JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Characterization of ESKAPE pathogens in urinary tract infections among Jordanian patients

Rawan H Alsharedeh[1], Alaa Yehya[2], Othman Beni Yonis[3], Omran Alameri[4], Nida Alshraiedeh[5]

[1] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan
[2] Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Yarmouk University, Jordan
[3] Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
[4] Department of Basic Medical Sciences, Jordan University of Science and Technology, Irbid, Jordan
[5] Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan

Abstract

Introduction: ESKAPE pathogens are a small group of pathogens of remarkable importance. The present study was carried out to determine the prevalence of ESKAPE pathogens in urinary tract infections (UTIs) and their antibiotic susceptibility patterns at the Jordan University of Science and Technology Health Center in Irbid, Jordan.

Methodology: A one-year retrospective study was conducted from April 2021 to April 2022. A total of 444 samples of "clean-catch" (midstream) urine from outpatients were studied.

Results: Our study showed that the vast majority of urinary tract infected patients were females (92%) compared to males (8%) and were most frequent in the age group 21-30 years old. The most associated co-morbidities with UTIs were hypertension followed by diabetes mellitus and hypothyroidism. ESKAPE pathogens were responsible for about 87.4% of the UTIs in this study, and all were identified in the urine samples except *Acinetobacter baumannii*. In this study, isolates were most sensitive to levofloxacin, ciprofloxacin, and third-generation cephalosporin's and least sensitive to doxycycline, amoxicillin, and clindamycin.

Conclusions: This research work has shown that patients with UTI-associated ESKAPE pathogens in Jordan are at high risk of antibiotic resistance. To the best of our knowledge, this is the first study in the region that studies the association between ESKAPE pathogens and UTIs.

Key words: ESKAPE pathogens; UTIs; risk factors; antimicrobial resistance; Jordan.

J Infect Dev Ctries 2023; 17(4):374-380. doi:10.3855/jidc.17490

(Received 02 October 2022 – Accepted 08 January 2023)

Introduction

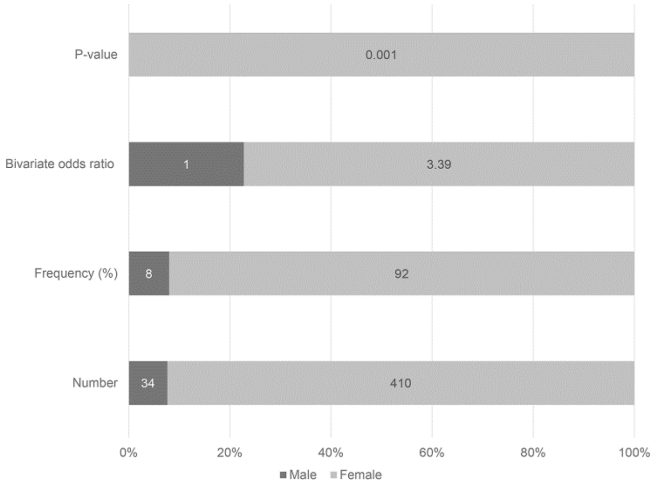
The ESKAPE pathogens were reported for the first time in 2008 by Rice based on data collected from hospital surveillance studies and from the Infectious Diseases Society of America (IDSA) which emphasized a clique of multidrug-resistant bacteria (MDR). This faction is made up of six pathogens (both Gram-positive and Gram-negative species) [1]. The word ESKAPE is consists of the first letter of each pathogen in the group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter/Escherichia coli* species) [1,2]. This acronym is used to indicate the capability of those pathogens of "escaping" the biocidal action of antibiotics [3,4]. This small group of pathogens have exceptional importance as they are the leading cause of nosocomial infections in both developed and developing countries, and they have various paradigms in virulence, pathogenesis, mode of transmission, and multidrug resistance. Globally, multidrug resistance is one of the most important health challenges. It comes among the top three health threats and is typically instigated by high frequencies of using and/or prescribing of antibiotics, antibiotic misuse, patient self-medication, and exposure to infections in health settings [3,5-8]. MDR in ESKAPE pathogens is increasingly associated with both clinical and economic impact. It has a significant disease burden, high mortality and morbidity rates, high treatment and healthcare cost, prolonged admission times, high rates of treatment failure, limited treatment options, and an increase in diagnostic uncertainties [3,5,6,9,10]. Other effects also include triggering life-threatening infections in critically ill and immunocompromised patients [11]. Furthermore, ESKAPE pathogens can form biofilms making treatment even more challenging [12]. In response to MDR's global health threats and

diminishing antibiotic discovery and development pipeline, the World Health Organization (WHO) in 2017 announced a global priority list of the most important antibiotic-resistant bacteria to encourage research and development of new antibiotics. This list contains 12 bacteria and it includes the ESKAPE pathogens labelled with a "priority status" [8,13,14].

Urinary tract infections (UTIs) are among the most prevalent types of infections reported in patients visiting outpatient clinics and emergency rooms, or hospitalized patients. UTIs can be divided into lower UTIs that involve infections in the bladder and urethra or upper UTIs in the kidneys and ureters. UTIs have a wide range of variable symptoms, severity, causative pathogen and treatment plan. The European Association of Urology (EAU) guidelines have indicated the critical levels of midstream sample urine (MSU) to be in the range of 10^3 CFU/mL for uncomplicated UTIs and 10^5 CFU/mL in complicated cases [15,16]. Treatment and management of UTIs must take into consideration various factors; the type of UTI (uncomplicated or complicated), the host factors, the severity of illness, and the association between causative pathogen and MDR [17]. IDSA has standard treatment guidelines for the treatment of both upper and lower UTIs [18]. One of the major challenges in UTIs treatment is UTI recurrence, either relapses or reinfection. UTI recurrence is defined as ≥ 3 UTIs per year or ≥ 2 UTIs per six months [19].

This study is a retrospective study aiming to examine patients diagnosed with UTIs by physicians to determine the prevalence of ESKAPE pathogens in UTIs among diagnosed patients. To the best of our knowledge, this is the first study locally and regionally to research the association between UTIs and ESKAPE pathogens.

Figure 1. Gender distribution and its frequency in urinary tract infections. *p*-value and odds ratios (OR) are presented.



Methodology

Four hundred and forty-four Jordanian patients diagnosed with UTIs at the clinics of Jordan University of Science & Technology (JUST) Health Centre, Irbid, Jordan were included in this retrospective study from April 2021 to April 2022. Medical files of all patients admitted for UTIs during the study period were extracted. Data forms were designed to collect and record demographic and clinical information of each patient. The Institutional Review Board (IRB) approved the study protocol under the reference number 13/1/2719.

Assessment of infectious pathogens and the sensitivity of antibiotics

A sample of "clean-catch" (midstream) urine was cultured in order to determine the microorganisms that cause UTIs. The antibiotic sensitivity of bacterial isolates was assessed using the Kirby-Bauer test for susceptibility. A standard chart was used to look up the zone sizes (in millimeters) and determine if they were "sensitive, resistant, or intermediate." The data of antibiotic susceptibility results were extracted for all patients from laboratory test results performed at the health center.

Statistical analysis

Data were obtained from JUST health centre registries and transferred to standard forms describing demographic/clinical characteristics, including gender, age, clinical symptoms, and comorbidities. Percentages were compared to demonstrate the trends of UTIs among the study group. Association between UTIs and potential risk factors was assessed with the percent prevalence as well as odds ratios (OR) and *p* values based on the results from bivariate logistic regression. Statistical significance was defined at $p < 0.05$. Pearson correlation (r) was calculated to describe the relationship between the characteristics of UTIs and antibiotic resistance. The data obtained were entered in Microsoft® Excel 2016 (Microsoft Corporation, USA) and analyzed using the Statistical Package SPSS (SPSS® Version 21.0, NY, USA).

Results

Demographic data and clinical characteristics of patients with UTIs

This study assessed 444 patients with UTIs. 92% of the studied patients were females and 8% were males

(Figure 1). The age of the studied patients ranged from 1 to 72 years (Figure 2). Regarding clinical presentations, 343 patients (77.3%) presented multiple symptoms, including fever, dysuria, polyuria, lower back pain, and pelvic pain (Figure 3). More than half of the patients (55.4%) had no concomitant chronic diseases, while the rest suffered from commonly diagnosed illnesses such as hypertension (16.2%), diabetes mellitus (13.5%), and hypothyroidism (5.4%) (Figure 4). The statistically significant OR and *p* values for the risk factors were being a female (OR = 3.39; *p* = 0.001), and aged 21-30 years (OR = 1.42; *p* = 0.023). Suffering from multiple symptoms when presenting at the clinic was also a predictor of UTIs (OR = 2.46; *p* = 0.003).

Distribution of ESKAPE pathogens among patients with UTIs

Out of the total 444 patients; the frequency of Gram-negative bacteria causing the UTIs was 74.3%, compared to Gram-positive bacteria which caused 25.7% of the UTIs. *Escherichia coli* was responsible for more than 62% of the infections. Figure 5 shows the results of urine cultures. ESKAPE pathogens were responsible for about 87.4% of the UTIs in this study except *Acinetobacter baumannii*, which was not associated with any UTI cases in the study.

Risk factors for UTIs

The demographics and characteristics of UTIs, including bacterial isolates and sensitivity to the prescribed antibiotic were plotted to describe the relationship using Pearson's correlation. The analysis showed a strong correlation between gender and the risk of UTIs. Similarly, a strong correlation was noted between the type of bacterial isolate and the risk of UTIs. In addition, a weak correlation between the

Figure 4. Urinary tract infections comorbidities and their frequencies. *p*-value and odds ratios (OR) are presented.

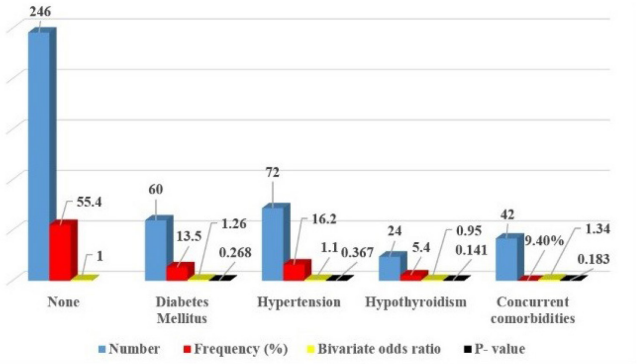


Figure 2. Age distribution and its frequency in urinary tract infections. *p*- value and odds ratios (OR) are presented.

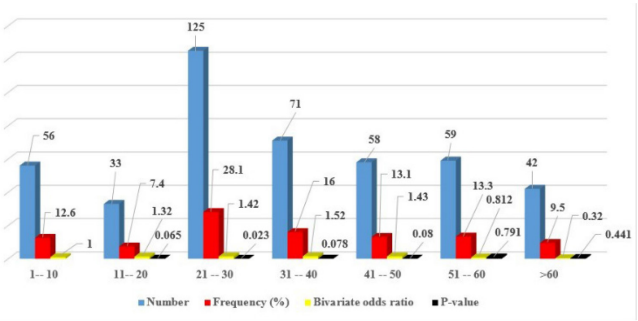


Figure 3. Clinical presentations and their frequencies in urinary tract infections. *p*value and odds ratios (OR) are presented.

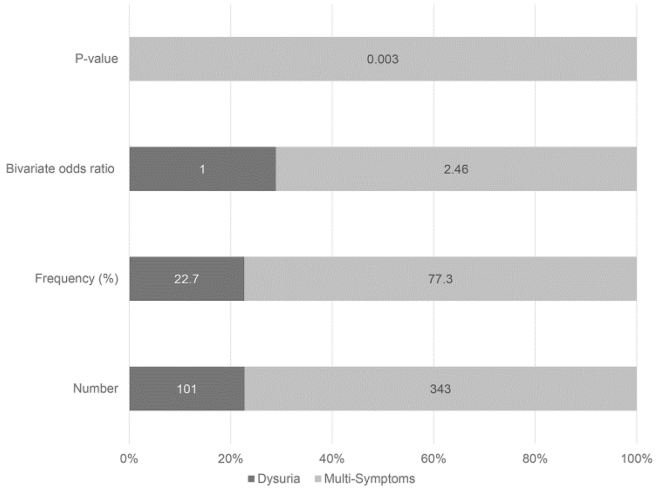
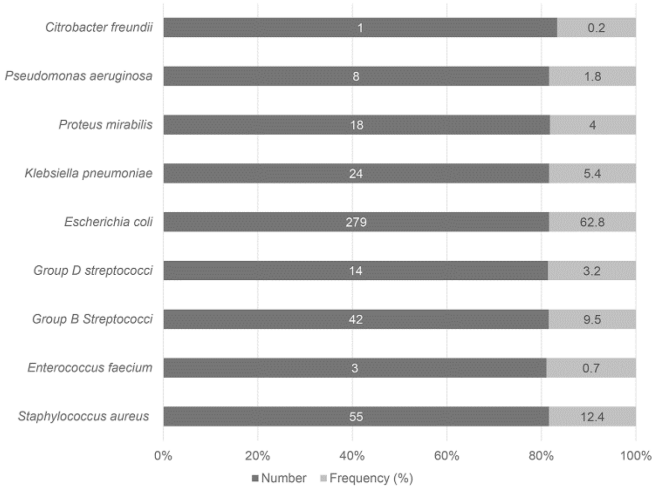


Figure 5. Distribution, frequency and characteristics of pathogens responsible for urinary tract infections (UTIs). In total Gram-positive bacteria are responsible for 114 (25.7%) of UTIs and Gram-negative bacteria are responsible for 330 (74.3%) of UTIs.



bacterial isolates and sensitivity to the antibiotics were identified (Figure 6).

Antibiotic susceptibility test

The Kirby-Bauer test was used to determine antibiotic susceptibility. Results were presented as S (sensitive), I (intermediate), and R (resistance) as shown in Supplementary Table 1. Susceptibility test of Gram-positive bacteria showed that *Staphylococcus aureus* was most resistant to cefixime (78.85%) and most sensitive to cefotaxime (100%), clindamycin (100%), and vancomycin (80%). All the tested isolates of *Enterococcus faecium* were resistant to amoxicillin, cefdinir, and azithromycin, but sensitive to ceftriaxone. Group B streptococci, showed the highest resistance rate for azithromycin (48.6%) and the most sensitivity to cefdinir (100%), clindamycin (100%), and vancomycin (91.7%). Group D streptococci showed highest resistance rates to cefixime (76.9%) and azithromycin (75%) while being the most sensitive to vancomycin (100%), ciprofloxacin (76.9%), and levofloxacin (76.9%).

Gram-negative bacteria showed a more comparable resistance profile. *Escherichia coli*, was completely resistant to doxycycline (100%), vancomycin (95.6%), and amoxicillin (93.4%) while most sensitive to cefdinir (75%). *Proteus mirabilis* showed the highest resistance to amoxicillin (81.8%) and vancomycin (75%) and most sensitivity to cefotaxime (100%) and cefuroxime (81.8%). In the case of *Klebsiella pneumonia*, the highest resistance rates were for vancomycin (100%) and amoxicillin (100%) but they were most sensitive to cefdinir (100%), cefotaxime (100%), and cefuroxime (85%). All isolates of *Pseudomonas aeruginosa*, were resistant to azithromycin, vancomycin, amoxicillin, and cefuroxime (100%) and were most sensitive to cefotaxime (100%). Similarly, *Citrobacter freundiis* was resistant to the entire list of tested antibiotics with the exception of an intermediate sensitivity to ciprofloxacin.

Discussion

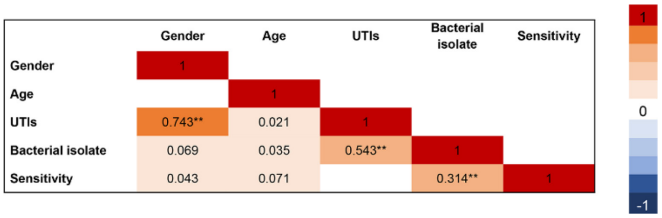
This paper describes the association of ESKAPE pathogens and UTIs among 444 Jordanian patients, over the period of one year. To the best of our knowledge, this study is the first study to determine the association between ESKAPE pathogens and UTIs in Jordan and nearby regions.

UTIs are common in all age groups and genders, however they have a higher prevalence rate in younger females compared to males and a similar prevalence in both genders in the geriatric age group [20-22]. This correlates to the findings of this study. According to our data, the vast majority of UTIs (92%) were in females (OR = 3.39; $p = 0.001$) compared to only 8% in males. Additionally, this is further corroborated by the statistical analysis performed in which a strong correlation was identified between gender and risk of UTI ($0.7 < r < 0.5$). Various anatomical factors and behavioral practices like the short urethral length, the closeness of the urethral meatus to the anus, sexual intercourse, absence of prostatic secretions, pregnancy, easy contamination with gastrointestinal tract flora and fecal flora, incontinence, and bad toilet habits explain these findings [23-26].

According to studies, the prevalence and frequency of a symptomatic UTI in some form rises as people get older [15,17]. The younger groups, between the ages of 21 and 30, and those between the ages of 31 and 40, are considered to be child-bearing. Members of these groups would therefore be sexually active, pregnant and exposed to contraception, whether it be spermicide, condoms, or hormonal birth control, and engaging in other related sexual behaviors like incomplete emptying, the use of lubricants, and delayed micturition after intercourse [20,27,28]. Menopause and hormonal imbalances, catheterization and other medical procedures for institutionalized patients are additional risk factors that become important as the age groups get older [17;29].

In this study, more than three-quarters of the patients were suffering from multi-UTI symptoms including fever, dysuria, polyuria, lower-back pain, and pelvic pain, and these were the most common reported symptoms. This is comparable with other studies that reported these similar symptoms in UTI patients [26,30,31]. However less than one-quarter of the patients suffered solely from dysuria. Even though it is statistically insignificant, 101 patients reported this symptom. It is noteworthy to mention though, that the presence of some or all these symptoms is not enough to diagnose UTIs, and it is imperative in this case to run

Figure 6. Correlation matrix for the urinary tract infections risk factors.



** Correlation is significant at the 0.001 (2-tailed).

a urine culture test to determine whether a type of pathogen is present and the appropriate medication needed according to the resistance and susceptibility profile of the pathogen [32,33].

In this study, around 55% of the patients did not suffer from any comorbidities. However, the remaining 45% have reported associated comorbidities including hypertension, diabetes mellitus, and hypothyroidism. This finding is similar to the comorbidities reported by Zavala-Cerna *et al.* [34].

Gram-negative bacteria cause almost 90% of all UTIs diagnosed, 65-90% of these cases are due to *Escherichia coli* [31,35,36]. In this study, the highest prevalence was of Gram-negative bacteria (74.3%) of which 92.8% of the cases were attributed to *Escherichia coli*. On the other hand, Gram-positive bacteria were responsible for only 25.7% of the cases, half of which were due to *Staphylococcus aureus*. These findings are in agreement with other studies [37,38].

ESKAPE pathogens were responsible for about 87.4% of UTIs studied here. All pathogens in the list were identified in the urine samples except for *Acinetobacter baumannii*. In this study, a strong correlation was detected between the type of bacterial isolate and the risk of UTIs ($0.5 < r < 0.5$), and this is indicated by the predominance of *Escherichia coli* (62.8%) in UTIs. In addition, *Klebsiella pneumoniae* (5.4%) was identified as the second most prevalent Gram-negative bacteria in this analysis. We also assessed the presence of Gram-positive bacteria in the cultures studied; *Staphylococcus aureus* (12.4%), followed by Group B *Streptococci* (9.5%) were the most predominant among Gram-positive microorganisms isolated from urine samples of patients with UTIs. Our findings are in line with data from Arab countries, including Saudi Arabia [39], Lebanon [40], and studies from various regions of the world [41,42]. In Jordan a previous study described the clinical patterns among Jordanian patients with UTIs, however, the analysis was only limited to patients with positive *Escherichia coli* or *Klebsiella pneumonia* urine cultures [43] and did not include the rest of the pathogens from the ESKAPE pathogens group. This study performed an extended analysis to include all ESKAPE pathogens among patients with UTIs.

Based on our data, about two-thirds of the overall UTIs were caused by *Escherichia coli*. An understanding of the reasons behind the high prevalence of *Escherichia coli* in UTIs are given by the presence of uropathogenic *Escherichia coli* (UPEC). This pathogen includes *Escherichia coli* with a set of genes encoding for virulence factors allowing them to persist at the site of infection and successfully establish an infection [44]. Moreover, fimbria, flagella, biofilm formations, and the external lipopolysaccharide in the bacterial *Escherichia coli* membrane and its capsule are additional virulence factors. These factors help bacterial cells in adhesion to the site of infection, finding new nutrient sources, escape the host's immune system, evade antibiotics and reach into the upper urinary tract [44-47]. Our data analysis has also shown that *Acinetobacter baumannii* has not been associated with any UTI cases reported by the JUST health centre. This can be attributed to the fact that *Acinetobacter baumannii* is associated with UTIs when percutaneous nephrostomy tubes or urinary catheters are inserted in hospitalized patients. It has also been connected to patient's infrequent contact with the healthcare system. In our study, patients visiting the JUST health centre are treated as outpatients; thus, limited or no cases of UTIs caused by *Acinetobacter baumannii* would be expected [14,48].

Overall, the bacterial isolates analyzed in this study showed a wide range of antibiotic resistance pattern. The tested isolates were resistant to doxycycline (100%), amoxicillin (80%), clindamycin (80%), azithromycin (53%), cefixime (51%), vancomycin (50%), amoxicillin/clavulanic acid (44.6%), cefdinir (30.8%), cefotaxime (27.8%), cefuroxime (26%), ceftriaxone (20%), ciprofloxacin (16.9%) and levofloxacin (16.55%). The detailed susceptibility pattern for each isolate is presented in Supplementary Table 1. Gram-positive bacteria were found to be most sensitive to vancomycin, clindamycin, and cephalosporins, while being most resistant to azithromycin. Bacteria in this category have also shown good to moderate susceptibility to both ciprofloxacin and levofloxacin.

In general, Gram-negative bacteria are highly resistant to vancomycin, and amoxicillin while having good sensitivity to cephalosporins. In addition, Gram-negative bacteria are intrinsically resistant to vancomycin. This is due to its bulky structure and incapability to penetrate the outer bacterial cell membrane [49]. However, some bacteria developed a high resistance against some cephalosporins including cefuroxime (100%) and cefixime (87%) against *Pseudomonas aeruginosa*, as well as ceftriaxone (100%), and cefixime (100%) against *Citrobacter freundii*. Levofloxacin has shown a near 50% activity against Gram-negative bacteria, except for *Citrobacter freundii* which is completely resistant to it. Similarly, ciprofloxacin has been active in treating infections of *Klebsiella pneumoniae*, *Proteus mirabilis* and, to a

lesser extent, *Escherichia coli*, with a complete resistant profile against *Citrobacter freundiis*, and *Pseudomonas aeruginosa* [37,50-55].

Conclusions

Overall, the data indicated that ESKAPE pathogens were responsible for about 87.4% of UTIs in this study. In addition, the data indicated that the highest resistance rates were associated with doxycycline, amoxicillin, and clindamycin. While the lowest resistance rates were associated with levofloxacin and ciprofloxacin. This reflects the need for accurate and periodic assessment and surveillance data of ESKAPE pathogens prevalence as uropathogens and their susceptibly pattern. This continuous update in susceptibility profiles will directly affect the selection of empiric therapy for UTIs and aid in outlining and updating the primary healthcare guideline in the Jordanian health centers. This study will help in establishing a national policy regulating the use of antibiotics, notably against ESKAPE pathogens in patients with UTIs.

Acknowledgements

The authors would like to acknowledge the deanship of scientific research and graduate studies at Yarmouk University for funding this project and the JUST health centre for the help in this work.

References

1. Rice LB (2008) Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis 197: 1079-1081.
2. Vadivoo NS, Usha B (2018) ESKAPE pathogens: trends in antibiotic resistance pattern. MedPulse Int J Microbiol 7: 26-32.
3. Pendleton JN, Gorman SP, Gilmore BF (2013) Clinical relevance of the ESKAPE pathogens. Expert Rev Anti Infect Ther 11: 297-308.
4. Navidinia M (2016) The clinical importance of emerging ESKAPE pathogens in nosocomial infections. Archives of Advances in Biosciences 7: 43-57.
5. Fadare JO, Ogunleye O, Iliyasu G, Adeoti A, Schellack N, Engler D, Massele A, Godman B. (2019) Status of antimicrobial stewardship programmes in Nigerian tertiary healthcare facilities: findings and implications. J Glob Antimicrob Resist 17: 132-136.
6. Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR (2019) Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front Microbiol 10: 1-24.
7. Gipson KS, Nickerson KP, Drenkard E, Llanos-Chea A, Dogiparthi SK, Lanter BB, Hibbler RM, Yonker LM, Hurley BP, Faherty CS. (2020) The great ESKAPE: exploring the crossroads of bile and antibiotic resistance in bacterial pathogens. Infect Immun 88: e00865-19.
8. Songhita M, Mehta CH, Nayak UY (2020) Antimicrobial peptide polymers: no escape to ESKAPE pathogens - a review. World J Microbiol Biotechnol 36: 131-145.
9. Santajit S, Indrawattana N (2016) Mechanisms of antimicrobial resistance in ESKAPE pathogens. BioMed Res Int 2016: 2475067.
10. Ma YX, Wang CY, Li YY, Li J, Wan QQ, Chen JH, Tay FR, Niu LN (2020) Considerations and caveats in combating ESKAPE pathogens against nosocomial infections. Adv Sci 7: 1901872-1901915.
11. Zhen X, Lundborg CS, Sun X, Hu X, Dong H (2019) Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. Antimicrob Resist Infect Control 8: 1-23.
12. Lewis K (2007) Persister cells, dormancy and infectious disease. Nat Rev Microbiol 5: 48-56.
13. Group WPPLW (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 18: 318-327.
14. De Oliveira DM, Forde BM, Kidd TJ, Harris PN, Schembri MA, Beatson SA, Paterson DL, Walker MJ. (2020) Antimicrobial resistance in ESKAPE pathogens. Clin Microbiol Rev 33: e00181-19.
15. Tan CW, Chlebicki MP (2016) Urinary tract infections in adults. Singapore Med J 57: 485–490.
16. Smelov V, Naber K, Johansen TEB (2016) Improved classification of urinary tract infection: future considerations. European Urology Supplements 15: 71-80.
17. Abou Heidar NF, Degheili JA, Yacoubian AA, Khauli RB (2019) Management of urinary tract infection in women: a practical approach for everyday practice. Urol Ann 11: 339–346.
18. Gupta K, Grigoryan L, Trautner B (2017) Urinary tract infection. Ann Intern Med 167: ITC49-ITC64.
19. Jhang J-F, Kuo H-C (2017) Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. Tzu-Chi Medical Journal 29: 131-137.
20. Harrington RD, Hooton TM (2000) Urinary tract infection risk factors and gender. J Gend Specif Med 3: 27-34.
21. Griebling TL (2005) Urologic diseases in America project: trends in resource use for urinary tract infections in men. J Urol 173: 1288-1294.
22. Griebling TL (2007) Urinary tract infection in women. Urologic Diseases in America 7: 587-619.
23. Khanal L, Shrestha R, Barakoti A, Timilsina S, Amatya R (2016) Urinary tract infection among males and females-a comparative study. Nepal Medical College Journal 18: 97-99.
24. Vranic SM, Zatric N, Rebic V, Aljicevic M, Abdulzaimovic A (2017) The most frequent isolates from outpatients with urinary tract infection. Mater Sociomed 29:17-20.
25. Pardeshi P (2018) Prevalence of urinary tract infections and current scenario of antibiotic susceptibility pattern of bacteria causing UTI. Indian J Microbiol Res 5: 334-338.
26. Kaur R, Kaur R (2021) Symptoms, risk factors, diagnosis and treatment of urinary tract infections. Postgrad Med J 97: 803-812.
27. Foxman B (2010) The epidemiology of urinary tract infection. Nat Rev Urol 7: 653-660.
28. Strom BL, Collins M, West SL, Kreisberg J, Weller S (1987) Sexual activity, contraceptive use, and other risk factors for symptomatic and asymptomatic bacteriuria: a case-control study. Ann Intern Med 107: 816-823.

29. Garibaldi RA, Burke JP, Dickman ML, Smith CB (1974) Factors predisposing to bacteriuria during indwelling urethral catheterization. N Engl J Med 291: 215-219.
30. Holm A, Siersma V, Cordoba GC (2021) Diagnosis of urinary tract infection based on symptoms: how are likelihood ratios affected by age? A diagnostic accuracy study. BMJ Open 11: e039871-e8
31. Matthews SJ, Lancaster JW (2011) Urinary tract infections in the elderly population. Am J Geriatr Pharmacother 9: 286-309.
32. Bagga A (2008) Revised guidelines for management of steroid-sensitive nephrotic syndrome. Indian J Nephrol 18: 31-39.
33. Zavala-Cerna MG, Segura-Cobos M, Gonzalez R, Zavala-Trujillo IG, Navarro-Perez SF, Rueda-Cruz JA, Satoscoy-Tovar FA (2020) The clinical significance of high antimicrobial resistance in community-acquired urinary tract infections. Can J Infect Dis Med Microbiol 2020: 1-7.
34. Weekes LM (2015) Antibiotic resistance changing management of urinary tract infections in aged care. Med J Aust 203: 352.
35. Gupta K, Hooton TM, Stamm WE (2001) Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med 135: 41-50.
36. Shaifali I, Gupta U, Mahmood SE, Ahmed J (2012) Antibiotic susceptibility patterns of urinary pathogens in female outpatients. N Am J Med Sci 4: 163-169.
37. Muhammad A, Khan S, Ali N, Rehman M, Ali I (2020) Prevalence and antibiotic susceptibility pattern of uropathogens in outpatients at a tertiary care hospital. New Microbes New Infect 36: 100716-100720.
38. Ahmad S, Ahmad F (1995) Urinary tract infection at a specialist hospital in Saudi Arabia. Bangladesh Med Res Counc Bull 21: 95-98.
39. Soubra L, Kabbani S, Anwar M, Dbouk R (2014) Spectrum and patterns of antimicrobial resistance of uropathogens isolated from a sample of hospitalised Lebanese patients with urinary tract infections. J Glob Antimicrob Resist 2: 173-178.
40. Valera B, Gentil M, Cabello V, Fijo J, Cordero E, Cisneros J (2006) Epidemiology of urinary infections in renal transplant recipients. In Transplantation. New York, NY: Elsevier. 2414-2415.
41. Flokas ME, Detsis M, Alevizakos M, Mylonakis E (2016) Prevalence of ESBL-producing Enterobacteriaceae in pediatric urinary tract infections: a systematic review and meta-analysis. J Infect 73: 547-557.
42. Almomani BA, Hayajneh WA, Ayoub AM, Ababneh MA, Al Momani MA (2018) Clinical patterns, epidemiology and risk factors of community-acquired urinary tract infection caused by extended-spectrum beta-lactamase producers: a prospective hospital case-control study. Infection 46: 495-501.
43. Bien J, Sokolova O, Bozko P (2012) Role of uropathogenic *Escherichia coli* virulence factors in development of urinary tract infection and kidney damage. Int J Nephrol 2012: 1-15.
44. Karam MRA, Habibi M, Bouzari S (2019) Urinary tract infection: pathogenicity, antibiotic resistance and development of effective vaccines against uropathogenic *Escherichia coli*. Mol Immunol 108: 56-67.
45. Totsika M, Gomes Moriel D, Idris A, A Rogers B, J Wurpel D, Phan M, L Paterson D, A Schembri M. (2012) Uropathogenic *Escherichia coli* mediated urinary tract infection. Curr Drug Targets 13: 1386-1399.
46. Johnson JR (1991) Virulence factors in *Escherichia coli* urinary tract infection. Clin Microbiol Rev 4: 80-128.
47. Bagińska N, Cieślik M, Górski A, Jończyk-Matysiak E (2021) The role of antibiotic resistant *A. baumannii* in the pathogenesis of urinary tract infection and the potential of its treatment with the use of bacteriophage therapy. Antibiotics 10: 281.
48. Saito H, Sakakibara Y, Sakata A, Kurashige R, Murakami D, Kageshima H, Saito A, Miyazaki Y. 2019. Antibacterial activity of lysozyme-chitosan oligosaccharide conjugates (LYZOX) against *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus*. PloS One 14: e0217504.
49. Seifu WD, Gebissa AD (2018) Prevalence and antibiotic susceptibility of uropathogens from cases of urinary tract infections (UTI) in Shashemene referral hospital, Ethiopia. BMC Infect Dis 18: 1-9.
50. Assafi MS, Ibrahim NM, Hussein NR, Taha AA, Balatay AA (2015) Urinary bacterial profile and antibiotic susceptibility pattern among patients with urinary tract infection in Duhok city, Kurdistan region, Iraq. Int J Pure Appl Sci Technol 30: 54-63.
51. Chowdhury S, Parial R (2015) Antibiotic susceptibility patterns of bacteria among urinary tract infection patients in Chittagong, Bangladesh. SMU Medical Journal 2: 114-126.
52. Angami S, Jamir N, Sarma PC, Deka AC (2015) Urinary tract infection, its causative microorganism and antibiotic susceptibility in Nagaland. Archives of Medicine and Health Sciences 3: 40-43.
53. Qiao L-D, Chen S, Yang Y, Zhang K, Zheng B, Guo HF, Yang B, Niu YJ, Wang Y, Shi BK, Yang WM, Zhao XK, Gao XF, Chen M, Tian Y. (2013) Characteristics of urinary tract infection pathogens and their in vitro susceptibility to antimicrobial agents in China: data from a multicenter study. BMJ Open 3: e004152-e9.
54. Mukherjee M (2013) Multidrug-resistance and extended spectrum beta-lactamase production in uropathogenic *E. coli* which were isolated from hospitalized patients in Kolkata, India. J Clin Diagn Res 7: 449-453.

Corresponding author
Dr. Rawan H. Alsharedeh, PhD
Department of Pharmaceutics and Pharmaceutical Technology,
Faculty of Pharmacy,
Yarmouk University, P.O Box 566, Zip code 21163, Jordan
Tel: +962 2 7211111
Email: r.sharedeh@yu.edu.jo

Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Bacterial antibiotic susceptibility testing.

Staphylococcus aureus	**Sensitive**	**Intermediate**	**Resistance**
Amoxicillin	4 (23.5%)	3 (17.7%)	10 (58.8%)
Amoxicillin/clavulanic acid	29 (55.8%)	13 (25%)	10 (19.2%)
Ciprofloxacin	28 (52.8%)	14 (26.4%)	11 (20.8%)
Levofloxacin	29 (54.7%)	14 (26.4%)	10 (18.9%)
Cefuroxime	27 (56.25%)	18 (37.5%)	3 (6.25%)
Cefotaxime	1 (100%)	0 (0.0%)	0 (0.0%)
Cefdinir	1 (33.33%)	1 (33.33%)	1 (33.33%)
Ceftriaxone	34 (65.4%)	9 (17.3%)	9 (17.3%)
Cefixime	9 (17.3%)	2 (3.85%)	41 (78.85%)
Vancomycin	12 (80%)	0 (0.0%)	3 (20%)
Clindamycin	1 (100%)	0 (0.0%)	0 (0.0%)
Doxycycline	-	-	-
Azithromycin	15 (30%)	3 (6%)	32 (64%)
Enterococcus faecium	**S**	**I**	**R**
Amoxicillin	0 (0.0%)	0 (0.0%)	2 (100%)
Amoxicillin/clavulanic acid	0 (0.0%)	1 (50%)	1 (50%)
Ciprofloxacin	1 (33.3.%)	2 (66.7%)	0 (0.0%)
Levofloxacin	2 (66.7%)	0 (0.0%)	1 (33.3.%)
Cefuroxime	1 (50%)	1 (50%)	0 (0.0%)
Cefotaxime	-	-	-
Cefdinir	0 (0.0%)	0 (0.0%)	1 (100%)
Ceftriaxone	2 (100%)	0 (0.0%)	0 (0.0%)
Cefixime	2 (66.7%)	1 (33.3.%)	0 (0.0%)
Vancomycin	-	-	-
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	0 (0.0%)	0 (0.0%)	3 (100%)
Group B Streptococci	**S**	**I**	**R**
Amoxicillin	14 (70%)	1 (5%)	5 (25%)
Amoxicillin/clavulanic acid	17 (40.5%)	21 (50%)	4 (9.5%)
Ciprofloxacin	33 (78.6%)	0 (0.0%)	9 (21.4%)
Levofloxacin	32 (78.1%)	0 (0.0%)	9 (21.9%)
Cefuroxime	15 (50%)	12 (40%)	3 (10%)
Cefotaxime	-	-	-
Cefdinir	2 (100%)	0 (0.0%)	0 (0.0%)
Ceftriaxone	19 (48.7%)	19 (48.7%)	1 (2.6%)
Cefixime	28 (68.3%)	2 (4.9%)	11 (26.8%)
Vancomycin	11 (91.7%)	1 (8.3%)	0 (0.0%)
Clindamycin	1 (100%)	0 (0.0%)	0 (0.0%)
Doxycycline	-	-	-
Azithromycin	18 (51.4%)	0 (0.0%)	17 (48.6%)
Group D streptococci	**S**	**I**	**R**
Amoxicillin	3 (42.86%)	1 (14.3%)	3 (42.86%)
Amoxicillin/clavulanic acid	4 (30.8%)	9 (69.2%)	0 (0.0%)
Ciprofloxacin	10 (76.9%)	0 (0.0%)	3 (23.1%)
Levofloxacin	10 (76.9%)	0 (0.0%)	3 (23.1%)
Cefuroxime	3 (30%)	3 (30%)	4 (40%)
Cefotaxime	-	-	-
Cefdinir	-	-	-
Ceftriaxone	3 (23.1%)	4 (30.8%)	6 (46.1%)
Cefixime	3 (23.1%)	0 (0.0%)	10 (76.9%)
Vancomycin	4 (100%)	0 (0.0%)	0 (0.0%)
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	2 (16.7%)	1 (8.3%)	9 (75%)
Escherichia coli	**S**	**I**	**R**
Amoxicillin	8 (6.6%)	0 (0.0%)	114 (93.4%)
Amoxicillin/clavulanic acid	118 (43.5%)	0 (0.0%)	153 (56.5%)
Ciprofloxacin	122 (43.9%)	109 (39.2%)	47 (16.9%)
Levofloxacin	155 (56.8%)	73 (26.7%)	45 (16.5%)
Cefuroxime	147 (66.8%)	3 (1.4%)	70 (31.8%)
Cefotaxime	8 (57.2%)	1 (7.1%)	5 (35.7%)
Cefdinir	3 (75%)	0 (0.0%)	1 (25%)
Ceftriaxone	125 (48.1 %)	73 28.1%)	62 (23.8%)
Cefixime	115 (42.9%)	24 (9%)	129 (48.1%)
Vancomycin	1 (0.04%)	0 (0.0%)	22 (95.6%)
Clindamycin	1 (12.5%)	0 (0.0%)	7 (87.5%)

Doxycycline	0 (0.0%)	0 (0.0%)	6 (100%)
Azithromycin	125 (46%)	4 (1.6%)	143 (52.5%)
Klebsiella pneumoniae	**S**	**I**	**R**
Amoxicillin	0 (0.0%)	0 (0.0%)	7 (100%)
Amoxicillin/clavulanic acid	11 (45.8%)	1 (4.2%)	12 (50%)
Ciprofloxacin	12 (50%)	10 (41.7%)	2 (8.3%)
Levofloxacin	14 (66.7%)	6 (28.6%)	1 (4.7%)
Cefuroxime	17 (85%)	0 (0.0%)	3 (15%)
Cefotaxime	1 (100%)	0 (0.0%)	0 (0.0%)
Cefdinir	1 (100%)	0 (0.0%)	0 (0.0%)
Ceftriaxone	16 (69.6%)	6 (26.1%)	1 (4.3%)
Cefixime	9 (37.5%)	2 (8.3%)	13 (54.2%)
Vancomycin	0 (0.0%)	0 (0.0%)	2 (100%)
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	13 (59.1%)	0 (0.0%)	9 (40.9%)
Proteus mirabilis	**S**	**I**	**R**
Amoxicillin	2 (18.2%)	0 (0.0%)	9 (81.8%)
Amoxicillin/clavulanic acid	11 (68.75%)	1 (6.25%)	4 (25%)
Ciprofloxacin	9 (52.9%)	7 (41.2 %)	1 (5.9%)
Levofloxacin	9 (52.9%)	7 (41.2 %)	1 (5.9%)
Cefuroxime	9 (81.8%)	0 (0.0%)	2 (18.2%)
Cefotaxime	1(100%)	0 (0.0%)	0 (0.0%)
Cefdinir	1 (50%)	0 (0.0%)	1 (50%)
Ceftriaxone	7 (46.7%)	6 (40%)	2 (13.3%)
Cefixime	6 (37.5%)	5 (31.25%)	5 (31.25%)
Vancomycin	0 (0.0%)	1 (25%)	3 (75%)
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	12 (75%)	0 (0.0%)	4 (25%)
Pseudomonas aeruginosa	**S**	**I**	**R**
Amoxicillin	0 (0.0%)	0 (0.0%)	4 (100%)
Amoxicillin/clavulanic acid	0 (0.0%)	1(14.3%)	6 (85.7%)
Ciprofloxacin	0 (0.0%)	7 (87.5%)	1 (12.5%)
Levofloxacin	4 (50%)	3 (37.5%)	1 (12.5%)
Cefuroxime	0 (0.0%)	0 (0.0%)	4 (100%)
Cefotaxime	1 (100%)	0 (0.0%)	0 (0.0%)
Cefdinir	-	-	-
Ceftriaxone	4 (57.1%)	1 (14.3%)	2 (28.6%)
Cefixime	0 (0.0%)	1 (12.5%)	7 (87.5%)
Vancomycin	0 (0.0%)	0 (0.0%)	1 (100%)
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	0 (0.0%)	0 (0.0%)	3 (100%)
Citrobacter freundii	**S**	**I**	**R**
Amoxicillin	0 (0.0%)	0 (0.0%)	1 (100%)
Amoxicillin/clavulanic acid	0 (0.0%)	0 (0.0%)	1 (100%)
Ciprofloxacin	0 (0.0%)	1 (100%)	0 (0.0%)
Levofloxacin	-	-	-
Cefuroxime	0 (0.0%)	0 (0.0%)	1 (100%)
Cefotaxime	-	-	-
Cefdinir	-	-	-
Ceftriaxone	0 (0.0%)	0 (0.0%)	1 (100%)
Cefixime	0 (0.0%)	0 (0.0%)	1 (100%)
Vancomycin	-	-	-
Clindamycin	-	-	-
Doxycycline	-	-	-
Azithromycin	-	-	-