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Evaluation of Antibiotic Sensitivity of Urinary Tract Pathogens among Children in Zahedan, South East of Iran

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Abstract

Background

Urinary tract infection (UTI), are the most frequent and serious infection in childhood around the world. The present study aimed to evaluate antibiotic sensitivity of urinary tract pathogens among children in Zahedan, South East Iran.

Materials and Methods

This cross-sectional study analyzed 396 patients aged 1-18 years with positive urine and suspected UTI. Gender and age of children, kind of isolated bacteria in urine culture, susceptibility and resistance of these bacteria to current antibiotics were studied. Bacterial growth for more than 10^5 CFU/ml was considered as positive. Data analyzed by SPSS version 21.0.

Results

The most common age of urinary tract infection were < 1 year and 1-7 years for boys and girls, respectively, and the variation of sex distribution was significant in different age groups (P = 0.003). The most prevalent cause of UTI was Escherichia coli (E.coli) (77%), in total ages and both gender, afterward was Enterobacter (8.1%) and Klebsiella (7.1%). E.coli sepsis was highly sensitive to nitrofurantoin (74.7%), ciprofloxacin (72.5%), and amikacin (64.6%), both highly resistant to trimethoprim and sulfametoxazole (74.8%), ampicillin (66.9%), and nalidixic acid (51.1%); and its resistance to ceftriaxone was increasing.

Conclusion

In this study resulted that E. coli was the first responsible pathogen in proven culture of UTI in children, which was increased in resistance to popular antibiotics like Ampicillin, Sulfamethoxazole-trimethoprim and Nalidixic acid. In several countries, emphasize the need for local population specific surveillance for guiding empirical therapy for UTI in children.

Key Words: Antibiotic, Bacteria, Children, Urinary tract infection.

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1- INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections in childhood with prevalence of 1-3% in girls and 1% in boys. UTI has been considered in clinical performs and is noticed with high morbidity. Moreover, it has long-term complications like renal scarring and hypertension in pediatric population (1-6). In most cases, it characterized by high incidence, high recurrence, and mild severity of evolution. It often forces physicians to introduce antibiotic for prior treatment to obtain the culture results because of the uncomfortable symptoms (7, 8). The incidence has a peak in girls specially, in toilet training period and adolescence, but in boys, mostly occurs during the first year of life; specially uncircumcised ones (3, 4, 9).

The most common causative pathogen for UTI is Escherichia coli (3-6, 9-11), and followed by Klebsiella species (spp.), Proteus spp., Enterococcus spp., Pseudomonas aeruginosa and Staphylococcus spp., (6, 8, 12, 13). Proteus is as common as E.coli in boys higher than one year. Staphylococcus saprophyticus and enterococci are pathogenic in both genders. The most common causes of UTI are ascending pathway from normal flora in the perineum. In uncircumcised boys, the prepuce is the origin of pathogenic bacterial flora. The factors that affect increasing urinary tract infections included of age, gender, circumcision, meatal stenosis, and obstruction of the urinary tract, vesicoureteral reflux, constipation, anatomical abnormalities, neuropathic bladder. Sign and symptoms of UTI are very varied from asymptomatic bacteriuria to full sepsis depending age, underlying disease, responsible pathogen (3, 14).

Community acquired UTIs could be uncomplicated in the majority of cases, but those of the hospital settings resulting in high rate of morbidity and economy cost (3, 14, 15). As above-mentioned, the maximum morbidity and mortality rate due to UTI occurs in age less than one year, therefore could be resulted that early diagnosis and treatment of UTI is needed to prevent complications such as Pyelonephritis, Urosepsis, hypertension, protein urea, kidney dysfunction and renal scarring (9, 10). The majority of these patients receive empirical antibiotic therapy before preparing the result of urine culture and antimicrobial sensitivity and resistance. The recent studies have showed that unfortunately, the antibiotics and resistance of uropathogens are increasing and this is a worldwide concern (1, 2, 4-11). In the geographic area of the study, a research resulted that all isolates were in resistance to amoxicillin and any were in resistance to imipenem and Colistin sulfate. In the mentioned research, among the tested strains, amikacin, gentamicin and ciprofloxacin had the lowest antibiotic resistance and have been proved that these antibiotics were the best therapeutic options for treatment of outpatients with UTI accordance with side effects of imipenem and Colistin sulfate in this region (16). In an attempt, this study aimed to assess the prevalence of main UTI causative agents and to find antimicrobial resistance pattern in the southeast area of Iran that enables physicians to prescribe an appropriate empirical antimicrobial therapy.

2- MATERIALS AND METHODS

2-1. Design and samples

In this cross-sectional study, 396 children with UTI were enrolled after exclusion criteria. The study children were aged one month to eighteen years old. These children with signs and symptoms of UTI were referred to the pediatric clinics of Ali Ibn Abi Talib hospital in Zahedan city, Sistan and Baluchestan province, Iran, from January 2013 to September 2015.

2-2. Method and clinical measurements

In the laboratory, urine samples were cultured in blood agar and MacConkey agar Medias under sterile condition and incubated for 24h at 36°C. Microbial growth identification performed by gram stain and disc diffusion technique (17). The disc that have been used (MAST, Merseyside, UK) were included of Cefepime (30µg), Aztreonam (30µg), Imipenem (10µg), Gentamicin (10µg), Streptomycin (10µg), Amikacin(30µg), Ciprofloxacin (5µg), Cefotaxime (30µg), Cef-tazidime (30µg), Ceftriaxone (30µ), Cefpodoxime (10µg), Nalidixic acid (30µg), Ni-trofurantoin (300µg), Colistin sulfate (25µg), Amoxicillin (25µg), and Trimetho-prim / Sulfamethoxazole (1.25/23.75µg). For screening Extended-spectrum beta-lactamases (ESBL) producing isolates, the clinical and laboratory standards institute (CLSI) confirmatory test was done by disc diffusion method with discs containing Ceftazidime (30µg) and Ceftazidime / Clavulanicacid (30/10µg), as well as Cefotaxime (30µg) and Cefo-taxime/Clavulanic acid (30/10µg) (18).

Patients were classified into three groups: sensitive, intermediate and resistant according to the clinical and laboratory standards institute procedure. Criteria were based on usual dosage regimens and routes of administration in the United States. Susceptible, intermediate, or resistant interpretations reported and defined based on Clinical, Laboratory Standards Institute (18). 1. Susceptible (S): The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used. 2. Intermediate (I): The "intermediate" category includes isolates with antimicrobial agent minimum inhibitory concentrations (MICs) that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (eg, quinolones and β-lactams in urine), or when a higher than normal dosage of a drug can be used (eg, β-lactams). This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmaco-toxicity margins. 3. Resistant (R): The "resistant" category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules, and/or that demonstrate MICs or zone diameters that fall in the range where specific microbial resistance mechanisms (eg, -lactamases) are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

2-3. Criteria

Children with mixed bacterial growth and those who had history of genitourinary abnormalities, recent hospitalization, or antibiotic usage were excluded from the study and the urine cultures were considered as negative when bacterial growth was lower than 103 CFU/mL.

2-4. Ethical consideration

After permission from the patients' parents or guardians, data on age, sex and needed information about urine culture were obtained from the medical records of patients. Urine samples were collected using midstream method in toilet-trained children and using clean catch methods or sterile bladder catheter in younger children and infants in the consideration of the parents or guardians' permission.

2-5. Statistical analysis

Data collection carried out from sheet information and entered to SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). For the analyses, the frequency and percentage were used as descriptive statistics and for the inferential statistics Chi-square test applied to test the study's hypotheses. The level of significant considered as 0.05 errors.

3-RESULTS

In the present study, 396 children with signs and symptoms of UTI entered to the study and referred to Ali Ibn Abi Talib hospital's pediatric clinics in Zahedan city, Sistan and baluchestan province, Iran. The patients aged one month to 18 years. Sex distribution was 328 (82.8%) and 68 (17.2%), for female and male, respectively, and the sex ratio was 4.8:1(female to male). The most frequent UTI occurred in female 1 to 7 years old (52.7%) then in boys under one year old (50%) (**Table.1**).

The **Table.1** also illustrated that the sex distribution of participants was variable accordance with age groups, so that boys were higher in age lower than 1 year compared to other age groups. This variation of sex distribution was significant in different age groups (P=0.003). Gram-negative and Gram-positive UTIs were found in 97% and 3% of the patients, respectively. The most common pathogen causing UTI was E.coli with 77.02% relative frequency, and afterwards Enterobacter with 8.08% relative frequency.Gram-positive bacteria were the minimum micro-organisms that caused UTI, with relative frequency 1.26%. According to the age structure, E.coli was the most micro-organisms that caused UTI in all age groups. Klebsiella was in the second place and Proteus was in last place. Klebsiella and Enterobacter prevalence with a relative frequency of 5.9% were similar. Minimum organism causing the infection in this group was Proteus with a relative frequency 2.9%. In the age group of 15 to 7 years after E.coli, Enterobacter was common with frequency of 6 patients (21.4%). In this age group, 2 patients (1.7%) were infected with Proteus. Also, no case of infection with Klebsiella and other Gram-positive bacteria were reported (**Table.2**). Escherichia coli (305 patients) with relative frequency 77% was the most common gram-negative organisms in culture positive UTI which was maximum sensitivity to Nitrofurantoin (74.4%), Ciprofloxacin (72.5%), Amikacin (64.6), Gentamicin (62.3%). The maximum resistance of E.coli was Trimethoprim and Sulfamethoxazole (74.8%), Ampicillin (66.9%) and Nalidixic acid (51.1%). It seems that Ceftriaxone (45.6%) was becoming to be resistant in this group. Enterobacter had most sensitivity to ciprofloxacin (87.5%), Nitrofurantoin (75%) the same as Gentamicin, Amikacin (68.8) the same as Cefotaxime (69.6 %), Ceftriaxone (65.6%) and then to Cefixime (56.2%). The maximum Enterobacter resistance was to Ampicillin (53.1%), Trimethoprim and Sulfamethoxazole (43.8%) (**Table.3**).

Pseudomonas was reported in 12 cases (3%), with equal frequency in both genders. Its most sensitivity was to Ciprofloxacin (83.3%), Gentamicin (76%), Amikacin (66.7%) Nitrofurantoin (58.3%), and was resistant to others. Staphylococcus aureus and Staphylococcus epidermidis were Gram-positive bacteria in this study. They were found in 1.3% of the positive cultures and had most sensitivity to Amikacin (100%), Gentamicin and Ciprofloxacin (80%) and Ceftriaxone (60%), and were resistant to the rest. Klebsiella (28 cases) was with relative frequency 7.1%. It had the greatest sensitivity to Ciprofloxacin (92.2%), Nitrofurantoin (78.6%), Gentamicin (60.7%) the same as Amikacin and Ceftriaxone (50%). Klebsiella strains were resistant to Trimethoprim and Sulfamethoxazole (78.6%), Ampicillin (57.1%) and Cefixime (46.4%). In this study, Proteus was with relative frequency 2.5%. The most cases of UTI with Proteus reported in girls (90%). The maximum Proteus sensitivity was to Ciprofloxacin (70%) and then to Amikacin and Gentamicin (60%), and Cefotaxime (50%).There was no sensitivity to other antibiotics. Citrobacter freundii was the minimum underlying pathogens in our patients, only in 4 cases (1%) with peak sensitivity to Nalidixic acid, Ciprofloxacin and Amikacin. It was also sensitive to Gentamicin, Nitrofurantoin and Ceftriaxone (**Table.3**).

Table-1: Participant sex distribution based on age groups

Gender	<1 year	1_7 years	7_18 years	Total	P-value
Boy, number (%)	34(50)	23(33.8)	11(16.2)	68(100)	0.003
Girl, number (%)	94(28.7)	173(52.7)	61(18.6)	328(100)	
Total	128(32.3)	196(49.5)	72(18.2)	396(100)	

Table-2: Organisms that cause UTI based on gender and ages

Organisms	Gender		Age, year			Total
Microorganism	Boy	Girl	< 1	1_7	7_18	
Escherichia coli	43(14,1)	262(85.9)	99(32.5)	150(49.2)	56(18.4)	305(77.02)
Klebsiella	6(21.4)	22(78.6)	13(46.4)	15(53.6)	0(0)	28(7.07)
Proteus	1(10)	9(90)	2(20)	3(30)	5(50)	10(2.53)
Enterobacter	10(31.2)	22(68.8)	10(31.2)	15(46.9)	7(21.9)	32(8.08)
Gram-positive bacteria*	2(40)	3(60)	0(0)	3(60)	2(40)	5(1.26)
Citrobacter	0(0)	4(100)	3(25)	7(58.3)	3(16.7)	4(1.01)
Pseudomonas	6(50)	6(50)	1(25)	3(75)	0(0)	12(3.03)
Total	68(17.17)	328(82.83)	128(32.3)	196(49.5)	73(18.27)	396(100)

Table-3: The susceptibility of gram-negative and Staphylococcus bacteria

Antibiotic	Response	Enterobacter (%)	E.coli (%)	Pseudomonas (%)	Proteus (%)	Klebsiella (%)	Citrobacter	Staphylococcus (%)
Cefixime	Sensitive	18(56.2)	118(38.7)	2(16.7)	2(20)	8(28.6)	1(25)	2(40)
	Intermediate	8(25)	42(13.8)	0(0)	0(0)	7(25)	1(25)	0(0)
	Resistance	6(18.8)	145(47.5)	10(83.3)	8(80)	13(46.4)	2(50)	3(60)
Cefotaxime	Sensitive	22(68.8)	128(42)	2(16.7)	5(50)	12(42.4)	1(25)	2(40)
	Intermediate	4(12.5)	48(15.7)	3(25)	3(30)	7(25)	0(0)	3(60)
	Resistance	6(18.8)	129(42.3)	7(58.3)	2(20)	9(32.1)	3(75)	0(0)
Ceftriaxone	Sensitive	21(65.6)	129(42.3)	4(33.3)	4(40)	14(50)	2(50)	3(60)
	Intermediate	5(15.6)	37(12.1)	3(25)	0(0)	7(25)	1(25)	1(20)
	Resistance	6(18.8)	139(45.6)	5(41.7)	6(60)	7(25)	1(25)	1(20)
Ampicillin	Sensitive	4(12.5)	21(6.9)	3(25)	1(10)	5(17.9)	1(25)	1(20)
	Intermediate	11(34.4)	80(26.2)	3(25)	2(20)	7(25)	0(0)	0(0)
	Resistance	17(53.1)	204(66.9)	6(50)	7(70)	16(57.1)	3(75)	4(80)
Gentamicin	Sensitive	24(75)	190(62.3)	9(76)	6(60)	17(60.7)	3(75)	4(80)
	Intermediate	6(18.8)	78(25.6)	1(8.3)	4(40)	9(32.1)	1(25)	1(20)
	Resistance	2(6.2)	37(12.1)	2(16.7)	0(0)	2(7.1)	0(0)	0(0)
Trimethoprim/ sulfametoxazole	Sensitive	14(43.8)	48(15.7)	1(8.3)	1(10)	5(17.9)	0(0)	2(40)
	Intermediate	4(12.5)	29(9.5)	5(41.7)	4(40)	1(3.6)	1(25)	0(0)
	Resistance	14(43.8)	228(74.8)	6(50)	5(50)	22(78.6)	3(75)	3(60)

Nitrofurantoin	Sensitive	24(75)	227(74.7)	7(58.3)	3(30)	22(78.6)	3(75)	2(40)
	Intermediate	6(18.8)	45(14.8)	0(0)	2(20)	6(21.4)	1(25)	1(20)
	Resistance	2(6.2)	33(10.8)	5(41.7)	5(50)	0(0)	0(0)	2(40)
Nalidixic acid	Sensitive	12(37.5)	104(34.1)	2(16.7)	4(40)	13(46.4)	4(100)	1(20)
	Intermediate	11(34.4)	45(14.8)	3(25)	1(10)	6(21.4)	0(0)	1(20)
	Resistance	9(28.1)	156(51.1)	7(58.3)	5(50)	9(32.1)	0(0)	3(60)
Ciprofloxacin	Sensitive	28(87.5)	221(72.5)	10(83.3)	7(70)	26(92.2)	4(100)	4(80)
	Intermediate	1(3.1)	39(12.8)	1(8.3)	1(10)	1(3.6)	0(0)	0(0)
	Resistance	3(9.4)	45(14.8)	1(8.3)	2(20)	1(3.6)	0(0)	1(20)
Amikacin	Sensitive	22(68.8)	197(64.6)	8(66.7)	6(60)	17(60.7)	4(100)	5(100)
	Intermediate	7(21.9)	89(29.2)	4(33.3)	4(40)	7(25)	0(0)	0(0)
	Resistance	3(9.4)	19(6.2)	0(0)	0(0)	4(14.3)	0(0)	0(0)

4- DISCUSSION

UTI is the most frequent cause of fever and infection. It is one of the most common and serious infections among children, particularly among infants and young children (19). Delay in diagnosis or treatment leads to irreversible side effects such as renal failure and hypertension (20). So, the present study directed on various aspects of 396 patients (aged 1 month to 18 years with positive urine culture). From the study observed that UTI was more common in girls with the ratio of 4.8:1.

Many studies received to the same trends with present study (4, 21-23). Ghorashi et al. (4) resulted that the sex-ratio was about 4:1, and Esmaeili (22) received to similarity with Ghorashi et al. (4), both were consistent with the present study. Ghorashi et al. (4), resulted that the sex ratios (male to female) had the highest in ages more than 2 years. In a study, the infection rate was higher in 0-1 year age group among males and in females, the rate was higher in 6-12 years; also, Escherichia coli were the commonest pathogen, which was isolated in all age groups, followed by Klebsiella species and Enterococcus species. Also, higher sensitivity was against Gentamicin, Amikacin and Nitrofurantoin and maximum resistance was observed against Ampicillin and Norfloxacin. In the second line antibiotics, all strains were sensitive to imipenem (1). In the present study the highest incidence of UTI was in boys less than one year and followed by the age group of 1-7 years old; also preschool girls had the highest incidence about fifty percent and followed by the period of age less than one year. In comparison, our results would be confirmed by these two studies with similar results approximately. In the present study the highest sensitivity was for Escherichia coli to Gentamicin (75%0 and Amikacin (68.8%).

Klebsiella species also had the highest sensitivity to Ciprofloxacin (92%), Nitrofurantoin (76.8%) and gentamicin (60.7%), and Escherichia coli (E.coli) had the maximum resistance against amicline. These two studies results would be confirmed by Eliana Biondi. Medeiros Guidoni et al., conducted a study on antibiotic resistance patterns of pediatric urinary infections and resulted that the most frequently isolated microorganism was E. coli. It was revealed that among the oral antibiotics, Nitrofurantoin, Fluoroquinolones and 2nd generation cephalosporins were the most active antimicrobials against E. coli, followed by Nalidixic acid (21). In the paper published by Miranda et al., 11,943 positive urine samples were studied and resulted that E.coli was the most common etiological pathogen in all ages (70%), approximately similar to the present study (77%) (24). If needs more results to be reported, the Ronald study was a review (25), reported that E. coli (80%), and Staphylococcus Saprophyticus (5% to 15%) were the most common causative pathogens associated with uncomplicated cystitis or acute pyelonephritis. So many similarities could be observed with the present study and a little difference due to the pattern of age groups. In the Barnett and Stephens's study revealed that for detecting Carbapenemases, including Klebsiella Pneumoniae Carbapenemase (KPC), the susceptibility to Ertapenem was high among isolates of Enterobacteriaceae (E. coli, 100%; Proteus mirabilis, 99.5%; Klebsiella pneumoniae, 98.5%; and E. aerogenes, 100%) (26). In a study by Ghorashi et al. (4) the most frequent isolated pathogen was Escherichia coli spp. and followed by Klebsiella spp., Enterobacter spp., and Enterococcus spp., in the order given. It was revealed that isolated pathogens were highly resistant to Ampicillin, Co-trimoxazole, and cephalexin, intermediate sensitivity to third-generation cephalosporins, and highly sensitive to ciprofloxacin, amikacin, and nitrofurantoin.

In comparison with our findings, obviously resulted that Escherichia coli was more resistant to Ampicillin (53%) and Cotrimoxazole (43.8%). In comparison, our results could be confirmed by Ghorashi et al.'s results. Tseng et al., in Taiwan (20), reported that E. coli was the most common pathogen and followed by Klebsiella pneumoniae, Enterococcus spp., and Proteus mirabilis in the order given. The susceptibility to antimicrobial agents of individual pathogens E. coli isolates, almost were susceptible to nitrofurantoin, while only low percent were susceptible to ampicillin. The overall resistance to antimicrobial agents showed that Ampicillin had the highest overall resistance rate while nitrofurantoin had the lowest. We found that Escherichia coli spp. was the most frequent pathogen, so that in compare with Tseng et al. results (20) ampicillin were in same line of highest resistance while amikacin had the lowest. Lu et al., performed an epidemiologic study on antimicrobial susceptibility profiles of gram-negative bacteria causing UTI, resulted that E. coli and Klebsiella pneumoniae were the most common amongst Gram-negative bacilli, and were resistant to many antimicrobial agents. The rates of susceptibility of the gram-negative pathogens causing UTIs to antimicrobial agents showed that amikacin had the highest frequency, followed by ertapenem, imipenem and piperacillin-tazobactam, respectively.

The rates of susceptibility to the other beta-lactam agents had percentages higher than half. For ciprofloxacin and levofloxacin, the susceptibility rates were 51.4% and 54.4%, respectively. Pseudomonas aeruginosa ranked at the third order and most common UTI pathogens, but had the lowest rates of susceptibility to most antimicrobials. For Pseudomonas aeruginosa, the rates of susceptibility to the tested drugs had high values up to 76.2% (27).

In our study, the Pseudomonas aeruginosa had the resistance rate of 0% to 83% to the tests of selected antibiotics and Pseudomonas aeruginosa had the highest level of susceptibility to ciprofloxacin, gentamicin, and amikacin in the order given. The Lu et al. study results (27) were difference with our results on ranking of Pseudomonas aeruginosa which was dropped in the rank of fourth when E.coli, Enterobacter, Klebsiella placed on the first to the third, respectively. But in some other studies, most cases of UTIs were caused by gram-negative organisms, especially E.coli (77%), Enterobacter (8.1%), and Klebsiella (7.1%) (24, 26). Mirsoleymani et al. (28) conducted a study on 19,223 samples and resulted that 1,513 (7.87%) samples were positive for bacterial infection. E. coli was reported the most common etiological agent of UTI (65.2%), followed by Klebsiella spp. (26%), Pseudomonas aeruginosa (3.6%), and Staphylococcus coagulase positive (3.7%). They also resulted that for E. coli antibiotics were Amikacin (79.7%), Ofloxacin (78.3%), Gentamicin (71.6%), Ceftriaxone (41.8), Cefotaxime (41.4%), and Cefixime (27.8%). The results of this study showed that empirical antibiotic selection should be based on awareness of the local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal or even national guidelines that is has same message as the present study.

4-1. Limitations of the study

Although our study was the first to investigate the provincial evidence regarding the prevalence of bacterial resistance in children's urinary tract infection and associations with the routine use of antibiotics in primary care in children and adolescent population of Sistan and Baluchestan province, it is important to note certain limitations.

The present study only looked at inpatients and outpatients who referred to the pediatric ward of Ali Ibn Abi Talib hospital with UTI, and therefore our findings may not apply to the general pediatric population even children with UTI in overall. Furthermore, the number of cases included in our study was restricted by our criteria for defining UTI. A significant number of cases excluded due to exclusion criteria.

5- CONCLUSION

According to the results of this study, although E. coli still was in top of pathogens list children's UTI in this area, but it showed an increase in resistance to popular empirical antibiotics such Ampicillin, Cotrimoxazole and Nalidixic acid. This resistance is due to the convenience of taking some of these antibiotics such as Ampicillin, Cotrimoxazole. Therefore more sensitive drugs like Nitrofurantoin, Ciprofloxacin and Amikacin, should be considered alternative antibiotic in children's UTI.

6- CONFLICT OF INTEREST

The authors would like to confirm no conflict of interests.

7- ACKNOWLEDGMENTS

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