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Aetiology, antimicrobial susceptibility and predictors of urinary tract infection among febrile under-fives at Muhimbili National Hospital, Dar es Salaam-Tanzania

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Urinary tract infection (UTI) is a common cause of fever in children and contributes to morbidity and mortality. This study aimed at determining prevalence, aetiology and antimicrobial susceptibility pattern of the isolates at Muhimbili National Hospital (MNH), Dar es Salaam- Tanzania. Demographic data were collected using a pretested questionnaire. 382 febrile children below five years admitted in the general paediatric wards were recruited. Urine specimens were obtained for urinalysis, culture and antimicrobial sensitivity testing. UTI was detected in 16.8% (64/382). Children who presented prolonged duration of fever (7 days or longer) were more likely to have UTI (p< 0.01). Duration of fever, positive leukocyte and nitrite tests were independent predictors of UTI. Isolated bacteria included *Escherichia coli* (39.1%), *Klebsiella* spp (31.2%), *Staphylococcus epidermidis* (6.2%), *Staphylococcus aureus* (4.7%) and *Pseudomonas aeruginosa* (4.7%). We observed high resistance of the isolated uropathogens to ampicillin (79.9%), co-trimoxazole (89%) and clavulanate-amoxillin (70.3%). Amikacin had the least resistance (12.5%) from the isolated pathogens.

Key words: Urinary tract infection, uropathogens, antimicrobial susceptibility.

INTRODUCTION

Febrile illnesses account for most hospital attendance and may lead to significant morbidity and mortality (Campbell et al., 2004). The underlying causes of fever in Sub-Saharan Africa are predominantly infectious in nature and urinary tract infection (UTI) is among the leading causes (Adjei et al., 2004; Jeena et al., 1996). There is co-existence of UTI with other febrile conditions including malaria and acute respiratory tract infections (Okwara et al., 2004; Mussa-Aisien et al., 2003); therefore UTI may be easily missed if it is not considered as one of the differential diagnosis in a febrile child. In a study conducted in one of the consultant hospitals in north western Tanzania, UTI was detected in 39.7% of febrile children (Festo et al., 2011).

Generally, Gram-negative organisms are the common organisms causing UTI in children. In Tanzania, Festo et al. (2011) reported *E. coli* and *Klebsiella pneumonia* as the commonest isolates among febrile under-fives who had UTI. Gram positive organisms, including *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Staphylococcus faecalis* have also been reported as pathogens in children with UTI (Adjei et al., 2004; Festo et al., 2011).

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Table 1. Demographic and baseline characteristics of study participants.

Variable	n (%)
Age (month)	
1-11	177 (46.3)
12-23	108 (28.3)
24-35	48 (12.6)
36-47	32 (8.4)
48-59	17 (4.5)
Sex	
Male	212 (55.5)
Use of antibiotic	
Yes	213 (55.8)
Duration of fever	
<7 days	207 (54.2)
Mean temperature (°C)	38.5±0.7
Total number of study participants (N) = 382	

Most urinary tract infections among under-fives result from ascent of faecal flora colonising the perineum into the bladder through the urethra. Pyelonephritis may cause acute morbidity and can result in long term complications such as renal scarring, hypertension and end stage renal disease (Coulthard et al., 1997).

Children admitted at Muhimbili National Hospital (MNH) are referred from lower health facilities. Febrile children are usually exposed to multiple antibiotics prior to admission, and these children are initially treated empirically at MNH following WHO recommendations. Recommended first line antibiotics for treatment of UTI include amoxillin and co-trimoxazole (WHO, 2005). Recently, Festo et al. (2011) in a study conducted among febrile children in Bugando Medical Centre, Tanzania reported high resistance to ampicillin (98.4%) and co-trimoxazole (95.3%) from isolated E coli.

In our setting, there was a need to determine the magnitude of UTI and the antimicrobial susceptibility of the common causative organisms which will guide clinical decision for initial empirical treatment of UTI in febrile children. We conducted this study to determine the prevalence, aetiology, antimicrobial susceptibility and predictors of UTI among febrile children admitted at MNH.

MATERIALS AND METHODS

We conducted a hospital based cross-sectional study and recruited febrile under-fives admitted in paediatric wards at MNH between October 2009 and February 2010. Sample size was calculated using *Epi info version 6* statistical package using a prevalence of 13.3% from a study conducted in Kenya by Okwara et al. (2004) with a target of recruiting a minimum sample size of 276 participants. During the study period, 382 children admitted with informed written parental/guardian consent. This study was approved by MUHAS ethical committee and we used the laboratory fever (axillary temperature ≥38°C) were recruited after obtaining findings to provide appropriate UTI management to all recruited study participants.

A standardized questionnaire was used to collect demographic data and symptoms from participants. 5 ml of urine specimens were obtained by supra-pubic aspiration which was performed under aseptic technique.

Urinary catheterization using number five and eight French gauge polythene feeding tubes were used to obtain specimens in cases of dry tap and when time lapse from last void was less than 2 h. Specimens were transported in sterile containers and were sent to the laboratory within 1 h of collection. If the specimens were not analyzed within 1 h of collection, they were kept refrigerated at 4°C and were subsequently analyzed not later than 18 h from the time of collection.

Dipstick urinalysis for the presence of nitrites and leukocyte esterase was carried out in the admission room using CYBOW^{TM} test strips for urinalysis (DFI Co., Ltd, Korea). In the laboratory, microscopy was carried out to determine presence of white blood cells and bacteria. Specimens were inoculated onto Cysteine-lysine electrolyte deficient (CLED) medium using a standard 1 µl loop and incubated aerobically at 37°C for 24 h. Bacterial colonies on solid agar were identified based on characteristic morphology, Gram stain appearance and standard prepared biochemical tests (Barrow et al., 2003). UTI was defined by any growth on the culture medium for supra-pubic aspiration specimen and ≥50,000 CFU/ml for specimens obtained by catheterization (IPNG-IAP 2001).

We performed antimicrobial sensitivity testing for routinely used antimicrobials including amoxillin and co-trimoxazole which are WHO recommended first line for treatment of UTI.

Ampicillin (10 µg), clavulanate-potentiated-amoxillin (30 µg), co-trimoxazole (25 µg), gentamycin (10 µg), amikacin (30 µg) and ceftriaxone (30 µg) sensitivity testing were performed by Kirby Bauer diffusion method using Mueller Hinton agar with incubation of 24 h at 37°C. Sensitivity was determined according to Clinical Laboratory Standard Institute standards (CLSI, 2006). Antimicrobial sensitivity was reported as resistant, intermediate and sensitive, however, in data analysis we merged intermediate and resistant into one category.

Statistical Package for Social Sciences (SPSS) version 17 was used for data entering, cleaning and analysis. Chi square and Fischer's exact test were used to determine association between categorical variables. We performed univariate and multivariate logistic regression to determine the predictors of UTI. Probability (p) value of <0.05 was considered statistically significant.

RESULTS

Demographic and baseline characteristics of participants

Participants included 382 children aged between 1 and 59 months. 212 (55.5%) out of those recruited were males. 177 (46.3%) out of all participants were aged between 1 to 11 months. 175 (45.8%) were reported to have had fever for seven days or longer. 213 (55.8%) had used antibiotics within 72 h prior to admission (Table 1).

Sixty four (64) children had UTI giving overall prevalence of 16.8%. Table 2 shows distribution of children with UTI according to age and sex.

Clinical features and predictors of UTI

Frequencies of reported symptoms were vomiting (144 / 382, 37.7%), failure to gain weight (111/382, 29.1%) and

Table 2. Relationship between UTI and clinical features.

Parameter	Has UTI	No UTI	p value
	n (%)	n (%)	
Age			
<12 months	27 (15.3)	150 (84.7)	0.466
1-<5years	37 (18.0)	168 (82.0)	
Sex			
Male	32 (15.1)	180 (84.9)	0.332
Female	32 (18.8)	138 (81.2)	
Antimicrobial use			
Yes	34 (16)	179 (84)	0.642
No	30 (17.8)	139 (82.2)	
Duration of fever			
<1 week	19 (9.2)	188 (90.8)	0.010
≥1 week	45 (25.7)	130 (74.3)	
Temperature			
<38.5°C	38 (18.0)	173 (82.0)	0.465
≥38.5°C	26 (15.2)	145 (84.8)	
Vomiting			
Yes	26 (18.1)	118 (81.9)	0.596
No	38 (16.0)	200 (84)	
Poor weight gain			
Yes	25 (22.5)	86 (77.5)	0.053
No	39 (14.4)	232 (85.6)	
Haematuria			
Yes	0 (0)	3 (100)	1.000*
No	64 (16.9)	315 (83.1)	
Frequency			
Yes	0 (0)	6 (100)	0.595*
No	64 (17.0)	312 (83.0)	
Dysuria			
Yes	11 (22.4)	38 (77.6)	0.253
No	53 (15.9)	280 (84.1)	
Diarrhoea			
Yes	9 (16.4)	46 (83.6)	0.933
No	55 (16.8)	272 (83.2)	
Leucocyte esterase			
Positive	49 (52.1)	45 (47.9)	0.000
Negative	15 (5.2)	273 (94.8)	
Nitrite			
Positive	44 (64.7)	24 (35.3)	0.000
Negative	20 (6.4)	294 (93.6)	

* Fisher's exact test.

diarrhoea (55/382, 14.4%). Dysuria was reported in 49 (12.8%) out of all participants while increase frequency of micturition and haematuria were reported in 6 (1.6%) and 3 (0.8%) respectively.

Children who were reported to have fever for less than one week were found to have a lower prevalence of UTI; 9.2% as compared to those with fever for 7 days or longer, 25.7%, ($p<0.01$). Children with urine dipstick positive for leukocyte esterase and nitrite were more likely to have UTI (Table 2). Duration of fever, leukocyte esterase and nitrite tests were noted to be independent predictors of UTI on univariate and multivariate analysis as described in Table 3.

Isolated microorganisms

Most of the isolates were Gram-negative bacteria (49/64, 76.6%). *E. coli* was the most common isolated organism (25/64, 35.7%) followed by *Klebsiella* spp (20/64, 28.6%). Five (7.8%) of the isolates were non-lactose fermenters which could not be identified. Table 3 summarizes the distribution of isolated microorganisms.

Antimicrobial resistance pattern

High resistance to co-trimoxazole, ampicillin and clavulanic acid-potentiated amoxillin by all isolated pathogens was observed in this study. Of the *E coli* isolates, 100 and 96% were resistant to co-trimoxazole and ampicillin respectively while for *Klebsiella spp.* 85% were resistant to co-trimoxazole and 95% were resistant to ampicillin. 12% of the *E coli* isolates were resistant to Amikacin while none of the *Klebsiella spp.* isolates were resistant to Amikacin. Table 4 shows the frequency of resistance of isolated uropathogens.

Sensitivity and specificity of urine dipstick

Nitrite test used in evaluating urine specimen in this study showed a sensitivity of 68.8% (95% CI: 56.6 to 78.8) and specificity of 92.4% (95%CI: 89.0 to 94.9). Leukocyte esterase test had sensitivity of 76.6% (95%CI: 64.9 to 85.2) and specificity of 85.9% (95%CI: 81.6 to 89.2) (Table 5).

DISCUSSION

This study was conducted to evaluate the magnitude of UTI among febrile under-fives at MNH which is the largest referral hospital in Tanzania. 64 children out of 382 (16.8%) febrile children admitted at MNH and recruited in this study had culture proven urinary tract infection. This finding is comparable to 20.3% reported by Msaki et al. (2012) in a study which was conducted among febrile under-fives in Mwanza, north-western Tanzania. However, our prevalence was lower than 39.7% reported by Festo et al. (2011) in a study which was conducted among under-fives in a consultant hospital in Mwanza, north western Tanzania.

In this study, duration of fever for seven days or longer, positive nitrite and leukocyte esterase tests were independent predictors of UTI. Similar findings were reported

Table 3. Predictors of UTI (univariate and multivariate analysis of demographic, clinical features and urinalysis results).

Variable	Has UTI n (%)	Univariate			Multivariate		
		OR	CI	p value	OR	CI	p value
Age							
<1 year	27 (15.3)	1.2	0.7- 2.1	0.466	1.1	0.5-2.4	0.864
1-<5years	37 (18.0)						
Sex							
Male	32 (15.1)	1.3	0.7- 2.2	0.333	0.9	0.4-2.1	0.875
Female	32 (18.8)						
Fever duration							
<1 week	19 (9.2)						
≥1 week	45 (25.7)	3.4	1.0-4.1	0.000	8.2	2.9-23.0	0.000
L. esterase							
Positive	49 (52.1)	19.8	10.2-38.3	0.000	12.6	5.5-28.8	0.000
Negative	15 (5.2)						
Nitrite							
Positive	44 (64.7)	26.9	13.7-52.8	0.000	30.2	11.6-78.7	0.000
Negative	20 (6.4)						

Table 4. Isolated microorganisms.

Organism	Frequency (%)
Escherichia coli	25 (39.1)
Klebsiella spp	20 (31.2)
Pseudomonas aureginosa	3 (4.7)
Proteus spp	1 (1.6)
Staphylococcus Epidermidis	4 (6.2)
Staphylococcus aureus	3 (4.7)
Streptococcus faecalis	3 (4.7)
UINLF*	5 (7.8)
Total	64 (100)

*UNLF, un-identified non-lactose fermenters.

Table 5. Antimicrobial resistance pattern.

Organism	Resistance to antimicrobials* n (%)						
	CTX	AMP	AMC	CEF	GEN	AMK	Total
E. coli	25(100)	24(96)	22(88)	9(36)	15(60)	3(12)	25
Klebsiella spp	17(85)	19(95)	14(70)	11(55)	14(70)	0(0)	20
P. aureginosa	3(100)	3(100)	3(100)	2(66.7)	0(0)	0(0)	3
Proteus spp	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	1
S. epidermidis	4(100)	0(0)	1(25)	3(75)	3(75)	2(50)	4
S. aureus	3(100)	3(100)	2(66.7)	3(100)	1(33.3)	0(0)	3
S. faecalis	3(100)	1(33.3)	1(33.3)	1(33.3)	0(0)	2(66.7)	3
UNLF	2(40)	1(20)	2(40)	3(60)	1(20)	1(20)	5
Total	57(89.1)	51(79.9)	45(70.3)	32(50)	35(54.7)	8(12.5)	64

CTX, co-trimoxazole; AMP, ampicillin; AMC, amoxillin-clavulanic acid; CEF, ceftriaxone; GEN, gentamycin; AMK, amikacin. *Resistance represent intermediate and resistant.

Table 6. Sensitivity and specificity of dipstick urinalysis.

Test	Sensitivity % (95% CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
Nitrite	68.8 (56.6-78.8)	92.4 (89.0-94.9)	64.7 (52.1-75.6)	93.6 (90.2-96.0)
LE	76.6 (64.9-85.2)	85.9 (81.6-89.2)	52.1 (41.6-62.5)	94.8 (91.4-97.0)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LE, leukocyte esterase.

by other studies in the region (Festo et al., 2011; Musa-Aisien et al., 2003). Dysuria, haematuria, diarrhea, failure to gain weight and increased frequency of micturition did not show a significant association with occurrence of UTI, in keeping with the non-specific presentation of UTI in young children (Shaikh et al., 2007; Zorc et al., 2005) Fever of seven days duration or longer in a child should prompt clinicians to consider a diagnosis of UTI and in the presence of a positive urine dipstick results for nitrites and leukocyte esterase, the diagnosis of UTI is highly suggested.

Isolated bacteria in this study were predominantly Gram-negative organisms which is similar to other reports from the region (Tessema et al., 2007; Festo et al., 2011; Msaki et al., 2012). *E. coli* was the most common isolate followed by *Klebsiella* spp. Other Gram negative bacteria included *Proteus* spp. and *P aeruginosa*. Gram positive bacteria were also isolated in this study, including *S epidermidis*, *S. aureus* and *S. faecalis*, which agrees with reports from Nigeria (Asinobi et al., 2003; Aiyegoro et al., 2007; Okunola et al., 2012) These findings suggest similar bacterial aetiology for UTI in children regionally; however we had a limitation of not being able to identify some isolates which were non-lactose fermenters.

High resistance of isolated bacteria to ampicillin, co-trimoxazole and clavulanate potentiated amoxillin were noted in this study which is in agreement with other reports (Musa-Aisien et al., 2003; Brown et al., 2003; Asharam et al., 2003; Rabasa et al., 2009; Okunola et al., 2012). Msaki et al. (2012) and Festo et al. (2011) reported high resistance to ampicillin and co-trimoxazole in studies which were conducted in north-western Tanzania. These antibiotics are widely available at the primary health care level and due to lack of binding restrictions antibiotics are accessed from local chemists without prescriptions, resulting in irrational use of antibiotics. High resistance to co-trimoxazole may also be attributed to its routine use as prophylaxis against Pneumocystis jirovecii.

In this study, resistance of isolates to gentamycin and ceftriaxone was high compared to that reported by Msaki et al. (2012). The latter study was conducted among febrile under-five year olds in a primary care facility in north-western Tanzania and the isolates were 100% susceptible to gentamycin and ceftriaxone. Our study was carried out in a tertiary care hospital and most of the patients were referred from primary care facilities and could have been exposed to these antimicrobials.

Among the tested antimicrobials, amikacin had the least resistance from bacterial isolates, making it a suitable choice in the empirical treatment of UTI in our centre. Findings of this study indicate the importance of performing a urine culture and antimicrobial susceptibility test in the evaluation of a child suspected to have a UTI in a secondary and tertiary care centre, as these children could have had multiple previous exposures to routinely utilized antimicrobials. Therefore, the WHO recommended first line antimicrobials may not be useful in the empirical treatment of UTI in our setting.

High specificity was noted for both nitrite and leukocyte esterase tests, but the leukocyte esterase test was noted to be more sensitive than the nitrite test (Table 6). This is similar to reports from other studies in the region (Munyi et al., 1998; Brown et al., 2004; Festo et al., 2011). It is evident from this study and other reports that a urine dipstick test is a cost effective tool for making a diagnosis of a UTI in a febrile child and supports the notion that it may be used in settings, without laboratory support, for the empirical treatment of febrile children for UTI.

This was a cross sectional study which was conducted in one tertiary hospital only and the findings may not be generalizable to other parts of Tanzania. We have however observed a similar prevalence of UTI as reported in other studies in Tanzania (Msaki et al., 2011). We did not look for other causes of fever or evaluate children for congenital malformations predisposing to UTI in this study because of financial and time constraints. Findings of this study will provide important information on the magnitude of UTI and the choice of antimicrobials for the management of febrile children at MNH.

Conclusions

Urinary tract infection is prevalent in febrile under-five year old children admitted at MNH, and UTI could be independently predicted by duration of fever, positive nitrite and leukocyte esterase tests. The commonest isolates were *E coli* and *Klebsiella* spp. which had a high resistance to ampicillin and co-trimoxazole. There is a need to stress the importance of screening for UTI in children presenting with fever in our setting and, to reconsider the use of ampicillin and co-trimoxazole for empirical treatment as uropathogens have been shown to be highly resistant to these antimicrobials. Although these antimicrobials are recommended by WHO and in guideline from developed countries (Finnell et al., 2011), they may not be useful in our setting. Therefore there is a need

to develop locally appropriate guideline which should be reviewed frequently to meet the dynamic changes in local antimicrobial susceptibility pattern.

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