Community Urinary Tract Infections: Guideline Adjustment

Infeções Urinárias da Comunidade: Adaptação da Norma de Orientação Clínica

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ABSTRACT

INTRODUCTION: Urinary tract infections are very common in the community and are one of the most common reasons for antibiotic prescription.

Our objective was to identify the most frequent microorganisms present in urine cultures in Primary Health Care, at a Local Health Unit and their sensitivity profile to some antibiotics.

METHODS: Observational and retrospective study based on bacteriological identification in urine cultures obtained between January/2020 and December/2021. Individuals of both genders and ages 15 and over were included.

RESULTS: The total number of urine cultures obtained was 2788, 83% from female patients, and 17% from males. In males, unlike females, there were no significant differences between age groups regarding the isolates agents. The most frequently isolated agent in both sexes was *Escherichia coli* (64.89%), and its sensitivity to fosfomycin is over 98% in all age groups, and equal to or less than 75% to amoxicillin-clavulanic acid.

CONCLUSION: Empirical treatment of uncomplicated cystitis should target *Escherichia coli*. Amoxicillin-clavulanic acid should not be considered as empirical treatment, except in patients with a history of lithiasis. Pivmecillinam would be a viable option if available for prescription in the community. Antibiotic selection should be appropriate and in accordance with local resistance patterns and based on data from more recent studies, since the variability of antibiotic sensitivities can change.

KEYWORDS: Community-Acquired Infections/drug therapy; Community-Acquired Infections/microbiology; Drug Resistance, Microbial; Practice Guidelines as Topic; Practice Patterns, Physicians; Urinary Tract Infections/drug therapy

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RESUMO

INTRODUÇÃO: As infeções do trato urinário são muito comuns na comunidade e são uma das razões mais comuns para a prescrição de antibióticos.

O nosso objetivo foi identificar os microrganismos mais frequentes em uroculturas nos Cuidados de Saúde Primários, numa Unidade Local de Saúde e seu perfil de sensibilidade aos antibióticos.

MÉTODOS: Estudo observacional e retrospetivo, baseado na identificação bacteriológica em uroculturas obtidas entre janeiro/2020 a dezembro/2021. Incluídos indivíduos de ambos os sexos e idade igual ou superior a 15 anos.

RESULTADOS: Obtidas um total de 2788 uroculturas, 83% relativas a utentes do sexo feminino e 17% do sexo masculino. No sexo masculino, ao contrário do sexo feminino, não existiram diferenças significativas entre os grupos etários relativamente aos agentes isolados. O agente mais frequentemente isolado em ambos os sexos foi a *Escherichia coli* (64,89%), e a sua sensibilidade à fosfomicina é superior a 98% em todos os grupos etários, e igual ou inferior a 75% à amoxicilina-ácido clavulânico.

CONCLUSÃO: O tratamento empírico da cistite não complicada deve visar *Escherichia coli*. A amoxicilina-ácido clavulânico não deve ser considerada como tratamento empírico, com exceção nos doentes com antecedentes de litíase renal. O pivemecilinam seria uma opção viável em caso de disponibilidade para prescrição na comunidade. A seleção de antibióticos deve ser apropriada e de acordo com os padrões de resistência locais e com base em dados de estudos mais recentes, uma vez que a variabilidade das sensibilidades aos antibióticos pode alterar.

PALAVRAS-CHAVE: Infecções Comunitárias Adquiridas/microbiologia; Infecções Comunitárias Adquiridas/tratamento farmacológico; Infecções Urinárias/tratamento farmacológico; Norma de Orientação Clínica; Padrões de Prática Médica; Resistência Microbiana a Medicamentos

INTRODUCTION

Antibiotic resistance is a major public health problem worldwide, resulting in increased morbidity and mortality.[1] Urinary tract infections (UTIs) occur frequently in the community and are therefore a common reason for resorting to primary healthcare and, for antibiotic prescriptions.[2]

The most common etiological agent of urinary tract infections belongs to the *Enterobacteriaceae* family, namely *Escherichia coli*, being responsible for 75%-95% of cases, followed by *Klebsiella pneumoniae* and *Proteus Mirabilis*, with *Staphylococcus saprophyticus* or *Enterococcus* spp. as possible alternative infectious agents. In the past years, an increase in antimicrobial resistance has been noted, particularly to the pharmacological class of cephalosporins, trimethropim-sulfamethoxazole and fluoroquinolones.[3]

In Portugal, despite the existence of National Clinical Guidelines, referred to as "Normas de Orientação Clínica" (NOC), drawn up by the national health authority, high rates of resistance have been described, probably as a result of the incorrect use of these antibiotics.[4] Understanding the local epidemiology and the antimicrobial resistance profile is crucial to optimizing treatments and reducing the emergence of resistance to the therapeutic regimens instituted.

In order to achieve a global commitment and effort in the prevention, control and management of infections, the authors believe that the surveillance of the etiological agents of community-acquired uncomplicated cystitis in users of a Local Health Unit in the northern region of Portugal, as well as knowledge of their local antibiotic sensitivity and resistance profile, could contribute to the development of clinical guidelines for the empirical treatment of these infections, leading to a possible reduction in resistance rates.

The goals for this study were to determine the prevalence of the most frequent microorganisms in uncomplicated cystitis in Primary Health Care in patients of our institution, to assess their sensitivity and resistance profile to antimicrobials and, based on this data, to draw up an empirical therapeutic proposal taking for reference the national guidelines. There is an urgent need to alert healthcare professionals to a global commitment and effort at the primary healthcare level in infection prevention and control, antimicrobial stewardship and ongoing surveillance to limit antibiotic resistance and healthcare costs.

METHODS

An observational, descriptive, and retrospective study was carried out at the Local Health Unit based on urine

cultures relating to uncomplicated cystitis at Primary Health Care level with bacteriological identification, obtained between January 2020 and December 2021.

The inclusion criteria were patients of both sexes, aged 15 or over. Pregnant women, urine cultures from catheterized patients or urine cultures whose identified microorganisms did not correspond to bacteria were excluded.

The samples list was extracted using the Clinidata XXI® software program (5.3.22 version, Maxdata). The following variables were studied: gender, age, microorganism isolated in the urine culture and antibiotic susceptibility. The variable "age" was categorized in age groups according to the consensus of the authors and based on different studies with similar characteristics, and were considered as follows: Men: 15-44; 45-64; 65-84; ≥ 85. Women: 15-24; 25-44; 45-64; 65-84; ≥ 85).[5-7]

Descriptive statistics were analyzed using Excel® and SPSS® (26.0 version). To evaluate the categorical variables, relative and absolute frequencies were calculated, and the chi-square test was used to compare the prevalence of the microorganisms isolated between the age groups considered. A p value < 0.05 was considered statistically significant.

This study was approved by the Ethics Committee of the institution and favorable reports were obtained from the Clinical and Health Council.

RESULTS

In this study, the total number of urine cultures obtained was 2788, of which 2313 were from female patients (83%), 475 from males (17%) and 142 corresponded to pregnant women, who were excluded.

In terms of gender distribution, we found that, in males, the highest number of bacterial isolations were found in the age group between 65 and 84 (54.90%). On the other hand, the age group between 15 and 44 had the lowest number of isolations (5.60%). With regard to the most frequent microorganisms, in general, *Escherichia coli* was the most common etiological agent, identified in 47.6% (n = 226) of urine cultures from all age groups and representing around 66.7% (n = 18) of the results between the ages of 15 and 44; 57.6% (n = 72) between the ages of 45 and 64; 43.7% (n = 114) between the ages of 65 and 84; and 37.9% (n = 22) over the age of 85. The second most frequent microorganism that was also identified in all age groups was *Klebsiella pneumoniae*, with 15.4% (n = 73) of the total, which also presented a growing prevalence concerning the age groups, unlike *Escherichia coli*, which showed a progressive decrease in the number of cases with advancing age.

The sensitivity of the most commonly observed microorganisms in this study to some existing antibiotics was checked. In the male group, there was no statistical difference regarding the prevalence of the microorganisms isolated between the age groups considered (p>0.05), so the antibiotic sensitivity was evaluated for the group as a whole. Regarding the most common microorganism found in males, *Escherichia coli*, we observed sensitivity levels of 98.21% (219/223) to fosfomycin; 97.73% (215/220) to nitrofurantoin; 88.79% (198/223) to cefuroxime and 85.53% (65/76) to pivmecillinam.

In females, as in males, the age group with the highest number of bacterial isolations was the 65-84 age group (38.90%), with the 15-24 age group having the fewest isolations (4.90%). In terms of the frequency of microorganisms, *Escherichia coli* was the bacterium that came first in all age groups, with a frequency of 52.8% (n = 66) between the ages of 15 and 24; 72.5% (n = 288) between the ages of 25 and 44; 73.3% (n = 404) between the ages of 45 and 64; 69.1% (n = 622) and 57.2% (n = 202) over the age of 85. *Klebsiella pneumoniae* came second in all age groups, except in the 15-24 age group, where *Staphylococcus saprophyticus* came second with 12.8% (n = 16). In general, it was again found that the prevalence of *Escherichia coli* decreased with age, while the prevalence of *Klebsiella pneumoniae* progressively increased.

Regarding the sensitivity of the microorganisms to the antibiotics evaluated in this study, in the female group, there were differences between the age groups considered (p<0.05), which led to this analysis being carried out separately. Between the ages of 15 and 24, *Escherichia coli* showed a sensitivity of 100% (65/65) to nitrofurantoin; 86.36% (57/66) to cotrimoxazole; 98.46% (64/65) to fosfomycin and 92% (23/25) to pivmecillinam. *Staphylococus saprophyticus* was 100% (16/16) sensitive to nitrofurantoin.

In the other age groups, *Escherichia coli* showed a sensitivity of over 98% to fosfomycin and nitrofurantoin and over 86% to pivmecillinam. Above the age of 85, the sensitivity to cefuroxime was 84.0%. The sensitivity of *Escherichia coli* to ciprofloxacin also decreased with age (96.97% in females of aged group 15-24 and 82.5% in females over 85; 83.11% in male group).

DISCUSSION

This study determined the etiology of community-acquired uncomplicated cystitis in a Local Health Unit,

as well as the local antibiotic sensitivity and resistance profile for the main bacteria isolated in men and women. The national guidelines for treatment of these infections were then adapted to the local ecology. The results of this investigation corroborate what is described in the literature, as the percentage of urine cultures with bacteriological isolation was much higher in women (83.0%).[5,8,9] The high occurrence of uncomplicated cystitis in women may be due to the anatomy of the female urethra, which is shorter than the male urethra, making it more susceptible to the ascension of enterobacteria, along with the influence of antibacterial compounds found in the male prostatic fluid.[10,11] Other risk factors can be considered in premenopausal women, namely sexual activity, delayed post-coital urination, the use of spermicides and a personal history of UTIs.[12]

The most isolated microorganism in both females (68.40%, n = 1582) and males (47.79%, n = 227) was *Escherichia coli*, regardless of the age group considered, which is in line with what has been identified in similar studies.[13-17] The overall prevalence of *Escherichia coli* was 64.89% (n = 1809), similar to the prevalence identified in other Portuguese studies,[11,18] but lower than that reported in international studies, where it varies between 75% and 90%.[17,19]

Klebsiella pneumoniae was identified in 15.79% (n = 75) of urine cultures with bacterial isolation in males and 12.15% (n = 281) in females, which represents an overall prevalence of 12.77%, similar to that reported in a Portuguese study carried out in the central region (12%),[18] but higher than that reported in two national studies carried out in Lisbon and in the Vale do Tâmega e Sousa region, where the figure was between 3.7%[20] and 10%,[11] respectively.

The appropriate choice of empirical antibiotic therapy for the treatment of uncomplicated cystitis should be based on knowledge of the microorganisms primarily involved and their susceptibility to antibiotics.[21] In females, the distribution of bacterial agents was different between the age groups considered, so the therapeutic proposals made by the researchers were adjusted according to the age group considered and the antimicrobial sensitivity profile analyzed.

According to the current NOC, in non-pregnant women with uncomplicated cystitis, the recommended first-line therapy is fosfomycin or nitrofurantoin.[22] A meta-analysis comparing the therapeutic effects of fosfomycin with other antibiotics in the treatment of cystitis in non-pregnant, pregnant and elderly women concluded that fosfomycin produced similar effects to fluoroquinolones, trimethoprim-sulfamethoxazole, β-lactams and nitrofurantoin, with fewer associated adverse effects.[23] However, in the 15-24 age group, *Escherichia coli* accounts for approximately half of the isolations, followed by *Staphylococcus saprophyticus*, so the researchers considered that nitrofurantoin would be a better first-line option for women in this age group, always taking into account the therapeutic adherence factor.

The authors highlight the relevance of pivmecillinam as an empirical therapy option for uncomplicated cystitis in women aged 25 and over, as recommended by other guidelines.[24,25] This drug is not available for prescription in the community in Portugal and has been used for a limited time at hospital level. However, this study highlights its relevance in dealing with this very prevalent pathology, particularly in primary healthcare, and the potential benefit of its use, reserving the use of other antibiotics more commonly used in other infectious pathologies.

From the age of 85, in females, the resistance profile changes due to the presence of factors such as urinary incontinence, atrophic vaginitis, deterioration in functional status, with frequent urinary catheterizations, which is why it is important to carry out a bacteriological examination prior to antimicrobial treatment, and to adjust therapy if necessary.[26] It should be noted that all recommended drugs should be adjusted to each patient's history, including renal function and known drug allergies.

Regarding antibiotic sensitivities in males, *Escherichia coli* had a sensitivity of 98.21% to fosfomycin, 97.73% to nitrofurantoin, 88.79% to cefuroxime and 85.53% to pivmecillinam, which is why these were selected by the researchers as the first-line antibiotics to implement for uncomplicated cystitis. The approach to uncomplicated cystitis in men is not straightforward due to the frequent involvement of the prostate,[27] with approximately 10% of men presenting symptoms suggestive of prostatitis and 50% presenting these symptoms at least once in their lives.[19] It is therefore important that in young men with uncomplicated cystitis without systemic symptoms, no personal history of UTI and a physical examination that does not suggest a causal factor, treatment for uncomplicated cystitis should be considered, with a shorter treatment duration.[24,27]

In the presence of symptoms suggestive of prostatitis, the use of ciprofloxacin as first-line therapy and cotrimoxazole as second-line therapy is recommended. It should be noted that ciprofloxacin and cotrimoxazole

are not therapeutic options if the agent responsible for the prostatitis is *Klebsiella pneumoniae*. For these patients, it is recommended to carry out a urine culture before starting empirical antibiotic therapy, which should then be adjusted based on the antibiotic susceptibility test.[24]

The following Tables 1 and 2 summarizes our proposal for treating community UTIs in our geographic area.

Based on the present analysis, the authors consider that amoxicillin-clavulanic acid conjugate should not be an option for the treatment of local uncomplicated cystitis, contrary to what is suggested in the NOC, since the sensitivity to *Escherichia coli* is less than 75% in all the analyses carried out. According to the European Urology Guidelines, it is a strong recommendation to avoid using aminopenicillins and fluoroquinolones to treat uncomplicated cystitis.[24] However, in patients with a previous history of renal lithiasis who present with symptoms compatible with uncomplicated cystitis, empirical treatment with amoxicillin-clavulanic acid conjugate may be considered, since the presence of infected calculi involves urease-producing bacteria in the vast majority of cases, and infection by *Proteus mirabillis* is therefore considered more likely in these patients.[28,29] The authors found in their data analysis that antibiotic sensitivity decreases with age. This pharmacological class is not recommended as first-line antibiotics and should not be prescribed for uncomplicated cystitis, but only for more serious infections.[26]

Considering our study's limitations, the following stand out: 1) bias related to not knowing the clinical suspicion of the diagnosis; 2) possible inclusion of samples from the same patient related to recurrent UTIs; 3) the possibility that not all urine cultures from catheterized

TABLE 1. Proposal for empirical outpatient therapy for uncomplicated cystitis in FEMALE patients, belonging to the community served by the Local Health Unit.

Infection	Age (years)	Antibiotic	Dose	Duration
Uncomplicated cystitis	15-24	**1st line:** Nitrofurantoin	100 mg 6/6 hours	5-7 days
		2nd line: Cotrimoxazole	160/800 mg 12/12 horas	3-5 days
		3rd line:		
		Fosfomycin	3000 mg	One-time
		or Pivmecillinam	400 mg 12/12 hours	3-7 days
	25-64	**1st line:**		
		Fosfomycin	3000 mg	One-time
		Pivmecillinam	400 mg 12/12 hours	3-7 days
		Nitrofurantoin	100 mg 6/6 hours	5-7 days
		2nd line: Cefuroxime axetil	250 mg 12/12 hours	5-7 days
	≥ 65	**1st line:**		
		Fosfomycin	3000 mg	One-time
		Pivmecillinam	400 mg 12/12 hours	3-7 days
		2nd line: Cefuroxime axetil	250 mg 12/12 hours	5-7 days
		3ª linha: Cotrimoxazole	160/800 mg 12/12 hours	3-5 days
Uncomplicated cystitis and history of renal lithiasis	15 – 64	Amoxicilin+Clavulanic acid	875/125 mg 12/12 hours	7 days

TABLE 2. Proposal for empirical outpatient therapy for UTIs in MALE patients belonging to the community served by the Local Health Unit.

Infection	Antibiotic	Dose	Duration
Uncomplicated cystits	Fosfomycin	3000 mg	One-time
	Nitrofurantoin	100 mg 6/6hours	5-7 days
	Cefuroxime	500 mg 12/12 hours	3 days
	Pivmecillinam	400 mg 12/12 hours	3-7 days
Acute Prostatitis	**1st line:** Ciprofloxacin	500 mg 12/12 hours	3-4 weeks if acute, 6 weeks id subacute 12 weeks if chronic
	2nd line: Cotrimoxazole	160/800 mg 12/12 hours	7 days
Uncomplicated cystitis and history of renal lithiasis	Amoxicilin+Clavulanic acid	875/125 mg 12/12 hours	7 days

patients in the community were excluded, due to omission of clinical information or unrequested urine culture as "catheter urine"; 4) the pandemic period may have intensified the already recognized problem of antimicrobial resistance, due to their excessive use. In the management of infections, the rational use of antibiotics is essential, since their choice has an impact not only on an individual, but also on a collective dimension.

CONCLUSION

In general, the empirical treatment of uncomplicated cystitis should target *Escherichia coli*. Antibiotic selection should be appropriate and in line with local resistance patterns and based on data from the most recent studies, since the variability of sensitivities can change. The NOC does not differentiate between age groups in their recommendations, so the development of this local protocol is a significant gain for the population covered by the study. These results allowed the promotion of rational antibiotic prescription adjusted to the local reality, with a significant contribution to reducing antibiotic resistance.

In the future, we think it would be important to compare this data with recent data from the post-pandemic period and see if this situation may have altered antimicrobial sensitivity profiles.

CONTRIBUTORSHIP STATEMENT/ DECLARAÇÃO DE CONTRIBUIÇÃO

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