An Investigation Into Carbapenem Resistance in Enterobacteriaceae Among Outpatients With Urinary Tract Infection in Southwestern Uganda

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Abstract

Background and aim

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, primarily caused by Enterobacteriaceae. The rise of carbapenem-resistant Enterobacteriaceae (CRE), complicates treatment of UTIs, yet the distribution of CRE and carbapenemase genes in Uganda's hospitals is not sufficiently explored. This study aimed to examine the distribution of carbapenemases genes in Enterobacteriaceae isolated from urinary tract infections in outpatients in southwestern Uganda.

Methods

A cross-sectional hospital-based study was conducted in southwestern Uganda. The study involved 111 participants who tested positive for carbapenemase genes. These participants were selected from a total of 2,371 patients presenting with urinary tract infections (UTIs) at Bwizibwera Health Center IV and Rubaya Health Center III. Enterobacteriaceae were identified using a series of biochemical tests, and the presence of carbapenemase resistance genes (blaVIM, blaOXA-48, blaNDM, blaKPC, and blaIMP) was confirmed through polymerase chain reaction (PCR) genotyping. Data were analyzed and presented as frequencies and proportions, displayed in tables and charts.

Results

We screened a total of 2,371 participants with symptoms of urinary tract infections (UTI) for Enterobacteriaceae, 455 (19.2%) tested positive for at least one of the Enterobacteriaceae species. Disk susceptibility testing (DST) for carbapenems (meropenem and ertapenem) revealed a phenotypic carbapenem resistance prevalence of 5.7% (26/455), while polymerase chain reaction (PCR) identified a genotypic prevalence of 24.4% (111/455). *Klebsiella spp.* was the most common carbapenemase gene carrier (60/111, 54.1%), with blaIMP being the most frequent gene detected (32.4%). PCR detected more carbapenemase-producing organisms compared to DST. Notably, 14.4% of the isolates harbored multiple carbapenem resistance genes, with one sample carrying four different genes.

Conclusion

Our study revealed a high genotypic prevalence of CRE, especially in *Klebsiella spp.* and *Escherichia spp.* isolates with a low phenotypic expression. This suggests that relying solely on DST could miss resistant strains, emphasizing the importance of molecular diagnostics like PCR for accurate detection. Carbapenemase inhibitors should be prescribed alongside carbapenem drugs where CREs are suspected, combined with continued surveillance to help manage CRE and reduce their spread in resource-limited settings.

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, primarily caused by Enterobacteriaceae. The rise of multidrug-resistant (MDR) pathogens, particularly carbapenem-resistant Enterobacteriaceae (CRE) including *Klebsiella*, *E. coli*, *Proteus spp.*, and *Serratia spp.* complicate the treatment of UTIs. CRE are recognized as a high-priority threat by the World Health Organization (WHO) due to their resistance, even to last-resort carbapenem antibiotics [1].

Carbapenem resistance largely results from carbapenemase enzymes, with genes like Verona imipenemase (blaVIM), imipenemase (blaIMP), oxacillinase-48 (blaOXA-48), New Delhi (blaNDM), and *Klebsiella*

pneumoniae carbapenemase (blaKPC) driving the resistance. These genes are often located on mobile genetic elements, facilitating the spread of resistance, notably in healthcare settings [2]. CRE infections extend beyond hospitals, with patients serving as reservoirs and transmitting resistant strains into communities. This is particularly concerning in low-resource settings like Uganda, where inadequate infrastructure and poor sanitation exacerbate the issue [3]. Limited data on CRE prevalence in Uganda's hospitals raises concerns about healthcare facilities as potential sources of resistance. Discharged patients may unknowingly spread CRE to others, highlighting the need for research into the genetic makeup of carbapenemase-producing Enterobacteriaceae from UTI patients.

In Uganda, the threat posed by antibiotic resistance is growing, exacerbated by factors such as the improper use of antibiotics in both human and veterinary medicine and a lack of robust antimicrobial resistance (AMR) monitoring systems [4]. Understanding the distribution of key resistance genes in southwestern Uganda can inform strategies to curb the spread of CRE. A One Health approach, considering human, animal, and environmental factors, is critical to tackling this growing threat [5].

Materials And Methods

A cross-sectional hospital-based study was conducted in southwestern Uganda, involving 111 participants who tested positive for Enterobacteriaceae harboring carbapenemase genes. These participants were selected from a total of 2,371 outpatients presenting with urinary tract infections (UTIs) at Bwizibwera Health Center IV and Rubaya Health Center III. Enterobacteriaceae isolated from urine samples were identified using a series of biochemical tests including oxidase, citrate utilization, indole, urease production, triple-sugar iron, and motility tests [6]. For susceptibility testing, we used the Kirby-Bauer diffusion method following the Clinical Laboratory Standards Institute (CSLI) guidelines 2019, as described previously [7].

The presence of carbapenemase resistance genes (blaVIM, blaOXA-48, blaNDM, blaKPC, and blaIMP) was confirmed through polymerase chain reaction (PCR) genotyping. To extract DNA, colonies were washed with 1X TE buffer twice. Then, 100 µL TE elution buffer was added to the pellet and vortexed for 1 min. The mixture was incubated at 95°C for 1 hour and 30 min using a heating dry bath and centrifuged at 15,000 rpm for 5 min. The supernatant containing the DNA was transferred to a new ultracentrifuge tube, and the DNA was stored at -20°C until usage within 4 hours [8].

We purchased the PCR kit for gene amplification from New England Biolabs Inc. (M0258L Deep Vent DNA Polymerase, ThermoPol reaction buffer, and magnesium sulfate ($MgSO_4$) solution. Each of the open reading frames of specific targets was amplified separately for each sample using forward and reverse primers each with a unique sequence as follows: blaKPC forward primer - TCGTCGCGGAACCATTC, reverse primer - ACAGTGGGAAGCGCTCCTC; blaIMP forward primer - CATGGTTTGGTGGTTCTTGT, reverse primer - ATAATTTGGCGGACTTTGGC; blaVIM forward primer - GATGGTGTTTGGTCGCATA, reverse primer - CGAATGCGCAGCACCAG; blaOXA-48 forward primer - GATTTGCTCCGTGGCCGAAA, reverse primer - CCTTGATCGCCCTCGATT; blaNDM forward primer - CCAATATTATGCACCCGGTCG, reverse primer - ATGCGGGCCGTATGAGTGATTG.

Initial denaturation was at 95°C for 30 s, followed by elongation at 72°C for 1 min, and a final extension at 72°C for 5 min. DNA amplicon was electrophoresed using 1.5% agarose gel, in 1x Tris-Borate EDTA buffer (TBE), 5 µL DSView Nucleic acid stain (cat. no.: M7011), 6X loading buffer (GDSBio Lot 050), and DNA ladder/marker 100 bp (GDSBio Lot 076). Electrophoresis was run at 200V and 80 mA for 1 hour. Bands were visualized using the gene-flash transilluminator. Data were analyzed and presented as frequencies and proportions, displayed in tables and charts. We used KPC-positive control *K. pneumoniae* ATCC BAA-1705, NDM-positive control *K. pneumoniae* ATCC BAA-2146, and a multidrug-resistant strain of *E. coli* harboring multiple carbapenemase genes (blaIMP, blaVIM and blaOXA-48). Distilled water was used as a negative control.

Results

Study profile

A total of 2,371 participants with symptoms of urinary tract infections (UTI) were screened for Enterobacteriaceae, and 455 participants had at least one of the causative organisms identified as Enterobacteriaceae. The identified Enterobacteriaceae were subjected to disk susceptibility testing (DST) using the Kirby-Bauer diffusion method for carbapenem (meropenem and ertapenem) sensitivity and polymerase chain reaction (PCR) for the presence of the carbapenemase genes (Figure *1*).
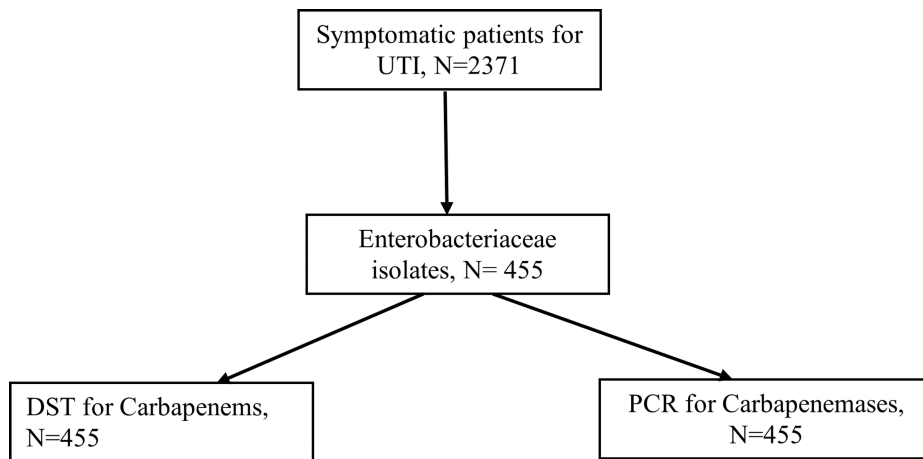
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FIGURE 1: Study flowchart: UTI participants with Enterobacteriaceae.

DST: disk susceptibility test; PCR: polymerase chain reaction; UTI: urinary tract infection

Characteristics and overview of the resistance patterns to carbapenems among study participants

Out of the screened 2,371 participants, 455 (19.2%) were positive for Enterobacteriaceae, with the majority of the organisms being *Escherichia* and *Klebsiella spp.* (Figure 2). The DST-based phenotypic prevalence of carbapenem resistance was 26/455 (5.7%, 95% CI: 3.8-8.3).
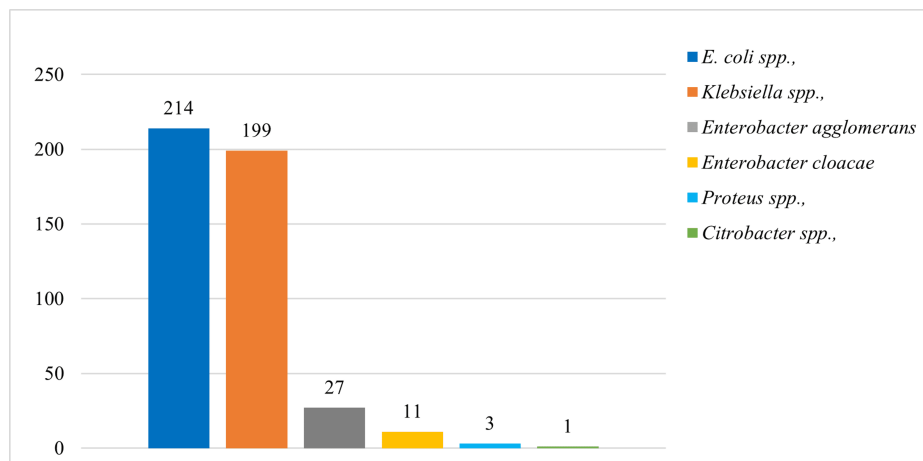

FIGURE 2: A bar chart showing the Enterobacteriaceae isolated from the study participants.

Escherichia and *Klebsiella spp.* were the predominant organisms.

The genotypic prevalence with PCR was 111/455 (24.4%, 95% CI: 20.5-28.6), with more than half of the organisms harboring a carbapenemase gene being *Klebsiella spp.* (60/111, 54.1%) (Figure 3). PCR method identified more carbapenemase-encoding genes harboring organisms than the DST method with the majority of the genes identified in *Klebsiella* and *Escherichia spp.* (Table 1).
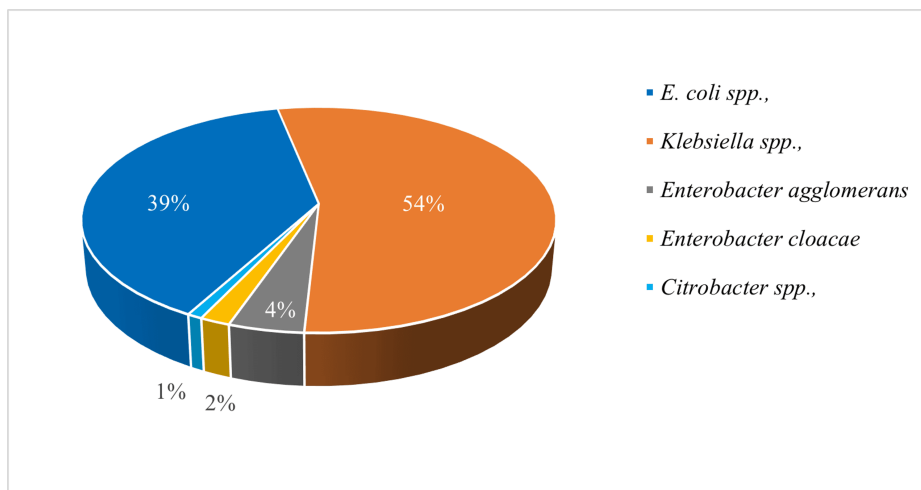
FIGURE 3: Distribution of carbapenemase genes in Enterobacteriaceae.

Klebsiella spp. had the highest number of organisms that harbored carbapenemase genes as identified by PCR method.

PCR: polymerase chain reaction

Organism isolated	Resistance pattern	
	DST-based	PCR-based
Escherichia coli spp.	7	43
Klebsiella spp.	17	60
Enterobacter cloacae	1	2
Enterobacter agglomerans	1	5
Citrobacter spp.	0	1
Proteus spp.	0	0

TABLE 1: DST- and PCR-based carbapenem resistance

DST: disk susceptibility testing; PCR: polymerase chain reaction

In general, the carbapenemase genes were disproportionately distributed among the different isolates. blaIMP was the most prevalent carbapenemase-encoding gene (36/111, 32.4%), while blaVIM and blaOXA-48 had similar distribution (23/111, 20.7%) (Table 2).

Species	Carbapenemase-encoding genes				
	blaIMP	blaNDM	blaKPC	blaVIM	blaOXA-48
Escherichia coli spp.	17	6	12	5	9
Klebsiella spp.	15	17	12	17	10
Enterobacter cloacae	1	0	0	0	1
Enterobacter agglomerans	3	2	0	0	2
Citrobacter spp.	0	0	0	0	1
Proteus spp.	0	0	0	0	0
Total	36	25	24	23	23

TABLE 2: The distribution of carbapenemase encoding genes in the study isolates.

In addition, *Proteus spp.* showed neither phenotypic expression nor harbored any resistant gene (Tables *1*, *2*). The proportion of isolates that harbored more than one resistance gene was 16/111 (14.4%), with blaNDM being the most shared carbapenemase gene. Multiple genes were only carried in *Klebsiella spp.*, *Escherichia coli spp.*, and *Enterobacter agglomerans*. Interestingly, one *Klebsiella spp.* harbored four out of the five studied genes (Table *3*).

Species	Number of isolates	Genes per isolate	bla genes
Klebsiella spp.	1	4	VIM, NDM, IMP, and KPC
Klebsiella spp.	1	3	VIM, NDM, and IMP
Escherichia coli spp.	1	3	VIM, NDM, and KPC
Escherichia coli spp.	1	2	KPC and NDM
Escherichia coli spp.	1	2	VIM and NDM
Klebsiella spp.	3	2	VIM and NDM
Klebsiella spp.	1	2	NDM and XA-48
Enterobacter agglomerans	1	2	NDM and OXA-48
Escherichia coli spp.	2	2	IMP and KPC
Escherichia coli spp.	1	2	IMP and OXA-48
Escherichia coli spp.	1	2	NDM and IMP
Klebsiella spp.	2	2	NDM and IMP
Escherichia coli spp.	36	1	IMP or VIM or NDM or KPC or OXA-48
Klebsiella spp.	52	1	IMP or VIM or NDM or KPC or OXA-48
Enterobacter agglomerans	5	1	IMP or NDM or OXA-48
Enterobacter cloacae	2	1	IMP or OXA-48
Citrobacter spp.	1	1	OXA-48
Proteus spp.	3	0	None

TABLE 3: Bacterial isolates positive for carbapenemase genes and number of genes per organism.

Discussion

Out of the total 2,371 participants screened, 455 (19.1%) tested positive for Enterobacteriaceae, with the majority being Escherichia and Klebsiella species. Carbapenem resistance was phenotypically detected in 5.7% of the isolates using the disk susceptibility test (DST), while genotypic analysis using PCR identified carbapenemase genes in 24.4% of the isolates. This discrepancy highlights the higher sensitivity of molecular techniques in detecting carbapenem resistance, as many CREs may not show phenotypic resistance despite harboring resistance genes. Among the carbapenemase genes identified, blaIMP was the most prevalent (32.4%).

Our study revealed *Escherichia* and *Klebsiella spp.* to be the most predominant organisms responsible for causing UTIs. These Enterobacteriaceae have been reported to cause UTIs in outpatient visits with 72.8% of infections caused by *E. coli* in the 338 US health facilities [9] and 87.6% of the UTIs were due to Enterobacteriaceae in the Chicago Emergency Department [10]. In addition, in a review of causative organisms of UTI in Spain, Mancuso et al. reported up to 85% of the UTI being caused by Enterobacteriaceae [11]. An earlier study in Uganda reported more than half (59.2%) of UTIs were due to *Klebsiella* and *E. coli spp.* [12]. These organisms have the ability to form biofilms which enable them to adhere to the urogenital mucous membrane [13,14]. Similar to our current study, *Citrobacter* and *Enterobacter spp.* have been reported in a few studies to be uropathogenic [10,15].

A number of studies have continued to report an increased production of carbapenemases hydrolyzing β-lactam antibiotics, including carbapenems, worldwide [2,16,17]. Our study has revealed a phenotypic and genotypic prevalence of carbapenemase resistance of 5.7% and 22.4%, respectively, among uropathogenic Enterobacteriaceae. Our prevalence is comparable to a study conducted earlier in Uganda, which reported a prevalence of 4.92% in hospital isolates [18]. In addition, Tuhamize et al. reported a comparable prevalence of 5% in human community isolates [7]. The similarity in the findings could be due to the fact that the studies are conducted in similar settings and use similar methods to determine the resistance patterns (DST). Another study carried out in Uganda had a contrasting DST-based prevalence of 18.4% [19]. The difference in the study findings could be because many organisms were studied, isolated from several samples, and used automated methods with better sensitivities to study phenotypic expression. In our study, only urine samples were analyzed using the Kirby-Bauer disk diffusion method with lesser sensitivity.

Lower prevalence has been reported in China (1.0%) [20], Germany (0.3%) [21], and a surveillance study in Spain (0.04%) in hospital isolates with larger sample sizes [22]. In the above countries, there are restrictions on the use of antibiotics by only licensed individuals, contrary to the liberal nature of acquiring drugs from pharmacies over the counter even without a prescription in Uganda [23]. The differences in prescription habits could be responsible for the lower resistance prevalences in China, Spain, and Germany.

Our study revealed that blaIMP was the most prevalent (32.4%) carbapenemase-encoding gene in the studied Enterobacteriaceae. These findings are comparable to an earlier study in neighboring Tanzania, where resistant Gram-negative clinical isolates harbored blaIMP as the prevalent carbapenemase-encoding gene [24]. In contrast, an earlier study of clinical isolates in southwestern Uganda, where our study was carried out, reported no blaIMP in the isolates [18]. Our study findings highlight an emerging gene pool of carbapenemase genes to include blaIMP, likely from neighboring countries or societies. However, the prevalence of blaIMP reported by Mushi et al. was higher than in our study, an observation that could be due to the fact they studied various sample isolates and many Gram negatives other than Enterobacteriaceae, while our study only analyzed urine samples with a focus on Enterobacteriaceae [24].

blaVIM has been reported to possess the broadest range of substrate hydrolysis when compared with other carbapenemase genes, with the capability to degrade nearly all β-lactams except monobactams [25]. It is worrisome that in our study, the prevalence of blaVIM was high at 20.7% when compared to previous studies in the region, which reported rates of 19.6% and 12.3%, posing a threat to the use of carbapenems as one of the last-resort antibiotic treatments [18,24]. Surprisingly, a recent study in China reported no blaVIM among the CRE strains isolated from adult and pediatric patients, suggesting a possible differential distribution of carbapenemase-encoding genes [26].

Furthermore, the current study detected blaNDM as highly prevalent (22.5%) among study strains. This is a bothersome statistic given that the NDM-1 encoding gene is documented to be found on different large and easily transmissible plasmids at a high frequency to competent bacteria. These plasmids are thought to confer resistance to several antibiotics [2,27]. Moreover, our study revealed blaNDM as the most prevalent carbapenemase-encoding gene in organisms that harbored multiple genes. In addition, the blaNDM reported in earlier related studies was lower, indicating an increase in the NDM gene pool in the CREs [19,24,28]. Notably, 14.4% of the isolates harbored multiple carbapenem resistance genes, with one isolate containing four genes. The presence of multiple carbapenemase genes within a single organism is concerning, as it may contribute to the heightened resistance of these strains to carbapenems and complicate the use of carbapenems for the treatment of bacterial infections.

Routine implementation of molecular diagnostic tools, such as PCR, should be prioritized in healthcare settings for the detection of carbapenemase genes. Clinicians should consider the use of carbapenemase

inhibitors, such as avibactam, alongside carbapenem antibiotics when carbapenemase genes are detected, even in instances where phenotypic resistance is absent, as an approach to hamper the development of resistance [29].

Conclusions

Our study revealed a high prevalence of carbapenemase genes among Enterobacteriaceae isolated from outpatients with UTIs. *Klebsiella spp.* and *Escherichia spp.* were the most predominant organisms, and blaIMP was the most identified carbapenemase gene. The study also revealed the presence of multiple carbapenem resistance genes in the organisms studied. The blaNDM was the most prevalent carbapenemase-encoding gene in organisms that harbored multiple genes. The routine use of molecular techniques to identify carbapenem-resistant Enterobacteriaceae (CRE) and the co-prescription of carbapenems with a carbapenemase inhibitor require careful consideration.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Barbra Tuhamize, Joel Bazira, Deusdedit Tusubira, Charles Masembe, Pascal Bessong

Acquisition, analysis, or interpretation of data: Barbra Tuhamize

Drafting of the manuscript: Barbra Tuhamize, Joel Bazira

Critical review of the manuscript for important intellectual content: Barbra Tuhamize, Joel Bazira, Deusdedit Tusubira, Charles Masembe, Pascal Bessong

Supervision: Joel Bazira

Disclosures

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References

1. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. (2017). Accessed: September 30, 2024: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12.
2. Nordmann P, Naas T, Poirel L: Global spread of carbapenemase-producing Enterobacteriaceae . Emerg Infect Dis. 2011, 17:1791-8. 10.3201/eid1710.110655
3. Gorrie CL, Mirceta M, Wick RR, et al.: Gastrointestinal carriage is a major reservoir of Klebsiella pneumoniae infection in intensive care patients. Clin Infect Dis. 2017, 65:208-15. 10.1093/cid/cix270
4. Byarugaba DK: A view on antimicrobial resistance in developing countries and responsible risk factors . Int J Antimicrob Agents. 2004, 24:105-10. 10.1016/j.ijantimicag.2004.02.015
5. Robinson TP, Bu DP, Carrique-Mas J, et al.: Antibiotic resistance is the quintessential One Health issue . Trans R Soc Trop Med Hyg. 2016, 110:377-80. 10.1093/trstmh/trw048
6. Zakrzewski AJ, Zarzecka U, Chajęcka-Wierzchowska W, Zadernowska A: A comparison of methods for identifying enterobacterales isolates from fish and prawns. Pathogens. 2022, 11:10.3390/pathogens11040410
7. Tuhamize B, Asiimwe BB, Kasaza K, Sabiiti W, Holden M, Bazira J: Klebsiella pneumoniae carbapenamases in Escherichia coli isolated from humans and livestock in rural south-western Uganda. PLoS One. 2023, 18:10.1371/journal.pone.0288243
8. Dilhari A, Sampath A, Gunasekara C, et al.: Correction to: evaluation of the impact of six different DNA

extraction methods for the representation of the microbial community associated with human chronic wound infections using a gel-based DNA profiling method. AMB Express. 2020, 10: 10.1186/s13568-020-01145-w

9. Dunne MW, Aronin SI, Yu KC, Watts JA, Gupta V: A multicenter analysis of trends in resistance in urinary Enterobacterales isolates from ambulatory patients in the United States: 2011-2020. BMC Infect Dis. 2022, 22:10.1186/s12879-022-07167-y

10. Khawcharoenporn T, Vasoo S, Singh K: Urinary tract infections due to multidrug-resistant Enterobacteriaceae: prevalence and risk factors in a Chicago emergency department. Emerg Med Int. 2013, 2013:10.1155/2013/258517

11. Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo C: Urinary tract infections: the current scenario and future prospects. Pathogens. 2023, 12:10.3390/pathogens12040623

12. Odoki M, Aliero AA, Tibyangye J, et al.: Fluoroquinolone resistant bacterial isolates from the urinary tract among patients attending hospitals in Bushenyi district, Uganda. Pan Afr Med J. 2020, 36:10.11604/pamj.2020.36.60.18832

13. Miyazaki J, Ba-Thein W, Kumao T, Obata Yasuoka M, Akaza H, Hayshi H: Type 1, P and S fimbriae, and afimbrial adhesin I are not essential for uropathogenic Escherichia coli to adhere to and invade bladder epithelial cells. FEMS Immunol Med Microbiol. 2002, 33:23-6. 10.1111/j.1574-695X.2002.tb00567.x

14. Schroll C, Barken KB, Krogfelt KA, Struve C: Role of type 1 and type 3 fimbriae in Klebsiella pneumoniae biofilm formation. BMC Microbiol. 2010, 10:10.1186/1471-2180-10-179

15. Ranjan KP, Ranjan N: Citrobacter: an emerging health care associated urinary pathogen . Urol Ann. 2013, 5:313-4.

16. Touati A, Mairi A: Carbapenemase-producing Enterobacterales in Algeria: a systematic review . Microb Drug Resist. 2020, 26:475-82. 10.1089/mdr.2019.0320

17. Kim SH, Kim GR, Jeong J, Kim S, Shin JH: Prevalence and characteristics of carbapenemase-producing Enterobacteriaceae in three tertiary-care Korean university hospitals between 2017 and 2018. Jpn J Infect Dis. 2020, 73:431-6. 10.7883/yoken.JJID.2020.043

18. Ampaire LM, Katawera V, Nyehangane D, Boum Y, Bazira J: Epidemiology of carbapenem resistance among multi-drug resistant Enterobacteriaceae in Uganda. Br Microbiol Res J. 2015, 8:418-23. 10.9734/BMRJ/2015/17055

19. Okoche D, Asiimwe BB, Katabazi FA, Kato L, Najjuka CF: Prevalence and characterization of carbapenem-resistant Enterobacteriaceae isolated from Mulago National Referral Hospital, Uganda. PLoS One. 2015, 10:10.1371/journal.pone.0135745

20. Hu L, Zhong Q, Shang Y, et al.: The prevalence of carbapenemase genes and plasmid-mediated quinolone resistance determinants in carbapenem-resistant Enterobacteriaceae from five teaching hospitals in Central China. Epidemiol Infect. 2014, 142:1972-7. 10.1017/S0950268813002975

21. Ehrhard I, Karaalp AK, Hackel T, et al.: Prevalence of carbapenemase-producing bacteria in hospitals in Saxony, Germany. [Article in German]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2014, 57:406-13. 10.1007/s00103-013-1914-z

22. Miró E, Agüero J, Larrosa MN, et al.: Prevalence and molecular epidemiology of acquired AmpC β-lactamases and carbapenemases in Enterobacteriaceae isolates from 35 hospitals in Spain. Eur J Clin Microbiol Infect Dis. 2013, 32:253-9. 10.1007/s10096-012-1737-0

23. Mukonzo JK, Namuwenge PM, Okure G, Mwesige B, Namusisi OK, Mukanga D: Over-the-counter suboptimal dispensing of antibiotics in Uganda. J Multidiscip Healthc. 2013, 6:303-10. 10.2147/JMDH.S49075

24. Mushi MF, Mshana SE, Imirzalioglu C, Bwanga F: Carbapenemase genes among multidrug resistant Gram-negative clinical isolates from a tertiary hospital in Mwanza, Tanzania. Biomed Res Int. 2014, 2014:10.1155/2014/303104

25. Docquier JD, Lamotte-Brasseur J, Galleni M, Amicosante G, Frère JM, Rossolini GM: On functional and structural heterogeneity of VIM-type metallo-beta-lactamases. J Antimicrob Chemother. 2003, 51:257-66. 10.1093/jac/dkg067

26. Han R, Shi Q, Wu S, et al.: Dissemination of carbapenemases (KPC, NDM, OXA-48, IMP, and VIM) among carbapenem-resistant Enterobacteriaceae isolated from adult and children patients in China. Front Cell Infect Microbiol. 2020, 10:10.3389/fcimb.2020.00314

27. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR: Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother. 2009, 53:5046-54. 10.1128/AAC.00774-09

28. Poirel L, Revathi G, Bernabeu S, Nordmann P: Detection of NDM-1-producing Klebsiella pneumoniae in Kenya. Antimicrob Agents Chemother. 2011, 55:934-6. 10.1128/AAC.01247-10

29. Cano Á, Guzmán-Puche J, García-Gutiérrez M, et al.: Use of carbapenems in the combined treatment of emerging ceftazidime/avibactam-resistant and carbapenem-susceptible KPC-producing Klebsiella pneumoniae infections: report of a case and review of the literature. J Glob Antimicrob Resist. 2020, 22:9-12. 10.1016/j.jgar.2019.11.007