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Patterns of Antibiotic Resistance in Children Hospitalized with Urinary Tract Infection in a Teaching Hospital in South-West Nigeria

[1]Adeyemo A.T.,[2]Ojewuyi A.R., [3]Odeyemi A.O., [4]Adeyemo A.T., [5]Olumakinde T.S., [4]Akokhia A.O., [6]Bolaji O. S., Adekunle O.C.[6], [7]Hassan A.O.

[1]Department of Medical Microbiology and Parasitology, UNIOSUN Teaching Hospital, Osogbo, Nigeria. Email- adeyemoat@gmail.com, [2]Department of Medical Microbiology and Parasitology, College of Health Science, Osun State University, Osogbo, Nigeria. Email- ojewuyia@gmail.com, [3]Department of Paediatrics and Child Health, College of Health Science, Osun State University, Osogbo, Nigeria. Email- bimbolaodeyemi@uniosun.edu.ng, [4]Department of Medical Microbiology and Parasitology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria. Email- adeyemiadeyemo3@gmail.com, [5]Multidisciplinary Research Laboratory, Osun State University, Osogbo, Nigeria. Email- taiwo.olumakinde@uniosun.edu.ng, [6]Department of Medical Microbiology and Parasitology, College of Health Science, Osun State University, Osogbo, Nigeria. Oloyede.bolaji@uniosun.edu.ng, [7]Department of Medical Laboratory Science, Achievers University, Owo, Nigeria. Email- hassan4ever2006@yahoo.com

Corresponding Author: Dr A.T. Adeyemo;adeyemiadeyemo3@gmail.com

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Corresponding Author:
Adeyemi Temitayo Adeyemo

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ABSTRACT

Background: Efforts at effective treatment of urinary tract infection (UTI) have been largely compromised by evolution and spread of antibiotic resistance in the causative pathogens leading to restricted therapeutic options. This study aimed to determine the burden of antibiotic drug resistance in UTI among hospitalized paediatric patients in a university teaching hospital in Nigeria.

Methods: It is a descriptive cross-sectional study in which 250 hospitalized paediatric patients with features of UTI were consecutively recruited at UniOsun Teaching Hospital Osogbo from March to September 2022. Appropriately collected urine samples were processed by standard microbiological methods and antibiotic susceptibility test according to guidelines.

Results: One hundred and sixty-three bacteria were isolated from 250 urine samples showing predominance of Gram-negative bacilli (GNB) 137 (82.5%). The common bacterial isolates were Escherichia coli (43, 25.9%), Klebsiella species (23, 13.9%), Proteus species (19, 11.4%), Citrobacter species (16, 9.6%), Enterobacter species (15, 9.0%) and Staphylococcus aureus (15, 9.0%). The uropathogens showed high resistance to first- and second-line antibiotics; GNB particularly showed alarming rates to trimethoprim-sulfamethoxazole (77.0%), gentamicin (51.8%), amoxicillin-clavulanate (47.6%), third and fourth generation cephalosporins (39.4- 46.8%) and fluoroquinolones (44.5-47.4%). Overall rate of multidrug resistance (MDR) among the pathogens was 54.6% with common phenotypes being Extended-spectrum beta-lactamase-producing GNB (31.4%, 43/137), AmpC beta-lactamase-producing GNB (25.5%, 35/137), Carbapenemase-producing GNB (8%, 12/137), and methicillin-resistant Staphylococcus aureus (40%, 6/15).

Conclusions: High rates of antibiotic resistance is observed among pathogens of UTI in children highlights a need to curtail inappropriate use of antimicrobials which is the most important driver of AMR.

Key words: UTI, Children, Antibiotic-resistance, Uropathogen, Nigeria

1. INTRODUCTION

Urinary tract infection (UTI) is among the common infections in childhood and it is one of the reasons for paediatric consultations and hospital admission.[1] It is a common indication for antibiotic use in children, particularly in developing countries, most of these children receive antibiotics empirically without the knowledge of causative organism and their antibiotic susceptibility. UTI in children typically has a bimodal age peak with one in the first year of life and the second between ages 2 and 4 years which corresponds to the age of toilet training.[1,2] UTI is by far more common in girls; it is estimated that 7.8% of girls and 1.7% of boys will have had UTI by the age of 7 years, and 11.3% of girls and 3.6% of boys will have had UTI by the age of 16 years.[2-4]

Bacterial pathogens of UTI in children are diverse and are commonly from intestinal flora with Escherichia coli being the leading accounting for 80-90%, other important bacterial genera include Klebsiella, Enterobacter, Proteus, Citrobacter, Serratia, Pseudomonas, Enterococcus and Staphylococcus.[1] Streptococcus agalactiae is relatively more common in neonatal age group and early infant-

Table 2: Clinical Characteristics of In-Patients (n is 250 Unless Otherwise Stated)

Clinical Patameters	Frequency	Percentage
Admitting Ward		
Neonatal Ward	37	14.8
Children's Ward	121	48.4
Surgical Ward	23	9.2
Emergency Ward	67	26.8
Intensive Care Unit	2	0.8
Comorbidities		
Sepsis	66	26.4
Congestive cardiac failure	19	7.6
Infective endocarditis	4	1.6
Haematologic malignancy	5	2.0
Chronic glomerulonephritis	3	1.2
HIV infection	10	4.0
Pulmonary tuberculosis	6	2.4
Pneumonia	53	21.2
Type I diabetes mellitus	3	1.2
Prematurity	14	5.6
Meningitis	27	10.8
HBSS with VOC	13	5.2
Hydrocephalus	9	3.6
Congenital heart diseases	4	1.6
Malaria	89	35.6
Duration of Hospital Stay (n= 239) *		
<1 Week	117	49.0
1 Week – 1 Month	88	36.8
>1 Month	34	14.2
Duration of Antibiotic Treatment (n=242)†		
1-3 Days	23	9.5
4-7 Days	93	38.4
8-14 Days	87	36.0
15-30 Days	30	12.4
>1 Month	9	3.7
Undergone non-urologic surgery	16	6.4
Antibiotic use in the past 1 month before admission	179	71.6
Outcomes of treatment of UTI (n= 221)‡		
UTI resolved without complication	169	76.5
Complicated with sepsis	43	19.5
Died of UTI or its complication	9	4.1

*HBSS-Haemoglobin SS, VOC-Vaso-Occlusive Crisis, *Indicating number after excluding patients who were discharged against medical advice, †Indicating total number after excluding patients who were still on antibiotics when they discharged against medical advice, ‡Indicating total number after excluding patient who died from non UTI-related condition and those who were discharged against medical advice before UTI symptoms re-*

Table 1: Demographic Characteristics of Patients (250 Hospital-

Age	Male	Female	Total
1-28 Days	12 (46.2%)	14 (53.8%)	26
1 Month- 1 Year	13 (40.6%)	19 (59.4%)	32
1-5 Years	21 (39.6%)	32 (60.4%)	53
5-10 Years	31 (53.4%)	27 (46.6%)	58
10-14 Years	42 (51.9%)	39 (48.1%)	81
Total	119 (47.6%)	131 (52.4%)	250

hood while Staphylococcus saprophyticus is seen more among sexually active female adolescents.[1,5,6]

Resistance of uropathogens to antibiotics is increasing and the common predisposing factors are prior antibiotic exposure, urinary malformations as well as use of prophylactic antibiotics for a prolonged period.[7] The most important driver of antimicrobial resistance (AMR) among UTI cases is overuse and misuse of antibiotics in form of indiscriminate and widespread use in hospitals and communities, and high empiric use for treatment of patients due to lack of culture results.[8] Excessive use of antibiotics for UTI is a global problem, in the United States for example, up to 15% of antibiotics prescribed in the communities are for treatment of UTI with the situation likely to be worse in resource-constrained developing countries where access to antibiotics is largely unrestricted.[9,10] Emergence and spread of multidrug resistant uropathogens have a serious impact on effective treatment of UTI, the bugs cause huge therapeutic difficulties leaving little options of highly expensive drugs which are often toxic to vital organs. In some occasion, the available option for patients is polymyxin (colistin) which is highly toxic to kidneys and can only be safely giving topically by bladder irrigation with reduced efficacy.[11] The inability to identify patients with resistant organisms leads to inappropriate treatment with grave implications; renal scarring is most likely to occur in young children, and delayed treatment is an additional risk.[12]

Antibiotic use for UTI is mostly unguided in our environment and this promotes selective pressure and evolution of MDR infection. The situation is made worse by the unspecific nature of clinical presentations and general tendencies to by-pass routine laboratory testing in cases of UTI in paediatric age group due to several factors including social and financial. This study sought to elucidate the resistance profile of bacterial agents of UTI as well as burden of MDR UTI in paediatric patients. This was aim of promoting rational use of antibiotics and putting up efforts at mitigating and preventing emergence drug-resistant UTI.

2. METHODOLOGY

2.1 Study Design

It is a descriptive cross-sectional study carried out from March 2022 to September 2022

2.2 Study Population

Two hundred and fifty hospitalized children with clinical features of Urinary tracts infection were recruited consecutively at UniOsun Teaching Hospital Osogbo, Osun State, Nigeria.

2.3 Data Collection

Patients' clinical and socio-economic information was collected directly form care-giver and patients' clinical records with the aid of proforma. Informed consent was taken from the parents or care givers.

2.4 Sampling Technique

Two hundred and fifty properly collected urine samples (midstream or specimen from newly passed urinary catheter) were collected from the younger children by the attending nurses, while the older children were supervised to collect the appropriate samples. The urine samples were immediately transported to the laboratory for processing within 1 hour of collection.

2.5 Specimen Processing

The urine samples were examined microscopically for white blood

cell count, cultured on cysteine lactose electrolyte deficient (CLED) agar and immediately incubated at 35-370C. Identification of bacterial pathogens was by colonial morphology, conventional biochemical tests and the use of appropriate analytical profile index (API) kits. Antibiotic susceptibility testing was done using modified Kirby-Bauer method using antibiotic discs appropriate for each organism, and the zone of inhibition (in millimeters) interpreted according to clinical and laboratory standard institute (CLSI) guidelines.[13] Quality control was performed using Escherichia coli ATCC 25922, Staphylococcus aureus ATCC 25923 and Pseudomonas aeruginosa ATCC 27853.

2.6 Resistance Testing

Gram negative isolates with reduced susceptibility to one or more third- generation cephalosporins were tested for extended-spectrum beta-lactamase and AmpC beta- lactamase production by combination disc diffusion test (CDDT) and AmpC disc test respectively and interpreted according to the guidelines.[13-15] Testing for carbapenemase production was by modified Modified Carbapenemase Inactivation Method (mCIM).[13]

2.7 Data Analysis

Data entry and analysis was performed using SPSS version 20. The descriptive statistics was used and variables expressed as percentages.

2.8 Ethical Consideration

Ethical approval for this study was obtained from the ethics and research committee of UniOsun Teaching Hospital, Osogbo (Protocol Number: LAUTECH/REC/2022/03/615). Patient confidentiality was ensured throughout the phases of data collection, sample processing and statistical analysis using appropriate codes to replace patient identifiers and use of passworded electronic device.

2.8 Data Availability

The data that support the findings of this study are openly available at the Open Science Framework (OSF) repository at https://osf.io/e2m3t/

3. RESULTS

3.1 Sociodemographic Characteristics of Patients

A total of 250 hospitalized children recruited into this descriptive cross-sectional study were distributed as 199 (47.6%) male and 131 (52.4%) female. Children within the age group 10-14 years constituted the highest number (81, 32.4%). In addition, there were 26 (10.4%) neonates and 32 (12.8%) infants. (Table 1).

3.2 Clinical Characteristics of Patients

A large proportion of participants recruited for this study were from the children's ward 121, (48.4%) and emergency ward 67 (26.8%) (Table 2). Malaria, sepsis, pneumonia and meningitis were the common co-morbid conditions recorded in 89 (35.6%), 66 (26.4%), 53 (21.2%) and 27 (10.8%) of patients respectively. Forty-nine percent of the hospitalized patients were discharged within the first week of admission while 88 (36.8%) were discharged after the first week but within the first month of admission. Most of the patients had antibiotic treatment for a duration of 4-7 days (93, 38.4%) and 8-14 days (87, 36.0%). One hundred and seventy-nine (71.6%) patients had used antibiotics in the previous month before admission. Forty-three (19.5%) of UTI cases were complicated by sepsis and 9 (4.1%) died from complications of UTI. (Table 2)

Table 4: Microbial Profile of UTI in Children (n=166)

Organisms	Frequency	Percentage
Gram-Negative Bacilli	137	82.5
Escherichia coli	43	25.9
Klebsiella pneumoniae	15	9.0
Klebsiella oxytoca	8	4.8
Citrobacter freundii	16	9.6
Enterobacter cloaca	4	2.4
Enterobacter aerogenes	11	6.6
Proteus mirabilis	12	7.2
Proteus vulgaris	7	4.2
Acinetobacter baumanii	10	6.0
Pseudomonas aeruginosa	11	6.6
Gram-positve cocci	26	15.7
Staphylococcus aureus	15	9.0
Coagulase-negative staphylococci	2	1.2
Enterococcus faecalis	7	4.2
Enterococcus faecium	2	1.2
Yeast		
Candida albican	3	1.8
Total	166	

3.3 Urinary Symptoms and Urinary Tract Disorders

Lower urinary tract infection (cystitis) was the predominant type of UTI and common presenting UTI symptoms were pain/burning sensation (36.4%), lower abdominal pain (27.2%), urinary frequency (21.6%), and fever (20.8%). Fifty-seven (21.6%) of patients did not show specific symptoms. The presence of indwelling urinary catheter in 38 (15.2%) patients prior to the diagnosis of UTI noted and it remained in situ for less than one week in 31.6% of patients and up to one month in 50% of the patients. Some associated urinary tract disorders found in these children included nephro-

Table 3: Urinary Tract Infection Symptoms, Abnormalities & Procedures (n is 250 Unless Otherwise Stated)

Presenting Features of UTI	Frequency	Percentage
Pain or burning sensation when urinating	91	36.4
Urinary frequency	54	21.6
Urgency	15	6.0
Lower abdominal pain	68	27.2
Flank pain	23	9.2
Fever	52	20.8
Cloudy urine	32	12.8
Bloody urine	4	1.6
Unspecific	54	21.6
Types of UTI		
Acute pyelonephritis	29	11.6
Cystitis	164	65.6
Undefined	57	22.8
Urinary Tract Disorders		
Posterior urethral valve	2	0.8
Vesico-ureteric reflux	1	0.4
Nephrolithiasis	6	2.4
Neurogenic bladder	1	0.4
Presence of indwelling urinary catheter	38	15.2
Duration of Catheterization (n= 38)		
< 1 Week	12	31.6
1 Week- 1 Month	19	50.0
>1 Month	7	18.4

UTI- Urinary Tract Infection

Table 5: Antibiotic Resistance Pattern of Gram-Negative Bacilli

Antibiotics (n)	AMC n(%)	TZP n(%)	CTX n(%)	CRO n(%)	CAZ n(%)	AZN n(%)	FEP n(%)	GEN n(%)	AMK n(%)	NIT n(%)	SXT n(%)	CIP n(%)	OFL n(%)	IMI n(%)	MEM n(%)
Escherichia coli (43)	19 (44.2)	8 (18.6)	18 (41.9)	17 (46.5)	17 (39.5)	14 (32.6)	15 (34.9)	20 (46.5)	6(14.0)	10 (23.3)	33 (76.7)	19 (44.2)	18 (41.9)	4(9.3)	3(7.0)
Klebsiella pneumoniae (15)	8 (53.3)	3 (20.0)	8(53.3)	9(60.0)	8(53.3)	6(40.0)	7(46.7)	8(53.3)	2(13.3)	6 (40.0)	12 (80.0)	7 (46.7)	6 (40.0)	2 (13.3)	2 (13.3)
Klebsiella oxytoca (8)	4 (50.0)	2 (25.0)	4(50.0)	4(50.0)	4(50.0)	3(37.5)	3(37.5)	5(62.5)	1(12.5)	2 (25.0)	6 (75.0)	4 (50.0)	3 (37.5)	1 (12.5)	1 (12.5)
Citrobacter freundii (16)	7 (43.8)	4 (25.0)	7(43.8)	7(43.8)	6(37.5)	5(31.3)	4(25.0)	8(50.0)	2(12.5)	5 (31.3)	13 (81.3)	8 (50.0)	8 (50.0)	2 (12.5)	2 (12.5)
Enterobacter cloacae (4)	2 (50.0)	1 (25.0)	2(50.0)	2(50.0)	2(50.0)	2(50.0)	2(50.0)	2(50.0)	0(0.0)	1 (25.0)	3 (75.0)	2 (50.0)	2 (50.0)	0(0.0)	0(0.0)
Enterobacter aerogenes (11)	5 (45.5)	2 (18.2)	5(45.5)	6(54.5)	5(45.5)	4(36.7)	4(36.7)	6(54.5)	1(9.1)	4 (36.7)	8 (72.7)	5 (45.5)	5 (45.5)	1(9.1)	1(9.1)
Proteus mirabilis (12)	5 (41.7)	2 (16.7)	4(33.3)	5(41.7)	4(33.3)	4(33.3)	4(33.3)	5(41.7)	2(16.7)	4 (33.3)	8 (66.7)	5 (41.7)	4 (33.3)	1(8.3)	1(8.3)
Proteus vulgaris (7)	3 (42.9)	1 (14.3)	3(42.9)	3(42.9)	3(42.9)	3(42.9)	3(42.9)	3(42.9)	1(14.3)	3 (42.9)	5 (71.4)	3 (42.9)	3 (42.9)	0(0.0)	0(0.0)
Acinetobacter baumannii (10)	7 (70.0)	4 (40.0)	7(70.0)	6(60.0)	6(60.0)	6(60.0)	6(60.0)	7(70.0)	3(30.0)	6 (60.0)	9 (90.0)	6 (60.0)	6 (60.0)	3 (30.0)	3 (30.0)
Pseudomonas aeruginosa (11)	NT	5 (45.5)	NT	NT	6(54.5)	6(54.5)	6(54.5)	7(63.6)	4(36.7)	NT	NT	6 (54.5)	6 (54.5)	4 (36.7)	4 (36.7)
Total	60 (47.6)	32 (23.4)	58 (46.0)	59 (46.8)	61 (44.5)	53 (38.7)	54 (39.4)	71 (51.8)	22 (16.1)	41 (32.5)	97 (77.0)	65 (47.4)	61 (44.5)	18 (13.1)	17 (12.4)

AMC- Amoxicillin-Clavulanate, TZP- Piperacillin-Tazobactam, CTX- Cefotaxime, CRO- Ceftriaxone, CAZ- Ceftazidime, AZN- Aztreonam, FEP- Cefepime, GEN- Gentamicin, AMK- Amikacin, NIT- Nitrofurantoin, SXT- Trimethoprim-Sulfamethoxazole, CIP- Ciprofloxacin, OFL- Ofloxacin, IMI- Imipenem, MEM Meropenem, NT- Not tested

lithiasis (n=6), posterior urethral valve (PUV) (n=2), vesico-ureteric reflux (n=1) and neurogenic bladder (n=1), Table 3.

3.4 Microbial Pathogens of UTI in Patients

A total of 166 microorganisms were isolated from 250 urine samples; 133 samples yielded a single organism each while 18 samples yielded two organisms each, and 99 samples yielded no growth of organisms. There were 163 bacterial isolates; 137 (82.5%) Gram-negative bacilli and 26 (15.7%) Gram-positive cocci. The most common bacterial pathogen was Escherichia coli 43 (25.9%). Other common isolates were Klebsiella species (23, 13.9%), Proteus species (19, 11.4%), Citrobacter species (16, 9.6%), Enterobacter species (15, 9.0%) and Staphylococcus aureus (15, 9.0%). (Table 4).

3.5 Antibiotic Resistance Pattern of Bacterial Uropathogens

Overall, Gram-negative bacilli (GNB), showed high resistance to trimethoprim-sulfamethoxazole (77.0%), gentamicin (51.8%), amoxicillin-clavulanate (47.6%), third and fourth generation cephalosporins (39.4-46.8%) and fluoroquinolones (44.5-47.4%). Resistance was however low to carbapenems (12.4-13.1%) and amikacin (16.1%). Among specific GNB, Escherichia coli, Klebsiella, Enterobacter and Citrobacter showed high resistance rates to commonly used antibiotics such as third generation cephalosporins (37.5 - 60%), gentamicin (46.5 - 62.5%), fluoroquinolones (37.5 - 50%), and trimethoprim-sulfamethoxazole (72 - 80%). Also, Acinetobacter baumanii and Pseudomonas aeruginosa showed alarming resistance (45.5-90%) to all tested antibiotics except carbapenems and amikacin to which they also showed considerable resistance ranging from 30 to 36.7%. (Table 5)

Gram-positive cocci (GPC) showed high resistance ranging from 33.3% (doxycycline) to 73.1% (penicillin). Their overall resistance to vancomycin and linezolid was low (11.1% each). Forty percent of Staphylococcus aureus were methicillin-resistant, it also showed high resistance to clindamycin (40.0%), trimethoprim-sulfamethoxazole (46.7%), erythromycin (40%), and gentamicin (46.7%). Of the Enterococcus species, Enterococcus faecalis, unlike Enterococcus faecium, showed zero resistance rates to vancomycin and linezolid, and low rates of less than 30% to all other tested antibiotics. (Table 6).

3.6 Prevalence and Pattern of Multi-Drug Resistance Uropathogens

The overall prevalence of Multidrug resistance (MDR) among pathogens of UTI in the children was 54.6% with more MDR bacteria among GNB (56.2%) compared to GPC (46.2%). High rates of MDR were particularly seen in Acinetobacter baumannii (70%, 7/10), Klebsiella species (69.6%, 16/23). (Table 7).

Extended-spectrum beta-lactamase-producing and AmpC beta-lactamase-producing strains respectively accounted for 31.4% (43/137) and 25.5% (35/137) of total GNB. Carbapenemase production was seen in 12 (8.0%) of GNB with Klebsiella species being the commonest producers (13.0%, 3/23). Among GPC, methicilllin-resistant was seen in 40% of Staphylococcus aureus while high-level gentamicin resistance was seen in 28.8% (2/7) of Enterococcus faecalis and 100% (2/2) of Enterococcus faecium. (Table 7)

4. DISCUSSION

This study sought to determine the clinical and bacteriological burdens of urinary tract infection (UTI) among 250 hospitalized paediatric patients in a University Teaching Hospital, Osogbo, Nigeria. There was a wide range of comorbid conditions among children's cases of UTI with malaria being the most common. This

Table 6: Antibiotic Resistance Pattern of Gram-Positive Cocci

Antibiotics	AMP	PEN	FOX	CLN	SXT	NIT	ERY	AZT	CIP	OFL	DOX	GEN	VAN	LNZ
Staphylococcus aureus (15)	NT	13(86.7)	6(40.0)	6(40.0)	7(46.7)	NT	6(40.0)	5(33.3)	5(33.3)	5(33.3)	4(26.7)	7(46.7)	NT	2(13.3)
CONs (2)	NT	2(100.0)	1(50.0)	1(50.0)	1(50.0)	NT	1(50.0)	1(50.0)	1(50.0)	1(50.0)	1(50.0)	1(50.0)	NT	1(50.0)
Enterococcus faecalis (7)	2(28.6)	2 (28.6)	NT	NT	NT	2(28.6)	2(28.6)	NT	2(28.6)	NT	2(28.6)	2(28.6)*	0(0.0)	0(0.0)
Enterococcus faecium (2)	2(100.)	2(100.0)	NT	NT	NT	2(100)	2(100.0)	NT	2(100.0)	NT	2(100.)	2(100.0)*	1(50.0)	1(50.0)
Total	4(44.4)	19(73.1)	7(41.2)	7(41.2)	8(47.1)	4(44.4)	11(42.3)	6(35.3)	10(37.0)	6(35.3)	9(33.3)	12(44.4)	1(11.1)	1(11.1)

*AMP- Ampicillin, PEN- Penicillin, FOX- Cefoxitin, CLN- Clindamycin, SXT- Trimethoprim-Sulfamethoxazole, NIT- Nitrofurantoin, ERY-Erythromycin, AZT-Azythromycin, CIP- Ciprofloxacin, OFL- Ofloxacin, DOX- Doxicycline, GEN- Gentamicin, VAN- Vancomycin, LNZ- Linezolid, *High-level Aminoglycoside testing using 120µg of Gentamicin, NT- Not tested. The number in brackets are percentages*

corroborates a known fact that malaria is still endemic in sub-Saharan Africa with attributable morbidity and mortality in children especially under five age group.[16] Despite that majority of patients in this study had lower urinary tract infections which should indicate a short duration of hospitalization and antibiotic course, there was prolonged hospitalization in 51% of patients; 36.8% stayed for duration of one week to one month and 14.2% stayed for longer than one month. Likewise, 52.1% of patients had antibiotic treatment for longer than 7 days. Long duration of hospitalization and antibiotic treatment observed in this study is due to the many comorbid conditions necessitating either antibiotic treatment or prophylaxis. The study also showed a high level of antibiotic use in the preceding month of admission (71.6%) reflecting excessive use of antimicrobials in our setting, which is the leading driver of antimicrobial resistance (AMR) with a negative impact on morbidity, mortality and healthcare cost.

Antimicrobial resistance threatens effective treatment of common diseases and constitutes a huge economic burden in form of health expenditures, especially in settings with huge out-of-pocket payments for healthcare. In this study, 19.5% of UTI cases were complicated by sepsis and 4.1% died from serious UTI complications. Sepsis is an important complication of urinary tract infection, especially pyelonephritis in which there is a high possibility of bacteria seeding to other body sites causing substantial mortality.[17] Symptoms of UTI in children are diverse and depend on the type of infection and age of patient among other factors, many patients may however not have definable symptoms as noted in 21.6% of patients in this study. Urosepsis is a serious complication in neonates and infants in whom the unspecific nature of symptoms poses a barrier to early diagnosis and prompt treatment.[18]

Out of 250 urine samples processed, 166 microorganisms were isolated; 133 samples yielded one microorganism each while 18 samples yielded two microorganisms each. Urinary tract infection is commonly caused by a single organism but can be caused by two or more organisms in patients with long-standing catheterization. This study noted that most of the patients with indwelling urinary catheters had them in situ for prolonged periods (50% for up to one month and 18.4% for more than a month). Polymicrobial culture is common among patients with long-term catheterization which is often associated with biofilm formation.[19]

Results obtained in this study showed that Gram-negative bacilli (GNB) constituted 82.5% while Gram-positive cocci (GPC) constituted 15.7%. This compares well with the report of Otajevwo who found that GNB and GPC constituted 86.1% and 13.9% respectively.[20] Our findings agree with the well-known fact that GNB are the primary and most common agent of urinary tract infection.8 The most frequent bacterial pathogen isolated among the pure cultures was Escherichia coli (25.9%). This result is consistent with reports from several local studies.[21-25] Urinary tract infections are most commonly caused by uropathogenic Escherichia coli and accounted for up to 80% of urinary tract infections.[26,27] It is noteworthy that studies had reported a preponderance of Klebsiella as a causal pathogen of UTI.[20,28] Klebsiella species was also not uncommon in our study with a prevalence of 13.8% which is second to Escherichia coli, bringing to light that they are increasingly becoming more important as causative agents of UTI.[29] Other common organisms isolated in this study were Proteus species (19, 11.4%), Citrobacter species (16, 9.6%), Enterobacter species (15, 9.0%) Staphylococcus aureus (15, 9.0%), Pseudomonas aeruginosa (11, 6.6%) and Acinetobacter baumannii (10, 6.0%). In the same vein, in addition to Escherichia coli, Klebsiella, Pseudomonas aeruginosa, Enterobacter and Acinetobacter had been reported as clinically important urine pathogens,[30,31] associated with about 90% of both community and hospital acquired UTIs.[32,33] Our finding confirms that spectrum of uropathogens is wide including varieties bacteria and yeasts and may be affected by factors such as age, gender, presence of indwelling catheters, urinary tract abnormalities, antibiotic exposure as well as immunosuppression.[26]

Bacterial pathogens in this study showed high resistance to trimethoprim-sulfamethoxazole (77.0%), gentamicin (51.8%), amoxicillin-clavulanate (47.6%), third and fourth generation cephalosporins (39.4-46.8%) and fluoroquinolones (44.5-47.4%). Resistance was however low to carbapenems (12.4-13.1%) and amikacin (16.1%). A study conducted in Ghana by Agyepong et al.,[25] also documented a high degree of resistance among the isolates to trimethoprim-sulfamethoxazole and amoxicillin-clavulanate (84.5% and 51.5% respectively) which also aligns with findings from some other countries in sub-Sahara Africa.[34-37] A systematic review and meta- analysis of 90 studies in an Asian country spanning 1991 to 2015 incorporating 35,118 cases of UTI showed that the predominant organism, Escherichia coli, was highly resistant to commonly used antibiotics including amoxicillin (76%), ampicillin (86%), trimethoprim-sulfamethoxazole (64%), tetracycline (71%), cephalexin (61%), and cefalothin (60%).[38] In another systematic review which determined the global prevalence of antibiotic resistance in paediatric urinary tract infections, 58 observational studies were included which investigated 77783 uropathogenic Escherichia coli isolates. The findings showed high resistance rates in many countries to common agents such as ampicillin (79.8%), amoxicillin-clavulanate (60.3%) and ciprofloxacin

Table7: Resistance Mechanisms of Bacteria Causing UTI in Children

Organisms	MDR n (%)	ESBL– P n (%)	AMPC β Lactamase Production n(%)	Carbapenemas Production n(%)	Methicillin Resistance n(%)	High-Level GentamicinResistance n(%)
Gram-Negative Bacilli (137)	77(56.2)	43(31.4)	35(25.5)	12(8.0)		
Escherichia Coli (43)	24(55.8)	15(34.9)	7(16.3)	3(7.0)	NA	NA
Klebsiella Pneumoniae (15)	11(73.3)	6(40.0)	4(26.7)	2(13.3)	NA	NA
Klebsiella Oxytoca (8)	5(62.5)	3(37.5)	2(25.0)	1(12.5)	NA	NA
Citrobacter Freundii (16)	8(50.0)	5(31.3)	6(37.5)	1(6.3)	NA	NA
Enterobacter Cloaca (4)	2(50.0)	1(25.0)	1(25.0)	0(0.0)	NA	NA
Enterobacter Aerogenes (11)	6(54.5)	4(36.4)	5(45.5)	1(9.1)	NA	NA
Proteus Mirabilis (12)	5(41.7)	3(25.0)	1(8.3)	1(8.3)	NA	NA
Proteus Vulgaris (7)	3(42.9)	2(28.6)	3(42.9)	0(0.0)	NA	NA
Acinetobacter Baumannii (10)	7(70.0)	3(30.0)	3(30.0)	1(10)	NA	NA
Pseudomonas Aeruginosa (11)	6(54.5)	2(18.2)	3(27.3)	1(9.1)	NA	NA
Gram-Positve Cocci (26)	12(46.2)					
Staphylococcus Aureus (15)	7(46.7)	NA	NA	NA	6(40.0)	NA
Coagulase-Negative Staphy (2)	1(50.0)	NA	NA	NA	1(50.0)	NA
Enterococcus Faecalis (7)	2(28.6)	NA	NA	NA	NA	2(28.6)
Enterococcus Faecium (2)	2(100.0)	NA	NA	NA	NA	2(100.0)
Total (163)	89 (54.6)					

MDR- Multi-drug Resistance, ESBL– P Extended Spectrum Beta-Lactamase Production

(26.8%).[39] A recent study by Ahmed et al. conducted over an 11-year period (2009-2019) among infants and children between 0 and 16 years of age also revealed high resistance rates to commonly prescribed antibiotics, especially amoxicillin, trimethoprim and cephalexin which peaked at 65.2%, 49.3% and 33.3% respectively.[40] Another study by Gunduz and Altum in Turkey agrees with our findings and showed similar Escherichia coli predominance (64,2%); high resistance to ampicillin, cotrimoxazole, cephalotin and cefuroxime; and zero or low resistance to imipenem (0%) and amikacin (0.2%). However, resistance rates in Gunduz and Altum's study are clearly better than those observed in our study to ceftazidime (10.7% vs 44.5%), ceftriaxone (2.4% vs 46.8%), cefepime (8.3% vs 39.4%), ciprofloxacin (7.5% vs 47.4%), and gentamicin (10.8% vs 51.8%).[41] A study carried out among children in a General Hospital in Greece also showed lower resistance rates to third- generation cephalosporins (1.7%), ciprofloxacin (1.4%), nitrofurantoin (2.3%), and amikacin (0.9%)[42] which may be a pointer to excessive use of these agents in our environment. The high resistance tendency in many African countries may be due to effect of easy availability, misuse and overuse of antimicrobial agents, especially the first-line choice in many healthcare settings.[43,44]

The overall prevalence of multidrug-resistant UTI in children in this study was 54.6%. Two separate studies from Nepal reported similarly high rates of MDR among uropathogens in children within the last 6 years; the first, by Parajuli et al, noted an MDR rate of 64.9% with Extended spectrum beta lactamase (ESBL) enzyme detected in 38.9%,45 and the second, by Raya et al, reported 34.5% with MDR significantly higher among under five children.[46] In addition, a systematic review and meta-analysis of uropathogenic Escherichia coli in Asia which included 15 articles also recorded an overall rate of MDR as high as 49.4%.[47] These attest to a fact that global burden of drug resistant infections remains enormous and will continue to snowball with developing countries bearing the greatest brunt as reported by O'Neil that AMR will cause an estimated 10 million mortality yearly by 2050 and 88.8% of these deaths is projected to happen in Africa and Asia.48 The rates of extended-spectrum beta-lactamase (ESBL)-producing and AmpC beta-lactamase-producing strains among GNB uropathogens in our study were alarming at 31.4% (43/137) and 25.5% (35/137) respectively. Similar to our findings, a study by Kocak et al in Turkey, like many others, showed a higher rate of ESBL-producing UTI pathogens which is associated with increased duration of hospitalization (49.3%).[49] The high ESBL-production rate among GNB in our study also aligns with the report of a review of African studies which also revealed a high pooled ESBL prevalence (38%). These findings underscore high magnitude of ESBL-producing GNB across African regions.[50] The evolution and wide spread of ESBL-producing bacterial infections have remained a global health concern for the past two decades reaching an endemic level, especially among Enterobacteriales.[51] Also, AmpC beta-lactamase production is becoming a big issue; a report of a study from a developing country documented a prevalence of 29.2% (Shafiq et al., 2013).[52] Although resistance due to AmpC beta-lactamase is not as common as that caused by ESBL, our study established that AmpC is still very common especially among Enterobacter, Citrobacter and Proteus vulgaris, and that bacteria such as Escherichia coli and Klebsiella which traditionally lack or poorly express chromosomal AmpC gene are fast acquiring plasmid transmissible genes for enzyme production. Our study further revealed that carpapenem-resistant GNB were 12.4% and 13.1% for meropenem and imipenem respectively; carbapenemase production was 8.0% (12/137) with Klebsiella species being the commonest producers (13.0%, 3/23). Being among the last resort antibiotics, resistance to carbapenem constitutes a huge threat to effective treatment of difficult to treat infections, the situation is made worse by the drought in pipeline of antibiotic production in the last decades.[16] Among Staphylococcus aureus, methicilllin-resistant strains accounted for 40% in our study which supports the established knowledge that Methicillin-resistant Staphylococci aureus (MRSA) is common in patients on prolong catheterization (Klein and Hultgren, 2020). The high magnitude of drug-resistant infections in this study will have a multiplied effect considering the vulnerability of age of some of the patients and many underlying health conditions and co-morbidities as well as socioeconomic

challenges inherent in our population.

4.1 Conclusion

The clinical presentation of UTI observed in this study is non-specific and variable. There was high resistance to first- and second line antibiotics. These findings, including high prevalence of multidrug-resistant bacterial urinary tract infection, poses huge therapeutic challenges with the use of the commonly available antibacterial agents.

Contributor Roles Taxonomy (CRediT) Statement

Adeyemo A.T.: Conceptualization, study design, sample collection and laboratory processing, data collection and analysis, review of manuscript.
Ojewuyi A.R.: Laboratory processing of sample, data collection, review of manuscript.
Odeyemi A.O.: Conceptualization, sample collection, review of manuscript
Adeyemo A.T.: Conceptualization, study design, sample collection and laboratory processing, data collection and analysis, writing of original manuscript draft, review of manuscript.
Olumakinde T.S.: Data collection, data analysis, review of manuscript
Akokhia A.O.: Sample collection, laboratory processing of sample, review of manuscript
Bolaji O.S: Data collection, data analysis, review of manuscript.
Adekunle O.C: Data collection, data analysis, review of manuscript.
Hassan A.O.: Data collection, laboratory processing of sample, review of manuscript

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