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ORIGINAL ARTICLES

Urinary tract infections in a Pediatric Emergency Department – Etiology and antibiotic susceptibility patterns

Infeções do trato urinário num Serviço de Urgência Pediátrico - Etiologia e padrões de suscetibilidade aos antibióticos

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ABSTRACT

Introduction: Urinary tract infections are common in children. The decision to start empiric antibiotic therapy before isolation of the causative agent must be made based on the clinical presentation and antimicrobial resistance profile of each population. The aim of the present study was to identify the most common etiological agents in urinary tract infections in children and adolescents attending the Pediatric Emergency Department of a level II hospital and the antimicrobial susceptibility pattern, in order to optimize the use of empiric and prophylactic therapy.

Material and Methods: A retrospective analysis of urine cultures with a positive result between January 2019 and December 2021 was performed.

Results: A total of 774 urine cultures were evaluated. The most frequently isolated etiological agents were *Escherichia coli* (68.5%), *Proteus mirabilis* (18.1%), and *Staphylococcus saprophyticus* (4.7%). *Escherichia coli* showed 4.9% resistance to cefuroxime and 26.2% resistance to amoxicillin-clavulanic acid. *Proteus mirabilis* showed an adequate susceptibility profile to all empirically used antibiotics. In adolescents, 26.8% of urinary tract infections were caused by *Staphylococcus saprophyticus*. Ten cases (1.3%) of extended-spectrum beta-lactamase-producing Enterobacteriaceae were identified.

Discussion: Cefuroxime showed an adequate susceptibility profile for all microorganisms. *Escherichia coli* showed a high resistance rate to amoxicillin-clavulanic acid, exceeding the acceptable resistance threshold for empirical antibiotic therapy. The results suggest an increase in the incidence of urinary tract infections caused by *Staphylococcus saprophyticus*, which means that the prescription of fosfomycin as first-line empirical therapy for female adolescents should be discouraged.

Keywords: antimicrobial susceptibility; Pediatrics; urinary tract infection

RESUMO

Introdução: As infeções urinárias são comuns em idade pediátrica. A decisão de iniciar antibioterapia empírica antes do isolamento do agente etiológico deve ser tomada com base na clínica e no perfil de resistência antimicrobiana de cada população. O presente estudo teve como objetivo identificar os agentes etiológicos mais frequentes em infeções urinárias em crianças e adolescentes seguidos no Serviço de Urgência Pediátrico de um hospital de nível II e analisar o seu padrão de suscetibilidade aos antimicrobianos, com o objetivo de otimizar o uso da terapêutica empírica e profilática.

Material e Métodos: Foi realizada uma análise retrospetiva das uroculturas com resultado positivo entre janeiro de 2019 e dezembro de 2021.

Resultados: Foram analisadas 774 uroculturas. Os agentes etiológicos mais frequentemente isolados foram *Escherichia coli* (68,5%),

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Proteus mirabilis (18,1%) e *Staphylococcus saprophyticus* (4,7%). *Escherichia coli* apresentou 4,9% de resistência ao cefuroxime e 26,2% de resistência à amoxicilina-ácido clavulânico. *Proteus mirabilis* apresentou um perfil de suscetibilidade adequado a todos os antibióticos usados empiricamente. Nas adolescentes, 26,8% das infeções urinárias foram causadas por *Staphylococcus saprophyticus*. Foram identificados 10 casos (1,3%) de enterobactérias produtoras de beta-lactamases de amplo espetro.

Discussão: O cefuroxime apresentou um perfil de suscetibilidade adequado para todos os microrganismos. A *Escherichia coli* mostrou uma taxa de resistência elevada à amoxicilina-ácido clavulânico, ultrapassando o limiar de resistência aceitável para antibioterapia empírica. Os resultados sugerem um aumento da frequência de infeções urinárias causadas por *Staphylococcus saprophyticus*, pelo que a prescrição de fosfomicina como antibioterapia empírica de primeira linha para adolescentes do sexo feminino deve ser desaconselhada.

Palavras-Chave: infeção urinária; Pediatria; suscetibilidade aos antimicrobianos

INTRODUCTION

Urinary tract infections (UTIs) are common in children and are a frequent reason for Emergency Department (ED) visits.[1,2] The decision to start empirical or prophylactic antibiotic therapy should be based on factors such as age, clinical condition, and the most commonly isolated bacteria in urine cultures (UCs), and should be adapted to the antimicrobial susceptibility profile of the pediatric population in each geographic region.[1,3,4]

UTIs are more common in females of all ages, except during the first three months of life, when they are more common in males.[2]

UTIs are defined by the presence of a significant number of microorganisms in aseptically collected urine associated with concordant clinical symptoms.[1,3,4] Most UTIs are caused by bacteria, with *Escherichia coli* accounting for approximately 70-90% of all cases·.[2,4] Other common uropathogens include *Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus* spp, and *Staphylococcus saprophyticus*, the latter being more common in UTIs in female adolescents.[2]

The diagnosis requires urine collection using an aseptic technique, with growth of bacteria in sufficient numbers in the UC.[1-3] In Portugal, according to Direção-Geral da Saúde (DGS) Regulation 008/2012, urine samples are considered positive with growth of ≥ 1 colony-forming unit (CFU)/mL by suprapubic aspiration (SPA); ≥ 10^4-10^5 CFU/mL by catheterization; or ≥ 10^5 CFU/mL by midstream urine (MSU).[3]

When UTI is clinically and analytically suspected, it is imperative to initiate antibiotic therapy immediately after urine collection for UC.[1-3] The choice of empirical antibiotic therapy depends on factors such as patient age, clinical presentation, and local antimicrobial susceptibility patterns.[3] In addition, the presence of known renal or urinary system abnormalities, previous antibiotic therapy, and ongoing prophylactic antibiotic therapy (treatment with a different antibiotic) should be considered.[3]

The empirical antibiotic therapy of choice for UTIs in children includes cefuroxime and amoxicillin-clavulanic acid.[3] In female adolescents with cystitis, nitrofurantoin or fosfomycin may be an option.[3,5] These recommendations exclude neonates and patients with previously known renal or urinary system abnormalities.[3]

The main complication of lower UTI (cystitis) is its spread to the upper urinary tract, causing pyelonephritis. Some pyelonephritis, especially those occurring in the first years of life, may be complicated by lesions of the renal parenchyma, which may later evolve to renal scarring and progressive kidney dysfunction. In some situations, namely in children with recurrent UTIs, prophylactic antibiotic therapy may be indicated, with trimethoprim-sulfamethoxazole and nitrofurantoin being the recommended antimicrobials for this purpose.[3,6]

The indiscriminate and excessive use of antimicrobial agents, facilitated by their easy accessibility, has led to the emergence of resistant and multi-resistant bacteria, which has become a major public health problem today.[1,4-12] Therefore, it is essential to promote the rational use of antimicrobial agents at the community level.[8,11,12]

One of the consequences of the overuse of broad-spectrum antibiotics is the increase in the prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, which are responsible for a growing number of cases of UTIs in children.[4,9,11-12] *Escherichia coli* and *Klebsiella pneumoniae* are the most common causative organisms.[4,9,13-15] The majority of ESBL-producing Enterobacteriaceae are resistant to the most commonly used antimicrobial agents.[9,10,14] To overcome this resistance, combinations of beta-lactams and beta-lactamase inhibitors, as well as broader-spectrum antibiotics, have been used. According to the latest Infectious Diseases Society of America guidelines, ESBL-producing Enterobacteriaceae are universally susceptible to carbapenems, making these agents the treatment of choice for pyelonephritis and complicated UTIs. Alternatively, trimethoprim-sulfamethoxazole or fluoroquinolone can be used. The first-line treatment for cystitis includes nitrofurantoin or trimethoprim-sulfamethoxazole, while the second-line treatment includes amoxicillin-clavulanic acid, fosfomycin, or an aminoglycoside. Piperacillin-tazobactam therapy is not recommended.[15]

In most cases of UTI, initial antimicrobial therapy is empirical, and this choice should be based on the prevalence of pathogens and their susceptibility to antimicrobial agents. Given the large geographic variability of both parameters, epidemiologic surveillance studies conducted by each health unit are crucial for prescribing empirical therapy.[8,16]

The latest Clinical Microbiology consensus, published in 2017, recommended that antimicrobial susceptibilities be presented in microbiology charts using the color green for susceptibility greater than 80%, yellow for susceptibility between 50 and 80%, and red for susceptibility less than 50%.[8] Therefore, a susceptibility rate of 80% seems to be the acceptable susceptibility threshold for initiating empirical antibiotic therapy.

The latest updates of the expected susceptibility phenotypes for the different bacterial species were published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 2022.[17] According to EUCAST, susceptibility patterns for fosfomycin and nitrofurantoin should only be reported for uncomplicated UTIs caused by *Escherichia coli* and are not recommended for other Enterobacteriaceae.[17,18]

The aim of this study was to analyze the UC results of urine samples collected using an aseptic technique in the pediatric ED of a level II hospital in Portugal between January 2019 and December 2021 with the purpose of characterizing the pediatric population diagnosed with UTIs and analyzing positive UC results to identify the most frequently isolated bacterial agents and analyze their antimicrobial susceptibility profile. The ultimate goal was to optimize the use of empirical and prophylactic therapy.

MATERIAL AND METHODS

This was a retrospective, descriptive study of all UC results of children and adolescents referred from the Pediatric ED to the Clinical Pathology Department of a level II hospital between January 2019 and December 2021. All urine specimens collected by aseptic non-touch (drainage bag) or unknown technique or by puncture catheterization in patients with chronic catheterization were excluded. All UCs with isolation of a single agent in colony count ≥ 1 CFU/mL by SPA, ≥ 10^4 CFU/mL by catheterization, and ≥ 10^5 CFU/mL by MSU were considered positive.[3]

Regarding laboratory procedures, urine samples were inoculated onto cystine-lactose-electrolyte-deficient (CLED) agar culture and incubated in an aerobic atmosphere at 35°C for 18-24 hours, after which bacterial growth was assessed. From January 2019 to December 2019, isolated colonies were identified using the Vitek®2 automated identification system. From January 2020, identification of these isolates was performed using MALDI-TOF (MALDI Biotyper®).

The Vitek®2 system was used to determine the minimum inhibitory concentration of the isolates and the susceptibility was interpreted according to the current EUCAST standards.[17,18]

Susceptibilities to the following antimicrobials were provided and analyzed: ampicillin, oxacillin, amoxicillin-clavulanic acid, cefuroxime, ceftazidime, fosfomycin, nitrofurantoin, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, and vancomycin.

Data analyzed included patient age and sex, collection technique, isolated microorganism, isolation of ESBL-producing Enterobacteriaceae, and antimicrobial susceptibility pattern.

Statistical analysis was performed using IBM SPSS version 26.0. Categorical variables were presented as absolute (n) and relative (%) frequencies. Collection techniques were defined as SPA, catheterization, or MSU. The antimicrobial susceptibility pattern was classified as standard dose susceptibility (S), increased exposure susceptibility (I), and resistance (R) according to the EUCAST classification in effect since 2019.[19] The only continuous variable in study was age, defined in years and characterized by mean and median. All children and adolescents aged between one month and 17 years were included.

The study was approved by the Ethics Committee of the participating hospital.

RESULTS

During the study period, the Clinical Pathology Department received and analyzed 3222 urine specimens from the pediatric ED, of which only 774 (24%) were collected using an aseptic technique and were positive, according to previously defined criteria. The urine collection techniques are shown in **Table 1**.

The 774 UCs included in the study were from a total of 610 patients, 73.8% of whom were female, with a mean age of five years and a median age of three years; 49% were children up to two years of age.

The distribution of positive UCs by age and sex is shown in **Figure 1**. There was a predominance of UTIs in females of all ages, and a higher prevalence of UTIs during the first year of life, followed by a significant decrease (especially after four years of age) in males.

Eighteen different bacterial strains were identified in positive UCs (**Table 2**). The most commonly isolated etiological agents were *Escherichia coli* (68.5%), *Proteus mirabilis* (18.1%), and *Staphylococcus saprophyticus* (4.7%), followed by *Klebsiella pneumoniae* (2.8%) and *Pseudomonas aeruginosa* (0.9%).

The distribution of bacterial strains by age group is shown in **Table 3**. *Escherichia coli* was the most frequently isolated etiological agent in all age groups. In the group of female adolescents aged between 14 and 17 years, most UTIs were caused by *Escherichia coli* (52.9%) and *Staphylococcus saprophyticus* (26.8%).

The antimicrobial susceptibility pattern of the five most common etiological agents is shown in **Table 4**.

Ten cases (1.3%) of ESBL-producing Enterobacteriaceae were identified, and this phenotype was detected in 1.5% of *Escherichia coli* (n=8) and 9% of *Klebsiella pneumoniae* (n=2) cases. ESBL-producing *Escherichia coli* were identified in all age groups, with 50% of cases in children less than two years of age. *Klebsiella pneumoniae* was identified only in adolescents between 14 and 17 years of age. The susceptibility pattern of these bacteria to recommended antibiotics is shown in **Table 5**.[16] The susceptibility pattern to fluoroquinolones and carbapenems was not available and therefore not analyzed in this study.

Table 1 - Distribution of urine collection techniques by age group

	Suprapubic aspiration	Catheterization	Midstream urine	TOTAL
1-3 months	5	24	0	29
4-24 months	6	225	21	252
2-6 years	0	65	201	266
7 – 17 years	0	7	220	227
TOTAL	11	321	442	**774**

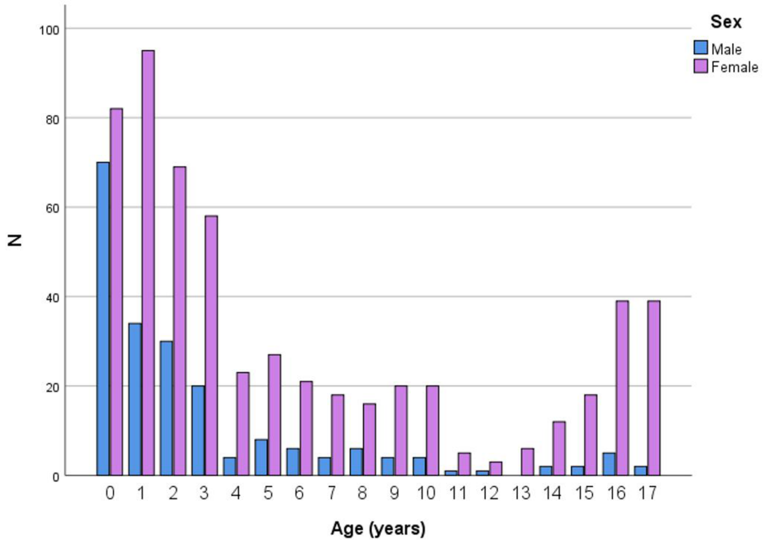

Figure 1 - Distribution of positive UCs by age and sex

Table 2 - Bacterial strains identified in positive UCs

Bacterial strain	N (%)
Escherichia coli	530 (68.5%)
Proteus mirabilis	141 (18.2%)
Staphylococcus saprophyticus	36 (4.7%)
Klebsiella pneumoniae	22 (2.8%)
Pseudomonas aeruginosa	7 (0.9%)
Other *	38 (4.9%)

* Other bacterial strains identified include: *Aerococcus urinae* (n=1); *Citrobacter koseri* (n=5); *Enterobacter aerogenes* (n=2); *Enterobacter cloacae* (n=4); *Enterococcus faecalis* (n=11); *Klebsiella oxytoca* (n=4); *Morganella morganii* (n=2); *Proteus hauseri* (n=2); *Pseudomonas putida* (n=1); *Staphylococcus epidermidis* (n=1); *Staphylococcus simulans* (n=1); *Streptococcus agalactiae* (n=2); *Streptococcus viridans* (n=2)

Table 3 - Distribution of bacterial strains by age group

	Escherichia coli	*Proteus mirabilis*	*Staphylococcus saprophyticus*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	Outros	Total
1-3 months	25 (3.2%)	2 (0.2%)	0	0	0	2 (0.2%)	29 (3.7%)
4-24 months	197 (25.4%)	33 (4.2%)	0	9 (1.2%)	1 (0.1%)	12(1.5%)	252 (32.5%)
2-6 years old	162 (20.9%)	82 (10.6%)	0	6 (0.8%)	4 (0.5%)	12(1.5%)	266 (34.4%)
7-13 years old	83 (10.7%)	13 (1.7%)	4 (0.5%)	1 (0.1%)	0	7 (0.9%)	108 (14%)
14-17 years old	63 (8.1%)	11 (1.4%)	32 (4.1%)	6 (0.8%)	2 (0.2%)	5 (0.6%)	119 (15.4%)
Total	530 (68.5%)	141(18.2%)	36 (4.7%)	22 (2.8%)	7 (.9%)	38(4.9%)	**774**

Table 4 - Antimicrobial susceptibility pattern of the most common etiological agents

	Escherichia coli			*Proteus mirabilis*			*Klebsiella pneumoniae*		*Staphylococcus saprophyticus*		*Pseudomonas aeruginosa*	
	S	**I**	**R**	**S**	**I**	**R**	**S**	**R**	**S**	**R**	**I**	**R**
Ampicillin	330 (62.3%)	-	200 (37.7%)	117 (83%)	-	24 (17%)	-	-	*	*	-	-
Oxacillin	-	-	-	-	-	-	-	-	32* (88.9%)	3* (8.3%)	-	-
Amoxicillin-clavulanic acid	391 (73.8%)	-	139 (26.2%)	129 (91.5%)	-	12 (8.5%)	17 (77.3%)	5 (22.7%)	*	*	-	-
Cefuroxime	504 (95.1%)	-	26 (4.9%)	139 (98.6%)	-	2 (1.4%)	20 (90.9%)	2 (9.1%)	*	*	-	-
Ceftazidime	525 (99.1%)	2 (0.4%)	3 (0.6%)	140 (99.3%)	-	1 (0.7%)	20 (90.9%)	2 (9.1%)	*	*	7 (100%)	0
Piperacillin-tazobactam	515 (97.2%)	3 (0.6%)	12 (2.3%)	141 (100%)	-	0	20 (90.9%)	2 (9.1%)	-	-	7 (100%)	0
Fosfomycin	524 (98.9%)	-	6 (1.1%)	-	-	-	-	-	-	-	-	-
Nitrofurantoin	529 (99.8%)	-	1 (0.2%)	-	-	-	-	-	36 (100%)	0	-	-
Trimethoprim-sulfamethoxazole	449 (84.7%)	-	81 (15.3%)	126 (89.4%)	1 (0.7%)	14 (9.9%)	16 (72.7%)	6 (27.3%)	36 (100%)	0	-	-
Vancomycin	-	-	-	-	-	-	-	-	36 (100%)	0	-	-

I – Susceptible, increased exposure; R – Resistant; S – Susceptible, standard dosing regimen [19]
* Oxacillin screening allows to know the susceptibility to isoxazolyl penicillins, penicillin + beta-lactamase inhibitors, and cephalosporins.

Table 5 - Susceptibility pattern of ESBL-producing Enterobacteriaceae to the recommended antibiotic

	Escherichia coli		*Klebsiella pneumoniae*	
	S	**R**	**S**	**R**
Amoxicillin-clavulanic acid	1 (12.5%)	7 (87.5%)	1 (50%)	1 (50%)
Cefuroxime	0	8 (100%)	0	2 (100%)
Fosfomycin	8 (100%)	0	-	-
Nitrofurantoin	9 (100%)	0	-	-
Trimethoprim-sulfamethoxazole	2 (25%)	6 (75%)	0	2 (100%)

I – Susceptible, increased exposure; R – Resistant; S – Susceptible, standard dosing regimen [19]

DISCUSSION

In this study, *Escherichia coli* was the most frequently isolated etiological agent in all age groups, which is consistent with data from other studies.[2,4] This agent showed a resistance profile of 26.2% to amoxicillin-clavulanic acid, which exceeds the resistance threshold considered acceptable. According to the latest Clinical Microbiology consensus, when the resistance profile is greater than 20%, the empirical use of the antibiotic in infections caused by the identified etiological agent should be questioned.[8] Thus, according to this study's results, amoxicillin-clavulanic acid should not be recommended as first-line empirical therapy for the pediatric population in the region. Cefuroxime resistance rate was 4.9% and should therefore be recommended as the empirical antibiotic of choice.

Proteus mirabilis has a suitable susceptibility profile for all empirical antibiotics used for UTIs in different age groups.

Staphylococcus saprophyticus was the third most frequently isolated microorganism in this study. Oxacillin screening allows to know the susceptibility to isoxazolyl penicillins, penicillin beta-lactamase inhibitors, and cephalosporins. The analysis showed over 80% susceptibility to oxacillin, which means that amoxicillin-clavulanic acid and cefuroxime can still be used as empirical antibiotic therapy for UTIs caused by *Staphylococcus saprophyticus*. Likewise, it is 100% susceptible to nitrofurantoin, which makes this antibiotic a suitable option for UTIs without fever in female adolescents, as indicated in DGS Rule 008/2012.[3] On the other hand, *Staphylococcus saprophyticus* has an expected resistance phenotype to fosfomycin, so its prescription as first-line empirical antibiotic therapy for UTIs in female adolescents should be discouraged.

Klebsiella pneumoniae is intrinsically resistant to ampicillin. According to this study, it has less than 80% susceptibility to amoxicillin-clavulanic acid (77.3%) and trimethoprim-sulfamethoxazole (72.7%), which is why these antibiotics are not recommended as empirical therapy for infections caused by this microorganism.[8] However, it has an adequate susceptibility profile to cefuroxime (90.9%), so this agent should still be used as the empirical antibiotic of choice.

Pseudomonas aeruginosa is rarely responsible for UTIs in children. This microorganism shows intrinsic resistance to amoxicillin-clavulanic acid and cefuroxime and 100% susceptibility to piperacillin-tazobactam and ceftazidime. In the present study, seven cases (0.9%) of UTIs caused by this bacterium were identified in a total of five patients. Therefore, the empirically initiated antibiotic should be changed if this organism is isolated in culture, even before the result of antimicrobial susceptibility testing is known, since it is intrinsically resistant to amoxicillin-clavulanic acid and cefuroxime.

Although a significant number of cases of *Escherichia coli* with ESBL-producing phenotype were isolated, this phenotype was proportionally more common in *Klebsiella pneumoniae* strains, which is in line with data retrieved in other studies.[10,13] In this study, these bacteria showed a high resistance profile to amoxicillin-clavulanic acid and cefuroxime. *Escherichia coli* with an ESBL-producing phenotype showed a 100% susceptibility profile to fosfomycin and nitrofurantoin. Therefore, if ESBL-producing Enterobacteriaceae are identified in culture before the result of antimicrobial susceptibility testing is available, the recommendation is to switch therapy to the recommended antimicrobials, namely fosfomycin, nitrofurantoin, or carbapenems.[15] However, alarmingly, the susceptibility profile for trimethoprim-sulfamethoxazole was much lower than 80% for both bacterial strains, so its use as first-line empirical antibiotic therapy for the treatment of UTIs in the pediatric population of the region should be discouraged in these cases .[8,15]

Regarding antibiotic prophylaxis, *Escherichia coli* was found to have a susceptibility profile greater than 80% for both trimethoprim-sulfamethoxazole (84.7%) and nitrofurantoin (99.8%). *Proteus mirabilis* and *Staphylococcus saprophyticus* were susceptible to trimethoprim-sulfamethoxazole in 89.4% and 100% of cases, respectively. In contrast, *Klebsiella pneumoniae* was susceptible to this antibiotic in only 72.7% of cases.

CONCLUSIONS

The present study showed that cefuroxime maintains an adequate susceptibility profile for all microorganisms and should therefore continue to be recommended as the empirical antibiotic of choice for UTIs in the pediatric population of the geographical area considered. *Escherichia coli* showed a high rate of resistance to amoxicillin-clavulanic acid, exceeding the acceptable resistance threshold for empirical antibiotic therapy. *Staphylococcus saprophyticus* was the second most common cause of UTIs in female adolescent. However, it showed an expected resistance phenotype to fosfomycin, so its prescription as empirical antibiotic therapy in this group should be discouraged. Trimethoprim-sulfamethoxazole and nitrofurantoin remain appropriate prophylactic antibiotics in most cases.

Establishing appropriate empirical and prophylactic antibiotic therapy for UTIs requires periodic assessment of the susceptibility of the most common etiological agents to various antimicrobials. Since there is variability in the pattern of antibiotic susceptibility between different age groups and geographic regions, periodic updating of this information is essential not only for choosing the most appropriate empirical treatment, but also for controlling and preventing the emergence of bacterial resistance to antibiotics.

LIST OF ABBREVIATIONS

Abbreviation	Definition
UTI	Urinary tract infection
ED	Emergency Department
UC	Urine culture
CFU	Colony-forming unit
SPA	Suprapubic aspiration
MSU	Midstream urine
DGS	Direção-Geral da Saúde
ESBL	Extended-spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing

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Catarina Ribeiro - Conceptualization; Supervision; Validation; Writing – review & editing

Julieta Morais - Validation; Writing – review & editing

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