URINARY TRACT INFECTION IN FEBRILE UNDER-FIVE CHILDREN ADMITTED IN PAEDIATRIC WARDS AT MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA IN 2010

By

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: ***Urinary tract infection in febrile under-five children admitted in paediatric wards at Muhimbili national Hospital, Dar es Salaam, Tanzania in 2010,*** in partial fulfillment of the requirements for the degree of Master of Medicine (Pediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam.

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DECLARATION AND COPYRIGHT

I, **Francis Fredrick**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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ABSRTACT

Background: Urinary tract infection (UTI) is a common and significant cause of morbidity and long-term complications in paediatric population. These infections are caused mainly by gram negative bacteria, which constitute the normal flora of gastrointestinal tract colonizing the perineum and ascending into the genital urinary system through the urethra. Children present with non specific symptoms and signs making the diagnosis of UTI in children challenging, furthermore obtaining urine specimen for confirming the diagnosis of UTI is difficult resulting in presumptive treatment of these patients. Effective and appropriate treatment depends on clinician's high index of suspicion which is influenced by knowledge of the prevalent bacteriological uropathogens and antimicrobial susceptibility pattern in the specific area of practice. There is limited information on clinical epidemiology of UTI in children in Dar es Salaam, and the few studies that are available were conducted several years ago. Therefore findings of those studies may not be applicable in the current circumstances bearing in mind the dynamic nature of antimicrobial susceptibility pattern of uropathogens.

Objective: To determine the prevalence of UTI, aetiological uropathogens and antimicrobial susceptibility pattern in febrile children under-five years of age admitted in general paediatric wards of Muhimbili National Hospital, Dar es Salaam, Tanzania.

Methodology: This was a cross-sectional hospital based study which was conducted among febrile children less than five years of age. The children were consecutively recruited at admission in the general paediatric wards and the study was carried out for six months, from September, 2009 to February, 2010. Standardized questionnaires were used to collect socio-demographic characteristics and clinical presentation of study participants. The diagnosis of UTI was confirmed by urinalysis and bacteriological culture of urine specimens, which were obtained by supra-pubic aspiration or catheterization. The laboratory investigations were performed in accordance with the standard operating laboratory procedures. After isolation of bacterial uropathogens on a urine specimen antimicrobial susceptibility testing was performed using discs for the following antimicrobials ampicillin, co-trimoxazole, clavulanate-potentiated amoxillin, ceftriaxone, gentamycin and amikacin.

Results: A total of 382 children fulfilled the eligibility criteria and were enrolled into the study; out of which 212 (55.5%) were males and 170 (44.5%) were females. Among the 382 children sixty four children were confirmed to have UTI by urine culture, giving an overall prevalence of UTI of 16.8%. Females were noted to have higher prevalence of UTI than males, however, the difference was not statistically significant (p=0.332). *Escherichia coli* was the most commonly isolated organism accounting for 35.7%, followed by *Klebsiella spp.* Gram positive organisms were also isolated and these included *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Streptococcus faecalis*. Resistance rates of the isolated uropathogens to ampicillin, co-trimoxazole and clavulanate-potentiated amoxillin were 79.7%, 89.1% and 70.3% respectively, while gentamycin and ceftriaxone had slightly lower resistance rates of 54.7% and 50% respectively. Amikacin had least resistance rate of 12.5%. Nitrite test had sensitivity and specificity of 68.8% and 92.4%, while leukocyte esterase test had sensitivity and specificity of 76.65 and 85.9%. When used in combination the nitrite and leukocyte esterase tests had a sensitivity and specificity of 85.9% and 79.6% respectively. Patients with fever for seven days or more were noted to have higher prevalence of UTI as compared to those with fever for less than seven days (OR 3.42; 95%CI 1.91-6.12, p<0.01) while patients with history of convulsion had lower prevalence of UTI than those without (OR 2.37; 95%CI 1.16-4.85, p=0.016).

Conclusion: Urinary tract infection was prevalent in children less than five years of age admitted with fever, particularly those with fever of longer than seven days duration. The isolated bacterial uropathogens have shown a relatively high resistance to ampicillin, co-trimoxazole and clavulanate-potentiated amoxillin.

Recommendations: Children admitted with fever should be evaluated for UTI and urine culture and sensitivity should guide the choice of antimicrobials in their treatment.

LIST OF ABBREVIATIONS

CFU	=Colony Forming Unit
CLED	=Cysteine Lysine-Electrolyte-Deficient
MNH	=Muhimbili National Hospital
MUHAS	=Muhimbili University of Health and Allied Sciences
UTI	=Urinary Tract Infection
SD	=Standard Deviation
CI	=Confidence Interval
WHO	=World Health Organisation
HIV	=Human Immunodeficiency Virus
AIDS	=Acquired Immunodeficiency Syndrome
UNLF	=Un-identified Non-Lactose Fermenters

TABLE OF CONTENTS

CERTIFICATION	II
DECLARATION AND COPYRIGHT	III
ACKNOWLEDGEMENT	IV
ABSRTACT	VI
LIST OF ABBREVIATIONS	VIII
LIST OF TABLES	XI
1.0 INTRODUCTION AND LITERATURE REVIEW	1
2.0 PROBLEM STATEMENT	9
3.0 RATIONALE OF THE STUDY	10
3.1 RESEARCH QUESTIONS	10
4.0 OBJECTIVES	11
4.1 Broad objective	11
4.2 Specific objectives	11
5.0 METHODOLOGY	12
5.1 Study design	12
5.2 Study duration	12
5.3 Study area	12
5.4 Study population	12
5.5 Inclusion criteria	12

5.6 Exclusion criteria 13

5.7 Sample size 13

5.8 Sampling technique 13

5.9 Data collection 14

5.11 Laboratory investigations 15

6.0 DATA MANAGEMENT 18

7.0 ETHICAL CONSIDERATION 19

8.0 RESULTS 20

9.0 DISCUSSION 28

10.0 STUDY LIMITATION 33

11.0 CONLUSIONS 33

12.0 RECOMMENDATIONS 33

13.0 REFERENCES 34

APPENDIX NO 1 38

Informed Consent Form 38

APPENDIX NO 2 40

Informed Consent Form (Swahili version) 40

APPENDIX NO 3 42

Questionnaire 42

APPENDIX NO 4 44

Suprapubic aspiration 44

LIST OF TABLES

Table 1	**Demographic and baseline characteristics of study population**	**20**
Table 2	**Distribution of children with of urinary tract infection by age and sex**	**21**
Table 3	**Organisms isolated from urine culture**	**22**
Table 4	**Uropathogens and susceptibility pattern to antimicrobials**	**24**
Table 5	**Relationship between clinical features and urinary tract infection**	**26**
Table 6	**Predictors of urinary tract infection**	**27**
Table 7	**Sensitivity and specificity of urinalysis**	**27**

1. INTRODUCTION AND LITERATURE REVIEW

Fever is fairly a common problem in children less than 5 years of age accounting for most hospital attendances and leading to significant morbidity and mortality.[1] The underlying causes of fever in Sub-Saharan Africa are predominantly infectious in nature and urinary tract infection is among the leading causes.[2, 3] Okwara et al in a study conducted among febrile children admitted with no obvious focus of infection, in Kenyatta Hospital in Nairobi, Kenya in 2004 showed that two thirds had malaria and one fifth had significant bacteriuria or bacteremia.[4]

Although UTI is reported as an important cause of fever and hospital attendances, several studies have reported co-existence of UTI with other febrile conditions including malaria and acute respiratory tract infections, and UTI may be missed if it is not considered in a febrile patient. [4-6]

High grade fever and prolonged duration of fever lasting for more than seven days are associated with the likelihood of UTI. Mussa –Aisien et al reported a significantly high frequency of UTI with temperature $\geq 38.3^{o}C$ and duration of fever lasting 7 days or more.[6] Similar findings were reported by Hoberman in which infants with fever of $39^{o}C$ were likely to have UTI.[7] However, low grade fever has also been reported with UTI.

Urinary tract infection (UTI) is the infection by pathogenic microorganisms of urine and genitourinary tract which include urethra, urinary bladder and kidney.[8, 9] Acute UTI can be divided anatomically into upper urinary tract infections (pyelonephritis, renal abscess), and lower urinary tract infections with involvement of the urethra (urethritis) and bladder (cystitis). UTI can also be categorized in three clinical forms which are pyelonephritis, cystitis and asymptomatic bacteriuria indicating positive urine culture with no symptoms; however it is difficult to distinguish the three forms clinically. [8]

Urinary tract is a common site of infections in children and these infections are important cause of acute morbidity and sometimes may also result in long-term medical

complications including hypertension and reduced renal function.[10] Infants and young children are at higher risk of acute renal injury as a result of UTI and usually present with non-specific features of UTI as compared to older children.[8, 10-12] Coulthard et al reported renal scar occurrence rate of 5% among paediatric patients less than 16 years referred because of UTI to Royal Victoria Infirmary and Newcastle General Hospital.[13] Lin et al also reported a high incidence of renal scarring following the first febrile UTI with incidence of acute pyelonephritis of 70% among 191 children of less than 17 years who under-went (99m)Tc-dimercaptosuccinic acid renal single-photon computed tomography, 57% of which had developed renal scars.[14]

Prevalence and incidence rates of UTI in children are reported to vary with age and sex.[8, 15, 16] Boys are more affected during early infancy with a male: female ratios of 2.8-5.4:1 and 1:10 during the first year of life and beyond two years respectively,[8] Jeena et al reported a male: female ratio of 1.7:1 in children 4-24 months in South Africa.[3]

Several studies have reported varying incidence and prevalence rates of UTI, Shaw et al in a cross-sectional study of febrile infant male less than one year of age and female less than two years of age carried out at children's hospital of Philadelphia in United States, reported overall prevalence of 3.3% with a higher prevalence in females.[17] Garcia et al reported an incidence of 7.5% in a study conducted in Los Angeles, California, among 160 infants less than eight weeks of age with jaundice[18] indicating importance of considering UTI even during early infancy. Hoberman et al reported prevalence of 4.6% and 5.9% in febrile infants aged less than two months of age and above two months of age respectively with overall prevalence of 5.3% in a study which was conducted in Pittsburgh children hospital, in United States.[7]

In India Kaushal et al studying 131 children of up to five years of age presenting with fever, reported an incidence of 8.4%, with incidence rates of 6.1%, 12.2%, 12.3% and 5.4% in boys, girls, infants and in 13-60 months age group respectively.[19] A high frequency of UTI of 37.5% was reported in Pakistan by Anis et al in study of 1000 children aged between 0-15 years, with prevalence of UTI in male children being the highest below one year of age declining gradually with increasing age.[12]

Jeena et al reported prevalence of UTI as a single major diagnosis of 14% in a retrospective study conducted among 54 paediatric patients in a tertiary hospital in Durban.[3] In Nigeria Mussa-Aisien reported prevalence of 9% in a study of 300 children aged one to 60 months who presented with fever in emergency room, with a significantly higher prevalence of UTI among girls.[6]

In a study conducted by Okwara et al, among febrile paediatric patient aged between three months and 12 years, hospitalized in Kenyatta Hospital, UTI was prevalent among 13.3% of patients with malaria and 16% of those who had no malaria. Okwara et al did not report association between prevalence of UTI and recent use of antibiotics.[4]

In a study done by Munubhi at Muhimbili Medical Centre in Dar es Salaam, Tanzania in 1982 among paediatric patients who presented with gastroenteritis, incidence rates of UTI reported were 7.9% among 900 paediatric patients who presented with gastroenteritis and 7.5% among their 400 controls.[20]

Most of urinary tract infections are ascending infections resulting from faecal flora colonising the perineum and eventually ascending to the bladder through the urethra.[8, 9, 11] The organisms may also ascend to the kidneys resulting in pyelonephritis or renal abscess. In some rare cases haematogenous spread has been implicated,[8] most commonly during the neonatal period.[21]

Clinical features of UTI vary with age at occurrence and the type of infection. Newborns present with non-specific signs including fever, hypothermia, jaundice, vomiting, and poor feeding.[8, 11] Abdominal or flank pain, vomiting, fever, urinary frequency, dysuria, urgency and enuresis are common in pre-school aged children.[11] Classic symptoms of cystitis which include frequency, dysuria and urgency are usually present in school age children, who may also present with suprapubic pain and incontinence .[8, 11]

Anis et al reported fever to be the commonest presentation of UTI with frequency of 91% followed by dysuria (65%) and failure to thrive (40%) in a study conducted in among children aged 0-15 years.[12] Similar findings were reported by Qureshi et al with most of

patients presenting with fever (92%), dysuria (68%) and failure to thrive (31%).[22] In a prospective study conducted in India to evaluate 130 children presenting with fever, 15% of patients with UTI presented with dysuria, increased frequency of micturation and malodorous turbid urine.[19] Garcia et al reported high incidence of jaundice in newborn younger than 8 weeks of age who were asymptomatic and diagnosed to have UTI by urine culture.[18]

The aetiology of UTI in children is predominantly Gram negative bacteria, which is part of faecal flora and colonize the perineum.[8] *Escherichia coli* is widely reported as the commonest isolated uropathogen in both children and adults followed by other enterobacteria especially Klebsiella, Proteus and Pseudomonas species.[8, 9, 11] In some instances gram positive organisms, viruses and fungi have also been isolated as causative agents of UTI in children.[8]

Yuksel et al reported *E. coli* as the commonest isolate (87% of cases) followed by *Klebsiella pneumoniae* (10%) in a study conducted in Turkish children.[23] Wu et al in a clinical analysis of 597 admitted patients reported similar findings with *E. coli* accounting for 74.7% followed by *Proteus spp* 6.7% and *Klebsiella spp* 6.4%.[24] In Israel Sakran et al reported *E coli* to have contributed to 87% of the isolates followed by *Klebsiella pneumoniae* (4%) and *Proteus mirabilis* (4%).[25]

Similar findings were reported in studies conducted in African setting, Asinobi et al reported *E. coli* and *Klebsiella spp* as the predominant isolates in UTI among febrile sickle cell paediatric patients and their controls.[26] In Ghana Adjei et al reported *E. coli* and Proteus spp to have accounted for 32% and 22% respectively, of isolates in a study conducted among young infants aged up to 12 months.[2] Tessema et al reported *E. coli* (40.2%) as the most predominant isolate in a study conducted in Ethiopia.[27]

Munyi et al reported *E. coli* and *Klebsiella spp* to be responsible for 93.4% of UTI among children on treatment for malignancy in Kenyatta Hospital.[28] Ashram et al reported gram negative bacteria as the commonest organisms causing UTI in a study conducted in South

Africa to determine the impact of HIV and AIDS on UTI and *E. coli* was the most cultured uropathogen.[29]

Munubhi reported *Klebsiella spp* 49.9%, *E. coli* 39.4%, *Proteus spp* 4.2% and *Pseudomonas aureginosa* 2.8% as the predominant isolates in a study conducted in Muhimbili Medical Centre among paediatric patients with gastroenteritis.[20] Similar findings were reported by Isaack et al in a study conducted at Muhimbili Medical Centre in 1991, in which 164 admitted paediatric patients with severe malnutrition were evaluated for nosocomial infections, and UTI was reported among common infections. [30]

Gram positive organisms have also been reported as important cause of UTI, Adjei et al reported the contribution of *Staphylococcus aureus* to be 11% of the isolates in a study conducted in Kumasi, Ghana,[2] while Azubike reported *Staphylococcus epidermidis* to have highest incidence in causing symptomatic UTI in school aged children. In that study *S. aureus*, *Streptococcus faecalis* and *Candida albicans* were also isolated.[31] Okwara et al reported isolation of coagulase negative staphylococcus species with no isolation of *S. aureus* in study conducted in Nairobi.[4] A study conducted at Muhimbili Medical Centre reported similar findings in which *S. aureus* contributed to 1.4 percent.[20]

The diagnosis of UTI in children poses a big challenge to the practitioner, and the difficult is more marked in children less than 2 years of age. There are several reasons for the difficulties in establishing the diagnosis of UTI, among these is the non-specific clinical presentations and the difficulty in getting urine specimen for laboratory investigations.[16, 32] Several methods are used for urine specimen collection in children which include mid-stream clean catch, catheterization, supra-pubic aspiration and urine bag applied to the perineum. Regardless of the method employed in urine collection, the most important factor to consider in the diagnosis of UTI is prevention of contamination of the specimen especially from periurethral flora.[21]

A clean midstream catch is a widely used method in older children with adequate bladder control, in this method the first passed urine is ignored to clear the urethra of contamination and the midstream urine is collected into a sterile container. This method

has an advantage of being non-invasive however, in uncircumcised males the prepuce must be retracted, if the prepuce is not retractable this method becomes unreliable.[8] Positive culture results from urine specimen obtained by midstream catch is defined by growth of colony counts of more than 10^5/ml of a single pathogen.[8, 21]

Transurethral catheterization and suprapubic aspiration provide specimens which are unlikely to be contaminated making these two preferred methods for documenting UTI.[10] Catheterization requires good skills and experience to obtain an uncontaminated specimen, proper lubrication and use of number five and eight French polyethylene feeding tubes for infants and older children respectively, to minimize the chance of urethral trauma and contamination.[8, 10] Urine specimen obtained by transurethral catheterization for culture has been reported to have sensitivity and specificity of 95% and 99% respectively, and with this method UTI is defined by growth of at least 50,000 CFU/ml on cultures.[7, 10, 21]

Urine obtained by suprapubic aspiration is the least likely to be contaminated and this method has been considered the gold standard for detecting bacteria in the bladder,[10, 21] however this method has variable success rates for obtaining urine sample and parents and physicians perceive it to be invasive as compared to catheterization.[10] With this method UTI is defined by growth of any number of colony forming unit.[10, 21]

Urinary bags applied to the perineum provide specimens which are heavily contaminated, resulting in high false positive rates on culture,[10, 21] however this method has the advantages of convenience, noninvasiveness and minimal requirement of personnel time. Urine specimen obtained by this method can be used for urinalysis, but because of delayed voiding after application of a bag positive urinalysis results will need to be confirmed by a second specimen. However, when results are negative they exclude UTI provided there was no use of antimicrobials.[10]

Evaluation of urine specimen for UTI requires quantitative urine culture which is the standard test for diagnosis,[10] however urinalysis plays an important role in screening patients whose specimens will subsequently be cultured.[7] Of the components of urinalysis

the most useful in evaluating a patient for possible UTI are microscopy, nitrite test and leukocyte esterase test.[10, 21, 33] Nitrite and leukocyte esterase tests are dipstick based tests.

Nitrites in urine results from bacterial reduction of urinary nitrates, many gram negative organisms and some gram positive organisms are capable of this process,[33] nitrates must be exposed to nitrate reducing-bacteria for several hours before this reaction can take place[7] resulting in low sensitivity of this test in young infants who void frequently.[21] Nitrite reducing reagent is sensitive to air and false positive reaction will be obtained if dipstick containers are not tightly covered when stored, and false negative results may be obtained with non-nitrate reducing bacteria.[33]

Brown et al reported specificity and sensitivity rates of 99.2% and 18.9% respectively for nitrite test in detecting bacteriuria in a study conducted in Nigeria among febrile sickle cell children,[34] in this study positive nitrite test was associated with bacteriuria and a negative test associated significantly with absence of bacteriuria. Munyi et al in a study conducted in Kenyatta National Hospital among children receiving cancer treatment reported sensitivity and specificity rates of 60% and 97.7% for nitrite test in diagnosing UTI.[28]

Leukocyte esterase component of dipstick urinalysis detects esterases released from leukocytes that have broken down, therefore it is an indirect test for presence of white blood cells.[7, 21, 33] This test is more sensitive but less specific for UTI, making the combination of nitrite and leukocyte esterase tests highly sensitive and specific in diagnosing UTI.[21]

Microscopy urinalysis involve microscopic examination of urine specimen to enumerate white blood cells/ mm^3 of centrifuged or uncentrifuged urine, as well as gram stain microscopy for identification of bacteria,[7]leukocyturia, which is defined as more than five white cells/high power field in centrifuged urine and 10 or more white cells/high power field in uncentrifuged urine, is found in symptomatic UTI.[21] Munyi et al reported leukocyturia defined as more than five white cells per high power field , to have sensitivity of 80% and specificity of 97.1% in screening for UTI, in a study which was conducted among cancer patients in Kenyatta Hospital.[28] Presence of white cells in urine points

towards inflammatory response against offending microorganisms, however their absence does not exclude UTI.[8, 10, 21]

The sensitivity pattern of isolated uropathogen is changing and is posing a growing problem in the empirical treatment of UTI in children, amoxillin and co-trimoxazole which are recommended first line treatment for UTI by World Health Organization (WHO) are reported to be among the most affected antibiotics.[35] Yen et al reported *E. coli* to be the exclusively resistant to ampicillin (90.2%) with relative resistance to co-trimoxazole (57.1%) in a study of 285 under 15 years conducted in China,[36] similar findings were reported by Yuksel et al with resistant rate of 74.2% and 61.3% to amoxillin and co-trimoxazole respectively, in the study by Yuksel et al nitrofurantoin was found to be the most active agent (2.2% resistant isolates) against *E. coli* followed by amikacin (4.9%) and ceftriaxone (7.5%). [23]

Ashram et al reported high resistance of gram negative isolates to amoxillin, ampicillin, erythromycin and co-trimoxazole, while they were sensitive to cefuroxime, nalidixic acid, gentamycin and amikacin in a study conducted in South Africa.[29] Similar findings were reported by Brown et al in a study conducted in Nigeria among febrile sickle cell paediatric patients in which most of the isolates were resistant to amoxillin, ampicillin, gentamycin and co-trimoxazole,[37] similarly Adeyemo et al reported high resistance of isolates to ampicillin and co-trimoxazole with good sensitivity to nitrofurantoin, nalidixic acid and ofloxacin in a study conducted in Ibadan, Nigeria.[38]

A study conducted in Muhimbili Medical Centre in 1982 by Munubhi had shown high sensitivity rates (90.9-100%) to nitrofurantoin and nalidixic acid, intermediate sensitivity rate (43.8-50%) to co-trimoxazole and low sensitivity rate (0-33%) to ampicillin, of the *E. coli* isolates.[20] However, susceptibility to antimicrobial drugs is a dynamic process and changes in microbial resistance occur with time.

2.0 PROBLEM STATEMENT

UTI is an important cause of morbidity in paediatric population,[8, 10, 16] and has been reported to result in both short and long term medical complications.[13, 14] To confirm the diagnosis of UTI in children is difficult especially in developing countries,[2, 32] and as a result most patients with UTI are either misdiagnosed or are given presumptive treatment without laboratory confirmation of the infection. This approach carries the risk of providing inadequate treatment and consequently leading to complications of UTI.

Empirical treatment of paediatric patients with UTI depends on high index of suspicion of the clinician, which is also dependant on knowledge of the magnitude of the problem as well as knowledge on aetiology and antibiotic sensitivity pattern prevailing in the area. Few studies have been conducted on UTI in children, in Dar es Salaam, Tanzania, and these were conducted several years ago, therefore those findings may not reflect the current situation.

Limited data on UTI among paediatric population in Tanzania, which lead to constraints in providing good quality of care and rational use of antimicrobials has prompted the need to carry out this study in order to determine the current microbial sensitivity pattern in febrile children with UTI.

3.0 RATIONALE OF THE STUDY

This study was conducted in the light of the paucity of information on UTI in children at Muhimbili National Hospital and the findings of this study are expected to improve the management of children with UTI by defining its magnitude in febrile under-fives admitted in general paediatric wards at MNH.

The antimicrobial sensitivity pattern of isolated uropathogens is expected to provide up-to date information on susceptibility pattern of routinely used antimicrobials. This information is important in rational choice of antibiotics and will help in managing children presenting with UTI in secondary and tertiary level hospitals in Tanzania.

3.1 RESEARCH QUESTIONS

Is UTI prevalent among febrile paediatric patients admitted in general paediatric wards of MNH in Dar-es-Salaam, Tanzania? And are the routinely used antimicrobials sensitive to the isolated uropathogens?

3.2 STUDY HYPOTHESIS

UTI is prevalent in febrile paediatric patients admitted in general paediatric wards.

4.0 OBJECTIVES

4.1 Broad objective

To determine the prevalence of UTI, aetiology and antimicrobial susceptibility pattern in febrile children under-five years of age admitted in general paediatric wards at Muhimbili National Hospital (MNH).

4.2 Specific objectives

4.2.1 To determine the prevalence of UTI in febrile under-five children admitted in general paediatric wards at Muhimbili National Hospital.

4.2.2 To identify the aetiology of UTI in febrile under-five children admitted in general paediatric wards.

4.2.3 To determine antimicrobial susceptibility pattern of the isolated uropathogens.

5.0 METHODOLOGY

5.1 Study design

This was a hospital based descriptive study to determine the magnitude of UTI among paediatric patients admitted at MNH.

5.2 Study duration

The study was conducted in a period of six months, from September, 2009 to February, 2010.

5.3 Study area

This study was carried out in general paediatric wards of Muhimbili National Hospital (MNH). Muhimbili National Hospital is one of the four tertiary hospitals in the country, it also serve as second level referral for three municipal hospitals in Dar es Salaam. MNH serves as a University teaching hospital for Muhimbili University of Health and Allied Sciences. Paediatric department of MNH have five wards two of which are for general paediatric patients, and the remaining three are for sub-specialty care for patients with diarrhoea, severe malnutrition and sick neonates.

These wards admit an average of ten patients per day and the leading causes of admission are infections. In the year 2007/2008, malaria was the leading cause of admission accounting for 26% of the 4000 children admitted, this was followed by pneumonia (24.6%) and UTI accounted for 2.4% of diagnosis at admission.[39]

5.4 Study population

All paediatric patients aged between one and 59 months admitted in the general paediatric wards, presenting with fever (axillary temperature of 37.5°C and above).

5.5 Inclusion criteria

The following were the inclusion criteria into the study:

5.5.1 Children aged between one month and 59 months

5.5.2 Children presenting with fever, temperature 37.5^{o} C and above

5.5.3 Children of parents/guardian who gave written informed consent

5.6 Exclusion criteria

The exclusion criteria included the following:

5.6.1 Children with known co-existing renal diseases

5.6.2 Children with known co-existing Diabetes mellitus

5.6.3 Children with severe forms of malnutrition as co-morbid conditions

5.6.4 Very sick children in need of resuscitation during admission

5.6.5 Children whose parents/caregivers did not grant consent to participate in the study

5.7 Sample size

Sample size was calculated using

$$N = \frac{Z^2P(1-P)}{E^2}$$

Where;

Z is percentage point corresponding to significance level. For a significance level of 5%, **Z** is 1.96

P is the prevalence of UTI among febrile paediatric patients admitted in Kenyatta hospital in Kenya which is 13.3% [4]

E corresponds to maximum likely error and is 0.04

Therefore the minimum sample size **N** was 276, however, 382 participants were recruited to increase power of the study.

5.8 Sampling technique

All eligible participants whose parents/guardians granted written informed consent were recruited consecutively into the study until the required sample size was attained. Recruitment of participants was carried out exclusively on working days.

5.9 Data collection

Structured questionnaires were used to collect information from participants; the information included demographic data, clinical presentation and laboratory results of dipstick urinalysis, microscopy, culture and sensitivity.

5.9.1 Temperature

Body temperature was measured by using mercury clinical thermometer (Thermol®). This was placed in contact with skin on the participant's axilla for five minutes after which the reading was recorded. Participant was considered to be febrile when temperature was equal to or above 37.5° C.

5.9.2 Weight

Weight was taken using a standard beam balance (SECA®) with the child putting on light clothing and no shoes. Older children's weight was taken while standing on a weighing scale (SECA). Weight was measured to the nearest 10 grams. Calibration of weighing scale to zero was performed each day of recruitment.

5.9.3 Length/height

Length or height of participants was measured using either a length board or stadiometer. Parents/guardians assisted in removing shoes and gently laying the child in supine position on the board, with their heads placed at 90° to the fixed head piece. The investigator straightened the legs of the child at the knees and ensured that feet were at right angle to the sliding foot piece which was brought into contact to the child's heels.

Height of participants was measured with the child standing at right angle in front of height board and sliding head piece was brought into contact with the head and height measured. Height/length was recorded to the nearest 10 millimetres.

5.9.4 Nutritional status

Weight for height was used to interpret nutritional status; Z-score corresponding to the weight and height of each participant was looked for in WHO anthropometric assessment charts, and these scores were interpreted as

Z- Between Mean & -1SD: Normal nutritional status

Z- Between -1SD & -2SD: mild wasting

Z- Between -2SD & -3SD: moderate wasting

Z- Below –3SD: severe wasting, these were excluded from the study.

5.10 Specimen collection

After recruitment into the study, the study physician ascertained fullness of bladder of participants by inquiring about time when the participants last emptied their bladder and palpation of bladder. If it was deemed that the bladder had urine, then suprapubic puncture was carried out using aseptic technique and after cleaning the skin with 2% iodine solution and 70% alcohol. Five millilitres of urine specimen was collected. In the event that the lapsed time since last voiding was less than two hours or a dry suprapubic tap, urinary catheterization using number five and eight French gauge polythene feeding tubes for infants and older children respectively, was performed to obtain the specimen, sterile gloves were used and lubricating jelly was applied before introducing the catheter. All these procedures were carried out carefully to ensure collection of reliable and uncontaminated specimens.

Specimens were transported in sterile containers and were sent to the laboratory within one hour of urine collection. If the urine specimens were not analyzed within one hour of collection they were kept refrigerated at 4°C and were subsequently analyzed not later than 18 hours from time of urine collection.

5.11 Laboratory investigations

Urine specimens were processed and tested in the laboratory of the Department of Microbiology in the School of Medicine, Muhimbili University of Health and Allied Sciences. Urine specimens were analyzed by dipstick and microscopy, cultured and the isolated uropathogens were tested for antimicrobial susceptibility.

5.11.1 Urinalysis

The urine specimens were examined first by dipstick urinalysis for presence of nitrites and leukocyte esterase and later microscopically for presence of white blood cells. Dipstick urinalysis was performed at admission using CYBOW^{TM} test strips for urinalysis (DFI Co., Ltd, Korea), manufacturer's standard operation procedures were adhered to in performing these tests and commercially available controls were used to ensure quality control.

5.11.2 Urine culture

The urine specimen were inoculated on Cysteine-lysine electrolyte deficient (CLED) medium using a standard 1µml loop and incubated aerobically at 37°C for 24 hours. After 24 hours of incubation, bacterial colonies were identified based on characteristic colonial morphology, gram stain appearance and standard commercially prepared biochemical tests.

Antimicrobial susceptibility pattern of isolated bacterial pathogens were determined by Kirby Bauer diffusion method. In this method the isolated bacterial colonies were inoculated on Mueller Hinton agar on which discs containing antibiotics to be tested were placed together with the standard control, this was incubated aerobically at 37°C for 24 hours. After 24 hours each plate was examined and growth zones were measured to the nearest millimetre, using sliding caliper or ruler held at the back of the inverted media plate.

The Petri plate were held a few inches above a black, non- reflecting background and illuminated with reflected light. The zone margins were taken as the area showing no obvious, visible growth that can be detected with the unaided eye. Faint growth of tiny colonies, which can be detected only with a magnifying lens at the edge of the zone of inhibited growth, was ignored. However, discrete colonies growing within a clear zone of inhibition were sub cultured, re-identified, and retested. The results were reported as sensitive, intermediate or resistant to the agents that had been tested. For the purpose of this study intermediate sensitivity was considered resistant. The antibiotics which were tested in this study included ampicillin 10µg, clavulanate-potentiated-amoxillin 30 µg, co-trimoxazole 25 µg, gentamycin 10 µg, amikacin 30 µg and ceftriaxone 30 µg.

5.11.3 Quality control

Aseptic techniques were observed in all steps of urine sample collection and inoculation onto culture media to minimize contamination. All culture media were prepared according to the directions of the manufacturer. Three plates of each batch were incubated at 37^0C for 48 hours to check for sterility and the ability to support growth of the common organisms causing UTI was determined by inoculating the media with a typical stock culture. Negative and positive controls were included to validate the biochemical reagents/test kits.

5.11.4 Definition of UTI

UTI was defined by any growth on the culture medium for suprapubic aspiration specimen and 50,000 CFU/ml for specimens obtained by catheterization.[10,16] Results of the laboratory evaluation were ready after 72 hours of specimen collection.

6.0 DATA MANAGEMENT

6.1 Data entry and analysis

All filled questionnaires were coded before entering into the computer using EpiData version 3.1 statistical packages. Data cleaning was done by consistence checks. Statistical analysis was performed using Stata version 10.1 (StataCorp, 4905 Lakeway Drive, College station, Texas 77845, USA) statistical package. Frequency distribution and two way tables were used to summarize the data. Univariate and multivariate logistic regression were used to determine clinical predictors of UTI. Chi-square X^2 and Fisher's exact tests were used to determine the association between independent and dependent categorical variables. Student's t-test was used to determine association between means. P value of < 0.05 was considered statistically significant.

7.0 ETHICAL CONSIDERATION

Ethical clearance was sought and granted by MUHAS ethical committee and permission to conduct this study at MNH was granted by MNH administration. Parents/caretakers of participants signed informed consent forms prior to recruitment, this was done after receiving information regarding this study particularly benefits, risks involved and the importance of doing this study, also they were informed of the procedures that were involved when they chose to let their children to participate. Patients excluded from the study including those whose parents/caregivers did not grant consent for participating in the study received treatment in the hospital according to the existing protocols.

Results of dipstick urinalysis were immediately communicated to the parents/guardians and clinicians, while those of culture were reported after 24 hours for those who had no bacterial growth, for those with bacterial growth on their specimen; results were communicated after 48 hours after doing antimicrobial susceptibility testing.

The investigator worked in close collaboration with the attending health care team in the wards to which study participants were admitted, by providing results and facilitating continuum of care including the follow up of the participants.

8.0 RESULTS

8.1 Demographic and baseline characteristics of study population

During the study period 415 children with fever were seen by the study physician, three hundred and eighty two were recruited into the study while 33 were excluded. Nineteen out of those excluded had severe malnutrition, ten were very sick in need of resuscitation and four had underlying renal disorders out of which three had nephritic syndrome and one had acute renal failure. Two hundred and twelve (55.5%) out of those recruited were males and 170 (44.5%) were females. Temperature ranged from 37.6 to 41.0°C with a mean (SD) of 38.5°C (0.7). One hundred and seventy five (45.8%) were reported to have had fever for seven or more days. Participants' ages ranged from one to 59 months with most of participants 177 (46.3%) in 1-11 months category, the mean age was 16 months. Out of 382 children, 213 (55.8%) had used antibiotics within 72 hours prior to admission.

Table 1: Demographic and baseline characteristics of study population

Variable	**n (%)**
Age (Months)	
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)
Mean age (Months)	16
Sex	
Male	212 (55.5)
Use of antibiotics	
Yes	213 (55.8)
Duration of fever	
<7 days	207 (54.2)
Mean temperature	38.5±0.7° C
Total number of study participants N= 382	

8.2 Distribution with UTI according to age and sex

Sixty four (16.8%) of 382 children had confirmed UTI, females had a higher prevalence of UTI 18.8% (32/170) as compared to males 15.0% (32/212), however the difference was not statistically significant, p = 0.332. Urinary tract infection was more prevalent in the 36-47 months category 25.0% (8/32) and was least prevalent in 24-35months category 12.5% (6/48), the difference in UTI prevalence observed in the age categories was not statistically significant (p=2.71), (Table 2).

Table 2 Distribution of children with UTI according to age and sex

	Has UTI n (%)	Total	p value
Age (months)			
1-11	27 (15.3)	177	
12-23	20 (18.5)	108	
24-35	6 (12.5)	48	P=2.71
36-47	8 (25)	32	
48-59	3 (17.7)	17	
Sex			
Male	32 (15.0)	212	P=0.332
Female	32 (18.8)	170	

8.3 Organisms isolated from urine culture

Escherichia coli was the most common isolated organism, and was isolated in 25 (35.7%) of the 64 children with UTI, this was followed by Klebsiella spp which was isolated in 20 (28.6%) children with UTI, other isolates included *Staphylococcus epidermidis* (6.3%) *Staphylococcus aureus* (4.7%) and *Streptococcus faecalis* (4.7%). Five (7.8%) of the isolates were non-lactose fermenters which could not be identified. *Candida albicans* were isolated in six specimens, however this was not considered as the cause of UTI, (Table 3).

Table 3: Organisms isolated from urine culture

Organism	**Frequency**	**%**
Escherichia coli	25	35.7
Klebsiella spp	20	28.6
Pseudomonas aureginosa	3	4.3
Proteus spp	1	1.4
Staphylococcus Epidermidis	4	5.7
Staphylococcus aureus	3	4.3
Streptococcus faecalis	3	4.3
Candida albicans	6	8.6
UNLF*	5	7.1
Total	**70**	**100**

*UNLF-Un-identified Non-Lactose Fermenters

8.4 Uropathogens and susceptibility pattern to antimicrobial

High resistance to co-trimoxazole, ampicillin and clavulanic acid-potentiated amoxillin by all isolated pathogens was observed in this study. Table 4 shows the frequency of resistance of isolated uropathogens. Of all isolated bacteria 89.1% were resistant to co-trimoxazole, 79.7% to ampicillin while 70.3% were resistant to clavulanate-potentiated ampicillin. All *E. coli* isolates were resistant to co-trimoxazole, while 96% were resistant to ampicillin and 88% to clavulanic acid-potentiated amoxillin. Of all isolated Klebsiella spp 95% were resistant to ampicillin, 85% resistant to co-trimoxazole and 70% to clavulanic acid-potentiated amoxillin.

Amikacin was the most active agent against all isolated bacteria (12.5% resistant isolates) in this study. Only 3% of *E. coli* and none of Klebsiella spp isolates were found to be resistant to amikacin. Frequency of resistance to ceftriaxone was relatively lower as compared to gentamycin. Fifty percent of all isolates were resistant to ceftriaxone while 54.7% were resistant to gentamycin.

Table 4: Uropathogens and susceptibility pattern to antimicrobials

	Resistance of organisms to antimicrobial n (%)						
Organisms	**Cotrimoxazole**	**Ampicillin**	**Amoxillin-clavulanic acid**	**Ceftriaxone**	**Gentamycin**	**Amikacin**	**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 (3)	3 (3)	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
UINLF	2 (40)	1 (20)	2 (40)	3 (60)	1 (20)	1 (20)	5
TOTAL	**57 (89.1)**	**51 (79.7)**	**45 (70.3)**	**32(50)**	**35 (54.7)**	**8 (12.5)**	**64**

8.5 Relationship between UTI and clinical features

Among the presenting clinical features, vomiting, failure to gain weight, convulsion and diarrhea were reported in 144 (37.7%), 111 (29.1%), 107 (28%) and 55 (14.4%) respectively. Dysuria was reported in 49 (12.8%) while increased frequency of micturation and haematuria were reported in 6 (1.6%) and 3 (0.8%) respectively.

The mean duration of fever for participants with UTI was longer, 14.8 days (95% CI 10.6, 19.0) as compared to 9.5 days (95% CI 7.7, 11.4) for those without UTI. Children who were reported to have fever for less than one week were found to have lower prevalence of UTI 9.1% (19/207) as compared to those reported with fever duration of 7 days or longer 25.7% (45/175), $p<0.01$.

Children reported to have had convulsion were found to have lower prevalence of UTI 9.3% (10/107) as compared to those who were reported to have had no convulsion 19.6% (54/275), $p<0.02$. Other reported symptoms did not show any statistically significant difference with UTI, (Table 5).

Table 5: Relationship between UTI and clinical features

	Has UTI n (%)	**No UTI n (%)**	**p-value**
Antimicrobial use			
Yes	34 (16)	179 (84)	p=0.642
No	30 (17.8)	139 (82.2)	
Duration of fever			
<1 week	19 (9.2)	188 (90.8)	p<0.01*
≥1 week	45 (25.7)	130 (74.3)	
Temperature			
<38.5°C	38 (18.0)	173 (82.0)	p=0.465
≥38.5°C	26 (15.2)	145 (84.8)	
Vomiting			
Yes	26 (18.1)	118 (81.9)	p=0.596
No	38 (16.0)	200 (84)	
Poor Wt gain			
Yes	25 (22.5)	86 (77.5)	p=0.053
No	39 (14.4)	232 (85.6)	
Convulsion			
Yes	10 (9.3)	97 (90.7)	p=0.016*
No	54 (19.6)	221 (80.4)	
Haematuria			
Yes	0 (0)	3 (100)	p=1[F]
No	64 (16.9)	315 (83.1)	
Frequency			
Yes	0 (0)	6 (100)	p=0.595[F]
No	64 (17.0)	312 (83.0)	
Dysuria			
Yes	11 (22.4)	38 (77.6)	p=0.253
No	53 (15.9)	280 (84.1)	
Diarrhea			
Yes	9 (16.4)	46 (83.6)	p=0.933
No	55 (16.8)	272 (83.2)	

* Statistically significant; F- Fisher's exact test

Predictors of UTI

Among clinical features duration of fever and history of convulsion were subjected to univariate and multivariate analysis and were observed to be significant predictors of UTI.

Table 6: Predictors of UTI

	Univariate analysis			Multivariate analysis		
Variable	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Fever duration	3.42	1.91,6.12	<0.001	3.52	1.96,6.33	<0.001
Convulsion	2.37	1.16,4.85	0.018	2.50	1.20,5.19	0.014

8.6 Sensitivity and specificity of urinalysis

Nitrite test used in evaluating urine specimen in this study showed a sensitivity of 68.8% (95%CI: 56.6-78.8) and specificity of 92.4% (95%CI: 89.0-94.9). Leukocyte esterase test had sensitivity of 76.6% (95%CI: 64.9-85.2) and specificity of 85.9% (95%CI: 81.6-89.2). When used together in combination nitrite and leukocyte esterase tests had sensitivity of 85.9% (95%CI: 75.4-92.4) and specificity of 79.6% (95%CI: 74.8-83.6). Microscopic pyuria had sensitivity of 20.3% (95%CI: 12.3-31.7) and specificity of 99.7% (95%CI: 98.2-99.9)

Table 7: Sensitivity and specificity of 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)
L E	76.6(64.9,85.2)	85.9(81.6,89.2)	52.1(41.6,62.5)	94.8(91.4,97.0)
Combined*	85.9(75.4,92.4)	79.6(74.8,83.6)	45.8(36.8,55.2)	96.6(93.4,98.3)
Pyuria	20.3(12.3,31.7)	99.7(98.2,99.9)	92.9(64.2,99.6)	86.1(82.1,89.4)

* Either one or both positive, L E; leukocyte esterase, PPV/NPV; positive/negative predictive values

9.0 DISCUSSION

Urinary tract infection contributes to morbidity and mortality in children particularly those of less than 5 years of age. The aim of this study was to determine the prevalence of UTI, causative agents and their antimicrobial susceptibility pattern among febrile under-fives admitted in general paediatric wards at Muhimbili National Hospital.

The overall prevalence of UTI in this study was 16.8%. This finding is comparable to 14% reported by Okwara et al in a study which was conducted in similar setting in Kenyatta hospital.[4] Shaw et al reported prevalence of 3.3% in Philadelphia, [17] while Mussa-Aisien et al reported a prevalence of 9% in a study which was conducted in Nigeria. [6] The high prevalence observed in this study could be explained by the fact that recruited participants represent a highly selected group of patients, out of which 45.8% had fever more than seven days which could have necessitated their referral to MNH and 55.8% had been on antibiotics in the last 72 hours before admission. Therefore it is important to consider UTI in patients presenting with fever in secondary and tertiary hospitals.

Females had a higher prevalence of UTI (18.8%) as compared to males (15.0%) in this study, although not statistically significant, this difference points to more predisposition of female children to UTI. Similar findings were reported by Mussa-Aisien et al, in a study which was conducted in Nigeria.[6] Female children have short urethra which is in close proximity to the anus, this facilitates easy ascent of bacterial pathogens from the gastro-intestinal tract to the urinary tract.

Most participants with UTI 73.4% (47/64) in this study were below two years of age, although there was no statistically significant difference between age and occurrence of UTI in this study, this finding shows preponderance of UTI in early childhood, which agrees with other reports from studies conducted by Anis et al[40] and Mussa-Aisien et al.[6] Urinary tract infection is reported to be more common in early childhood and this is probably because of immature immune system and toilet training problems during early childhood. Structural anomalies which are known to resolve spontaneously later in childhood may also account for UTI in early childhood.[41] UTI in early childhood is

reported to be more likely to result in long-term complications which include scarring and end stage renal failure.[41, 42] It is important for clinicians to consider UTI when evaluating young children presenting to health care facilities with fever, with special emphasis for those with fever for duration of seven days or longer, which was noted to have two fold likelihood of having UTI in this study.

Escherichia coli was the commonest bacterial isolate from cultured urine specimens accounting for 35.7% (25/70), this was followed closely by Klebsiella spp which accounted for 28.6% (20/70). This finding is in accordance with other findings reported by Yuksel et al,[23] Sakran et al,[25] Munyi et al[28] and Munubhi[20] in studies which were carried out in Turkey, Israel, Kenya and Muhimbili, Tanzania respectively. This was not observed in school aged children as reported by Azibuke et al in which *Staphylococcus epidermidis* was the commonest isolate in symptomatic school aged children and *Pseudomonas aureginosa* was highest in asymptomatic participants.[31] The difference could be due to the fact that school aged children are less likely to contaminate their urinary tract as they have attained control of micturation and bowel evacuation.

Pseudomonas aureginosa accounting for 4.3% and Proteus spp 1.4% were isolated in this study. Munubhi in a study conducted at Muhimbili Medical Centre, reported similar finding in which Proteus spp accounting for 4.2% and *Pseudomonas aureginosa* 2.8% were isolated.[20] However, Adjei et al in a study which was conducted among infants in Ghana reported Proteus spp to be second most common isolate accounting for 22%,[2] this difference may be accounted for by the difference in the study population as only infants participated in Adjei et al study.

Gram positive organisms were also isolated in this study and included *Staphylococcus epidermidis* (5.7%), *Staphylococcus aureus* (4%) and *Streptococcus faecalis* (4%). This finding is in accordance with other reported findings in studies by Azubike et al,[31] Adjei et al,[2] Okwara et al[4] and Munubhi[20] conducted in Nigeria, Ghana, Kenya and Tanzania respectively, in which gram positive organisms were isolated. These bacteria, in particular *Staphylococcus epidermidis* and *Streptococcus faecalis*, are known to colonize gastro-

intestinal tract as normal flora and may result in ascending UTI. It is therefore important to consider gram positive organisms as potential uropathogens.[43]

Five of the isolates accounting for 7.1% were non-lactose fermenters which could not be identified because of limited resources in this study. *Candida albicans* were also isolated in this study accounting for 8.6% of all isolated organisms. This finding is comparable to those reported by Azubike et al[31] and Asharam et al[29] in studies conducted in Nigeria and South Africa respectively reporting isolation of *Candida albicans.* Candiduria has been reported with use of antibiotics, which may account for isolated Candida spp in this study as 55% of participants had been on antibiotics within 72 hours at the time of recruitment.[44] The role of *Candida albicans* in causing UTI in immuno-competent children in the absence of invasive instrumentation is still largely unknown.

Bacteria isolated in UTI have recently been reported to have high resistant against ampicillin and co-trimoxazole, which are WHO recommended first line drugs for treatment of UTI. In this study the frequency of isolated bacteria pathogens' resistance was observed to be high against ampicillin, co-trimoxazole and clavulanate potentiated-amoxillin as compared to ceftriaxone and gentamycin.

E. coli and Klebsiella spp which were the predominant isolates in this study showed significantly high resistance against co-trimoxazole, ampicillin and clavulanate-potentiated amoxillin. These findings are similar to those reported by Yuksel et al[23] and Yildiz et al[45] in Turkey, Asharam et al in south Africa,[29] and in studies conducted in Nigeria by Adeyemo et al,[38] Mussa-Aisien et al[6] and Rabasa et al.[46] Munubhi in a study which was conducted at Muhimbili Medical Centre reported *E. coli* isolates to have intermediate sensitivity rate to co-trimoxazole and low sensitivity to ampicillin,[20] however, this study was carried out in 1982 which reflects the dynamic nature of antimicrobial sensitivity pattern over time.

Fifty four percent of all isolates were resistant to gentamycin, while 50% were resistant to ceftriaxone. Resistance of *E. coli* isolates to gentamycin was 60% while to ceftriaxone was 36%, Klebsiella spp had resistance of 70% to gentamycin and 55% to ceftriaxone. These

findings are at variance to those reported by Yuksel et al [23] and Mussa-Aisien et al [6] in studies conducted in Turkey and Nigeria respectively which reported low resistance rates of *E. coli* and Klebsiella spp to gentamycin and ceftriaxone. Amikacin was observed to have the least resistance from bacterial isolates in this study, with only 12.5% of all isolates being resistant. Twelve percent (12%) of *E. coli* isolates were resistant while none of Klebsiella spp isolate was resistant to amikacin. This finding agrees with reports by Yuksel et al[23] and Asharam et al[29] in studies conducted in Turkey and South Africa respectively. Observed higher resistance to gentamycin and ceftriaxone as opposed to amikacin may be accounted for by the frequent use of these antimicrobial in the primary care facilities which might have resulted in irrational prescription and use.

In this study no difference was noted in the prevalence of UTI, between participants who were and those who were not on antibiotics at time of recruitment. Participants with fever for seven days or longer had higher prevalence of UTI which is consistent with reports by Mussa-Aisien et al[6] and Hoberman et al[7]. The high resistance of isolated bacteria to antimicrobial observed in this study, and lack of difference between participants who were on and those who were not on antimicrobials, shows that most of tested antimicrobials, which are routinely used, may be ineffective in treating UTI in children at secondary or tertiary hospitals as a result of previous exposure at primary care level. Therefore culture and sensitivity should guide appropriate treatment of UTI.

Dipstick urinalysis and microscopy were used in this study to evaluate urine specimen. Nitrite test had a sensitivity of 68.8% and a specificity of 92.4% while leukocyte esterase test had sensitivity of 76.6% and specificity of 85.9%. Combined nitrite/leukocyte esterase test had sensitivity and specificity of 85.9% and 79.6% respectively. Similar findings were reported by Munyi et al[28] and Brown et al[34] in studies conducted in Kenya and Nigeria respectively, which reported high specificity and low sensitivity of nitrite test for UTI. Pyuria showed a sensitivity of 20.3% and a specificity of 99.7% in detecting UTI in this study, which are in contrast to report by Munyi et al (sensitivity 97.1%, specificity 80%)[28] in Kenya and Mussa-Aisien et al (sensitivity 81%, specificity 99%).[6] This difference could be explained by the fact that pyuria can be caused by other factors including fever and having pyuria may not necessarily indicate UTI.

Both types of urinalysis are effective ways of screening for UTI. However, dipstick method is cheap and more convenient and can be used in out-patient set up and at bedside as opposed to microscopy which require use of microscopes which are not readily available in our wards. It is important to combine the two tests in dipstick urinalysis to improve sensitivity and specificity because leukocyte esterase test may be positive in febrile children in the absence of UTI and nitrite test is positive only after several hours of nitrate exposure to bacteria.[7, 47] From the findings of this study, urinalysis should be used to screen for UTI in all children presenting with fever to outpatient departments and those admitted in health facilities. It may also be useful in making decision for presumptive treatment of UTI in settings with no facilities for performing urine culture and sensitivity.

Participants reported to have had convulsion in this study had lower prevalence of UTI as compared to those without convulsion, this finding is at variance with report by Mussa-Aisien et al[6] in a study conducted in Nigeria which showed no association between history of convulsion and UTI. This finding emphasizes the importance of considering common causes of convulsions in a febrile patient in addition to UTI.

Classical features of UTI including dysuria, increased frequency of micturation and haematuria were subjectively reported by parents/guardians who were accompanying children. Presence or absence of these features did not show difference with occurrence of UTI. These symptoms are usually more reliable in older school age children with urinary tract infection as these children can express themselves,[41] therefore making diagnosis of UTI in under-five is a challenge which calls for high index of suspicion and clinical acumen on the part of health care providers to consider UTI even in the absence of these clinical features.

10.0 STUDY LIMITATION

This was a highly selected hospital based study so the results may not be generalized to the community, however they could be generalized for secondary and tertiary level hospitals. Also in this study five of isolated organisms, which were non-lactose fermenters could not be identified because of limited resources in the laboratory.

11.0 CONLUSIONS

Prevalence of UTI is 16.8% among admitted febrile children. Children who presented with prolonged duration of fever lasting seven days or more were more likely to have UTI. The isolated uropathogens had high resistance to ampicillin, co-trimoxazole and clavulanate-potentiated amoxillin.

12.0 RECOMMENDATIONS

1. Children less than five years of age presenting with fever in health facilities especially secondary and tertiary level of care should be evaluated for UTI.
2. The routine use of ampicillin and co-trimoxazole as first line drugs for treatment of UTI in children in our setting especially at secondary and tertiary levels of care need further evaluation with regard to its efficacy because of the relatively high in-vitro resistance pattern.
3. While the gold standard to confirm the diagnosis of UTI is bacteriological culture of urine specimen, the leukocyte esterase and nitrite tests used together in combination is useful and makes the diagnosis of UTI highly probable and would justify giving presumptive treatment with close follow up.
4. Children presenting with fever and suspected of having UTI who are not very sick, should first have their urine specimen submitted for culture and sensitivity testing before starting presumptive antimicrobial therapy.
5. On-going surveillance for antimicrobial susceptibility pattern for isolated uropathogens should be established to provide basis for the presumptive treatment of UTI.

13.0 REFERENCES

1. Campbell JD, Sow SO, Levine MM, Kotloff KL. The causes of hospital admission and death among children in Bamako, Mali. J Trop Pediatr. 2004 Jun; 50(3):158-63.
2. Adjei O, Opoku C. Urinary tract infections in African infants. Int J Antimicrob. 2004 Sep; 24 Suppl 1:S32-4.
3. Jeena PM, Coovadia HM, Adhikari M. Probable association between urinary tract infections (UTI) and common diseases of infancy and childhood: a hospital-based study of UTI in Durban, South Africa. J Trop Pediatr. 1996 Apr; 42(2):112-4.
4. Okwara FN, Obimbo EM, Wafula EM, Murila FV. Bacteraemia, urinary tract infection and malaria in hospitalised febrile children in Nairobi: is there an association? East Afr Med J. 2004 Jan; 81(1):47-51.
5. Jeena PM, Coovadia HM, Adhikari MA. Bacteriuria in children attending a primary health care clinic: a prospective study of catheter stream urine samples. Ann Trop Pediatr. 1996 Dec; 16(4):293-8.
6. Musa-Aisien AS, Ibadin OM, Ukoh G, Akpede GO. Prevalence and antimicrobial sensitivity pattern in urinary tract infection in febrile under-5s at a children's emergency unit in Nigeria. Ann Trop Pediatr. 2003 Mar; 23(1):39-45.
7. Hoberman A, Wald ER. Urinary tract infections in young febrile children. Ped Infect Dis J. 1997 Jan; 16(1):11-7.
8. Elder JS. Urinary tract infections. Nelson textbook of pediatrics. 17 Ed: Saunders; 2004. p. 1785-90.
9. Stamm WE. Urinary tract infections and pyelonephritis. Harrison's principles of internal medicine.16 Ed: McGraw Hill; 2005. p. 1715.
10. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children.. Pediatrics. 1999 Apr; 103(4 Pt 1):843-52.
11. Lum GM. Kidney and urinary tract. Current diagnosis and treatment in pediartics. 18 Ed: McGraw Hill; 2007. p. 684-707.

12. Anis ur R, Jahanzeb M, Siddiqui TS, Idris M. Frequency and clinical presentation of UTI among children of Hazara Division, Pakistan. J Ayub Med Coll Abbottabad. 2008 Jan-Mar; 20(1):63-5.

13. Coulthard MG, Lambert HJ, Keir MJ. Occurrence of renal scars in children after their first referral for urinary tract infection. BMJ (Clinical research ed. 1997 Oct 11; 315(7113):918-9.

14. Lin KY, Chiu NT, Chen MJ, Lai CH, Huang JJ, Wang YT, et al. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. Pediatr Nephrol (Berlin, Germany). 2003 Apr; 18(4):362-5.

15. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Ped Infect Dis J. 2008 Apr; 27(4):302-8.

16. Downs SM. Technical Report: Urinary Tract Infections in Febrile Infants and Young Children. 1999. p. e54-59.

17. Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics. 1998 Aug; 102(2):e16.

18. Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics. 2002 May; 109(5):846-51.

19 Kaushal RK, Bansal S, Sharma VK, Sood A, Goyal A. Urinary tract infection among children presenting with Fever. Indian Pediatr. 2003 Mar;40(3):269-70.

20. Munubhi EK. Urinary tract infections among children admitted with gastroenteritis in padiatric ward, Muhimbili medical centre, Dar-es-salaam, Tanzania: Dar-es-salaam University; 1982.

21. Hari P, Mantan M, Bagga A. Management of urinary tract infections. Indian J Pediatr. 2003 Mar; 70(3):235-9.

22. Qureshi AM. Clinical presentation of urinary tract infection among children at Ayub Teaching Hospital, Abbottabad. J Ayub Med Coll Abbottabad. 2005 Apr-Jun; 17(2):79-81.

23. Yuksel S, Ozturk B, Kavaz A, Ozcakar ZB, Acar B, Guriz H, et al. Antibiotic resistance of urinary tract pathogens and evaluation of empirical treatment in Turkish children with urinary tract infections. Int J Antimicrob. 2006 Nov; 28(5):413-6.

24. Wu CY, Chiu PC, Hsieh KS, Chiu CL, Shih CH, Chiou YH. Childhood urinary tract infection: a clinical analysis of 597 cases. Acta paediatrica Taiwanica = Taiwan er ke yi xue hui za zhi. 2004 Nov-Dec; 45(6):328-33.

25. Sakran W, Miron D, Halevy R, Colodner R, Smolkin V, Koren A. [Community acquired urinary tract infection among hospitalized children in northern Israel: pathogens, susceptibility patterns and urinary tract anomalies]. Harefuah. 2003 Apr; 142(4):249-52, 320, 19.

26. Asinobi AO, Fatunde OJ, Brown BJ, Osinusi K, Fasina NA. Urinary tract infection in febrile children with sickle cell anaemia in Ibadan, Nigeria. Ann Trop Pediatr. 2003 Jun; 23(2):129-34.

27. Tessema B, Kassu A, Mulu A, Yismaw G. Pridominant isolates of urinary tract pathogens and their antimicrobial susceptiblity patterns in Gondar University Teaching Hospital, nothwest Ethiopia. Ethiop Med J. 2007 Jan; 45(1):61-7.

28. Munyi ST, Macharia WM, Alwar AJ, Njeru EK. Screening for urinary tract infection in children with cancer. East Afr Med J. 1998 May; 75(5):264-7.

29. Asharam K, Bhimma R, Adhikari M. Human immunodeficiency virus and urinary tract infections in children. Ann Trop Pediatr. 2003 Dec; 23(4):273-7.

30. Isaack H, Mbise RL, Hirji KF. Nosocomial bacterial infections among children with severe protein energy malnutrition. East Afr Med J. 1992 Aug; 69(8):433-6.

31. Azubike CN, Nwamadu OJ, Oji RU, Uzoije N. Prevalence of urinary tract infection among school children in a Nigerian rural community. West Afr J Med. 1994 Jan-Mar; 13(1):48-52.

32. Van der Voort J, Edwards A, Roberts R, Verrier Jones K. The struggle to diagnose UTI in children under two in primary care. Fam Pract. 1997 Feb; 14(1):44-8.

33. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005 Mar 15; 71(6):1153-62.

34. Brown BJ. Evaluation of the Nitrite Test in Screening for Urinary Tract Infection in Febrile Children with Sickle Cell Anaemia. Nigerian J Pediatr. 2004; 30(1):10-3.

35. WHO. Guidelines for the management of common illnesses with limited resources WHO Press; 2005.

36. Yen CW, Chen DH. Urinary tract infection in children. J Microb Immunol Infect = Wei mian yu gan ran za zhi. 1999 Sep; 32(3):199-205.

37. Brown BJ, Asinobi AO, Fatunde OJ, Osinusi K, Fasina NA. Antimicrobial sensitivity pattern of organisms causing urinary tract infection in children with sickle cell anaemia in Ibadan, Nigeria. West Afr J Med. 2003 Jun; 22(2):110-3.

38. Adeyemo AA, Gbadegesin RA, Onyemenem TN, Ekweozor CC. Urinary tract pathogens and antimicrobial sensitivity patterns in children in Ibadan, Nigeria. Ann Trop Pediatr. 1994;14(4):271-4.

39. MNH. Department of Paediatrics and Child Health annual report: Muhimbili National Hospital; 2007/08.

40. Anis ur R, Jahanzeb M, Siddiqui TS, Idris M. Frequency and clinical presentation of UTI among children of Hazara Division, Pakistan. J Ayub Med Coll Abbottabad. 2008 Jan-Mar; 20(1):63-5.

41. RCOG. Royal College of Obstetrician and Gynaecologist Clinical Guideline for Diagnosis, Treatment and Long Term Management of Urinary Tract Infections in Children. August 2007.

42. Berg US, Johansson SB. Age as a main determinant of renal functional damage in urinary tract infection. Arch Dis Child. 1983;58:963-9.

43. Brooks GF, Butel JS, Morse SA. Jawetz, melnick, & Adelberg's Medical Microbiology. Mc Graw-Hill Companies, Inc; 2004 [cited 2010 April, 2010].

44. Goldberg PK, Philip J. Kozzin M, Gilbert J. Wise M, Nabil Nouri, Richard B. Brooks M. Incidence and Significance of Candiduria. JAMA. February 9, 1979; 241(6).

45. Yildiz B, Kural N, Durmaz G, Yarar C, Ak I, Akcar N. Antibiotic resistance in children with complicated urinary tract infection. Saudi Med J. 2007 Dec;28(12):1850-4.

46. Rabasa AI, Gofama MM. Urinary tract infection in febrile children in Maiduguri north eastern Nigeria. Niger J Clin Pract. 2009 Jun; 12(2):124-7.

47. Turner GM, Coulthard MG. Fever can cause pyuria in children. BMJ. October, 1995;311:924.