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Etiology and Antimicrobial Susceptibility Pattern of Uropathogens in Children and Adolescents in a Tertiary Hospital: Moving from the Known to the Unknown

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Abstract

Background: Urinary tract infection is a frequent health problem in children and an important cause of morbidity and mortality, with the highest rate seen in the first 2 years of life. Management of a patient with urinary tract infection depends on good knowledge of the causative agents and local antimicrobial susceptibility patterns. This study was designed with the aim to investigate the aetiology and antimicrobial susceptibility pattern of uropathogens in children and adolescents at the University of Nigeria Teaching Hospital, Ituku-Ozalla Enugu.

Methods and findings: This was a hospital-based cross-sectional study conducted in Department of Medical Microbiology, University of Nigeria Teaching Hospital, Ituku-Ozalla Enugu. The laboratory records of all the mid-stream urine samples of children and adolescents analysed from 2014 to 2019 were reviewed. Urine sample results from neonates were excluded. Information extracted from the records included: age, sex, date of submission of urine samples, provisional diagnosis, microbial isolates and their susceptibility patterns to various antibiotics. Analysis was done using descriptive and inferential statistics.

Of 2199 urine samples that were analysed, 650 (29.9%) yielded significant bacteriuria with females accounting for more than half (363/650: 55.8%) of the cases; (χ2=4.204; P=0.040). Isolated organisms were mostly Gram negative bacilli predominantly E. coli (346/650; 53.2%) occurring more in females (220/650; 33.8%) than males (126/650; 19.4%); (χ2=13.009; p<0.001). The least isolated Gram negative organisms was Pseudomonas aeruginosa seen in 20/650 (3.1%) of the urine samples The Gram positives cocci isolated were Staphylococcus aureus (59/650; 9.1%) and Streptococcus species (12/650; 1.9%). Candida spp was also isolated in 32/650; 4.9% of the urine samples. Most of the isolated organisms showed very high resistance to ampicillin and cotrimoxazole. Moderate resistances were seen with nitrofurantoin, cephalosporins, amoxicillin-clavulanic acid and quinolones. The least resistances were shown with carbapenems piperacillin/tazobactam, linezolid and cefoxitin.

Conclusion: The resistance pattern of organisms causing urinary tract infections in children and adolescents to common antibiotics as highlighted in this study is worrisome. Facility specific guideline for antibiotics therapy is urgently advocated for better management of the patients and to ensure good antibiotics stewardship in line with universally accepted standards.

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Abbreviations: ATCC: American type culture collection; AMP: Ampicillin; AUG: Augmentin; CEF: Cefoxitin; CTX: Cefotaxime; CTZ: Ceftazidime; CIP: Ciprofloxacin; CLSI: Clinical and Laboratory Standard Institute; COT: Cotrimoxazole; GEN: Gentamicin; LEV: Levofloxacin; LIZ: Linezolid; IMI: Imipenem; MEM: Meropenem; NITRO: Nitrofurantoin; P: Probability factor; P/TA: Piparacillin/tazobactam; SPSS: Statistical Package for Social Sciences; UTI: Urinary Tract Infection; UK: United Kingdom.

Introduction

Urinary Tract Infection (UTI) is a common infection that is encountered in children, accounting for 5% to 14% of paediatric emergencies [1,2]. UTI can be grouped into upper and lower infection [3]. It is an important cause of morbidity and mortality [4], with the highest rate seen in the first two years of life [5]. Long-term complications such as renal scarring, hypertension, and chronic renal failure are mainly seen in children with recurrent, poorly treated or undiagnosed UTI [6,7]. In the past 30-50 years, the natural history of urinary tract infection in children has changed as a result of the introduction of antibiotics and improvements in health care [8]. This change has contributed to uncertainty about the most appropriate and effective way to manage UTI. It may be difficult to recognize urinary tract infection in children because of absence or non-specific symptoms [9,10]. A high index of suspicion is appropriate when making diagnosis in children that presented with fever [11].

Urine collection and interpretation of urine tests in children are not easy and therefore it may not always be possible to unequivocally confirm the diagnosis [12]. There are variations in etiologic features and antimicrobial sensitivity patterns which may be due to gender, age and region. Effective treatment of patients requires the knowledge of the aetiologic organisms and the local resistance patterns within the region are for a favourable outcome [13]. Our aim was to investigate the aetiology and antimicrobial susceptibility patterns of uropathogens in children and adolescent at the University of Nigeria Teaching Hospital, Ituku-Ozalla Enugu, in order to evaluate options for empirical antibiotic therapy. This information will also assist the clinicians in optimizing antibiotic management and ensure good antibiotic stewardship.

Materials and Methods

Methods Study design and study setting

This was a hospital-based cross-sectional study conducted in the Department of Medical Microbiology, University of Nigeria Teaching Hospital, and Enugu from 2014 to 2019. The laboratory records of all the urine samples of children and adolescents submitted were reviewed. Urine sample results from neonates were excluded. Information extracted from the records included: age, sex, date of submission of urine samples, provisional diagnosis, microbial isolates and their antibiotic susceptibility patterns.

Culture and antibiotics susceptibility testing

Routinely, midstream urine samples were collected in wide-mouthed, sterile, leak-proof containers. The urine samples were examined microscopically and cultures done on MaCconkey and 5% sheep blood agars (Oxoid, UK) using a calibrated wire loop (0.001 ml). The cultured plates were incubated at 370 °C overnight in aerobic condition. After, the overnight incubations, the plates with growth were checked and bacterial counts done to check the presence of significant bacteraemia. Bacterial colony count yielding growth of ≥ 105 CFU/ml of urine was considered significant according to the infectious Diseases Society of America [14]. Identification of the positive isolates was done by their colony morphologic characteristics and standard biochemical tests [15]. Antibiotics susceptibility testing was done on all significant positive cultures using disc diffusion method on Muller Hinton agar (Oxoid, UK) plate and interpreted according to Clinical and Laboratory Standard institute (CLSI) guidelines. The antibiotics included in the susceptibility testing were Levofloxacin (LEV), Augmentin (AUG), Cotrimoxazole (COT), Ampicillin (AMP), Gentamicin (GEN), Ciprofloxacin (CIP), Nitrofurantoin (NITRO), Cefoxitin (CEF), Cefotaxime (CTX), Piparacillin/Tazobactam (P/TA), Imipenem (IMI), Meropenem (MEM), ceftazidime (CTZ), linezolid (LIZ).All the antibiotics were from Oxoid, UK. *E coli* American type culture collection (ATCC) 25922 and *Pseudomonas aeruginosa* (ATCC 27853) were used as the control strains in the antibiotic susceptibility testing.

Data management and statistical analysis

All the patient's data were carefully collected from the laboratory records, recorded and a number issued on all of them. The data were secured adequately and analysed using the Statistical Package for Social Sciences (SPSS) version 25.0. The results were presented using descriptive statistics, chi square and Fischer's exact. Tables were used to explain the descriptive data. Probability factor (P) less than 0.05 was regarded as statistically significance.

Results

Two thousand, one hundred and ninety-nine urine samples of children and adolescents were analysed within the review period. Of these 650 (29.6%) samples yielded significant bacteriuria, 408 (62.8%) were samples from patients more than 12 years old. Females (363/650:55.8%) accounted for more than half of the population. There was no significant difference among the gender distribution (χ^2=3.002; p=0.083) (**Table 1**).

Isolated organisms were mostly Gram negative bacilli predominantly *E.coli* (346/650; 53.2), which was higher in females (220/650; 33.8%) than males (χ^2=13.009; p<0.001). The least isolated Gram negative organism isolated was *Pseudomonas spp* 11/650 (1.7%) (χ^2=0.100; p=0.752); (**Table 2**).

The Gram positives cocci isolated were *Staphylococcus aureus* (59/650; 9.082%) (χ^2=0.306; p=0.580 and *Streptococcus species* (12/650; 1.9%) (χ^2=0.168; p=0.682). *Candida spp* were also isolated (32/60; 4.9%) (χ^2=1.016; p=0.313) as shown in **Table 2**. There were statistical difference between distribution of isolates (F=10.28; p=0.00) and also among they gender (χ^2=18.385;

Table 1: Distribution of patients according to age and gender, %-Percentage.

Age (yr)	Male (%)	Female (%)	Total (%)
<12	90 (13.8%)	142(21.8%)	232 (35.7%)
≥ 12	197 (30.3%)	221 (34.0%)	418 (64.3%)
Total	287 (44.2%)	363 (55.8%)	650 (100.0%)
Statistical difference: χ^2 =3.002; df=1; *P*=0.083.			

Table 2: Distribution and frequency of the isolated organisms according to gender.

Isolates	Female (%)	Male (%)	Total	χ^2	P-value
Escherichia coli	220 (33.8)	126 (19.4)	346(53.2)	13.009	0.001
Klebsiella species	34 (5.2)	27 (4.1)	61(9.4)	0.526	0.468
Other coliforms	45 (6.9)	36 (5.5)	81(12.5)	0.397	0.529
Staphylococcus aureus	26 (4.0)	33 (5.1)	59(9.1)	0.306	0.580
Candida species	12 (1.8)	20 (3.1)	32(4.9)	1.016	0.313
Streptococcus species	7 (1.1)	5 (0.8)	12(1.9)	0.168	0.682
Proteus species	27 (4.1)	12 (1.8)	39(6.0)	3.391	0.066
Pseudomonas species	9 (1.4)	11 (1.7)	20(3.1)	0.100	0.752
Total	380 (58.5)	270 (41.5)	650(100%)		
Statistical difference (by gender): χ^2 *=18.385; df=7; p=0.010.* Statistical difference (by isolates): *F=10.28; p=0.002.*					

Table 3: The Antimicrobial susceptibility pattern of the isolates. **Abbreviations**: LEV:Levofloxacin; AUG: Augmetin; COT:Cotrimoxazole; AMP:Ampicillin; GEN: Gentamicin; CIP:Ciprofloxacin; NITRO:Nitrofurantoin; CEF:Cefoxitin; CTX:Cefoxitin; P/TA:Piparacillin/tazobactam; IMI:Imipenem; MEM:Meropenem; CTZ: Ceftazidime; LIZ:Linezolid; S:Sensitive; R:Resistance.

Isolates	LEV		AUG		COT		AMP		GEN		CIP		NITRO		CEF		CTX		P/TA		IMI		MEM		CTZ		LIZ	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
E.coli	65	35	62	38	40	60	9	91	66	34	63	37	72	28	-	-	77	23	84	16	94	6	89	11	85	15	-	-
Kleb. spp	75	15	54	46	22	78	8	92	70	30	72	28	81	19	-	-	65	35	80	20	90	10	85	15	89	11	-	-
Others	70	30	67	33	35	65	15	85	54	46	69	31	82	18	-	-	71	29	84	16	85	15	90	10	82	18	-	-
Proteus spp	87	13	72	28	42	58	12	88	71	29	55	45	90	10	-	-	65	35	70	30	85	15	85	15	75	25	-	-
Pseudo	55	45	-	-	-	-	-	-	77	23	56	44	-	-	-	-	-	-	92	8	96	4	96	4	92	8	-	-
S.aureus	67	33	84	16	55	45	23	77	62	38	68	32	70	30	92	8	-	-	-	-	85	15	85	15	-	-	95	5
Strep spp	75	25	78	22	43	57	22	78	-	-	67	33	-	-	-		-	-	-	-	-	-	-	-	-	-	97	3

p=0.010)

Antimicrobial susceptibility test showed variable degrees of resistance (**Table 3**). Gram negative organisms isolated showed very high sensitivity to imipenem, meropenem, piperacillin/ tazobactam and linezolid, cefoxitin in Gram positives. Most of the isolated organisms showed very high resistance to ampicillin and cotrimoxazole. Moderate resistances were seen in nitrofurantoin, cephalosporins, amoxicillin-clavulanic acid and quinolones.

Discussion

Urinary tract infection is a common paediatric condition that is treated in most hospitals [1,16]. Diagnosis and management significantly affect the health of the child, cost of treatment; and development of antibiotic resistance. Our study has shown that *E. coli* is the most prevalent uropathogenic bacteria associated with UTI in the paediatric age group; and significantly so in females than males. This finding is comparable with many studies [17-20]. In a study by Lok et al. in 2019 [19], *Escherichia coli* was noted to account for 50-90% of UTI in paediatric age-groups irrespective of age, sex, community or country [19]. In the pediatric population, females are at greater risk of developing UTIs after approximately 6 months of age *E.coli* is a normal inhabitant of gastro intestinal tract so can easily spread across the perineum, adhere and invade the urinary tract through the urethral opening [11,18,21]. This invasion is more frequent in females, coupled with their unique anatomical structure and moist warmth environment of their genitalia [22-24] Prostatic fluid has antibacterial properties, so may protect males from UTI infections [25].

Contrary to the finding in this index study and other works in other parts of the world [17-19], Muoneke and colleagues in Abakaliki, reported that *Klebsiella spp* was the predominate organisms causing UTI [26]. Gram negative organisms such as *E. coli* and *Klebsiella spp* are widely known to be the main causative pathogens for UTI in children. Thus, it is not surprising that *Klebsiella spp* predominated in the study done in Abakaliki.

Despite the fact that Gram negative organisms are the causative agents for UTI generally, the prevalence rates for Gram-positive organisms are gradually on the increase [27]. In the index study *Staphylococcus aureus* was the predominant Gram positive organism isolated. This was consistent with many studies done in different part of the world. Muoneke et al. [26] and Lok et al. [19], in their respective studies reported *Staphylococcus aureus* as the second uropathogen isolated in their study.

Antimicrobial resistance patterns of uropathogens may vary with time and geographical area so continuous surveillance is advocated for better management of the patient especially with empirical treatment. The higher resistance rates detected with cotrimoxazole and ampicillin are worrisome because they are common drugs used in the treatment of UTI in children. This is in agreement with many other studies [20,28-30]. The reason for the high resistance rates might be attributed to frequent use of these drugs in routine medical practice. This may be explained by the ease of administration *via* the oral route of administration, cheap cost and easy availability. The main driving force of antimicrobial resistance is Inappropriate and continuous use of antibiotics agent [21]. Continuous treatment with these antibiotics leads to treatment failure, increased cost, longer hospital stay, increased morbidity and mortality [31].

Nitrofurantoin, cephalosporins and quinolones have lower resistant rates in our study and may be appropriate for use in uncomplicated UTI. Nitrofurantoin is known to be sensitive to resistant organisms, [32,33] however, its use in children with febrile UTI, suspected cases of urospesis and pyelonephritis is not recommended because it is excreted in urine and does not achieve therapeutic concentration in the blood stream. [34,35].

Carbapenems, piperacillin/tazobactam and linezolid are recommended for use in treatment of complicated UTI. These drugs are sensitive to organisms that resistant to commonly used antibiotics [36,37].

A very pertinent but worrisome finding in the current study is the high rate of sensitivity of all the isolated organisms to carbapenems. The implication of this finding is the possible rise in the rates of prescription of these drugs as first line drugs for both complicated and uncomplicated UTI among doctors in our facility. It is worrisome because, it is expected that with rise in rate of prescription of these drugs as first line, resistance may build up over time. They should be prescribed with caution because currently, there are limited evidences for newer drugs that may replace these novel drugs in the treatment of UTI. Unless researchers put all hands on deck to provide newer drugs that may be relied on, the future of antibiotic treatment of UTI both in our centre and other centres that may be experiencing this paradigm shift in antibiotic sensitivity may remain bleak.

We acknowledge the limitations inherent in our study design, data were extracted from the laboratory records so there was no opportunity of interaction with the subjects to get more information from them.

Conclusion

Antibiotic sensitivity to uropathogens in our facility is experiencing a paradigm shift from the widely recommended empiric first line regimen to those reserved for use as last resort or when there are complications. It is of paramount importance that clinicians take into consideration the increasing prevalence of multidrug resistant uropathogen, in their everyday practice, and ensure judicious and appropriate administration of antibiotics where indicated in line with the principles of good antibiotic stewardship. This will curb the impending doom with the emergence of the ‘super bug’ when all antibiotics fail in the treatment of UTI in children in our setting.

Declarations

Ethics approval

Ethical approval was obtained from Health Research and Ethic Committee of University of Nigeria Teaching Hospital Enugu.

Consent for Publication

Not applicable

Availability of Data and Materials

The datasets used and/or analysed during the study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author’s Contributions

Conception and design of study: MEO, JNE, INN. Data collection: INN. Analysis and/or interpretation of data: MEO, INN, JE. Drafting the manuscript: MEO, INN, JNE. Revising the manuscript critically for important intellectual content: MEO, INN, JNE. Approval of the version of the manuscript to be published: MEO, INN, JNE. All authors read and approved the final manuscript.

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