

Antimicrobial resistance in urine cultures of residents of North and Northeast Porto Alegre

Resistência antimicrobiana em uroculturas de moradores das Zonas Norte e Nordeste de Porto Alegre

Resistencia a los antimicrobianos en urocultivos de residentes de las Zonas Norte y Noreste de Porto Alegre

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Abstract

Introduction: Urinary tract infection is a common reason for consultation in primary care, requiring empirical treatment. For the selection of the antimicrobial, it is necessary to know the resistance profile of uropathogens in the community. **Objective:** To analyze the profile of antimicrobial resistance in urine cultures performed on primary health care patients from the Community Health Service of Grupo Hospitalar Conceição from July 2017 to June 2019. **Methods:** Cross-sectional, observational and descriptive study with urine cultures of outpatients from the Health Units from the Community Health Service of Grupo Hospitalar Conceição, in North and Northeast Porto Alegre, Brazil, from July 2017 to June 2019. The data on urine cultures were provided by the Grupo Hospitalar laboratory and analyzed through proportions, by sex, microorganism, and antimicrobial resistance. **Results:** Two thousand positive urine cultures were found in the period, mainly for *Escherichia coli* (75.50%), *Klebsiella pneumoniae* (7.80%), *Staphylococcus saprophyticus* (4.95%), *Enterococcus specie* (3.35%) and *Proteus mirabilis* (2.85%). Among the oral antibiotics tested, the most frequent resistance was to ampicillin (48.95%), followed by trimethoprim+sulfamethoxazole (25.85%), norfloxacin (18.05%), ciprofloxacin (18.00%), amoxicillin-clavulanate (11.05%) and nitrofurantoin (8.60%). Considering only *E. coli*, resistance was 47.75% to ampicillin, 29.74% to trimethoprim+sulfamethoxazole, 19.74% to norfloxacin and ciprofloxacin, 8.08% to amoxicillin-clavulanate and 1.99% to nitrofurantoin. **Conclusions:** The profile of antimicrobial resistance in the North and Northeast Zones of Porto Alegre suggests that nitrofurantoin or amoxicillin-clavulanate should be used for empirical treatment of urinary tract infection in this locality.

Keywords: Urinary tract infections; Drug resistance; Bacterial drug resistance; Community-acquired infections; *Escherichia coli*.

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Resumo

Introdução: Infecção urinária é motivo comum de consulta na Atenção Primária, requerendo tratamento empírico. Para a seleção do antimicrobiano, é necessário conhecer o perfil de resistência dos uropatógenos na comunidade. **Objetivo:** Analisar o perfil de resistência antimicrobiana em uroculturas realizadas em pacientes da Atenção Primária à Saúde do Serviço de Saúde Comunitária do Grupo Hospitalar Conceição, de julho de 2017 a junho de 2019. **Métodos:** Estudo transversal, observacional e descritivo com uroculturas de pacientes ambulatoriais das Unidades de Saúde do Serviço de Saúde Comunitária do Grupo Hospitalar Conceição, nas Zonas Norte e Nordeste de Porto Alegre, de julho de 2017 a junho de 2019. Os dados das uroculturas foram fornecidos pelo laboratório do Grupo Hospitalar e analisados por meio das proporções, por sexo, micro-organismo e resistência antimicrobiana. **Resultados:** Encontraram-se 2.000 uroculturas positivas no período, principalmente por *Escherichia coli* (75,50%), *Klebsiella pneumoniae* (7,80%), *Staphylococcus saprophyticus* (4,95%), *Enterococcus specie* (3,35%) e *Proteus mirabilis* (2,85%). Entre os antibióticos orais testados, a maior resistência foi para ampicilina (48,95%), seguida por sulfametoxazol+trimetoprima (25,85%), norfloxacino (18,05%), ciprofloxacino (18,00%), amoxicilina+clavulanato (11,05%) e nitrofurantoína (8,60%). Considerando-se apenas *E. coli*, as resistências foram 47,75% para ampicilina, 29,74% para sulfametoxazol+trimetoprima, 19,74% para norfloxacino e ciprofloxacino, 8,08% para amoxicilina+clavulanato e 1,99% para nitrofurantoína. **Conclusões:** O perfil de resistência antimicrobiana nas Zonas Norte e Nordeste de Porto Alegre sugere que sejam utilizados para tratamento empírico de infecção do trato urinário nessa localidade nitrofurantoína ou amoxicilina+clavulanato.

Palavras-chave: Infecções urinárias; Resistência a medicamentos; Farmacorresistência bacteriana; Infecções comunitárias adquiridas; *Escherichia coli*.

Resumen

Introducción: La infección del tracto urinario es un motivo frecuente de consulta en atención primaria, requiriendo tratamiento empírico. Para la selección del antimicrobiano, es necesario conocer el perfil de resistencia de los uropatógenos en la comunidad. **Objetivo:** Analizar el perfil de resistencia antimicrobiana en urocultivos realizados en pacientes de atención primaria de salud de Serviço de Saúde Comunitária de Grupo Hospitalar Conceição de julio de 2017 a junio de 2019. **Métodos:** Estudio transversal, observacional y descriptivo con urocultivos de pacientes ambulatorios de las Unidades de Salud de Serviço de Saúde Comunitária de Grupo Hospitalar Conceição, en las Zonas Norte y Nordeste de Porto Alegre, de julio de 2017 a junio de 2019. Los datos de urocultivos fueron proporcionados por el laboratorio de Grupo Hospitalar y analizados a través de proporciones, por sexo, microorganismos y resistencia a los antimicrobianos. **Resultados:** En el período se encontraron 2.000 urocultivos positivos, principalmente por *Escherichia coli* (75,50%), *Klebsiella pneumoniae* (7,80%), *Staphylococcus saprophyticus* (4,95%), *Enterococcus especie* (3,35%) y *Proteus mirabilis* (2,85%). Entre los antibióticos orales probados, la mayor resistencia fue para la ampicilina (48,95%), seguida de sulfametoxazol+trimetoprima (25,85%), norfloxacina (18,05%), ciprofloxacina (18,00%), amoxicilina+clavulanato (11,05%) y nitrofurantoína (8,60%). %. Considerando solo a *E. coli*, la resistencia fue del 47,75% para ampicilina, 29,74% para sulfametoxazol + trimetoprima, 19,74% para norfloxacina y ciprofloxacina, 8,08% para amoxicilina + clavulanato y 1,99% para nitrofurantoína. **Conclusiones:** El perfil de resistencia a los antimicrobianos en las regiones Norte y Nordeste de Porto Alegre sugiere que se utilizan para el tratamiento empírico de la infección del tracto urinario en esta localidad nitrofurantoína o amoxicilina+clavulanato.

Palabras clave: Infecciones urinarias; Resistencia a medicamentos; Farmacorresistencia bacteriana; Infecciones comunitarias adquiridas; *Escherichia coli*.

INTRODUCTION

Urinary tract infections (UTIs) are extremely prevalent worldwide, accounting for 0.9% of all outpatient visits in the United States.¹ In Brazil, its annual incidence is 8.0–10.8%.^{2,3} About 60% of women will have at least one episode of UTI during their lifetime, and of these, around 44% will have a recurrence in the following year.

Because of laboratory requirements and time for urine culture and drug sensitivity testing (48–72 hours), UTI treatment in primary health care (PHC) is usually empirical, and drug selection is based on an assumption of the probable pathogen and its local antimicrobial susceptibility.^{4,5} Such a pathogen must be inferred according to the location in which the diagnosis occurs and with the knowledge of the profile of its sensitivity to the available antibiotics. This knowledge is essential for treatment to be effective and to have lower risk of complications.

The Community Health Service of Grupo Hospitalar Conceição has existed for 40 years, is composed of 12 PHC units in North and Northeast Porto Alegre and is responsible for health care in an area with 105,428 inhabitants, according to the 2010 Census. For the city of Porto Alegre and the vast majority of locations in Brazil, the resistance and sensitivity profile of the pathogens that cause community UTIs is currently unknown. The treatment of this infection is based especially on data from studies carried out in other locations, where the antimicrobial resistance profile is often different. To guide the empirical treatment of community UTIs in the region, this study aimed to assess the profile of antimicrobial resistance in urine cultures of PHC patients in North and Northeast Porto Alegre.

METHODS

A cross-sectional observational descriptive study was carried out analyzing all positive urine cultures collected from outpatient from living in the areas covered by the 12 health units of the Community Health Service of Grupo Hospitalar Conceição, located in neighborhoods in North and Northeast Porto Alegre, from July 2017 to June 2019.

All urine samples were collected at home, with midstream sampling, and delivered by the patients to the laboratory of Grupo Hospitalar Conceição, where they were processed. Urine cultures were performed in a specific medium, with a Veitec2c identification card, and the antimicrobial sensitivity test was performed using the Kirby and Bauer disk diffusion technique.⁶ Antibiogram reading was based on BrCast standards.

Urinary culture data were provided by the Grupo Hospitalar Conceição laboratory, upon written request to its technical manager. A spreadsheet was sent by the laboratory containing the test identification number, patient's name, registration number at the Institution, date of collection, isolated microbe, number of colony-forming units (CFU) and list of tested antibiotics, with the symbols "R" and "S", when there was resistance and sensitivity to that drug, respectively. All urine cultures showing growth of a single agent over 100,000 CFU/mL were considered positive.^{5,7,8}

The variables analyzed were sex, microorganism isolated and antimicrobial resistance profile. The spreadsheet sent by the laboratory was imported by the Numbers program (Apple Inc.), in which the descriptive analysis was performed, by calculating the proportions of the variables. The study was approved by the Research Ethics Committee of Grupo Hospitalar Conceição, under No. 3,279,803, CAAE 08030819.6.0000.5530.

RESULTS

A list containing 2,038 positive urine cultures from outpatients of the Community Health Service of Grupo Hospitalar Conceição from July 2017 to June 2019 was sent to the laboratory. Of these, 38 showed growth below 100,000 CFU/mL, and were therefore excluded from the study. A total of 2,000 urine cultures were included in the analysis.

The vast majority of these, 1750 (87.50%), were from female patients. In most cases, the isolated agent was *Escherichia coli* (75.50%), followed by *Klebsiella pneumoniae* (7.80%), *Staphylococcus saprophyticus* (4.95%), *Enterococcus* sp. (3.35%) and *Proteus mirabilis* (2.85 %) (Table 1). The other bacteria were isolated in less than 1% of the urine cultures.

The antibiotics that showed the highest levels of resistance, regardless of the microbe isolated, were ampicillin (48.95%), trimethoprim+sulfamethoxazole (25.85%), norfloxacin (18.05%) and ciprofloxacin

Table 1. Bacteria identified in urine cultures of outpatients of the Community Health Service of Grupo Hospitalar Conceição between July 2017 and June 2019.

Bacterium	Absolute No.	Percentage (%)
<i>Escherichia coli</i>	1,510	75.50
<i>Klebsiella pneumoniae</i>	156	7.80
<i>Staphylococcus saprophyticus</i>	99	4.95
<i>Enterococcus</i> sp.	67	3.35
<i>Proteus mirabilis</i>	57	2.85
<i>Staphylococcus aureus</i>	17	0.85
<i>Enterobacter cloacae</i> complex	17	0.85
<i>Citrobacter koseri</i>	14	0.70
<i>Enterobacter aerogenes</i>	13	0.65
<i>Morganella morganii</i>	12	0.60
<i>Serratia marcescens</i>	11	0.55
<i>Pseudomonas aeruginosa</i>	10	0.50
<i>Klebsiella oxytoca</i>	6	0.30
<i>Enterococcus faecalis</i>	2	0.10
<i>Klebsiella ozaenae</i>	2	0.10
<i>Streptococcus agalactiae</i>	2	0.10
<i>Raoultella planticola</i>	1	0.05
<i>Proteus penneri</i>	1	0.05
<i>Staphylococcus epidermidis</i>	1	0.05
<i>Staphylococcus hominis</i>	1	0.05
<i>Serratia rubidaea</i>	1	0.05
Total	2,000	100.00

(18.00%) (Table 2). Regarding *E. coli*, the main etiologic agent of UTIs in the community, the most common resistance was to ampicillin (47.75%), trimethoprim+sulfamethoxazole (29.74%), ciprofloxacin (19.74%) and norfloxacin (19.74%) (Table 3).

DISCUSSION

E. coli was the most frequently found pathogen in positive urine cultures of patients from the health units of the Community Health Service of Grupo Hospitalar Conceição, from July 2017 to June 2019. The antibiotics with greatest resistance to this agent and to all that grew in the urine cultures were ampicillin, trimethoprim+sulfamethoxazole, ciprofloxacin and norfloxacin.

There are several studies describing the profile of antimicrobial susceptibility in urine cultures, including ones conducted in Brazil.^{5,9-31} However, many have older data,^{5,9,10} include a small sample¹¹⁻²⁰ or are from tertiary services.²¹⁻²⁴ But considering only studies from the last decade, evaluating at least 220 positive urine cultures of outpatient origin (community UTIs), excluding tertiary outpatient clinics, the results are, in general, similar to those of the present study. In all studies found with these criteria and that evaluated both sexes, the proportion of women with UTI was almost always greater than 80%, as in this study, especially if all age groups were included. In all these studies, *E. coli* was the most frequent pathogen; in most of them, it was responsible for UTI in more than 70% of cases, as in our study.

Table 2. Antibiotic resistance of pathogens in urine cultures of outpatients of the Community Health Service of Grupo Hospitalar Conceição between July 2017 and June 2019 (n=2,000).

Antibiotic	Resistance (%)
Ampicillin	48.95
Trimethoprim+sulfamethoxazole	25.85
Norfloxacin	18.05
Ciprofloxacin	18.00
Amoxicillin-clavulanate	11.05
Nitrofurantoin	8.60
Cefazolin	8.25
Gentamicin	6.70
Ceftriaxone	3.85
Aztreonam	3.00
Cefepime	2.55
Tetracycline	2.00
Piperacillin-tazobactam	1.65
Ertapenem	1.15
Imipenem	0.90
Meropenem	0.85
Erythromycin	0.70
Clindamycin	0.50
Amikacin	0.35
Oxacillin	0.05
Vancomycin	0.00
Rifampicin	0.00
Tigecycline	0.00
Linezolid	0.00

Table 3. Antibiotic resistance of *E. coli* in urine cultures of outpatients of the Community Health Service of Grupo Hospitalar Conceição between July 2017 and June 2019 (n=1,510).

Antibiotic	Resistance (%)
Ampicillin	47.75
Trimethoprim+sulfamethoxazole	29.74
Ciprofloxacin	19.74
Norfloxacin	19.74
Amoxicillin-clavulanate	8.08
Gentamicin	6.62
Cefazolin	4.83
Ceftriaxon	2.25
Nitrofurantoin	1.99
Aztreonam	1.99
Cefepime	1.79
Piperacillin-tazobactam	0.20
Amikacin	0.13
Ertapenem	0.13
Imipenem	0.07
Meropenem	0.07

In 2014, a study in Florianópolis outpatients of all age groups analyzed 4,603 urine cultures, where 1,035 were positive.²⁵ Of these, 89.1% were in women, and 77.1% were caused by *E. coli*, where antibiotic resistance was: high for cephalothin (56.3%), ampicillin (52.8%), amoxicillin-clavulanate (33.1%), trimethoprim+sulfamethoxazole (31.7%) and nalidixic acid (31.6%); intermediate for ciprofloxacin (22.7%) and norfloxacin (22.2%); and low for nitrofurantoin (14.1%) and gentamicin (7.6%). Of the antibacterials tested, the resistance levels were similar to those in our study, except for amoxicillin+clavulanate and nitrofurantoin, with much lower resistance compared to our findings.

Another study evaluating community UTIs in Divinópolis (MG), collected from January to June 2015, involved 3,995 urine cultures, 802 with bacterial growth.²⁶ Of these positive ones, 86.9% were in women and 72.8% were caused by *E. coli*. Resistance of this bacterium was highest to ampicillin (49.7%), trimethoprim+sulfamethoxazole (38.6%), norfloxacin (33.0%) and ciprofloxacin (31.8%), and lowest to gentamicin (19.2%), cephalothin (18.6%), amoxicillin-clavulanate (16.0%) and nitrofurantoin (9.0%). Considering the resistance of all bacteria found in this work, the proportions did not change much for the large majority of antibiotics: 55.8% for ampicillin, 37.6% for trimethoprim+sulfamethoxazole, 32.1% for norfloxacin, 31.1% for ciprofloxacin, 18.3% for amoxicillin-clavulanate and 22.5% for nitrofurantoin. *E. coli* resistance in that study was greater than that found in the present work to almost all antibiotics.

A study with data from 2012 to 2016 from a private laboratory in Uberlândia (MG) involved 6,691 urine cultures, 1,065 of which were positive.²⁷ The prevalence of women was 84.6%, and the proportion of those caused by *E. coli* was slightly lower than in our results and in the other studies reported so far, i.e., 64.2%. The resistance of *E. coli* to ampicillin (77%), trimethoprim+sulfamethoxazole (56%) and amoxicillin-clavulanate (17%) was much higher than in the present study and in those by others, and substantially lower to ciprofloxacin and norfloxacin (11%) compared to other studies. No resistance to nitrofurantoin was reported.

Another study evaluated only the 1,654 positive urine cultures for *E. coli* (about 79% of all samples collected) from outpatients at the Federal University of Triângulo Mineiro Hospital, from 2010 to 2015, of which 83% were in women.³ Antibiotics with resistance to *E. coli* were cephalothin (31.8%), ciprofloxacin (28.9%) and norfloxacin (30.7%), with a linear increase in resistance to these last two drugs (resistance that was, on average, significantly higher than what we found here), and low resistance to nitrofurantoin (5.9%), but higher than that observed by us.

A study analyzing community UTIs in the elderly (over 60 years old) in Goiânia concluded that 75.6% of them were caused by *E. coli*, and 77.6% of positive urine cultures in symptomatic affected elderly women.²⁸ Compared to what we found, there was much greater resistance to quinolones (39.5%), lower resistance to trimethoprim+ sulfamethoxazole (16.2%) and similar resistance to nitrofurantoin (3.76%).

Outside Brazil, a study tried to evaluate urine cultures from all over France, but, for logistical reasons, it ended up having losses.²⁹ It included only women, who went to see their general physician for bladder pain, urinary frequency or urinary urgency. That study showed much lower *E. coli* resistance than other studies for ciprofloxacin (1.5%), nitrofurantoin (0.4%) and amoxicillin-clavulanate (3.5%), although not so much lower for trimethoprim+sulfamethoxazole (17.8%) and amoxicillin (38%).

Another French study, including only Paris laboratories, with 1,123 positive urine cultures, 81.4% in women, 69% for *E. coli*, obtained similar results as ours for resistance of this pathogen to ampicillin (50.5%), trimethoprim+sulfamethoxazole (26.0%), ciprofloxacin (15.5%), norfloxacin (22.1%) and nitrofurantoin (1.1%), but higher for amoxicillin-clavulanate (38.2%).³⁰

Finally, a study in the French territory of Guadeloupe, in the Caribbean, with 1,293 positive urine cultures, 73.5% in women, 57.0% due to *E. coli*, showed resistance of this bacterium similar to that found in our work for nitrofurantoin (1.2%), slightly higher for amoxicillin-clavulanate (18.6%) and slightly lower for trimethoprim+sulfamethoxazole (18.6%).³¹

Differences in the proportion of *E. coli* as the etiologic agent of UTIs and in its resistance to antibiotics between studies are likely due to the pattern of antimicrobial use in each location, as well as possible demographic differences.

The profiles we found, as well as reported by other authors, demonstrate great bacterial resistance to some of the main antibiotics used in PHC. Because *E. coli* is the most frequent pathogen in our study and in all studies found in the last 10 years involving patients with community-acquired UTIs and with more than 220 positive urine cultures, antimicrobial selection for the empirical treatment of community-acquired UTI should be guided by the resistance profile of this bacterium, as well as by the clinical effectiveness of the drug in the urinary spectrum.³²

Therefore, the results of this study reinforce the use of nitrofurantoin as the drug of choice for the empirical treatment of community-acquired lower UTI also in the Porto Alegre region.³² For upper UTI or contraindication for the use of nitrofurantoin (for example, renal from stage G3a onwards), the best alternative is amoxicillin-clavulanate.

It is worth highlighting the results for trimethoprim+sulfamethoxazole, an antibiotic combination widely used empirically for this type of infection. *E. coli* resistance to these drugs was greater than 20% in the present study, as well as in most studies on outpatient UTI published in recent years,^{25-27,30,32} which contraindicates its empirical use also in the Porto Alegre region. The fluoroquinolone class, also widely used empirically for cystitis, should also be avoided in this type of treatment. Initially a class with high sensitivity in uropathogens, it has shown a progressive increase in resistance due to wide use, currently greater than 10% in *E. coli* in ours and in almost all the studies found.^{3,25-28,30,31} The same applies to ampicillin, formerly used for empirical treatment of UTI as monotherapy, but whose resistance proportion is around 50% or more, in our study and in others carried out recently.^{25-27,30}

The strength of this work is the number of positive urine cultures (2000) and the fact that it is the first known study of this magnitude in the Porto Alegre region. In addition, all urine cultures collected in the period at the Grupo Hospitalar Conceição laboratory requested by the 12 PHC units of the Institution were evaluated.

The main limitations of this research are the lack of records of patients' age in the analysis sheets sent by the laboratory, as well as sex, which had to be inferred through the patient's name and, in case of doubt, from research in the register in the Conceição Hospital Group's information system. We also did not have access to the presence of symptoms, to separate asymptomatic bacteriuria, detected in pregnant women and candidates for urinary procedures, from upper and lower UTIs, and cases of recurrence were not analyzed separately, which according to the literature show higher resistance levels when compared to primary infections. Another limitation, inherent to studies that evaluate urine cultures, is that since lower UTIs are usually treated empirically, the cases in which the examination was performed were possibly more complex than those that did not require laboratory confirmation, which may cause actual resistance levels to be lower than those found in this study. Finally, fosfomicin and pivmecillinam, which are important alternatives in the empirical treatment of UTI in the community, are not routinely tested in the Institution's laboratory.

As already mentioned, this study is the first known to evaluate a considerable number of positive urine cultures in the region of Porto Alegre and to be able to propose the drugs of choice for the

empirical treatment of UTI in the region. The differences found between the studies in the proportion of *E. coli* as the cause of UTI and in its resistance to antibiotics reinforce the importance of regional research on the resistance of uropathogens, to determine the best choice of empirical treatment in other locations in the country.

CONCLUSION

The antimicrobials with the highest proportions of resistance in urine cultures of PHC patients in the areas covered by the health units of the Community Health Service of the Grupo Hospitalar Conceição, in North and Northeast Porto Alegre, from July 2017 to June 2019, were ampicillin, trimethoprim+sulfamethoxazole, ciprofloxacin and norfloxacin. The antibiotic most indicated for empirical treatment of community-acquired lower UTIs in this city, due to its efficacy and resistance profile in the region, is nitrofurantoin. For upper UTIs or in patients with contraindication to this antimicrobial, amoxicillin-clavulanate is a good alternative. For cases in which there is no clinical improvement with empirical treatment using one of these drugs, a urine culture with an antimicrobial sensitivity test should be performed to guide the selection of another drug.

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CONFLICTS OF INTEREST

None to declare.

AUTHORS' CONTRIBUTIONS

RPR: project conceptualization and management, formal analysis, data curation, writing – first draft, research, methodology, resources and software. AK: project conceptualization and management, formal analysis, writing – proofreading & editing, research, methodology, resources, software, supervision, validation and visualization.

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