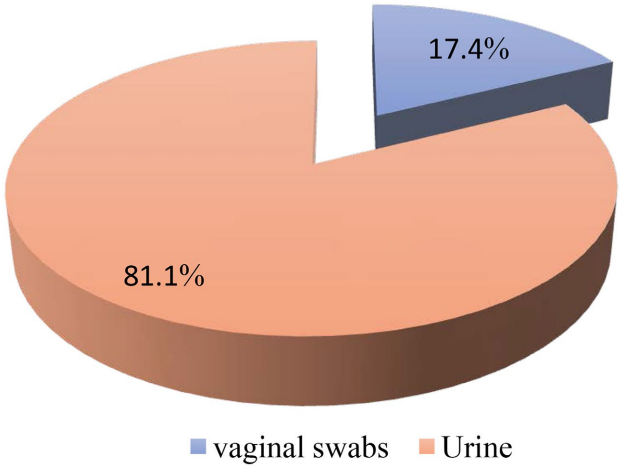

Figure 1. Distribution of positive samples according to specimen type.

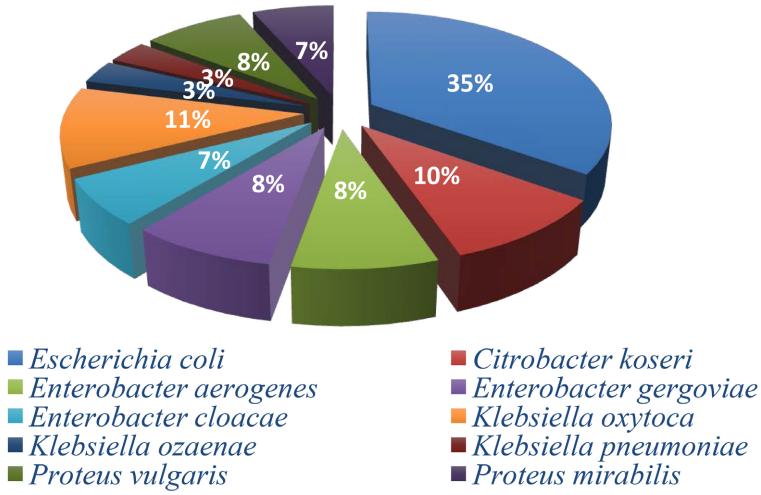

Figure 2. Different types of Enterobacteriaceae identified.

3.3. Antibiotic Susceptibility

Table 1 shows the results of antibiotic susceptibility testing performed on 123 Enterobacteriaceae strains. The strains were most susceptible to ertapenem (79.67%) and meropenem (69.92%). In contrast, they exhibited lower susceptibility to doripenem (33.33%).

Table 1. Overall resistance and susceptibility of the tested strains to carbapenems.

Antibiotics	Susceptibility N (%S)	Resistance N (%R)
DOR, 10 µg	41 (33.33%)	82 (66.67%)
IMI, 10 µg	63 (51.22%)	60 (48.78%)
MRP, 10 µg	86 (69.92%)	37 (30.08%)
ERP, 10 µg	98(79.67%)	25 (20.33%)

Legend: N: Number of strains, %S: Percentage of susceptibility, %R: Percentage of resistance, DOR: Doripenem, IMI: Imipenem, MRP: Meropenem, ERP: Ertapenem.

Table 2(a) and Table 2(b) present the rates of antibiotic resistance. These tables show that resistance rates vary depending on the strains and the antibiotics; however, the strains were less resistant to ertapenem and meropenem. The chi-square test revealed a significant difference in bacterial resistance among the different strains with respect to imipenem, meropenem, doripenem, and ertapenem.

Table 2. (a) Overall resistance and susceptibility of tested strains to carbapenems; (b) Overall resistance and susceptibility of tested strains to carbapenems.

(a)

Antibiotiques	*Escherichia coli* (N = 43)		*Citrobacter koseri* (N = 12)		*Enterobacter aerogenes* (N = 10)		*Enterobacter gergoviae* (N = 10)		*Enterobacter cloacae* (N = 08)		P-value
	N (%R)	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	
IMI, 10 µg	30 (69.76)	13 (30.24)	6 (50)	6 (50)	6 (60)	4 (40)	6 (60)	4 (40)	3 (37.5)	5 (62.5)	**0.0003***
MRP, 10 µg	18 (41.86)	25 (58.14)	0	12 (100)	2 (20)	8 (80)	3 (30)	7 (70)	4 (50)	4 (50)	**0.0182***
DOR, 10 µg	28 (65.11)	15 (34.89)	12 (100)	0	5 (50)	5 (50)	6 (60)	4 (40)	5 (62.5)	3 (37.5)	**0.0009***
ERP, 10 µg	5 (11.62)	38 (88.38)	4 (33.33)	8 (66.64)	2 (20)	8 (80)	3 (30)	7 (70)	1 (12.5)	7 (87.5)	**0.0292***

(b)

Antibiotiques	*Klebsiella oxytoca* (N = 14)		*Klebsiella ozaenae* (N = 04)		*Klebsiella pneumoniae* (N = 04)		*Proteus vulgaris* (N = 10)		*Proteus mirabilis* (N = 08)		P-value
	N (%R)	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	**N (%R)**	**N (%S)**	
IMI, 10 µg	5 (35.71)	9 (64.29)	1 (25)	3 (75)	2 (50)	2 (50)	1 (10)	9 (90)	0	8 (100)	**0.0003***
MRP, 10 µg	5 (35.71)	9 (64.29)	2 (50)	2 (50)	3 (75)	1 (25)	0	10 (100)	0	8 (100)	**0.0182***
DOR, 10 µg	8 (57.12)	6 (42.88)	4 (100)	0	4 (100)	0	7 (70)	3 (30)	3 (37.5)	5 (62.5)	**0.0009***
ERP, 10 µg	2 (14.28)	12 (85.72)	0	4 (100)	3 (75)	1 (25)	3 (30)	7 (70)	2 (25)	6 (75)	**0.0292***

Legend: N: Number of strains; %S: Percentage susceptible; %R: Percentage resistant; *: $p < 0.05$ (statistically significant difference); DOR: Doripenem; IMI: Imipenem; MRP: Meropenem; ERP: Ertapenem.

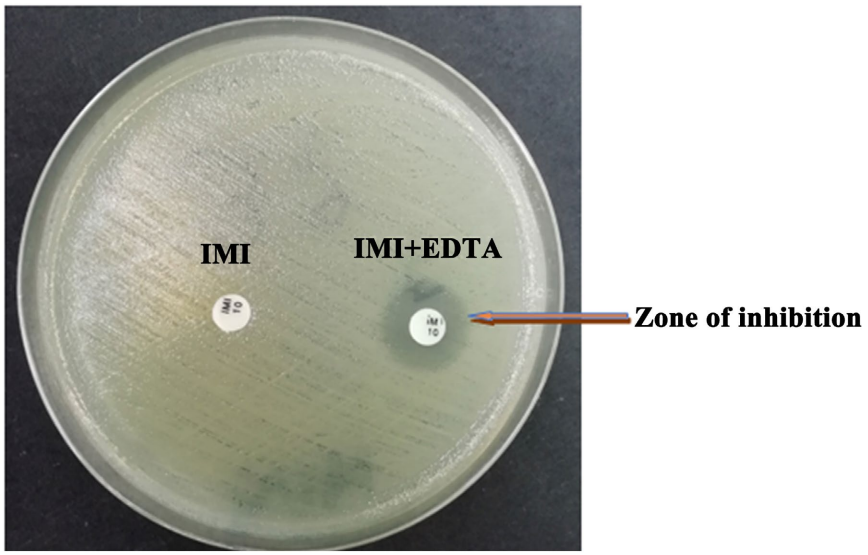

Figure 3. Combined imipenem/imipenem + EDTA disk test.

3.4. Results of Combined Carbapenem/Carbapenem + EDTA Disk Tests

The combined disk tests revealed Metallo-β-Lactamase (MBL) production among imipenem-resistant strains. All strains (100%) resistant to imipenem tested positive in the combined imipenem/imipenem + EDTA disk test (Figure 3). These MBL-producing strains also exhibited significant resistance to other antibiotics. Only *E. coli* and *Enterobacter aerogenes* produced MBLs in the presence of meropenem, with respective rates of 40% and 20% (Figure 4).

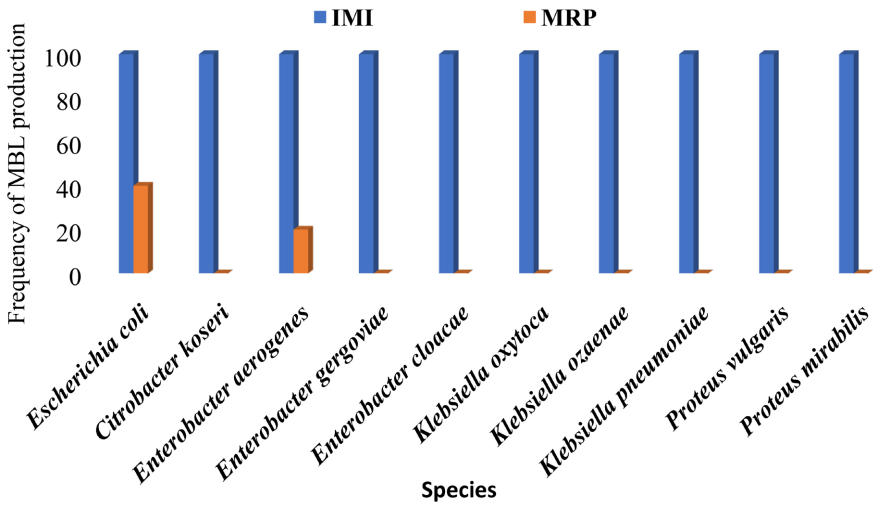

Figure 4. Distribution of MBL-producing strains.

4. Discussion

Antibiotic resistance among Enterobacteriaceae, particularly to carbapenems, represents a major public health challenge. This issue is critical both in industrialized countries and in developing countries, where self-medication and the uncontrolled sale of antibiotics outside legal frameworks are common. The main objective of this study was to describe the carbapenem resistance profile of Enterobacteriaceae strains isolated from urogenital tract infections at the National Public Health Laboratory. These strains were obtained from urine and vaginal swab samples. A total of 123 strains, distributed across five genera of Enterobacteriaceae, were isolated and identified. The distribution of the 123 strains according to sample type showed that urine was the specimen from which Enterobacteriaceae were most frequently isolated. These results are consistent with those obtained by Al-Mayahie *et al.* [23], who reported urine as the most common sample type in hospitals in Iraq. In contrast, our results are higher than those reported by Alsamarai and Ali [24] in Kirkuk, Iraq, where only 41.6% of urine samples were culture-positive. The predominance of Enterobacteriaceae in urine samples in our study may be explained by the larger sample size of urine specimens compared to vaginal swabs. Bacterial identification revealed 12 different species, with *E. coli* being the most predominant, accounting for 35% of isolates. This finding is comparable

to Moyen *et al.* [14], who reported a predominance of *E. coli* (36%) in studies of *β*-lactam resistance transmission among mothers and children in the Republic of Congo. Similarly, Goro [25] reported comparable results in Bamako. The predominance of *E. coli* in these samples can be explained by its role as a normal component of the intestinal microbiota. Although generally harmless, uropathogenic strains of *E. coli* can cause urinary and extra-intestinal infections, possessing virulence factors, including adhesins, that allow colonization of the urinary epithelium and resistance to clearance during bladder voiding [3].

The antibiotic susceptibility study revealed significant and variable resistance depending on the tested carbapenem. The highest resistance was observed for doripenem (66.67%), followed by imipenem (48.78%). Ertapenem was the most active molecule, with a resistance rate of 20.32%. These results are consistent with previous studies. For example, in Latin America, Costa *et al.* [26] reported 100% resistance to carbapenems (imipenem, meropenem, and ertapenem). Similar results were obtained in Tunisia by Ben *et al.* [27], who reported a resistance rate of 55.8% to imipenem.

However, our results differ from those of Moyen *et al.* [13], who studied *β*-lactam activity and *β*-lactamase production in bacteria isolated from wound infections in Brazzaville, Congo, where strains were more sensitive to imipenem (resistance rate 10.82%). Ya-Ting *et al.* [28] in Taiwan region reported resistance rates of 95.5%, 74.26%, 61.6%, and 96.2% for the four tested antibiotics. Makaya *et al.* [3] reported 68.8% resistance to imipenem in *E. coli* in Brazzaville. Rodríguez *et al.* [29] observed 100% resistance to imipenem and 98% resistance to meropenem and doripenem in Colombia. In our study, ertapenem was highly effective against all tested strains, contrasting with Ben *et al.* [27], who reported 100% resistance to ertapenem. Differences in resistance may be attributed to temporal evolution, geographic location, antibiotic selection pressure, consumption patterns, and genetic transfer mechanisms.

Overall, the studied strains exhibited simultaneous resistance to multiple carbapenems. *E. coli*, along with other species, showed resistance to three carbapenem disks. These results are consistent with Moyen *et al.* [14], who demonstrated *β*-lactam resistance transmission among Enterobacteriaceae between mothers and children in Brazzaville. In that study, *E. coli* and *K. oxytoca* showed 30% resistance to ertapenem, while *K. oxytoca* strains were fully susceptible to imipenem compared to 30% resistance in *E. coli*. The observed carbapenem resistance rates are concerning, as carbapenems constitute the last line of defense against bacterial infections. The predominance and broad-spectrum resistance of *E. coli* pose a serious public health threat, undermining the effectiveness of available antibiotics. This may result from selection pressure due to the excessive use of antibiotics in hospital and community settings, as well as plasmid-mediated horizontal transfer of resistance genes [30]. Similar observations were made by Habibou *et al.* [7] in Senegal, reporting a prevalence of 60.83%. All genera studied, *Enterobacter*, *Klebsiella*, *Proteus*, *E. coli*, and *Citrobacter*—showed resistance to

the tested carbapenems. Mellouli *et al.* [31] reported similar findings in Tunisia. Abera *et al.* [32] observed low resistance rates in *E. coli* and *K. pneumoniae* producing ESBLs.

Carbapenem resistance can result from the selection of resistant bacteria favored by frequent use of these antibiotics in empirical treatment of severe nosocomial infections [33]. Literature data indicate that mechanical ventilation and treatment with carbapenems, alone or in combination with vancomycin, are major risk factors for acquiring imipenem resistance [34]. Resistance mechanisms may include non-enzymatic processes such as loss of *OprD* porin, active efflux systems (*MexAB*), or production of carbapenemases of the *IMP* and *VIM* types [35].

To contextualize the results of our study on carbapenem resistance in our institution, it is relevant to compare them with the global data provided by the 2023 GLASS report of the World Health Organization (WHO). This report reveals that carbapenem resistance in *Escherichia coli* and *Klebsiella pneumoniae* remains high in many regions of the world, particularly in Asia, Africa, and Latin America [36]. This situation is mainly attributed to the spread of certain carbapenem resistance genes, such as *KPC* and *NDM*, as well as to person-to-person transmission within healthcare facilities [37]. Moreover, socio-economic factors, such as limited access to healthcare and the overuse of antibiotics, contribute to this alarming trend [36]. In our local context, these global data confirm that carbapenem resistance is a major public health issue, especially in developing countries. The results of our study, showing a high prevalence of carbapenem resistance in our institution, therefore fit within a worrisome global context. It is imperative to strengthen surveillance, prevention, and infection control strategies to effectively combat this emerging threat [37].

In this study, all imipenem-resistant strains produced Metallo-β-Lactamases (MBLs), representing a 100% rate. This is higher than the 78.25% reported in India by Debasrita *et al.* [38]. These results differ from those of Makaya *et al.* [3] in Brazzaville, where 16.66% of strains were MBL producers. Gba *et al.* [39] in Côte d'Ivoire reported 78.6% of imipenem-resistant *P. aeruginosa* producing MBLs. In this study, 40% of *E. coli* produced MBLs in the presence of meropenem, lower than the 86.61% reported by Nu *et al.* [40] in Pakistan. Genetic variability among strains may explain these differences. A recent study in Morocco (2019 - 2023) found that all carbapenem-resistant Enterobacteriaceae (n = 74) produced MBLs, with *bla_NDM* predominating (83.78%), often associated with *bla_OXA*-48 [41], similar to our findings. According to the international ATLAS program (2018 - 2020), nearly 50% of carbapenem-resistant Enterobacteriaceae in Africa and the Middle East carried MBLs [42]. A systematic review of 39 studies (2013 - May 2023) reported MBL-producing strain prevalence ranging from 6.8% to 100%, particularly high in Southern Europe and Asia [43]. Among MBL-producing strains, *E. coli* was the most prevalent, with 100% producing MBLs in the presence of imipenem, exceeding the 36.1% reported by Mudathir *et al.* [44] in Khartoum, Sudan. The

combined test for the detection of Metallo-β-Lactamases (MBLs) using meropenem was limited to *E. coli* and *Enterobacter aerogenes* because these species are the main Enterobacteriaceae in which MBL production represents a frequent and clinically relevant mechanism of carbapenem resistance. Moreover, the interpretation criteria and reliability of the meropenem + EDTA combined test have been better validated for these Enterobacteriaceae in the CASFM/EUCAST recommendations, unlike other species in which alternative mechanisms (porin loss, AmpC overproduction, or production of KPC or OXA-48) may also contribute to resistance [22].

This study presents certain limitations that should be acknowledged. First, its monocentric nature limits the generalization of the results to other healthcare facilities in Brazzaville and in other departments. Second, the short duration of the investigation does not allow conclusions to be drawn regarding the temporal dynamics of carbapenem resistance. Finally, the absence of molecular confirmation of the genes encoding Metallo-β-Lactamases (MBLs) prevents the precise identification of the enzyme types involved and the assessment of their genetic distribution among the isolates studied.

5. Conclusion

This study aimed to establish the carbapenem resistance profile of Enterobacteriaceae strains isolated from urogenital tract infections at the National Public Health Laboratory. A total of 123 strains were isolated from various biological samples, comprising five bacterial genera: *Escherichia*, *Klebsiella*, *Enterobacter*, *Citrobacter*, and *Proteus*, representing 10 species. *E. coli* was the most dominant species. The majority of strains were isolated from urine. The results show that the studied strains exhibited resistance to the tested carbapenems: 66.67% to doripenem, 48.78% to imipenem, 30.08% to meropenem, and 20.32% to ertapenem. Simultaneous resistance to imipenem, meropenem, and doripenem was observed. Significant differences in bacterial resistance among strains were noted for imipenem, meropenem, doripenem, and ertapenem. All imipenem-resistant strains produced MBLs, while only *E. coli* and *Enterobacter aerogenes* produced MBLs in the presence of meropenem. However, meropenem and ertapenem should be used as first-line agents for the treatment of infections caused by these bacterial genera.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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