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Frequency of Urinary Tract Pathogens and the Pattern of Antibiotic Resistance among Iranian Children

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Abstract

Background: One of the most typical reasons for pediatric hospitalization is urinary tract infection. The purpose of this study was to identify the prevalence of urinary tract pathogens and the distribution of antibiotic resistance in children with urinary tract infections referred to Shahid Beheshti Kashan Hospital in 2018–2019. This information would assist physicians in choosing more potent medications.

Methods: Children with urinary tract infections were the subject of this cross-sectional study, carried out in 2018–2019 at Shahid Beheshti Kashan Hospital. The presence of an active urine test, a positive urine culture, and clinical symptoms of a urinary tract infection were the inclusion criteria. Data were examined using SPSS 16 software.

Results: Out of the 400 children studied, 153 (38.2%) were males and 247 (61.8%) females. Among 153 boys, 96.1% had undergone circumcision, while 3.9% had not. Gender and UTI bacteria had a significant connection (p=0.023). *Escherichia coli* had the highest prevalence in female children's urinary tract bacteria. Males were more likely to contract *Escherichia coli*. Results indicated that ampicillin resistance pattern significantly correlated with gender (p=0.011). Amikacin, an antibiotic, proved most effective against *Escherichia coli*, the most prevalent pathogen. *Escherichia coli* also showed the highest level of ampicillin resistance. To combat antibiotic resistance, it is crucial to prescribe medicines in a methodical and scientific manner.

Conclusion: Pediatric urinary tract infections are most likely to be caused by *Escherichia coli*. This study's isolated bacteria showed a high sensitivity to Amikacin and resistance to Ampicillin, a penicillin beta-lactam antibiotic used to treat UTIs.

Key Words: Antibiotic Resistance, Pediatrics, Urinary Tract Infection.

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1- **INTRODUCTION**

A single pathogen growing with colony forming units (CFU) > 10^5 per ml of clean catch midstream urine is considered to be an infection of the urinary tract (UTI). Acute respiratory infections are the most prevalent infection in children, followed by UTIs (1). High morbidity and long-term consequences such renal scarring, hypertension, and chronic renal failure are linked to pediatric urine infections (1, 2). Approximately 7% of infants between the ages of 2 months and 2 years who have an unexplained febrile illness and 8% of children between the ages of 2 and 19 years who arrive with potential urinary symptoms are thought to have UTIs. During the first six years of life, there are 7% more recorded cases of UTI in females than in males (3). Generally, for all children, the highest incidence is observed in the first year of life (1%) but among boys, it significantly declines following infancy. Boys are more likely to develop UTI before the age of one-year; in the first year of life, particularly in the first three months, boys are more likely to develop UTI (3.7%) than girls (2%). After that, it was revealed that girls (3%) were far more likely than boys (1.1%) to have a UTI (4). The prevalence of asymptomatic bacteriuria is higher in females.

Pyelonephritis, an infection of the renal parenchyma, is caused by tissue invasion, inflammation, and bacterial proliferation in UTI (5).

According to the severity of the condition, UTI is divided into two categories: normal and atypical (complex) UTI. UTIs can be categorized based on whether they predominantly affect the lower urinary tract, known as cystitis, or the upper urinary tract, known as pyelonephritis. Age, gender, and other factors all affect the epidemiology of UTI in children (6). Clinical UTI presentation varies from patient to patient depending on the patient's age, the pathogen that is causing the UTI, any structural defects in the urinary tract, and the time since the patient last presented. The typical signs and symptoms include fever, stomach ache, vomiting, frequent urination, dysuria, burning micturition, and on rare occasions, either urinary retention or outright pyuria. When a child exhibits uraemia-related signs and symptoms (acidosis, anemia, hypertension), or symptoms of sepsis-like hypotension and convulsions, children can present an abnormal or difficult course. Hospitalization is necessary in these complex cases (atypical UTIs), as well as a comprehensive septic work-up that includes urinalysis, blood and/or urine cultures; and intensive treatment possibly including dialysis or urological therapies like catheterization is required (5, 7, 8). For prompt treatment to choose the proper antibiotic, follow-up imaging workup for underlying problems, and long-term observation for recurrence and Chronic kidney disease (CKD), a definitive diagnosis of UTI and the sensitivity pattern of the causative agents are critical. The treatment of UTI is more complicated in children with underlying obstructive disorders, refluxing kidneys, neurogenic bladder, or immunocompromised children, such as those who have undergone organ transplants.

Gram-negative bacteria from the Enterobacteriaceae family, of which *Escherichia coli* is the most common and responsible for more than 70% of UTIs in children, are the main cause of most pediatric UTIs. The same family also includes the common infections *Klebsiella* spp., *Enterobacter* spp., and *Proteus* spp. (3, 9). Despite being a less frequent Gram-negative infection, *Pseudomonas* aeruginosa is frequently linked to more severe UTIs. Gram-positive bacteria are only sometimes responsible for UTIs, and *Enterococcus spp* is the most frequent cause. Even in UTI, which has a varying

prevalence across different geographical areas, the development and spread of antibiotic resistance are significant global public health issues. The prevalence of uropathogen resistance to frequently used antibiotics for pediatric UTI has increased globally in recent years (10). Prior antibiotic use and abnormalities of the urinary tract are the most common risk factors linked to the development of UTIs caused by pathogens that are resistant to antibiotics (11-13).

In light of this, the purpose of this study was to investigate the incidence of uropathogens and antibiotic resistance patterns in pediatric UTI patients referred to Kashan Shahid Beheshti Hospital in 2019-2020 to guide physicians in selecting more effective antibiotics.

2- MATERIALS AND METHODS

2-1. Design and Population

The study was conducted at Beheshti hospital in Kashan, Iran. In this cross-sectional study, medical records for pediatric patients - of both sexes in the age group of one year and above - admitted to Shahid Beheshti Hospital in Kashan for UTI between January 1, 2018, and June 30, 2019, were analyzed. And Consent for publication was obtained from the patients.

A popular non-invasive sampling technique that is advised by numerous standards, including NICE, is midstream clean catch. For younger children Suprapubic needle aspiration (SPA) as well as Urine collection bags are mentioned as sampling methods. Only patients who had UTI symptoms and had positive urine cultures according to Shahid Beheshti Hospital's definition were mentioned. Positive urine culture (bacterial count greater than 10^5 CFU/ml) with active urine test and clinical signs of urinary tract infections were concluded. Standard procedures were followed during study. Age, sex, and the kind of admission were recorded together with demographic information. Following sampling with a standard loop at 0.01 volume, samples were cultured for up to 30 minutes on Blood Agar (BA) and Eosin Methylene Blue (EMB), both made by the German company Merck. The cultures spent 24 hours in the incubator at 37 degrees Celsius. If pee with 10^{-5} bacteria per ml of a colony-forming unit was discovered after this time; it was meant to be an infectious sample (Any counts obtained after SPA should be regarded as significant if urine is taken by catheterization; 1000–50 000 CFU/ml is deemed positive). The samples were then stored in the incubator at 37 °C for a further 24 hours. Colonies are produced using biochemical assays and common microbiological conditions, such as Gram staining, catalase, coagulase, bacitracin sensitivity, novobiocin sensitivity, urease, Triple Sugar Iron Agar (TSI) differential environment, indole synthesis test, and Sulfide Indole Motility. After preparing a microbial suspension equating to Half McFarland in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines, susceptibility was assessed using nine antibiotic discs (PattenTeb, Iran) including ampicillin, co trimoxazole (25 µgr), tetracycline(10 µgr), nitrofurantoin (300 µgr), Amikacin (30 µgr), cefixime (5µgr), cefotaxime cefixime (5µgr), gentamicin (10 µgr), and ciprofloxacin (5 µgr). Chi-square test ($P<0.05$) was used to examine the data through SPSS software version 21(14). The study was approved by Kashan University of Medical Sciences (KAUMS).

2-2. Data Evaluation

Retrospective reviews of all medical records of the participants with 1 year or older age range who met the inclusion and exclusion criteria were conducted. When it comes to young children, fever may be the only sign of a UTI. The signs of pyelonephritis or urosepsis in newborns can include failure to thrive, jaundice,

vomiting, hyperexcitability, lethargy, hypothermia, and occasionally even no fever. Unless there is an obstruction or the infant is in some other way compromised, septic shock is uncommon, even with a high temperature. Lower urinary tract symptoms in older children include dysuria, stranguria, frequency, urgency, malodorous urine, incontinence, haematuria, and suprapubic discomfort; upper urinary tract symptoms include fever and flank pain. Infant UTI may also be accompanied by temporary pseudohypoaldosteronism, significant hyponatremia, and either hyperkalaemia or neither (15, 16). Mixed cultures point to contamination. Age, circumcision status, and history of receiving antibiotics as well as fever (>37℃) are demographic factors mentioned in this study.

2-3. Data Analysis

Descriptive statistics (frequency distribution) and inferential statistics were used to analyze the data through SPSS software version 16 program. P-values lower than 0.05 were regarded as statistically significant.

3- RESULTS

To examine the prevalence of urinary tract infections and patterns of antibiotic resistance in children referred to Shahid Beheshti Hospital, Kashan, between 2018 and 2019, 400 cases were examined as part of this study (Total cases are 1100). Girls are more common than boys, with a frequency of 61.8%, additionally, 73.5% of children were older than one year of age. 96.1% of the boys had circumcisions as well. On the other hand, 61% of the kids in the study had previously taken antibiotics and 96.1% had circumcision status.

With 283 cases (70.8%), *Escherichia coli* was found to be the most frequently isolated microorganism from urine samples, followed by *Klebsiella pneumonia* (17.8%), Proteus (5.2%), and *Pseudomonas*.spp (2.3%). *Acinetobacter.spp* was the least prevalent, with three instances (0.8 percent) shown in **Fig. 1**.

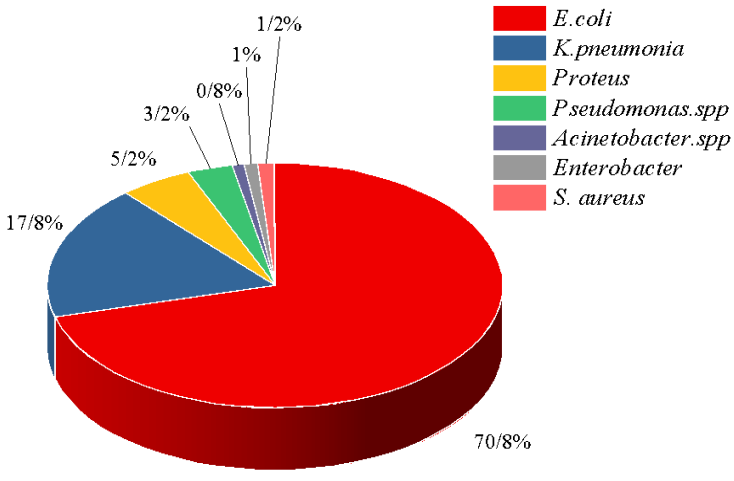

Fig. 1: The proportion of bacteria isolated from UTI urine samples

As shown in **Table 1**, there is a strong link between gender and the bacteria caus ing urine infection (p=0.016), with *Escherichia coli* being the source of urinary infection in 75.7% of females. The percentage for boys is 62.7%. Additionally, there was no correlation between age and the microorganisms that

cause urine infections (p=0.092); therefore, *Escherichia coli* bacteria caused urinary infections in 69.7% of infants under the age of one year and 71.1 percent of children above the age of one year.

Table-1: The frequency of pathogens isolated from urine samples of patients with UTI, according to gender

UTI pathogens	Gender			Age		
	Male	Female	Chi-square test	< 1 year	>1 year	Chi-square test
E. coli	96(62.7%)	187(62.7%)	0.016	74(69.7%)	209(71.1%)	0.093
K. pneumonia	34(22.2%)	37(15%)		20(18.9%)	51(17.3%)	
Proteus	8(5.2%)	13(5.3%)		4(3.8%)	17(5.8%)	
Pseudomonas	6(3.9%)	7(2.8%)		4(3.8%)	9(3.1%)	
Acinetobacter	2(1.3%)	1(0.4%)		0	3(1%)	
Enterobacter	2(1.3%)	2(0.8%)		0	4(1.4%)	
Staphylococcus	5(3.4%)	0		4(3.8%)	1(0.3%)	

Fig. 2 demonstrates that antibiotics ampicillin (98%), tetracycline (89%), and cotrimoxazole (83%) are associated with the greatest number of isolated microorganism resistance instances. On the other hand, amikacin (98%), nitrofurantoin (97%) and gentamicin (96%) caused the greatest occurrences of sensitivity. Additionally, the antibiotic ampicillin is associated with the majority of *Escherichia coli* resistance cases (

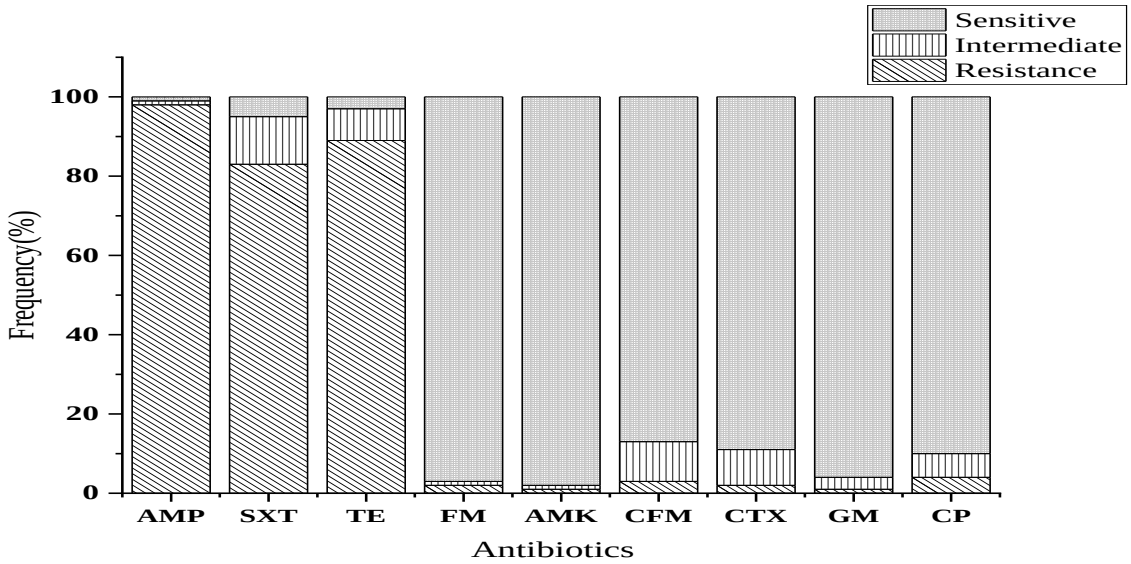

Fig. 2: The prevalence of antibiotic susceptibility. AMP: Ampicillin, SXT: co-trimoxazole, TE: tetracycline, FM: nitrofurantoin, AMK: Amikacin, CFM: cefixime, CTX: cefotaxime, GM: gentamicin, CP: ciprofloxacin

92.2%) and the least (1.4%) of instances is associated with the antibiotics amikacin and gentamicin. The lowest sensitivity, on the other hand, was associated with ampicillin (1.4%), while the maximum sensitivity was related to amikacin (97.2%). Antibiotic susceptibility percentage of bacteria isolated from both males and females using the disk diffusion method shown in **Table 2**.

Table-2: Antibiotic susceptibility percentage of bacteria isolated from gender using the disk diffusion method

Antibiotic	Susceptibility (%)	Bacteria						
		E.coli	*K.pneumonia*	*Proteus*	*Pseudomonas*	*Acinetobacter*	*Enterobacter*	*Staphylococcus*
AMP	Resistant	275(92.7%)	71(100%)	21(100%)	13(100%)	3(100%)	4(100%)	5(100%)
	Intermediate	4(1.4%)	0	0	0	0	0	0
	Susceptible	4(1.4%)	0	0	0	0	0	0
SXT	Resistant	240(84.8%)	58(81.7%)	13(62%)	13(100%)	3(100%)	3(75%)	4(80%)
	Intermediate	35(12.4%)	9(12.7%)	4(19%)	0	0	0	0
	Susceptible	8 (2.8%)	4(5.6%)	4(19%)	0	0	1(25%)	1(20%)
TE	Resistant	251(88.7%)	67(94.4%)	17(81%)	9(69.2%)	3(100%)	4(100%)	5(100%)
	Intermediate	20(7.1%)	4(5.6%)	4(19%)	4(30.8%)	0	0	0
	Susceptible	12(4.2%)	0	0	0	0	0	0
FM	Resistant	8(2.8%)	0	0	0	0	0	0
	Intermediate	4(1.4%)	0	0	0	0	0	0
	Susceptible	271(95.8%)	71(100%)	21(100%)	13(100%)	3(100%)	4(100%)	5(100%)
AMK	Resistant	4(1.4%)	0	0	0	0	0	0
	Intermediate	4(1.4%)	0	0	0	0	0	0
	Susceptible	275(97.2%)	71(100%)	21(100%)	13(100%)	3(100%)	4(100%)	5(100%)
CFM	Resistant	8(2.8%)	4(5.6%)	0	0	0	0	0
	Intermediate	24(8.5%)	8(11.3%)	4(19%)	4(30.8%)	0	0	0
	Susceptible	251(88.7%)	59(83.1%)	17(81%)	9(69.2%)	3(100%)	4(100%)	5(100%)
CTX	Resistant	8(2.8%)	0	0	0	0	0	0
	Intermediate	28(9.9%)	4(5.6%)	4(19%)	0	0	0	0
	Susceptible	247(87.3%)	67(94.4%)	17(81%)	13(100%)	3(100%)	4(100%)	5(100%)
GM	Resistant	4(1.4%)	0	0	0	0	0	0
	Intermediate	12(4.2%)	0	0	0	0	0	0
	Susceptible	267(94.4%)	71(100%)	21(100%)	13(100%)	3(100%)	4(100%)	5(100%)
CP	Resistant	16(5.7%)	0	0	0	0	0	0
	Intermediate	12(4.2%)	4(5.6%)	4(19%)	4(30.8%)	0	0	0
	Susceptible	255(90.1%)	67(94.4%)	17(81%)	9(69.2%)	3(100%)	4(100%)	5(100%)

AMP: Ampicillin, **SXT**: co-trimoxazole, **TE**: tetracycline, **FM**: nitrofurantoin, **AMK**: Amikacin, **CFM**: cefixime, **CTX**: cefotaxime, **GM**: gentamicin, **CP**: ciprofloxacin

4- DISCUSSION

This study was carried out with the intention of determining the prevalence of urinary tract pathogens and the distribution of antibiotic resistance in children referred to Kashan's Shahid Beheshti Hospital between 2018 and 2019. In the first year of life, both boys and girls experienced the same rate of UTIs, which thereafter shifted to favoring girls. Most kids exhibited no clinical signs. According to three previous studies, breastfeeding may influence the likelihood of UTIs. The risk of UTI in children may be decreased by breastfeeding and maintaining a healthy weight (17-19). The treatment of UTIs in Iran is known to be severely complicated by antibiotic resistance (20, 21). Uncontrolled antibiotic use and unproven methods of treating urinary tract infections have decreased the drugs' sensitivity to uropathogenic bacteria (22, 23).

Ecoli was found to be the most frequently isolated bacteria from the urine cultures of the children in this study (70.8%), followed by *Klebsiella*, *Proteus*, and *Pseudomonas*. Acinetobacter was the least isolated microorganism. The results of a study by Renjbar et al. (24) that looked at the pattern of antibiotic resistance and the prevalence of microbial species in children with urinary tract infections sent to Motahari Hospital in Urmia, Iran, revealed that *Ecoli* was the most common strain isolated from urine cultures (81.3%); this finding is consistent with the findings of the current study. *Ecoli* and *Klebsiella* were found to be the most prevalent organisms in another study by Mollazadeh et al. (25) which examined the pattern of antibiotic resistance of bacteria causing urinary tract infections in children in Fasa City, Iran. Consistently, the study's findings are presented. *Ecoli* was the most isolated microbe in the investigations of Hanna-Wakim et al.(26) and Elder et al. (27); and the results are supported by the present study.

According to the study's goals, the frequency of antibiotic sensitivity and resistance patterns in each microbe isolated from the urine culture of study participants was examined. According to the findings of the current investigation, regardless of the disease-causing strain, the isolates had the maximum sensitivity to amikacin. The next two drugs in line were gentamicin and nitrofurantoin. Additionally, independent of the strain responsible for the condition, the isolates exhibited the highest levels of resistance to ampicillin, with tetracycline and cotrimoxazole medicines coming in at the bottom of the list. According to the findings by Ranjbar et al., the most efficient antibiotics were nitrofurantoin and gentamicin in the order of microbial sensitivity; the findings of the current study verify these findings (24). A similar research was conducted in Croatia by Ili et al., (28) but their findings were different in that there was less cotrimoxazole, cephalexin, and nitrofurantoin resistance there.

Ampicillin, Amoxicillin-clavulanic acid, cotrimoxazole, cefuroxime, and ciprofloxacin had the highest rates of antibiotic resistance in the study conducted by Duicu et al., but Amikacin, and carbapenem were the most effective medications and showed that they might be utilized for the empirical treatment of febrile or complex UTI in children (29). Antibiotic resistance patterns frequently change and worsen, mostly because of variations in the types of organisms, organism types, processes, and methods used. Amino-glycosides and carbapenems have been identified as the most effective antibiotics against gram-negative isolates isolated from UTIs in studies from Oman (30), Iran (31), and Lebanon (32), which are comparable to our findings.

In contrast to the current study, the resistance of the isolates to ciprofloxacin, cefixime, ceftriaxone, nitrofurantoin, and

cotrimoxazole was lower in the study by Gökçe et al., in Istanbul (33). It can be claimed that these disparities may be brought on by the pattern of prescription antibiotics to patients in various locations. As a result, the pattern of antibiotic sensitivity and antibiotic resistance may shift due to this variation in antibiotic prescription patterns. Additionally, self-treatment can play a role in some general strata and influence the frequency of both antibiotic sensitivity and resistance in various societies. Ecoli, the most prevalent pathogen in this study, responded most favorably to amikacin, followed by nitrofurantoin and gentamicin. The highest level of ampicillin resistance was seen in *Ecoli*. The resistance rate of *Ecoli* to amikacin, gentamicin, and nitrofurantoin in the study of Mirsoleymani et al. was comparable to the findings of the current study, but the resistance rate to other antibiotics was higher (34). The antibiotic nitrofurantoin had the highest level of sensitivity in the investigation by Ranjbar et al., which is also congruent with the results of the current study (24).

The selected antibiotics were not the same in all studies, and different types of antibiotics were chosen in different ways, which is consistent with the variation in the results of some studies. Another potential affecting element is the pattern of antibiotic prescriptions in various locations.

4-1. Limitations of the study

One of the study's drawbacks is the absence of an analysis of demographic factors like residency and hospitalization history, which were not fully included in the patient records but can be important environmental variables in studies of antibiotic resistance. Another restriction of the current study was the incompleteness of some files.

5- CONCLUSION

Ecoli was the most prevalent urinary tract infection pathogen among the study's participants, according to the study's findings. This study's isolated bacteria showed high sensitivity to Amikacin and resistance to Ampicillin, a penicillin beta-lactam antibiotic used to treat UTIs. However, the optimal course of treatment for this form of infection requires a careful examination of each patient's infectious agent's drug resistance before prescribing antibiotics. Finally, pediatricians in Kashan region are strongly adviced to use Amikacin for UTIs.

6- CONFLICT OF INTEREST

None.

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