A Nine-Year Follow-Up of Antimicrobial Resistance Profile in Children with Urinary Tract Infection in Northern Iran

Hadi Sorkhi[1], Fazeleh Shahhoseini[1], Mahmoud Hajiahmadi[1], Abazar Pournajaf[2], Mehrdad Halaji[2], Mohsen Mohammadi[1]*

1. *Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran*
2. *Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran*

ABSTRACT

Background and Aim: Urinary tract infection (UTI) is one of the most common infections in children. Arbitrary use of antibiotics has increased the resistant strains and transmits these resistant factors to other pathogens. Therefore, this study was designed to follow the resistance trend in 9-years in children with urinary tract infections referred to the Amirkola Children's hospital (Northern Iran).

Materials and Methods: In this cross-sectional study, all children who had Urinary tract infections between 1994 to1998 and 2013 to 2018 with one month to 18 years old were included. Data (covering 9 years), such as age, sex, antibiotic resistance profile, urine culture results, and history of UTI, were collected retrospectively from patients' records. Cases were selected based on clinical and microbiological criteria. Antimicrobial susceptibility was determined by the Kirby–Bauer disk diffusion method.

Results: *Escherichia coli* was the most predominant organism isolated from urine samples. The highest drug resistance was related to cefazolin (83.3%). Resistance to nitrofurantoin was higher in children older than 5 years ($P \leq 0.001$). Moreover, the resistance pattern to gentamicin, amikacin, ceftriaxone, cephalexin, and imipenem differed in females and males ($P > 0.05$).

Conclusion: A 9-year study showed that 91.4% of the strains are still sensitive against amikacin which is a suitable treatment option in the studied strains. The establishment of antimicrobial stewardship programs and regular monitoring of antimicrobial resistance could help to reduce inappropriate prescribing for UTIs.

Keywords: Antibiotic resistance, Children, Iran, Urinary tract infection

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1. Introduction

Urinary tract infections (UTIs) are common infections in 3-5% female and 1% male children and are the commonest proven bacterial infection in febrile infants without localizing signs **(1, 2)**. UTI is one of the main causes of hospitalization in children with significant complications and high healthcare costs **(2, 3)**. Children with UTI may show non-specific symptoms, which can be challenging to diagnose. Therefore, timely diagnosis and proper treatment can reduce severe complications such as hypertension, renal scarring, pyelonephritis, and chronic kidney disease (CKD) **(4, 5)**. A urine culture should be performed in children with fever of unknown origin (FUO) to rule out UTI **(6)**. On the other hand, UTIs in children with vesicoureteral reflux (VUR) are very important in order not to cause renal scarring and CKD **(7)**.

Long-term use of antibiotics is essential to prevent kidney damage in high-risk children. Proper treatment of UTIs has become challenging due to high resistance to frequently prescribed antibiotics (e.g., amino-penicillins, aminoglycosides, and quinolones) and the internationally increasing frequency of multidrug-resistant (MDR) organisms causing UTIs. Evidence has shown a high frequency of MDR in Gram-negative organisms (GNOs), which are the commonest cause of UTIs (7). Among the GNOs, uropathogenic *Escherichia coli* (UPEC) is the pathogen most frequently associated with UTIs. For example, resistance to ampicillin and SXT in the study of Vazouras *et al.* (2019) was reported to be more than 51% and 29%, respectively (8). The exact burden of antimicrobial resistance (AMR) in children in Iran is poorly understood, as few studies have been done in this area. The aims of this study were *(i)* to introduce antibiotic prescribing profiles for clinical and empirical treatments and *(ii)* to investigate the AMR rates of uropathogens isolated from hospitalized children with UTI in the Amirkola Children's hospital (Babol, north of Iran) over 9 years.

2. Materials and Methods

Study Design

This descriptive cross-sectional retrospective study was performed in 2019 and followed the trend of antibiotic resistance pattern over 9 years from 1994-1998 and 2013-2018. The Amirkola Children's hospital is a 110-registered bed hospital and is one of the most equipped teaching therapeutic centers affiliated to the Babol Medical University in the north of Iran. This work was approved (ethic code: IR.MUBABOL.HRI.-REC.1398.191) by the Research Ethics Committee of the Babol University of Medical Sciences, Iran.

Inclusion Criteria

Children from 1 month to 18 years of old with UTIs were included in the study. UTIs was defined based on the following criteria: (i) positive urine culture with pathogen growth ≥10^4 CFUmL^{-1} for catheter samples or suprapubic aspiration or ≥10^5 CFUmL^{-1} for clean-catch specimens; and (ii) pyuria (≥5 white blood cells per high-power field) in centrifuged urine OR positive dipstick (leukocyte esterase or nitrites) (9). Patients with incomplete records were excluded from the study.

Laboratory Methods

Erythrocyte sedimentation rate (ESR) was measured by the micro (capillary tube) laboratory method. The rate of RBC deposition per hour indicates a systemic inflammation and is more likely to indicate an upper UTI. The serum level of CRP was measured quan-titatively according to the manufacturer's instruction (Bionic, Iran). Antibiotic susceptibility pattern was performed using the Kirby–Bauer disk diffusion method on the Mueller-Hinton agar (Merck, Germany) recommended by the Clinical and Laboratory Standards Institute (CLSI) guideline. Commonly used antibiotics include, amikacin (AK; 30 µg), gentamicin (GM; 10 µg), nalidixic acid (NA; 30 µg), ceftizoxime (CZ; 30µg), ceftriaxone (CRO; 30 µg), trimethoprim-/sulfamethoxzale (SXT, 1.25/23.75 µg) nitrofurantoin (FT; 300µg), and ampicillin (AMP; 10 µg) (10).

Statistical Analyses

All statistical analyses were performed by SPSS 22 (SPSS Inc., Chicago, Ill., USA), and a P-value < 0.05 was considered significant. The results were analyzed using the Chi-square and Kruskal-Wallis tests, followed by residual analysis.

3. Results

A total of 253 children (n= 227; 89.7% of female, n=26; 10.3% of male) with a diagnosed UTI were followed during the study period. The mean age of patients included in the study was 38.8 ±40.9 months. UTI was diagnosed for the first time in 76.7% (n; 194/253) of children, and recurrent UTI (rUTI) was reported in 23.3% (n; 59/253) of cases.

The length of hospitalization was 9.42±3.13 days. The mean ±SD of CRP (mg/ dl), ESR (mm/ h) and WBC (cell/ mcl) were 75.61 ± 37.4, 61.59 ± 28.17 and 16187.63±6479.83, respectively. The mean level of WBC was 16187.63±6479.83 m/mm^3. The highest and lowest CRP rate were 7 and 230 mg/dL, respectively. The ESR was in a range of 21 - 163 mm/h. The most commonly identified pathogen was *E. coli* (84.9%; 215/253), followed by *P. aeruginosa* (3.9%; 10/253), *K. pneumoniae* (4.3%; 11/253), and *Enterobacter* spp. (2.8%; 7/253). *Enterococcus* spp. (1.6%; 4/253) and *Proteus* sp. (1.2%; 3/ 253) were the least frequent isolates in this population.

Antibacterial susceptibility tests showed that the highest resistance rates were related to AMP (71.8%) and SXT (66.3%). In contrast, the most susceptible antibiotics were AK (93.4%) and FT (93.1%). Examination of the trend of resistance pattern over 9 years showed that the sensitivity of AK at 2013-2018 was 93.4%, while at 1994-1998 was 91.4%. However, this antibiotic was the most effective. Between 2013 and 2018, sensitivity to FT was 93.1%, while in 1994-1998, it was 52.9%. Resistance to AMP was 96.4% from 1994-1998, whereas decreased to 71.8% over time (Figure 1 and Table 1).
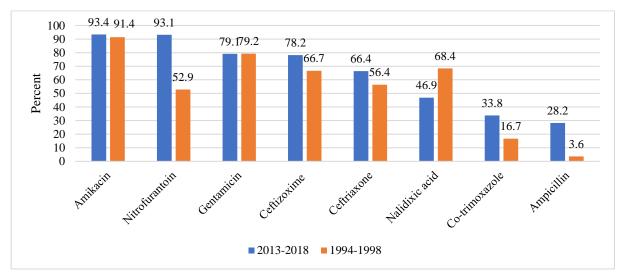
Figure 1. A trend of antibiotic susceptibility pattern over time.

However, there was no significant difference between the trend of antibiotic-resistant rate between the first and second periods of study (P>0.05). Only gram-negative isolates demonstrated increased resistance to NA in the second period. A trend of antibiotic susceptibility patterns over time has been shown in Figure 1. Moreover, the details of antibiotic susceptibility patterns of Gram-negative isolates recovered from UTIs are presented in Table 1.

Table 1. Antibiotic Susceptibility Patterns of Gram-negative Isolates Recovered From UTIs in 2013-2018

Antimicrobials	E. coli N=215 (%)	P. aeruginosa N=10 (%)	K. pneumoniae N=9 (%)	Enterobacter N=7 (%)
Amikacin	11 (5.1)	1 (10)	0	0
Nitrofurantoin	6 (2.8)	9 (90)	1 (11.1)	0
Gentamicin	37 (17.2)	2 (20)	2 (22.2)	3 (42.8)
Ceftizoxime	33 (15.3)	5 (50)	3 (33.3)	2 (28.6)
Ceftriaxone	61 (28.4)	2 (20)	3 (33.3)	3 (42.8)
Nalidixic acid	110 (51.2)	8 (80)	2 (22.2)	5 (71.4)
Co-trimoxazole	133 (61.9)	8 (80)	5 (55.6)	5 (71.4)
Ampicillin	141 (65.6)	9 (90)	9 (100)	7 (71.4)

4. Discussion

The widespread spreading of bacterial isolates with the extensive ability to resist a broad spectrum of antibiotics is a severe challenge for physicians faced with these organisms (11, 12). Therefore, to monitor the clinicians to proper and accurate prescription for prophylaxis purposes, updated and awareness of antimicrobial susceptibility pattern is necessary (13, 14). Therefore, the present study investigated the etiology of UTIs and bacterial resistance patterns in UTIs of children admitted to the teaching hospital in the two periods of 1994-1998 and 2013-2018. Accordingly, *E. coli* was the most frequent isolate, followed by *P. aeruginosa*, *K. pneumoniae*, *Enterobacter* spp., *Enterococcus* spp., and *Proteus* spp (11, 12).

In agreement with a previous study performed by Ronald *et al.*, in our study, *E. coli* with an isolation rate of 85% was the most frequent isolate (15). Moreover, in accordance with our results, Motamedifar *et al.* from Shiraz city of Iran reported that *E. coli* (50.6%) was the most common gram-negative isolate, followed by *Klebsiella spp*. And *Enterobacter spp.*, respectively (16). Farajnia *et al.* reported that *E. coli*, *P. aeruginosa,* and *Staphylococcus saprophyticus* were three prevalent causes of UTIs in patients aged less than 9 years old and older. However, in contrast with our finding, they revealed that *S. saprophyticus* was among three frequent isolated bacteria in patients(17).

Similar to findings in previous studies performed by Raya *et al.* **(18)**, Vazouras *et al.* **(8)** and Duicu *et al.* **(19)**, on the same subject, *E. coli* was the most frequently encountered etiological agent in our research as well. Therefore, the role of *E. coli* as the predominant causative agent of UTIs was confirmed in most previous studies **(20)**. These variations rely on the type of isolation, type of infection, studied population, and geographical distribution **(21)**.

E. coli with a frequency of 120 (56.1%) cases in the age group of 1 month to 24 months was the most common cause of UTIs in children. However, in our results, the patterns for the commonest etiologic agent of UTIs other than *E. coli* were similar in different age groups. So, according to the type of bacteria causing the infection, there is no statistically significant difference in children with different age groups. In contrary to our finding, Fesharakinia *et al.* revealed that there was a significant association between type of microorganism and the age of patients with UTIs, where the most frequent cause of UTIs in all ages was *E. coli* (75%), followed by *Proteus* (11%) **(22)**.

The acceptable treatment of UTIs in pediatrics depends on the early identification of infecting etiology and antibiotic susceptibility patterns **(23)**. In this regard, antibiotic susceptibility results showed that the susceptibility rate of AK in the first period of study was 93.4%, while in the second period of study was 91.4%. However, in the second period of study, this antibiotic was the most sensitive and effective; therefore, it seems that the sensitivity rate of AK in the studied population during these two periods has not significantly changed.

Moreover, according to our results, the sensitivity rate of FT was observed to be 93.1%. In contrast, in the previous period, its sensitivity was 52.9%, probably due to the limited use of FT antibiotics. In addition, in the first period of study, the antibiotic resistance of AMP was 96.4%. In the second period of study, its resistance was reduced to 71.8%, which may be due to the reduction in the use of this antibiotic in children.

However, compared to the previous period (1994-1998), the trend susceptibility rate of all antibiotics except NA in the current period (2013-2018) has increased. In 1994, 31.6% of isolates were resistant to NA, while in 2003 reached over 53% were resistant. In a study conducted by Wang *et al.,* uropathogens had a low susceptibility to imipenem (5.74%) and AMC (3.17%), but they had a high level of susceptibility against cefotaxime (71.41%), cefazolin (73.41%), cefuroxime (72.52%), and aztreonam (70.11%) **(24)**.

Furthermore, in the study performed by Duicu *et al.,* the highest rates of antibiotic resistance were related to ampicillin, AMC, TMP/SMX, cefuroxime, and ciprofloxacin, while FT, CRO, AK, and carbapenem were the most effective agents which suggested may be used for the empirical treatment for febrile or complicated UTI in children **(19)**. Antibiotic resistance patterns are usually wildly changing and increasing, mostly due to variation in the geographical area, type of organisms, different mechanisms, and used methods. However, similar to our study, studies from Oman **(25)**, Iran **(16)**, and Lebanon **(26)** introduced aminoglycosides and carbapenems as the most effective antibiotics against gram-negative isolates obtained from UTIs. This study had the main limitation; the study was only performed in a children's center; therefore, generalization of the results to other regions requires further investigations.

4. Conclusion

According to the present study, the pattern of drug sensitivity has not changed significantly. Recognition and timely detection of antibiotic resistance and the proper use of antibiotics to reduce drug resistance are the most important principles that should be followed when selecting antibiotics. Moreover, the alarmingly high rates of antibiotic resistance in hospitalized children with UTI and the emergence of carbapenemases emphasize that susceptibility testing should be carried out on all clinical isolates.

Ethics approval and consent to participate

This study was also confirmed and permitted by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.HRI.REC.1398.191). These patients were routinely referred to the microbiology laboratory, and a urine sample was taken, and then we only used bacteria isolates obtained from urine culture.

Author's Contributions

HS and MM; designed the study, reviewed the manuscript and edited the final version. FSH, MH, AP, and MeH contributed to designing the study, collected the data, and drafted the manuscript. FSH and MH contributed to designing the study, collected the data, and participated in drafting the manuscript. AP and

MeH analyzed the data, reviewed the manuscript, and edited the final version.

Conflict of Interest

The authors report no conflicts of interest in this work.

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