Prevalence patterns of bacterial urinary tract infections among febrile children under-five years of age at Kampala International University Teaching Hospital

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Susceptibility patterns of bacterial urinary tract infections among febrile children under-five years of age at Kampala International University Teaching Hospital

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ABSTRACT

A reliable diagnosis of UTI in children is critical because they are usually underdiagnosed or over-diagnosed especially in children under five years of age. Antimicrobial susceptibility results are key to effective intervention. This study was done to determine the prevalence, predictors, and susceptibility patterns of bacterial urinary tract infections among febrile children aged less than 5 years presenting at Kampala International University Teaching Hospital. A hospital-based cross-sectional study was conducted in entry points of the pediatric ward of KIU-TH between December 2020 and March 2021. The study enrolled a total of 350 children 2-59 months by consecutive enrolment. Urinalysis and urine culure was done, clinical and demographic data was collected using questionnaires and data analysed using SPSS version 27 with significance at 95% confidence interval. Isolates had a sensitivity pattern to Imipenem of 93.4%, Ciprofloxacin (85.4%), Amikacin (77.4%) and were extremely resistant to Cotrimoxazole (83.3%), Amoxicillin (80.0%) and Ampicillin (74.4%). There is a high resistance to commonly used antibiotics thus need to review the treatment protocols of UTI.
Keywords: Susceptibility patterns, bacterial, urinary tract and infections.

INTRODUCTION

During the ancient days in Babylon, diagnosis of UTIs was made by visual inspection of the colour and cloudiness of urine and in the 20th century diagnosis was transformed by the use of assays for white cell and bacterial counts in urine [1]. Almost 100 years ago, the nitrite test was developed [2] but had a limitation of inability to identify the pathogen because it measures the conversion of dietary nitrate to nitrite by Gram-negative bacteria, currently its used as a screening test where a positive nitrite test makes UTI very likely but the test may be falsely negative if the bladder is emptied frequently or if an organism that does not metabolize nitrate (including all Gram-positive organisms) is the cause of infection.

At the beginning of the 20th century, urine culture proved valuable in diagnosis of UTIs [1] and use of antimicrobial agents such as hexamine, pyridium, hexylresorcinol and mercurochrome was recognized [3; 4]. During the first half of the twentieth century, penicillins were introduced but had limited effectiveness in management of UTIs [5; 6]. In 1937, sulfanilamide ushered the era of antimicrobial therapy which was effective in management of several types of UTIs such as cystitis and pyelonephritis but poor for different bacterial isolates and in 1953, nitrofurantoin was introduced which was a safe and more effective antibiotic for UTI and was an antimicrobial agent with good activity against *E. coli*, and a more favourable tolerability and had safety profile than sulphanilamide [7]. Since then different antimicrobial agents such as Cephalosporin and augmented Penicillin have been developed and this has led to great improvement in management of UTIs in children.

During the past 30–50 years, the natural history of UTIs in children has evolved as a result of the introduction of antibiotics and significant improvements in health care [8]. Earlier guidelines for paediatric UTIs advocated for extensive imaging and

aggressive treatment [9], but this is not the case today. Worldwide, resistant bacterial strains are increasing at an alarming rate replacing almost all susceptible bacterial populations especially when compared with antibiotic resistance which was virtually zero three decades ago [10]. Until recently, this increasing trend in antimicrobial resistant infections in infants and children has been relatively unrecognised.

AIM OF THE STUDY

The aim of this study was to determine the susceptibility patterns of bacterial urinary tract infections among febrile children aged less than 5 years presenting at Kampala International University Teaching Hospital.

Specific objective

To describe the susceptibility patterns of bacterial isolates of urinary tract infections among febrile children aged < 5 years presenting at Kampala International University Teaching Hospital.

Research questions

What are the susceptibility patterns of bacterial isolates of urinary tract infections among febrile children aged < 5 years presenting at Kampala International University Teaching Hospital?

METHODOLOGY

Study design

This was a hospital-based cross-sectional descriptive and analytical study to determine the prevalence, describe susceptibility patterns of bacterial isolates and predictors of UTIs among febrile children aged 2 to 59 months presenting at Kampala International University Teaching Hospital. The study was conducted at all entry points of paediatric patients in the hospital; out-patient clinic and A and E, where all eligible children age 2 to 59 months with fever or history of fever were enrolled into the study. Informed consent was sought from the caregiver, then data was collected by use of paper-based investigator-administered questionnaire that was designed in English and translated in Runyankole, based on the problem statement and objectives. Urine samples were collected for urinalysis and culture and bacterial uropathogen susceptibility patterns described as explained in the details below.

Study site

The study was conducted on the Pediatrics outpatient and A and E department/all entry points of KIU-TH which is a university teaching hospital located in Ishaka- Bushenyi municipality approximately 319.7km from Kampala, on Kampala-Mbarara-Kasese highway, 60 km west of Mbarara. KIUTH is private not for profit hospital and one of the general hospitals in western Uganda started in 2008. It is a specialized hospital with the following departments: Pediatrics, Internal medicine, Surgery, Obstetrics and Gynecology, and other specialized clinics with a bed capacity of 700 with a fully functional laboratory (level III) with microbiology, chemistry, hematology and pathology unit departments. The microbiology unit of KIU-TH offers diagnostic bacteriology,mycology,parasistology,virology and mycobacteriology and contains major equipements such as autoclave sterilizers, cell culture incubators, light microscopes, refrigerators, busern burners among others and the chemistry offers both sample preparation and analysis and the major equipments include a centrifuge, spectrometers, dry ovens and other minor apparatuses used. The facility serves as a tertiary point of care for referrals from lower facilities in the districts of Mitooma, Sheema, Rubirizi and Ntungamo. The Paediatric outpatient department receives an average of 350 patients monthly and it is managed by a Pediatrics specialist, a senior house officer, an intern doctor and a nurse on a daily basis.

Target population

Febrile children aged 2 to 59 months attending to KIU-TH.

Study population

All febrile children aged 2 to 59 months attending the paediatric outpatient clinic/all entry points of KIU-TH. Children were considered to be febrile if axillary temperature was $\geq 37.5^0$C and this was put into consideration because of easy infection control and axillary temperature is $0.5\,^0$C less than rectal temperature which is 38.0^0C

Study duration

This study was conducted over a period of three months from December 2020 to March 2021.

Sample size determination

To determine the prevalence [11] was used

$$N = \frac{z^2 \rho (1-\rho)}{r^2}$$

N= desired sample size

Z= Standard normal deviate (1.96 for a 95% confidence interval)

P= Proportion of children <5 years diagnosed with a UTI [12], in a cross-sectional study done at Nsambya hospital found a prevalence of 26.8% among children <5 years presenting with fever.

r= the acceptable margin of error (0.05)

Sample size = 302

To estimate the sample size for the predictors of UTIs, the method for calculating sample size for two proportions(Kelsey's formula) was employed and a study by [13] in Tanzania using age as predictive factor for UTIs found a percentage of 45.2%(P1) for children below 2years and Percentage 30.7(P2) for children above 2 years

$$n = \frac{(Z_1 + Z_2)^2 \, 2P(1-P)}{(P_2 - P_1)^2}$$

Where;

Z1 is Z value at 95% level of significance = 1.96,

Z2 is Z value at 80% power = 0.84,

P1 is proportion of patient with UTI among patients below 2 years=45.2%

P2 is proportion of patient with UTI among patients above 2 years=30.7%

$$P = \frac{(P_1 + P_2)}{2}$$

Sample size = 350.

The sample size calculated (350) was more than the sample size for the prevalence so 350 was used, which is the bigger of the two sample sizes.

Selection criteria

Inclusion criteria

All children from 2-59 months presenting with history of fever or axillary temperature of ≥37.5°C at the paediatric outpatient clinic/all entry points of KIU-TH.

Exclusion criteria

Children with a contraindication to urethral catheterization were also be excluded such as children with hypospadias, evidence of urethral infection, gross hematuria and blood at meatus.
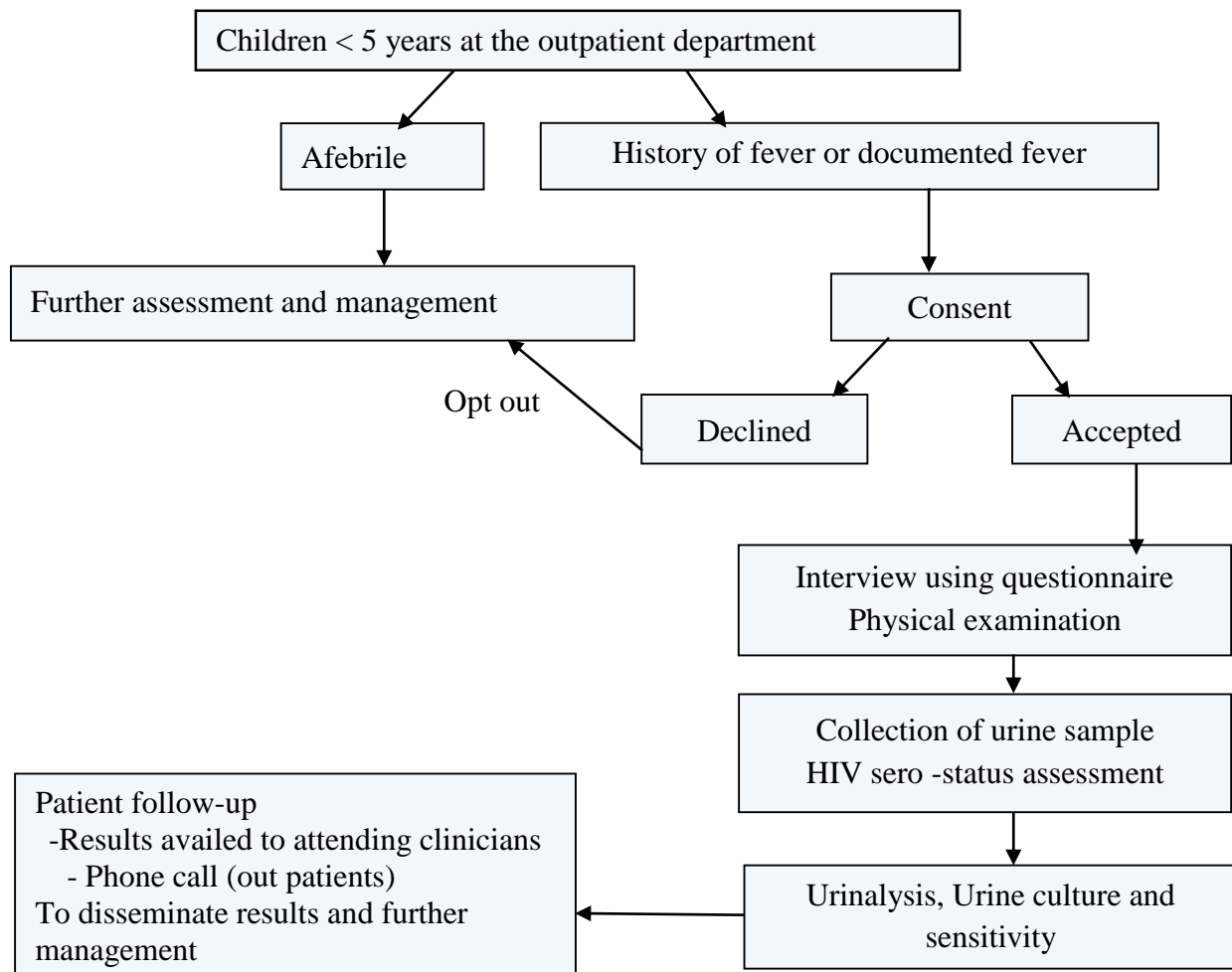
Sampling technique

Consecutive enrollment into the study was done for children who met the inclusion criteria until the desired sample size was obtained.

Study procedure

Identification of study participants and screening for eligibility

At the outpatient clinic KIU-TH, all children age 2 to 59 months with history of fever or fever on examination were enrolled into the study.

Figure 1: Patient flow chart

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            ┌─────────────────────────────────────────────┐
            │  Children < 5 years at the outpatient department │
            └─────────────────────────────────────────────┘
                   │                          │
                   ▼                          ▼
            ┌──────────┐       ┌──────────────────────────────────┐
            │ Afebrile │       │ History of fever or documented fever │
            └──────────┘       └──────────────────────────────────┘
                   │                          │
                   ▼                          ▼
 ┌────────────────────────────────┐      ┌──────────┐
 │ Further assessment and management │     │ Consent  │
 └────────────────────────────────┘      └──────────┘
                   ▲                     │          │
            Opt out │                    ▼          ▼
            ┌──────────┐          ┌──────────┐
            │ Declined │          │ Accepted │
            └──────────┘          └──────────┘
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Interview using questionnaire
Physical examination

Collection of urine sample
HIV sero -status assessment

Urinalysis, Urine culture and sensitivity

Patient follow-up
 -Results availed to attending clinicians
 - Phone call (out patients)
To disseminate results and further management

Validity and Reliability of data collection tools

The questionnaires contained both open and close ended questions and was pretested in a similar study population at KIU-TH in Bushenyi. The pretesting was helpful in obtaining data by a pre-determined questionnaire using the Cronbach's coefficient alpha of more than 0.8 which means that the items of the questionnaire were reproducible and consistent. Standard operating procedures for urethral catheterization and mid-stream urine (MSU) sample collection were followed at all times. Urine samples were stored in a cool box at a temperature of 5ºC-7 ºC and then delivered to the laboratory within one hour of collection. Standard operating procedures for urine culture and antibiotic susceptibility testing were followed and a clinical microbiologist was consulted at all levels of the procedure. The antimicrobial susceptibility tests were performed using the Kirby Bauer disk diffusion technique [14] with commercially available disks on Mueller Hinton agar plates. Antibiotics disks validity were controlled using *E. coli* (ATCC 25922). Run control tests for dipsticks on each new batch and weekly.

Data collection instruments

Patient information including socio-demographic details, physical examination findings and past medical history was obtained upon enrollment using a questionnaire that was designed in English and translated in Runyankole. The children were examined for fever by taking the

axillary temperature using a digital thermometer. Cotton swabs, normal saline, urine sample bottles (50ml) and small sized appropriate urine catheters were used to collect urine samples as described in details below and urine samples which were not processed immediately were kept in a cooler box and processed within one hour for urinalysis and urine culture.

Data collection

Based on the problem statement and objectives. Patients were given information about the study, and then a written consent sought and signed. Predictors including age, sex, place of residence and education level of the caregiver were under social demographics while under medical predictors we had factors such as circumcision, HIV status, malnutrition, exclusive breastfeeding and clinical features which may predict UTI in children included; constipation, diarrhea, vomiting, character of fever (fever of $\geq 39^\circ C$ at the time of recruitment, >24 hours, fever without definite source), sudden onset bedwetting and foul smelling urine in past two weeks. Behavioral predictors included wiping from back to front, toilet training habits, and use of diapers. Laboratory predictors were nitrites, leucocytes and microscopy results. Physical assessment of study participants included taking temperature,checking for oedema and taking anthropometric measurements including MUAC , weight, height, then indices weight for height, height for age and weight for age were compared to the WHO growth standard charts to determine the nutritional status which was classifiesd as moderate or severe malnutrition using under nutrition parameters(wasting,under weight or stunting). The result of MUAC was interpreted as normal, moderately wasted and severely wasted if it is above 12.5cm, between 11.5-12.4 cm, and less than 11.5 cm respectively. Children with bilateral pitting oedema were not assessed for MUAC. The child was regarded as normal if height for age is $\geq$-2 SD, moderately stunted if is $\geq$-3SD to <-2SD and severely stunted if is <-3SD. The child was regarded as normal if weight for age is $\geq$-2 SD, moderately underweight if is $\geq$-3SD to <-2SD and severely underweight if is <-3SD. The child was considered as normal if

the weight-for-length is $\geq$ -2 SD, moderately wasted if is $\geq$-3 SD to <-2SD and severely wasted if is <-3SD. All children with bilateral pitting oedema were not assessed for weight-for-length but were considered as malnourished after ruling out other causes of oedema. The subjects' weight in kilograms was taken using a weighing scale manufactured by SECA®. Before the weight was taken, the subject took off his/her shoes and any heavy clothing. The weighing was calibrated every morning according to the manufacturer's manual, for those who cannot stand, a two in one weighing scale will be used and the caregiver carried the participant. The height was recorded to the nearest 0.1 centimeter. The subject's height was measured using a SECA® wall mount station meter and a tape measure for those who cannot stand. The height was recorded as the maximum distance from the floor to the highest point on the head. Sources of other causes of fever were recorded on the questionnaire according to physical examination findings (clinically) done by the principal investigator and this was refined according to the investigations such as CBC,lumbar punctures,malaria tests, thyphoid tests etc requested by the clinician attending to the patient. However it was a limitation in that the research principal investigator couldn't directly be involved in the decision of the investigations requested.

Urine sample collection

One urine sample was collected on the same day of recruitment of study participants. For children older than two years (toilet-trained children) who were able to follow instructions, a mid-stream (clean catch) was collected. For girls, the labia were spread and the perineum cleansed two to three times with non-foaming antiseptic solution or mild soap and for boys, the meatus was cleansed, The foreskin was retracted before cleaning for those who were uncircumcised. For uncircumcised males, the foreskin was reduced to its normal position so that a paraphimosis does not develop. Midway through urination, voided sample of urine was obtained under the observation of the principal investigator [15; 16]. For children aged less than 2 years and those who were

unable to follow instructions, transurethral catheterization was performed; the child was gently restrained in the supine and frog leg position to permit adequate stabilization of the pelvis and complete visualization of the external genitalia, the anterior urethra was cleansed thoroughly with an antiseptic (povidone-iodine solution) and a sterile lubricant jelly was applied to the end of an appropriately sized catheter (5 French for children younger than six months; 8 French for those between 6-59 months, the catheter was passed through the urethra and into the bladder as follows:For boys, the foreskin of the glans was retracted gently to permit complete visualization of the urethral meatus if the boy was uncircumcised, the urethra was straightened by using the non-dominant hand to hold the penis perpendicular to the lower abdomen. Gentle traction was applied; the catheter was inserted with the dominant hand until urine returns. As the catheter was being advanced, it was palpated along the posterior aspect of the penis. If Resistance was encountered near the base of the penis due to contraction of the external bladder sphincter. This was generally overcome by maintaining traction on the penis, while applying gentle pressure with the catheter. For girls, an assistant often was needed to retract the labia majora, having an assistant lift the labia majora anteriorly, laterally, and cephalad to provide better urethral exposure, Swabbing the introitus and the surrounding area from front with the povidone-iodine solution was done, the catheter was inserted into the urethral meatus until urine comes [17]. About 5ml of urine specimen was collected from each patient in a sterile screw-capped, wide-mouth, leak-proof container and labelled with the unique sample number, date and time of collection. Voided sample of urine was obtained under the observation of the principal investigator or research assistants. Urine samples were taken immediately to the laboratory and samples which were not processed immediately were kept in a cooler box for one hour till when urinalysis and urine culture could be done. One drop was utilized for culture and the remaining sample processed for urinalysis.

Diagnosis of UTIs

This was made based entirely on urine culture results and this study considered a threshold of $\geq 100,000$ CFU/ml (10^5) for mid- stream catch urine and $\geq 10,000$ CFU/ml (10^4) for catheter-collected urine sample for a positive culture test for UTI. Rapid techniques were carried out to predict UTI but not making diagnosis and these included urine dipstick tests for leukocyte esterase and nitrites and standard microscopy as described in detail below.

Urine dipstick and microscopy

Immediately after collection of the urine specimen, it was delivered and processed in the microbiology laboratory at KIU-TH. A spot urine dipstick test (Neotest® urine multistix, Neomedic Ltd, Rickmansworth, UK) was performed to detect leucocyte esterase and nitrites then microscopic examination was performed by centrifugation of urine at 3000 rpm for 3 minutes and thereafter the supernatant was discarded aseptically. The sediment was placed on the slide and a cover slip was applied before being examined under the microscope at 40X objective. An average count of white blood cells (WBC) was taken per number of fields examined. The increased number of leucocytes is mostly observed in urinary tract diseases, and thus presence of ≥ 5 WBCs per hpf (high-power field) was considered positive.

Isolation of bacteria in pure culture

The cysteine lactose electrolyte deficient (CLED) and Chrom Agar were used as selective media for isolation. The media was prepared according to the manufacturer's instructions and 0.001 ml of urine sample was inoculated onto the media using a platinum wire loop. Plates were then incubated for 24 hours at 37°C. Colony counts yielding bacterial growth of 10^4 CFU/ml and 10^5 CFU/ml of urine collected by catherisation and mid stream methods were regarded as significant for bacteriuria respectively [18]. Plates with no growth or tiny colonies were returned to the incubator for another 24 hours before discarding the plates since antimicrobial

treatment or other factors may inhibit initial growth [19].

Colony characteristics, morphology and staining

The shape, size, color, elevation and hemolysis of the colony formed on the culture plate was observed after 24 hours of incubation at 37º C. Gram staining was done to determine the microscopic appearance (for-example clusters, rods or cocci) and gram reaction (positive or negative bacteria) of a stained preparation.

Biochemical characteristics

The following biochemical tests were done to determine chemical changes related to different micro-organisms identified including: Methyl red test, Indole test, Catalase test, Urease test, Citrate utilization test and Triple iron agar.

Triple sugar iron test (TSI)

This test was used in Gram negative colonies. TSI agar had glucose with a 0.1 % concentration and lactose and sucrose with a concentration of 1 %. Sterile TSI slants with agar were taken from the refrigerator and wiped using a dry cotton wool. The cap was removed and then the neck was flamed [19]. An inoculating straight loop was sterilized in the blue flame of the Bunsen burner and then allowed to cool. A colony of the suspected organism from CLED agar was picked, stabbed into the medium up to the butt of the TSI tube and then it was streaked back and forth along the surface of the slant. Again the neck of the TSI was flamed, capped and placed in the incubator for 24 hours at a temperature of 37º C. Triple sugar iron agar tube was used to test for the fermentation of only glucose (yellow butt), fermentation of lactose and sucrose (all over yellow), CO_2 formation (crack in agar), or ferrous ammonium sulphate produced (black precipitate) [19].

Catalase test

This test was used to differentiate suspected *Staphylococci spp.* colonies which appeared with a uniform yellow color. Two drops of 3% hydrogen peroxide was put onto a clean glass slide using a dropper; a pure colony of the organism was picked from CLED agar using a wooden applicator stick [19]. Placing the colony on the hydrogen peroxide on the glass slide; emulsification was done. Observation for bubble formation was done within 30 seconds [19].

Mannitol Salt (MSA) Agar

This tests for the bacteria's ability to tolerate 7% salt concentration and ferment mannitol. The media is selective because it selects for salt tolerant bacteria. It was done following results of catalase test for the confirmation of *S. aureus*. A plate of MSA was inoculated with a discrete colony of the test organism using a sterile wire loop by a streak plate method and was incubated at 37ºC for 24-48 hours. If the organism was tolerant to salt it grew. If the organism was not tolerant to salt it did not grow. If the tolerant organism fermented mannitol, then there were yellow zones around the colonies indicating *staphylococcus aureus*. If the salt tolerant organism could ferment mannitol, then the media would remain pink.

Indole, Methyl Red, Voges-Proskauer and Citrate test (IMVIC) tests

This test was used in organisms suspected to be *E. coli* and *Klebsiella*. Indole test determines the presence or absence of the tryptophanase, an enzyme which breaks down tryptophan [19]. A 1 % Tryptone broth was used during the test [19]. Kovac's reagent was added to the tryptone broth and if indole was present then a red coloration formed at the top indicating the presence of *E. coli* [19]. A MR-VP broth was used to look for mixed acid and butanediol fermenters in the test organisms. One tube was used for each test. Half of the broth, once incubated, was removed and placed into a different tube. Methyl red was added to one tube to see if the pH was neutral (yellow) indicating negative while the development of red colour after addition of methyl red indicated positive, *E. coli* [19]. Barritt's solution (alpha hapthol and potassium hydroxide) was added to the other tube to test the Butanediol fermenters and if the bacteria were butanediol fermenters then the broth turned red indicating *Klebsiella spp.* Citrate test was used to test for the presence of citrate which was the sole source of carbon for bacteria [19]. An agar slant with synthetic medium containing small amounts of mineral salts (citrate and ammonium) was used to perform the test

[19]. Bromothymol blue (pH indicator) was added to the agar slant and if there was growth (presence of citrate) the agar was blue indicating the presence of *Klebsiella spp.* and if there was no growth the agar is green.

Urease test

Urease test was used to determine the bacteria's ability to hydrolyze urea to make ammonia using the enzyme urease. It was conducted by inoculating Urea broth with a sterile inoculating wire loop. ammonia. If ammonia is made, the broth turned a bright pink color, and was positive indicating the presence of *Proteus spp.* If test was negative, broth had no color change and no ammonia was made.

Antimicrobial susceptibility tests

The antimicrobial susceptibility tests were performed using the Kirby Bauer disk diffusion technique [14] with commercially available disks on Mueller Hinton agar plates. Antibiotics disks validity were controlled using *E. coli* (ATCC 25922). This was performed weekly. The agar was poured to a uniform depth of 4 mm and allowed to cool and solidify according to Clinical and Laboratory Standards Institute (CLSI, 2007) and International Guidelines. A 0.5 McFarland turbidity standard was prepared according to the method described by [20]. A solution with 9.95 ml of 1 % chemically pure sulphuric acid was mixed with 0.05 ml of 1.175 % barium chloride to form a barium sulfate precipitate which would cause turbidity. This standard was used to adjust the turbidity of the inoculums for the antimicrobial susceptibility test. Well isolated single colonies were transferred to the tube with sterile saline and suspensions and were compared to 0.5McFarland turbidity. Then the turbidity of the inocula was adjusted, and a sterile cotton swab was dipped into the suspension, and pressed firmly against the inside wall of the tube. The swab was then streaked over the surface of the medium 3 times rotating the plate after each application to ensure an even distribution and was allowed to stand at room temperature for 10 minutes [21].

Antimicrobial disks containing specified concentrations in micrograms were placed on the agar plates after 10 minutes (to allow the agar to dry) using a pair of sterile forceps and then gently pressed down on the agar to ensure contact. The plates were inverted, and incubated at a temperature of 37°C for 24 hours. After incubation the zone diameters with complete inhibition, including the diameter of the disk were measured using a ruler and were recorded in millimeter on the under surface of the plate without opening the lid. The diameter of the zone of inhibition for each antibiotic was measured and interpreted as resistant, intermediate and sensitive according to Clinical Laboratory Standards Institute criteria (2007) and commercially available discs containing commonly prescribed antibiotics were used and the results were recorded as per the manufacturer's instructions. The criteria used to select the antimicrobial agents was based on both their availability for the management of UTIs and their recommendation for use by the World Health Organisation and Clinical Laboratory Standard Institute (CLSI) guideline.

Safety of the environment

All cultured microorganisms were autoclaved, packed and incinerated and the ash was buried to prevent spread of the cultured bacteria.

Data quality control

Pre-testing was done at KIU-TH located in Bushenyi district in western Uganda, using ten (10) questionnaires. This checked if the questions were accurate and easily understandable by the caregivers. The pre-test questionnaires were not included in the data analysis. All research assistants who were involved in data collection during the study period were trained on how to collect a non-contaminated urine sample. Each filled questionnaire was cross-checked for inconsistencies and incompleteness before the interview was terminated.

Data management

Data from completed questionnaires was arranged, summarized and entered using the statistical computer software package, Microsoft Excel 2019. The data was cleaned, checked for errors and corrected, then imported to SPSS for analysis.

Data analysis

Data was analyzed using IBM SPSS 27.0 statistics for windows (Armonk. NY: IBM Corp).

Objective 1: The prevalence of urinary tract Infections was determined as a proportion using frequencies, percentages. This was presented using a pie chart.

Ethical considerations

For the study to be ethical, the following were considered;

Institutional consent

Ethical approval of the research protocol was obtained from the Research Ethics Committee (REC) of Kampala International University, Western Campus (Nr.UG-REC-023/202017). Permission to conduct the study was obtained from the director of KIU-TH as shown in appendices X and XI.

Privacy, confidentiality and non-maleficence

All questionnaires did not have provisions for participant's names, and the interviews were carried out in the side room in the pediatric clinic, to ensure privacy and confidentiality. Collection of urine samples was done from the procedure room near the out-patient clinic. Completed questionnaires were kept under lock and key, only accessible by the Principal Investigator and authorized individuals. Data was kept in password-protected files, where it remained until dissemination and didn't include patient identifiers. There was sensitization and training of research assistants about the study, specifically on urine sample collection procedure to minimize the risks.

Informed consent

Written informed consent was sought from each caregiver and the purpose of the study was well explained to the participants in a language they understood before they started answering the questions. In order to participate in the study, the caregiver was requested to sign a written informed consent document or use a thumb print for those who could not write. A copy of the signed consent form was given to the participant and another copy kept by the Principal Investigator. The consent forms were written both in English and Runyankole, and the participants had a right to decline to participate or withdraw from the study at any time without any penalty.

Respect of individual persons

Participants who declined to participate in the study at whatever stage of the interview were respected and this did not interfere with the quality of medical care that was provided to them.

Benefits and risks

Some participants experienced some pain and discomfort during urethral catheterization, to minimize that, an appropriate size of urethral catheters and a lubricant was used to minimize patient discomfort, pain and urethral trauma which might have occurred during urine sample collection. Least harm was expected during urine sample collection and less invasive procedures were considered; mid-stream urine sample collection method was used for children above to two years and in and out catheterisation for those below 2 years and the smallest appropriate catheters were used to avoid the complications which may have risen if suprapubic catheterisation is used. The results of urine culture and sensitivity were immediately availed and discussed with the clinician and caregiver of each study participant. Those who were found with a UTI were started on effective antimicrobial therapy as per urine culture results. A courtesy call was made to inform patient who had left the hospital premises without their results especially OPD patients.

Dissemination of results

The research findings are to be disseminated to the office of the director of KIU- TH, department of Pediatrics and child health at KIU-TH, and KIU western campus library. The results of this study will also be disseminated to a peer-review journal and presented at scientific conferences

RESULTS

Study participants

A total of 927 children presented to Kampala International University Teaching Hospital from 1st December 2020 to 31th March 2021. Of these, 152 did not fit in the age group (were either below 2 months or

above 59 months) and 419 had no fever or history of fever. Six participants were excluded because four failed produce urine, one had hypospadias, one had local urethral infection 350 participants met the inclusion criteria and were consecutively enrolled into the study. Out of 350, 97 had positive urine culture of a single uropathogen, 250 had no growth on urine culture and 3 had mixed growth on culture.
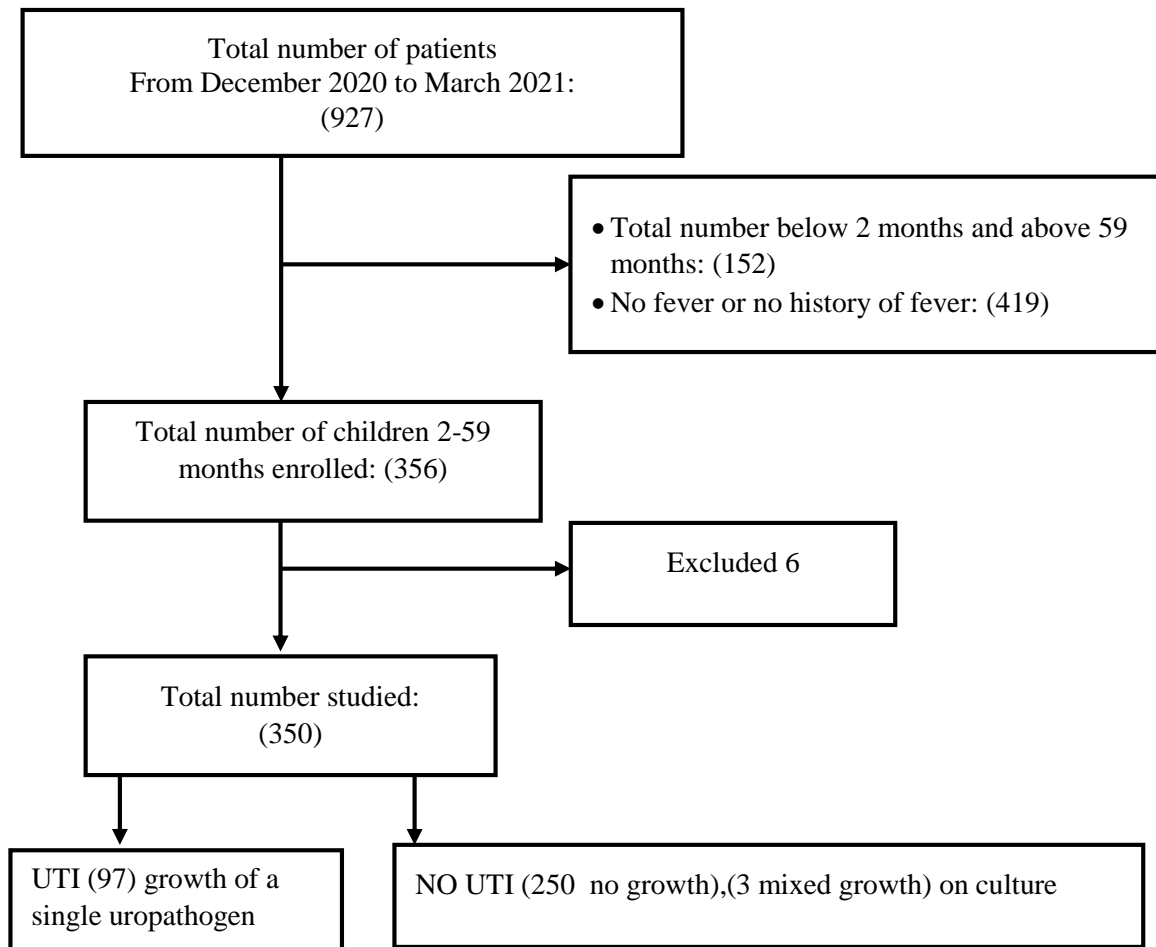
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┌─────────────────────────────────────┐
│   Total number of patients          │
│ From December 2020 to March 2021:   │
│              (927)                   │
└─────────────────────────────────────┘
                │
                │          ┌──────────────────────────────────────────┐
                │────────▶ │ • Total number below 2 months and above 59│
                │          │   months: (152)                          │
                │          │ • No fever or no history of fever: (419)  │
                │          └──────────────────────────────────────────┘
                ▼
┌─────────────────────────────────────┐
│  Total number of children 2-59      │
│   months enrolled: (356)            │
└─────────────────────────────────────┘
                │
                │          ┌──────────────────────┐
                │────────▶ │     Excluded 6        │
                │          └──────────────────────┘
                ▼
┌─────────────────────────────────────┐
│   Total number studied:             │
│              (350)                   │
└─────────────────────────────────────┘
         │                    │
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┌──────────────────┐  ┌──────────────────────────────────────────────┐
│ UTI (97) growth  │  │ NO UTI (250 no growth),(3 mixed growth) on    │
│ of a single      │  │ culture                                       │
│ uropathogen      │  │                                               │
└──────────────────┘  └──────────────────────────────────────────────┘
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Figure 1. Study profile.

Baseline characteristics of study participants

Socio-demographic characteristics

Out of 350 children, more than half of study participants were aged less than 24 months of age, 208(59.4%). Study participants were aged 2 to 59 months with the overall mean age of 10.13 ± 1.44 months, that for children with no UTI was 14.10 ± 1.26 months while that of children with UTI was 8.21 ± 1.63 months, majority of the study participants were males 224(64%). and other socio-demographic characteristics of the participants were distributed as shown in table 1 below.

Table 1. Baseline socio-demographic characteristics of study participants

Variable	Frequency	Percentage
Age		
< 24 months	208	59.4
≥ 24 months	142	40.6
Sex		
Female	126	36.0
Male	224	64.0
Residence		
Urban	153	43.7
Peri-urban	86	24.6
Rural	111	31.7
Education level of care giver		
Utmost primary	156	44.4
Secondary	98	28.2
Tertiary	96	27.4

Medical characteristics,clinical presentation and behavioural characteristics of participants

Most of the study participants had a known source of fever 262 (74.9%) and of the 350 participants, 230(65.7%) had fever for less than 24 hours. Almost one third of the study participants were undernourished 105(30.0%). More than two thirds of the study participants were using diapers 257(73.4%). Other baseline clinical presentation, bevavioural and medical characteristics of study participants are detailed in Tables 2 and 3 below.

Table 2. Baseline medical characteristics and clinical presentation of study participants

Variable	Frequency	Percentage
Circumcision		
No	185	82.6
Yes	39	17.4
Undernutrition		
No	245	70.0
Yes	105	30.0
Exclusive breastfeeding		
No	196	56.0
Yes	154	44.0
Constipation		
No	326	93.1
Yes	24	6.9
Diarrhoea		
No	205	58.6
Yes	145	41.4
Vomiting		
No	169	48.3
Yes	181	51.7
Foul smelling urine		
No	243	69.4
Yes	107	30.6
Duration of fever		
< 24 hours	120	34.3
≥24 hours	230	65.7
Intensity of fever		
< 39°C	232	66.3
≥39°C	118	33.7
Source of fever		
Unknown	88	25.1
Known	262	74.9
Sudden bed wetting		
Yes	258	73.7
No	92	26.3
HIV		
Negative	346	98.9
Positive	4	1.1

Table 3. Baseline Behavioural characteristics of study participants

Variables	Frequency	Percentage
Wiping from back to front		
No	136	38.9
Yes	214	61.1
Toilet training		
No	218	62.3
Yes	132	37.7
Use of diapers		
No	93	26.6
Yes	257	73.4

Urinalysis laboratory predictors of the participants

The urinalysis predictive parameters were distributed as shown in table 4 below.

Table 4. Baseline urinalysis laboratory predictors of study participants

Variable	Frequency	Percentage
Leucocyte esterase		
Absent	278	79.4
Present	72	20.6
Nitrites		
Absent	295	84.3
Present	55	15.7
Microscopy		
< 5 WBC/hpf	256	73.1
≥ 5 WBC/hpf	94	26.9

Bacterial isolate and their Susceptibility patterns

Bacterial isolates

Gram negative microorganisms were the most commonly isolated, with *E. coli* being the predominant (56.7%) and among the gram positives isolated, *enterococcus* was the most common (4.1%) and other isolated uropathogens are shown in table 5.

Table 5:Table showing bacterial isolates frequency and percentage

Bacterial isolate	Frequency	Percentage
E. coli	55	56.7
Proteus spp	17	17.5
Klebsiella spp	10	10.3
Enterococcus fecalis	4	4.1
Enterobacter spp	3	3.1
Citrobacter spp	2	2.1
Pseudomonas spp	1	1.0
Staphylococcal saprophyticus	2	2.1
Staphylococcal aureus	3	3.1
Total	97	100.0

Susceptibility patterns of Bacterial isolates

The sensitivity of isolated organisms to the commonly used antibiotics including Gentamicin, Ampicillin, Azithromycin, Ceftriaxone, Amikacin, Cefixime, Amoxiclav, Ciprofloxacin, Amoxicillin, Cephalexin, Nitrofurantoin, Cotrimoxazole and Imipenem was assessed. Generally, isolated uropathogens were highly sensitive to imipenem (93.4%), Ciprofloxacin (85.4%), Amikacin (77.4%), Amoxiclav (58.6%), Gentamicin (50.6%), and Ceftriaxone (43.4%) in that order. On average, the highest resistance observed was to Cotrimoxazole (83.3%), Amoxicillin (80.0%) and Ampicillin (74.4%). The study findings show that majority of the bacterial isolates demonstrated multiple drug resistance to first line antibiotics used in our settings including: Ampicillin, Cotrimoxazole, Amoxicillin, Cephalexin and Ceftriaxone with Pseudomonas Spp demonstrating the highest resistance profile. Sensitivity and resistance patterns of isolated uropathogens to commonly used antibiotics is shown in table 6 and 7 respectively with a full antibiotics susceptibility profile showing uropathogens with intermediate pattern shown in appendix VII.

Table 6. A table showing bacterial isolates sensitivity to commonly used antibiotics

	E.coli (n=55)	Proteus (n=17)	Klebsiella (n=10)	Pseudomonas (n=01)	S. aureus (n=03)	Enterococcus fecalis (n=04)	Enterobacter (n=03)	Citrobacter(n=02)	S. Saprophiticus (n=02)	Average sensitivity(%)
Gentamicin	56.4	82.4	50.0	0.0	66.7	50.0	100.0	50.0	0.0	50.6
Ampicilin	12.7	0.0	0.0	0.0	33.3	0.0	0.0	0.0	0.0	5.1
Azythromicin	34.5	52.9	90.0	0.0	33.3	50.0	0.0	0.0	0.0	29.0
Ceftriaxone	74.5	29.4	70.0	0.0	66.7	50.0	0.0	0.0	100.0	43.4
Amikacin	83.6	88.2	100.0	0.0	100	75.0	100.0	50.0	100.0	77.4
Cefixime	47.3	11.8	70.0	0.0	33.3	50.0	0.0	0.0	0.0	23.6
Amoxiclav	72.7	76.5	70.0	0.0	100.0	75.0	33.3	0.0	100.0	58.6
Ciprofloxacin	92.7	94.1	90.0	100.0	66.7	75.0	100.0	50.0	100.0	85.4
Amoxicillin	3.6	0.0	0.0	0.0	33.3	0.0	0.0	0.0	0.0	4.1
Cephalexin	20.0	0.0	50.0	0.0	33.3	50.0	0.0	0.0	50.0	22.6
Nitrofurantoin	89.1	0.0	0.0	0.0	66.7	25.0	0.0	0.0	0.0	20.1
Imipenem	96.4	94.1	100.0	100.0	100.0	100.0	100.0	50.0	100.0	93.4
Cotrimoxazole	1.8	0.0	0.0	0.0	33.3	25.0	0.0	0.0	0.0	6.7

Table 7. A table showing resistance of bacteria isolates to commonly used antibiotics

	E. Coli (n=55)	Proteus (n=17)	Klebsiella (n=10)	Pseudomonas (n=01)	S. aureus (n=03)	Enterococcus fecalis (n=04)	Enterobacter (n=03)	Citrobacter(n=02)	S. Saprophiticus (n=02)	Average resistance (%)
Gentamicin	32.7	5.9	0.0	0.0	0.0	25.0	0.0	50.0	50.0	18.2
Ampicilin	87.3	94.1	80.0	100.0	66.7	75.0	66.7	0.0	100.0	74.4
Azythromicin	12.7	0.0	0.0	100.0	66.7	0.0	0.0	100.0	0.0	31.0
Ceftriaxone	14.5	11.8	0.0	100.0	33.3	50.0	66.7	50.0	0.0	36.3
Amikacin	14.5	5.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.3
Cefixime	36.4	70.6	10.0	100.0	33.3	0.0	66.7	100.0	50.0	51.9
Amoxiclav	20.0	11.8	10.0	100.0	0.0	25.0	33.3	50.0	0.0	27.8
Ciprofloxacin	7.3	0.0	0.0	0.0	33.3	0.0	0.0	0.0	0.0	4.5
Amoxicillin	96.4	35.3	80.0	100.0	33.3	75.0	100.0	100.0	100.0	80.0
Cephalexin	63.6	94.1	20.0	100.0	0.0	25.0	66.7	100.0	0.0	52.2
Nitrofurantoin	9.1	64.7	70.0	100.0	0.0	50.0	100.0	0.0	0.0	43.8
Imipenem	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Cotrimoxazole	96.4	88.2	90.0	100.0	100.0	75.0	0.0	100.0	100.0	83.3

DISCUSSION

Bacterial isolates and their susceptibility patterns

In conformity with many other studies, many cases of UTIs in this study were attributable to Gram negative uropathogens with *E. coli* being the predominant (56.7%), followed *by proteus* (17.5%). A study by [22] in Ethiopia found that Gram-negative bacteria were the predominant etiologic agents of UTIs in children and *E. coli* was the most frequently occurring pathogen (54.88%), followed by *S.aureus* and *P.aeruginosa* (9.75% for both), *P.vulgaris* (4.88%) and *Enterococcus spp* (3.66%). In the study by [13] in Tanzania, *E. coli* (43.5%) and *Klebsiella pneumoniae* (35.4%) were the most common isolated bacteria. In the Democratic Republic of Congo [23] found that *Proteus mirabilis* was the main Gram-negative bacteria causing UTI (41.2%), followed by *Pseudomonas aeruginosa* (23.5%), *E. coli* (12.8%), *Citrobacter* (8.8%, and *Yersinia enterocolitica* (2.9%). Among the Gram-positives isolated, in our study, *Enterococcus species* (17.6%) was the most predominant, followed by *Enterococcus fecalis* (2.9%), and *Staphylococcus species* (2.9%). The discrepancy in the aetiological causes or order of the commonly isolated uropathogens in a few different studies could be because of the different age groups studied and different characteristics of these participants. However, *E. coli* remains the predominant aetiological cause of UTIs in children in most studies.

In line with antimicrobial susceptibility profiles, the highest resistance was recorded with Cotrimoxazole. All the 9 bacterial isolates were resistant to

Cotrimoxazole with an average resistance of 83.3%. According to previous studies in developing countries, a high rate of resistance to Cotrimaxazole was reported in several studies ranging from 80-100% such as [24] (83.9%), Msaki et al (97 %) and Ojambo 2012 (92.4 %) which was in line with this study.

On the other hand, lower resistance rates were reported with Cotrimoxazole in developed countries where in Belgium, [25] and in Turkey, [26] reported resistance of 38% and 58% respectively. This discrepancy could be attributed to wide use of Cotrimoxazole for simple bacterial infections and prophylaxis in immunosuppressed patients in the developing countries and also to the fact that bacteria undergo mutation which makes their susceptibility vary from one geographical region to the other. A high resistance to ampicillin and amoxicillin of 74.4% and 80.0% respectively was also reported in this study which was slightly lower than that reported by other studies; [24] (100% for ampicillin,87.9% amoxicillin), [27] (91.2% for Ampicillin. [12] also reported significant resistance to all the three antibiotics (Cotrimoxazole, Ampicillin and Amoxicillin). Although resistance was high, the percentage of resistance in this study is lower than that of other studies, this slight difference may be because of the different prescription practices in different hospital settings hence organisms develop resistance to the commonly prescribed drugs.

Generally, Isolates were susceptible to Imipenem (93.4%), Ciprofloxacin (85.4%), Amikacin (77.4%), Gentamicin (50.6%), Amoxiclav (58.6%), and Ceftriaxone (43.4%). This is in line with previous studies showing a high sensitivity pattern for both Imipenem and Ciprofloxacin; [28] in Tanzania (imipenem 100%, Ciprofloxacin 91.2%, Ceftriaxone 73.5%), [27,28,29,30] in Uganda (Ciprofloxacin 73.8%, Ceftriaxone 93.2%). This study also reveals comparable results as a study done in Nigeria by West and colleagues 2019, where Amoxiclav and Ciprofloxacin showed high sensitivity patterns. However, there is a noted disparity in sensitivity pattern of Ceftriaxone of 43.4% in this study and could be due to increased indiscriminate use of Ceftriaxone in management of bacterial infections and its inbuilt potential to develop resistance.

CONCLUSION

There was high resistance to the first line antibiotics used in management of UTIs our setting with pseudomonas demonstrating the highest resistance profile and isolated uropathogens were highly susceptible to Imipenem, Ciprofloxacin, and Amikacin, averagely susceptible to Gentamicin and Amoxiclav and highly resistant to Cotrimoxazole, Amoxicillin and Ampicillin.

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