Antimicrobial susceptibility patterns and their correlate for urinary tract infection pathogens at Kitwe Central Hospital, Zambia.

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Citation style for this article:
Chisanga J, Mazaba ML, Mufunda J, Besa C, Kapambwe-muchemwa MC, Siziya S. Antimicrobial susceptibility patterns and their correlate for urinary tract infection pathogens at Kitwe Central Hospital, Zambia. Health Press Zambia Bull. 2017;1(1) [Inclusive page numbers]

Inadequate data on antimicrobial susceptibility patterns in the Africa region and indeed in Zambia have led to ineffective empirical treatment before the culture and sensitivity results are made available. The purpose of this study was to determine the antimicrobial susceptibility patterns amongst the most common bacterial causes of UTIs amongst patients presenting at Kitwe Central Hospital (KCH), Zambia. A 5-year record review of data captured in the laboratory urine register from 2008 to 2013 was conducted. Demographic data, culture and antimicrobial susceptibility data were entered in Epi Info version 7 and analysed using SPSS version 17.0. Associations were determined using the Chi-squared test at the 5% significance level. A total of 1854 records were extracted from the laboratory register. The highest frequency of UTI (43.9%) was in the 15–29 years age group. The overall sensitivity patterns indicated that *E.coli* was mostly sensitive to ciprofloxacin (69.8%), *Klebsiell*a species to ciprofloxacin (68.2%), *Proteus* species to cefotaxime (66.7%) and *Staphylococcus saprophyticus* to nitrofuratoin (63.7%). Sensitivity for *E. coli* to nalidixic acid was higher for males (58.6%) than females (39.5%). Sensitivity for *E. coli* to cefotaxime and norfloxacin varied with age (Chi-squared for trend=10.32, p=0.001). Our results have shown that UTI pathogens isolated at KCH were less than 70% sensitive to the recommended and used antibiotic. Studies to establish highly sensitive antibiotics to UTI pathogens are needed to effectively treat patients.

Introduction

Urinary tract infections (UTIs) account for one of the major reasons for most hospital visits and the determination of the antimicrobial susceptibility patterns of uropathogens will help to guide physicians on the best choice of antibiotics to recommend to affected patients [1]. Bacterial infections that cause community-acquired urinary tract infections and upper respiratory tract infections are most frequently treated empirically. However, an increase in antimicrobial resistance has raised challenges in treating outpatients [2]. The increases in antibiotic resistance of urinary tract pathogens can be attributed mainly to frequent and indiscriminate use of antibiotics [3]. Increasing resistance in bacterial pathogens been reported widely [4]. Despite the widespread availability of antimicrobial agents, UTIs have continued to be increase resistance to antimicrobial agents [5]. The prevalence of antibiotic resistance in UTIs varies according to geographical and regional location [4]. Studies conducted in Pakistan and Washington showed variations in resistance to antibiotics by sex and age group [6,7]. UTIs are caused by different microbial pathogens. The most prevalent bacteria causing UTI are *Escherichia coli*, *Staphylococcus saprophyticus*, *S. aureus*, *Proteus* sp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and enterococci [1].

The Ministry of Health [Zambia] recommends antibiotic prescription for UTIs to be guided by sensitivity results [8]. The recommended drugs for the treatment of UTI in Zambia are as follows: amoxicillin, nitrofurantoin, nalidixic acid, ciprofloxacin, cefotaxime and ceftriaxone [8]. Limited data on urinary tract pathogens and their in-vitro susceptibility pattern hinder effective empirical treatment. A retrospective study was conducted to determine susceptibility patterns for some of the commonly used antibiotics for the treatment of urinary tract infections at Kitwe Central Hospital, Zambia.

Methods

The study was conducted at the Kitwe Central Hospital, which is a provincial referral facility for Copperbelt, North Western and Luapula provinces of Zambia.

Ethics clearance was obtained from the Tropical Diseases Research Centre Ndola reference number TRC/C4/07/2015 to conduct the study.

An analysis of secondary data was performed on data captured in the microbiology laboratory register from 2008 to 2013. The data were captured using Epi info version 7 and analyzed using SPSS version 17.0. Proportions were compared in 2 x 2 contingency tables using the Yates' corrected Chi-squared test, while the uncorrected Chi-squared test was used to determine associations in higher contingency tables. The Chi-squared test for trend was used to determine linear associations. The cut off point for statistical significance was set at the 5% level.

The culture and sensitivity results that were analysed were results from routine analysis of urine specimen collected from both in- and out-patients. Mid-stream urine and occasionally urine specimen collected suprapubically were analysed as outlined in the standard operating procedure. Culture was done on CLED agar. Susceptibility testing was done on Mueller Hinton agar using Disk diffusion method with the inoculums suspension in sterile distilled water prepared using a 0.5 McFarland standard.

Table 1 Susceptibility patterns of commonly isolated UTI pathogens at Kitwe Central Hospital (Zambia) from 2008-2013

Bacteria		**Antibiotic**						
		Cefotaxime	Chloramphenicol	Ciprofloxacin	Cotrimoxazole	Nalidixic acid	Nitrofurantoin	Norfloxacin
Escherichia coli	Total n(%)	326 199(61.0)	331 161(48.6)	368 257(69.8)	299 38(12.7)	588 229(38.9)	583 348(59.7)	505 323(64.0)
***Klebsiella* Species**	Total n(%)	144 86(59.7)	99 53(53.5)	154 105(68.2)	83 7(8.4)	230 103(44.8)	231 116(50.2)	180 121(67.2)
***Proteus* species**	Total n(%)	114 76(66.7)	116 49(42.2)	127 77(60.6)	96 17(17.7)	196 75(38.3)	211 102(48.3)	176 108(61.4)
Staphylococcus saprophyticus	Total n(%)	87 45(51.7)	66 29(43.9)	130 82(63.1)	60 7(11.7)	177 49(27.7)	193 123(63.7)	124 75(60.5)

Results

Table 1 shows susceptibility patterns of commonly isolated UTI pathogens to antibiotics. *E.coli* isolates were more sensitive to ciprofloxacin (69.8%), norfloxacin (64.0%) and cefotaxime (61.0%) and least to cotrimoxazole (12.7%). *Klebsiella* species isolates were more sensitive to ciprofloxacin (69.8%), norfloxacin (67.2%) and least to cotrimoxazole (8.4%). *Proteus* species were more sensitive to cefotaxime (66.7%), norfloxacin (61.4%), ciprofloxacin (60.6%) and least to co-trimoxazole (17.7%). *Staphylococcus saprophyticus* isolates were more sensitive to nitrofurantoin (63.7%), ciprofloxacin (63.1%) and norfloxacin (60.5%).

Sensitivity levels for *E. coli* to antibiotics varied by year. Overall, *E.coli* was most sensitive to ciprofloxacin (69.8%), norfloxacin (64.0%) and cefotaxime (61.0%) with least sensitivity to co-trimoxazole (12.7%) as shown in Table 2. Apart from ciprofloxacin and co-trimoxazole, sensitivity levels for the other drugs remained constant as shown in table 3. For both ciprofloxacin and co-trimoxazole, sensitivity levels declined between 2008 and 2013. A unit change in the year corresponded to about 6%(-6.48 for ciprofloxacin and -5.93 for co-trimoxazole).

No significant differences in antibiotic sensitivity to *E. coli* were observed between females and males, except for nalidixic acid (p<0.001) with higher levels of sensitivity for males (58.6%) than females (39.5%) as shown in table 5.

Table 2. Susceptibility by year for *E.coli* to antibiotics at Kitwe Central Hospital (Zambia) from 2008-2013

Year	Cefotaxime		Chloramphenicol		Ciprofloxacin		Cotrimoxazole		Nalidixic acid		Nitrofurantoin		Norfloxacin	
	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
2008	40	14(35.0)	-	-	45	37(82.2)	30	8(26.7)	121	49(40.5)	97	50(51.6)	102	60(58.8)
2009	42	28(66.7)	79	42(53.2)	135	101(74.8)	39	12(30.8)	152	64(42.1)	155	96(61.9)	139	83(59.7)
2010	39	29(74.4)	29	16(55.2)	54	43(79.6)	34	6(17.7)	89	47(52.8)	79	48(60.8)	76	54(71.0)
2011	29	21(72.4)	38	23(60.5)	23	16(69.6)	31	3(9.7)	83	38(45.8)	97	66(68.0)	101	66(65.3)
2012	91	62(68.1)	113	51(45.1)	56	34(60.7)	102	9(8.8)	7[a]	2(28.6)	8[a]	2(25.0)	73	48(65.8)
2013	85	45(53.0)	72	29(40.3)	55	26(47.3)	63	0(0.0)	136	29(21.3)	147	86(58.5)	14[a]	12(85.7)
Total	326	199(61.0)	331	161(48.6)	368	257(69.8)	299	38(12.7)	588	229(38.9)	583	348(59.7)	505	323(64.0)

[a]Caution: denominator less than 30

Sensitivity levels varied by age for cefotaxime (p=0.010) and norfloxacin (p=0.010) as shown in Table 4. Sensitivity levels for cefotaxime linearly decreased with age (Chi-squared test for trend=10.32, p=0.001) but not for nalidixic acid (Chi-squared test for trend=2.20, p=0.138). The lowest sensitivity level was observed among the 45 years or older patients (48.4% for cefotaxime and 54.5% for norfloxacin).

Discussion

This study provides the information about the antibiotic susceptibility patterns of common bacterial pathogens isolated from urine specimen of patients with urinary tract infections at Kitwe Central Hospital on the Copperbelt province of Zambia. In this study, 1854 urine culture and sensitivity results were analyzed covering the period 2008 to 2013.

Of the 1854 culture results that were analyzed, the most common organisms were *E.coli* (46.7%), *Klebsiella* species (17.1%), *Proteus* species (15.4%) and *Staphylococcus saprophyticus* (12.6%). These findings are slightly to what Ekwealor et al found in Nigeria that the most prevalent isolates were *S. aureus* (28%), *E. coli* (24.6%), and *S. saprophyticus* (20%) [1]. Analysis of the susceptibility pattern excluded *Enterobacter* species, *Enterococcus faecalis* and *Pseudomonas* because of small numbers. Susceptibility by age and sex were only done for *E.coli* because of large numbers.

Table 3 Linear trends in sensitivity levels by year

Drug	Equation	Standard error	p-value	R^2
Cefotaxime	52.38+2.63 year	3.796	0.526	10.7
Chloramphenicol	65.22-3.59 year	2.106	0.187	49.2
Ciprofloxacin	91.71-6.48 year	1.339	0.008	85.4
Cotrimoxazole	36.37-5.93 year	0.985	0.004	90.0
Nalidixic acid	52.88-4.10 year	2.313	0.151	44.0
Nitrofurantoin	61.20-1.97 year	3.970	0.646	5.8
Norfloxacin	53.01+4.20 year	1.596	0.058	63.4

In the current study, *E.coli* isolates were more sensitive to ciprofloxacin (69.8%), norfloxacin (64.0%) and cefotaxime (61.0%). The analysis of the trends revealed that apart from ciprofloxacin and co-trimoxazole, sensitivity levels for the other drugs in the table remained constant. For both ciprofloxacin and co-trimoxazole, sensitivity levels declined between 2008 and 2013. A unit change in the year corresponded to about 6%(-6.48 for ciprofloxacin and -5.93 for co-trimoxazole). A study conducted in Tumkur, Bangalore, revealed lower sensitivity level for *E.coli* to ciprofloxacin (24%), norfloxacin (25.5%) and co-trimoxazole (37%) [10]. Another study conducted in Chandigarh, northern India [11], revealed similar sensitivity for *E.coli* to ciprofloxacin (62%) among outpatients but higher than 48% sensitivity observed in in-patients. However, the sensitivity level for *E. coli* to cefotaxime in the current study was lower than the 96% observed among out-patients and 80% among inpatients. A retrospective study carried out in Brazil revealed rate of resistance of *E.coli* to ciprofloxacin was higher than expected with highest of 36.0% [12**]**. A study by Cho et al placed ciprofloxacin (20.7%), levofloxacin (22.7%), co-trimoxazole (34.3%) and ampicillin-clavulanate (42.9%) as the least active substance compared to nitrofurantoin (93.1%) and fosfomycin (100%) [13]**.** A study by Ahmad et al revealed that *E.coli* had higher rates of rates of resistance to ampicillin (90%), tetracycline (70%), erythromycin (70%) and Cotrimoxazole (50%) [14]. Fasugba et al concluded that ciprofloxacin resistance in UTI caused by *E.coli* is increasing hence a need to reconsidered

norfloxacin (67.2%) and the least sensitive to co-trimoxazole (8.4%). The study in Tumkur, Bangalore also showed that *Klebsiella* species had sensitivity of 63% (ciprofloxacin), 66% (norfloxacin) and 58% (co-trimoxazole) [11]. *Proteus* species were more sensitive to cefotaxime (66.7%),

Table 4 *E.coli* Susceptibility by age group at Kitwe Central Hospital (Zambia) from 2008-2013

Antibiotic			**Age groups (years)**				**x^2; p value**
		Total	**<15**	**15-29**	**30-44**	**45+**	
Cefotaxime	Sensitivity	199 (61.0)	12(70.6)	102(69.9)	55(54.5)	30(48.4)	11.45; 0.010
	Total	326	17	146	101	62	
Chloramphenicol	Sensitivity	162 (48.8)	6(30.0)	75(53.2)	48(48.0)	33(47.1)	4.02; 0.260
	Total	332	20	141	100	70	
Ciprofloxacin	Sensitivity	257 (69.8)	15(75.5)	110(68.7)	86(74.5)	46(60.5)	6.04; 0.110
	Total	368	20	160	112	76	
Co-trimoxazole	Sensitivity	38 (12.7)	0(0.0)	19(13.7)	9(10.5)	10(17.2)	4.01; 0.260
	Total	299	17	139	85	58	
Nalidixic acid	Sensitivity	229 (38.9)	13(56.5)	107(40.7)	64(38.1)	45(33.6)	5.16; 0.160
	Total	588	23	263	168	134	
Nitrofurantoin	Sensitivity	348 (59.7)	14(51.9)	161(61.2)	101(59.8)	72(58.1)	1.08; 0.782
	Total	583	27	263	169	124	
Norfloxacin	Sensitivity	323 (64.0)	20(80.0)	136(61.8)	106(71.6)	61(54.5)	11.30; 0.010
	Total	505	25	220	148	112	

empirical treatment [15]. A study by Bryce et al revealed high rates of resistance ampicillin (23.6%), trimethoprim (8.2%), co-amoxiclav (26.8%) and lower rates for ciprofloxacin (2.1%) and nitrofurantoin (1.3%) [16].

Klebsiella species isolates were more sensitive to ciprofloxacin (68.2%), norfloxacin (61.4%) and ciprofloxacin (60.6%). A study done in Portugal revealed the sensitivity of *Proteus* species as 2.9% for nitrofurantoin, 75.1% for norfloxicin,75.0% for ciprofloxacin and 73.2% for cefotaxime [17]. *Staphylococcus saprophyticus* isolates were more sensitive to nitrofurantoin (63.7%), ciprofloxacin (63.1%) and norfloxacin (60.5%). A study in Iran showed the sensitivity of coagulase negative *staphylococci* as 100% for ciprofloxacin and nitrofurantoin, 69.2% for co-trimoxazole, 23.1% for cefotaxime and 0% for nalidixic acid [18].

The Sensitivity levels of *E.coli* varied with age for cefotaxime and norfloxacin. Furthermore, the sensitivity variation was linearly related to age for cefotaxime suggesting that the drug should be limited to younger age groups of <15 years. Although no similar pattern emerged for norfloxacin, the least sensitivity was observed in the 45 years or older age group, indicating that the drug should not be used for persons in this age group. Sensitivity to cefotaxime decreased as age increased and this was the same for nalidixic acid and nitrofurantoin. Cefotaxime had the highest sensitivity in the under 15 years of age (70.6%) and lowest in the 45 years or older age group (48.8%). Chloramphenicol had the highest sensitivity in the 15-29 years age group (53.2%) and lowest in the <15 years age group (30.0%). Ciprofloxacin had highest sensitivity in the under 15 years age group (75.5%) and lowest in the 45 years or older age groups (60.5%). Co-trimoxazole had the highest sensitivity in the 45 years or older age group (17.2%) and the lowest in the under 15 years age group (0.0%). Nalidixic acid had the highest sensitivity in the under 15 years age group (56.5%) and lowest in the 45 years or older age group (33.6%). Nitrofurantoin had the highest sensitivity in the 15-29 years age group (61.2%) and the lowest in the under 15 years age group. Norfloxacin had the highest sensitivity in the under 15 (80.0%) and lowest in the 45+ age group (54.5%).

The only sex difference in sensitivity levels was observed for nalidixic acid, with higher sensitivity for males (58.6%) than females (33.8%). However, the level of sensitivity was too low to recommend the use of nalidixic acid among males only.

A study done in Pakistan on the resistance of *E.coli* across age groups and sex revealed variation in resistance patterns of *E.coli* to antibiotics. Nitrofurantoin was about 2-fold more resistant in males than females, while trimethoprim, co-trimoxazole and ceftazidime showed 11% more resistance in males than females. Ceftriaxone, ciprofloxacin showed 13%, 14%, more resistance in males as compared to females, respectively. *E.coli* also manifested almost complete resistance to trimethoprim and co-trimoxazole in all the age groups. The isolates from below 40 years male patients and age groups 50-59 and 70-79 showed almost complete resistance to ciprofloxacin, while it was effective in half of male patients in age groups 40-49 and 60-69. Nitrofurantoin showed 33% resistance in age groups 0-9, 20-29 and 30-39 and was found almost sensitive in all other age groups. Ceftriaxone showed 60% resistance in age group 60+. Ceftriaxone was sensitive in age group 10-19, while it showed variable resistance among other age groups.

antibiotic susceptibility to common urinary anti-infectives among *E. coli* isolated from males versus females was meaningful hence recommending that male sex alone cannot be used as a basis for empirical treatment [7].

Conclusions

Our results have shown that the UTI

Table 5 *E.coli* Susceptibility by sex at Kitwe Central Hospital (Zambia) from 2008-2013

Antibiotic		**Total n (%)**	**Sex**		**x^2 ;p value**
			Female n (%)	**Male n (%)**	
Cefotaxime	Sensitivity	198 (60.7)	152(63.3)	46(53.5)	2.57; 0.140
	Total	326	240	86	
Chloramphenicol	Sensitivity	162(48.9)	117(49.4)	45(47.9)	0.02; 0.902
	Total	331	237	94	
Ciprofloxacin	Sensitivity	257(70.2)	186(71.3)	71(67.6)	0.32; 0.573
	Total	366	261	105	
Co-trimoxazole	Sensitivity	38(11.4)	23(9.7)	15(15.6)	1.78; 0.182
	Total	332	236	96	
Nalidixic acid	Sensitivity	229(33.8)	160(39.5)	160(58.6)	23.12; 0.000
	Total	678	405	273	
Nitrofurantoin	Sensitivity	348(59.7)	253(61.3)	95(55.9)	1.23; 0.207
	Total	583	413	170	
Norfloxacin	Sensitivity	325(64.5)	228(66.1)	95(59.9)	1.63; 0.201
	Total	504	345	159	

Ciprofloxacin, co-trimoxazole and trimethoprim showed variable resistance patterns in all age groups except 40-49 in which these antibiotics were effective among half the female patients [6]. A study done in USA reported that differences in

pathogens isolated at KCH were less than 70% sensitive to the recommended and used antibiotic. Studies to establish high sensitive antibiotics to UTI pathogens are needed to effectively treat patients.

Authors' contributions

JC obtained the data, conducted preliminary analysis and drafted the manuscript. JM revised the manuscript. CB research protocol development, analysed the findings and revised the manuscript. SS interpreted the findings and edited the manuscript MLM reanalyzed the data, interpreted the results and edited the manuscript.

Acknowledgement

We would like to thank the management of Kitwe Central Hospital for allowing us to use their records.

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