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ORIGINAL ARTICLE

COMMUNITY-ACQUIRED URINARY TRACT BACTERIAL INFECTIONS AND DRUG RESISTANCE AMONG PATIENTS FOLLOWED AT A REFERENCE CENTER IN FORTALEZA, CEARÁ, BRAZIL

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ABSTRACT

Background: The aim of this study was to assess the antimicrobial resistance pattern of the most frequent pathogens responsible for community-acquired urinary tract infection (UTI). *Methods*: This is a retrospective, descriptive epidemiological survey involving all urine samples submitted for culture and antimicrobial susceptibility testing from patients with clinical diagnosis of UTI followed at the outpatient clinic of the Núcleo de Atenção Médica Integrada, University of Fortaleza, Brazil. The study period was from September 2012 to July 2013. Urine cultures were processed with clean-catch midstream urine samples in the local laboratory employing standard methods. A questionnaire was used to collect patient demographic data and the results of the bacterial identification and susceptibility testing. The data were analyzed by SPSS software. *Results*: A total of 514 urine samples were analyzed. Most patients were females (78.6%). Patients' mean age was 39 years old. Bacterial growth was observed in 16.5% of the samples. This rate was lower in women (13.6%) than in men (27.3%). The most prevalent pathogen was *Escherichia coli* (57.6%), followed by *Klebsiella* sp. (35.3%) and *Proteus* sp. (4.7%). *E. coli* showed a high frequency of resistance to ampicillin (88.2%) and sulfamethoxazole/trimethoprim (77.1%), as well as significant resistance to ciprofloxacin (38.9%) and norfloxacin (39.4%). Isolates from elderly patients (>60 years) had higher resistance to all tested antibiotics. *Conclusions*: There is a trend toward increasing bacterial resistance among the main UTI pathogens. Resistance to sulfamethoxazole/trimethoprim follows a worldwide increase rate tendency and it should be avoided as a first-line empirical treatment for UTIs. A significant resistance to quinolones was also observed.

KEY WORDS: Urinary tract infections; drug resistance; anti-bacterial agents; epidemiology.

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RESUMO

Infecções do trato urinário adquiridas na comunidade e resistência bacteriana em pacientes seguidos em um centro de referência em Fortaleza, Ceará, Brasil

Introdução: O objetivo deste estudo foi identificar o perfil de resistência dos patógenos mais frequentes responsáveis por infecções do trato urinário (ITU) adquiridas na comunidade. *Métodos*: Foi realizado estudo retrospectivo, pesquisa epidemiológica descritiva, incluindo todas as amostras de urina enviadas para cultura e teste de sensibilidade antimicrobiana de pacientes com diagnóstico clínico de ITU acompanhados no ambulatório do Núcleo de Atenção Médica Integrada da Universidade de Fortaleza, Ceará, Brasil. O período do estudo foi de setembro de 2012 a julho de 2013. As urinoculturas foram processadas a partir de urinas colhidas do jato médio utilizando os métodos padrões de laboratório. Foi utilizado um questionário para coletar dados demográficos e os resultados da identificação bacteriana e teste de susceptibilidade. Os dados foram analisados pelo programa SPSS. *Resultados*: Um total de 514 amostras de urina foram analisadas. A maioria dos pacientes era do sexo feminino (78,6%). A média de idade dos pacientes foi de 39 anos. Foi observado crescimento bacteriano em 16,5% dos casos. Esta taxa foi menor entre as mulheres (13,6%) que nos homens (27,3%). O patógeno mais prevalente foi a *Escherichia coli* (57,6%), seguida de *Klebisiella* sp. (35,3%) e *Proteus* sp. (4,7%). A *E. coli* apresentou alta resistência à ampicilina (88,2%) e ao sulfametoxazol-trimetoprim (77,1%), bem como resistência significativa ao ciprofloxacino (38,9%) e norfloxacino (39,4%). Os pacientes idosos (>60 anos) apresentaram alta resistência a todos os antibióticos testados. *Conclusões*: Há uma tendência ao aumento da resistência bacteriana entre os principais patógenos causadores de ITU. A resistência so Sulfametoxazol-trimetoprim segue uma tendência mundial de aumento e seu uso deve ser evitado como tratamento empírico de primeira escolha nas ITUs. Resistência significante às quinolonas também foi observada.

DESCRITORES: Infecções urinárias; resistência a medicamentos; antibacterianos; epidemiologia.

INTRODUCTION

Urinary tract infection (UTI) is a disease with high prevalence in the population, affecting both sexes at all ages; the disease can manifest as symptoms ranging from those of little or no clinical significance to complex scenarios of extreme severity (Nardozza Júnior et al., 2010).

In Brazil, symptomatic UTIs appear as the second most common infection in the general population (Sociedade Brasileira de Infectologia e Sociedade Brasileira de Urologia, 2004). Approximately 48% of the female population has at least one event of UTI throughout life. After the fifth decade of life, the presence of prostatic hyperplasia makes men more susceptible to UTIs (Brandino et al., 2007).

UTIs may be classified as complicated and uncomplicated. Uncomplicated UTI is a community-acquired infection that occurs in non-pregnant females with no anatomical or functional abnormalities of the urinary

tract, in the absence of urinary catheters and immunological alterations. A complicated UTI is associated with obstructive (benign prostate hypertrophy, tumors, urolithiasis, ureteropelvic junction stenosis, foreign bodies, etc.); anatomofunctional (neurogenic bladder, vesicoureteral reflux, medullary sponge kidney, nephrocalcinosis, renal cysts, bladder diverticula); and metabolic causes (renal failure, diabetes mellitus, renal transplantation), as well as indwelling urethral catheters or any type of instrumentation and ileal derivations (Heilberg et al., 2003).

The most prevalent etiologic agents in community-acquired UTI in the general population are, in order of frequency: *Escherichia coli, Staphylococcus saprophyticus, Proteus* sp., *Klebsiella* sp. and *Enterococcus faecalis. E. coli* alone is responsible for 70% to 85% of community-acquired urinary tract infections and 50% to 60% in elderly patients admitted to institutions. However, when the UTI is hospital-acquired, the etiologic agents are usually more diverse, with a predominance of Enterobacteriaceae, with reduced frequency of *E. coli* (although still generally being the main cause), and an increase in *Proteus* sp., *Pseudomonas aeruginosa, Klebsiella* sp., *Enterobacter* sp., *Enterococcus faecalis* and fungi, especially *Candida* sp. (Sociedade Brasileira de Infectologia e Sociedade Brasileira de Urologia, 2004). The prevalence of these pathogens remains unchanged to the present day.

The increase in bacterial resistance has generated a global mobilization of the medical class to perform epidemiological studies aiming to characterize the prevalence of pathogens and their characteristics, including the antimicrobial resistance profiles. The World Health Organization (WHO) released a report in 2014 that considers antibiotic resistance a global threat to public health (World Health Organization, 2014).

Studies from different parts of the world have indicated *E. coli* as the main cause of UTIs (Nardozza Júnior et al., 2010; Alzohairy et al., 2011; Lagacé-Wiens et al., 2011; Peco-Antic et al., 2012; Santana et al., 2012; Tantry et al., 2012; Linhares et al., 2013; Korb et al., 2013; Jalilian et al., 2014; Park et al., 2014), and warned of its increased resistance to first-choice antimicrobials such as ampicillin and trimethoprim-sulfamethoxazole (TMP-SMZ). High rates of resistance have also been attributed to quinolones, which are probably one of the most widely used groups of antibacterial drugs for the treatment of urinary tract infections. Quinolone resistance may be indicative of resistance to one of the last available oral treatment options, in some cases (World Health Organization, 2014).

The aim of this study was to assess the antimicrobial resistance pattern of the most frequent pathogens responsible for community-acquired UTIs.

MATERIAL AND METHODS

Patients and collaborating center

This is a retrospective, descriptive epidemiological survey, involving all urine samples submitted for culture and susceptibility testing from patients with a clinical diagnosis of urinary tract infection (UTI) followed at the outpatient clinics of Núcleo de Atenção Médica Integrada, University of Fortaleza, Brazil. The study period was from September 2012 to July 2013.

Sampling

Urine cultures were processed with clean-catch midstream urine samples in the local laboratory employing standard methods. A questionnaire was used to collect patient demographic data, as well as the results of the bacterial identification and susceptibility testing.

Microorganism identification

Urine samples were plated on cystine-lactose electrolyte-deficient (CLED) agar up to 20 min after collection and then incubated at 37 ºC for 24 h. Bacterial counts were considered negative in cases of precarious growth and then rejected. Only pure growth of a single uropathogen at $\geq 10^5$ CFU/mL was considered for analysis. The Muller-Hinton method was used to determine antimicrobial susceptibility of causative strains, in accordance with established norms of the Clinical and Laboratory Standards Institute (CLSI). The susceptibility profile of the majority of isolated strains was tested against the following antibiotics: ampicillin, ampicillin-sulbactam ceftriaxone, ciprofloxacin, gentamicin, nitrofurantoin, norfloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ). Isolates were classified as resistant, intermediate and susceptible. The intermediate isolates were excluded for analysis in this study.

Ethics

The protocol of this study was approved by the Ethical Committee of the University of Fortaleza (protocol number 213.087).

Statistical Analysis

The data were analyzed by SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA). Stratification by age and sex was performed. Pearson's

chi-square test was used for bivariate correlations. An exact 2-tailed P value was computed (values below 0.05 were considered significant) and the strength of association was assessed in selected variables by calculation of odds ratios. We considered that all cases have the same odds of entering the analysis.

RESULTS

A total of 514 culture samples were analyzed during the study period. Of these, 78.6% of samples were from women and 21.4% from men. The mean age of the enrolled patients was 39 years, being higher among men (56.2 years) than women (34.6 years). Out the 514 culture samples, 18.3% (n=94) of the medical records did not have the patient's age or date of birth. Of the women, 3.3% were less than 12 years old, 72.2% were aged between 12 and 40 years, 14.6% between 40 and 60 years and 9.9% were older than 60 years. Among men, the majority (51.8%) were 60 years old or older, 5.9% were less than 12 years old, 22.4% were aged between 12 and 40 years and 20% between 40-60 years.

Of the 514 cultures carried out in the study, bacterial growth was observed in 16.5% (85 samples). This rate was lower in women (13.6%) than in men (27.3%). *Escherichia coli* was the most prevalent isolated microorganism, with a prevalence of 57.6% among positive cultures, representing 46.7% and 63.6% of the bacterial species isolated from men and women, respectively, followed by *Klebsiella* sp., with a prevalence of 35.3%, which was more frequent in men (43.3%) than in women (30.9%). The prevalence of *Proteus* sp. was 6.7% of cultures from men and only 3.6% in women (Table 1).

Antibiotic susceptibility was tested for most of the strains. Ciprofloxacin and gentamicin were tested in 64.7% of the positive cultures; sulfametoxazol/trimethropim in 63.5%; ampicillin and ampicillin/sulbactam in 62.3%; norfloxacin, in 61.2%; nitrofurantoin in 56.5% and ceftriaxone in 50.8%.

A high frequency of *E. coli* strains resistant to ampicillin (88.2%) or trimethoprim/sulfamethoxazole (TMP-SMX) (77.1%) was observed. There was also a significant resistance of *E. coli* to norfloxacin (39.4%) or ciprofloxacin (38.9%) (Table 2). Patients aged 60 years or older had higher rates of resistance to all tested antibiotics (Table 3).

Despite the fact that 18.3% of the patients' age information was not available, it is possible to see a distinction between the antibiotic susceptibility profile in patients of different age groups. There was also a significant difference between men and women. A higher resistance was observed among men (Tables 4 and 5).

Table 1. Prevalence of microorganisms isolated from 514 urine samples from patients with clinical diagnosis of UTI treated at a referral service in Fortaleza, Ceará, Brazil, between September 2012 and July 2013.

Isolated microorganism	n	%	n	Men %	n	Women %
Escherichia coli	49	57.6%	14	46.7%	35	63.6%
Klebsiella sp.	30	35.3%	13	43.3%	17	30.9%
Proteus sp.	4	4.7%	2	6.7%	2	3.6%
Coagulase negative *S. aureus*	1	1.2%	0	-	1	1.8%
Acinetobacter	1	1.2%	1	3.3%	0	-

Table 2. Susceptibility profile of *E. coli* and non-*E. coli* bacteria isolated from urine samples of 514 patients treated at a referral service in Fortaleza, Ceará, Brazil, between September 2012 and July 2013.

Antimicrobial agent	*E. coli* Total n = 49			Non-*E. coli* Total n = 36			*P*
	Tested n	Resistant		Tested n	Resistant		
		n	%		n	%	
Ampicillin	34	30	88.2%	19	18	94.7%	0.250
Ampicillin/ sulfabactam	34	7	20.6%	19	6	31.6%	0.198
Ceftriaxone	32	2	6.3%	18	2	11.1%	0.291
Ciprofloxacin	36	14	38.9%	19	3	15.8%	0.043
Gentamicin	36	1	2.8%	19	3	15.8%	0.062
Nitrofurantoin	33	4	12.1%	15	8	53.3%	0.002
Norfloxacin	33	13	39.4%	19	3	15.8%	0.042
Sulfametoxazol/ trimethoprim	35	27	77.1%	19	2	10.5%	0.0001

Table 3. Susceptibility profile of *E. coli* urine cultures according to different age groups.

Antimicrobial	up to 60 years			60 years or older			*P*
	Resistance			Resistance			
	Total	n	%	Total	n	%	
Ampicillin	19	18	94.4%	8	8	100%	0.351
Ampicillin/sulbactam	20	4	20.0%	9	2	22.2%	0.441
Ceftriaxone	18	0	0.0%	8	1	12.5%	0.153
Ciprofloxacin	20	6	30.0%	9	6	66.7%	0.042
Gentamicin	20	0	0.0%	9	1	11.1%	0.155
Nitrofurantoin	19	4	21.1%	8	0	0.0%	0.110
Norfloxacin	17	5	29.4%	9	6	66.7%	0.045
Sulfametoxazol/ trimethoprim	20	16	80.0%	8	8	100%	0.118

Table 4. Susceptibility profile of *E. coli* urine cultures according to gender among individuals younger than 60 years.

Antimicrobial	Men			Women			*P*
	Resistance			Resistance			
	Total	n	%	Total	n	%	
Ampicillin	5	5	100%	26	25	96.2%	0.419
Ampicillin/ sulbactam	5	3	60.0%	27	5	18.5%	0.046
Ceftriaxone	3	0	0.0%	27	0	0.0%	-
Ciprofloxacin	5	3	60.0%	27	3	11.1%	0.018
Gentamicin	5	0	0.0%	27	0	0.0%	-
Nitrofurantoin	4	0	0.0%	25	7	28.0%	0.153
Norfloxacin	5	3	60.0%	24	2	8.3%	0.012
Sulfametoxazol/ trimethoprim	5	3	60.0%	27	13	48.1%	0.333

Table 5. Susceptibility profile of *E. coli* urine cultures according to gender among individuals older than 60 years.

Antimicrobial	Men			Women			*P*
	Resistance			Resistance			
	Total	n	%	Total	n	%	
Ampicillin	4	4	100%	7	7	100%	-
Ampicillin/sulbactam	7	3	42.9%	5	1	20.0%	0.247
Ceftriaxone	6	3	50.0%	5	0	0.0%	0.060
Ciprofloxacin	7	7	100%	5	2	40.0%	0.022
Gentamicin	7	3	42.9%	5	1	20.0%	0.247
Nitrofurantoin	5	2	40.0%	5	0	0.0%	0.111
Norfloxacin	7	7	100%	5	2	40.0%	0.022
Sulfametoxazol/ trimethoprim	7	6	85.7%	4	4	100%	0.318

DISCUSSION

The choice of antimicrobial therapy should be based on the knowledge of two basic principles: first, the prevalence of the most common etiologic agents for each age group and sex; and second, the knowledge of the antimicrobial susceptibility profile of these uropathogens, which may be variable in each community and over time (Lo et al., 2013). Recent studies in our region have pointed to a growing increase in bacterial resistance in urinary tract infections (Araújo et al., 2011).

Corroborating the literature data, it was observed that in men, the mean age of patients with UTIs (61 years) was older than in women (30 years). This is related to the fact that, in women, the main risk factors for developing UTI are pregnancy and the onset of sexual activity. After the neonatal period, urinary infection is more common in females, with incidence increasing with each decade, until it reaches 10% to 15% at 60-70 years of age. Asymptomatic bacteriuria is also more common in females, although there is an increased prevalence in males after the sixth decade of life. Urinary tract infection and asymptomatic bacteriuria are common in males, especially if associated with obstructive factors, such as Benign Prostatic Hyperplasia (BPH), and urinary tract instrumentation (Riella, 2010). According to Litza and Brill (2010), the type and duration of UTI treatment should be based on comorbidities and

complications shown by each patient, not their age. We have observed a higher frequency of positive cultures in men than in women, and this is probably due to the fact that UTI in men tends to be more severe, with more aggressive pathogens that are consequently easier to identify in urine cultures.

Recent studies carried out in several countries, such as India (Tantry et al., 2012), Canada (Lagacé-Wiens et al., 2011), Iran (Jalilian et al., 2014), Serbia (Peco-Antic et al., 2012), Portugal (Linhares et al., 2013), United States (Fleming et al., 2014) and Brazil (Nardozza Júnior et al., 2010; Korb et al., 2013; Santana et al., 2012) have demonstrated that the pathogen most commonly found in urine samples was E. coli, showing the global range of this microorganism in these infections.

In the present study, *Klebsiella* sp. was the second most prevalent bacterium, detected in 35.3% of cases. A similar result was found by others (Alzohairy et al., 2011; Araújo et al., 2011; Dibua et al., 2014; Irenge et al., 2014). Infections by *Proteus, Klebsiella, Serratia, Pseudomonas* and *Enterococcus* are frequent in elderly men (Barros et al., 2007).

The continuous increase in bacterial resistance is a matter of concern, as it is directly related to additional costs for the patient and the health care system and because it involves hospitalization, costly and very often long treatments, as well as the decrease in available therapeutic options. The matter of bacterial resistance is often debated, especially the increase of *E. coli* strains resistant to quinolones and sulfonamides. Much of this is due to the indiscriminate use of these drugs for too long (Nardozza Júnior et el., 2010).

A study carried out by Irenge et al. (2014) found that, of the 643 samples that showed bacterial growth, 16.3% were multidrug resistant strains. Of these, 92.4% had the ESBL phenotype, with high prevalence of *E. coli*.

Our study shows a pattern of antimicrobial resistance that is above those found in other Brazilian studies. In the analysis of *E. coli* resistance to ampicillin, for instance, a percentage of 88.2% was observed, compared to 52% in São Luís/MA (Santana et al., 2012), 52.1% in Presidente Prudente/SP (Braoios et al., 2009) and 77% in Fazenda Rio Grande/PR (Korb et al., 2013). These differences may be related to several factors, including the epidemiological profile of the region and the predominant clinical management. According to these data, ampicillin is confirmed as one of the antimicrobials with lower therapeutic success against *E. coli*. International studies also corroborate this assertion (Alzohairy et al., 2011; Linhares et al., 2013; Dash et al., 2012). It is noteworthy that, among the non-*E. coli* pathogens found in the sample, ampicillin resistance was 94.7%.

In the present study, *E. coli* resistance was higher than that of other pathogens regarding ciprofloxacin (38.9%), norfloxacin (39.4%) and TMP-SMX (77.1%). This is probably due to the fact that *E. coli* is the most prevalent pathogen and thus, the most often exposed to these antibiotics. Moreover,

TMP-SMX and ciprofloxacin are antibiotics found in the pharmacies of basic public health facilities and popular pharmacy networks, at low cost, which increases their availability for use, although indiscriminately.

Marques et al. (2012) observed that *E. coli* was present in cultures from patients with urinary tract infections, as well as those with asymptomatic bacteriuria. In both cases, *E. coli* was resistant to TMP-SMX and fluoroquinolones.

Araújo et al. (2011), in a study carried out with adult women, also found that TMP-SMX and quinolones, especially ciprofloxacin, follow the global trend of increased resistance of the most prevalent strains.

The selection of an empirical therapy should be based on the history of prior antimicrobial therapy (Marques et al., 2012), tolerance of the patient and suspected or known local prevalence of *E. coli* resistance (Nicolle, 2008).

Resistance to TMP-SMX was observed in 100% of samples from patients older than 60 years, an increase of 20.0% compared to younger patients (80.0% resistance). A study carried out in Portugal in 2013 discourages the use of this combination of antimicrobials for the treatment of UTIs due to their observed ineffectiveness (Linhares et al., 2013).

Ampicillin, TMP-SMX, cephalothin and nalidixic acid showed the lowest levels of susceptibility in general, indicating that these antibiotics should be used only after the results of susceptibility testing are available (Santana et al., 2012).

The present study also showed a level of resistance above that recommended for empirical treatment with quinolones. In the analysis of ciprofloxacin, resistance was 38.9%. The high resistances to quinolones indicate cause for concern, as the World Health Organization recommends caution when these rates are close to 20% due to the compromised results of antibiotic therapy without antibiograms in emergency cases (Korb et al., 2013). Several studies have warned about the increasing rates of resistance to fluoroquinolones (Dash et al., 2012; Kamenski et al., 2012; Dibua et al., 2014; Park et al., 2014; Singhal et al., 2014).

Elderly patients had higher rates of resistance to the tested antibiotics, which is in accordance with Brazilian and international studies (Lagacé-Wiens et al., 2011; Almeida, 2012) and can be explained by the increased number and duration of hospitalizations with the increasing age of patients (Linhares et al., 2013).

The tested quinolones, norfloxacin and ciprofloxacin, also showed a significant increase of resistance in elderly patients. The increase was similar among the quinolones: 36.7% for ciprofloxacin (66.7% in the elderly *versus* 30.0% in those younger than 60 years) and 37.3% for norfloxacin (66.7% in the elderly versus 29.4% in those younger than 60 years). The increase in bacterial resistance to quinolones is a matter of concern, as studies have confirmed the association between resistance to ciprofloxacin and resistance

to other antibiotics (Strand et al., 2014). Therefore, the empirical use of this class of antimicrobial agents must be reviewed and possibly be discouraged in the treatment of UTIs. Fleming et al. (2014) also recommend the empirical use of fluoroquinolones in cases of community-acquired UTIs in Georgia (USA), as the resistance remains at the 10% limit. However, alternative therapies may be necessary in patients with health care-related UTIs.

Regarding differences in overall resistance of urine cultures between men and women in the age groups studied, it was demonstrated that men have a higher resistance to the tested antibiotics. This may be related to the fact that women show a higher rate of return to health services to reassess the empirical therapeutic approach based on the result of the urine culture. Linhares et al. (2013) showed that the pathogens isolated in urine cultures of women had a better profile regarding resistance to multiple drug classes and therefore, these results indicate that the choice of empirical therapy should take the patient's sex into consideration.

The present study has some methodological limitations. The study has a retrospective design and data collection was carried out from the database of a secondary care center laboratory. Consequently, in some cases it was not possible to get the complete patient information due to incomplete medical records, such as patient's age and the bacteria susceptibility testing. Also, we had no control of how the material was collected, or the conditions of cleanliness and time between collection and examination. A more comprehensive study with a larger number of positive samples would be necessary for further inferences to be made.

In short, pathogen sensitivity to antibiotics regularly used in clinical practice, disclosed by antibiograms, as well as the prevalence of these agents in the obtained cultures, to counteract the high incidence of therapy failure of initial empirical treatment, requires that each service knows these data, in order to optimize treatment (to reduce costs, morbidity, time required for cure, inappropriate use of antimicrobial agents) and therefore prevent the emergence of new resistances.

The emergence of increasingly resistant strains to regularly used antibiotics, either caused by inadequate choice, poor patient compliance or microbial mutations, has caused major changes in the morbidity and mortality profile of patients, resulting in longer and more expensive treatments requiring invasive access, which do not always yield the desired result. The financial impact of this fact in the long term is yet to be calculated, but it is undeniable that it generates a burden to patients, health facilities, the government and society as a whole.

The perpetuation of this condition may cause serious harm to future generations with the emergence of multiresistant strains to the known antibiotics, when there might not be any alternatives for the treatment of these patients.

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