

ORIGINAL ARTICLE**Pediatric Urinary Tract Infection as a Cause of Outpatient Clinic Visits in Southern Ethiopia: A Cross Sectional Study****Enkosilassie Mitiku¹, Anteneh Amsalu², Birkneh Tilahun Tadesse^{3*}****OPEN ACCESS**

Citation: Enkosilassie Mitiku, Anteneh Amsalu, Birkneh Tilahun Tadesse. Pediatric Urinary Tract Infection as a Cause of Outpatient Clinic Visits in Southern Ethiopia: A Cross Sectional Study. *Ethiop J Sci*.2018;28(2):187. doi:<http://dx.doi.org/10.4314/ejhs.v28i2.10>

Received: October 11, 2017
Accepted: October 21, 2017

Published: March 1, 2018

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Funding: Nil

Competing Interests: The authors declare that this manuscript was approved by all authors in its form and that no competing interest exists.

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ABSTRACT

BACKGROUND: Failure to timely diagnose and treat urinary tract infections is associated with grave long term consequences. The objectives of this study included assessing the proportion and predictors of Urinary Tract Infection (UTI) as a cause of pediatric outpatient department (OPD) visits and determining common uropathogens with antimicrobial susceptibility pattern.

METHODS: A cross sectional study was conducted from May to September 2015 among children of less than 15 years old at a tertiary center in Hawassa, Ethiopia. Children who fulfilled predefined eligibility criteria were recruited to undergo urine culture and urine analysis.

RESULTS: A total of 863 children visited the OPD during the study period among which 269(31.2%) fulfilled the predefined eligibility criteria. Urine culture was positive for 74/269(27.5%) of the clinically suspected children. Male uncircumcision (adjusted odds ratio (aOR) 3.70; 95% CI 1.34-10.16) and under nutrition (aOR 5.41; 95%CI 2.64-11.07) were independent predictors of culture positivity. More than 5 WBC per high power field (aOR 4.7, 95% CI 1.8-12.7) on microscopy, urine PH > 5.0 (aOR 2.6, 95%CI 1.2-5.8), and positive leukocyte esterase (aOR 9.9, 95%CI 4.1-25.7) independently predicted positive growth on urine culture. *Escherichia coli* (34/74, 45.9%) and *Klebsiella spp* (18/74, 24.3%) were the most frequent isolates. High resistance was noted against amoxicillin (70.6%) and cotrimoxazole (97.1%) by *E. coli*.

CONCLUSION: UTI accounted for a tenth of total OPD visits. Commonly used first line antibiotics showed high level resistance to common etiologies of UTI. UTI should be suspected in febrile children, and antibiograms should be done to tailor prescription of antibiotics.

KEYWORDS: Bacterial profile, antibiotic resistance, children, urinary tract infection

INTRODUCTION

Urinary Tract Infection (UTI) is the most common childhood bacterial infection associated with high morbidity and long-term complications like renal scarring, hypertension, and chronic renal failure (1). To reduce the adulthood complications, early diagnosis,

proper investigation, adequate therapy and prolonged follow-up are of outmost importance. The epidemiology of UTI during childhood varies by age, gender, circumcision status and other factors. Boys are more susceptible during the first year of life, mostly the first 3 months; thereafter the incidence is substantially higher in girls (2). Among boys, uncircumcised infants have an eightfold higher risk (3). About 5% of girls and 2% of boys experience at least one episode of UTI up to the age of seven years (4). Clinically, important UTIs usually occur due to bacteria, although viruses, fungi, and parasites can also cause infection (5). Gram negative enteric bacilli such as *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Pseudomonas* spp., and *Citrobacter* spp. and Gram-positive organisms, including group B streptococci, *Enterococcus* spp, and *Staphylococcus aureus* are commonly associated with pediatric UTI (1,4,5).

Effective management of patients suffering from severe UTI commonly relies on the identification of pathogenic organisms and the selection of an effective antibiotic agent to the organism in question. However, diagnosis of UTI is often delayed due to obscure clinical findings, particularly in infants and children of less than two years (2,3,6). Moreover, it is difficult to collect urine and interpret the results to confirm the diagnosis unequivocally in this age group (3). Hence, empirical antibiotic prescription is often endorsed even without culture and sensitivity. On the other hand, the emergence of antibiotic resistant uropathogens in pediatric urology is increasing worldwide; particularly in developing countries where empirical treatment is the mainstay of treatment in the absence of proper diagnostic modalities and the availability of antibiotics over the counter (7,8).

The antibiotic susceptibility profile of uropathogens is variable and usually depends on time, geographical location, demography and clinical characteristics of patients (9). An updated information in a specific location may aid clinicians in choosing the appropriate antibiotic for empirical treatment. However, shortage of data regarding the antibiogram of commonly encountered uropathogens, empirical antibiotic

treatments following the WHO empiric guidelines is the common practice in the study setting.

Given the prescription practices following the WHO empiric guidelines in the study setting, understanding the common etiologies of pediatric UTI and their antibiograms would assist clinicians to optimize treatment strategies for such patients. This study tries to address three important questions:

1. How common is UTI as a cause of OPD visits?
2. What are the common etiologies of UTI in the study setting?
3. What is the antibiotic susceptibility profile of pediatric uropathogens?

METHODS

Study setting: A hospital based cross-sectional study was conducted from May to September 2015 at the Outpatient Department (OPD) of Hawassa University Comprehensive Specialized Hospital (HUCSH) in Southern Ethiopia. The hospital serves as both primary care and referral teaching hospital for both Southern Nations Nationalities and Peoples Region (SNNR) and Oromia regions. It is located 275 km south of the capital city, Addis Ababa.

Eligibility criteria: We recruited children of less than 15 years of age who were attending at the pediatric OPD of HUCSH. For enrolment to the study, we followed predefined inclusion criteria which were adapted from Grabe et al, 2015 (2,10). We included children who had one or more of the following:

- 1) Fever which was defined as axillary temperature of 37.5 °C or higher at presentation;
- 2) At least two episodes of vomiting within two days of presentation at OPD;
- 3) Dysuria as complained by older children or crying during urination for young children as reported by the mother;
- 4) Urinary frequency which is defined as passing urine more frequently than the previous normal for the child;

- 5) Urinary urgency as complained in older children;
- 6) Loin pain/tenderness or urinary color change.

We excluded children who had taken antibiotics within the last two weeks and if mothers or the child refused to give consent for participation. A sample size of 192 children was calculated based on the assumptions of a 25% culture positive rate according to Ali E and Osman H (10), power of 80%, with 95% confidence interval and 5% margin of error and 10% non-response rate. A study period was decided based on the predefined patient flow and the sample size. However, we have ultimately taken all the children who fulfilled the inclusion criteria during the study period.

Data collection: After obtaining informed written consent from parents/guardians and assent from older children, socio-demographic and clinical data were collected using structured questionnaires. Nutritional status, weight and height of children were assessed by trained nurses and clinical examination was carried out by the attending physician. For patients who fulfilled the inclusion criteria, midstream urine sample was collected in a wide mouthed sterile container after cleansing the urethral meatus after thoroughly instructing their guardians. The collected urine sample was delivered to the hospital microbiology laboratory within 30 minutes.

Urine culture: All urine specimens were inoculated into blood agar and MacConkey agar plate (Oxide, Ltd., Basingstoke, and Hampshire, England), using a calibrated loops (0.002ml) for the semi-quantitative method. Streaked culture plates were incubated at 37°C overnight. More than 10⁵ colony forming units per milliliter of urine (cfu/mL) and growth of a single organism was considered as culture positive to further decrease the possibility of contamination. Pure isolates of bacterial pathogen were preliminary characterized by colony morphology and Gram-stain. All positive urine cultures showing significant bacteriuria were further identified by their characteristic appearance on their respective media and confirmed by the pattern of

biochemical reaction using the standard procedures (11). Urine culture was done by experienced graduate medical microbiology students under the close supervision of experienced microbiologists.

Antibiotic susceptibility test: The antibiotic susceptibility test was performed by Kirby-Bauer disk diffusion method (12). In brief, pure culture was transferred into a tube containing 5 ml nutrient broth and mixed gently until it forms a homogenous suspension. The turbidity of the suspension was compared with 0.5 McFarland standards in order to standardize the inoculum density. A sterile cotton swab was dipped into the suspension and the excess were removed by gentle rotation of the swab against the surface of the tube. The swab was then used to distribute the bacteria suspension evenly over the entire surface of Mueller-Hinton agar (Oxoid). The inoculated plates were left at room temperature to dry for 3-5 minutes. The antibiotics for disc diffusion testing were obtained from Oxoid that include: ciprofloxacin (5µg), norfloxacin (10µg), nitrofurantoin (300µg), ceftriaxone (30µg), cefotaxime (30µg), cefazolin (30µg), gentamicin (10µg), co-trimoxazole (1.25/23.75µg), ampicillin (10µg), cefoxitin (30µg), penicillin G (10IU) and erythromycin (15µg). After 18-24 hours incubation at 37°C, zone of growth inhibition was measured to the nearest whole millimeter using a caliper. The zone diameters were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guideline (13) as susceptible (S), intermediate (I) or resistant (R).

Quality control: The completeness of the questionnaire was verified by the principal investigator daily. Sterility of culture media and biochemical tests were checked by overnight incubation of un-inoculated media from each batch of preparation. Standard strains of *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 25923 were used during culture and antibiotic susceptibility testing for internal quality assurance.

Data analysis: Data were coded, entered and analyzed using R software version 3.3.2. Data were presented as percentage, mean (standard deviation (SD)) and median (range). Differences

in proportions were evaluated by Pearson's chi-square and Fisher exact tests; $p < 0.05$ was considered to be significant. Bivariate and multivariate logistic regression were used to determine the predictors of culture proven UTI. Adjusted odds ratio (aOR) with 95% CI was also computed using multivariable logistic regression analysis, taking all factors yielding a p -value ≤ 0.05 in bivariate analysis for adjusting possible confounders. In this study, undernutrition is defined as having a weight-for-height/length (WFH) below-2SD based on the WHO growth standards (14).

Ethics approval and consent to participate:

Ethical approval was obtained from Hawassa University, College of Medicine and Health Sciences, Institutional Review Board (IRB). A permission letter was obtained from the hospital administration. Informed written consent and/or assent were obtained from children and/or guardians. Patient information was anonymized and de-identified prior to analysis. Culture results were given to the physician, and patients were treated accordingly.

RESULTS

From May 1, 2015 to September 30, 2015, a total of 269/863(31.2%) children fulfilled the inclusion criteria for clinically suspected UTI. Two-third (61.7%) of the children were male. The mean age of the participants was 4.8 (SD=3.6) years. The majority (195/269, 72.5%) presented with fever; whereas 81/269(31.1%), 92/269(34.2%), 33/269(12.3%), and 33/269(12.3%) presented with dysuria, vomiting, urinary frequency and lower abdominal pain respectively. More than half (149/269, 55.4%) were rural residents, 31/269(11.5%) had any degree of under nutrition (mild moderate or severe) and 8/269(3.0%) of the children had diabetes mellitus. Previous history of UTI was reported in 20/269(7.4%) of the children, and 71/269(26.4%) had taken any antibiotics in the last three months prior to current presentation (Table 1). None of the subjects reported any history of previous renal problems.

Table 1: General characteristics of children who had clinical signs and symptoms suggestive of UTI at the OPD of Hawassa University Comprehensive Specialized Hospital, 2015.

Variable (total 269)	Frequency(%)
Age (years)	
<1	54(20.5)
1-5	107(39.8)
6-14	108(40.1)
Sex	
Female	103 (38.3)
Male	166 (61.7)
Circumcision in boys (166)	
Yes	47(28.3)
No	119(71.7)
Residence	
Rural	120(44.6)
Urban	149(55.4)
Previous antibiotic intake	
No	16(5.9)
Unknown	182(67.7)
Yes	71(26.4)
Previous history of UTI	
Yes	20(7.4)
No	208(77.3)
Unknown	41(15.2)
Clinical presentation at the time of diagnosis	
Fever	195(72.5)
Dysuria	81(31.1)
Vomiting	92(34.2)
Urinary frequency	33(12.3)
Lower abdominal pain	33(12.3)
Under-nutrition	
Yes	31(11.5)
No	238(88.5)
Diabetes mellitus	
Yes	8(3.0)
No	261(97.0)

UTI: urinary tract infection

Bacterial isolation: Midstream clean catch urine culture was positive for 74/269(27.5%) of the patients who had suspected UTI. Overall, UTI contributed for 74/863(8.6%) of the total pediatric OPD visits in five months. Males had a slightly higher isolation rate of 40/74(54.5%) (p -value=0.147). Among males, 119(71.7%) were not circumcised; and 36/40(90.05) of the boys who had a positive urine culture were not circumcised ($X^2=7.6$, p -value=0.006). The majority (61/74, 82.4%) of the isolates were Gram negative bacteria. *E. coli* (36/74, 48.6%) was the most frequent isolate followed by *Klebsiella* spp. (18/74, 24.3%); *S. aureus* (7/74, 9.5%);

Enterococcus spp. (6/74, 8.1%); *Citrobacter* spp.(4/74, 5.4%); *Enterobacter* spp. (2/74, 2.7%); *Proteusspp.* (2/74, 2.7%), and *Salmonella* spp. (1/74, 1.4%). Isolation of *E. coli* was significantly more frequent in females (25/36, 69.4%) than in males (11/36, 30.6%) ($X^2= 15.6$, p -value<0.0001). On the other hand, all the 7(100%) of the *S. aureus* isolates (p -value=0.04), and the majority (15/18, 83.3%) of *Klebsiella* spp, though statistically insignificant, were isolated from boys ($X^2=2.9$, p -value=0.089). Culture positivity of urine culture was much higher for children who presented with fever, dysuria and vomiting ($X^2=33.53$, $df = 8$, p -value < 0.0001) (Figure 1).

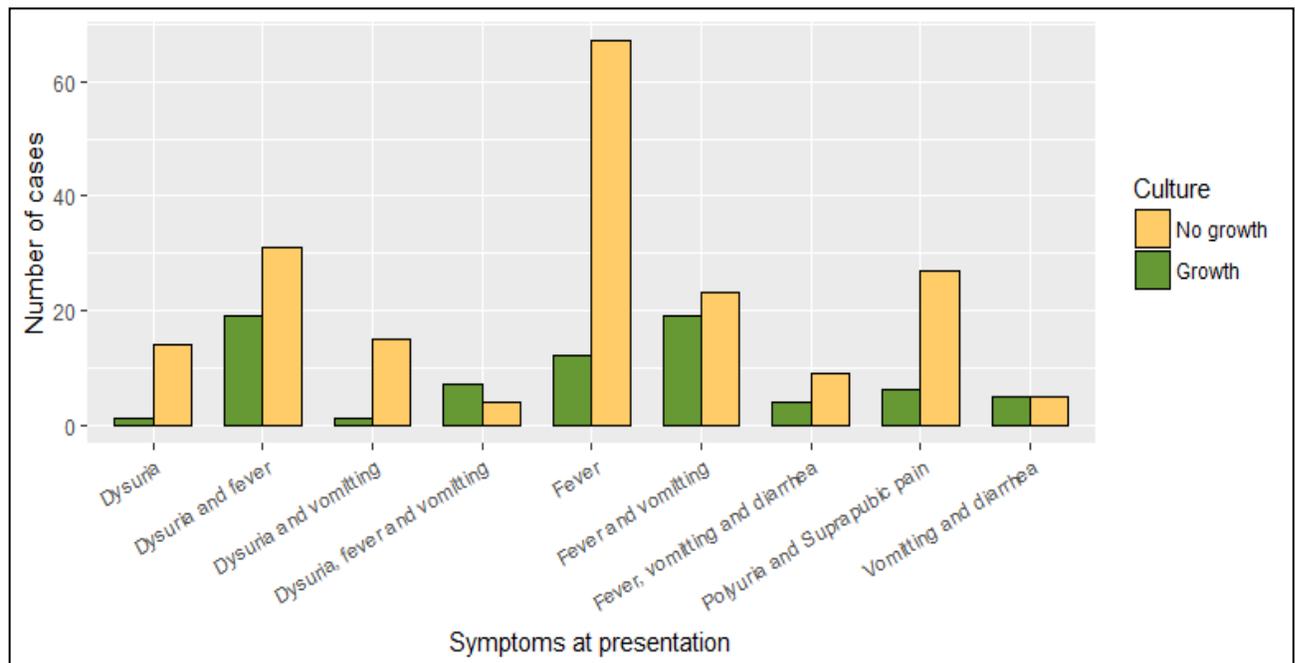


Figure 1: Number cases of positive and negative culture result based on symptoms at presentation to the hospital from May 2015 to September 2015

Predictors of culture confirmed UTI: Rural residence (aOR 2.84, 95% CI 1.74-4.64), any degree of under nutrition (aOR 5.41, 95%CI 2.64-11.07) and absence of circumcision in boys (aOR 3.70, 95%CI 1.34-10.16) have been found to be independent predictors of culture confirmed UTI. However, on including circumcision in the

multivariate regression model, we observed that residence is no more an independent predictor (aOR 0.97, 95% CI 0.46-2.03) (Table 2). Further looking into the relationship between residence and circumcision, it is noted that rural residents are more likely to be uncircumcised ($X^2 = 40.41$, $df=1$, p -value < 0.0001).

Table 2: Predictors of urinary tract infection among children who visited pediatric outpatient department of Hawassa University Comprehensive Specialized Hospital between May and September 2015.

Variable (total patients)	No UTI N (%)	UTI N (%)	p- value	Crude OR(95% CI)	Adjusted OR (95% CI)
Age, mean(SD) (n=269)	4.85(3.88)	4.78(3.53)	0.903	1.01(0.93-1.08)	
Sex (n=269)			0.113		
Male	69(67.0)	34(33.0)	1	1	
Female	126(75.9)	40(24.1)	0.113	0.64(0.41-1.02)	
Residence (n=269)					
Rural	95(63.8)	54(36.2)	0.000	2.84(1.74-4.64)*	0.97 (0.46-2.03)
Urban	100(83.3)	20(16.7)	1	1	1
Previous history of UTI (n=269)					
No	152(73.1)	56(26.9)	1	1	
Unknown	30(73.2)	11(26.8)	0.990	1.0(0.53-1.88)	
Yes	13(65.0)	7(53.0)	0.443	1.46(0.65-3.29)	
Under-nutrition (n=269)					
Yes	10(32.3)	21(67.7)	0.000	7.33(3.71-14.50)*	5.41(2.64-11.07)
No	185(77.7)	53(22.3)	1	1	1
Previous antibiotic intake (n=269)					
No	54(29.7)	128(70.3)	1	1	
Unknown	5(31.2)	11(68.8)	0.985	1.07(0.43-0.55)	
Yes	15(21.1)	56(78.9)	0.172	0.63(0.37-1.10)	
Previous hospital admission (n=269)					
Yes	20(62.5)	12(37.5)	0.181	0.59(0.31-1.13)	
No	175(73.8)	62(26.2)	1	1	
Circumcision in boys (n=166)					
Yes	43(91.5)	4(8.5)	1	1	1
No	83(69.7)	36(30.3)	0.006	4.66(2.00-13.02)*	3.70(1.34-10.16)

UTI: urinary tract infection, * p-value :< 0.05

All the patients underwent urine microscopy and dipstick. The findings of more than five white blood cells (WBC) per high power field (HPF) (aOR 4.7, 95% CI 1.8-12.7) on urine microscopy, urine PH higher than 5.0 (aOR 2.6, 95%CI 1.2-5.8), and a positive leukocyte esterase (aOR 9.9,

95% CI 4.1-25.7) independently predicted a higher chance of bacterial isolation on urine culture. Moreover, all the four patients who had a positive nitrite test had a positive urine culture (Table 3).

Table 3: Urine analysis findings and their association with urine culture positivity among children seen at OPD of Hawassa University Comprehensive Specialized Hospital, 2015.

Variable	Urine Culture		P-value	Crude OR (95% CI)	Adjusted OR (95% CI)
	No (%)	Yes (%)			
White Blood Cell (per HPF)			<0.0001		
Less than 5 cells	152(93.3)	11(6.7)		1	1
More than 5 cells	43(40.6)	63(59.4)		20.2(10.2-43.7)*	4.7(1.8-12.7)
Urine PH			0.0005		
PH less than 5.0	120(81.1)	28(18.9)		1	1
PH 5.0 and above	75(62.0)	46(38.0)		2.6(1.5-4.6)*	2.6(1.2-5.8)
Urine Specific Gravity			0.975		
1.0 - 1.015	61(72.6)	23(27.4)		1	-
1.020 - 1.030	134(72.4)	51(27.6)		1.0(0.6-1.8)	
Red Blood Cells (per HPF)			0.123		
Less than 5 cells	168(74.3)	58(25.7)		1	-
More than 5 cells	27(62.8)	16(37.2)		1.7(0.9-3.0)	
Cast			<0.0001		
No cast	189(77.5)	55(22.5)		1	1
Cellular or Granular	6(24.0)	19(76.0)		10.9(5.0-25.9)*	2.5(0.7-9.5)
Nitrite			0.006†		
Negative	195(73.6)	70(26.4)			
Positive	0	4(100)			
Leukocyte Esterase			<0.0001		
Negative	180(89.6)	21(10.4)		1	1
Positive	15(22.1)	53(77.9)		30.3(15.0-64.9)*	9.9(4.1-25.7)
Urinary Crystals			0.437†		
None	190(73.1)	70(26.9)			
Yes	5(55.6)	4(44.4)			
Urine protein					
None	172(76.4)	53(23.6)	1	1	1
Trace	14(70.0)	6(30.0)	0.519	1.4(0.5-3.7)	1.4(0.3-5.1)
More than 1+	9(37.5)	15(62.5)	0.0002	5.4(2.3-13.6)*	1.5(0.4-5.4)
Urine Glucose			0.899†		
None	192(72.7)	72(27.3)			
Trace and above	3(60.0)	2(40.0)			

HPF: high power field, **p-value* <0.05; †bivariate logistic regression was not done as there are zero or few cases in a category.

Antibiogram of isolates: All the *E. coli* isolates-the commonest cause of UTI in children-were resistant to ampicillin, penicillin and oxacillin, while the majority (97.1%) were resistant to cotrimoxazole, which is the first line drug for pediatric uncomplicated UTI. On the other hand,

resistance of *E. coli* to nitrofurantoin (0%) and quinolones (11.8%) was the lowest of all the tested antibiotics. Gentamicin resistance to *Klebsiella* spp, which is naturally resistant to ampicillin, was observed to be high (66.7%) (Table 4).

Table 4: Antimicrobial resistance pattern of bacterial isolates described as number of resistant isolates over total number of isolates tested for the specific antibiotic among pediatric UTI patients at Hawassa University Comprehensive Specialized Hospital, 2015

Antibiotic	<i>E. coli</i> (n=34)	<i>Klebsiella</i> <i>spp.</i> (n=18)	<i>Citrobacter</i> <i>spp.</i> (n=3)	<i>Enterobacter</i> <i>spp.</i> (n=2)	<i>Salmonella</i> <i>spp.</i> (n=1)	<i>S. aureus</i> (n=7)	<i>Enterococcus</i> <i>spp.</i> (n=6)
Ampicillin	100	88.9	100	100	0	85.7	83.3
Amoxicillin	70.6	77.8	100	100	0	14.3	33.3
Cotrimoxazole	97.1	94.4	100	100	100	14.3	16.7
Gentamicin	41.2	66.7	66.7	0	0	57.1	50
Ciprofloxacin	11.8	44.4	0	0	0	57.1	50
Norfloxacin	23.5	11.1	0	0	0	71.4	50
Ceftriaxone	47.1	38.9	66.7	0	0	71.4	50
Cephalexin	44.1	72.2	0	100	0	0	0
Cefotaxime	29.4	16.7	33.3	0	0	0	16.7
Nitrofurantoin	0	22.2	0	50	0	71.4	50
Oxacillin	100	100	100	100	100	42.9	83.3
Penicillin G	100	100	-	-	-	85.7	66.7
Erythromycin	-	100	-	-	-	71.4	50

DISCUSSION

Although UTI causes significant illness in children, the definitive diagnoses of UTI in most developing countries are often overlooked due to lack of facilities and laboratory cost in addition to difficulties of obtaining urine from children especially those who would not void voluntarily (6,15,16). In this study, culture confirmed UTI among clinical suspected children was 27.5% which is concordant with a study conducted in India (32.2%) but higher than a study reported in Iran (3.6%) (17,18). The differences could be explained by the retrospective study design they used and other demographic differences such as the majority of study subjects being females in contrast to our study. Moderate and severe degrees of undernutrition were independently associated with higher risk of UTI which could be explained by immunosuppression associated with undernutrition (2,19). Additionally, the finding of significantly more boys with uncircumcision from rural settings could explain the higher isolation.

In this study, *E. coli* and *Klebsiella spp.* accounted for about three fourth of the total isolates. The presence of unique structures such as adhesion, pili, fimbriae and P1-blood group phenotype

receptor in *Enterobacteriaceae* which help for their attachment to the uroepithelium increases risk for infection (20). We found a relatively higher rate of isolation of *Klebsiella spp.* and *S. aureus* as compared to previous reports (1,15,18). *E. coli*, which is the most common pathogen in both sexes, was significantly more frequently isolated in females than in males which is congruent with previous studies (21,22). On the other hand, similar with our findings, isolation rates of *Klebsiella spp.* and *S. aureus* have been reported to be higher in males than females (21,22). The differences in the preputial flora have been proposed as the possible reasons for differences in isolation rates (23). Moreover, findings of higher frequency of dilating vesicoureteral reflux (VUR) in boys (24) could be the explanation for the differences (22,25).

The more antibiotics are used in a community, the more likely it is that resistant strains will be selected and maintained in the environment (8,15,26). This complements the current high rate of resistance following ampicillin, co-trimoxazole, gentamicin and ceftriaxone exposure within three months prior to the diagnosis of UTI in our hospital. High resistance to these antibiotics is perhaps due to their widespread and erroneous use as empirical therapy even when guidelines suggest that when resistance rate exceeds 20%, the drug should not be

used empirically (27). In this study, rates of antimicrobial resistance profile of *E. coli* to ampicillin were high similar to studies from another African setting (15) but higher than Asian (79.3%) (28) and European settings(50%)(29). Our finding of high resistance profile of the common etiologies of UTI to the first line antibiotics is high and calls for more studies in this area in order to revise guidelines.

In this study, nitrofurantoin showed low level of resistance which makes this drug a reasonable alternative in management of UTI. This might have been due to its multiple mechanisms of action (1), underusage and narrow-spectrum nature of the drug. However, it cannot be used to treat UTI in complicated and febrile infants because it is excreted in the urine and does not achieve therapeutic concentrations in the bloodstream (30).

This study tried to address important research questions regarding the contribution of UTI for pediatric OPD visits, rate of isolation of bacterial causes among suspected cases based on signs and symptoms and the predictors of a culture confirmed UTI. It also revealed the antimicrobial resistance pattern of clinically relevant pathogens that caused UTI. However, it also had limitations including being hospital/suspicion based study where less severe or asymptomatic cases of UTI might have been missed further limiting its generalizability to the whole pediatric population. It also involved a small sample size especially for antimicrobial testing which limits the recommendations for revising treatment guidelines. Moreover, even though we took measures to minimize any risk of contamination, for younger age groups, the urine collection mechanism we have used might have increased the risk of contamination.

In conclusion, clinically suspected UTI accounted for nearly a third of the total OPD visits, and around a third of these were culture confirmed UTI. Moderate and severe degree of undernutrition and male uncircumcision were associated with increased risks of culture confirmed UTI. The commonly used first line antibiotics like amoxicillin, ampicillin and cotrimoxazole showed a high level resistance limiting their use for OPD treatment of UTIs. The findings of the current study call for a more robust study with a larger isolate number to better understand the resistance pattern of

the common bacterial isolates and advise guideline change.

ACKNOWLEDGEMENTS

We are most grateful to express our gratitude to staff members of pediatric and microbiology laboratory department for their professional assistance during the data collection and analysis.

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