Shiraz E-Med J. 2024 September; 25(9): e143958. https://doi.org/10.5812/semj-143958.

Published online: 2024 August 3. **Research Article**

Frequency of Bacteria Causing Urinary Tract Infection and Their Antibiotic Resistance Among Children

Shiva Rafati [1,*], Reyhaneh Tavousian [2], Ali Davati [3], Azadeh Afshin [4], Mohammadmehdi Attarpour Yazdi [5], Masood Soltanipur [2,6], Sina Shahshenas [2]

[1] Department of Pediatric, Faculty of Medicine, Shahed University, Tehran, Iran
[2] Medical Students Research Committee, Shahed University, Tehran, Iran
[3] Department of Social Medicine, Faculty of Medicine, Shahed University, Tehran, Iran
[4] Department of Pediatric Nephrology, Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran
[5] Department of Microbiology, Faculty of Medicine, Shahed University, Tehran, Iran
[6] Department of Quality of Life, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran

[*] *Corresponding author:* Department of Pediatric, Faculty of Medicine, Shahed University, Tehran, Iran. Email: 1

Received 2023 December 13; **Revised** 2024 May 26; **Accepted** 2024 June 1.

Abstract

Background: Childhood urinary tract infections (UTIs) are among the most prevalent diseases. In recent years, the overuse of common antibiotics has increased antibiotic resistance among urinary tract pathogens worldwide, with changes in the pattern of microbial resistance varying by geographical area and time.

Objectives: This study aims to investigate the pattern of microbial resistance of UTI pathogens in pediatric patients.

Methods: In this cross-sectional study, children aged < 13 years with UTI and positive urine cultures, who were admitted to Bahrami Hospital in Tehran, Iran, between 2015 and 2019, were evaluated. The pathogens' frequency, their antimicrobial resistance, and clinical and demographic information were extracted from the patients' files. Statistical relationships between clinical and demographic data and antibiotic resistance were analyzed using appropriate statistical tests.

Results: The files of 202 patients were evaluated. The majority of patients were female (79.2%). UTI was more common among the 12 - 60 months age group (36.3%) in females and the 1 - 12 months age group (50%) in males. The most common UTI pathogen was *Escherichia coli* (85.1%). The lowest rates of microbial resistance were related to Meropenem (0% resistance), Gentamicin (9.2%), and Amikacin (10.8%). Conversely, the highest resistance rates were observed for Cotrimoxazole (74.6%), Ampicillin (74.5%), and Cephalothin (64.9%).

Conclusions: UTI is more common in females aged 1 to 60 months. *E. coli* is the most common cause of UTI. Microbial resistance to antibiotics used for empirical treatment, such as ceftriaxone, is high and changes over time. It is recommended to use alternative antibiotics and avoid the inappropriate administration of antibiotics.

Keywords: UTI, Pediatric, Resistance, Antibiotic, *E. coli*

1. Background

Infectious diseases such as urinary tract infections (UTIs), meningitis, and otitis are very common in children (1-3). Childhood urinary tract infections can lead to severe complications, including chronic kidney failure, high blood pressure, scarring in the kidney tissue, and voiding dysfunctions (2, 4, 5). The exact prevalence of UTI depends on age, sex, and circumcision status (6). Generally, UTI is more common in females (about 3 - 5% in girls and about 1% in boys), but its prevalence changes with age. In the first year of life, these infections occur more frequently in boys; however, after one year, they are more common in girls (7, 8). Other factors that increase the risk of UTI include urinary reflux, overactive bladder, adhesions and tightness in the foreskin region, structural abnormalities in the lower urinary tract, and constipation (2). Therefore, timely diagnosis and

appropriate management of these infections are imperative.

Childhood urinary tract infections can occur in children due to a variety of microorganisms. Gram-negative bacteria are the most common microorganisms affecting the urinary system across all age groups (9). These bacteria mostly reach the urethra through feces and ascend through the urethra (9, 10). Meanwhile, *E. coli* alone is the cause of 90 - 95% of pediatric UTIs acquired from the community and 50% of these infections acquired in medical centers and hospitals (11, 12). Other causes of these infections include Pseudomonas species, members of the Enterobacteriaceae family, including Klebsiella, Enterobacter, and Citrobacter, and Gram-positive bacteria such as Staphylococcus and Enterococcus (5, 13).

In recent years, the inappropriate use of common antibiotics has increased antibiotic resistance among urinary pathogens worldwide (14, 15). Timely diagnosis, correct treatment, and proper patient follow-up can significantly reduce complications (14, 15). In general practice, the therapeutic approach is often conducted empirically (7, 8, 16). Empirical treatment is implemented to relieve symptoms, suppress infection, prevent urosepsis, and reduce the possibility of kidney damage (7, 8, 16). However, these empirical treatments sometimes involve the inappropriate use of antibiotics, which contributes to the prevalence of antibiotic resistance (5, 17, 18).

One of the most critical threats to public health is the problem of antibiotic-resistant bacteria, which cause a high percentage of hospital deaths every year (5, 18). Genetic changes in the causative strains and differences in the access and consumption of antibiotics are major factors influencing drug resistance worldwide (8). Identifying antibiotic resistance patterns in UTIs is crucial for selecting appropriate antibiotics and their proper use in treating these diseases (19). Therefore, periodic research in this area is necessary.

2. Objectives

The present study aimed to investigate the frequency of bacteria causing UTIs and their antibiotic susceptibility in children admitted to the Bahrami Children's Hospital, Tehran, Iran.

3. Methods

3.1. Patients and Sample Collection

This study was approved by the local ethical committee (IR.SHAHED.REC.1400.097). The archive of Bahrami Hospital in Tehran, Iran, was reviewed for pediatric inpatients aged < 13 years, diagnosed with UTI based on confirmed positive urine culture (colony count > 100,000) from 2015 to 2019. Cases were excluded if the patient's record was incomplete or the urine culture result was reported as a mixed growth culture.

Clinical information, including demographic data (age, sex, history of UTI, and history of oral antibiotic use in the previous six weeks), clinical symptoms, complications related to urinary infection (presence or absence of urinary reflux history), and laboratory information (type of microbe isolated from urine culture, microbial sensitivity and resistance to antibiotics, urine gravity, and pyuria), were extracted from patients' medical files. Only the results of urine samples taken at admission and before antibiotic therapy were included in the analysis.

3.2. Statistical Analysis

Finally, the collected information was entered into SPSS version 16 statistical software (IBM SPSS Statistics, New York, United States). Descriptive data were expressed as frequency percentages and mean ± standard deviation (SD). Analytical tests, including the chi-square test, were used to analyze the data and check the statistical relationship between the variables and the antibiotic resistance profile. A P-value of < 0.05 was considered statistically significant.

4. Results

A total of 202 inpatient children's urinary samples were analyzed in this study. Histories of urinary reflux, previous UTIs, and antibiotic use were present in 7.4%, 17.8%, and 30.35% of cases, respectively. The most common clinical symptoms were fever (75.2%) and vomiting (37.6%), while the most common laboratory findings were urine with low gravity (75.2%) and pyuria (72.3%).

Table 1 shows the distribution of age and isolated bacteria from urine cultures according to sex. The majority of patients were female (79.2%). The highest percentage of female patients were children aged 12 - 60 months (36.3%). Conversely, most male patients were

Table 1. The Age Distribution and Isolated Bacteria from Urine Culture According to Sex

Variables	Male (42, 20.8%)	Female (160, 79.2%)	Total (202, 100%)
Age groups			
<1 mo	12 (28.6)	18 (11.3)	30 (14.9)
1 - 12 mo	21 (50)	42 (26.3)	63 (31.2)
12 - 60 mo	4 (9.5)	58 (36.3)	62 (30.7)
60 mo <	5 (11.9)	42 (26.3)	47 (23.3)
Pathogen			
E. coli	34 (81.0)	138 (86.3)	172 (85.1)
Klebsiella Pneumoniae	4 (9.5)	18 (11.3)	22 (10.9)
Other	4 (9.5)	4 (2.4)	8 (4.0)

[a] Values are expressed as No. (%).

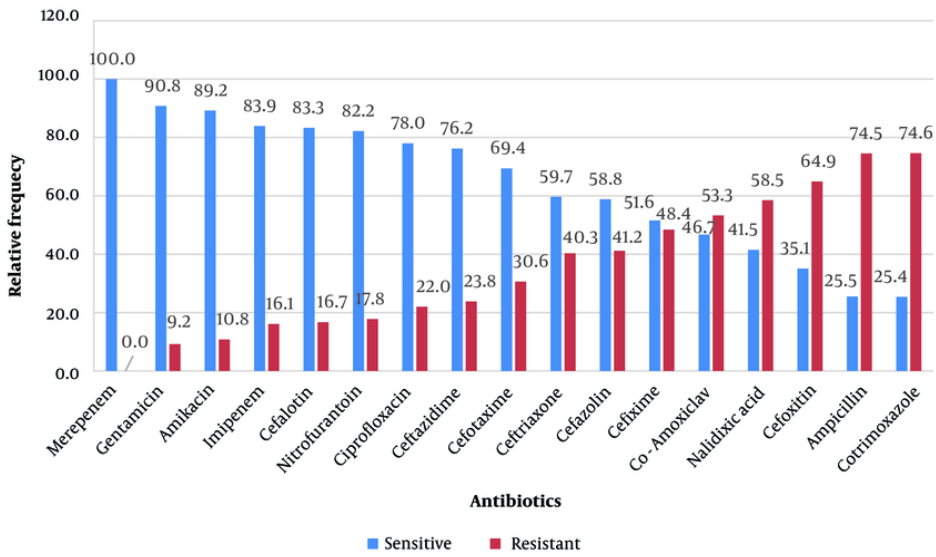

Figure 1. Relative frequency of antibiotic resistance in different types of antibiotics

children aged 1 - 12 months (50%). The most common pathogen isolated from the urine culture, in both females and males, was *E. coli* (85.1%), followed by Klebsiella pneumoniae (10.9%). Other pathogens (4%) included Enterococcus and Pseudomonas.

Figure 1 shows the resistance rates to different types of antibiotics. The lowest antibiotic resistance in pathogens obtained from urine cultures was to meropenem, gentamicin, and amikacin (no resistance, 9.2%, and 10.8%, respectively), while the highest resistance rates were to cotrimoxazole, ampicillin, and cefoxitin (74.6%, 74.5%, and 64.9%, respectively).

The antibiotic resistance of *E. coli* is shown in Table 2. The resistance rates of cephalosporins were not related to demographic variables (P-Value > 0.05). However, resistance to ampicillin significantly increased with age (P-Value = 0.038).

5. Discussion

In this study, we retrospectively investigated the demographic characteristics of UTIs, the frequency of

causative pathogens, and their antibiotic sensitivity in admitted pre-pubertal children. The findings showed that most cases of UTIs occurred in females (79.2%). The most common age range for UTIs was 1 to 60 months (61.9%). *E. coli* and Klebsiella were responsible for 96% of UTIs. Many other studies also show that UTIs are more common in females (15, 20-23) and at younger ages (15, 24). In this study, the most common clinical symptoms were fever and vomiting, and the most common laboratory findings were low urine gravity and pyuria. Previous studies have also identified fever and vomiting as common symptoms (4, 25).

Our study confirmed that *E. coli* and Klebsiella are the most common causes of UTIs, consistent with other research findings (22-24). Similarly, Kalantar et al. (26) found that *E. coli* and Klebsiella are the most common UTI pathogens in a study that examined data from 55 hospitals across 12 different cities in Iran. In our study, the highest microbial resistance was to cotrimoxazole, ampicillin, cephalothin, nalidixic acid, and co-amoxiclav, with resistance observed in more than 50% of UTIs. In contrast, resistance to carbapenems and aminoglycosides was very low, which is consistent with findings from other studies (8, 15, 20, 27).

Kalantar et al. (26) reported a resistance rate of 85.9% to cotrimoxazole, with high resistance rates also noted for cephalothin, cephalexin, cefixime, and ampicillin. However, resistance to aminoglycosides and carbapenems was low (8, 15, 20, 21, 26, 28). In a meta-analysis by Hadifar et al. (29), the overall prevalence of multidrug-resistant *E. coli* (MDR-UPEC) in Iran was reported to be 49.4%, ranging from 27.7% to 77%. In contrast, studies from other countries reported much lower microbial resistance to cotrimoxazole (24, 30).

In a meta-analysis by Bryce et al. (31), the pattern of antimicrobial resistance differed between member countries of the Organization for Economic Co-operation and Development (OECD) and non-member countries. In OECD member countries, resistance rates were 53.4% for ampicillin, 23.6% for trimethoprim, 8.2% for co-amoxiclav, and 2.1% for ciprofloxacin. In non-member countries, resistance rates were 79.8% for ampicillin, 60.3% for co-amoxiclav, and 26.8% for ciprofloxacin, with the results of non-member countries being much closer to those observed in our study.

One of the most important factors influencing the pattern of microbial resistance in different regions is the pattern of antibiotic prescription, as repeated exposure to an antibiotic can lead to resistance mutations in pathogens (32). In the study by Datta et al. (33), it was observed that frequent exposure of *E. coli* to cotrimoxazole is associated with multiple resistance mechanisms, whereas this was less common for imipenem and amikacin. Similar results have been observed in other studies (34). Therefore, it is recommended to avoid the inappropriate prescription of antibiotics.

In the present study, there was no correlation between demographic characteristics or patient histories and *E. coli* antibiotic resistance. Limited studies have investigated such a relationship. Unlike previous research, our study did not find an association between a history of antibiotic use and increased *E. coli* resistance. In the study by Long et al. (35), frequent and high doses of antibiotic prescriptions were linked to increased resistance. However, in our research, the quality and quantity of antibiotic consumption were not investigated.

Additionally, the prophylactic antibiotic prescribed for individuals with urinary reflux varies according to its grade and clinical course. Our study did not examine the duration of reflux or the length of antibiotic use, which could explain the lack of significance in the history of antibiotic use concerning *E. coli* resistance. Overall, in our study, *E. coli* resistance to cephalosporins was unrelated to age, sex, history of urinary reflux, history of UTI, and antibiotic use.

In the study by Mantadakis et al. (24), the resistance of *E. coli* to co-amoxiclav and ampicillin was higher in males than in females. In contrast, our study found no such difference, although we observed that resistance to ampicillin increased with age. In the study by Mostafavi et al. (28), the sensitivity of *E. coli* to cephalosporins and carbapenems was higher in females under 20 years of age. For instance, sensitivity to cefazolin was 28.1% in males and 40.6% in females, but we did not observe similar results in our study.

Finally, considering the high microbial resistance and the significant differences between OECD member and non-member countries, future studies should focus on identifying the causes of this high resistance, exploring the reasons for differences between OECD member and non-member countries, and providing solutions to reduce it.

Table 2. Distribution of *Escherichia coli* Antibiotic Resistance According to Demographic Variables

Antibiotic	Cephalosporins		Ampicillin	
	Resistant	P-Value	Resistant	P-Value
Age (mo)		0.947		0.038
<1	25.0		50	
1 - 12	30.4		84.6	
12 - 60	28.6		72.7	
60 <	32.5		100	
Gender		0.526		0.484
Male	34.4		72.7	
Female	28.7		73.3	
History of taking oral antibiotics		0.300		0.826
No	27.4		81.5	
Yes	35.3		78.6	
History of UTIs		0.299		0.484
No	27.7		83.3	
Yes	36.8		72.7	
History of urinary reflux		0.506		0.169
No	29.0		79.5	
Yes	38.9		100	

[a] Values are expressed as No. (%).

5.1. Limitations

Some limitations need to be noted. This study was retrospective and confined to the geographical area of Tehran, with samples obtained from only one center. Therefore, the results should be cautiously generalized to other areas. Future studies should conduct prospective multi-center research in different geographical regions and include a larger sample size.

5.2. Conclusions

In this study, fever, vomiting, low urine gravity, and pyuria were the most common clinical manifestations of UTIs. Most cases of UTIs were female, with ages 1 to 60 months being the most common age group. *E. coli* and Klebsiella were the most common causes of UTIs. Microbial resistance to antibiotics used to treat UTIs was relatively high. In our study, the highest antibiotic resistance was to cotrimoxazole and ampicillin, while the lowest antibiotic resistance was to meropenem and gentamicin. Considering the dynamic course of microbial resistance, it is recommended to prescribe antibiotics based on the resistance pattern in any region and avoid the inappropriate administration of antibiotics.

Footnotes

Authors' Contribution: The study design was conducted by S.R. and A.D., while A.A. and R.T. extracted data. M.M.A.Y. reviewed the samples and contributed to writing the first draft. M.S. and S.S. conducted the statistical analysis. The initial draft was written by M.S., S.S., A.A., and R.T., and was finalized by S.R., M.M. A.Y., and A.D. All authors reviewed and approved the final manuscript.

Conflict of Interests Statement: The authors confirm that no known conflicts of interest are associated with this publication.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The study protocol was approved by the Ethics Committee of Shahed University (IR.SHAHED.REC.1400.097).

Funding/Support: This work was not funded.

Informed Consent: Legal guardians of patients in the study had written informed consent in their files for using their file information for research purposes.

References

1. DeAntonio R, Yarzabal JP, Cruz JP, Schmidt JE, Kleijnen J. Epidemiology of otitis media in children from developing countries: A systematic review. *Int J Pediatr Otorhinolaryngol*. 2016;**85**:65-74. [PubMed ID: 27240499]. https://doi.org/10.1016/j.ijporl.2016.03.032.
2. Gondim R, Azevedo R, Braga A, Veiga ML, Barroso UJ. Risk factors for urinary tract infection in children with urinary urgency. *Int Braz J Urol*. 2018;**44**(2):378-83. [PubMed ID: 29368878]. [PubMed Central ID: PMC6050565]. https://doi.org/10.1590/S1677-5538.IBJU.2017.0434.
3. Yarmohammadi H, Razavi A, Shahrabi Farahani M, Soltanipur M, Amini M. Characteristics of HHV-7 meningitis: a systematic review. *J Neurol*. 2023;**270**(12):5711-8. [PubMed ID: 37620518]. https://doi.org/10.1007/s00415-023-11950-5.
4. Kocak M, Buyukkaragoz B, Celebi Tayfur A, Caltik A, Koksoy AY, Cizmeci Z, et al. Causative pathogens and antibiotic resistance in children hospitalized for urinary tract infection. *Pediatr Int*. 2016;**58**(6):467-71. [PubMed ID: 26513232]. https://doi.org/10.1111/ped.12842.
5. Rezaee MA, Abdinia B. Etiology and Antimicrobial Susceptibility Pattern of Pathogenic Bacteria in Children Subjected to UTI: A Referral Hospital-Based Study in Northwest of Iran. *Medicine (Baltimore)*. 2015;**94**(39). e1606. [PubMed ID: 26426643]. [PubMed Central ID: PMC4616821]. https://doi.org/10.1097/MD.0000000000001606.
6. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*. 2008;**27**(4):302-8. [PubMed ID: 18316994]. https://doi.org/10.1097/INF.0b013e31815e4122.
7. Amini FATEMEH, Vaziri SIAVASH, Karimpour HA, Hassani S, Mohamadi S, Azizi MOHSEN. [Antibiotic resistance pattern of urinary tract infection pathogens in children of Kermanshah in 2015]. *Razi J Med Sci*. 2017;**24**(155):20-7. Persian.
8. Asadi MF, Sharifi A, Mohammad HZ, Nasrolahi H, Kalantari A, Khosravani S. [Antibiotic resistance of urinary tract infection of children under 14 years admitted to the pediatric clinic of Imam Sajjad hospital, 2012]. *Armaghan Danesh*. 2014;**19**(5):411-20. Persian.
9. Khan S, Maroof P, Amin U. Microbial Etiology and Resistance Patterns of Urinary Tract Infection at a Tertiary Care Centre-A Hospital based Study. *J Pure Applied Microbiol*. 2023;**17**(3):1659. https://doi.org/10.22207/JPAM.17.3.28.
10. Gamit SC, Singel HV, Jain AA, Jain JN, Jain KP, Jain MS. Bacteriological Profile and Antibiotics Sensitivity Pattern of Patients with Urinary tract infection in tertiary Care Center, Pipariya, Vadodara, Gujarat. *J Pure Applied Microbiol*. 2022;**16**(4). https://doi.org/10.22207/JPAM.16.4.24.
11. Alishah M, Amini K, Zahraei Salehi T. [Detection of virulence genes in Escherichia coli strains isolated from pediatric with urinary tract infection and their antibiotic resistance profile]. *Studies Med Sci*. 2017;**27**(11):942-9. Persian.
12. Abedi Samakoosh M, Aghaei N, Babamahmodi F, Dawodi AR. [Frequency and pattern of urinary pathogens and their antibiotic resistance in patients with urinary tract infection]. *J Mazandaran Univ Med Sci*. 2015;**25**(131):155-8. Persian.
13. Khan A, Jhaveri R, Seed PC, Arshad M. Update on Associated Risk Factors, Diagnosis, and Management of Recurrent Urinary Tract Infections in Children. *J Pediatric Infect Dis Soc*. 2019;**8**(2):152-9. [PubMed ID: 30053044]. [PubMed Central ID: PMC6510945]. https://doi.org/10.1093/jpids/piy065.
14. Lutter SA, Currie ML, Mitz LB, Greenbaum LA. Antibiotic resistance patterns in children hospitalized for urinary tract infections. *Arch Pediatr Adolesc Med*. 2005;**159**(10):924-8. [PubMed ID: 16203936]. https://doi.org/10.1001/archpedi.159.10.924.
15. Fesharakinia A, Malekaneh M, Hooshyar H, Aval M, Gandomy-Sany F. [The survey of bacterial etiology and their resistance to antibiotics of urinary tract infections in children of Birjand city]. *J Birjand Univ Med Sci*. 2012;**19**(2):208-15. Persian.
16. Zare M, Vehreschild M, Wagenlehner F. Management of uncomplicated recurrent urinary tract infections. *BJU Int*. 2022;**129**(6):668-78. [PubMed ID: 34741796]. https://doi.org/10.1111/bju.15630.
17. Baig MIR, Kadu P, Bawane P, Nakhate KT, Yele S, Ojha S, et al. Mechanisms of emerging resistance associated with non-antibiotic antimicrobial agents: a state-of-the-art review. *J Antibiot (Tokyo)*. 2023;**76**(11):629-41. [PubMed ID: 37605076]. https://doi.org/10.1038/s41429-023-00649-4.
18. Megantara I, Sylviana N, Amira PA, Pradini GW, Krissanti I, Lesmana R. Potential of waterbodies as a reservoir of Escherichia coli pathogens and the spread of antibiotic resistance in the Indonesian aquatic environment. *J Water, Sanitation Hygiene for Develop*. 2023;**13**(10):776-92. https://doi.org/10.2166/washdev.2023.040.
19. Nateghian A, Parvin M, Rouhani P, Tabrizi M. [Incidence and risk factors for gentamicin and ceftriaxone resistant E. coli causing urinary tract infection in children admitted in Hazrat-e-Ali Asghar Hospital]. *Razi J Med Sci*. 2009;**16**. Persian.
20. Alaei V, Salehzadeh F. [The clinical manifestations and antibiogram results in children with UTI]. *J Ardabil Univ Med Sci*. 2008;**8**(3):274-80. Persian.
21. Norouzi F. [Antibiotic resistance pattern of bacteria causing urinary tract infections in children of Fasa during the years 2012 and 2014]. *J Advanced Biomed Sci*. 2014;**4**(4):493-9. Persian.
22. Mortazavi-Tabatabaei SAR, Ghaderkhani J, Nazari A, Sayehmiri K, Sayehmiri F, Pakzad I. Pattern of Antibacterial Resistance in Urinary Tract Infections: A Systematic Review and Meta-analysis. *Int J Prev Med*. 2019;**10**:169. [PubMed ID: 32133087]. [PubMed Central ID: PMC6826787]. https://doi.org/10.4103/ijpvm.IJPVM_419_17.
23. Fahimi D, Khedmat L, Afshin A, Noparast Z, Jafaripor M, Beigi EH, et al. Clinical manifestations, laboratory markers, and renal ultrasonographic examinations in 1-month to 12-year-old Iranian children with pyelonephritis: a six-year cross-sectional retrospective study. *BMC Infect Dis*. 2021;**21**(1):189. [PubMed ID: 33602159]. [PubMed Central ID: PMC7890627]. https://doi.org/10.1186/s12879-021-05887-1.
24. Mantadakis E, Tsalkidis A, Panopoulou M, Pagkalis S, Tripsianis G, Falagas ME, et al. Antimicrobial susceptibility of pediatric uropathogens in Thrace, Greece. *Int Urol Nephrol*. 2011;**43**(2):549-55. [PubMed ID: 20524067]. https://doi.org/10.1007/s11255-010-9768-x.
25. Tullus K, Shaikh N. Urinary tract infections in children. *Lancet*. 2020;**395**(10237):1659-68. [PubMed ID: 32446408]. https://doi.org/10.1016/S0140-6736(20)30676-0.
26. Kalantar EA, Motlagh ME, Lornezhad H, Reshadmanesh N. Prevalence of urinary tract pathogens and antimicrobial susceptibility patterns in children at hospitals in Iran. *Iran J Clinical Infectious Dis*. 2008;**3**(3):149-53. Persian.
27. Mamishi S, Shalchi Z, Mahmoudi S, Hosseinpour Sadeghi R, Haghi Ashtiani MT, Pourakbari B. Antimicrobial Resistance and Genotyping of Bacteria Isolated from Urinary Tract Infection in Children in an Iranian Referral Hospital. *Infect Drug Resist*. 2020;**13**:3317-23. [PubMed

ID: 33061479]. [PubMed Central ID: PMC7535122]. https://doi.org/10.2147/IDR.S260359.

28. Mostafavi SN, Rostami S, Rezaee Nejad Y, Ataei B, Mobasherizadeh S, Cheraghi A, et al. Antimicrobial Resistance in Hospitalized Patients with Community Acquired Urinary Tract Infection in Isfahan, Iran. *Arch Iran Med*. 2021;**24**(3):187-92. [PubMed ID: 33878876]. https://doi.org/10.34172/aim.2021.29.
29. Hadifar S, Moghoofei M, Nematollahi S, Ramazanzadeh R, Sedighi M, Salehi-Abargouei A, et al. Epidemiology of Multidrug Resistant Uropathogenic Escherichia coli in Iran: a Systematic Review and Meta-Analysis. *Jpn J Infect Dis*. 2017;**70**(1):19-25. [PubMed ID: 27000462]. https://doi.org/10.7883/yoken.JJID.2015.652.
30. Gunduz S, Uludag Altun H. Antibiotic resistance patterns of urinary tract pathogens in Turkish children. *Glob Health Res Policy*. 2018;**3**:10. [PubMed ID: 29568806]. [PubMed Central ID: PMC5856228]. https://doi.org/10.1186/s41256-018-0063-1.
31. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ*. 2016;**352**. i939. [PubMed ID: 26980184]. [PubMed Central ID: PMC4793155]. https://doi.org/10.1136/bmj.i939.
32. van Staa TP, Palin V, Li Y, Welfare W, Felton TW, Dark P, et al. The effectiveness of frequent antibiotic use in reducing the risk of infection-related hospital admissions: results from two large population-based cohorts. *BMC Med*. 2020;**18**(1):40. [PubMed ID: 32114981]. [PubMed Central ID: PMC7050123]. https://doi.org/10.1186/s12916-020-1504-5.
33. Datta N, Nugent M, Amyes SG, McNeilly P. Multiple mechanisms of trimethoprim resistance in strains of Escherichia coli from a patient treated with long-term co-trimoxazole. *J Antimicrob Chemother*. 1979;**5**(4):399-406. [PubMed ID: 385578]. https://doi.org/10.1093/jac/5.4.399.
34. Erol B, Culpan M, Caskurlu H, Sari U, Cag Y, Vahaboglu H, et al. Changes in antimicrobial resistance and demographics of UTIs in pediatric patients in a single institution over a 6-year period. *J Pediatr Urol*. 2018;**14**(2):176 e1-5. [PubMed ID: 29428362]. https://doi.org/10.1016/j.jpurol.2017.12.002.
35. Long H, Miller SF, Strauss C, Zhao C, Cheng L, Ye Z, et al. Antibiotic treatment enhances the genome-wide mutation rate of target cells. *Proc Natl Acad Sci U S A*. 2016;**113**(18):E2498-505. [PubMed ID: 27091991]. [PubMed Central ID: PMC4983809]. https://doi.org/10.1073/pnas.1601208113.