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ORIGINAL ARTICLE

Urinary Tract Infections are prevalent among febrile under-five children presenting to the University Teaching Hospital- Children's Hospital in Lusaka, Zambia

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ABSTRACT

Background: Urinary tract infections (UTIs) account for a significant proportion of fevers in paediatric patients. In low resource settings where diagnostic testing for fever is not readily available, children with UTIs may be left at risk of adverse outcomes due to inadequate treatment. This study investigated the burden of UTIs in under-five children presenting with fever to the outpatient department of the University Teaching Hospitals, Children's Hospital in Lusaka, Zambia.

Method: This cross-sectional study was conducted between October 2019 and March 2020, in children with an axillary temperature greater than 37.5°C. Clinical data were collected and urine specimens were obtained for analysis by dipstick, microscopy, culture, and sensitivity testing. Ultrasonography was performed on all children with culture positive UTIs. Data was analysed using IBM ™-SPSS ™ version 29 (IBM Corp., Armonk, NY, USA) and a p-value of <0.05 was considered significant.

Results: Most participants (79,54%) were males and the median age was 26.5 months (IQR, 11.3 – 42.0). The prevalence of UTIs was 28.8% (42)/146) and a history of diarrhoea (p=0.031) and presence of leucocytes in urine (p=0.016) were predictive of UTIs. *Escherichia coli* 12(26%) and *Enterococcus species* 10(22%) were the commonest uropathogens and were most susceptible to co-amoxiclav 19(83%) and ciprofloxacin 15(83%) but 15 (83%) were resistant to co-trimoxazole.

Conclusion: A third of febrile under-five children had UTI and most uropathogens were susceptible to the most used antibiotics. However, there is evidence of emergent resistance to cefazolin which raises concerns for use of cephalosporins particularly in treatment of complicated UTI.

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INTRODUCTION

Fever is one of the most common presenting complaints of children brought to the Outpatient Department (OPD).[1] In Zambia, during the Health and Demographic Survey of 2018, it was found that about 16% of children under the age of five years had experienced fever in the two weeks preceding the survey.[2,3] Studies have shown that urinary tract infections (UTIs) account for a significant proportion of these fevers.[4, 5, 6] Yet in most low-resource settings such as Zambia, the use of the Integrated Management of Childhood Illness (IMCI) guideline emphasizes diagnostic workup of fever as malaria and advises the use of antibiotics if given at all, for only 5 days.[7] This blanket approach may contribute to malaria over diagnosis and inappropriate antibiotic utilization. Furthermore, clinical features of UTIs in young children may be non-specific and may closely mimic features of other causes of febrile illnesses[8]. This suggests that children presenting with fever because of UTI may be misdiagnosed or inappropriately treated.[7,8] Untreated UTIs are important in the paediatric population as they may result in several complications such as urosepsis, meningitis and in the long-term, renal scarring, hypertension, chronic kidney disease and an increased risk of pregnancy-associated hypertension for females.[9,10]

The prevalence of UTIs varies with age, sex, race, nutrition and circumcision status in males.[11] Worldwide, the most common causative agent of UTIs is *Escherichia coli.*[12] Local antibiotic sensitivities tend to vary but generally, there is now increasing recognition of the emergence of resistance of uropathogens to commonly used antibiotics.[13,14]

There is paucity of empirical evidence regarding prevalence of UTI among the Zambian paediatric population and thus information on clinical characteristics of children with UTIs, common causative organisms and local antibiotic susceptibility patterns to guide in the treatment of UTIs is scanty.[15,16] We present for the first time, to our knowledge, data on the magnitude of culture-proven UTI, predictors of UTI, causative organisms and their antibiotic susceptibility among Zambia children.

METHODS

This study was carried out to determine the prevalence, risk factors, and the common causative pathogens of UTIs in children under five presenting with fever as well as determine the antibiotic susceptibility patterns of the identified pathogens.

Study design, setting and population

This was a cross-sectional study conducted at the OPD of the UTH Children's Hospital, Lusaka, Zambia. The hospital is a tertiary referral centre for all Lusaka urban clinics as well as first and second level hospitals countrywide with a 350-capacity bed space. In the year 2019, a total of 15,361 children were seen in the OPD and about 10,600 were children under the age of 60 months.

Eligibility criteria and sample size calculation

The study was targeted at under five children who presented to the UTHs Children's Hospital with an axillary temperature greater than 37.5 °C. Children who had taken antibiotics for more than 48 hours were excluded from the study. We consecutively recruited 162 participants, and the sample size was calculated as follows: $\mathbf{N = Z^2 x\, p(1-p)/e^2}$. We assumed a loss to follow up rate of 10%, Z= 1.96; prevalence= 11.9%, the proportion of morbidity (presence of a UTI) taken from the study by Masika et al., 2017 in Kenya; e =precision (0.05).[15] There was no local data on UTI prevalence among hospitalised children thus regional data from Kenya for the UTI prevalence for the purposes of estimating the sample size.

Data collection procedure

Children with febrile illness were recruited from the OPD after obtaining consent from parents/guardians. Upon sensitisation and informed consent, baseline data and clinical characteristics were collected using a data extraction sheet. Thereafter, a physical examination was performed by the study doctor and two urine samples were collected from the participants.

Sample collection

For non-toilet trained children (under 3 years) urine was collected using the in and out catheter method, using the smallest size Foley Catheter (size 6Fr) to minimise pain and discomfort as urine was being collected. To further minimise pain, children were allowed to breastfeed during catheter insertion as a non-pharmacological method of pain management.[17,18] Other modes of pain reduction included distracting the children with play therapy during the collection of urine. For children above 3, urine was collected via the mid-stream urine (MSU) method. The collection was done after thorough cleaning of the perineum using swabs dipped in normal saline. The urine was collected in two sterile urine specimen bottles.

Sample analysis

The urine samples were initially inspected macroscopically for colour and clarity. Then the first sample was subjected to a dipstick test (*Mission*® Urinalysis Strips, ACON, laboratory Inc., San Diego CA) immediately after collecting the urine. A urinalysis strip (dipstick) was dipped into the sample and the colour on the strips checked within 60 seconds. The information noted was urobilinogen, glucose, ketones, bilirubin, protein, nitrite, pH, blood, specific gravity as well as leukocytes status in the urine sample.[19]

The second sample was sent to the UTH microbiology laboratory for microscopy, culture and antimicrobial sensitivity. The samples were taken to the laboratory within an hour of collection using a cooler box. Any sample not worked on immediately was refrigerated. Standard methods for processing of urine samples were used, in brief, the samples were centrifuged at 3000 revolutions for 5 minutes after which the supernatant was discarded. The remaining sediment was used to prepare a smear on a slide for urine microscopy.[20] The sample was considered positive for a UTI if 5 white blood cells were seen per high power field on microscopy.[21]

For the urine culture, a well-mixed sample of urine was inoculated on blood and cysteine lactose electrolyte deficient (CLED)/MacConkey agsar using a standardised wire loop [1µl (0.001 ml)]. After inoculation, plates were incubated aerobically at 35-37?C for 18-24 hour. Blood agar plates were incubated in 5% CO_2 for better growth of Gram-positive organisms. The plates were examined for growth after 24 hours. Colony counts were performed for pure growth. If the colony count was $\geq 10^5$ it was considered as significant bacteriuria and subjected to susceptibility tests. On the other hand, colony counts of $< 10^4$ were considered as insignificant bacteriuria and recorded as negative in the final analysis. Mixed cultures were indicated as contaminated.

Organisms were identified by colony morphology, gram stain and bio-chemical tests. Antimicrobial sensitivity testing was carried out by Kirby Bauer disc diffusion technique according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI).[22] The sensitivity discs that were tested against the isolates included the commonly used antimicrobial agents: trimethoprim/sulfamethoxazole (TMP-SMX), ampicillin, nitrofurantoin, amoxicillin-clavulanate, nalidixic acid, gentamicin, penicillin and ciprofloxacin. Cefazolin was used as a surrogate marker for cephalosporins.[22]

Variables

Study dependent variable was UTI (Yes or No). The independent variables included age, sex, temperature at admission, irritability, dysuria, constipation, diarrhoea, poor appetite, nausea, vomiting, history of previous UTI, urinalysis findings, history of poor weight gain and ultrasonography findings. The area of residence of participants was classified into high-, medium- and low- density. For the purposes of this study, unplanned settlements were classified as high-density areas, while council gazetted and serviced areas that are low income were classified as medium-density and the suburbs were classified low-density areas.

Data Analysis

Data was collected and entered on Excel spreadsheet and later exported into IBM ™-SPSS ™ version 29 (IBM Corp., Armonk, NY, USA). Continuous variables such as age and temperature were tested for normality using the Shapiro-Wilk test before analysis. To determine the association between the outcome variable (UTI or no UTI) with categorical variables such as sex, irritability, dysuria, constipation, diarrhoea, nausea and vomiting, Chi-square test was used. However, in instances where any of the cell frequency was less than 5, Fisher's exact test was used. To determine the correlation of continuous variables Mann-Whitney U test was used since both continuous variables had a non-normal distribution. All independent variables showing correlation to the UTI with chi-square $p < 0.25$ and variables known from literature to predict UTI were used to construct a logistic regression model to determine the association between outcome and independent variable[23,24]. For all statistical test, a p-value of 0.05 was considered significant.

Ethical Considerations

The study was conducted according to the ethical standard of ERES Converge Institutional Review Board and the Helsinki declaration. Ethical clearance was obtained from ERES Converge Institutional Review Board (Ref. No.2019- May-035). Permission to conduct the study was granted by the National Health Research Authority as well as the hospital administration. Written informed consent was obtained from participants before enrolment. The potential participants were interviewed in either English Nyanja, Bemba, Tonga or Lozi depending on their language of preference and were handed a printed information sheet. They were informed that they were free to withdraw from the study at any time without any consequences. For participants who were unable to read and write a witness was asked to follow along during the consenting process and to counter sign the consent form. Patient information was anonymized and de-identified prior to analysis. Participants were informed that they were free to withdraw from the study anytime without any consequences.

RESULTS

Recruitment of study participants

In this study, conducted between October 2019 and March 2020, 180 children under five years were screened out of which 162 were recruited. Of those recruited, 18 children were excluded due use of antibiotics for more than 48 hours. Sixteen children were excluded from the final analysis due to incomplete lab data and mixed growth on urine culture, Figure 1.

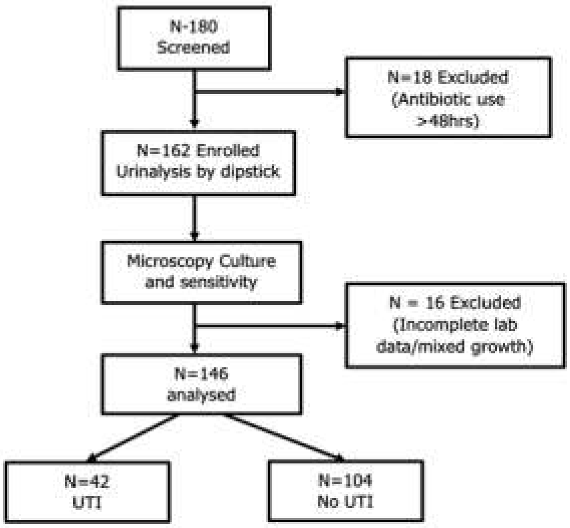

Figure 1: Study recruitment algorithm.

Prevalence of UTI

Of the 146 children 42 had growth on culture giving a UTI prevalence of 28.8%.

Demographic and baseline characteristics of study participants and their association to UTI

The demographic and baseline clinical characteristics of the participants are illustrated in Table 1. The median age of the children enrolled was 26.5 months (IQR, 11.3 – 42.0) but children with UTI were significantly younger (15 months versus 29.6 months, p=0.029). Of the children enrolled the majority (77, 52.7%) were in the age range 25 to 59 months while only 8 (5.5%) were neonates.

Of all the study participants 54.1% (79/146) were boys and being male was significantly associated to UTI (66.7% boys with UTI versus 49% boys without UTI, p=0.053). Most participants (79, 58.9%) were from high density areas, but areas of residence were not statistically associated with UTI.

Most of parents/guardians 91(62.3%), cleaned their children/wards front to back after defecation or urination with only 11(7.5%) cleaning them back to front but cleaning pattern was not correlated to UTI (p=0.406). More than half 83 (56.9%) had their urine samples collected via mid-stream collection method, but method of urine collection was not associated to UTI (p=0.265).

At presentation most of the children, 89 (60.9%), were irritable and 74 (54.3%) had a history of poor appetite. The use of bubble bath was not common, only 4 (2.7%) of participants had reported use of bubble bath. The analysis was done on all variables which had a p-value of <0.05 in univariate logistic regression. The children with diarrhoea were more likely to develop UTI (AOR=1.66, 95% CI [0.80–5.90]; p=0.031).

Less than half of children 63(43.2%) presented with fever only as the main presenting complaint followed by less than one-third 42(28.8%) who came with gastrointestinal complaints that included diarrhoea, vomiting or constipation. Other children presented with fever with respiratory symptoms 16(11.0%), fever with musculo-skeletal symptoms 8(5.5%), central nervous system (CNS) signs 5(3.4%) while only two presented with fever and both respiratory and CNS symptoms.

Table 1: Baseline Demographic and clinical characteristics of study participants

Characteristics	Category	Total N (%)	No UTI N (%)	UTI N (%)	COR	95 % CI	P-value
Sex	Male Female	79 (54.1) 67 (45.9)	51 53	28 14	0.48	0.23-1.02	0.055
Age (Months)	0 -1 2-12 13-24 25-59	8 (5.5) 32(21.9) 29 (19.9) 77 (52.7)	7(6.7) 15 (14.4) 23 (22.1) 59 (56.7	1(2.4) 17 (40.5) 6 (14.3) 18 (42.9)	0.79	0.41 -1.53	0.488
Residence (Density)	High Medium Low	86 (58.9) 53 (36.3) 7 (4.8)	4 (3.8) 37 (35.6) 63 (60.6)	3 (7.1) 16 (38.1) 23 (54.8)	ref 1.18 2.05	0.56-2.52 0.43-9.89	0.661 0.369
Cleaning Pattern	Back to front Front to back No pattern	11 (7.53) 91 (62.33) 44 (30.1)	6 (5.8) 65 (62.5) 33 (31.7	5 (11.9) 26 (61.9) 11 (26.2)	ref 0.48 0.40	0.13- 1.00 0.10-1.00	0.258 0.190

Signs And Symptoms							
Irritable	Yes No	89 (61) 57 (39)	64 (61.5) 40 (38.5)	25 (59.5) 17 (40.5)	0.92 Ref	0.44 – 1.91	0.821
Poor Appetite	Yes No	74 (50.7) 72 (49.3)	50 (48.1) 54 (51.9)	24 (57.1) 18 (42.9)	1.44	0.07 – 2.96	0.322
Vomiting	Yes No	36 (24.7) 110 (75.3	21 (20.2) 83 (79.8)	15 (35.7) 27 (64.3)	2.20	0.99 – 4.85	0.052*
Diarrhoea	Yes No	31 (21.2) 115 (78.8)	17 (16.3) 87 (83.7)	14 (33.3) 28 (66.7)	2.56	1.12 – 5.84	0.026*
Constipation	Yes No	7 (4.8) 139 (95.2)	3 (7.9) 101 (97.1)	4 (9.5) 38 (90.5)	3.54	0.76 – 16.6	0.108
Abdominal Pain	Yes No	26 (17.8) 120 (82.2)	18 (17.3) 86 (82.7)	8 (19.0) 34 (81.0)	1.15 ref	0.45 – 2.96	0.769
Pain/Crying On Passing Urine	Yes No	4 (2.7) 142 (97.2)	4 (3.8) 100 (96.2)	0 (0) 42 (100)	2.18	0.90 – 5	1.72
Foul Smelling Urine	Yes No	1 (0.7) 144 (97.3)	1 (1.0) 103 (99.0)	0 (0.0) 41 (100)	1	**OMIT	
Change In Colour Of Urine	Yes No	2 (1.4) 142 (98.6)	1 (100)	0	1	**OMIT	
Increase In Frequency Of Passing Urine	Yes No	1 (0.7) 144 (98.6)	1 (100) Ref	0	1	**OMIT	
Day Or Bedwetting When Previously Dry	Yes No	1 (0.7) 102 (69.9)	1 (100) ref	0	1	**OMIT	
Use Bubble Bath	Yes No	4 (2.7) 142 (97.3)	2 (1.9) 102 (98.1)	2 (4.8) 40 (95.2)	2.55	0.35 -18	0.357
Mode Of Collection	Catheter Mid-stream Clean-catch	62 (42.5) 83 (56.9) 1 (0.7)	40 (38.6) 63 (60.6) 1(1)	22 (52.4) 20 (47.6) 0(0)			
OMIT – omitted due to collinearity. CI = Confidence interval **, COR = Crude odds ratio, N/A = Not applicable							

The sensitivity and specificity of the urinalysis parameters in detecting UTI are displayed in Table 2. All the parameters had a low sensitivity; leucocytes 59%, nitrites 11.9%, blood 21.4%, protein 54.8% and pH 4.8%. The use of all these parameters combined still showed a low sensitivity with both leucocytes and nitrites positive giving a sensitivity of 9.52. Specificity was high for nitrites (91.4%), pH (100%) and when both leucocytes and nitrites were positive (95.2%).

Table 2: Sensitivity and specificity of urinalysis in detecting UTI

Parameter Of Urinalysis	Sensitivity (%)	Specificity (%)
Leucocytes	59.5	63.5
Nitrites	11.9	91.4
Blood	21.4	85.6
Protein	54.8	51.9
pH	4.8	100
Both Leucocytes and Nitrites positive	9.52	95.2
Negative Nitrites with positive leucocytes	50	69
Negative Leucocytes with positive nitrites	2.4	95.2

Predictors of UTI

A logistic regression model was constructed (table 3) to ascertain the effects of various independent variables on the likelihood that the participants had UTI. All variables with chi-square $p < 0.25$ and variables known from literature to predict UTI used to construct the logistic regression model. A total of 143 cases were used to construct the model while 3 cases were omitted due to missing data. The model was a good fit and explained 42.0% (Nagelkerke R^2) of the variance in UTI and correctly classified 79% of all cases, increasing accuracy from 71.3% to only 79.0 %. Being female and wiping front to back were protective against UTI but being from a low-density residential area was predictive of UTI

Table 3: multivariable logistic regression

Characteristic	Category	COR	AOR	Sig.	95% C.I. for AOR	
					Lower	Upper
Sex	Female	-1.433	0.238	0.011	0.08	0.72
Area of Residence	High density Medium density Low density	.267 2.129	1.305 8.403	0.173 0.625 0.061	0.448 0.907	3.80 77.82
Cleaning pattern	Back to front Front to back no pattern	-0.829 -2.074	0.447 0.126	0.081 0.337 0.043	0.080 0.017	2.374 0.934
Leucocytes on Urinalysis	Positive	1.205	3.338	0.019	1.216	9.166
	Constant	9.953	21010	0.444		

Model statistics:
Nagelkerke R-Square= 0.39, Cox-Snell R-Square= 0.273
Testing Global Null Hypothesis: omnibus model coefficient chi-square= 49.577, df= 26, p= <0.004
Hosmer and Lemeshow Goodness-of-Fit Test: chi-square= 14.55, df=8, p= 0.067
AOR= Adjusted odds ratio, CI = Confidence interval, COR = Crude odds ratio

Spectrum of Microorganisms isolated from urine

The uropathogenic organisms isolated are shown in Table 4. Most 12 (26%) of the organisms identified in culture-positive urine was *E. coli* followed by 10 (22%) *Enterococcus sp.* Other microorganisms that were cultured include *Providencia stuartii, Morganella morganii, Pseudomonas sp.* and *Citrobacter sp.* There were 12 cultures with insignificant growth which were recorded as negative.

Antibiotic susceptibility of bacterial isolates

The bacteria isolates were all subjected to antibacterial sensitivity testing as per Clinical and Laboratory Standards Institute (CLSI, 2018) guidelines. The drugs used for susceptibility testing were co-trimoxazole, ciprofloxacin, nitrofurantoin, co-amoxiclav, cefazolin, ampicillin, nalidixic acid, gentamicin and penicillin because these are the most utilized drugs for treatment of UTIs in clinical practice.

Out of 146 urine samples cultured, 42 (28.9%) were positive for uropathogens. Most 15 (83%) of the isolates demonstrated resistance to co-trimoxazole. In contrast, most of the organisms were susceptible to norfloxacin, co-amoxiclav and ciprofloxacin 8 (100%), 19 (83%) and 15 (83%) respectively) as shown in Figure 2.

Table 4: Spectrum of Microorganisms isolated from urine

Bacteria species isolated (N=42)	Number	Percent
E. coli	12	26.1 %
Enterococcus sp.	10	22 %
Staphylococcal sp.	7	15 %
Klebsiella	7	15 %
Proteus mirabilis	2	4.4 %
Morganella morganii	1	2.2 %
Pseudomonas sp.	1	2.2 %
Citrobacter sp.	1	2.2 %
Providencia stuartii	1	2.2 %

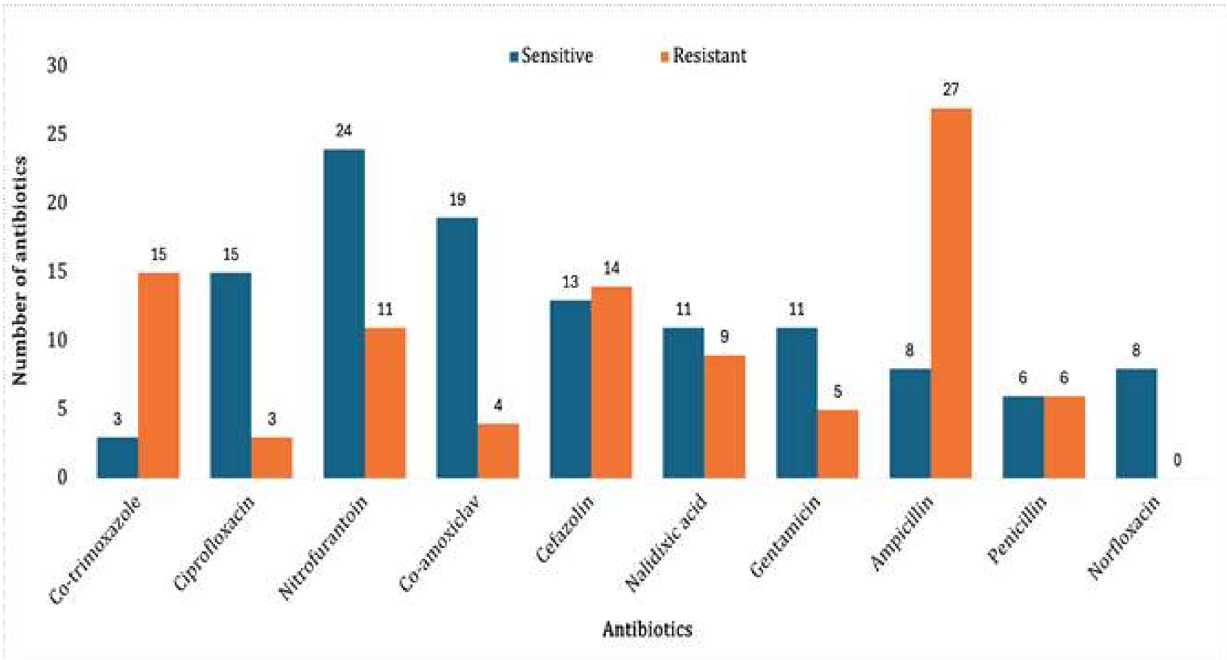

Figure 2: Overall antimicrobial sensitivity pattern.

The sensitivity and resistance of individual isolates are displayed in Figure 3 and 4. *E.coli* was susceptible to ciprofloxacin, nitrofurantoin, co-trimoxazole and norfloxacin. *Keblsiella* was sensitive to co-amoxiclav and nitrofurantoin while isolates tested against Ciprofloxacin, ampicillin and gentamicin were resistant. The single isolate of *Pseudomonas sp.* was only tested against ciprofloxacin to which it was susceptible.

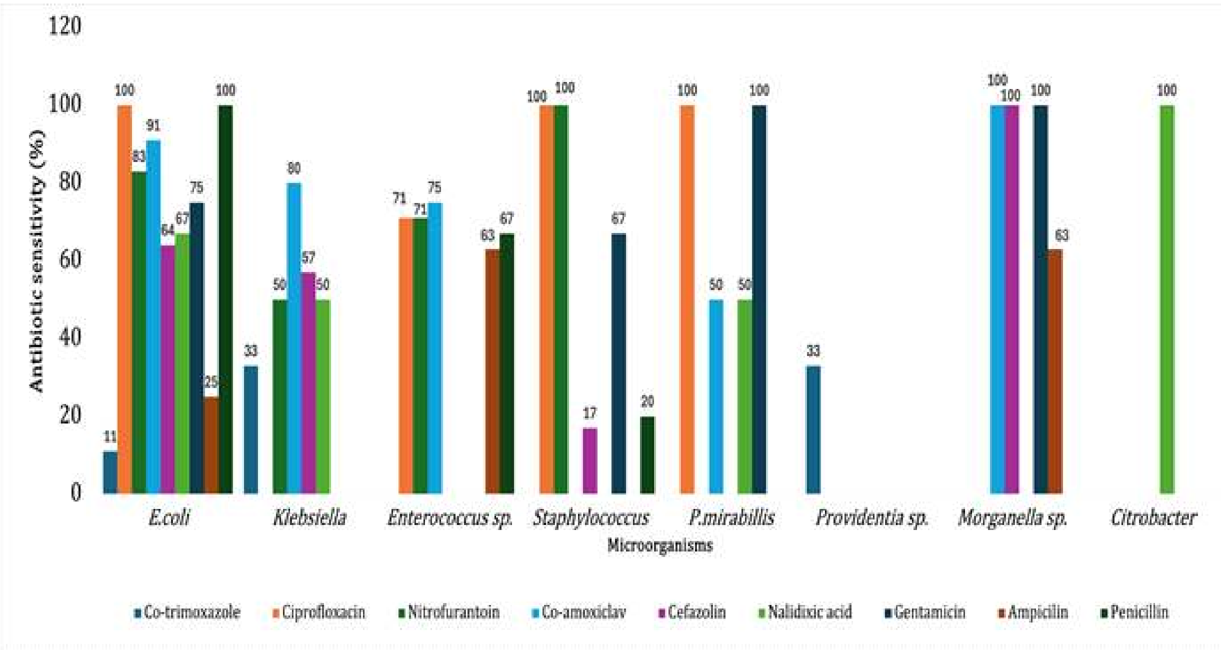

Figure 3: Sensitivity patterns of individual bacterial isolates to various drugs.

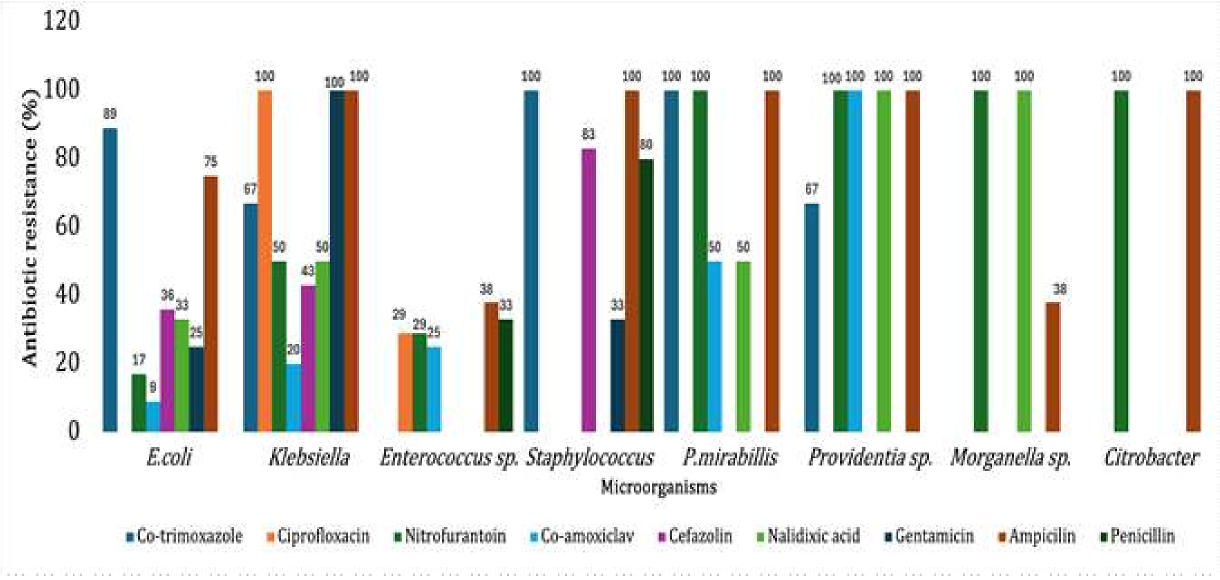

Figure 4: Resistance patterns of individual bacterial isolates to various drugs.

Ultrasonography findings

Out of 42 participants with positive culture only 15 returned for KUB ultrasonography, 13 were normal and 2 abnormal. One was a male, and one was female. The male participant had bilateral hydronephrosis while the female had hydronephrosis plus thickened bladder wall.

DISCUSSION

This study was conducted to establish the magnitude associated risk factors, causative agents as well as the antimicrobial susceptibility patterns of UTI among under-five children in the Zambian context. The prevalence of UTI was 28.8% and the factors that were associated with UTI were presence of leucocytes in urine while female sex and having a non-back to front pattern of wiping were protective. *Escherichia coli* and *Enterococcus species* were the commonest uropathogens and were most susceptible to co-amoxiclav and but resistant to co-trimoxazole.

Most of the children enrolled were aged between 25 and 59 months old. Children in this age group are known to be at higher risk of UTI because they are not yet toilet trained.[25] There were twice as many boys with UTI as girls. It is known that male infants are at higher risk of UTI[26] due partly to their physiologic detrusor sphincter dyscoordination.[27] In addition, it is known that circumcision offers protection as was shown by Laway *et al.* who compared uropathogenic bacteria on the prepuce of boys before and after circumcision.[28] None of the boys in this study were circumcised.

The prevalence of UTIs is dependent on sex, age and male circumcision status.[11,29–31] Our rate of UTI was much lower than the prevalence reported in similar studies in southern Africa.[32,33] For instance, one study done in Tanzania had a prevalence of 40%.[32] The noted discrepancy in prevalence between these two studies could be because urine specimens that grew mixed urine cultures in the Tanzanian study were re-cultured and any growth regardless of the number of CFU was considered positive for samples collected via SPA. Other studies have shown lower prevalence rates. For example, a study done in rural Kenya reported a prevalence of only 12%.[15] One plausible reason for this lower prevalence in the Kenyan study could be that in that study urine culture was only performed on urine samples that showed prior positivity for leucocytes on either dipstick or microscopy. In our study however, all patient urine specimens were cultured regardless of urinalysis findings since a negative urinalysis by urine dipstick does not rule out UTI.[34,35] This could explain our higher UTI prevalence. Generally, the reported prevalence of UTI in high income countries is lower than that in developing countries. Our reported prevalence was much higher than the rate from a similar study carried out in the UK (5.9%).[35]

Surprisingly, there was no sufficient evidence to suggest that there was an association between features such as irritability, poor appetite, constipation, abdominal pain, dysuria, foul-smelling urine, frequency, change in colour of urine and bedwetting with UTI. This may be because only a few children presented with these complaints. Previous studies have found that these clinical features were risk factors for UTI.[21,36] Our findings, however, did not demonstrate such an association.

In this study only 4 children reported using bubble bath and none of them had UTI. Due to the small number of children, no firm conclusion can be made about this association. Similarly, the cleaning pattern (after urination and defection) was not demonstrated to be a risk factor for UTI in our study. Most of the children enrolled were being cleaned correctly i.e., front to back. Cleaning from front to back is one of the methods described in the prevention of UTI.[36]

Dipstick urinalysis is often used as a screening tool for the diagnosis of UTI although various studies have disputed its utility as a standalone tool for diagnosis of UTI.[37–39] In our study, the presence of leucocytes on urinalysis was associated with a positive urine culture although the sensitivity was only 59.5% and specificity 63.5%. This reaffirms previous guidance that urinalysis cannot be used to exclude UTI.[39,40] The presence of nitrites alone had a specificity of 11.9% and a sensitivity of 91.4%. However, most studies have shown that nitrites are poor indicators of UTI as they have a low sensitivity and a high specificity particularly in infants.[39,41] When the presence of leucocytes was combined with the presence of nitrite the sensitivity was 9.5% and the specificity rose to 95.2%. This is in keeping with other studies that show a significant increase in sensitivity when the two tests are combined (i.e., nitrites and leucocytes)[37]. However, in our study, even in combination sensitivity was low. This finding was consistent with the meta-analysis which showed that a negative urinalysis did not rule out UTI[19]. Thus, primary care health workers need to be alerted to the limitations of urine dipsticks and encourage to culture urine as a means of excluding UTIs.

The commonest microorganisms cultured were *E.coli* and *Enterococcus sp.* This is in keeping with findings in other studies which demonstrated that children under the age of five years are more likely to be infected with organisms from the faecal flora.[15,25,42] Cultured uropathogens demonstrated good susceptibility to commonly used antibiotics. Susceptibility to both ciprofloxacin and co-amoxiclav was 83% while all the cultured uropathogens were susceptible to nitrofurantoin. There was a high resistance rate to co-trimoxazole (83%) by *E.coli*, *Klebsiella sp.,Staphylococcus, Proteus mirabilis and Providentia sp*. This is not surprising since co-trimoxazole is a commonly used drug especially for prophylaxis in HIV positive patients. This finding is similar to a retrospective study carried out in Gaborone, Botswana which examined antimicrobial susceptibility in both children and adults.[43] A total of 744 samples were included in the study of which greater than 60% of *E. coli* isolates were resistant to ampicillin and co-trimoxazole. The resistance to co-trimoxazole was more in the HIV positive patients who commonly use the drug for treatment and prophylaxis. Similarly, a study carried out on hospital and community isolates of uropathogens at a tertiary hospital in South Africa found high resistance levelled to amoxicillin and co-trimoxazole for all Gram-negative isolates.[44] These findings reaffirm the decision not to use cotrimoxazole as a first line treatment for UTI in the Zambian context.

Additionally, it is important to make the hospital microbiology surveillance reports that are routinely conducted on susceptibility of UTI pathogens, available to clinicians so that treatment guidelines are kept relevant.

Cefazolin which was used as a surrogate for cephalosporins showed an almost equal rate of resistance (52%) and susceptibility (48%). Worldwide, there is an emergence of resistance to antibiotics including cephalosporins.[13,45,46] This is of concern particularly in the very young infants who may present with the non-specific features of urosepsis and for whom cephalosporins form part of first-line empirical treatment. This underscores the need for all young infants presenting with febrile illness to have a urine culture as part of their septic workup. The emergence of resistance to broad-spectrum antibiotics such as cefazolin is a worrying trend. This can be attributed to an extent to the high level of misuse of drugs in part due to the ready availability of over-the-counter drugs.[45] In this study, the finding strengthens the argument that antibiotic acquisition should be by prescription. In terms of empirical treatment, the use of antibiotics should be restricted to drugs that fit the local antibiogram profile. In addition, broad-spectrum antibiotics should be reserved for the treatment of complicated UTIs. It is also important to insist that patients who are commenced on antibiotics should adhere closely to instructions as per prescription (duration and frequency) to further reduce the development of resistance.

The American Academy of Pediatrics recommends that children less than 2 years of age with culture-positive UTI and fever should have a follow-up ultrasonography done[39]. Unfortunately, as most parents were reluctant to come back to the hospital only 11 out of the 42 patients with UTI had ultrasonography done. Only two children had abnormal ultrasound findings. The participants with normal ultrasonography findings had UTIs due to either *E.coli* or *Enterococcus sp. The participants with abnormal ultrasound findings included one boy with* UTI positive *Klebsiella sp.* who had mild hydronephrosis with no features of renal failure. The other participant with abnormal ultrasonography was a female who also had mild hydronephrosis and had a thickened bladder wall. Due to the small number of children (less than half) who had ultrasonography done, it is difficult to draw any statistical conclusion from this data.

A study done in India reported the prevalence of abnormal ultrasonography in febrile children less than 2 years with positive urine culture as 34%.[47] In another study carried out in Kashmir province in India, VUR was detected in 25% of children with febrile UTI.[48] This is higher than the prevalence of 18% found in this study possibly because of the small number of patients who had ultrasonography done. The most common abnormality found in the Kashmir study was hydronephrosis similar to our study participants. In contrast a Spanish study that enrolled 306 children found that only 35(11.4%) children had positive renal findings. The conclusion reached in the study was that renal ultrasonography after first uncomplicated UTIs were of little value.[49] The recommendation, therefore, was that indication for ultrasonography be individualised and limited to children under the age of 3 months infected with microorganisms other than *E.coli.* A similar conclusion was arrived at in another retrospective study carried out in Riyadh, Saudi Arabia.[50]

This study is several limitations. Firstly, it was difficult to get all the children with culture-positive UTI back to the hospital to do ultrasounds to determine the most common urinary tract abnormality. Secondly, this study was conducted over a six-month period therefore any potential effect of seasonality on UTI may have been missed. Thirdly, response that required respondents to remember past events such as cleaning patterns, use of bubble bath may have introduced an element of recall bias.

CONCLUSION

A good number of under five children presenting with fever to UTH have UTI. Factors associated with UTIs were the presence of leukocytes in urine, but the specificity was poor. This implies that routine urine cultures for hospitalised febrile children in Zambia should be done. Urinalysis which had a low sensitivity, but high specificity is suitable only for screening purposes and should not be used as a stand-alone tool for diagnosis.

Female sex and a non-back to front wiping pattern were protective against UTI. Similar to what is found in literature, the commonest uropathogens isolated were *E.coli* and *Enterococcus sp.* These bacterial isolates were susceptible to commonly used drugs ciprofloxacin, co-amoxiclav and nitrofurantoin and thus these drugs can continue to be utilized for empirical treatment of UTI in this age group. Unfortunately, there was evidence of emergent resistance to cefazolin which raises concerns for use of cephalosporins particularly in treatment of complicated UTI. As expected, resistance to co-trimoxazole was widespread. There is continued need for pharmacovigilance and regulation of over-the-counter sell of antibiotics in order to prevent the widespread emergence of resistant species.

What is already known on this topic?

- UTI contribute to a significant number of children with fever in the paediatric out-patient department in children less than 60 months.
- UTI is caused largely by uropathogens *E.coli and Enterococcus sp. Which are susceptible to commonly used antibiotics co-amoxiclav, nitrofurantoin and ciprofloxacin.*

What this study adds

- A documentation of the prevalence of UTI among Zambian children
- A significant rate of emergent resistance to cefazolin (52%) which raises concerns particularly for infants being treated for sepsis in whom urosepsis is often the primary focus of infection.
- Documentation of widespread resistance of uropathogens to co-trimoxazole in the Zambian paediatric population.

Competing interests

The authors have no competing interests to declare.

Authors' contributions

Cheelo Mwiinga- Conceptualisation, design, analysis, interpretation of data, drafting of the manuscript, approval for publication.

Chisambo Mwaba- Conceptualisation, design, interpretation of data, review of the manuscript, approval for publications.

Somwe wa Somwe- Conceptualisation, design, interpretation of data, review of the manuscript, approval for publication.

Patrick Kaonga-Conceptualisation, design, analysis, interpretation of data, drafting of the manuscript, approval for publication.

Christone Kaile- Laboratory analysis, review of manuscript, approval for publication.

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