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Risk factors for resistance to antimicrobial drugs among extended-spectrum beta-lactamase producing *Escherichia coli* from urinary tract infection inpatients in tertiary health care facilities in Zanzibar: a retrospective health facility-based study

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Abstract

Introduction: *urinary tract infection (UTI) due to extended-spectrum beta-lactamase (ESBL) producing Escherichia coli (E. coli) has become a significant public health problem worldwide. The current study assessed the antimicrobial resistance profile and risk factors for ESBL-producing E. coli among patients receiving care and treatment for urinary tract infections (UTIs) in Zanzibar.* ***Methods:*** *a retrospective study was conducted from 2018 to 2020 in Zanzibar. The clinical records of antimicrobial resistance were retrieved from five (5) purposively selected microbiological and drug susceptibility testing laboratories in Zanzibar. All documented UTI patients aged 2 and above were included. Binary logistic regression analyses were used to look at the risk factors that predict ESBL E. coli antimicrobial resistance.* ***Results:*** *in total, 421 (23.1%) ESBL-producing E. coli were isolated from UTI patients. Seventy-one point one percent were female, and 28.9% were male (p=0.01). The majority of the patients were between the ages of 15 and 30. The resistance rate was high for ampicillin 95.9% 94.6% tetracycline, 93.2% ciprofloxacin, 90.8% norfloxacin, 89.5% nalidixic acid, 78.4% sulfamethoxazole/trimethoprim, 78.1% ceftriaxone, 73.5% cefotaxime, 71.8% gentamicin, and 70.7% ampicillin-amoxicillin. There was moderate resistance to chloramphenicol 51.6% and the lowest resistance to amikacin, 27.5%, with no resistance reported to meropenem. Multivariate analysis showed that the history of hospitalisation, long hospital stay, and antibiotic use history were significantly associated with antibiotic resistance of ESBL producing E. coli uropathogenic (<0.05).*

Conclusion: *antimicrobial drug resistance was high among ESBL-producing E. coli in Zanzibar. The main predictors of resistance were associated with a history of hospitalisation, recurrent attack of urinary tract infection, long hospital stay, and antibiotic use history. A strategic plan and interventions are needed to tackle antimicrobial resistance and target the identified risk factors.*

Introduction

Antibiotic resistance due to extended-spectrum beta-lactamases (ESBL) found in *Enterobacteriaceae* has rapidly become a public health threat [1]. In return, overuse of antibiotics accelerates the magnitude of the problem worldwide [2]. The predictive statistical models suggest an estimated 4.95 million bacterial-associated deaths, out of which the bacterial AMR claimed 1.27 million lives [3]. Africa is on the verge of facing the greatest AMR threat, with most countries currently dealing with infections caused by resistant organisms. The continent is threatened by a higher morbidity and mortality, expensive antimicrobial related illness resulting in extended hospital stays, and place a greater burden on health systems due to infections caused by microbial resistant organisms [4]. *Enterobacteriaceae* bacteria, including *Escherichia coli (E. coli)* have been pathogens of death associated with AMR, accounting for 3.57 million lives lost due to AMR in 2019 [5]. The overuse and misuse of extended-spectrum antibiotics contribute to the emergence of ESBL-producing *E. coli*. As a result, urinary tract infection (UTI) due to extended-spectrum β-lactamase (ESBL)-producing *E. coli* has become a significant public health problem worldwide [6]. The emergence of antibiotic resistance among ESBL-producing *E. coli* causing UTIs against commonly used antibiotics has been documented in different countries [7]. However, a few studies have been conducted in developing countries to determine the risk factors associated with resistance to ESBL-producing *E. coli* isolated from urine samples. Risk factors for antibiotic resistance differ due to prescription

practices and the use of antibiotics in the community [8]. In Zanzibar, there has been an increasing level of antimicrobial resistance of ESBL-producing *E. coli* from urinary tract infection to third-generation cephalosporin antibiotics each year. Identifying risk factors will help improve the treatment through the prescription of the right and effective antibiotics and preventive measures to limit the transmission of resistant infectious pathogens in hospital and community settings to alleviate the magnitude of the problem.

Methods

Study design: the retrospective analysis was carried out, covering three years from 2018 to 2020. All patients' medical information with UTIs admitted in tertiary hospitals was retrospectively recorded.

Setting: the study utilised data collected from five purposively selected clinical, microbiological laboratories that provide bacterial culture services and drug sensitivity testing and are also attached to the public and private tertiary hospitals in Zanzibar.

Participants: all documented UTI patients aged 2 to 72 years and who meet the inclusion criteria for the WHO definition of community and hospital-acquired UTI. The average age of patients is 33.33±11.62 years. In addition, 5220 (64.4%) participants were female, and 2812 males (35.1%) were male.

Variables: social demographics and clinical characteristic including, prior hospitalisation, recurrent UTI, prior antibiotic use, dose incompleteness, duration of hospital stay and prior use of a catheter were considered as dependent variables. Antimicrobial resistance of ESBL producing *E. coli* was considered as independent variable. A prior hospitalisation was defined as a case that had been hospitalised for more than one day before the diagnosis of a urinary tract infection [9]. Foley catheterisation history was defined as cases with catheterisation for more than three days before UTI diagnosis [10].

Data source/measurements: the study used patient´s data collected from medical records at tertiary health centres. Specific patient information, such as socio-demographic and clinical information, was gathered from admitted health care facilities. Positive urine cultures and sensitivity records were obtained from five purposively selected laboratories that provide bacterial culture services and drug susceptibility testing and are also attached to tertiary health care facilities. Medical records of all patients documented with UTIs and found cultured positive for ESBL producing *E. coli* from corresponding laboratories were used to obtain information on ESBL-producing *E. coli* isolates. The patient's information was retrieved from the sample request form upon arrival in the laboratory.

Samples collection: in all the participated laboratories, standardized urine collection, transportation procedures were implemented. Urine samples were obtained by clean midstream catch method or balder catheterization. The samples were transported in cold boxes and kept at 2-8°C until ready for processing as described in the standard operating procedures.

Laboratory sample analysis: in all laboratories, urine specimens were processed following standard operating procedures and Clinical and Laboratory Standards Institute (CLSI) guideline [11]. Conventional microbiological methods were used to identify the ESBL-producing *E. coli* isolate. Moreover, screening of ESBL-producing *E. coli* was carried out through a zone of inhibition of ≤ 25 mm for ceftriaxone and/or ≤ 22 mm for ceftazidime and or ≤ 17 mm cefpodoxime and or 27 mm for cefotaxime considered as positive ESBL producer [12]. ESBL-producing *E. coli* was confirmed phenotypically using the combined disc method. Discs containing ceftazidime (30 µg) and a combination of discs containing clavulanic acid (30 µg + 10 µg) were placed 25 mm apart. The isolate was considered

an ESBL producer when an increase in zone of the diameter of ≥5 mm in the zone of inhibitor for ceftazidime + clavulanic acid compared to ceftazidime alone was confirmed as ESBL-producing *E. coli* according to CLSI guideline [12]. For quality assurance, the reference strain of *E. coli* (ATCC 26122) and *Klebsiella* (ATCC 75674) were used in quality control for culture and susceptibility tests as well as for the detection of ESBL detection. Antibiotic's susceptibility test was carried out using Kirby-Bauer's disc diffusion method, and interpretation of the results, whether resistant, susceptible or intermediate, were based on recommendations by Clinical and Laboratory Standard Institute guidelines [12].

Bias: there was any bias carried out in this study. To ensure the validity and reliability of data, laboratories quality control measures were considered during this study. All laboratory procedures were done in accordance with standard operating procedures and CLSI guidelines. The reference strain of *E. coli* (ATCC 26122) and *Klebsiella* (ATCC 75674) were used in quality control for culture and susceptibility tests as well as for the detection of ESBL detection.

Study size: the study used retrospective data, therefore there was no statistic formula used to estimate sample size. A total of 8,104 urine samples of UTIs patients were collected for culture and sensitivity from five purposively laboratories, out of the 491294 suspicious cases of UTIs patients reported in five hospitals.

Data analysis: the data were analyzed using Statistical Package for Social Science version 21 (Chicago, Inc). The frequency, mean, media and standard deviation were used. The annually differences in antibiotics resistance were compared using the Chi-square test and Fischer's exact test. Univariates by binary logistic regression was performed to determine statistical significance with association of risk factors and resistance to ESBL producing *E. coli*. This was based on those variables with P-value 0.05 or less in the univariate logistic regression and was considered for the multivariable logistic analysis. Odds ratio (OR) and 95% confidence interval (95%Cl) were used to show the association between risk factors and antibiotics resistance of ESBL *E. coli*.

Ethics considerations: permission to use the data was obtained from the respective hospital administrations. Ethical approval was obtained from the Zanzibar Health Research Ethical Review Committee of the Zanzibar Health Research Institute, with approval number ZAHREC/O4/ST//32.

Results

Prevalence of urinary tract infections based on demographical characteristics: the average age of the study participants was 33.33±11.62 years, with a minimum age of 2 years and maximum age of 72 years. In terms of high age, prevalence of UTI was reported at the age between 16-30 years at 550 (30.4) as compared to the lowest of 320 (17.7%) in the age group <15(p=0.01). With respect to sex, the prevalence was 1120 (61.8%) in females and 691 (38.1%) in males. A total of 8,104 urine samples were cultured. A total of 8,104 urine samples were cultured, while ESBL-producing *E. coli* was isolated in 421 (23.2%) samples.

Distribution of urinary tract infection within three years period: a total of, 491294 suspicious cases of UTIs were reported; the least number of cases reported in 2018 at 29.0%, followed by 33.7% in 2019, while in 2020, 37.2% (p = 0.02). The overall prevalence of UTI caused by ESBL producing *E. coli* from UTI in patients was 23.3% during 3 years´ time period.

Trend of antimicrobial resistance of ESBL producing *E. coli* isolated in urinary tract infection: from Table 1, ESBL producing *E. coli* showed the highest level of resistance to antibiotics reported to ampicillin 406 (95.9%), 398 (94.6%) tetracycline, 393 (93.2%) ciprofloxacin, 384 (90.8%) norfloxacin, 379 (89.5%) nalidixic acid

respectively. Low level of resistance was reported to chloramphenicol 155 (51.6%) and least resistance to amikacin 116 (27.5%), and zero resistance to meropenem. Significant difference observed to ampicillin (p = 0.04) and ceftriaxone (p = 0.002) and nalidixic acid (p = 0.03).

Risk factors associated with antimicrobial resistance in ESBL producing *E. coli*: univariate logistic regression analysis of social-demographical and clinical characteristics with antimicrobial resistance in ESBL-producing *E. coli* shown in Table 2. The age, sex, recurrent urinary tract infection, previous use of the catheter, dose incompletion, prolonged hospital staying and history of taking antibiotics were subjected to regression model against antibiotics. All variables that had a statistical significance defined by a P-value < 0.05 were further entered in a multivariate logistic regression model. The only risk factors that impose the effect of antimicrobial resistance among *E. coli* isolate from urinary tract infections commonly used antibiotics were the previous hospitalisation to ciprofloxacin (OR 1.40) and ceftriaxone (OR 2.43). Recurrent urinary tract infection is significantly associated with the resistance to ceftriaxone (OR 2.31), ampicillin (OR 1.86), ciprofloxacin (OR 2.51), cefpodoxime (OR 3.42). Prior to taking antibiotic to ampicillin (OR 3.2), ciprofloxacin (OR 2.12) and ampicillin-cloxacillin (OR 2.78). Extended hospital stay to ampicillin (OR 1.62), ceftriaxone (OR 3.35) and ciprofloxacin (OR 2.33) and ampicillin-cloxacillin (OR 2.74). Our study did not find a significant association between age, sex, dose non-completion, catheter use to antibiotic resistance (p>0.05) (Table 3).

Discussion

In this study, a high prevalence of UTI was reported in the age group between 15-30 years compared to others; this is in line with a study from Nepal [13,14]. However, this contradicts studies which were conducted in Palestine [6]. This is the most reproductive age; hence are at high risk of UTIs [10,15]. Female patients reported the highest prevalence of UTIs compared to males. This finding is similar to studies reported in Korea [16]. However, other studies found statistical significance in male than female patients [15]. Having short urethra of the urinary tract in females makes it easy for uropathogens to reach the internal surface of the reproductive tract [17] and is easy for uropathogens to get into the internal surface of the female reproductive tract [18].

We found a greater significant association between antimicrobial resistance in urinary tract infections and previous hospitalisation, recurrent urinary tract infection, prolonged hospital stay, and previous antibiotic use. The risk factors have a strong association with resistance to ampicillin, ciprofloxacin, ceftriaxone, cefpodoxime, ampicillin-cloxacillin) respectively. Similar findings were reported in Tanzania Mainland [19] and China [20]. This could be explained as the indicator for hospital-acquired resistance associated with inadequate infection and prevention control measures in hospital settings. In addition, with received antibiotics in community pharmacies without a medical prescription [3]. Prolonged hospitalisation increases the duration of exposure to broad-spectrum antibiotics. This increased overuse of antibiotics causes mutations in gene sequences encoding for β-lactam antibiotics [21]. The association of recurrent UTIs with antibiotics resistance agrees with the study [22]. This suggests reducing the efficacy of most antibiotics for treating UTIs, including cephalosporin third generation.

The overall prevalence of UTI is 23.3% is relatively higher compared to the studies in Kenya at 15.7% [23], Uganda 19.5% [10]. The elevated levels of UTIs may be linked to the fact that the island, to a larger extent, relies on imported animal feeds and feed products from other places where hygiene is limited. A high level of resistance to the commonly used antibiotics, tetracycline, is similar to the recent reports in Nigeria [24]. Ultimately, most of these drug groups are

relatively cheap and are more likely to be dispensed over the counter. As a result, the over-use of antibiotics increases selection pressure and accelerates antimicrobial resistance [25]. Moreover, the broad-spectrum nature of these antibiotics such as ciprofloxacin, and their widespread used in the treatment of opportunist bacterial infections in AIDS patients and typhoid fever, can accelerate the risk of resistance [26]. These findings suggest the critical need to implement a hospital stewardship program to facilitate monitoring antimicrobial consumption and use in community and hospital settings for better treatment outcomes.

Cephalosporin resistance is the broad-spectrum third-generation antibiotics, including ceftriaxone and cefotaxime, and ampicillin-cloxacillin is attributed to their β-lactam nature, targeted by β-lactamase enzymes, resulting in the inactivation of the ESBL enzymes and hence accelerated resistance [13,27]. Similar findings were previously reported in Spain [28]. Nonetheless, a low level of resistance was reported in a study reported in Korea [29]. The low resistance rate to amikacin and chloramphenicol is similar to the findings in Egypt [30]. This is attributed to its clinical use through an intravenous (IV) or intramuscular (I.M.) administration in injectable formulation for the treatment of complicated and recurrent UTIs, and thereby, they are less available over the counter without a prescription. In addition, chloramphenicol, is rarely prescribed due to its high risk of aplastic anaemia. Surprisingly, as with the study by Moyo *et al*. (2020), this study could not find any resistance to meropenem, suggesting its best performance in treating UTIs and a drug of choice for ESBL.

Conclusion

The prevalence of urinary tract infections has risen steadily within three years. Antimicrobial resistance of ESBL-producing *E. coli* to commonly used antibiotics has been reported to be very high and alarming. Meropenem, cefotaxime, chloramphenicol, nalidixic acid, norfloxacin, and gentamicin are drugs of choice against ESBL-producing *E. coli*. Previous hospitalisation, extended hospital stay, recurrent urinary tract infection, and prior antibiotic use are significant risk factors for increasing antibiotic resistance in Zanzibar. A strategic plan and intervention are required, including establishing a national antimicrobial surveillance system and a hospital antimicrobial stewardship program. In addition, improvement of the existing laboratory capacity for detecting antimicrobial resistance pathogens with specific ESBL producing *Enterobacteriaceae* pathogens

What is known about this topic

- *Antimicrobial resistance is the global public health threat;*
- *There is an increase in the global mortality rate due to antimicrobial-resistant infectious diseases;*
- *The irrational of antimicrobial agents accelerate the magnitude of the problem.*

What this study adds

- *There is a high level of resistance among ESBL-producing E. coli to commonly used antibiotics;*
- *The study suggests that a history of hospitalisation, recurrent attack of urinary tract infection, extended hospital stay and antibiotic use history were associated with increasing antimicrobial resistance;*
- *They suggest the critical need to implement a hospital stewardship program to facilitate monitoring antimicrobial consumption in a community and in hospital settings.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Muhiddin Omar, Andrew Kilale, Emmanuel Kigadye, Angaza Gimbi contributed to the study design and data review and wrote the manuscript; Muhiddin Omar collected data. Isaack Onoka and Burhan Simai analysed the data and prepared the tables. All the authors have read and agreed to the final manuscript.

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Tables

Table 1: trend of antimicrobial resistance of ESBL producing *E. coli* isolated in urinary tract infection (2018-2020)

Table 2: univariate analysis of risk factors for ESBL *E. coli* antibiotics resistance

Table 3: multivariable analysis of independent risk factors for ESBL *E. coli* antibiotics resistance

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Table 1: trend of antimicrobial resistance of ESBL producing *E. coli* isolated in urinary tract infection (2018-2020)

Antimicrobial agents	**Resistance of antimicrobials (%) in year**			**Mean %**	**p-value**
	2018 n =105	2019 N =151	2020 n =165		
AMP	96(91.4).	147(97.3)	163(98.7)	95.9	0.04
CRO	57(54.2)	121(80.7)	134(81.2)	78.1	0.002
SXT	76(72.3)	114(75.4)	144(87.2)	78.4	0.23
CIP	97(92.3)	140(92.7)	156(94.5)	93.2	0.14
GN	61(58.0)	105(69.5)	145(87.8)	71.8	0.09
CTX	50(49.0)	125(82.7)	147(89.0)	73.5	0. 06
NOR	93(88.5)	137(90.7)	154(93.3)	90.8	0.38
AMK	33(31.4)	16(10.5)	67(40.6)	27.5	0.12
NAL	91(86.6)	136(90.0)	152(92.1)	89.5	0.03
CHL	40(38.0)	87(57.6)	89(59.3)	51.6	0.18
TER	100(2)	146(96.6)	152(92.1)	94.6	0.06
MEM	0(0.0)	0(0.0)	0(0.0)	0(0.0)	-
AMPC	41(56.9)	56(69.3)	91(86.6)	70.7	0.28

AMP = Ampicillin; CRO = Ceftriaxone; SXT = Sulfamethoxazole/Trimethoprim; CIP= Ciprofloxacin; GN= Gentamicin; CTX = Cefotaxime; NOR = Norfloxacin; AMK = Amikacin; NAL = Nalidixic acid; CHL = Chloramphenicol; TER = Tetracycline; MEM = Meropenem; and AMPC = Ampicillin-Amoxicillin

Table 2: univariate analysis of risk factors for ESBL *E. coli* antibiotics resistance

Risk factors	Label	AMP		P-value	CIP		P-value	CRO		P-value	SXT		P-Value	CEF		P-Value	AMP/CLAV	
		OR	(95% CI)		OR	95% CI		OR	95% CI		OR	95%CI		OR	95%CI		OR	95%CI
Age (yrs)	> 45	Ref			Ref			Ref			Ref			Ref			Ref	
	<15	0.3	(0.68 - 1.87)	0.06	1.35	0.18-10.0	0.7	0.5	0.88-3.11	0.45	0.26	0.03-2.72	0.26	0.076	00-11.95	0.31	2.79	0.146-53.42
	16 to 30	0.4	0.68-1.87	0.22	0.2	0.12.26	0.34	0.5	0.33-16.1	0.33	0.13	0.03-1.26	0.07	0.64	0.01-4.28	0.19	0.48	0.02-8.07
	31 to 45	0.37	0.01-43.56	0.71	0.4	0.38-14.8	0.11	0.5	0.13-5.55	0.88	0.13	0.01-1.61	0.12	0.01	7.62-1.9	0. 08	0.48	0.03-8.07
Sex	Male	Ref			Ref			Ref			Ref			Ref			Ref	
	Female	9.2	0.64-0.88	0.15	2.3	0.65-8.67	0.12	0. 42	0.10-1.796	0.245	0.52	0.12.182.	0.38	0.02	0.00-0. 59	0.23	0.1	0.01-.69
Recurrent UTI	Yes	Ref			Ref			Ref			Ref			Ref				
	No	1.86	0.57-12.3	0	2.5	0.59-11.23	0.006	0.313	0.081-1.85	0.01	0.17	0.02-1.28	0.08	2.1	0.00-3.36	0.028	3..28	0.03-2.20
Prior hospitalization	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	0.46	0.95-2.29	0.08	1.4	0.30-6.92	0.06	0.33	0.15-1.89	0.08	1.65	0.25-10.37	0.07	0.02	0 .00-.0. 60	0.23	0.98	0.11-8.62
Long Hospital staying	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	1.62	0.44-5.9	0	2.33	0.36-4.77	0.03	3.5	0.73-8.06	*0.001	0.08	1.83-11.24	0.09	0.31	0.00-1.50	0.06	0.41	0.01-0.72
Prior Use catheter	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	0.52	0.57-12.3	0.28	2.5	1.59-11.23	0.62	0.09	0.57-27	0.25	0.32	0.49-30.70	0.08	0.11	0.32-196	0.09	0.16	0.45-114.90
Dose incompletion	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	0.67	0.75-16.27	0.31	1.34	0.72-22.04	0.14	0.93	0.32.-2.60	0.89	0.78	0.16-3.85	0.76	0.05	0.00-0 .86	0.39	0.42	0.07-2.48
Prior taking antibiotic	Yes	Ref			Ref			Ref			Ref						Ref	
	No	0.2	0.4-0.9*	0.03	2.1	0.52-8.20	0.04	0.425	0.14-1.29	0.12	0.41	0.09-1.77	0.23	0.39	0.05-3.04	0.37	0.05	0.05-1.03

AMP= Ampicillin; CIP = Ciprofloxacin; CRO =Cefriaxone; SXT Sulfamethoxazole Trimethoprim; CEF=Cefpodoxime; AMP/CLAV=Ampicillin Clavulante, OR = Odd ratio and Cl = Confident interval

Table 3: multivariable analysis of independent risk factors for ESBL *E. coli* antibiotics resistance

Risk factors	Label	AMP		P-value	CIP		P-value	CEF		P-value	SXT		P-Value	CEFP		P-Value	AMPC	
		OR	(95% CI)		OR	95% CI		OR	95% CI		OR	95%CI		OR	95%CL		OR	95%CI
Prior hospitalization	**Yes**	**Ref**			**Ref**			**Ref**			Ref			Ref			Ref	
	No	2.41	0.99-11.11	0.002	1.77	0.45-9.22	0.001	1.56	0.78 - 9.12	0	2.22	0.80-6.99	0.04	1.75	0.44-8.75	0.02	2.85	0.90-12.34
Long Hospital stay	Yes	Ref			Ref			Ref			Ref						Ref	
	No	2.62	0.44-5.93	0.04	1.3	0.36-4.77	0.001	2.42	0.73 - 8.06	*0.003	1.82	1.83-11.24	0.08	2.54	0.45-14.48	0.08	3.34	0.56-9.09
Recurrent UTI	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	1.83	0.57-12.3	0.008	2.5	1.59-11.23	0.07	1.17	0.57 -27	0.25	3.62	0.49-30.70	0.23	2.11	0.32-19.60	0.08	2.72	0.33-5.67
Prior taking antibiotic	Yes	Ref			Ref			Ref			Ref			Ref			Ref	
	No	3.22	0.4-0.9*	0.03	2.1	0.52-8.20	0.01	2.425	0.14 - 1.29	0.01	3.41	0.09-1.77	0.03	2.49	0.053.04	0.03	2.78	0.99-10.33

AMP = Ampicillin; CIP = Cipropfloxacin; CRO =Cefriaxone; SXT= Sulfamethoxazole Trimethoprim; CEF = Cefpodoxime; AMP/CLAV = Ampicillin- clavulante; OR = Odd ratio and CI = Confident Interval