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ARTIGO ORIGINAL

Fatores associados com a resistência a ciprofloxacina e levofloxacina em bacilos Gram-negativos isolados de infecções do trato urinário

Factors associated with resistance to ciprofloxacin and levofloxacin in Gram-negative isolates from urinary tract infections

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RESUMO

Justificativa e Objetivos: As fluoroquinolonas representam uma classe de antimicrobianosque é frequentemente prescrita no tratamento de infecções do trato urinário (ITU), tanto de origem hospitalar como originárias da comunidade. Este estudo tem como objetivo, determinar a frequência de resistência à ciprofloxacina e levofloxacina, além de seus fatores associados em bacilos Gram-negativos (BGN) isolados de pacientes com ITU em um hospital no Sul do Brasil. **Métodos:** foi realizado um estudo transversal e analítico, baseado em casos de infecções do trato urinário causadas por bactérias gram-negativas provenientes de pacientes atendidos no Hospital Universitário Dr. Miguel Riet Correa Jr. em Rio Grande/RS, de agosto de 2012 a julho 2013. Foram analisadas variáveis independentes como idade, sexo, origem da infecção e características dos isolados clínicos bacterianos. **Resultados:** Dos 562 BGN isolados e analisados, foi encontrado uma frequência de resistência à ciprofloxacina e à levofloxacina de 25,5 e 23,3%, respectivamente, 62,6% de origem comunitária e 59% de origem hospitalar. Os fatores de risco associados à resistência a ciprofloxacina e levofloxacina, foram pacientes do gênero masculino, infecções adquiridas no ambiente hospitalar, com maior tempo de internação, e a presença de β-lactamases de espectro estendido (ESBL) nos isolados clínicos. **Conclusões:** Os resultados mostraram uma forte associação da resistência bacteriana de BGN com a permanência no ambiente hospitalar e a presença de ESBL. A fim de controlar a resistência antimicrobiana e a redução nos custos em saúde pública torna-se necessário que os hospitais tenham uma forte política de vigilância contínua do uso e da resistência de antibióticos.

ABSTRACT

Background and Objectives: Fluoroquinolones represent a class of antimicrobial agents that is often prescribed to treat urinary tract infections (UTI), both nosocomial ones and those originating in the community. This study aims to determine the frequency of resistance to ciprofloxacin and levofloxacin and its associated factors in Gram-negative bacilli (GNB) isolated from patients with urinary tract infection in a hospital in southern Brazil. **Methods:** A cross-sectional analytical study was carried out, based on cases of urinary tract infections caused by gram-negative bacteria in patients treated at Hospital Universitário Dr. Miguel Riet Correa Jr. in Rio Grande, state of Rio Grande do Sul, Brazil, from August 2012 to July 2013. Independent variables such as age, gender, infection origin and characteristics of the clinical and bacterial isolates were analyzed. **Results:** The resistance rate to ciprofloxacin and levofloxacin was 25.5 and 23.3%, respectively in the 562 BGN isolates

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that were analyzed, of which 62.6% were originated in community and 59% were nosocomial infections. Risk factors associated with resistance to ciprofloxacin and levofloxacin were male gender, infections acquired in the hospital environment, those with longer hospital stay, and the presence of extended spectrum β-lactamase (ESBL) in the clinical isolates. **Conclusions:** The results showed a strong association of GNB bacterial resistance with the permanence at the hospital environment and the presence of ESBL. In order to control antimicrobial resistance and reduce public health costs, it becomes necessary for hospitals to have a strong and continuous surveillance policy of antibiotic use and resistance.

INTRODUCTION

Urinary tract infections (UTI's) are clinically very relevant because they are among the most frequent causes of medical appointments and nosocomial infections, and they often result in an extended hospital stay and a consequent increase in health care costs.[1] The UTI's initiate when potential urinary pathogens originating from intestinal microbiota and in some cases from vagina are able to achieve the urinary system. These colonize the periurethral mucosa and ascend through the urethra to the bladder, being able to reach the ureters and kidneys.[2, 3]

Taking into account regional variations, UTIs are primarily caused by gram-negative bacilli (GNB) bacteria, including *Escherichia coli*, *Klebsiella* spp. and *Proteus* spp.; these bacteria account for up to 70-80% of community--acquired cases.[4] Therapies for these infections generally start before the results of the microbiological diagnosis are obtained, and empirical treatments are indicated in accordance with protocols based on the antimicrobial (ATM) activity spectrum and published studies of resistance standards.[5] Fluoroquinolones (FQ's) are one of the most commonly used ATMs for the treatment of UTIs acquired both in the community and in the hospital. However, studies have shown increased resistance to FQ's following its extensive use for the treatment of many infections in humans.[6]

GNB have shown resistance to multiple classes of antibiotics, including β-lactams, which reduces the therapeutic options and the infection control.[7] Higher rates of quinolone and FQ's resistance may be found in ESBL-producing strains like *E. coli* and *Klebsiella pneumoniae*, and continues to increase at alarming rates.[8] It is important also to point out that increasing bacterial resistance has major implications for urological practice, particularly in relation to catheter-associated UTI's and urological surgery.[8]

Understanding the incidence of bacterial resistance to FQs that are often used in the clinic, such as ciprofloxacin and levofloxacin, and the epidemiological factors associated with this resistance could inform rational therapy prescription and public control programs regarding ATM use. In this sense, this study aimed to determine the frequency of resistance and the factors associated with resistance to ciprofloxacin and levofloxacin in GNB isolated from patients with UTIs of hospital or community origin.

METHODS

It was performed a transversal, observational and analytical study of cases of UTI in patients treated at the Hospital Universitário Dr. Miguel Riet Correa Jr. in Rio Grande, Rio Grande do Sul between August 2012 and July 2013. The study used the following inclusion criteria: patients with a GNB urinary tract infection from whom samples were obtained and tested for susceptibility toFQ's. Patients were excluded if samples of their infections were not obtained or if there was a lack of sample data.

Microbiological analysis

The bacterial identification, assessment of susceptibility to ciprofloxacin and levofloxacin, and identification of extended-spectrum β-lactamases (ESBL) were performed using the Phoenix BD™ Diagnostic System following the manufacturer's standards. Urine samples were sent to the Analyzes Clinics Laboratory of HU-FURG and were plated on blood agar (or CLED agar when blood agar was not available) and MacConkey agar. After the incubation period (35° C for 18 to 24 hours), the colonies were quantified to determine if a UTI was present, and biochemical methods were used to characterize the bacterial species. To determine the susceptibility profile to ciprofloxacin and levofloxacin, 25 µl of standardized solution ID was transferred to TSA broth, and the solution was poured into the combined panel Phoenix compartment. This system was also used to check for resistance due to the presence of ESBLs by inoculating individual wells containing different concentrations of the following individual drugs and combinations: ceftazidime, cefpodoxime, ceftazidime plus clavulanic acid, clavulanic acid plus cefotaxime and clavulanic acid plus ceftriaxone. When the Phoenix system was not available, bacterial identification was performed using biochemical tests, and ciprofloxacin susceptibility testing was performed using the disk diffusion method.

Patient data were obtained from the hospital computer systems. It was evaluated the patient care sectors in the hospital and divided the patients into outpatients, emergency and hospitalized adults. To characterize the source of the infection, patients with UTIs beginning after 72 hours of hospitalization were considered of nosocomial origin; infections occurring prior to this time were considered to have originated in the community.[9]

For sample calculations, it was used a prevalence of 26% for resistance to ciprofloxacin and 28% for resistance to levofloxacin, with a sampling error of 24% and 27%, respectively. The necessary sample sizes with an increase of 5% to account for patient loss were 424 samples for ciprofloxacin and 514 samples for levofloxacin. Consistency analysis was performed by creating and categorizing variables and verifying frequencies in SPSS 17.0. Resistance

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to ciprofloxacin and levofloxacin was used as a dependent variable, and the following independent variables were considered: demographic data (age and gender), characteristics of the UTI (type of infection, the sample source, location and length of hospitalization) and features of the bacterial strains (species and presence or absence of ESBL). To compare the proportions, achi-square X^2 test was used at the 95% significance level. After obtaining the prevalence ratios (PR) and their respective confidence intervals (95% CI), the variables with $p \leq 0.20$ were included in the multivariate analysis. Poisson regression with robust adjustment of variance was used in the following hierarchical levels: age and gender, type of infection, the sample source, location and length of stay, bacterial species and the presence or absence of ESBL. Variables with $p \leq 0.05$ were considered significant.

Ethical aspects

This research followed the precepts introduced by Resolution 466/12 of Conselho Nacional de Saúde, which regulates research involving humans, and our study was approved by the Ethical Committee (Comitê de Ética em Pesquisa na Área da Saúde - CEPAS) of FURG (number n° 85/2013).

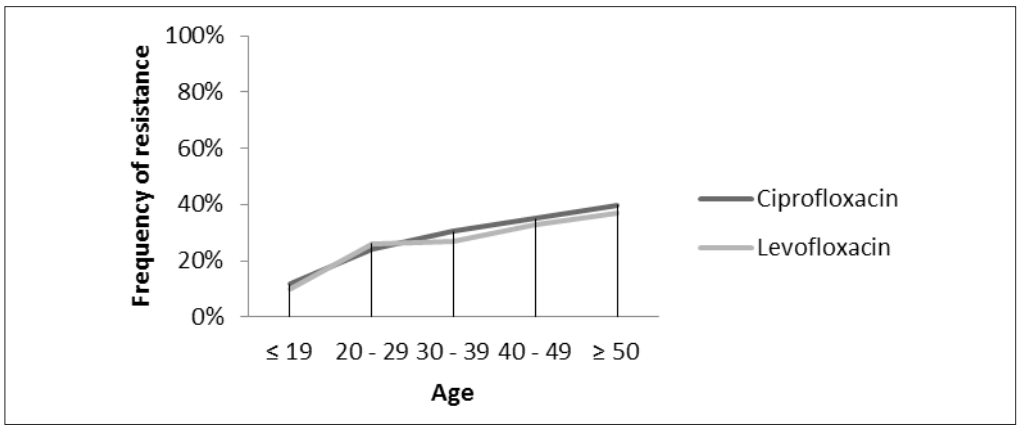
RESULTS

Samples were obtained from 562 cases of UTI caused by GNB; of these patients, 427 (76%) were females and 133 (24%) were male. Regarding age, 300 (53%) patients were older than 50 years. The majority of the infections originated in the community (n = 439), and 123 cases were characterized as nosocomial infections. Regarding the etiologic agents, *E. coli* was the most commonly isolated gram-negative microorganism, present in 375 samples, followed by *Klebsiella* spp. and the CESP group species (*Citrobacter* spp., *Enterobacter* spp., *Serratia* spp. and *Providencia* spp.). *Pseudomonas* spp., *Acinetobacter* spp. and other bacterial species (*Aeromonas hydrophila*, *Aeromonas caviae*, *Shigella flexneri* and *Pantoea agglomerans*) were isolated less frequently.

The overall frequency of ciprofloxacin resistance was 33.6% (Table 1). Patients who were 50 years of age or older were three times more likely to have an infection that was resistant to this antibiotic (Graphic 1). The analysis showed a significant difference when we analyzed the resistance frequencies of the strains according to the patient gender. Male patients had a frequency of 60.2% ciprofloxacin resistance and were twice as likely to acquire resistant strains compared to female patients. UTIs acquired in the community had a resistance prevalence of 25.5%, whereas more than 60% of the infections acquired in the hospital were resistant. Of the samples analyzed, more than 50% of the strains resistant to ciprofloxacin (PR 2.33; 95% CI: 1.41 – 3.83) were obtained from interned adults and cases treated at emergency rooms (PR 1.66; 95%CI: 1.46 – 4.56).

Hospitalization periods of seven days or more were also associated with resistance; patients hospitalized for this time were almost three times more likely to acquire bacterial species resistant to ciprofloxacin than patients hospitalized for shorter lengths of time. About the bacterial species, the adjusted analysis found high ciprofloxacin resistance rates in *Pseudomonas aeruginosa* (58.3%) and *Acinetobacter baumannii* (75%), even this species has not presented a significant difference. The presence of ESBLs in gram-negative bacterial species was the primary factor associated with resistance. The strains that produced this enzyme were fourteen times more likely to be resistant to ciprofloxacin.

The total percentage of levofloxacin-resistant isolates was 31.2% (Table 1). Age was not a risk factor for resistance, however, a linear trend of increased resistance to both ATMs with increasing age was observed. Males had a levofloxacin resistance rate (55.1%) that was twice that of females (24.2%). The sample origin was associated with levofloxacin resistance.Samples from hospital infections were three times more likely to be resistant to levofloxacin (PR: 2.42; CI95%: 1.43 -4.10) and ciprofloxacin; more than 50% of the samples from hospitalized adults



Graph 1. Frequencies of gram-negative bacilli resistance to ciprofloxacin and levofloxacin relative to patient age.

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Table 1. Ciprofloxacin and levofloxacin resistance prevalence, gross and adjusted analysis of associated factors in Rio Grande, 2013.

		Analysis PR (CI95%) Ciprofloxacin			Analysis PR (CI95%) Levofloxacin	
Variables (n^{CIP}) (n^{LEV})	**%**	**Unadjusted**	**Adjusted**	**%**	**Unadjusted**	**Adjusted**
Age (562) (546)		*p*<0.001	*p*=0.105		*p*<0.001	*p*=0.208
≤ 19 years (60) (60)	11.7	1	1	10.0	1	1
20 – 29 years (50) (50)	24	2.06 (0.88-4.83)	1.60 (0.51-4.96)	26.0	2.60 (1.07-6.34)	1.81 (0.55-5.53)
30 – 39 years (69) (67)	30.4	2.61 (1.19-5.70)	2.03 (0.71-5.79)	26.9	2.69 (1.14-6.32)	1.64 (0.57-4.47)
40 – 49 years (74) (70)	35.1	3.01 (1.41-6.45)	2.56 (0.91-7.19)	32.9	3,.29 (1.43-7.53)	2.17 (0.77-6.13)
≥ 50 years (309) (300)	39.8	3.41 (1.68-6.94)	2.92 (1.17-7.32)	37.1	3.71 (1.71-8.04)	2.60 (1.04-6.49)
Gender (560) (545)		*p*<0.001	*p*=0.001		*p*<0.001	*p*<0.001
Female (427) (418)	25.5	1	1	24.2	1	1
Male (133) (127)	60.2	2.36 (1.91-2.92)	3.12 (1.97-4.96)	55.1	2.28 (1.81-2.87)	2.67 (1.67-4.27)
Type of infection (562) (546)		*p*<0.001	*p*=0.001		*p*<0.001	*p*=0.001
Community (439) (424)	25.5	1	1	23.3	1	1
Nosocomial (123) (122)	62.6	2.45 (1.99-3.03)	2.47 (1.45-4.19)	59.0	2.53 (2.01-3.17)	2.42 (1.43-4.10)
Source location (548) (532)		*p*<0,001	*p*=0,035		*p*<0.001	*p*=0.007
Outpatients (303) (291)	20.8	1	1	19.2	1	1
Emergence (61) (61)	39.3	1.89 (1.29-2.77)	1.66 (0.88-3.12)	36.1	1.87 (1.25-2.82)	1.60 (0.84-3.03)
Hospitalized adults (184) (180)	54.3	2.61 (2.02-3.38)	2.33 (1.41-3.83)	51.1	2.66 (2.02-3.50)	2.25 (1.35-3.73)
Length of stay (561) (546)		*p*<0.001	*p*=0.003		*p*=0.006	*p*=0.003
≤ 3 days (439) (425)	25.5	1	1	23.3	1	1
4 – 6 days (24) (24)	54.2	2.13 (1.42-3.18)	2.33 (0.89-6.07)	54.2	2.33 (1.55-3.49)	2.67 (1.03-6.93)
≥ 7 days (98) (97)	65.3	2.57 (2.07-3.18)	2.58 (1.46-4.56)	60.8	2.61 (2.06-3.30)	2.47 (1.40-4.33)
Bacterial species (562) (562)		*p*<0.001	*p*=0.276		*p*=0,001	*p*=0.003
Escherichia coli (375) (375)	29.9	1	1	30.2	1	1
Klebsiella spp. (74) (74)	44.6	0.84 (0.31-2.26)	0.61 (0.30-1.24)	31.9	1.06 (0.72-1.54)	0.22 (0.09-0.51)
CESP (54) (54)	42.6	1.49 (1.11-2.01)	1.16 (0.58-2.31)	38.5	1.28 (0.87-1.86)	0.91 (0.45-1.87)
Pseudomonas spp. (12) (12)	58.3	1.43 (1.01-2.02)	1.59 (0.42-6.06)	60.6	1.66 (0.92-2.98)	1.02 (0.27-3.83)
Acinetobacter spp. (12) (12)	75.0	1.95 (1.18-3.13)	1.60 (0.37-6.83)	75.0	2.49 (1.73-3.57)	1.49 (0.35-6.35)
Others* (35) (35)	14.3	0.48 (0.21-10.9)	0.44 (0.15-1.29)	9.1	0.30 (0.10-0.90)	0.22 (0.60-0.83)
ESBL presence (449) (437)		*p*<0.001	*p*<0.001		*p*<0.001	*p*<0.001
No (390) (379)	24.4	1	1	23.2	1	1
Yes (59) (58)	84.7	3.07 (2.57-3.66)	13.93 (5.94-32.63)	77.6	3.00 (2.45-3.69)	12.18 (5.34-27.76)
Total (562) (546)	33.6			31.3		

**Aeromonas hydrophila, Aeromonas caviae, Shigella flexneri and Pantoea agglomerans; ESBL: extended-spectrum β-lactamase. CIP – ciprofloxacin; LEV – levofloxacina.*

were resistant to levofloxacin (PR: 2.25; CI: 1.35 – 3.73). The time of hospitalization was another factor associated with resistance. Patients hospitalized for seven days or more were more likely to acquire strains resistant to levofloxacin (PR: 2.47; 95% CI: 1.40 – 4.33) than patients who remained in the hospital for a shorter period of time.

Although the bacterial species was not found to be a risk factor for this antibiotic resistance in the adjusted analysis, two bacterial groups exhibited a reduced likelihood of levofloxacin resistance: the genus *Klebsiella* spp. (PR: 0.22; 95% CI: 0.09 – 0.51) and the group of bacterial species that were found in minor proportions (PR: 0.22; 95% CI: 0.60 – 0.83). Even with a lower frequency (77.6%) than that shown in the analysis, of ciprofloxacin resistance, the presence of ESBLs was also a risk factor for resistance to levofloxacin. Strains that produced ESBLs were twelve times more likely to demonstrate resistance to this second antibiotic.

DISCUSSION

Our study analyzed UTIs caused by GNB that were resistant to ciprofloxacin and levofloxacin and showed that the main risk groups were male patients, hospitalized patients and patients with a sevenday or longer hospital stay, as well as the presence of ESBLs in the strain responsible for the infection.

Although the result was not statistically significant, our study showed that FQ resistance tended to increase with the age of the patient. Similar studies have also correlated age and bacterial drug resistance, associating

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it especially with the greater permanence of this group in the hospital environment and subsequent exposure to multi-drug-resistant bacteria.[4,10] In our work andin other studies, male patients have been found to have a higher risk of antibiotic resistance a possible explanation for this condition is that men more often develop complicated UTIs that require a longer period of antimicrobial treatment.[10-12] Additionally, men of an advanced age have an increased number of underlying diseases, which is a significant risk factor for the development of bacterial resistance.[13]

According to the resistance frequencies in our study, the levels of resistance in the community were 25.5% for ciprofloxacin and 23.0% for levofloxacin, and the levels in the hospital were 62.6% and 59%, respectively. In a previous study in outpatients treated at the same hospital, the resistance to ciprofloxacin was 3.2% in 2000 e 15% in 2004.[10,14] In combination with our research, this result demonstrates a trend of increased fluoroquinolone resistance over time. In addition to the high nosocomial bacterial resistance rates, the data regarding resistance to these antibiotics in the community are alarming. Despite the restrictions imposed by the rules of the RDC 44/2010 (since replaced by the RDC 44/2011), which restricts the sale of antimicrobials, it can be observer a linear increase in bacterial resistance to antibiotics.[15] The correlation between the length of hospital stays and bacterial resistance that was demonstrated in this study can be corroborated by the results of other studies.[16,17] Hospitals introduce a high selective pressure for antibiotic-resistant strains of bacteria.[18] Over time, these strains become a permanent presence in hospital environments, and procedures involving catheterization, urogenital manipulation in surgery and patient care can increase the risk of infection and consequent exposure to multi-drug-resistant strains.[17]

In this study, we found similar levels of resistance for two antibiotics in one of the bacterial species studied. The *E. coli* isolates demonstrated 29.9% and 30.2% resistance frequencies to ciprofloxacin and levofloxacin, respectively. Although this study lacked information regarding the consumption of these antimicrobials by patients, similar levels of resistance result from cross resistance.[18] Furthermore, these antibiotics are in the same class and are affected by the same mechanisms of resistance. For example, a frequent mutation (Ser83) in *gyrA*, the gene encoding the GyrA subunit of DNA gyrase, leads to resistance to both FQs in *E. coli*.[19] The adjusted analysis also showed a chance of resistance to levofloxacin in *Klebsiella* spp. (PR 0.22, 95%CI: 0.09 – 0.51) and in the group of other bacteria (*Aeromonas hydrophila*, *Aeromonas caviae*, *Shigella flexneri* and *Pantoea agglomerans* – PR 0.22; 95%CI: 0.60 – 0.80). Variations in the molecular mechanisms of bacterial resistance to different ATMs in the same class, such as the acetylation of ciprofloxacin but not levofloxacin, can account for this type of event.[20] The FQs are the drugs that are most commonly implicated in bacterial resistance; this profile has been welldocumented in the cases of *A. baumannii* and *P. aeruginosa*.[21] Of the *A. baumannii* strains that were examined in this study (n = 12), only one strain was community acquired, and this strain was susceptible to both fluoroquinolones; all of the nine strains that were resistant to ciprofloxacin and levofloxacin were obtained from hospitalized patients.

For both antibiotics, the presence of ESBLs was a risk factor for resistance, and strains producing this enzyme were eleven times and seven times more likely to have resistance to ciprofloxacin and levofloxacin, respectively. Some studies have named the consumption of quinolones as a risk factor for the development of ESBLs.[22,23] Otherhave demonstrated an association similar to the present work and have suggested that the presence of ESBLs is a risk factor for the resistance to FQs, even though ESBLs are not directly related to resistance to FQ's.[6,24] Future studies of molecular mechanisms of resistance will be important because it is possible that a plasmid is present that encodes ESBL enzymes (bla_{ESBL}) and FQ's resistance determinants (*qnr*; *aac (6') – Ib – cr*; *qepA*).[25]

This work presented important factors associated with FQ resistance, including the strong association of bacterial resistance in gram-negative strains from UTIs with the presence of ESBLs. The use of antibiotics, especially in nosocomial environments, should be based on information regarding profiles of antibiotic resistance. Epidemiological data from the microbial ecology of each environment can support the clinician for a rational choice in need of star an empirically therapy. In addition, several publications contain data that were obtained worldwide; however, it is important to highlight that the profile of antibiotic resistance is strictly linked with site-specific factors.

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