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ANTIBIOTIC RESISTANCE PATTERNS OF URINARY TRACT INFECTIONS IN A NORTHEASTERN BRAZILIAN CAPITAL

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SUMMARY

Urinary tract infection is a common problem worldwide. Its clinical characteristics and susceptibility rates of bacteria are important in determining the treatment of choice and its duration. This study assessed the frequency and susceptibility to antimicrobials of uropathogens isolated from community-acquired urinary tract infections in the city of *Natal*, *Rio Grande do Norte* State capital, northeastern Brazil, from 2007 to 2010. A total of 1,082 positive samples were evaluated; *E. coli* was the most prevalent pathogen (60.4%). With respect to the uropathogens susceptibility rates, the resistance of enterobacteria to ciprofloxacin and sulfamethoxazole-trimethoprim was 24.4% and 50.6%, respectively. Susceptibility was over 90% for nitrofurantoin, aminoglycosides and third-generation cephalosporins. High resistance rates of uropathogens to quinolones and sulfamethoxazole-trimethoprim draws attention to the choice of these drugs on empirical treatments, especially in patients with pyelonephritis. Given the increased resistance of community bacteria to antimicrobials, local knowledge of susceptibility rates of uropathogens is essential for therapeutic decision making regarding patients with urinary tract infections.

KEYWORDS: Urinary tract infections; Antibacterial drug resistance; Enterobacteriaceae; Antibacterial agents.

INTRODUCTION

Urinary tract infections (UTI) are frequent problems, exceeded only by respiratory and gastrointestinal infections. It affects around 150 million people worldwide each year[1,2]. UTI is defined as a tissue invasion by means of bacterial colonization of any part of the urinary tract, from the urethra to the kidneys[3]. Thus, it may involve the lower or upper urinary tract. Episodes of UTI occurring in premenopausal, non-pregnant, women with no known urological abnormalities are classified as uncomplicated, while all others are considered complicated UTI. This concept and knowledge of local susceptibility rates are important in decision making of the optimal choice for empirical antimicrobial therapy and its duration[1,2].

Most UTIs are caused by Gram-negative bacteria, being *Escherichia coli* the most commonly isolated. Other bacteria involved are *Proteus mirabilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus* spp., *Enterobacter* spp., Group B *Streptococcus* and *Staphylococcus saprophyticus*[3-5]. Variations in microbial spectrum and susceptibility patterns may occur in different regions, and the previous use of antimicrobials is an important predictor of resistance[5,6].

The high incidence of these infections and the need to start treatment before the results of microbiological findings become available often lead to the adoption of empirical therapy[5]. National and international studies have shown increased resistance to commonly used antimicrobials[7-9]. Besides, knowledge of the resistance pattern of uropathogens is important in guiding optimal antimicrobial choice in the initial approach of the patient. The aim of this study was to describe pathogens frequency and their susceptibility patterns in community-acquired urinary tract infections in the city of *Natal, Rio Grande do Norte* State capital, northeastern Brazil.

MATERIALS AND METHODS

This is a retrospective study to evaluate the results of urine cultures taken at the Central State Laboratory (LACEN/RN), a reference center for microbiological examinations in the public health system of *Rio Grande do Norte* State, Brazil. Data were based on records collected from January 2007 to December 2010, precluding identification of the subjects involved.

The urine specimens were processed and incubated on CLED agar, at a temperature of 35 ± 2 °C, for 24-48 hours. A count ≥ 100,000 colony forming units (CFU) per milliliter of urine was considered positive after incubation, and these isolates were identified. The antimicrobial susceptibility was determined on urinary isolates using the disk diffusion method, according to CLSI (Clinical & Laboratory Standard Institute)

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Table 1
Antimicrobial susceptibility of the three main uropathogens from Family Enterobacteriaceae . January 2007 to December 2010, LACEN/RN.

Antimicrobials	% Susceptible		
	E.coli (n=653)	*Klebsiella* spp. (n=154)	*Proteus* spp. (n=52)
Amikacin	94.1	92.7	87.5
Gentamicin	92.1	81.7	78.1
Ampicillin	48.3	-	-
Ampicillin/sulbactam	52.0	72.2	80.0
Amoxicillin/Clavulanate	82.2	81.1	95.7
Cephalothin	42.8	72.3	55.6
Ceftriaxone	92.2	86.1	80.0
Cefepime	90.8	73.2	76.0
Ciprofloxacin	75.6	75.4	69.8
Norfloxacin	79.6	76.5	75.0
Nitrofurantoin	93.4	45.1	15.6
Sulfamethoxazole/Trimethoprim	49.4	65.6	46.2
Nalidixic Acid	68.4	60.6	44.4

recommendations. In addition, susceptibility test results were interpreted following CLSI standards and recommendations (2005)[10] and, for the purpose of the analysis, intermediate susceptibility was interpreted as resistance. Only aerobic bacterial infections were analyzed in this study. Cultures showing fungal growth, mixed growth and those not conclusive in the laboratory, irrespective of reason, were excluded.

The data were analyzed using Excel 2007®. Susceptibility to antimicrobials was calculated by species.

RESULTS

A total of 1,082 samples were considered positive, according to inclusion microbiological criteria. Of these, 836 (79%) were from women. The median age of patients at time of treatment was 68.3 years (range three months–95 years). Among those with positive samples, 346 (31.9%) were older than the age of 60; of these, 221 (63.9% of people aged 60 and over) were female. We do not have data on how many samples were from patients treated in primary care facilities, but, in *Natal*/RN, the LACEN/RN laboratory is responsible for the execution of exams sent from the primary care facilities, while nosocomial samples are analyzed in hospital laboratories.

Among the positive samples, the most common pathogen isolated was *E. coli* (653/60.4%), followed by *Klebsiella* spp. (154/14.2%), *Staphylococcus* spp. (78/7.2%), and *Proteus* spp. (52/4.8%). Data are summarized in Tables 1 and 2.

Resistance to ciprofloxacin was identified in 24.4% of *E. coli* and *Klebsiella* spp., 30.2% of *Proteus* spp., and 9.4% of *Staphylococcus* spp. Resistance to sulfamethoxazole-trimethoprim was 50.6% for *E. coli*, 34.4% for *Klebsiella* spp., 53.8% for *Proteus* spp., and 18.6% for *Staphylococcus* spp. Susceptibility to ceftriaxone was 92.2% for *E. coli*, 86.1% for *Klebsiella* spp., and 80.0% for *Proteus* spp. *E. coli* was susceptible to nitrofurantoin in 93.4% of the samples. Resistance to cephalothin was 57.2% for *E. coli*, 27.7% for *Klebsiella* spp., and 44.4% for *Proteus* spp.; 43.7% of *Staphylococcus* spp. were resistant to oxacillin. In relation to aminoglycosides, susceptibility to amikacin was 94.1% for *E. coli*, 92.7% for *Klebsiella* spp., and 87.5% for *Proteus* spp.

Table 2
Antimicrobial susceptibility of *Staphylococcus* spp.isolated from urine. January 2007 to December 2010, LACEN/RN.

Antimicrobials	% Susceptible
	Staphylococcus spp (n=78)
Amikacin	33.3
Gentamicin	84.3
Ciprofloxacin	90.6
Norfloxacin	94.4
Nitrofurantoin	98.2
Oxacillin	56.3
Sulfamethoxazole/Trimethoprim	81.4
Nalidixic Acid	14.3

DISCUSSION

The present study provides information regarding species that cause community-acquired urinary tract infection treated at public

health services in *Natal*, Brazil, and their susceptibility to the main antimicrobials. Most of the samples were from patients treated at primary care facilities, and 79% were from women. There was no discrimination between asymptomatic bacteriuria, complicated, and uncomplicated UTI. *E. coli* predominated among the isolated agents, accounting for 60% of the positive cultures. This value is lower than that found in a number of international studies and similar to that obtained in Brazilian studies[1,5,8,9,11], which might reveal a local characteristic, reaffirming the need to know the regional profile in order to choose the correct antibiotic and course of empirical treatment.

Furthermore, we had a high percentage of samples from people aged 60 and over (31.9%), predominantly women. Older people, especially women, have the highest incidence of asymptomatic bacteriuria and UTIs and more associated comorbidities, like diabetes, considered an important risk factor for recurrent UTIs in women[12]. The antimicrobial use in this group is very frequent, because of recurrent UTIs, mistaken treatment for asymptomatic bacteriuria, or treatment of others infections[12]. It is possible that part of the study population had history of previous antimicrobial use or previous hospitalization. These factors have probably contributed to pathogen distribution and the sensitivity profile in this study, with high resistance of Gram-negative *Enterobacteriaceae* to quinolones and high resistance of *Staphylococcus* spp. to oxacillin.

Escherichia coli, Klebsiella spp., and *Staphylococcus* spp. were isolated in 82% of the samples, and most were susceptible to nitrofurantoin (> 92%), excepting for *Klebsiella* spp. strains (45%). Therefore, these data reinforce the recommendation of various clinical guidelines related to the empirical prescription of nitrofurantoin for uncomplicated cystitis. Fosfomycin, also recommended for these situations, was not tested in our study[7,13-15].

Fluoroquinolones are widely used for empirical treatment of UTI, including the cases of upper urinary tract infections[9]. We observed high resistance rates of the main isolated species to the tested antimicrobials (> 25% for *E. coli*). Similar data were described by ANDRADE *et al*., in samples of five Latin American countries (Argentina, Chile, Brazil, Mexico, and Venezuela)[7]. The previous use of quinolones is an independent risk factor for resistance to ciprofloxacin[16]. The indiscriminate use of this class of antimicrobials in community-acquired infections may have contributed to the high percentage of resistance observed, considering that the Brazilian population had free over-the-counter access to antimicrobials until 2011 (Resolution No. 20 of the Collegiate Board – RDC, on May 5, 2011). Therefore, quinolones as empirical therapy must be considered carefully, especially for patients with pyelonephritis. In this respect, if susceptibility is confirmed by pathogen isolation, quinolones are alternatives for de-escalation therapy, given the possibility of their oral administration[17].

Most of the *E. coli* strains isolated (50.6%) and other species were resistant to sulfamethoxazole-trimethoprim, as described in earlier studies[5,7]. This finding is most probably due to the wide use of these antimicrobials in the treatment of community-acquired infections. Even though sulfamethoxazole-trimethoprim is one of the alternatives for the empirical treatment of uncomplicated cystitis, therefore this association is not a safe choice. Guidelines of the American Infectious Diseases Society and the European Society for Microbiology and Infectious Diseases suggest that antimicrobials with a resistance rate above 20% should not be prescribed empirically to patients with uncomplicated cystitis, unless susceptibility is determined by prior isolation in culture[17].

In pregnant women, asymptomatic bacteriuria and UTI are common problems that should be treated with proper antimicrobials, due to a greater risk of pyelonephritis and the relationship between asymptomatic bacteriuria and obstetric complications[18,19]**.** The high percentage of strains resistant to first-generation cephalosporins and amoxicillin in our sample limits the empirical use of these drugs in pregnant women. Under these circumstances, nitrofurantoin, fosfomycin or amoxicillin/clavulanate are safer alternatives for cystitis, while third-generation cephalosporins should be used for pyelonephritis, until the susceptibility test of the isolated bacteria is available[17,20].

The high susceptibility to third-generation cephalosporins and aminoglycosides (> 90% in most strains), as well as their pharmacokinetic characteristics, make them the first line of therapy for pyelonephritis, until microbiological data are known.

The authors underscore the importance of knowledge of the local antimicrobial susceptibility pattern in the decision making of the therapy for UTI, given the increased resistance of community bacteria to antimicrobials commonly prescribed for this condition.

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