Otaigbe et al. *Afr. J. Clin. Exper. Microbiol.* 2023; 24 (3): 299 - 304 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Jul 2023; Vol.24 No.3
AJCEM/2279. https://www.ajol.info/index.php/ajcem

Copyright AJCEM 2023: https://dx.doi.org/10.4314/ajcem.v24i3.10

Short Communication Open Access

Antibiotic susceptibility profiles of Gram-negative bacterial uropathogens in a tertiary hospital, southwest Nigeria

*[1,2]Otaigbe, I. I., [3]Ebeigbe, E., [2]Okunbor, H. N., [1,2]Oluwole, T. O., and [1,2]Elikwu, C. J.

[1]Department of Medical Microbiology, School of Basic Clinical Sciences, Benjamin Carson (Snr) College of Health and Medical Sciences, Babcock University, Ilishan Remo, Ogun State, Nigeria
[2]Department of Medical Microbiology, Babcock University Teaching Hospital, Ilishan Remo, Ogun State, Nigeria
[3]Department of Medical Microbiology, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria
*Correspondence to: otaigbei@babcock.edu.ng; +2348024406763; ORCID ID: 0000-0003-3140-1205

Abstract:

Background: Increasing rates of antibiotic resistance have made it necessary to regularly monitor antibiotic susceptibility patterns of gram negative bacterial uropathogens in order to optimize antibiotic therapy for urinary tract infections. The aim of this study was to analyze the antibiotic susceptibility patterns of Gram-negative bacterial uropathogens in Babcock University Teaching Hospital, Ilishan-Remo, southwest Nigeria.
Methodology: This study was a retrospective review of the Medical Microbiology Laboratory records of the hospital to analyze the *in vitro* antibiotic susceptibility patterns of Gram-negative urinary bacterial isolates between May 2016 and April 2022. The bacteria were isolated and identified from routine urine samples using standard bacteriological methods. *In vitro* antibiotic susceptibility test (AST) to amoxicillin-clavulanate, piperacillin-tazobactam, ceftriaxone, ceftazidime, nitrofurantoin, ciprofloxacin and meropenem was routinely performed by the modified Kirby-Bauer disk diffusion test and susceptibility break points determined using the Clinical and Laboratory Standards Institute (CLSI) guidelines.
Results: A total number of 3,549 urine samples were processed during the period of review, and 808 (22.8%) samples yielded positive bacterial cultures. Of the 808 isolates, 604 (74.8%) were Gram-negative bacteria. The most frequently isolated Gram-negative bacteria were *Escherichia coli* (41.9 %) and *Klebsiella* spp (27.5%) while *Pseudomonas* spp and *Proteus* spp accounted for 4.3% and 1.0% of all isolates respectively. Meropenem had the highest *in vitro* antibacterial activity (74.3% to 90.3% of isolates were sensitive) for all isolates. Overall, *E. coli, Klebsiella* spp., and *Proteus* spp. showed high resistance rates to amoxicillin-clavulanate (65.3% to 97.1%).
Conclusion: Effective antimicrobial stewardship programs must be in place in order to ensure the appropriate use of antibiotics for treating urinary tract infections.

Keywords: urinary tract infections; uropathogens; antibiotic resistance; *Escherichia coli*

Received Jun 21, 2023; Revised Jul 2, 2023; Accepted Jul 3, 2023

Profils de sensibilité aux antibiotiques des uropathogènes bactériens à Gram négatif dans un hôpital tertiaire du sud-ouest du Nigeria

*[1,2]Otaigbe, I. I., [3]Ebeigbe, E., [2]Okunbor, H. N., [1,2]Oluwole, T. O., et [1,2]Elikwu, C. J.

[1]Département de Microbiologie Médicale, École des Sciences Cliniques Fondamentales, Benjamin Carson (Snr) Collège des Sciences de la Santé et de la Médecine, Université Babcock, Ilishan Remo, État d'Ogun, Nigéria
[2]Département de Microbiologie Médicale, Hôpital Universitaire de Babcock, Ilishan Remo, État d'Ogun, Nigéria
[3]Département de Microbiologie Médicale, Hôpital Universitaire de l'Université du Bénin, Benin City, État d'Edo, Nigéria
*Correspondance à: otaigbei@babcock.edu.ng; +2348024406763; ID ORCID: 0000-0003-3140-1205

Résumé:

Contexte: L'augmentation des taux de résistance aux antibiotiques a rendu nécessaire la surveillance régulière des schémas de sensibilité aux antibiotiques des uropathogènes bactériens à Gram négatif afin d'optimiser l'antibiothérapie des infections des voies urinaires. Le but de cette étude était d'analyser les profils de sensibilité aux antibiotiques des uropathogènes bactériens à Gram négatif à l'hôpital universitaire de Babcock, à Ilishan-Remo, dans le sud-ouest du Nigeria.
Méthodologie: Cette étude était un examen rétrospectif des dossiers du laboratoire de microbiologie médicale de l'hôpital pour analyser les schémas de sensibilité aux antibiotiques in vitro des isolats de bactéries urinaires à Gram négatif entre mai 2016 et avril 2022. Les bactéries ont été isolées et identifiées à partir d'échantillons d'urine de routine à l'aide de méthodes bactériologiques classiques. Un test de sensibilité antibiotique in vitro (AST) à l'amoxicilline-acide clavulanique, à la pipéracilline-tazobactam, à la ceftriaxone, à la ceftazidime, à la nitrofurantoïne, à la ciprofloxacine et au méropénème a été systématiquement effectué par le test de diffusion sur disque de Kirby-Bauer modifié et les seuils de sensibilité ont été déterminés en utilisant les directives de l'Institut des Normes Cliniques et de Laboratoire (CLSI).
Résultats: Au total, 3,549 échantillons d'urine ont été traités au cours de la période d'examen, et 808 échantillons (22,8%) ont produit des cultures bactériennes positives. Sur les 808 isolats, 604 (74,8%) étaient des bactéries Gram-négatives. Les bactéries Gram-négatives les plus fréquemment isolées étaient *Escherichia coli* (41,9%) et *Klebsiella* spp (27,5%) tandis que *Pseudomonas* spp et *Proteus* spp représentaient respectivement 4,3% et 1,0% de tous les isolats. Le méropénem avait l'activité antibactérienne *in vitro* la plus élevée (74,3% à 90,3% des isolats étaient sensibles) pour tous les isolats. Dans l'ensemble, *E. coli*, *Klebsiella* spp et *Proteus* spp ont montré des taux de résistance élevés à l'amoxicilline-acide clavulanique (65,3% à 97,1%).
Conclusion: Des programmes efficaces de gestion des antimicrobiens doivent être en place afin d'assurer l'utilisation appropriée des antibiotiques pour le traitement des infections des voies urinaires.

Mots clés: infections des voies urinaires; uropathogènes; résistance aux antibiotiques; *Escherichia coli*

Introduction:

Urinary tract infections (UTIs) are common infections in both the community and hospital setting (1). In 1997, UTIs accounted for about 7 million visits to outpatient clinics, 1 million visits to emergency departments, and 100,000 hospitalizations annually in the United States of America (2). About 35% of healthcare associated infections are UTIs and UTIs are the second most common cause of bacteremia in hospitalized patients (3,4). UTIs also exert adverse economic impacts on patients (5), for example, the annual cost to the health care system of the United States attributable to community-acquired UTI alone is estimated to be approximately $1.6 billion (6).

Majority of UTIs are caused by bacteria (7). Amongst bacteria Gram-negative bacteria are the most prevalent uropathogens (7), and, of these, *Escherichia coli* accounts for 70% to 90% of cases (8). Also, the management of UTIs, particularly uncomplicated UTIs, has involved the use of antibiotics such as amoxicillin-clavulanate, nitrofurantoin, cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole and others. (9). However, increasing rates of antibiotic resistance are making many of these antibiotics ineffective resulting in considerable morbidity, mortality and increased healthcare costs (10). In addition, the rates of antibiotic resistance are higher in low-and-middle-income countries (LMICs) with high levels of inappropriate antibiotic use (11).

Studies conducted in Nigeria have shown high rates of antibiotic resistance among Gram-negative uropathogens (12,13) and this is associated with higher morbidity and mortality (14). The problem posed by antibiotic resistance is further worsened by the paucity of research and development in new antibiotics and lack of access to effective antibiotics in Africa and other developing parts of the world (15).

It is therefore imperative to ensure regular institutional and national surveillance of antibiotic susceptibility patterns of common bacterial uropathogens, to improve clinical decision making and optimize antibiotic use (16). The objective of this study therefore was to analyze the bacterial and antibiotic susceptibility profiles of Gram-negative bacterial uropathogens in Babcock University Teaching Hospital, with the aim of providing data that will guide empiric antibiotic therapy of UTIs in the hospital.

Materials and method:

Study setting:

The study was conducted in the department of medical microbiology and parasitology, Babcock University Teaching Hospital, a 240-bed tertiary centre located in Ilishan-Remo, Ikenne Local Government, southwest Nigeria. The hospital is dedicated to teaching, research and specialist services and serves Ogun State and neighboring States in southwest Nigeria.

Study design:

This was a retrospective study that involved a review of the medical microbiology laboratory records to analyze the antimicrobial susceptibility profiles of Gram-negative bacterial urinary isolates obtained between May, 2016 and April, 2022.

Isolation and antibiotic susceptibility pattern of bacterial isolates:

Routine processing of urinary samples in the laboratory during the period of the review involved macroscopic and microscopic examination. Subsequently urinary samples were inoculated into Cystine Lactose Electrolyte Deficient (CLED) and Blood agar plates and incubated aerobically at 35-37°C for 18-24 hours.

Isolates were identified by conventional biochemical tests and antimicrobial susceptibility testing (AST) was performed using the modified Kirby-Bauer disk diffusion method. The susceptibility break points were determined using the Clinical and Laboratory Standards Institute (CLSI) guidelines (17).

Data analysis

Data analysis was done using IBM SPSS software version 20.0 Descriptive statistics were used to analyze isolates based on frequency and AST patterns.

Ethical considerations:

Ethical approval for the study was obtained from Babcock University Health Research and Ethics Committee (Number: BUHREC 679/21). As data were retrospectively obtained from the laboratory records and did not involve contact with patients nor recruitment of patients, informed consent was not deemed necessary. However, privacy and confidentiality of patients' data were protected in accordance with the Declaration of Helsinki.

Results:

In the 6-year period under consideration, a total number of 3,549 urine samples were processed in the medical microbiology laboratory and 808 (22.8%) samples yielded positive cultures. Of the 808 isolates, 604 (74.8%) were Gram-negative bacteria (Table 1). The most frequently isolated Gram-negative bacteria were *Escherichia coli* (56.1 %) and *Klebsiella* spp (36.8%) while *Pseudomonas* spp and *Proteus* spp accounted for 5.8% and 1.3% of isolates respectively (Fig 1).

Most (90.3%) of the *E. coli* isolates were sensitive to meropenem (Table 2). In addition, *E. coli* isolates also showed sensitivity of 61.1% and 58.4% to ciprofloxacin and nitrofurantoin respectively (Table 2). The *E. coli* isolates however exhibited resistance to amoxicillin-clavulanate (69.6%), ceftriaxone (49.9%), piperacillin-tazobactam (46.9%), ceftazidime (44.5%) and ciprofloxacin (31. 6%) (Table 2).

Furthermore, the *Klebsiella* isolates exhibited sensitivity of 82.9% to meropenem but resistance to amoxicillin-clavulanate (65.3%), piperacillin-tazobactam (55.0%), ciprofloxacin (41.9%), ceftazidime (40.5%) and nitrofurantoin (40.5%) (Table 2). However, *Pseudomonas spp* showed sensitivity of 74.3% and 57.1% to meropenem and piperacillin-tazobactam respectively but showed resistance to piperacillin-tazobactam (42.9%), ciprofloxacin (42.9%) and ceftazidime (40%), (Table 2). Also, *Proteus* spp exhibited resistance to ceftriaxone (87.5%), amoxicillin-clavulanate (75.0%) and ceftazidime (62.5%) but sensitivity of 87.5% to meropenem and 50.0% to ciprofloxacin (Table 2).

Table 1: Frequency of bacteria uropathogens in Babcock University Teaching Hospital, Ilishan Remo, Nigeria

Microbial isolate	Frequency	Percentage
Gram negative		
Escherichia coli	339	41.9
Klebsiella spp	222	27.5
Pseudomonas spp	35	4.3
Proteus spp	8	1.0
Gram positive	124	15.3
Fungi (*Candida* spp)	80	10.0
Total	808	100

Discussion:

Gram-negative isolates were the most frequently (74.8%) isolated bacteria in this retrospective study. These findings are similar to previous studies done in India (18) in which Gram-negative isolates accounted for 90.32% of isolates. The most frequently isolated Gram-negative isolate was *E. coli* (56.1%). Again, this finding is similar to other studies done in Bangladesh (19), Chad (20), Ethiopia (21) and India (22) in which *E. coli* was the most frequently isolated Gram-negative bacteria from urinary tract infections.

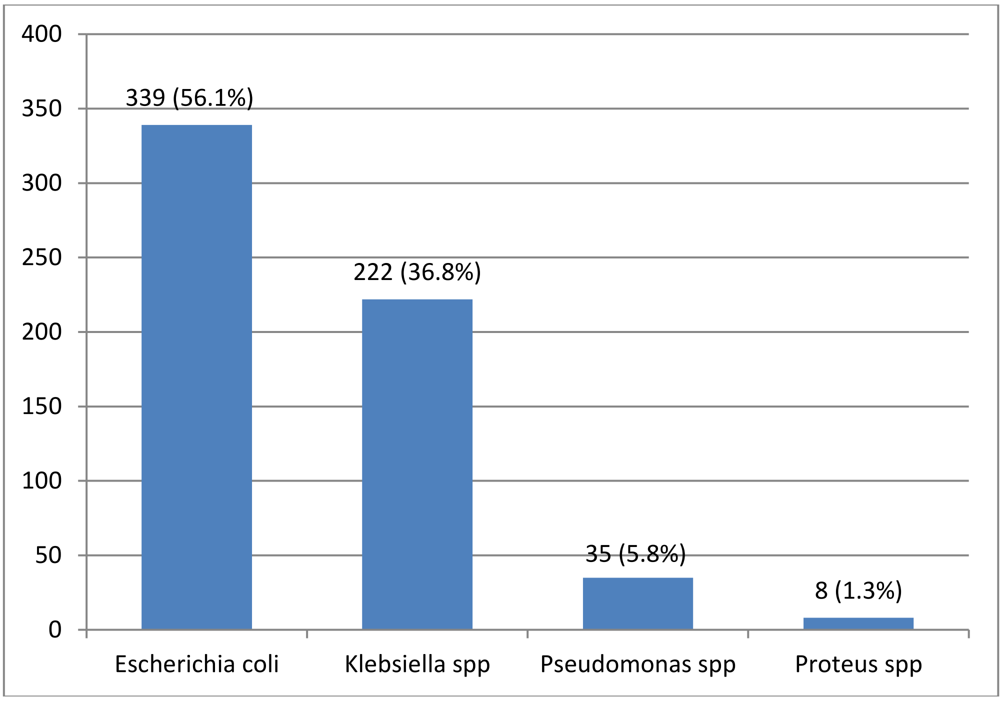

Fig 1: Frequency of Gram-negative bacterial uropathogens in Babcock University Teaching Hospital, Ilishan Remo, Nigeria

Table 2: Antibiotic susceptibility patterns of Gram-negative bacterial uropathogens in Babcock University Teaching Hospital, Ilishan Remo, Nigeria

Antibiotics/isolates/ Susceptibility breakpoint	***Escherichia coli* (%) (n=339)**			***Klebsiella* spp (%) (n=222)**			***Pseudomonas* spp (%) (n=35)**			***Proteus* spp (%) (n=8)**		
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
Amoxicillin-clavulanate	63 (18.6)	41 (12.1)	235 (69.3)	55 (24.8)	22 (9.9)	145 (65.3)	16 (45.7)	5 (14.3)	14 (40.0)	1 (12.5)	1 (12.5)	6 (75.0)
Piperacillin-tazobactam	161 (47.5)	20 (5.9)	158 (46.6)	80 (36.0)	20 (9.0)	122 (55.0)	20 (57.1)	0	15 (42.9)	3 (37.5)	2 (25.0)	3 (37.5)
Ceftriaxone	112 (33.0)	59 (17.4)	168 (49.6)	NT	NT	NT	NT	NT	NT	1 (12.5)	0	7 (87.5)
Ceftazidime	157 (46.3)	32 (9.4)	150 (44.3)	106 (47.8)	26 (11.7)	90 (40.5)	16 (45.7)	5 (14.3)	14 (40.0)	2 (25.0)	1 (12.5)	5 (62.5)
Nitrofurantoin	199 (58.7)	10 (2.9)	130 (38.4)	111 (50.0)	21 (9.5)	90 (40.5)	20 (57.1)	0	15 (42.9)	NT	NT	NT
Ciprofloxacin	208 (61.4)	25 (7.4)	106 (31.2)	100 (45.0)	29 (13.1)	93 (41.9)	18 (51.4)	2 (5.7)	15 (42.9)	4 (50.0)	1 (12.5)	3 (37.5)
Meropenem	307 (90.5)	7 (2.1)	25 (7.4)	184 (82.9)	7 (3.1)	31 (14.0)	26 (74.3)	2 (5.7)	7 (20.0)	7 (87.5)	0	1 (12.5)

S-sensitive; I = intermediate; R = resistant; NT = not tested

Our study showed that meropenem had the highest *in vitro* antibacterial activity (isolates sensitivity of 74.3% to 90.3%) for all isolates. This is similar to a study done in Somaliland in which 95.9% of urinary tract isolates were sensitive to meropenem (23). In another study from Japan, 100% of the Gram-negative urinary tract isolates were sensitive to meropenem (24). The highest sensitivity to meropenem was shown by *E. coli* (90.3%) while the lowest sensitivity was shown by *Pseudomonas* spp (74.3%). Similarly in a study from the USA, *E. coli* isolates from the urinary tract showed a sensitivity of ≥ 99.4% to meropenem (25). Overall, *E. coli, Klebsiella* spp and *Proteus* spp isolates showed high resistance to amoxicillin-clavulanate (65.3% to 97.1%). However, in a study from the Czech Republic, lower resistance rates to amoxicillin-clavulanate of 12.6%, 14.3% and 38.8% were respectively reported for *Proteus* spp, *E. coli* and *Klebsiella* spp (26).

The high sensitivity to meropenem should not encourage its use as a first line antibiotic to treat UTIs. This is because meropenem is an antibiotic on the Watch Group of the AWaRe antibiotic categorization by the World Health Organization (WHO) for purpose of antimicrobial stewardship (27). Antibiotics in this group have higher resistance potential and should be prioritized as key targets of anti-biotic stewardship programs and monitoring (27). Since meropenem is intravenously administered, this makes it a wrong choice for outpatients with uncomplicated UTIs. Therefore, the use of meropenem as a first line empiric antibiotic agent for treating UTIs should be discouraged in order to avoid the emergence of resistance.

However, the urinary isolates in this study have shown high resistance to most of the antibiotics that can be administered orally such as amoxicillin-clavulanate, nitrofurantoin and ciprofloxacin. It is therefore expedient for the hospital's antimicrobial stewardship (AMS) program to regularly monitor local antibiotic susceptibility patterns of urinary isolates and also draw up guidelines for empiric antibiotic therapy for UTIs. Furthermore, strict infection prevention and control (IPC) protocols should be adhered to, in order to prevent the spread of multidrug resistant pathogens in the hospital.

The limitations of the study included the fact that it was laboratory based and did not involve review of the medical records of patients, therefore, correlation of our *in vitro* findings with clinical UTIs was not possible.

Conclusion:

Rising rates of antibiotic resistance have made it necessary to regularly monitor antibiotic susceptibility patterns of Gram-negative bacterial uropathogens. This will help to optimize antibiotic therapy for UTIs. In addition, strict IPC protocols must be in place to prevent the spread of multidrug resistant pathogens in the hospital.

Conflict of interests:

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Contributions of authors:

IIO conceptualized and designed the study, and produced the manuscript draft; IIO and EE analyzed the data; EE and HNO contributed to drafting of the manuscript; CJE and TOO reviewed the manuscript. All authors approved the manuscript for submission.

Source of funding:

Authors received no external funding.

Data availability:

The data that support the findings of this study are openly available in Mendeley Data at https://data.mendeley.com/datasets/nd4w9wnmzc/1

References:

1. Horcajada, J. P., Shaw, E., Padilla, B., et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multi-centre cohort study in the era of antimicrobial resistance. Clin Microbiol Infect. 2013; 19: 962-968. doi: 10.1111/1469-0691.12089
2. Schappert, S. M. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997. Vital Health Stat 13. 2006; 159: 1-66.
3. Stamm, W. E. Scientific and clinical challenges in the management of urinary tract infections. Am J Med. 2002;113 (Suppl 1A):1S-4S. doi: 10.1016/s0002-9343(02)01053-7
4. Weinstein, M. P., Towns, M. L., Quartey, S. M., et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis. 1997; 24: 584 - 602. doi: 10.1093/clinids/5.1.35
5. Medina, M., and Castillo-Pino, E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019; 11: 175628721 9832172. doi: 10.1177/1756287219832172
6. Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002 ;113 Suppl 1A:5S-13S. doi: 10.1016/s0002-9343(02)01054-9
7. Wilson, M. L., and Gaido, L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis. 2004 ;38: 1150-1158. doi: 10.1086/383029.
8. Stamm, W. E. An Epidemic of Urinary Tract Infections? N Engl J Med 2001; 345: 1055–1057. doi: 10.1056/NEJM200110043451409
9. Jancel, T., and Dudas, V. Management of uncomplicated urinary tract infections. West J Med. 2002; 176: 51–55. doi: 10.1136/ewjm.176.1.51
10. Paul, R. State of the Globe: Rising Antimicrobial Resistance of Pathogens in Urinary Tract Infection. J Glob Infect Dis 2018; 10: 117-118. doi: 10.4103/jgid.jgid_104_17
11. Pokharel, S., Raut, S., and Adhikari, B. Tackling antimicrobial resistance in low-income and middle-income countries. BMJ Glob Health. 2019;4: 4–6. doi: 10.1136/bmjgh-2019-002104
12. Aboderin, O. A., Abdu, A. R., Odetoyin, B. W., and Lamikanra, A. Antimicrobial resistance in *Escherichia coli* strains from urinary tract infections. J Natl Med Assoc 2009; 10 (1): 1268 – 1273. doi: 10.1016/s0027-9684(15)31138-x
13. Dada-Adegbola, H. O., and Muili, K. A. Antibiotic susceptibility pattern of urinary tract pathogens in Ibadan, Nigeria. Afr J Med Med Sci. 2010;39: 173– 179.
14. Friedman, N.D., Temkin, E., and Carmeli, Y. The negative impact of antibiotic resistance. Clin Microbiol Infect. 2016; 22: 416-22. doi: 10.1016/j.cmi.2015.12.002.
15. Isabel, F., Jessica, C., Jyoti, J., Kim, F., and Ramanan, L. Access Barriers to Antibiotics. Was-

hington, DC: Center for Disease Dynamics, Economics & Policy. 2019.
16. Iregbu, K. C., and Nwajiobi-Princewil, P. I. Urinary tract infections in a tertiary hospital in Abuja, Nigeria. African J Clin Exp Microbiol. 2013; 14: 169–173. doi: 10.4314/ajcem.v14i3.9
17. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. M100. Wayne, PA: Clinical and Laboratory Standards Institute, 2020.
18. Prakash, D., and Saxena, R. S. Distribution and Antimicrobial Susceptibility Pattern of Bacterial Pathogens Causing Urinary Tract Infection in Urban Community of Meerut City, India. In: Deghmane, A. E., and Zunino, P. (eds). ISRN Microbiol. 2013; 2013:749629. doi: 10.1155/2013/749629
19. Chowdhury, S., and Parial, R. Antibiotic susceptibility patterns of bacteria among urinary tract infection patients in Chittagong, Bangladesh. SMU Med J. 2015; 2: 114–127.
20. Kengne, M., Dounia, A. T., and Nwobegahay, J. M. Bacteriological profile and antimicrobial susceptibility patterns of urine culture isolates from patients in Ndjamena, Chad. Pan Afr Med J 2017; 28: 258. doi: 10.11604/pamj.2017.28.258.11197
21. Girma, A., and Aemiro, A. The Bacterial Profile and Antimicrobial Susceptibility Patterns of Urinary Tract Infection Patients at Pawe General Hospital, Northwest Ethiopia. Scientifica (Cairo). 2022; 2022: 3085950. doi: 10.1155/2022/3085950
22. Shaifali, I., Gupta, U., Mahmood, S. E., and Ahmed, J. Antibiotic susceptibility patterns of urinary pathogens in female outpatients. N Am J Med Sci 2012;4: 163– 169. doi: 10.4103/1947-2714.94940
23. Ali, A. H., Reda, D. Y., and Ormago, M. D. Prevalence and antimicrobial susceptibility pattern of urinary tract infection among pregnant women attending Hargeisa Group Hospital, Hargeisa, Somaliland. Sci Rep. 2022; 12:1419. doi: 10.1038/s41598-022-05452-z
24. Kanda, N., Hashimoto, H., and Sonoo, T., et al. Gram-negative organisms from patients with community-acquired urinary tract infections and associated risk factors for antimicrobial resistance: a single-center retrospective observational study in Japan. Antibiotics. 2020; 9: 1–9. doi: 10.3390/antibiotics9080438.
25. Critchley, I.A., Cotroneo, N., Pucci, M.J., and Mendes, R. The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017. PLoS One. 2019;14: e0220265. doi: 10.1371/journal.pone.0220265
26. Hrbacek, J., Cermak, P., and Zachoval, R. Current Antibiotic Resistance Trends of Uropathogens in Central Europe: Survey from a Tertiary Hospital Urology Department 2011-2019. Antibiot (Basel, Switzerland). 2020; 9: 630. doi: 10.3390/antibiotics9090630
27. World Health Organization Electronic Essential Medicines List (eEML). AWaRe Portal. https://aware.essentialmeds.org/list.