Original article

Changing *Escherichia coli* susceptibility and increasing antimicrobial resistance in community urinary tract infections

Cambio en la susceptibilidad de Escherichia coli y aumento de la resistencia a los antimicrobianos en infecciones del tracto urinario comunitario

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ABSTRACT

Introduction: Urinary tract infections caused by antibiotic-resistant Gram-negative bacteria are a growing concern due to limited therapeutic options.

Objective: To analyze the antibiotic resistance trend in ciprofloxacin-resistant *Escherichia coli* isolated from community-acquired urinary tract infection.

Methods: Time series study analyzing records of urine cultures positive for ciprofloxacin-resistant *E. coli* in persons aged ≥18 years from 2011 to 2017. The trends in antibiotic resistance patterns were obtained using the *Prais-Winsten* generalized linear regression. Annual percent change (APC) and 95% confidence interval (CI 95%) were calculated from the regression analysis coefficient β_1 and standard error (SE). Values of $p<0.05$ were considered statistically significant.

Results: From the analyzed data, 3 363 (26.1%) were positive for ciprofloxacin-resistant *E. coli*. The increase in ciprofloxacin-resistant *E. coli* was 45.3%. Females suffered more infection by ciprofloxacin-sensitive *E. coli* (75.5%), but males had a higher chance of being infected with ciprofloxacin-resistant *E. coli*. [2.132 (1.891–2.402)]. Increase in resistance was highest for nitrofurantoin (<0.001) and ceftriaxone (<0.001). Prevalence of resistance was high for nitrofurantoin, norfloxacin, nalidixic acid, amoxicillin/clavulanate, ceftriaxone, and tobramycin. Except for gentamicin, which presented a downward trend in resistance, the other antimicrobials analyzed displayed no trends in antibiotic resistance.

Conclusions: There was an average increase in resistance to the main antibiotics used to treat community-acquired UTI. Among the antibiotics tested, only gentamicin displayed a downward trend in resistance. These results are important to direct the choice of antimicrobials for the empirical treatment of community-acquired UTI.

Keywords: Urinary tract infection; community-acquired infection; Anti-Bacterial Agents; *Escherichia coli*.

RESUMEN

Introducción: Las infecciones del tracto urinario causadas por bacterias gramnegativas resistentes a los antibióticos son una preocupación creciente debido a las limitadas opciones terapéuticas.

Objetivo: Analizar la tendencia de resistencia a los antibióticos en *Escherichia coli* resistente a la ciprofloxacina aislada de la infección del tracto urinario adquirida en la comunidad.

Métodos: Estudio de series de tiempo que analiza registros de urocultivos positivos para *E. coli* resistente a ciprofloxacina en personas de ≥18 años de 2011 a 2017. Las tendencias en los patrones de resistencia a los antibióticos se obtuvieron mediante la regresión lineal generalizada de Prais-Winsten. El cambio porcentual anual (APC) y el intervalo de confianza del 95 % (IC 95 %) se calcularon a partir del coeficiente de análisis de regresión $\beta 1$ y el error estándar (SE). Los valores de $p < 0,05$ se consideraron estadísticamente significativos.

Resultados: De los datos analizados, 3363 (26,1%) fueron positivos para *E. coli* resistente a la ciprofloxacina. El aumento de *E. coli* resistente a la ciprofloxacina fue del 45,3 %. Las mujeres sufrieron más infección por *E. coli* sensible a la ciprofloxacina (75,5 %), pero los hombres tuvieron una mayor probabilidad de infectarse con *E. coli* resistente a la ciprofloxacina [2,132 (1,891–2,402)]. El aumento de la resistencia fue mayor para la nitrofurantoína (<0,001) y la ceftriaxona (<0,001).

La prevalencia de resistencia fue alta para nitrofurantoína, norfloxacina, ácido nalidíxico, amoxicilina/clavulanato, ceftriaxona y tobramicina. A excepción de la gentamicina, que presentó una tendencia a la baja en la resistencia, los otros antimicrobianos analizados no mostraron tendencias en la resistencia a los antibióticos.

Conclusiones: Hubo un aumento promedio en la resistencia a los principales antibióticos utilizados para tratar la infecciones del tracto urinario adquirida en la comunidad. Entre los antibióticos probados, solo la gentamicina mostró una tendencia a la baja en la resistencia. Estos resultados son importantes para dirigir la elección de los antimicrobianos para el tratamiento empírico de la infección urinaria adquirida en la comunidad.

Palabras clave: infecciones urinarias; infecciones comunitarias adquiridas; antibacterianos; *Escherichia coli*.

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Introduction

The worldwide prevalence of community-acquired urinary tract infections (UTIs) is not well known. However, studies show that among gram-negative bacteria, *E. coli* is the most prevalent uropathogen, accounting for most of community-acquired UTIs.(1,2,3)

UTIs treatment is one of the major contributors to antibiotic use worldwide. (4) Over the last decades, the indiscriminate use of antibiotics led to an increase in antimicrobial resistance among uropathogens, which became a worldwide concern.(4)

Fluoroquinolone Resistance has increased since its introduction in the treatment of UTI and its consumption is associated with increasing resistance in *E. coli*.(5)

Substantial evidence points to an increase, over the last years, in ciprofloxacin resistance in community-acquired UTIs caused by *E. coli*, and this increase is particularly high in developing countries.(6) The goal of this study was to analyze the trends of antibiotic resistance in ciprofloxacin-resistant *Escherichia coli* isolated from community-acquired urinary tract infections from 2011 to 2017.

Methods

This was a time series study conducted from January 2011 to December 2017 in the city of Goiania (estimated population for 2019, 1 516 113),[7] in the mid-west of Brazil, analyzing data of community-originated, positive urine cultures from persons aged 18 years or older, in which ciprofloxacin-resistant *E. coli* was isolated and identified. These records were from four clinical laboratories, serving both public and private patients (including health insurance), with specimen collection offices distributed in all regions (North, South, East and West) of the city of Goiania, Goiás, Brazil.

Only results from the first record of each patient were considered to avoid data duplication, unless there was reinfection three months after the first infection, with a different antimicrobial susceptibility profile. Any non-conclusive result (for any reason), which was not followed by patient returning for new specimen collection were excluded.

The urine cultures performed by the participating laboratories were obtained from midstream urine, processed, and incubated in CLED Agar at an average temperature of 35°C. Urine cultures were deemed positive when bacterial count was above 100 000 colony forming units per milliliter of urine (CFU/mL).[8] Isolate identification and antimicrobial susceptibility test were performed with the VITEK2 automated system (BioMérieux).

Antimicrobials tested included nitrofurantoin, norfloxacin, nalidixic acid, ampicillin, amoxicillin/clavulanate, cefoxitin, ceftriaxone, ertapenem, piperacillin/tazobactam, meropenem, amikacin, gentamicin, and tobramycin. Results were interpreted according to guidelines from the *Clinical and Laboratory Standards Institute*.[9] For the purposes of this study, susceptibility was classified as susceptible or resistant; intermediate susceptibility was counted as resistance.

Demographic data and susceptibility profiles were stored in a Microsoft Excel database and analyzed with the softwares SPSS 20.0 and Stata 15.0.

Descriptive analysis of demographic data and antimicrobial bacterial resistance used absolute (n) and relative (%) frequencies. Bivariate logistic regression was employed to assess the association between sex and age and risk of resistance by ciprofloxacin-resistant *E. coli*.

Trends in the antibiotic resistance patterns were determined using the *Prais-Winsten* generalized linear regression;[10] then, the annual percent change (APC) and respective 95% confidence interval (CI 95%) were calculated from the β_1 coefficient and standard error (SE) of the regression analysis. Upward trends were identified when regression coefficients were positive and downward trends when they were negative; regression coefficients not significantly different from zero (p-value >0.05) indicated no trend. In addition, the change at both ends of the series (2011 and 2017) was calculated (Δ%) and its statistical significance was assessed with Pearson's chi-square test or Fisher's exact test. In all analyses, p-values <0.05 were considered statistically significant.

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Pontifical Catholic University of Goiás Research Ethics Committee (Opinion No. 348 549 and protocol No. 16242013.2.0000.0037).

Results

In this study, 20 272 positive urine culture reports were identified during the period from January 2011 to December 2017 of patients with community-acquired UTI, of which 3363 (26.1%) were ciprofloxacin-resistant E. coli infections.

The highest prevalence (40.91%) of UTIs for ciprofloxacin-resistant *E. coli* occurred in men, and are more likely to be infected with ciprofloxacin-resistant *E. coli* [2,132 (1,891–2,402)] (p = <0.001). Regarding age, the prevalence of ciprofloxacin-resistant *E. coli* infections was high in all age groups, but the greatest chance of being infected was in the ≥60 [2.392 (2.087–2.742)] age range (<0.001) (Table 1).

Table 1- Susceptibility pattern of ciprofloxacin resistant *E. coli* by sex and age in isolates from 2011 to 2017. Goiânia, Goiás, Brazil

Demographic Variables	Total		Resistant		Sensitivity		p-value*	Odds ratio (CI 95%)
	No.	%	No.	%	No.	%		
Sex								
Male	1 271	9,88	520	40,91	751	59,09		1
Female	11 595	90,12	2 843	24,51	8 752	75,49	<0.001	2.132 (1.891 - 2.402)
Total	12 866	100	3 363	26,14	9 503	73,86		
Age (years)								
18 -29	1 815	14,11	1 496	82,42	319	17,58		1
30-39	2 378	18,48	1 878	78,97	500	21,03	0.005	1.249 (1.068-1.459)
40-49	2 330	18,11	1 807	77,55	523	22,45	<0.001	1.357 (1.162-1.585)
50-59	2 092	16,26	1 507	72,04	585	27,96	<0.001	1.820 (1.561-2.124)
≥60	4 251	33,04	2 815	66,21	1 436	33,79	<0.001	2.392 (2.087-2.742)
Total	12 866	100	9 503	73,86	3 363	26,14		

* Univariate Logistic Regression.

An upward trend of ciprofloxacin-resistant *E. coli* isolated was observed between 2011 and 2017, with an APC of 5.2% (95% CI: 2.6; 7.8; p=0.001). In this period the fraction of ciprofloxacin-resistant isolates increased significantly from 19.2% to 27.9%, representing a variation of + 45.3% (Δ%) (p <0.001) (Figure 1).

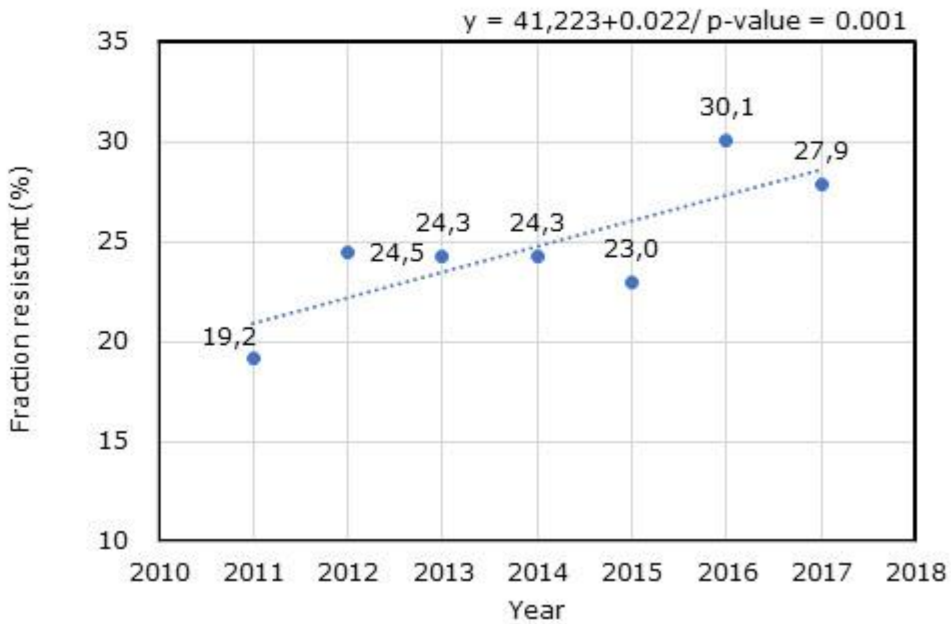

Fig. 1- Variation in the proportion of increased resistance of ciprofloxacin-resistant *E. coli* in the municipality of Goiânia, Goiás, Brazil in the period 2011-2017.

There was a significant increase in the resistance of ciprofloxacin-resistant *E. coli* to nitrofurantoin, 508.8% ($p < 0.001$), and to ceftriaxone, 250.0% ($p < 0.001$), from 2011 to 2017. For the other antibiotics, resistance either decreased or did not change significantly (Table 2).

Table 2- Change in the pattern of resistance of ciprofloxacin-resistant *E. coli* from 2011 to 2017

Antimicrobial agent	2011		2012		2013		2014		2015		2016		2017		Total		Δ% (2011-2017)	*p*-value
	n=211		n=249		n=235		n=479		n=541		n=773		n=875		n=3363			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	%	
Nitrofurantoin	22	10.4	14	5.6	14	6.0	84	17.5	33	6.1	104	13.5	620	70.8	891	26.5	+508.8	< 0.001*
Norfloxacin	141	66.8	37	17.9	196	83.4	461	96.2	315	58.2	694	89.8	159	18.2	2003	59.5	-72.8	<0.001*
Nalidixic acid	176	83.4	199	79.9	182	77.4	392	81.8	323	59.7	703	90.9	773	88.3	2748	81.7	+5.9	0.067*
Ampicillin	167	79.1	201	80.7	178	75.7	371	77.5	434	80.2	625	80.9	675	77.1	2651	0.8	-2.5	0.255*
Amoxicillin/ Clavulanate	62	29.4	38	1.5	54	23.0	121	25.3	92	17.0	285	36.9	261	29.8	913	27.1	+1.4	0.966*
Cefoxitin	27	17.8	20	8.0	5	2.1	2	0.4	40	7.4	11	1.4	19	2.2	124	3.7	-87.6	< 0.001*
Ceftriaxone	11	5.2	1	0.4	41	17.4	84	17.5	88	16.3	69	8.9	159	18.2	453	13.5	+250.0	< 0.001*
Ertapenem	1	0.5	1	0.4	0	0	2	0.4	2	0.4	4	0.5	0	0	10	0.3	-100.0	0.389**
Piperacillin/ Tazobactam	4	1.9	15	6.0	4	1.7	7	1.5	22	4.1	218	28.2	12	1.4	282	8.4	-26.3	0.744**
Meropenem	3	1.4	0	0	0	0	0	0	2	0.4	4	0.5	1	1.1	10	0.3	-21.4	0.050**
Amikacin	9	4.3	0	0	0	0	3	0.6	2	0.4	35	4.5	9	1.0	58	1.7	-76.7	0.006**
Gentamicin	47	22.3	39	15.7	32	13.6	70	14.6	39	7.2	48	6.2	22	2.5	297	8.8	-88.8	< 0.001*
Tobramycin	53	25.1	55	22.1	61	26.0	112	23.4	113	20.9	270	34.5	85	9.7	749	22.3	-61.4	< 0.001*

* Pearson's chi-square test; ** Fisher's exact test.

In the 2011-2017 time series, gentamicin displayed a downward trend in resistance, whereas for the other antibiotics there was no significant trend (Table 3).

Table 3- Trend analysis of the resistance pattern of ciprofloxacin-resistant *E. coli* from 2011 to 2017

Antibiotic	Equation	p-value	APC (CI 95%)	Trend
Nitrofurantoin	y = -246.895 +0.123x	0.209	32.8 (-14.7; 106.7)	–
Norfloxacin	y = 48.870 -0.023x	0.762	-5.3 (-35.2; 38.5)	–
Nalidixic acid	y = -3.225 +0.002x	0.781	0.6 (-3.8; 5.2)	–
Ampicillin	y = 2.685 -0.000x	0.853	-0.9 (-1.9; 0.1)	–
Amoxicillin/Clavulanate	y = -236.068 +0.118x	0.176	31.2 (-10.9; 93.1)	–
Cefoxitin	y = 4985.724 -2.471x	0.111	-99.7 (-100.0; 153.9)	–
Ceftriaxone	y =-327.240 +0.163x	0.133	45.5 (-9.1; 132.9)	–
Ertapenem	y = -2.514 +0.001x	0.979	0.3 (-17.1; 21.3)	–
Piperacillin/Tazobactam	y = -103.386 +0.051x	0.609	12.6 (-31.0; 83.8)	–
Meropenem	y = 1748.455 -0.869x	0.136	-86.5 (-98.8; 51.6)	–
Amikacin	y = 294.243 -0.145x	0.803	-28.4 (-95.9; 1143.0)	–
Gentamicin	y = 300.398 -0.149x	0.007	-29.0 (-40.3; -15.6)	↓
Tobramycin	y = 67.934 -0.033x	0.434	-7.3 (-24.2; 13.2)	–

Discussion

This study presents data on the antimicrobial resistance trends of ciprofloxacin-resistant *E. coli* isolated from community-acquired UTIs in a metropolis located in central Brazil.

UTIs is a disease with high prevalence, mainly caused by enteropathogens, that affects individuals of all age groups and sexes.(1) Females display higher prevalence of bacteriuria, as found in this study (90.12%) and described in Madrid, Spain. (85%).(3) These results show that females contracted more UTI than male. This occurs mainly in premenopausal women.(11)

Although the prevalence of UTIs is higher in females, this study showed that the exposure effect was 2.132 higher for males to contract ciprofloxacin-resistant *E. coli* UTIs than for females. Usually males are more susceptible to infectious diseases, and bacteria isolated from UTIs in males are more resistant to antimicrobials,[(1)] requiring longer treatment to eradicate the bacteria than in females, when treated with the same first-line antimicrobials.[(12)]

The increased incidence of UTIs in older men may be related to benign prostate hyperplasia, loss of prostate fluid and neurogenic bladder conditions, men's behavior towards their health and repeated use of antimicrobials.[(13,14,15)]

Community-acquired UTIs pathogens have displayed high resistance to fluoroquinolones, especially in developing countries.[(6)] Our data indicate that the ciprofloxacin resistance increased from 19.2% to 27.9% (p <0.001), contrasting with United States of America data, where the resistance rate increased from 3.6% to 11.8% between 2003 and 2012.[(16)] These results discourage the use of oral fluoroquinolone in the empirical treatment of community-acquired UTIs when the local resistance rate is >10%.[(17)]

Nitrofurantoin is the drug of choice for UTI treatment according to international guidelines,[(17)] and resistance to this drug is usually very low;[(2)] however, other studies have shown high resistance rates like this one.[(18, 19)] The wide variation in resistance rates may be due to local prescribing practices. In places with high prevalence of resistance to nitrofurantoin, its use should be guided by antibiogram, and, in empirical therapy, indication should consider local data on resistance, which should be periodically reviewed.

Considering the importance of this antimicrobial for the treatment of uncomplicated UTIs, it is important that other studies demonstrate the determinants of increased resistance to nitrofurantoin in *E. coli*.

Norfloxacin is another widely prescribed UTIs drug, in both the hospital and community settings. However, our results showed a resistance rate of 59.5%, higher than the recommended 20% limit for its use in empirical treatment of community-acquired UTI,[17] indicating that norfloxacin may not be an available option for empirical UTI treatment and its use should be judicious.

The resistance to nalidixic acid identified in this study suggests that *E. coli* has already acquired at least a first-step quinolone resistance and its use in the susceptibility test is useful as a predictor of fluoroquinolone resistance.[20, 21].

This study shows that, among ß-lactams, the prevalence of resistance was high for amoxicillin/clavulanate (27.1%) and low for ampicillin (0.8%); however, the use of these drugs in monotherapy should be avoided. They are less effective than other available agents[17,22] and therefore are not recommended for the empirical treatment of UTI.

The increase in resistance to ceftriaxone and the high prevalence of resistance (13.5%) identified, is similar to that described in another country (20.5%).[23] This resistance may be associated with more than one mechanism, including the production of extended spectrum ß-lactamase (ESBL).[24] Bacteria harboring quinolone-resistance plasmids often co-harbor genes encoding ESBL production, which increases the challenge in using these antibiotics, creating major public health management problems. In the in India 50% of fluoroquinolone resistant *E. coli*, also produce ESBL.[25].

Tobramycin is also used to treat community-acquired UTIs, but resistance rates are increasing, which may be associated with other classes of antimicrobials.[26]

Aminoglycosides resistance is associated with several resistance genes, including those that express beta-lactamase.[26] It is difficult to propose an empirical therapy when infections are caused by *E. coli* with multiple resistance mechanisms, as therapeutic failure may occur.

Although the study has shown significant increase in the resistance rate for nitrofurantoin (+508.8, p <0.001) and ceftriaxone (+250.0, *p* <0.001), it also showed no resistance trend for the antimicrobials considered in this study against ciprofloxacin-resistant *E. coli*, with the exception of gentamicin, which displayed a downward trend.

The analysis of the trend of resistance growth was stable for the studied antimicrobials, except for gentamicin, which showed a decline. This trend coincides with the Ministry of Health's ban on the sale of antimicrobials without a prescription,(27) which resulted in a decrease in the use of antibiotics.(28) Thus, the restriction of sales of antimicrobials may have contributed to the trend of decreasing resistance to gentamicin, but studies are needed to corroborate this conclusion.

The limitations of this study are related to the lack of data such as clinical manifestations (reason for requesting the exam, clinical picture), associated comorbidities, history of previous infections, recent exposure to antibiotics in the last 30 days, hospitalization or hospitalization for a long time, and use of permanent urinary catheter. However, the results presented here are important to guide empirical therapy in community-acquired UTIs.

Conclusion: This study demonstrated no resistance trend of ciprofloxacin-resistant *E. coli* to all antimicrobials tested except for gentamicin, which displayed a downward trend.

The change in resistance pattern of ciprofloxacin resistant *E. coli* was statistically significant for the following antimicrobials: nitrofurantoin, norfloxacin, cefoxitin, ceftriaxone, amikacin, gentamicin and tobramycin.

There was an increase in the proportion of ciprofloxacin resistant *E. coli* from 2011 to 2017, with oscillation between years. These findings are important in directing the choice of antimicrobials for empirical treatment of community-acquired UTI. Therefore, selection of empirical antibiotics should be based on data from different time periods and regions.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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