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ANTIBIOTIC RESISTANCE OF URINARY TRACT PATHOGENS IN SYRIAN FEMALES

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ABSTRACT

This study was performed to evaluate the resistance rates to antibiotics among bacteria isolated from urine culture from Syrian female's patients from different age categories. The most common uropathogen identified in urine isolates was *E. coli*. 2% of bacteria isolates were resistant to one antibiotic, while 98% bacteria isolates were resistant to at least 2 antibiotics. An extremely high *in-vitro* resistance rate (more than 90%) was remarked among bacteria isolates, especially toward Cefotaxime, Nalidixic acid, Cefexime, Cephalexin and Cefpodoxime. For Cefetriaxone, Cefuroxime, and Trimethoprim–Sulfamethoxazole, resistance rates ranged between 70%-80%. Resistance rates for Nitrofurantoin, Amoxicillin - Clavulanic acid, Ciprofloxacin and Norofloxacin were between 37% and 60%. For some antibiotics, resistance rates were high from early life and continue with nearly the same values along different age stages (Trimethoprim–Sulfamethoxazole, Cephalexin and Cefexime), for other, resistance rates progressively increased with increasing age of patients (Nitrofurantoin, Ciprofloxacin and Norfloxacin). Finally, Amikacin, Gentamycin, and Imipenem showed good sensitivity (more than 90%) in almost all age's groups.

Keywords:

Urine tract infections, Antibiotic, resistance, females, Syria.

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Introduction:

Urinary tract infection (UTI) is one of the most common infections affecting women at various stage of their life [1-6]. Nearly 50% to 60% of women will suffer from UTIs in their life time [1-6] . Compared to men, women are much more prone to develop UTI, mostly due to urinary tract anatomical differences [2,3]. The length of urethra is an important factor increasing female's susceptibility to develop UTIs. A short urethra, in women, facilitates uropathogen invasion of the urinary tract [6]. Pathogen causing UTI are known to have adhesions molecules on their surface, and can easily attach to mucosal epithelium of the urinary tract. On the other hand, colonization of lower urinary tract is easier in women due to proximity to both anus and genitalia [2, 3, 6].

Hormonal status variations during women's life stages influence UTIs occurrence [7-12]. Both estrogen and progesterone receptors are found in urinary organs [7, 8, 11], and estrogen decreasing levels during the post-menopausal period are related to morphological modifications leading to epithelial atrophy of the lower urinary tract, making it more vulnerable to infections [9]. It is to be mentioned that the presence of high levels of lactobacilli and acidic pH in lower urinary tract of pre-menopausal women helps reducing the opportunity of bacterial colonization. Increased pH in post-menopausal period is directly related to reduced lactobacilli presence, this leads to spreading infections by other pathogens such as *E. Coli* [9, 10].

Bacterial identification in UTIs is a key step for therapeutical strategy, UTIs are mainly caused by *Escherichia coli* , and other pathogen such as *Enterobacter aerogenes, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter*, *Pseudomonas aeruginosa*, *Enterococcus* spp., and *Serratia* spp. [13-15]. Due to the high empiric use of antibiotics for the treatment of UTIs, antibacterial resistance of Enterobacteriaceae, specifically the main uropathogens *Escherichia coli* and *Klebsiella pneumoniae*, has significantly increased [16-27].

Among Syrian population, resistance to antibiotics in patients suffering from UTIs has been examined previously, both in adults and children [28, 29]. In this study, we evaluate the resistance rates to antibiotics among bacteria isolated from urine samples collected from Syrian women.

Materials and methods:

Urine samples from one hundred eleven Syrian women from different age stages were collected in sterile urine containers during the period extended from August 2020 to June 2021. To detect and identify micro-organisms causing UTI, blood and MacConkey agar plates were used in the culture study of urine samples. 24 hours after the incubation of urine samples at 37°C, colony forming units CFU were counted. If CFU greater than 100,000/ml, antibiotic sensitivity tests were then carried out using Mueller Hinton Agar

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(MHA). The level of antibiotics susceptibility of bacteria was determined by measuring the zone of inhibition.

The studied antibiotics discs include; Amikacin 30µg, Gentamycin 10µg, Nitrofurantoin 300µg, Ceftriaxone 30µg, Ciprofloxacin 30µg, Imipenem 10µg, Nalidixic acid 30 µg, Norofloxacin 10µg, Cefpodoxime 30µg, Cefuroxime 30µg, Cefotaxime 30µg, Cephalexin 30µg, Cefixime 5µg, Amoxicillin-clavulanic acid 30µg and Trimethoprim-Sulfamethoxazole 75µg.

Results:

Female UTI patients were of classified according to their age into three groups (Figure 1): Group 1(below 18 years old), Group 2 (between 19 and 50 years old) and group 3 (above 51 years old). The three age groups roughly showed similar prevalence of UTIs (about 32% for both Group 1 and 3, 35% for Group2).

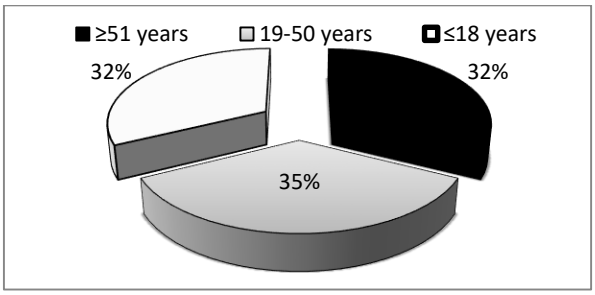

Figure 1: Prevalence of studied female UTI patients groups. Patients aged below the age of 18 are plotted in black, between the age of 19 and 50, above the age of 51 are plotted in black, gray, white color respectively .

Urine samples collected from women with UTI were analyzed in terms of uropathogens (Figure 2). *E. coli* was the first cause of UTIs in females (69%), followed by *Klebsiella pneumonia* (23%) and by others bacteria like *Enterobacter* and beta-hemolytic *streptococcus (*8%).

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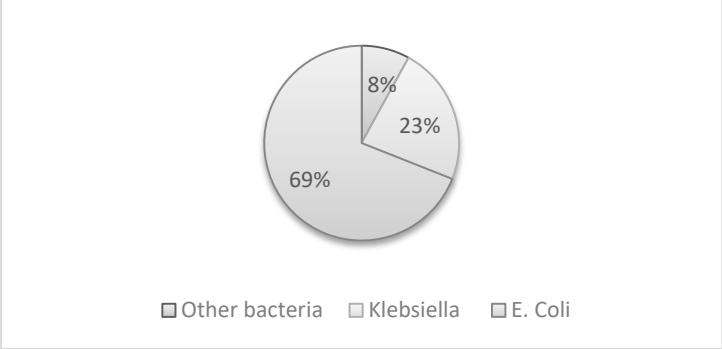

Figure 2: Prevalence of uropathogens in female UTI patients. *E. coli* has the highest prevalence (69%), followed by *Klebsiella pneumonia* (23%) and other types of pathogens (8%).

Susceptibility results

The susceptibility of isolated urine bacteria to fifteen antibacterial drugs were tested, including Amikacin, Gentamycin, Nitrofurantoin, Ceftriaxone, Ciprofloxacin, Imipenem, Nalidixic acid, Norofloxacin, Cefpodoxime, Cefuroxime, Cephalexin, Cefexime, Amoxicillin-Clavulanic acid, Trimethoprim-Sulfamethoxazole and Cefotaxime.

The Figure 3 presents susceptibility results of 111 bacteria isolates tested against the above cited antibiotics. All urine bacteria isolates were more sensitive to Amikacin (100%), Imipenem (97%) and Gentamaycin (89%). The percent of sensitivity for urine bacteria isolates were high for Nitrofurantoin (63%), Amoxicillin - Clavulanic acid (46%), Ciprofloxacin (44%) and Norofloxacin (40%). The percent of sensitivity for urine bacteria isolates were low for Cefetriaxone (29%), Cefuroxime (19%), Trimethoprim - Sulfamethoxazole (16%), Cefotaxime (7%), Nalidixic acid (8%), Cefexime (7%), Cephalexin (7%) and Cefpodoxime (5%).

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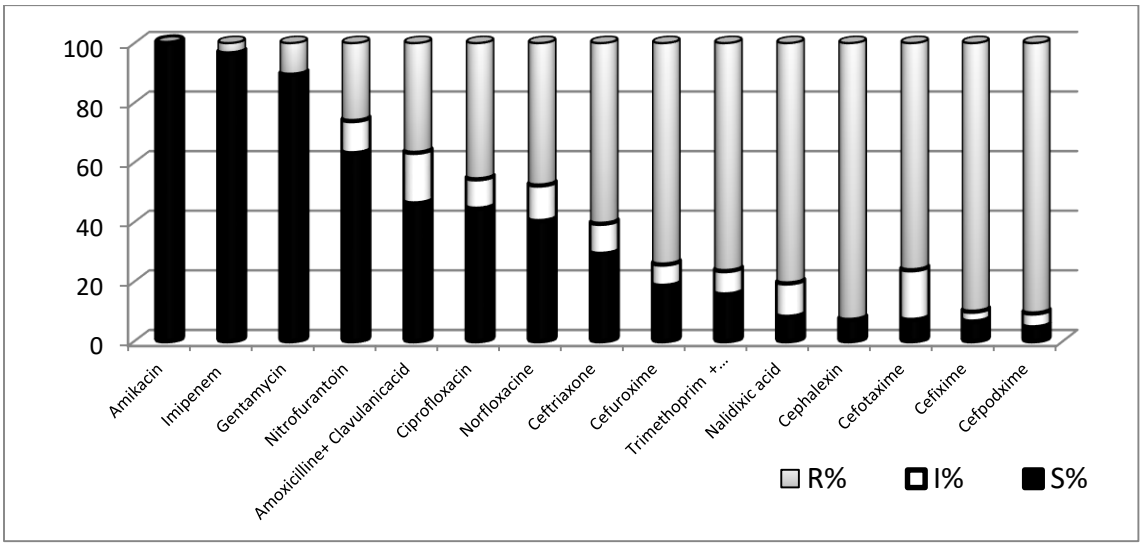

Figure 3: Antibiotic susceptibility results of 111 urine samples from female IUT patients. S: susceptible, I: intermediate, R: resistant.

A high rate of resistance (≥ 20%) was observed among isolated urine bacteria to twelve antibiotics. While only 3 antibiotics has a rate of resistance below 20% (Figure 4 A). These results are in agreement with several studies for the resistance of uropathogens in females which demonstrated high rates of resistance and multiple-antibiotic resistance [9, 12]. Susceptibility results of bacteria isolates from female UTI patients demonstrated a high multi-drug resistance prevalence. Only two bacteria isolates were resistant to one antibiotic (2%) while 98% bacteria isolates were resistant to at least 2 antibiotics (Figure 4B).

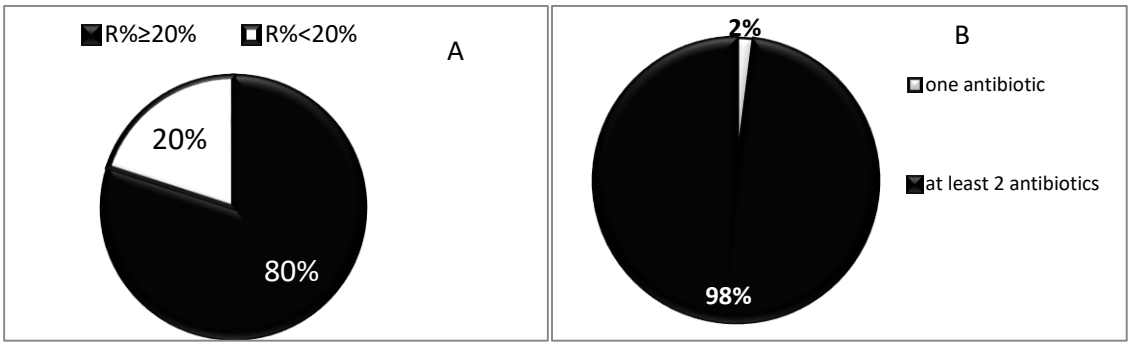

Figure 4: (A) Percent of multi-drug resistance isolates from female UTI patient. Resistances are plotted in white (below 20%), black (above 20%). (B) Percent of studied antibiotic according to resistance rate of isolated urine bacteria from female UTI patients . Only 2% were resistant to one antibiotic (white), 98% to at least two antibiotics (black).

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Type of pathogens

A comparison study of antibiotic resistance rates between *Escherichia Coli* and *Klebsiella Pneumoniae* was performed as shown in the Figure 5. The resistance rates to Cephalexin, Cefexime, Cefepodoxime, Naldixic acid, Cefotaxime, Trimethoprim-Sulfamethoxazole, Cefuroxime, Cefetriaxone, Ciprofloxacin, Nitrofurantoin, Gentamycin, and Amikacin were approximately similar for *Escherichia Coli* and *Klebsiella Pneumoniae. Escherichia Coli* urine isolates were more resistant to Norfloxacin than *Klebsiella Pneumoniae* (23%), whereas *Klebsiella Pneumoniae* urine isolates were more resistant to Amoxicillin-Clavulanic acid than *Escherichia Coli* (30%).

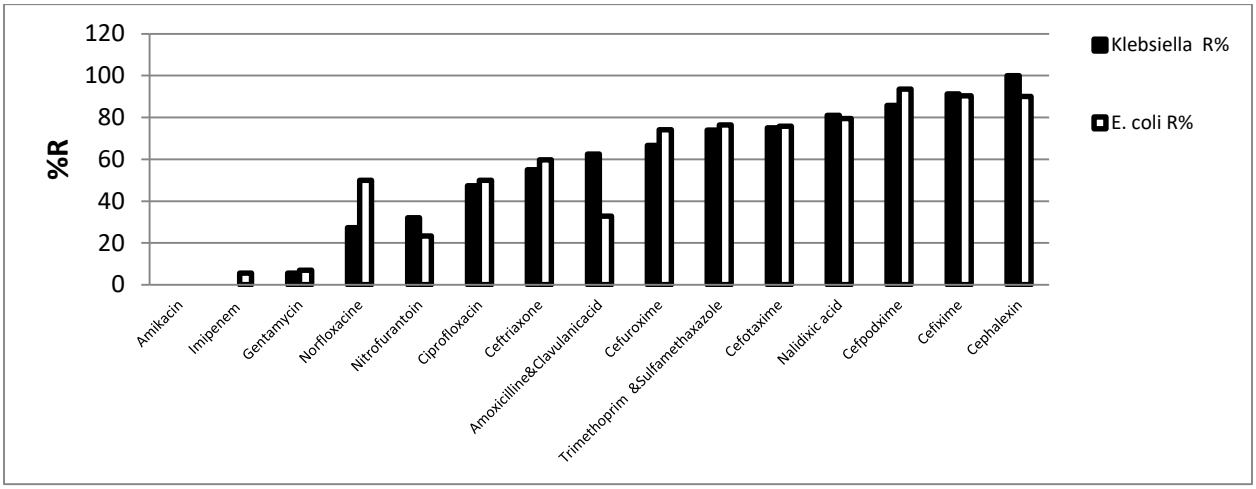

Figure 5: Resistance rates of *E. Coli* (white bars) and *Klebsiella Pneumoniae* (black bars) urine isolates to studied antibiotics. Note the resistance difference to Norfloxacin (23% in favor to *E. Coli*), and to Amoxicillin-Clavulanic acid (30% in favor to *Klebsiella Pneumoniae*).

Age of UTI female patients:

As resistance rates may vary according to age of patients, a comparative study for the three experimental groups was assessed. The effects of age on antibiotic resistance rates were studied by comparing susceptibility test results among urine isolates collected from pediatric female (Group 1, 0 to 18 years old), adult females (Group 2, 19 to 50 years old), and older adult females (Group 3, ≥ 51 years old). Comparison study results are demonstrated in the Figure 6.

Similar resistance rates for the three age groups was observed for Amikacin, Trimethoprim–Sulfamethoxazole, Cephalexin and Cefexime. On the other hand, resistance rates to Nitrofurantoin, Ciprofloxacin and Norfloxacin increased with female ages (respectively 6%, 29% and 40% in group 3 as compared to group 1)

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Urine bacteria isolated from UTI female patients of group 2 (19 to 50 years old) showed lower resistance rates than those obtained for both older or younger patients to Ceftriaxone, Nalidixic acid, Cefpodoxime, Cefuroxime Cefotaxime and Amoxicillin-Clavulanic acid (respectively 20%, 10%, 20%, 19%, 26% and 9% in group 2 as compared to group 1). Also, resistance of uropathogens isolated from UTI patients of group 3 demonstrated an increasing rates toward Ceftriaxone (10%), Cefuroxime (20%), Cefotaxime (21%) and Amoxicillin-Clavulanic acid (18%) as compared to group 1.

For Gentamycin, urine bacteria isolated from UTI female patients of group 2 (19 to 50 years old) was higher as compared to both younger and older females (16 % compared to Group 3). Only some urine bacteria isolated from pediatric UTI female patients were resistant to imipenem (14%).

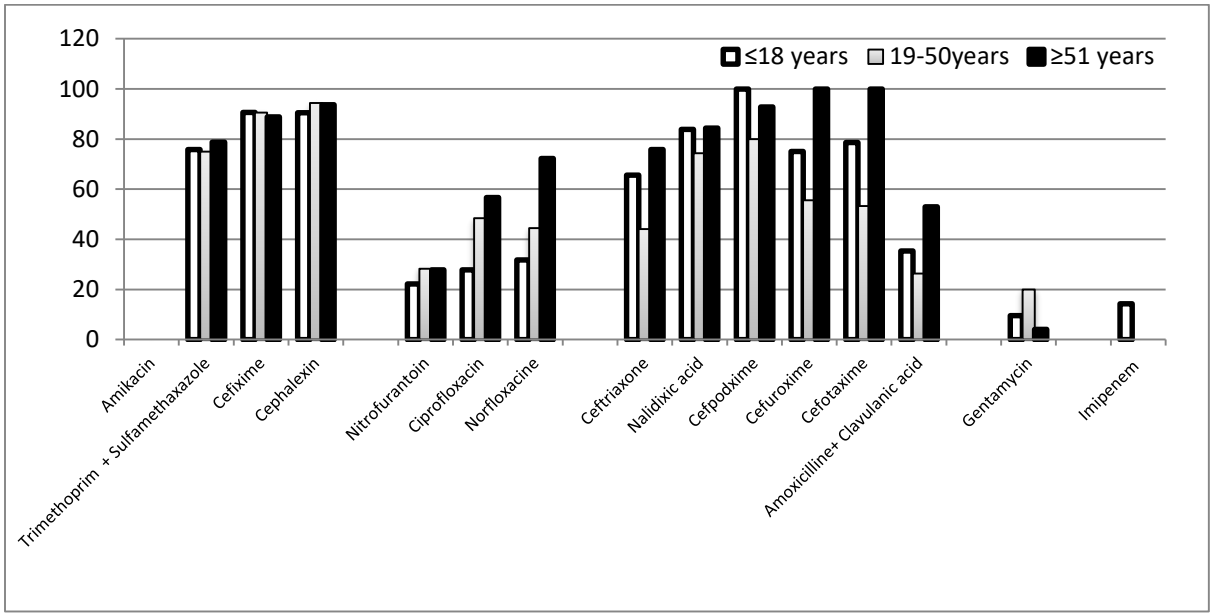

Figure 6: Resistance rate of uropathogens to studied antibiotics according to female age (white bars: between 0 and 18 years old, gray bars: between 19 and 50 years old, black bars: above 51 years old).

DISCUSSION:

In the present study, resistance of uropathogens to fifteen antibiotics was assessed in urine samples of UTI female patients from several age groups. The prevalence of bacterial UTIs in female is influenced by many factors, such as urethra both length and position, and estrogen variations with age. A shorter urethra facilitates germ propagation to the urinary bladder as well as being near the rectum [2, 3, 6]. Also, the well-known

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decreasing estrogen levels with age is often correlated with thinning the urethral epithelium and making lower urinary tract more vulnerable to infections [7-11].

Resistance to antibiotics has become a serious health issue in Syria, mainly caused by the inappropriate use of antibiotics in absence of medical prescription, and even sometimes without medical consultation. Increasing resistance to antibiotics makes it difficult to select the effective therapy and unfortunately may participate to worsening the health situation as it concern UTIs. In accordance with previous findings [30-36], uropathogen from urine samples of UTI female patients presented moderate to important resistance rates to twelve antibiotics including Nitrofurantoin, Amoxicillin-Clavulanic acid, Ciprofloxacin, Norofloxacin, Cefetriaxone, Cefuroxime, Trimethoprim-Sulfamethoxazole, Cefotaxime, Nalidixic acid, Cefexime, Cephalexin and Cefpodoxime. It is important to note that a high resistance rate was obtained for one of the most common antibiotic used in UTIs treatment in Syria, Cefexime, regardless of UTIs female patients age, which raises questions as to therapy effectiveness especially that resistance rates are importantly high in Groupe 1 and remain unchanged in both Groups 2 and 3. Important resistance rates toward Cefexime have been reported in previous studies [28, 29, 37-39], being one of the first effective antibiotics used in UTIs treatment [40]. On the other hand, antibiotics such as Ciprofloxacin and Nitrofurantoin, widely used as UTIs treatment in Syria, showed lower resistance rates as compared to Cefexime. In addition, resistance rates evolution for both Ciprofloxacin and Nitrofurantoin was progressive with age, suggesting a direct relation with the repetitive and sometimes the inappropriate use. Pathogen from urine samples was sensitive to three antibiotics: Amikacin, Imipenem and Gentamaycin, which is a very important finding that would suggest the use of these antibiotics in UTIs treatment. It is noteworthy to mention that Amikacin, Imipenem and Gentamaycin are used as treatment for UTIs in Syria, but under strict medical supervision via intravenous (Imipenem) or muscular (Amikacin and Gentamaycin) route. Taking in consideration the observed difference of resistance rates between *Escherichia Coli* and *Klebsiella Pneumoniae* both in the present study and in previous reports [28, 29,40-53], it is important to perform specific pathogen detection in urine samples of UTIs patients as a routine procedure.

CONCLUSION:

The aim of this research was to evaluate the antibiotic susceptibility of pathogen causing UTIs in Syrian female patients from different ages. Due to their high resistance rates, Cefexime, Ciprofloxacin and Nitrofurantoin must be avoided in treatment of UTIs patients. The best choice for UTIs treatment in young female patients was Amikacin, as for patients aged between 19 and 50 years old both Amikacin and Imipenem are effective, and for patients aged over 51 years old, Amikacin, Imipenem and Gentamaycin can be used.

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REFERENCE:

1. Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K , Stamm WE, Risk Factors for Recurrent Urinary Tract Infection in Young Women, *The Journal of Infectious Diseases*, Volume 182, Issue 4, October 2000, Pages 1177–1182, https://doi.org/10.1086/315827
2. Valiquette L. Urinary tract infections in women. Can J Urol. 2001 Jun;8 Suppl 1:6-12. PMID: 11442991.
3. Minardi D, d'Anzeo G, Cantoro D, Conti A, Muzzonigro G. Urinary tract infections in women: etiology and treatment options. *Int J Gen Med*. 2011;4:333-343. doi:10.2147/IJGM.S11767
4. Al-Badr A, Al-Shaikh G. Recurrent Urinary Tract Infections Management in Women: A review. *Sultan Qaboos Univ Med J*. 2013;13(3):359-367. doi:10.12816/0003256
5. Puebla-Barragan, S., Renaud, J., Sumarah, M. *et al.* Malodorous biogenic amines in *Escherichia coli*-caused urinary tract infections in women—a metabolomics approach. *Sci Rep* **10,** 9703 (2020). https://doi.org/10.1038/s41598-020-66662-x
6. Czajkowski K, Broś-Konopielko M, Teliga-Czajkowska J. Urinary tract infection in women. *Prz Menopauzalny*. 2021;20(1):40-47. doi:10.5114/pm.2021.105382
7. Walter E. Stamm, Estrogens and Urinary-Tract Infection, *The Journal of Infectious Diseases*, Volume 195, Issue 5, 1 March 2007, Pages 623–624,
8. Robinson D, Toozs-Hobson P, Cardozo L. The effect of hormones on the lower urinary tract. Menopause Int. 2013 Dec;19(4):155-62. doi: 10.1177/1754045313511398. PMID: 24336244.
9. Miotla P, Romanek-Piva K, Bogusiewicz M, Markut-Miotla E, Adamiak A, Wróbel A, Zebrowska M, Wawrysiuk S, Mendyk K, Rechberger E, Jakubczak A, Rechberger T. Antimicrobial Resistance Patterns in Women with Positive Urine Culture: Does Menopausal Status Make a Significant Difference? Biomed Res Int. 2017;2017:4192908. doi: 10.1155/2017/4192908. Epub 2017 Apr 13. PMID: 28497048; PMCID: PMC5406742.
10. Abelson B, Sun D, Que L, Nebel RA, Baker D, Popiel P, Amundsen CL, Chai T, Close C, DiSanto M, Fraser MO, Kielb SJ, Kuchel G, Mueller ER, Palmer MH, Parker-Autry C, Wolfe AJ, Damaser MS. Sex differences in lower urinary tract biology and physiology. Biol Sex Differ. 2018 Oct 22;9(1):45. doi: 10.1186/s13293-018-0204-8. PMID: 30343668; PMCID: PMC6196569.
11. Escobar C, Rosenblum N, Vaginal Estrogen—What a Urologist Should Know, Urology, **151**, (37-43), (2021).
12. Samir Issa Bloukh, Nageeb A. Hassan, Rand S. AlAni, Sabrina Ait Gacem, Urinary Tract Infection and Antibiotic Resistance among Pregnant and Non-pregnant females in UAE, Research J. Pharm. and Tech. 2021; 14(1):461-465. doi: 10.5958/0974-360X.2021.00084.6.
13. Klein RD, Hultgren SJ. Urinary tract infections: microbial pathogenesis, host-pathogen interactions and new treatment strategies. *Nat Rev Microbiol*. 2020;18(4):211-226. doi:10.1038/s41579-020-0324-0
14. Cui H. Distribution and drug resistance of pathogens causing urinary tract infection in patients with urinary calculi. Am J Transl Res. 2021 Sep 15;13(9):10554-10561. PMID: 34650726; PMCID: PMC8507078.
15. Vasudevan R. Urinary tract infection: an overview of the infection and the associated risk factors. J Microbiol Exp. 2014;1(2):42-54. DOI: 10.15406/jmen.2014.01.00008
16. Critchley IA, Cotroneo N, Pucci MJ, Mendes R. The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017. PLoS One. 2019 Dec 10;14(12):e0220265. doi: 10.1371/journal.pone.0220265. PMID: 31821338; PMCID: PMC6903708.
17. Schwaber MJ, Navon-Venezia S, Schwartz D, Carmeli Y. High levels of antimicrobial coresistance among extended-spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother. 2005;49(5):2137-2139. doi:10.1128/AAC.49.5.2137-2139.2005

ISSN:1673-064X
E-Publication: Online Open Access
Vol: 65 Issue 06 | 2022
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18. Morosini MI, García-Castillo M, Coque TM, et al. Antibiotic coresistance in extended-spectrum-beta-lactamase-producing Enterobacteriaceae and in vitro activity of tigecycline. Antimicrob Agents Chemother. 2006;50(8):2695-2699. doi:10.1128/AAC.00155-06

19. Astal Z, Sharif FA, Abdallah SA, Fahd MI. Multiresistant Escherichia coli isolated from women with community-acquired urinary tract infections in the Gaza Strip. J Chemother. 2002;14(6):637-8. doi: 10.1179/joc.2002.14.6.637. PMID: 12583559.

20. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-84. doi: 10.1038/nrmicro3432. Epub 2015 Apr 8. PMID: 25853778; PMCID: PMC4457377.

21. Can F, Kurt-Azap Ö, İspir P, Nurtop E, Seref C, Loçlar İ, Aktaş ON, Orhan YC, Ergonul O. The clinical impact of ST131 H30-Rx subclone in urinary tract infections due to multidrug-resistant Escherichia coli. J Glob Antimicrob Resist. 2016;4:49-52. doi: 10.1016/j.jgar.2015.10.006. Epub 2015 Nov 14. PMID: 27436393.

22. Nanda Anima, Dhamodharan S, Nayak BK, Antibiotic Resistance Pattern Exhibited by Esbl (Extended Spectrum β-Lactamases) in Multidrug Resistant Strains, Escherichia coli, Research J. Pharm. and Tech 2017; 10(11): 3705-3708. doi: 10.5958/0974-360X.2017.00672.2

23. Sreeja MK, Gowrishankar NL, Adisha. S, Divya. KC, Antibiotic Resistance-Reasons and the Most Common Resistant Pathogens – A Review, Research J. Pharm. and Tech., 2017; 10(6): 1886-1890. doi: 10.5958/0974-360X.2017.00331.6.

24. Joshi Y, Gurung P, Jain S, Evaluation and Assessment of Drug Utilization in Patients of Urinary Tract Infections, Asian J. Pharm. Res., 2018; 8(3): 167-169. doi: 10.5958/2231-5691.2018.00029.1.

25. Rajesh KS, Honey VS, Ullas Prakash D'souza, Ragava Sharma, Bharath Raj KC, Study of Antibiotic resistance pattern in uropathogens at a Tertiary Care Hospital. Research J. Pharm. and Tech., 2020; 13(3): 1253-1256. doi: 10.5958/0974-360X.2020.00231.0.

26. Ahmed Abduljabbar Jaloob Aljanaby, Israa Abduljabbar Jaloob Aljanaby, Profile of Antimicrobial Resistance of Aerobic Pathogenic Bacteria isolated from Different Clinical Infections in Al-Kufa Central Hospital –Iraq During period from 2015 to 2017, Research J. Pharm. and Tech., 2017; 10(10):3264-3270. doi: 10.5958/0974-360X.2017.00579.0.

27. Shireen Rana, Siddesh Basawaraj Sirwar, Vijayaraghavan. Prevalence and Antibiogram of Extended Spectrum beta- Lactamase Producing Klebsiella pneumoniae and Proteus mirabilis in UTI, Research J. Pharm. and Tech. 2015: 8(11): 1465-1468. doi: 10.5958/0974-360X.2015.00262.0.

28. Abbood A., Malek Z., Al-Homsh Y., Thallaj N., In vitro study for antibiotic resistance of bacteria causing urinary tract infection from Syrian adults, Research J. Pharm. and Tech. 2022, 15(10).

29. Abbood A., Malek Z., Thallaj N., Antibiotic resistance of urinary tract pathogens in Syrian children, Research J. Pharm. and Tech. 2022, *(under revision).*

30. Zhanel, G. G., Hisanaga, T. L., Laing, N. M., DeCorby, M. R., Nichol, K. A., Palatnick, L. P., … Hoban, D. J. (2005). Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). International Journal of Antimicrobial Agents, 26(5), 380–388.

31. Hummers-Pradier E, Koch M, Ohse AM, Heizmann WR, Kochen MM. Antibiotic resistance of urinary pathogens in female general practice patients. Scand J Infect Dis. 2005;37(4):256-61. PMID: 15871164.

32. J McIsaac W, Mazzulli T, Moineddin R, Raboud J, Ross S. Uropathogen antibiotic resistance in adult women presenting to family physicians with acute uncomplicated cystitis. *Can J Infect Dis Med Microbiol*. 2004;15(5):266-270. doi:10.1155/2004/947026

ISSN:1673-064X
E-Publication: Online Open Access
Vol: 65 Issue 06 | 2022
DOI 10.17605/OSF.IO/K56XY

33. McIsaac WJ, Moineddin R, Meaney C, Mazzulli T. Antibiotic-resistant Escherichia coli in women with acute cystitis in Canada. Can J Infect Dis Med Microbiol. 2013 Fall;24(3):143-9. doi: 10.1155/2013/547848. PMID: 24421825; PMCID: PMC3852451.
34. Stapleton AE, Wagenlehner FME, Mulgirigama A, Twynholm M. Escherichia coli Resistance to Fluoroquinolones in Community-Acquired Uncomplicated Urinary Tract Infection in Women: a Systematic Review. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e00862-20. doi: 10.1128/AAC.00862-20. Erratum in: Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0220921. PMID: 32747356; PMCID: PMC7508571.
35. Diorio de Souza H, Hase EA, Knippel Galletta MA, Rodrigues Mota Diorio G, Lippi Waissman A, Pulcineli Vieira Francisco R, Zugaib M. Urinary Bacterial Profile and Antibiotic Susceptibility in Pregnant Adolescents and Pregnant Low Obstetric Risk Adult Women. Infect Drug Resist. 2021 Jul 23;14:2829-2841. doi: 10.2147/IDR.S310696. PMID: 34326651; PMCID: PMC8316608.
36. Miotla P, Romanek-Piva K, Bogusiewicz M, Markut-Miotla E, Adamiak A, Wróbel A, Zebrowska M, Wawrysiuk S, Mendyk K, Rechberger E, Jakubczak A, Rechberger T, "Antimicrobial Resistance Patterns in Women with Positive Urine Culture: Does Menopausal Status Make a Significant Difference?", *BioMed Research International*, vol. 2017, Article ID 4192908, 6 pages, 2017. https://doi.org/10.1155/2017/4192908
37. Malmartel A, Ghasarossian C. Bacterial resistance in urinary tract infections in patients with diabetes matched with patients without diabetes. J Diabetes Complications. 2016 May-Jun;30(4):705-9. doi: 10.1016/j.jdiacomp.2016.01.005. Epub 2016 Jan 12. PMID: 26851821.
38. Gunduz, S., Uludağ Altun, H. Antibiotic resistance patterns of urinary tract pathogens in Turkish children. *glob health res policy* **3,** 10 (2018). https://doi.org/10.1186/s41256-018-0063-1
39. Sah SK, Regmi S, Upreti AR and Pathak S: Antibiotic resistance patterns and evaluation of treatment in out-patients with urinary tract infections in Nepal. Int J Pharm Sci Res 2016; 7(11): 4626-31.doi: 10.13040/IJPSR.0975-8232.7(11).4626-31.
40. Naber KG. Cefixime in urinary tract infections. Infection. 1990;18 Suppl 3:S132-9. German. doi: 10.1007/BF01644632. PMID: 2079373.
41. L. Labban, N. Thallaj, Z. Malek; International Journal of Medical Studies, 2020, 5, No 12, 23-36.
42. L. Labban, M. Kudsi, Z. Malek, N. Thallaj; Advances in Medical, Dental and Health Sciences, 2020,3, 3,45-48.
43. L. Labban, N. Thallaj, M. Al Masri; Journal of Advanced Research in Food Science and Nutrition, 2020,3,1,34-41.
44. Thallaj, N; agha, M. I ,H;, nattouf; A.H; katib, CH; karaali, A; Moustapha, A; Labban L;open access library journal, 2020,7,5,1-21.
45. L. labban; N. thallaj; A. labban; archives of medicine, 2020, 12, 2:8, 1-5.
46. L. labban; N. thallaj; international journal of herbal medicine,2020, 8, 2, 33-37.
47. L. Labban, N. Thallaj, Z. Malek; Journal of Medical Research and Health Sciences, 2019, 2, 11, 784-787.
48. L. labban N. Thallaj; acta scientific nutritional health, 2019, 3,10, 7-12.
49. Malek, Z.S.; Sage D.; Pevet, P.; Raison, S.; Endocrinology 2007, 148 (11), 5165-5173.
50. Malek, Z.S.; Dardente, H.; Pevet, P.; Raison, S.; European Journal of Neuroscience 2005, 22 (4), 895-901.
51. Malek, Z.S.; Pevet, P.; Raison, S.; Neuroscience 2004, 125 (3), 749-758.
52. Malek, Z.S.; Labban, L.; The International Journal of Neuroscience, 2020, 1-7.
53. Malek, Z.S.; Labban, L.; European Journal of Pharmaceutical and Medical Research 2019, 6 (11), 527-532.