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RESEARCH ARTICLE

CHILDHOOD URINARY TRACT INFECTION: CLINICAL SIGNS, BACTERIAL CAUSES AND ANTIBIOTIC SUSCEPTIBILITY

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Abstract

Background and objective: Urinary tract infections (UTIs) are the neglected infection in children from the side of study its clinical symptoms, causative organisms and their antibiotic sensitivity. This investigation searches for determine clinical symptoms frequency, prevalence rate, bacterial features, and antibiotic sensitivity of bacterial urinary tract infection in children attending private children's health center in Sana'a city.

Methods: In a prospective study carried out over a 24-month period, 1925 samples from children patients suspected of having a UTI were investigated, of which 175 were culture-positive. Clinical and demographic data were collected. Isolated bacteria were identified by standard tests, and antibiotic susceptibility was performed by the disk diffusion method.

Results: Fever was the most frequent symptom that occurred (88%) while other UTI symptoms were less frequent than that reported in adult patients for UTI. The most common etiological agent was *Escherichia coli* (89.7%), followed *Staphylococcus aureus* (3.4%), *Klebsiella* spp (2.9%), *Proteus* spp (2.3%), and beta haemolytic *streptococci* (1.7%). Results of antimicrobial resistant for *E. coli*, as the most prevalent cause of UTI, to commonly used antibiotics are ranged from less than 3% for levofloxacin, gentamicin, amikacin and cefoxitin to more than 75% for tetracycline, nalidixic acid, doxycycline, co-trimoxazol and amoxicillin .

Conclusions: The results show the most common symptom of UTI are fever and lack of more obvious symptoms of UTI in adult patients. The antimicrobial resistance patterns of the causes of UTI are highly changeable and constant surveillance of trends in resistance patterns of uropathogens among children is essential.

Keywords: antibiotic resistant, bacterial causes, children, Sana'a, UTI symptoms, UTI, Yemen.

INTRODUCTION

A urinary tract infection (UTI) is an infection that affects part of the urinary tract[1]. As the lower UTI, which is known as cystitis and as it affects the upper urinary tract, it is known as pyelonephritis[2]. As for the symptoms resulting from lower UTI, they include pain during urination, frequent urination, and the feeling of needing to urinate despite the presence of an empty bladder[2,3]. The symptoms of kidney infection include fever and flank pain and rarely, blood appears in the urine. In the elderly and the young, the symptoms are vague or non-specific[1,4]. In young children, researchers have found that the only symptom of UTI is fever[5]. Therefore, because there are no more obvious symptoms, when the fever appears in females under the age of two or in males less than a year old, it is recommended to do a bacterial culture of the child's urine. Also, one of the symptoms in children is that children feed poorly, vomit, sleep more than normal, or may show signs of jaundice. However, in older children, new onset of enuresis (loss of bladder control) may occur. Reports have documented that about 1 of 400 infants aged between 1 to 3 months having UTIs will develop bacterial meningitis[5,6]. Overall, urinary tract infections (UTIs) are one of the most common infectious diseases, and approximately 10% of people will likely develop a UTI during their lifetime[7,8]. It is known that UTIs are the most common after upper respiratory tract infections in humans[9].

This infection may be clinically symptomatic or asymptomatic, and upper or lower UTI infection may lead to serious consequences if left untreated[10]. Many different microorganisms can cause UTIs, consist of fungi and viruses, but bacteria are the main causative agents and cause more than 95% of UTI cases[11]. Since bacteria are the important cause of UTI, *Escherichia coli* is the most common UTI-causing bacterium and is exclusively responsible for more than 80% of these infections. Precise and rapid diagnosis of UTI is important in shortening the course of the disease and preventing transmission of infection to the upper urinary tract, which may lead to kidney failure[12,13]. The choice of antibiotics and the inappropriate dose leads to treatment failure and an increase in antibiotic resistance; and with recurrent UTIs, in particular, it may lead to permanent injuries such as renal parenchymal scarring, impaired renal function, high blood pressure, and chronic kidney disease[14]. In addition, frequent antibiotic use or urinary tract abnormalities are risk factors for developing resistance and although there are regional differences, resistance to antibiotics used in empirical therapy is gradually increasing worldwide and particularly in Yemen country[15-17,18-32].

An example of the importance of this topic in Sana'a and the situation where this information is useful in Sana'a as well. As the rates of antibiotic resistance are high, doctors depend on giving antibiotics experimentally without bacterial isolation and sensitivity testing to antibiotics[18-32]. Treatment for UTIs often begins with an experiment. Treatment is derived from specific information from the antimicrobial resistance pattern of urinary pathogens. Nevertheless, due to the developing and persistent phenomenon of antibiotic resistance, regular monitoring of resistance patterns is essential to improve the guidelines for empirical antibiotic therapy [30-32]. However, the availability of data about the type of isolated bacteria from childhood having UTIs and their antibacterial susceptibility profiles in Sana'a city, Yemen, are very limited.This study aimed to determine the frequency of clinical symptoms, prevalence, bacterial features, and antibiotic sensitivity of UTIs in children attending the private pediatric health center in Sana'a city, Yemen.

MATERIALS AND METHODS

Study design and area

This was a retrospective descriptive study. Clinical and microbiological data for the 2019-2020 bienniums were obtained from the Pediatric Department of Sam Medical Center (Private Childhood Hospital) in Sana'a City, Yemen. This time capsule was chosen for the completeness and correctness of the information, as it was reviewed and followed up by the first author.

Data collection

Clinical and demographic data were collected in a pre-designed questionnaire. The data were filled in by physicians and assistants and reviewed by the study supervisor.

Ethical approval

The written consent in all cases were obtained. Approval was obtained from the participants prior to including in the study. Ethical approval was obtained from the Medical Research and Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University with reference number (752) on 01/12/2018.

Inclusion and Exclusion criteria

The study included outpatient children with suspected UTI, who had not received antimicrobials within the past 2 months, referred to NCPHL for urine culture and obtained written consent.

Sample collection

Cultivation and identification were performed at the Microbiology Department of the National Center of Public Laboratories (NCPHL), Sana'a City. Urine samples were collected from 1925 outpatient children with suspected UTI, who had not received antimicrobials within the past two months, and referred to the NCPHL for Urine Culture. There were 1459 (75.8%) samples of female patients and 466 (24.2%) of male patients. The patient's age ranged from 7 months to 13 years (mean age 7.7±5.2 years). Children older than 3 years were sampled with clean urine midstream, and children younger than 3 years old were sampled using sterile urine bags.

Isolation and identification of bacteria

Urine samples were examined and cultured within an hour of sampling. All samples were inoculated on blood agar plus MacConkey agar and incubated at 37°C for 24 h, and for 48 h in negative cases. The sample was considered positive for urinary tract infection if a single organism was cultured at a concentration of 10^5 CFU/ml, or when a single organism was cultured at a concentration of 10^4 CFU/ml and 5 leukocytes per high-power field were observed on urine microscopy. The bacteria were identified on the basis of standard culture and biochemical characteristics of the isolates. Gram-negative bacteria were identified by standard biochemical tests[11,12]. Gram-positive bacteria were identified by the corresponding laboratory tests: catalase, coagulase, CAMP test (for *Streptococcus agalactiae*), and Esculin agar (for enterococci)[33].

Susceptibility testing

The isolates were tested for antimicrobial susceptibility by disc diffusion method consistent with the approvals of the National Committee for Clinical Laboratory Standards (NCCLS), employing Muller-Hinton medium[12]. The antimicrobial agents tested were: amikacin, amoxicillin, ampicillin, ampicillin-sulbactam, augmentin, azithromycin, aztreonam, cefaclor, cefadroxam, cefepime, cefixime, cefotaxime, cefoxitin, ceftazidime, ceftriaxin, ceftriaxone, cefuroxime, ciprofloxacin, clarithromycin, clindamycin, co-trimoxazol, etrapenem, erythromycin, doxycycline, gentamicin, fosfomycin, levafloxacin, lomefloxacin moxifloxacin, nalidixic acid, nitrofurantoin, piperacillin/tazobactam, tetracycline and vancomycin (BD-BBL-TM-Sensi-Disc-TM).

Statistical analysis

Discrete variables were expressed as percentages and proportions were compared using the Chi-square test[34].

RESULTS

Over a 24-month, 1925 urine samples from children outpatients were analyzed, of which 175 (9.1%) had significant bacteriuria. The rate of positive culture was 8.4% (124/1459) for female subjects and 10.9% (51/466) for male subjects (Table 1). Table 2 shows the frequency of clinical signs of UTI among children.

The usual clinical symptoms of upper and lower UTIs in the current study were significantly lower than those reported in adults, with the rate of pain above the pubic bone, lower back pain, flank pain, urine appearing bloody, and visible pus in urine <50 %. Whereas, the most important symptom was fever, which occurred in 88% of the children completely, followed by enuresis as a new onset (73.1%).

Table 1: The age and sex distribution of children suffering from UTI.

Charactheristics	Number	Percentage
Sex		
Male*	51	29.14
Female**	124	70.86
Total* **	**175**	**100**
Age groups		
Less than 1 year	7	4
1-5 years	48	27.4
6-10 years	106	60.6
More than 10 years	14	8.0
Total male investigated	51/466	10.9
Total female investigated	124/1459	8.4%
Total investigated	175/1925	9.1%
Max	13 years	
Min	7 months	

*Mean±SD age=7.5±4.3 year, *Mean ±SD age=7.89±5.3 year, *Mean±SD age=7.7±5.2 year.

Also, the symptom of poorly nourished children occurred at 57.1% in children under the age of one year, vomiting was recorded in 14.3%, and the presentation of sleeping more than usual in 58.9% and burning during urination was recorded in 56%. Gram-negative bacilli were responsible for 94.9% of cases followed by Gram-positive bacteria responsible for 5.1% of cases. Analysis of the results according to patient gender indicated that although *E. coli* is the predominant pathogen isolated from both sexes, it occurs significantly in female children (91.8% for females compared to 84.9% for males; $p<0.05$), whereas. The prevalence of urinary tract infection due to *Klebsiella* species and *Proteus* species was 2.9% and 2.5%, respectively. The prevalence of UTI caused by *S. aureus* in males (5.7%) was higher than in females (2.5%) (Table 3).

Table 2: The frequency of clinical signs of UTI among children.

Signs and symptoms	Number	Percentage
Burning while urinating	98	56
Pain above the pubic bone	89	50.9
Lower back pain	72	41.1
Loin pain	79	45.1
Fever	154	88
Urine looks bloody	72	41.1
Visible pus in urine	61	34.9
Babies are feeding poorly (n=7)	4	57.1
Vomiting	25	14.3
Sleep more	103	58.9
Urinary incontinence a new beginning	128	73.1

Table 3: The bacterial causes of children UTI according to gender.

Microorganisms	Male		Female		Total	
	No	%	No	%	No	%
Escherichia coli	45	84.9	112	91.8	157	89.7
Klebsiella spp.	2	3.8	3	2.5	5	2.9
Proteus spp.	1	1.9	3	2.5	4	2.3
Total gram negative	48	90.6	118	96.7	166	94.9
Staphylococcus aureus	3	5.7	3	2.5	6	3.4
Beta haemolytic streptococci	2	3.8	1	0.8	3	1.7
Total Gram positive *cocci*	5	9.4	4	3.3	9	5.1
Total	53	29.7	122	70.3	175	100

Table 4 shows the pattern of antibiotic resistance of microorganisms in children with UTI. The resistance rates of isolates to a group of antibiotics, including penicillins, cephalosporins, quinolones, amino-glycosides, and trimethoprim-sulfamethoxazole, that are routinely used to treat UTIs, are shown in Table 4.

Table 4: Bacterial antibiotic resistances pattern of children UTI.

Antibiotics	*E. coli* n=157 (%)	*Klebsiella* spp n=5 (%)	*Proteus* n=4(%)	*S. aureus* n=6(%)	*Beta* Gm+*Streptococci* n=3(%)
Amikacin	2.5	0	25	0	0
Amoxicillin	91.5	100	100	100	100
Ampicillin	33.3	100	75	100	66.7
Ampicillin -sulbactam	19.2	20	50	16.7	33.3
Augmentin	8.3	100	75	16.7	33.3
Azithromycin	14	80	75	100	100
Aztreonam	6.4	20	50	0	0
Cefaclor	53.5	80	75	50	66.7
Cefadroxam	54.8	80	75	50	66.7
Cefepime	15.3	40	25	0	0
Cefixime	44.6	60	75	0	0
Cefotaxime	7	40	50	0	0
Cefoxitin	2.5	40	50	0	0
Ceftazidime	15.9	40	50	0	0
Ceftriaxone	15.9	40	50	16.7	33.3
Cefuroxime	6.4	20	50	16.7	33.3
Ciprofloxacin	31.8	40	25	16.7	33.3
Clarithromycin	11.5	20	25	0	0
Clindamycin	11.5	20	25	16.7	33.3
Co-Trimoxazol	75.2	100	100	83.3	66.7
Doxycycline	95.5	100	100	16.7	33.3
Ertapenem	5.1	20	25	0	0
Erythromycin	-	-	-	50	66.7
Gentamicin	2.5	20	25	0	0
Fosfomycin	6.4	20	25	0	0
Levafloxacin	1.9	20	25	16.7	33.3
Lomefloxacin	3.8	20	25	0	0
Moxifloxacin	3.2	20	25	0	0
Nalidixic Acid	88.5	100	100	100	100
Nitrofurantoin	31.8	80	100	-	-
Piperacillin/Tazobactam	10.2	20	0	0	0
Tetracycline	88.5	100	100	100	100
Vancomycin	-	-	-	0	0

E. coli as the predominant cause of UTI, showed higher proportion of resistance to amoxicillin (91.5%), nalidixic acid (88.5%) and tetracycline (88.5%) while the least resistant to *E. coli* were to levafloxacin (1.9%), amikacin (2.5%), cefoxin (2.5%), gentamicin (2.5%), moxifloxacin (3.2%), lomefloxacin (3.8%), ertapenem (5.1%), and aztreonam (6.4%). *Klebsiella* spp as the second predominant UTI pathogen showed a similar resistance pattern and was 100% resistant to amoxicillin, ampicillin and augmentin, while 80% of this bacterium was resistant to azithromycin, cefaclor, cefadroxam, nalidixic acid, tetracycline and doxycycline. *Proteus* species also showed a high rate of antibiotic resistance to many of the antibiotics tested (Table 4). *S. aureus* was 100% resistant to amoxicillin, ampicillin and azithromycin, while all isolates of *S. aureus* were sensitive to vancomycin.

DISCUSSION

Urinary tract infection is a common disease in children, especially females, where in the current study 78.86% of cases were females, while only 21.24% of male cases, and this is similar to what was mentioned in the previous literature[35-37]. Infection generally occurs with the colonization of the lower urinary tract by bacteria, most of which are Gram-negative. The infection may extend from the bladder to the kidneys, depending on the characteristics of the pathogen. It is known that infection is rarely transmitted by the hematogenous route and may occur as a result of the transmission of the agent to the urinary tract through the blood during sepsis. Vesicoureteral reflux, voiding dysfunctions, neurogenic bladder, urinary incontinence, constipation, bladder neck obstruction, and the presence of a catheter are predisposing factors for UTI[35]. Another factor is familial and genetic predisposition[36].

Clinical outcomes in pediatric UTI vary according to age, location in the urinary tract, and severity of infection[37]. In the neonatal and pediatric period, the signs are mostly nonspecific[38]. Diagnosis is based mostly on the patient's symptoms and results of the physical examination and urinalysis, and treatment generally begins empirically[39]. However, increasing antibiotic resistance nowadays leads to treatment failure and an increase in acute cases. It is now known that antibiotic resistance has become an important problem for hospital infections, and for community-acquired infections[40]. Therefore, it is recommended that the resistance rate does not exceed 10-20% to start experimental treatment in any region of the world[41]. For that reason, the American Infectious Diseases Society emphasizes that regional pathogenic agents and antibiotic sensitivities in UTIs should be known[42].

Microbial infection of the urinary tract is one of the most common diseases worldwide. In this study, of 1925 children clinically diagnosed with a UTI, samples were taken and only 9.1% had a UTI while the others gave negative culture results. This is probably because UTI symptoms are not a reliable indicator of infection and also that children under 5 years of age have nonspecific UTI symptoms. This is similar to that reported by Farajnias, *et al.*, in Iran in their study, of the 5,136 patients from whom urine samples were taken; only 13.2% had a UTI[1]. In the current investigation, most urine samples were collected from pediatric patients who did not have a symptomatic group of UTI, and most of the subjects were referred by general practitioners and specialist physicians. These results indicate that urine culture is essential for the definitive diagnosis of urinary tract disease, and that empirical treatment should only be performed in the absence of urine culture examination[7]. The results of the current study show a higher number of females (124 females versus 51 males). This may be that males are less likely to develop UTIs due to the length of their urethra[7].

Even though the prevalence of UTIs causative agents in diverse parts of the world is to some extent similar, the patterns of antimicrobial resistance reported from different areas are considerably different and antimicrobial resistance is increasing in the world. The results of the current study illustrate that among the heterogeneous causative bacteria for UTI, *Enterobacteriaceae* are the dominant pathogens, followed by Gram-positive cocci. These results are consistent with reports published in Yemen previously and from other countries around the world[30-32,37,39]. In UTI, the causative agent is generally Gram-negative bacteria. The main pathogen is *E. coli*, *Klebsiella*, *Enterobacter* and *Proteus* spp. It has been reported at lower rates[37-39]. Consistent with previous studies, we found that the most common causative agent was *E. coli*, and the female sex was dominant in current study[37-39]. The highest resistances were found to amoxicillin (91.5%), ampicillin (90.7%), doxycycline (95.5%), trimethoprim-sulfamethoxazole (75.2%), and nalidixic acid (88.5%), while the least resistant to *E. coli* were to levofloxacin (1.9%), amikacin (2.5%), cefoxin (2.5%). %), gentamicin (2.5%), moxifloxacin (3.2%), lfomfloxacin (3.8%), Ertapenem (5.1%), aztronam (6.4%); these results are mainly consistent with other studies conducted previously in Yemen[18-32,44] and around the world[7-11]. The present study, as with previous studies, shows that *E. coli* is the predominant etiology of UTI[32,45,46] and also reveals a very high rate of bacterial resistance to antibiotics. This was particularly the case for the *Klebbsilla* species and *Proteus* sp. that were completely resistant to ampicillin, cephalexin, nitrofurantoin, nalidixic acid and trimethoprim-sulfamethoxazole; this resistance is higher than that of other reports[32,46,47]. Over the past decade, there has been a significant increase in the resistance of urinary pathogens to antibiotics. Resistance rates are increasing among strains of *Staphylococcus aureus*, and a significant portion of this species has become resistant to *beta-lactamase*-resistant penicillin[48]. For such resistant species, vancomycin is the effective drug choice. Vancomycin resistance has been reported among *Enterococci*[48], but this resistance has also begun to develop among *Staphylococci*. In this study, we focused on vancomycin resistance and fortunately no vancomycin-resistant strains were observed, but 100% of cases were resistant to ampicillin, aztreonam, and azithromycin. The regional variations of resistance to antibiotics may be explained partly by distinct local antibiotic practices[50]. The pressure of unnecessary and/or inappropriate antibiotic use on the development of antibiotic-resistant strains, mostly broad-spectrum agents prescribed empirically, has been demonstrated. Reducing the number of prescriptions of a particular antibiotic can lead to a decrease in resistance rates. Transmission of resistant isolates between people and/or by consumption of foods originated from animals that have received antibiotics and greater mobility of individuals worldwide has also be a factor of the expansion of antibiotic resistance. Regional differences in antibiotic resistance may be partially explained by different local antibiotic practices[50,51]. The outcome of unnecessary and/or improper use of antibiotics on the expansion of antibiotic-resistant strains, especially of broad-spectrum agents described experimentally, has been demonstrated. Reducing the number of prescriptions for a particular antibiotic can lead to lower rates of resistance. Transmission of resistant isolates between people and/or by consumption of foods originating from animals that received antibiotics and greater movement of individuals around the world has also play a role on the expansion of antibiotic resistance[50,52].

CONCLUSIONS

In conclusion, since the antibiotic susceptibility pattern of bacteria varies over time and in different geographic regions, antibiotic treatment of infection should be based on local experience of susceptibility and resistance patterns of culture and antibiotic susceptibility testing. In this study, it was found that augmentin and aztreonam two most suitable oral antibiotics, amikacin and third-generation cephalosporins were the most suitable parenteral antibiotics, for the empirical treatment of urinary tract infection. Also, *E. coli* was the most common causative agent of childhood UTIs.

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AUTHOR'S CONTRIBUTION

IshaK AA: writing original draft, methodology. **Alhadi AM:** investigation, conceptualization, literature survey. **Al-Moyed KAA:** interpretation of data. **Al-Shamahy HA:** data curation, conceptualization. All authors revised the article and approved the final version.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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