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Trimethoprim-sulfamethoxazole and fluoroquinolones Resistant *Escherichia Coli* in Community-Acquired and Nosocomial Urinary Tract Infections in Rio De Janeiro, Brazil

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Abstract

To investigate the multidrug resistance (MDR) patterns of *Escherichia coli* causative of urinary tract infections (UTI) in patients attending a tertiary university hospital of Rio de Janeiro, Brazil. Antibiotic susceptibility testing was performed by the disk diffusion method. MDR, extensively-resistance (XDR) and pan-resistance (PDR) were defined by using recently described criteria. Retrospective analyses of clinical, microbiological and demographic features of outpatients and inpatients with UTI (n=416) were also performed. High antibiotic resistance rates for trimethoprim-sulfamethoxazole - SXT-TMP (n=177; 46.7%) and fluoroquinolones - FQ [n=117; norfloxacin (27%) and ciprofloxacin (26.8%) – (FQ) were demonstrated for *E. coli* strains isolated from community and healthcare-onsets. Risk factors associated with UTIs due to MDR *E. coli* isolates included prior three-month hospitalization (OR: 2.4; CI 95%: 1.3-4.4; $p<0.005$), presence of neurogenic bladder (OR: 3.7; CI 95% :1.7-8.3; $p<0.01$) and kidney transplantation (OR: 3.1; CI 95%:1-0.5; $p<0.04$). A high prevalence of community-acquired and nosocomial urinary tract infections due SXT-TMP/FQ resistant *E. coli* strains was observed in Rio de Janeiro metropolitan area, Brazil. According to IDSA Guidelines, initial empirical therapy for community-associated UTI with SXT-TMP and FQ should be avoided in Rio de Janeiro. Nitrofurantoin, amoxicillin/clavulanic, piperacillin/tazobactam or gentamicin associations were effective for the empiric therapy for community-acquired and healthcare-associated UTIs, respectively.

Keywords: *Escherichia coli*; Healthcare-associated infections; Kidney transplantation trimethoprim-sulfamethoxazole resistance; Fluoroquinolones resistance; Urinary tract infection

Introduction

Urinary tract infection (UTI) is one of the most important causes of healthcare-associated infections in many clinical onsets worldwide, including Brazil [1,2]. UTI brings considerable risk on morbidity and mortality to patients, especially in catheter associated urinary tract infections (CAUTI) which prolonged the length of stay in intensive care units (ICU) and increased the risk of death [3]. Several epidemiological studies have shown increasing trends on multidrug resistant (MDR) *Escherichia coli* in UTI and bloodstream infections within the community as well as in hospitals and long-term care facilities [4-10]. Nowadays, the emergence of antimicrobial resistance among uropathogenic *E.coli* is one of the most impacting factors in UTI management. Recent published guidelines for the management of uncomplicated UTI [11] and CAUTI [12] have several limitations on antibiotic choices related to the regional epidemiologic variations of *E. coli* drug resistance. Therefore, periodically surveillance of antibiotic resistance patterns is a strategic tool to guide empiric antibiotic therapy in UTI, especially of patients presenting structural disturbs of urinary tract and/or submitted to prior hospitalization or kidney transplantation.

The aims of this study were to characterize the antibiotic susceptibility profiles of *E. coli* isolates recovered from community and healthcare-associated UTIs and to correlate these findings with risk factors and clinical features of patients attending a tertiary teaching 600-beds hospital in Rio de Janeiro metropolitan area, Brazil.

Methodology

Microbiological, clinical and demographic characteristics of patients with UTI

Urine cultures records from outpatients and inpatients (n=419) with *E. coli* growth in a recount higher than 10^5 colony-forming unit (CFU) (n=437) were retrospectively analyzed. Bacterial isolation and identification procedures were performed following institutional protocols and using biochemical tests described elsewhere [13]. Definition of community and healthcare-associated *E. coli* infection was based on the classification of the Centers for Disease Control and Prevention-CDC (USA) [14]. Community-associated *E. coli* isolates were considered when recovered from patients with 48 hours or less of hospitalization. Only one positive-culture by patient during a three-month period was selected for this survey. Urine samples presenting

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Characteristics	Episodes Total Number (%)	Hospital-Onset	Community-Onset		
			Total	Healthcare-Associated	Community-Associated
	437	62	375	116	259
	-100%	[N (%)]	-85.70%	-126.40%	-59.20%
Age in years, mean (range)	53.6 (0 - 91)	61.5 (11 - 91)	52.2 (0 - 91)	54.7 (1 - 88)	51 (0 - 91)
Female gender	340 (77.8)	36 (58)	304 (81)	84 (72.4)	220 (84.9)
Clinics					
Gynecology/obstetric	24 (5.5)	-	24 (6.4)	7 (6.1)	17 (6.7)
Internal Medicine	142 (32.5)	30 (48.4)	112 (29.8)	28 (24.4)	84 (32.5)
Nephrology	92 (21)	5 (8)	87 (23.2)	40 (34.1)	47 (18)
Urology	88 (20.1)	11 (17.4)	77 (20.5)	30 (25.6)	47 (18)
Surgery	22 (5)	11 (17.4)	11 (2.9)	1 (1.2)	10 (3.7)
Pediatric	37 (8.4)	2 (3.2)	35 (9.3)	3 (2.4)	32 (12.3)
Other	32 (7.3)	3 (4.8)	29 (7.7)	7 (6.1)	22 (8.9)
Prior 3-month hospitalization	139 (31.8)	24 (38.7)	116 (30.9)	116 (100)	NA
Prior time of hospitalization, month, mean (range)	10.3 (1 - 60)	8.9 (1 - 36)	10.6 (1 - 60)	10.7 (1 - 60)	NA
Time to positive urine culture,* days, mean (range)	6.3 (0 - 72)	6.3 (0 - 72)	NA	NA	NA
Prior antibiotic use					
Prior 3-month antibiotic use	139 (31.8)	35 (56.4)	104 (27.7)	45 (39.2)	59 (22.7)
Amino or carboxi-penicillins with or without ß-lactamase inhibitor	61 (43.8)	13 (37.1)	48 (46.1)	23 (50)	25 (42.2)
Fluoroquinolone 2nd	26 (18.7)	6 (17.1)	20 (19.2)	2 (5)	18 (30.3)
Cephalosporin 2nd	17 (12.2)	8 (22.6)	9 (8.6)	5 (10)	4 (6)
Fluoroquinolone 3rd	11 (7.9)	4 (11.4)	7 (6.7)	7 (15)	-
Fluoroquinolone 1st	10 (7.1)	-	10 (9.6)	3 (7.5)	7 (12.1)
Cephalosporin 3rd	4 (2.8)	1 (2.8)	3 (2.8)	3 (7.5)	-
Others	10 (7.1)	3 (8.7)	7 (6.7)	2 (5)	5 (9)
Co-morbidities					
Diabetes mellitus	112 (25.6)	9 (14.5)	103 (27.4)	26 (22.5)	77 (29.6)
Prior 6-month abdominal trauma	11 (2.5)	7 (11.3)	4 (1.6)	-	6 (2.2)
Prior abdominal or pelvic surgery	176 (40.2)	20 (32.2)	156 (40.5)	57 (49)	95 (36.5)
Neurogenic bladder	74 (16.9)	21 (33.8)	53 (14.1)	30 (25.6)	23 (8.9)
Chronic kidney insufficiency	60 (13.7)	9 (14.5)	51 (13.6)	19 (16.6)	32 (12.4)
Kidney transplantation	44 (10)	1 (1.6)	43 (11.4)	27 (23.5)	16 (6.2)
Inmunosupressor use	46 (10.5)	2 (3.2)	44 (11.7)	26 (22.5)	18 (6.9)

* From hospitalization date (for in-patients only); NA, Not applicable

Table 1: Demographic and clinical features of patients with urinary tract infection due to *Escherichia coli* attending a tertiary teaching hospital during a one-year period, Rio de Janeiro, Brazil.

more than one microorganism isolated in cultures were excluded from this study.

A retrospective analysis of the antibiotic susceptibility profiles of *E. coli* isolates recovered from community and healthcare-associated UTIs and the possible risk factors and clinical features of patients attending the Pedro Ernesto University Hospital, Rio de Janeiro, Brazil (a tertiary teaching 600-beds urban hospital, 5-intensive care units) was conducted in this descriptive serial study. Microbiological data were obtained from the records of the Laboratory of Microbiology at the HUPE/FCM/UERJ – RJ, Brazil and from clinical record of each patient.

The following clinical and epidemiological aspects of cases of UTI due to *E. coli* were analyzed in this study: age, gender, hospitalization setting and time, prior hospitalization, use of antimicrobial agents and surgical procedures, co-morbidities (i.e., diabetes mellitus, renal chronic insufficiency), immunosuppressive conditions, kidney transplantation and structural or functional anomalies of urinary tract (bladder dysfunction) (Table 1).

Antimicrobial susceptibility profiles. The sensitivity to antimicrobial agents (Oxoid, Hampshire, United Kingdom) amikacin (30 µg), amoxicillin (30 µg), amoxicillin plus clavulanic acid (30 µg), ampicillin (30 µg), ampicillin plus sulbactam (10/10 µg), cefepime (30 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), ciprofloxacin (5µg), norfloxacin (10µg), gentamicin (10 µg), imipenem (10µg), meropenem (10µg), nitrofurantoin (10 µg), piperacillin plus tazobactam (100/10 µg), and trimethoprim-sulfamethoxazole (SXT-TMP) (1.25/23.75 µg) was determined by the disk diffusion method in accordance with the Clinical Laboratory Standards Institute-CLSI (2013) guidelines [15]. MDR *E. coli* was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [16].

The presence of extended-spectrum beta-lactamase (ESBL) was determined by the double–disk synergy test. A zone of inhibition between any one of the disk containing beta–lactams and the disk containing clavulanic acid indicated the presence of ESBL [17].

Statistical Analysis

A descriptive analysis of the variables analyzed was performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for categorical variables and the χ^2 test was also used (the Fisher exact test was used if an expected value was less than 5). Logistic regression was used to examine potential associations between variables, and a multivariate analysis was performed to identify risk factors

Antimicrobial agents testing	Proportion (%)	Number (%) of *Escherichia coli* strains expressing antimicrobial resistance				
Features	***E. coli* strains tested**	**Total**	**Kidney Transplanted Patients**	**Healthcare-Onset**	**Community-Onset**	***P* values**
Antibiotics tested						
Nalidixic acid	23.8	62 (59.5)	5 (62.5)	23 (65.7)	39 (55.7)	0.3
Amicacin	93.3	20 (4.9)	1 (3)	6 (9.7)	14 (4)	0.06
Amoxicillin / Clavulanic Acid	99.5	30 (6.9)	3 (8.8)	3 (4.8)	27 (7.2)	0.4
Amoxicillin	52.6	96 (41.9)	7 (35)	25 (42.3)	71 (41.7)	0.9
Ampicillin	99.5	221 (50.9)	19 (55.8)	31 (50)	190 (51)	0.8
Ampicillin / Sulbactam	99.5	47 (10.8)	5 (14.7)	4 (6.4)	43 (11.6)	0.2
Aztreonam	98.6	19 (4.4)	2 (6)	3 (4.8)	16 (4.4)	0.8
Cefalotin	99.5	110 (25.3)	9 (27.2)	16 (25.8)	94 (25.2)	0.9
Cefepime	92.6	15 (3.7)	3 (9)	3 (4.9)	12 (3.5)	0.6
Cefotaxime	97	28 (6.6)	3 (8.8)	8 (12.9)	20 (5.5)	0.03
Cefoxitin	53	13 (5.6)	2 (10)	6 (10)	7 (4.1)	0.09
Ceftazidime	100	21 (4.8)	4 (11.7)	3 (4.8)	18 (4.9)	0.9
Cefuroxime	96.7	61 (14.2)	6 (18.1)	16 (25.8)	45 (12.2)	0.005
Ciprofloxacin	95.4	112 (26.8)	11 (32.3)	14 (22.6)	98 (27.5)	0.4
Gentamicin	88.5	24 (6.2)	3 (9.3)	2 (3.3)	22 (6.8)	0.3
Imipenem	91.5	2 (0.5)	-	-	2 (0.6)	0.5
Meropenem	100	1 (0.2)	-	-	1 (0.2)	0.6
Nitrofurantoin	100	21 (4.8)	6 (17.6)	2 (3.2)	19 (5.1)	0.5
Norfloxacin	99	117 (27)	13 (38.2)	16 (25.8)	101 (27.3)	0.8
Piperacillin / tazobactam	100	5 (1.1)	1 (2.9)	1 (1.6)	4 (1)	0.7
Trimethoprim / sulfamethoxazole	86.7	177 (46.7)	15 (44.1)	29 (46.7)	148 (39.7)	0.3
Aminoglycoside resistance	93.6	25 (6.1)	1 (3)	7 (11.3)	18 (5.2)	0.06
Presence of Extended Spectrum Beta- Lactamase	-	29 (6.7)	4 (11.7)	8 (12.9)	21 (5.6)	0.03
Multidrug resistance	-	130 (29.7)	13 (38.2)	26 (41.9)	104 (27.7)	0.02

Table 2: Antimicrobial susceptibility profiles of 437 *Escherichia coli* strains associated with urinary tract infection in patients attending a tertiary teaching hospital during a one-year period, Rio de Janeiro, Brazil.

Variable	Odds Ratio	95% Confidence Interval	*P* value
Prior 3-month antibiotic use	11.2	5.55 – 22.6	0.0001
Neurogenic bladder	3.7	1.7 – 8.3	0.001
Kidney transplantation	3.1	1.03 – 9.53	0.04

Table 3: Multivariate analysis of MDR *Escherichia coli* strains from hospital and community-onset patients with UTI (HUPE/UERJ).

Variable	Odds Ratio	95% Confidence Interval	*P* value
Prior 3-month antibiotic use	4.3	2.3 - 8.1	0.0001
Prior 3-month hospitalization	2.4	1.3 – 4.4	0.005
Aging	2.1	1.1 - 4	0.01
Renal chronic insufficiency	2.4	1 – 5.6	0.03

Table 4: Multivariate analysis of MDR *Escherichia coli* strains isolated from community patients with UTI.

independently associated with mortality. Variables with a p value>0.05 were excluded from the final model. STATA™ version 9.1 (Statacorp, Texas, USA. 2006) was used for all data analyses, and a p value ≤ 0.05 was considered statistically significant.

Results

Results of the analysis of demographic and clinical records from cases of UTI due to *E. coli* are shown in Table 1. Most of the patients were female (77.8%) with a mean age of 53.6 years-old (range 0-91). From a total of 437 UTI episodes, 375 were in the community-onset (85.7%): 116 (26.4%) healthcare-associated and 259 (59.2%) community-associated.

A number of 139 patients had 3-month prior hospitalization (31.8%); 32.5% of them were from internal medicine or related specialties. There were also patients from the nephrology (21%) and the urology (20%) settings, including a total of forty-four (10%) kidney-transplanted patients in the community (n=43) and hospital-onset (n=1).

Antimicrobial susceptibility profiles of *E. coli* strains associated with UTI are shown in Table 2. A total of 130 (29.7%) *E. coli* strains associated with UTI were MDR. In the transplanted group, one third of *E. coli* isolates were classified as MDR (38.2%); Microorganisms showed resistance to most of the antibiotics tested, especially to nitrofurantoin and fluoroquinolones.

Differences were observed between the *E.coli* isolated from community and healthcare-onsets. MDR, ESBL-producing cefotaxime and cefuroxime-resistant *E.coli* isolates were found more prevalent in the healthcare-onset (p<0.05). Generally, *E. coli* strains from UTI cases showed high resistance rates to norfloxacin (27%), ciprofloxacin (26.8%) and SXT-TMP (46.7%).

Results of multivariate analysis and the respective odds ratios (OR) and 95% confidence interval (CI) performed in order to examine possible associations between the clinic and demographic characteristics of the patients and the presence of MDR *E. coli* isolates in UTI are shown in Tables 3 and 4. The risk factors associated with the presence of MDR *E. coli* isolates in UTI were: prior 3-month antibiotic use, presence of neurogenic bladder and previous kidney transplantation. In a separated multivariate analysis of the community-onset, the presence of MDR isolates were associated with aging (65 years-old and older), renal chronic insufficiency, prior 3-month hospitalization and antibiotic use.

A proposal of an antibiotic guidance to initial empiric therapy in

Choices by UTI Class	Oral	Intravenous	Intramuscular
Community-Associated			
1	Nitrofurantoin	Cefepime or Amoxicillin/Clavulanic Acid	Amicacin†
2	Amoxicillin/ Clavulanic acid	Amicacin†	Gentamicin†
3	-	Aztreonam	-
4	-	Ceftazidime or Cefotaxime; Piperacillin/Tazobactam or Carbapenems*	-
Healthcare-Associated			
1	Nitrofurantoin	Piperacillin / Tazobactam	Gentamicin†
2	Amoxicillin / Clavulanic acid	Gentamicin†	Amicacin†
3	Ampicillin / Sulbactam	Aztreonam	-
4	Fosfomycin	Ceftazidime;	-
		Carbapenems*	

*, Recommended only in cases of therapeutic failure with selected agents; †, Not recommended in cases of kidney chronic disease, renal insufficiency or kidney transplant.

Table 5: Antibiotic guide to initial empiric therapy in urinary tract infections (UTI) due to *Escherichia coli*: a proposal of choices based on profiles of antibiotic resistance < 10%.

urinary tract infections (UTI) due to *Escherichia coli* based on profiles of antibiotic resistance < 10% is displayed in Table 5.

Discussion

UTIs due to *E. coli* are the most prevalent infectious diseases in the general population. They cause a substantial financial burden in the community and are associated with significant morbidity and mortality, particularly in hospitalized patients or patients with comorbidities. An optimal antimicrobial therapy should be based on local antimicrobial resistance patterns, specific risk factors of the patients, pharmacokinetic and pharmacodynamic principles and costs.

Regional studies of UTI in community and healthcare-onsets in order to evaluate the periodically modifications on the resistance patterns of *E. coli*, especially to fluoroquinolones, SXT-TMP, cephalosporins and carbapenems remain necessary. Presently, we found high rates of resistance to classes of antimicrobial agents recommended for treatment of UTI by the United States and European guidelines [11,12]. Interestingly, only two *E. coli* strains isolated from ITU showed resistance to carbapenems.

MDR *E. coli* strains are included among other MDR Gram-negative bacilli highly endemic in healthcare-onsets in Brazil, particularly critical settings, such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp [18]. The increase of resistance can be related to dissemination of MDR *E.coli* clones verified in others countries. Specifically, the *E. coli* clone O25b:H4-ST131 has recently emerged globally as a leading MDR pathogen causing UTI and bloodstream infections in hospitals and in the community [19]. This clone is the major contributors to what is known as 'the CTX-M pandemic; a recent worldwide increase in *E. coli* uropathogens that produce CTX-M type extended spectrum β-lactamases (ESBLs) [20]. *E. coli* ST131 are commonly identified among *E. coli* producing CTX-M-15; currently the most widespread CTX-M extended-spectrum β-lactamases (ESBL) enzyme [5,21]. Additionally, this clone is frequently resistant to **fluoroquinolones [6].** Nowadays, is widely recognized the transference of pathogenicity islands containing resistance genes to *E. coli* (*in vitro* and *in vivo*) from others species and this is particularly true for ESBL, ampC and ultimately carbapenemases [22-24]. Consequently, further studies remain necessary in order to define predominant MDR *E. coli* clones related with UTI in our environment.

Interestingly, some co-morbidities, such as, diabetes mellitus, surgical procedures of abdominal-pelvic cavity or others chronic pathology of bladder different of a neurogenic bladder were not currently associated with the presence of MDR *E. coli*. In the community onset data showed association of UTI due to MDR *E. coli* with aging (65 years-old and older) of the patients, which may indicate obstructive pathologies of the urinary tract. Once MDR *E. coli* was more frequently found among patients with 3-month prior hospitalization and with previous use of antibiotics, a new category in the guidelines of management of UTI should be considered for this "community with risk patients". Additionally, it should be recommended promptly antibiotic therapy directed to MDR microorganisms whenever menacing important programs such as kidney transplant or prosthetic advice use in urologic procedures. It is also necessary to seek for a more appropriate empirical scheme of treatment for UTI in those patients with prior hospitalization or contact with healthcare-onsets, especially in transplanted patients.

Unfortunately useful antibiotics such as fosfomycin are not tested routinely and there are not well established breakpoints for resistance isolates from the Clinical and Standard Laboratory Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations in complicate UTI [25]. Additionally, there are few studies correlating clinical responses of this antibiotic in UTI complicated and uncomplicated due to MDR *E. coli*. [26]. The new cephalosporins (ceftobiprole and ceftaroline) can select *P. aeruginosa* isolates worsening the prognosis of immunosuppressed patients. An issue of great concern it is the high resistance in *E. coli* isolates to fluoroquinolones, recognized inductors for MDR in methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenems-resistant *Acinetobacter* spp. and carbapenemase-producing *K. pneumonia* [27,28].

The use of fluoroquinolones in the healthcare-onset in many settings of Brazil may be questioned. Based in the proportion of antimicrobial resistance of *E. coli* isolates an antibiotic scheme for empirical therapy adapted to our local reality may be suggested. Despite the low rates of resistance to piperacillin/tazobactam *E. coli* isolates in both hospital and community-onsets, it is recommended in community-associated infections only in case of therapeutic failure with other agents in order to save this options for complicated UTI and avoid induction of resistance for other microorganisms (i.e., *P. aeruginosa, Acinetobacter sp.* and *K.*

pneumoniae). Neither fluoroquinolones nor SXT-TMP was considered in this proposal due to the high rates of resistance observed. It should be only recommended in cases of positive cultures for susceptible microorganisms. In community-associated UTI, the use of cefepime may be recommended as a first choice in cases that intravenous therapy is required due to the benefits on final outcome and costs.

Whereas the lowest prevalence of resistance to oral antimicrobials for *E. coli* was 5.1%, 7.2% for nitrofurantoin and amoxicillin /clavulanic acid association respectively, these drugs may be considered as the best options for community-acquired UTI. On the other hand, 1.6% of *E. coli* isolates showed resistance for piperacillin/tazobactam and 3.3% to gentamicin in our hospital. The association piperacillin/tazobactam or gentamicin seemed to be the best option for the empiric treatment of healthcare-associated UTIs considering that *E. coli* is still the main microorganism isolated in urine samples up to 30 days of hospitalization or bladder catheterization. Finally, it is important to reconsider the strategies recommended by laboratory procedure standardization international committees (i.e., CSLI and EUCAST) about the necessity of routinely testing antibiotics such as nalidixic acid or ampicillin in urine cultures showing increased resistance in *E. coli* (59.5 and 50.9% in our series). New prospective studies evaluating the proposed empirical scheme of antibiotic use in UTI should be done, including identification of specific *E. coli* clones disseminated locally in the community and healthcare-onsets.

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Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest. The authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work. All authors declare that they have no competing interests.

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