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Etiology and Antimicrobial Susceptibility Patterns of Bacterial Agents Causing Urinary Tract Infection in Children under Five years, dar es Salaam.

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Abstract

Background: The empirical therapy of urinary tract infections (UTI) relies on the predictability of the agents causing UTI and knowledge of their antimicrobial susceptibility patterns. This information need to be updated regularly. This study was conducted to assess the spectrum and patterns of antimicrobial resistance of UTI agents isolated from children aged less than five years of age presenting with clinical symptoms suggestive of UTI.

Methods: This was a cross-sectional study carried out at three hospitals in Dar es Salaam in which all children under five years of age with symptoms of UTI were enrolled. Demographic data was gathered using a structured questionnaire. Bacteriological information was obtained after culture of urine and sensitivity test using Kirby Bauer technique.

Results: Of the 270 cultured mid-stream urine samples, 80 (29.6%) revealed a significant single isolate growth of ≥ 10^5 colon-forming units per milliliter of urine, 33 (12.2%) had mixed growth, 27 (10%) non-significant growth, and the remainder 130 (48.1%) revealed no bacterial growth. Among the isolated bacteria, Escherichia coli was the most common isolate 34 (42.5%), followed by Klebsiella spp 32 (40%), Streptococcus spp 4 (5%) while Staphylococcus aureus, Proteus mirabilis and unidentified coliforms caused 3 (3.8%) each. Pseudomonas spp isolated only once. Isolates had high resistance to amoxicillin 79 (98.7%), trimethoprim-sulfamethoxazole 77 (96.2) and ampicillin 76 (95%), moderate resistance to nitrofurantoin (20%) and least resistance against amikacin 6 (7.5%).

Conclusion: Based on the results of this study, the empirical treatment of UTI should be done with amikacin and to a lesser extent nitrofurantoin. The high level of resistance shown by the isolates (95 – 98%) to a number of commonly prescribed antimicrobial calls for continuous surveillance of antibiotics.

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Introduction and Literature Review

Background

Urinary tract infection (UTI) results from the presence and multiplication of microorganisms in one or more structures of the urinary tract with associated tissues invasion. It is the presence of multiplying micro-organisms in significant number of more than 10^5 bacteria per milliliter of urine. This can give rise to a wide variety of clinical syndromes. These include acute and chronic pyelonephritis (kidney and renal pelvis), urethritis (urethra), epididymitis (epididymis) and prostatitis (prostate gland). Infection may spread to surrounding tissues (e.g. perinephric abscess) or to the blood stream, (Sobel, 1997). Urinary tract infection may involve just the lower tract or both the lower and upper urinary tracts. In children they are particularly important because their occurrence may be associated with some congenital abnormality of the urinary tract or an error in management. If not corrected, these may lead to recurrent infections causing damage to the urinary tract (Winberg, 1992).

In healthy children urine is sterile. The most important factor in maintaining the sterility of the urinary tract is emptying the bladder completely and frequently. The causative agent of most UTIs is bacteria that initially settle (colonize) around the urethra, and then ascend into the rest of the urinary tract. Several factors can make this process more likely to occur (Winberg, 1992).

Urinary tract infection (UTI) is a problem that is frequently encountered by pediatric healthcare providers. Over recent decades, the importance of UTI has been increasingly recognized, in particular the role of UTI as an occult cause of febrile illness in young children. The evolving state of knowledge about pediatric UTI leaves many questions and controversies.

Commonest causes of UTI

Clinically important infections usually occur due to bacteria, although viruses, fungi, and parasites can also cause infection.

Common bacterial pathogens include gram-negative species such as *Escherichia coli, Klebsiella, Proteus, Enterobacter, Pseudomonas,* and *Serratia* spp and gram-positive organisms, including group B streptococci, Enterococcus sp, and Staphylococcus aureus. In general, bacteria infect the urinary tract by ascending from the urethra, although hematogenous infection may occur in rare instances among young infants. (Zorc *et al*, 2005).

Common non-bacterial causes of UTI include hemorrhagic cystitis from adenovirus and Candida infection in immunocompromised individuals.

Symptoms of Urinary Tract Infections

Symptoms of UTI include dysuria, urinary frequency, urgency, burning, flank pain, suprapubic pain, fever and haematuria, it is generally accepted microbiologically, that urinary tract infection exists when pathogenic bacteria are detected in the urinary tract, and the infection is considered significant and requires treatment when more than 10^5 bacteria per milliliter of urine are present in a properly collected urine sample (Gleeson et al 1991).

Epidemiology and Public health Importance of UTI

The epidemiology of UTI during childhood varies by age, gender, and other factors. The incidence of UTI is highest in the first year of life for all children (1%) but decreases substantially among boys after infancy (Jakobsson et al, 1999).

Estimates of UTI incidence among infant boys have varied in different populations, likely due to factors such as circumcision, which has been associated with a reduction in risk of UTI. (Jakobsson et al, 1999). Infants and young children presenting with urinary tract infections have traditionally been investigated extensively due to a concern that developing kidneys are more susceptible to damage from pyelonephritis and that the risk of identifying associated urinary tract abnormalities is statistically higher in this group. Originally there appeared to be a difference in outcomes with infection occurring under the ages of 3 to 5 years based on studies which found a higher incidence of renal scarring in this age group (Berg et al, 1983).

Literature review

In many literatures UTI is defined as colonization of a pathogen occurring anywhere along the urinary tract: kidney, ureter, bladder, and urethra. Traditionally, UTIs have been classified by the site of infection (i.e., pyelonephritis [kidney], cystitis [bladder], urethra [urethritis]) and by severity (i.e., complicated versus uncomplicated). A complicated UTI describes infections in urinary tracts with structural or functional abnormalities or the presence of foreign objects, such as an indwelling urethral catheter. This model does not necessarily reflect clinical management, however. In children, a simpler and more practical approach is to categorize UTI as a first infection versus recurrent infection. Recurrent infections can be further subdivided into (1) unresolved bacteriuria, (2) bacterial persistence, and (3) reinfection (Smellie et al, 1998)

Infections of the urinary tract generally resolve with adequate treatment in most children. In neonates and infants, however, they are presumed to be complicated because of the high association between urinary tract malformation and concurrent bacteremia, which predispose children to acute morbidity and long-term renal insufficiency (Benador et al, 1997).

The recurrence of a UTI may be caused by several reasons. Unresolved bacteriuria is most commonly caused by inadequate antimicrobial therapy. Sub therapeutic levels of the antimicrobial agents may be a result of noncompliance, malabsorption, suboptimal drug metabolism, and resistant uropathogens unresponsive to attempted therapy (Pewitt et al, 1997). In these cases, infection typically resolves after altering the therapy according to antimicrobial sensitivities determined by a proper urine culture. Young children with UTIs may only have a fever, poor appetite, vomiting, or no symptoms at all.

The treatment for pediatric UTI varies considerably with several factors. The choice of antibiotic may be affected by local resistance patterns and other considerations. Amoxicillin was traditionally the first-line therapy for outpatient treatment of UTI in children. However, increased rates of Escherichia coli resistance have made amoxicillin a less acceptable choice, and studies have found higher cure rates for trimethoprim-sulfamethoxazole (AAP, 1999). Other choices include amoxicillin-clavulanate or cephalosporins such as cefoxime, cephalexin, cefprozil, or cefpodixime. Fluoroquinolones are widely used in adult patients, although concerns about potential effects on musculoskeletal joint development based on animal data have restricted their use in young children. A recent review of the use of fluoroquinolones for pediatric UTI noted a high rate of efficacy among patients with complex medical conditions or multidrug resistance, although data on the safety of these agents are limited (Koyle et al, 2003). Inpatient treatment regimens may include the combination of ampicillin and gentamicin or third-generation cephalosporins. Urine should always be obtained for culture in children so that sensitivities can be determined to guide antibiotic therapy.

A five year retrospective study was performed to identify organisms isolated from the urinary tract of 2815 children in the community and 1314 children with underlying renal problems and their antimicrobial susceptibilities. Isolates from children in the latter group were generally more resistant to commonly used antibiotics. In particular, up to a third of E coli isolates from children in the community and almost two thirds of E coli isolates from children with underlying renal damage was resistant to trimethoprim

Antimicrobial agents and mechanism of resistance

An antimicrobial agent is any chemical substance that is capable of inhibiting growth or causing the death of micro-organisms. They can either be bactericidal or bacteriostatic. They exert their activity through selective toxicity, by destroying the micro-organisms without causing harm to the body. Antibiotics first came to the forefront with the discovery of penicillin by Fleming in 1929. He observed that bacteria failed to grow in the vicinity of a colony of a fungus called Penicillin rotatum (Fleming, 1929). In 1940, Chain and Florey discovered that the above effect was due to a substance called Penicillin produced by these organisms (Chain et al, 1940). During the next 25 years, research on chemotherapeutic agents largely centered on substances of microbial origin called antibiotics. The isolation, concentration, purification and mass production of penicillin were followed by the development of streptomycin, tetracycline, chloramphenicol and many other agents (Brooks et al, 1998). These substances were originally isolated from filtrates of media in which their respective molds had grown. Subsequently, others have been synthesized and in recent year's biosynthetic modification of molecules have been a prominent technique for development of new antimicrobial agents (Brooks et al, 1998).

Mechanism of action of antimicrobial agents is based on selective toxicity. The selective toxicity may be a function of a specific receptor required for drug attachment, or it may depend on the inhibition of biochemical events essential to the organisms but not the host cells (Brooks et al, 1998).

Antimicrobial agents can act by inhibiting cell wall synthesis, which are found on bacterial cell and not human cells. Penicillins, vancomycin, cephalosporins, bacitracin and cycloserine inhibit various stages in the synthesis of the cell wall, making the bacterial cells fragile and easy to rupture. Amphotericin B, colistin, imidazoles, triazoles and polyene act by inhibiting bacterial cell membrane function, utilizing the existing structural and animal cells (Brooks et al, 1998).

Protein synthesis inhibitors, for example, erythromycin, tetracycline, chloramphenicol and aminoglycosides utilize the differences in the ribosomal make up between human and bacterial cells to achieve selective toxicity. Nucleic acid synthesis inhibitors, for example, quinolones, trimethoprim, sulphonamides and rifampin act

by inhibit various stages which are important in the synthesis of bacterial Deoxyribonucleic acid (DNA) (Brooks et al, 1998).

The antimicrobial resistance may be genetic or non-genetic. Non-genetic resistance includes failure to act on metabolically insert bacteria, intracellular bacteria and those bacteria that have lost the specific target structure for a drug (Brooks et al, 1998). Generic origin of antimicrobial resistance may be due to spontaneous mutation or due to acquisition of plasmids, which code for enzymes that are capable of destroying drugs. Bacteria have also evolved mechanisms of evading the action of antimicrobial agents, these include production of enzymes that destroy drugs, for example staphylococci produced β-lactamase which destroys the β-lactam ring in penicillin and hence rendering the drug ineffective (Brooks et al, 1998, O'Brien, 1997). Bacteria can also alter their outer membranes and hence impairing the permeability of the drug, for example, tetracyclines accumulate in susceptible bacteria but not in resistant bacteria. Other mechanisms include altered structural targets for the drug, for example, penicillin resistance in S. pneumoniae and enterococci is due to alteration in penicillin binding proteins (Brooks et al, 1998).

Bacteria can also develop an altered metabolic pathway that bypasses the reactions inhibited by antibiotics, for example, sulfonamide resistant bacteria can utilize preformed p-aminobenzoic acid (PABA) instead of extracellular PABA. Bacteria can alter their enzymes which are still functional but which are not affected many drugs, for example, in trimethoprim resistant bacteria, the dihydrofolic acid reductase is inhibited less efficiently than in trimethoprim sensitive bacteria (Brooks et al, 1998). There is a need for more studies in Tanzania to explore antimicrobial agents and mechanism of resistance so as to recommend appropriately.

Antimicrobial susceptibility patterns

The increasing prevalence of bacterial resistance to commonly prescribed antimicrobial agents, especially in the developing countries poses a major challenge in the management of bacterial infections (Kariuki et al, 1997, Kunin, 1993). The global magnitude of antimicrobial resistance is unknown and more so in the developing countries where the literature is very scanty and in most cases deficient (WHO, 1997). The frequency of resistance to antimicrobial agents for individual pathogens and the patterns of multiple resistances vary between countries and often in different parts of the same country. However, the situation has become worse in the last few years (Shears, 1993, Turnidge, 1998, Belihu et al, 1999). Antibiotic resistance pattern is rapidly evolving, hence a need for a constant surveillance. In Tanzania Blomberg et al in 1998 conducted a surveillance of antimicrobial resistance at a tertiary hospital Muhimbili. Certain trends in antimicrobial susceptibility were identified by comparison with data from other studies. While resistance to ampicillin, tetracycline and sulfonamides in Gram-negative bacteria was frequent already in the seventies, it was worrying that resistance to trimethoprim-sulfamethoxazole, chloramphenicol, nitrofurantoin, nalidixic acid and amoxicillin-clavulanate appeared to have increased compared to previous studies (Blomberg B et al, 1998).

Factors influencing antimicrobial resistance

Development of antimicrobial resistance occurs as a result of complex interactions, which encourage the emergence, persistence and enhance transmission of resistant organisms (Cohen, 1994). In a study done in a Finnish hospital between 1971 and 1984, the trimethoprim resistance pattern of E .coli isolates from urine specimen was related to the antimicrobial use (Huovinen et al, 1986). Cometta et al in a study done on patients with cancer and neutropenia reported that between 1983 and 1990, there was no resistance to fluoroquinolones amongst E. coli isolates, however, 28% were found to be resistant in 1991 through 1993. This change corresponded to an increase in the rate of fluoroquinolone use from 1.4% of patients between 1983 and 1985 to 45% between 1991 and 1993 (Cometta et al, 1994).

In another study done in Gonder, Ethiopia it was found that a high proportion of the common pathogens isolated were resistant to the frequently used antibiotics including tetracycline, chloramphenicol, sulphamethaxazole/trimethoprim and ampicillin (Asseffa, 1996). A similar relationship has been reported in a study that was done in Sidamo, Ethiopia between 1985 and 1997, which showed that resistance pattern correlated with the commonly prescribed antibiotics (Belihu et al, 1999). In a study done in Tanzania between 1978 and 1979, Maselle et al reported that 50%-90% of all coliforms were resistant to ampicillin, tetracycline and sulphonamides which were the commonly used antimicrobials (Maselle et al, 1980). Mhalu et al in a study done in Tanzania also reported that excessive use of tetracycline during the cholera epidemic in the late 1970's contributed to a significant increase in the widespread resistance to the antimicrobial agent (Mhalu et al,1979).

Self- medication is very common in many developing countries (Okeke et al, 1999). In a study done in Kenya, it was found that about 64% of all antibiotics sold by the chemists were without

prescriptions from a doctor (Indalo, 1997). Due to lack of control, broad-spectrum antibiotics can be found being sold freely over the counter and even at open market places (Kunin et al, 1987, Okeke et al 1999). Some antibiotics being sold are often of substandard qualities; these are therefore cheap and thus preferred by many people (Okeke et al, 1999)

Other factors that favor development of antimicrobial resistance include a heavy burden of infectious diseases, large populations with rudimentary primary health care. Others are poor diagnostic services prompting health care workers to prescribe indiscriminately, poor sanitation and overcrowding, all of which tend to favour the rapid spread of resistant organisms (Okeke et al, 1999, WHO, 1998). The consequences of antimicrobial resistance may include limitation in therapeutic options, high costs of alternative drugs and an increase in morbidity and mortality (Cohen, 1992).

Problem statement and Justification

In Tanzania treatment of UTI is done empirically due to little information regarding the spectrum, magnitude and patterns of antimicrobial resistance to urinary bacterial isolates from children. Also the existence of irrational drug use behaviors that contributes to development of antimicrobial resistance which includes taking medication at home without hospital prescription, incomplete dosage taking, use of counterfeit drugs from unregistered medical stores, and side effects following drug usage.

The previous study that investigated UTI among children was conducted more than ten years ago. Thus, updating knowledge of the prevailing causal bacteria and their susceptibility patterns is important for the proper selection and use of antimicrobial drugs and for the development of an appropriate prescribing policy.

Broad objective

To assess the spectrum of aetiological agents and antimicrobial resistance patterns of UTI agents in children aged less than five years in Dar es Salaam, Tanzania.

Specific objectives

1. To determine the spectrum of bacterial etiologic agents causing UTI to children with respect to sex and age.
2. To determine the spectrum and pattern of anti-microbial resistance among bacteria isolated from children with UTI
3. To relate antimicrobial use behaviors and antimicrobial resistance of bacterial agents causing UTI in children.

Methodology

Epidemiological Methods

Study design

A cross-sectional study design was used.

Study sites

Muhimbili National Hospital, Amana and Mwananyamala Hospitals-Dar es Salaam, Tanzania Muhimbili National Hospital is a tertiary hospital in Tanzania. With more than 1000 beds, MNH is the largest hospital in the country and serves as a national referral and university teaching hospital, as well as a primary and referral hospital for a population of approximately 3.6 million in the Dar es Salaam area. Amana and Mwananyamala are secondary hospitals serving as Municipal's health facility within Dar es Salaam Region.

Study population

Study subjects included children aged less than five years of age presenting with clinical symptoms suggestive of UTI (i.e. Dysuria, frequency, burning, fever and haematuria) at Muhimbili National Hospital, Amana and Mwananyamala Municipal Hospitals.

Inclusion criteria: All new cases aged less than five years presenting with symptoms of UTI at pediatric department.

Exclusion criteria: all cases aged five or more years with symptoms of UTI

Sampling technique

All new cases during the period of two months were reviewed by clinicians at Pediatric departments; those with clinical symptoms suggestive of UTI were selected to participate in the study after parental/guardian consent.

Data collection

A structured questionnaire was used to interview parents/guardians of children on demographic and antimicrobial use behaviors such as source of prescription, previous dosage completion and other history of medication of the child and urine samples was taken for invitro culture and sensitivity tests at MUHAS microbiology Laboratory.

Sample size

Sample size was calculated with the following formulae

$$n = \frac{z^2 p(1-p)}{\varepsilon^2} \quad \text{or} \quad n = \frac{z^2 p(100-p)}{\varepsilon^2}$$

$$n = \frac{1.96^2 \times 0.20(1-0.20)}{0.5^2}$$

$$\frac{3.84 \times 0.20 \times 0.80}{0.0025} =$$

$$\frac{3.84 \times 0.16}{0.0025} = 245.76$$

Sample size was 250.

By adding 10 percent for the non respondents the minimum sample size was 270 children under five years of age.

n = Minimum sample size

p = Proportion/Prevalence of antimicrobial resistance =20% (Urassa et al, 1997)

E = Tolerable error / level of significance = 5%.

z =Standard deviation of the normal distribution = 1.96

Antibiotic usage

The antibiotic use behavior of patients were explored using standard structured questionnaire where parents /guardians were interviewed to obtain information regarding the following; education level and occupation of parents/guardians, previous medical history and history of medication of the child. In addition; the following information was sought; source of prescription, completion of the dose and side effects following drug usage.

Laboratory Methods

Specimen Collection and Storage

Urine specimens were collected in sterile bottles by standard method for urine collection as stipulated on the Standard Operating Procedure (i.e. Parents were given a sterile, dry, wide-necked, leak-proof container, and explained the importance of collecting a specimen with no contamination [clean-catch specimen], they were instructed to cleanse the area around the urethral opening with clean water, dry the area and collect the urine, for female with the labia held apart) and transported to the laboratory for examination. Urine specimen was examined within six hours of collection and if not; it was stored at 4°C until the following day.

Urine Cultures

Urine samples were cultured in Cystine-Lactose-Electrolyte Deficient (CLED) agar media for isolation of uropathogens from children. Standard quantitative culture was performed in a laboratory. A loop calibrated to deliver approximately 0.001 mL was used to inoculate urine in CLED agar plates. All plates were incubated at 35°C and examined for growth after 24 hours. A significant bacteriuria result was defined as growth of a single urinary tract pathogen at $\geq 10^5$ CFU/mL. Bacterial isolates was identified using standard microbiological methods as described in Mackie & McCartney Practical Medical Microbiology (Collee, et al, 1996). An important biochemical feature of most E.coli strains is the production of indole from peptone water containing tryptophan, Proteus rapidly hydrolyzes urea (within 4 hours), Klebsiella gives a positive urease test after 18 – 24 hours, Pseudomonas spp are oxidase positive, catalase positive, indole negative and mostly citrate positive.

Sensitivity testing

Sensitivity testing was performed by Kirby-Bauer method (Bauer et al, 1966) on Mueller-Hinton agar plates. Isolates were suspended in peptone water, inoculated onto the agar plate and followed by antibiotic-impregnated discs within 15 minutes and the control strain at the respective media. The antibiotic disk was placed precisely at the interface between the surface areas inoculated with the clinical isolate and the control strain. After overnight incubation, the relative size of the inhibition zones of the clinical isolate and the control strains was compared in respect to the disc manufacturer guideline. The test results were classified as susceptible (S), intermediate (I) or resistant (R) by evaluation of the difference between the inhibition zones of the clinical isolate and the control strain. The control strains were used are S. aureus ATCC 25923, E. coli ATCC 25922 or Pseudomonas aeruginosa ATCC 27853.

The antibiotic discs and their concentrations per disc (mg) included: Trimethoprim-sulfamethoxazole (25), nitrofurantoin (300); representative antibiotics of aminoglycosides such as gentamicin (10), amikacin (10); quinolones such as nalidixic acid (30), ciprofloxacin (5); and cephalosporin such as, cefotaxime (30), as well as aminopenicillin, amoxicillin and clavulanic acid

Data management and Analysis

Demographic data collected by using a structured questionnaire, and laboratory results datasheet were checked for accuracy and entered into a computer and analyzed by using Epi info version 3.5.1 software package to calculate all necessary frequencies and cross tabulations regarding common bacterial aetiological agents in relation to sex and age, its sensitivity patterns to antibiotics. Statistical associations were tested using Chi-square test, Odds ratio, p-value at 95% significance level.

Ethical issues

The study proposal was cleared by the Research and Publication committee of Muhimbili University of health and Allied Sciences. Obligations of investigators were to adhere to all ethical issues. All information attained during the study was kept confidential.

Informed consents were sought from the parents or guardians of all children included in this study and code numbers were used instead of names. Refusal to participate or withdraw from the study did not attract any penalty or loss of any benefits to which non consenting participants were otherwise entitled. No risks were expected, as this was not an invasive procedure and results were shared with hospital authority for proper clinical management of patients

Results

The study recruited 270 children less than five years of age presenting with clinical symptoms suggestive of urinary tract infection at Pediatrics Departments of Muhimbili National Hospital, Amana and Mwananyamala Municipal hospitals. Of the recruited children 162 (60%) were male children. Majority 118 (43.7%) came from Kinondoni Municipality, while 100 (37%) and 52 (19.3%) were from Ilala and Temeke Municipalities respectively.

A total of 259 (95.9%) children were under care of their mothers, 10 (3.7%) under guardian and only 1 (0.4%) was under care of the father when brought him/her to hospital for treatments.

	Frequency	%
Sex		
Male	162	60.0
Female	108	40.0
Education (Parents)		
No formal education	32	11.9
Primary completed	149	55.2
Primary not completed	39	14.4
Secondary	49	18.1
Tertiary	1	0.4
Occupation		
Housewives	197	73.0
Business	53	19.6
Government *	20	7.4
Location		
Ilala	100	37.0
Kinondoni	118	43.7
Temeke	52	19.3

* Government included Teachers, health workers and other institutions

Table 1: *Socio-demographic characteristics of respondents (n =270).*

The majority of the children 149 (55%) had parents with primary education, followed by those 49(18.1%) with secondary school completed, 39 (14.4%) primary not completed, 32 (11.9%) had no formal education and only one had tertiary education. Most of the mothers 197 (73%) were housewives, 53 (19.6%) business entrepreneurship and only 20 (7.4%) were government employees (Table 1).

Culture results	Number	Percentages
i. E. coli	34	(42.5)
ii. Klebsiella spp	32	(40.0)
iii.P. mirabilis	3	(3.8)
iv. Pseudomonas	1	(1.3)
v. S. aureus	3	(3.8)
vi. Streptococci spp	4	(5.0)
vii. Unidentified coli	3	(3.8)
Total	80	100

Table 2: *Distribution of UTI pathogens by percentages (n = 80).*

Of the 270 cultured mid-stream urine samples, 80 (29.6%) revealed a significant single isolate growth of approximate 105 colon-forming units per milliliter of urine, 33 (12.2%) mixed growth, 27 (10%) non-significant growth, and while the remainder 130 (48.1%) had no bacterial growth. The most common bacteria isolated was Escherichia coli which accounted for 34 (42.5%), followed by Klebsiella spp 32 (40%), Streptococcus spp 4 (5%) while Staphylococcus aureus, Proteus mirabilis and unidentified coliforms caused 3 (3.8%) each, Pseudomonas spp isolated only once (Table 2).

Most isolates were from male children 49 (61.3%) while infants less or equal to one year of age accounted for 38 (47.5%) of all culture results with significant growth of uropathogens. (Table 3)

There is no significant difference (OR 1.077) on the risk of getting urinary tract infection on sex and age of children

Variable	Culture results		Crude or (95% CI)	P. value
	Positive	Negativ		
Sex				
Male	49	113	1.077 (0.6308, 1.839)	0.7856
Female	31	77		
Age				
Less than 1	38	67	x^2 (4.677)	0.3221
1 – 2	19	59		
2 – 3	11	23		
3 – 4	8	25		
Less than 5	4	16		
Occupation				
Housewives	60	137	x^2 (0.3151)	0.8543
Business	15	38		
Government	5	15		

Table 3: *Distribution of culture results with respect to Sex and Age (n = 270).*

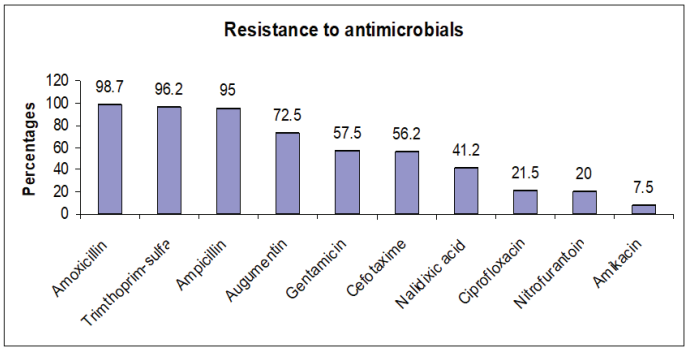

Figure 1: *Distribution of antimicrobial resistance patterns by percentages.*

High Antimicrobial resistance by bacterial isolates were seen with Amoxicillin 79 (98.7%), Trimethoprim-sulfamethoxazole 77 (96.2) and Ampicillin 76 (95%). Significant resistance revealed with Augumentin 58 (72.5%), Gentamicin 46 (57.5%) and Cefotaxime 45 (56.2%). Moderate to lower resistance seen with, Ciprofloxacin (21.5%), Nitrofurantoin 16 (20%) and Amikacin 6 (7.5%) (Figure 1).

Antibiotic susceptibility pattern of these isolates revealed that Amikacin, Nitrofurantoin and ciprofloxacin shown invitro effectiveness for treatment of urinary tract infection but Gentamicin and Nalidixic acid has significant resistance thus can need sensitivity pattern before administration.

The resistance pattern of the isolates to some prescribed antibiotics is shown in Table 4. While E. coli showed high resistance to amoxicillin and ampicillin (100%), it showed low resistance to amikacin (8.8%) and nitrofurantoin (14.7%). All isolates however showed high resistance to amoxicillin, trimethoprim-sulfamethoxazole and ampicillin. Of all bacteria isolated 99% were resistant to amoxicillin, and 95% were resistant to trimethoprim-sulfamethoxazole.

Antimicrobial use behaviors survey revealed that 188 (69.6%) of all interviewed parents/guardians had given their children antibiotics at home after symptoms onset before attending hospital, with 44 (24.4%) getting their prescribed drugs from private medical stores. Fifty-five percent of the kids were given antibiotics for three days during the previous episode of the disease.

Most of children 262 (97%) presented at pediatric clinics with persistent fever and 75 (97%) of those with positive culture results presented at hospital with fever symptoms only. Meanwhile 166 (63.1%) was recurrent cases of UTI

Antimicrobial agent (resistance in percent)											
Pathogen	n	CIP	AMP	AK	CTX	NA	F	GEN	AUG	SXT	AML
E. coli	34	29.4	100	8.8	47.0	47.0	14.7	50	79.4	97	100
Klebsiella spp	32	12.5	93.7	0	62.5	25	15.6	68.7	71.8	96.8	96.8
Proteus	3	33.3	100	66.6	66.7	33.3	66.7	100	100	100	100
Pseudomonas	1	0	100	0	100	100	100	0	100	100	100
S. aureus	3	0	66.7	0	33.3	66.7	0	33.3	0	100	100
Streptococcus	4	25	75	25	75	100	50	25	50	75	100
Unidentified coli	3	33.3	100	0	66.7	33.3	33.3	66.7	66.7	100	100
General (%)		19	90	14	64	58	40	49	66	95	99

Table 4: *Antimicrobial resistance patterns in specific isolated bacteria.*

Variable	Multiple drug resistance		Crude or (95% CI)	P.value
	Yes	No		
Self medication				
Yes	61	127	1.592 (0.8767, 2.8932)	0.1247
No	19	63		
Self medication	Antibiotic resistance (Amp)*			
Yes	58	3	1.074 (0.1051, 10.9752)	0.67
No	18	1		
(Gen)*				
Yes	34	27	0.734 (0.2544, 2.1210	0.756
No	12	7		
(Cip)*				
Yes	14	47	1.58 (0.369, 9.670)	0.754
No	3	16		

** Amp; ampicillin, Gen; Gentamicin, Cip; Ciprofloxacin*

Table 5: *Cross-tabulation relation of self medication to drug resistance.*

Self medication behavior shown no significant association with the development of multiple drug resistance revealed in this study.

Discussion

The objectives of this study was to assess the spectrum and patterns of antimicrobial resistance of UTI agents isolated from children aged less than five years of age presenting with clinical symptoms suggestive of UTI in major hospitals in Dar es Salaam.

The results of this study showed that 29.6% of suspect cases had significant growth of single isolate of approximate 10^5 cfu per milliliter of urine. The true prevalence of pediatric UTI is difficult to determine because there are varying presentations that range from an absence of specific urinary complaints to fulminant urosepsis. There are limited data on pediatric UTI as a significant health care burden to Tanzanian public, unlike in America where data from the Urologic Disease revealed that infections of the urinary tract affect 2.4% to 2.8% of children every year and account for more than 1.1 million office visits annually (Freedman, 2005).

When comparison is made between males and females; male children has shown higher percentage of infections and those of age less or equal to one year, but the difference was not statistically significant. Results of this study are similar to those described in other study showing that during the first year of life, boys have a higher incidence of UTI; but in all other age groups, girls are more prone to developing UTI (Wettergren et al, 1989). During the first year of life, the incidence of UTI in girls is 0.7% compared with 2.7% in boys (Wettergren et al, 1989). In this study E. coli was the most common bacterial agent isolated in the sample population. The predominance of E. coli as the commonest aetiological agent of UTI has also been reported in studies conducted previously in Tanzania (Bloomberg et al, 2005) and in Kuwait (Al Sweih et al, 2005). In most cases, E. coli which originates as a harmless microorganism in the intestines spreads to the vaginal passage where it invades and colonizes the UTI.

The results of antimicrobial susceptibility tests showed that the isolates were generally highly resistant to amoxicillin (99%) and trimethoprim-sulfamethoxazole (95%) and less resistance to amikacin (14%) and ciprofloxacin (19%). Also there are increased antimicrobial agent resistance to different bacteria, Escherichia coli shown 100% resistance to Ampicillin and Amoxicillin and 97% to Trimethoprim-sulfamethoxazole as shown by prior studies which have shown increasing rates of resistance to Ampicillin, trimethoprim-sulfamethoxazole, and first-generation cephalosporins (Gupta et al 1999). When compared with previous study done in Dar es Salaam, there is slight increase in resistance to specific antibiotics as shown in results of a study done in Tanzania which revealed that, among E. coli in urinary tract infections, more than 80% are currently resistant to ampicillin, cotrimoxazole and tetracycline while more than 80% of the isolates are still susceptible to nitrofurantoin, gentamicin and third generation cephalosporins (Urassa et al 1997).

This also is in consistent with the data previously reported from a study done in Muhimbili whereby more than 80% of Escherichia coli were resistant to ampicillin (Bloomberg et al, 2005), this could possibly be as a result of extensive use or misuse of the drugs by the correspondents since the drugs are commercially available, however this could not be proven in this study.

This result concludes the empirical treatment of UTI should be done with amikacin and ciprofloxacin, and to a lesser extent nitrofurantoin, which is not the case in the Country where the first line

treatment for UTI in children is trimethoprim-sulphamethaxazole, amoxicillin, ampicillin, gentamicin and Nitrofurantoin, (MOHSW-NEMLIT, 2007)

This study shown purchasing drugs from private medical stores, 44 (24.4%) and the habit of parents to give their children antibiotics at home (Self medication) prior to onset of fever symptoms 188 (69.6%) before attending hospital. Although self medication behavior shown no statistical significant association with the development of multiple drug resistance as revealed in this study, health education to community is needed, also reinforced guidelines on selling of antibiotics in irrelevant medical stores. Self- medication is very common in many developing countries (Okeke et al, 1999). In a study done in Kenya, it was found that about 64% of all antibiotics sold by the chemists were without prescriptions from a doctor (Indalo, 1997). Due to lack of control, broad-spectrum antibiotics can be found being sold freely over the counter and even at open market places (Kunin et al, 1987, Okeke et al, 1999). Some antibiotics being sold are often of substandard qualities; these are therefore cheap and thus preferred by many people (Okeke et al, 1999). Also this study show more than 149 (55%) of the parents complete primary education, while 32 (11.9%) had no formal education; this is significant proportion of ignorance within the community. Ignorance and poverty are other contributing factors such that some patients stop taking medication before completing recommended dose when they cannot afford the full dose (Okeke et al, 1999, Kunin et al, 1987).

The study also revealed that there is no significant difference (OR 1.077) on the risk of getting urinary tract infection on sex and age of children.

Conclusion and Recommendation

Conclusion

The study revealed that there is a reasonable increase in antimicrobial agent resistance to different bacteria, Escherichia coli shown 100% resistance to Ampicillin and Amoxicillin also 97% to Trimethoprim-sulfamethoxazole which are the first line antibiotic for treatment of UTI in Tanzania and commonly used antibiotics in the community. These drugs are mostly purchased from private unregistered medical stores and administered empirically, thus reflects to be the problem of public health importance, proper guideline is needed to ensure proper use of antibiotics to reduce the drug resistance burden.

In view of the high drug resistance amongst bacteria, (95 – 98%), therapy should only be advocated, as far as possible, after culture and sensitivity has been performed. This would not only help in the proper treatment of the patients but would also discourage the indiscriminate use of the antibiotics and prevent further development of bacterial drug resistance.

Based on the results of this study, the empirical treatment of UTI should be done with amikacin and to a lesser extent nitrofurantoin

Awareness of the community on health related matters is a crucial need that if developed will build their capacity on understanding the importance of acquiring appropriate drugs from appropriate suppliers and appropriate usage. This should be associated with legal guidelines to control sales of antibiotics in unauthorized medical stores and without prescriptions of a doctor.

Recommendations

Based on the study findings, it is recommended that there should be deliberate efforts to ensure that information on antimicrobial resistance patterns is updated regularly to ensure appropriate treatment is given to patients by avoiding the use of resistant antimicrobial agents.

There is a need for health education to the community on the proper use of antibiotics and adherence to the hospital prescribed dosage to reduce resistance and disease recurrence burden in the community

In this era of antimicrobial resistance there should be efforts for development of appropriate prescribing policy that will stipulate guidelines to be followed by clinicians for management of uropathogens infections; this will ensure the evidence based medicine by the use of laboratory results instead of empirical treatment.

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