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Clinical and Economic Outcomes Associated with Urinary Tract Infections Caused by Extended Spectrum Beta-lactamase Producing Bacteria in a Tertiary Care Hospital

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ABSTRACT Urinary tract infections (UTIs) are common community-acquired infections. Increasing antibiotic resistance rates have resulted in challenges of their treatment. The aim of this study was to assess the effects of UTIs caused by pathogens producing ESBL and ciprofloxacin-resistant bacteria during hospitalization and the cost of antibiotic treatment. ESBL production was present in 51.1 percent of bacterial isolates, and resistance to ciprofloxacin in 54.5 percent. Whereas the in cases where ESBL-producing hospital stay duration was approximately 9 days and non-ESBL-producing bacteria about 5 days, statistically significant differences were found (p=0.001). Whereas the average cost of antibiotics used in treatment was USD 37.5, in cases involving ESBL-producing bacteria, approximately USD110.6, the difference was statistically significant (p=0.001). Resistance to antibiotics is a major problem in the treatment of UTIs. Resistance to ciprofloxacin and b-lactam antibiotics, which are the preferred empiric treatment, prolongs hospitalization and increases the cost of antibiotic treatment.

INTRODUCTION

Urinary tract infections (UTIs) are the most common type of community-acquired infection; about 8 million individuals worldwide are treated for UTIs annually (Chomarat 2000). UTIs have a range of symptoms from asymptomatic bacteriuria to acute pyelonephritis with sepsis (Karlowsky et al. 2006). Oral empiric treatments for UTIs include trimethoprim/sulfamethoxazole, ciprofloxacin, fosfomycin, nitrofurantoin and derivatives of penicillin and cephalosporin (Gupta et al. 2010). The most important mechanism of resistance of Escherichia coli, which is recognized as the most common cause of UTIs, is the production of extended-spectrum beta-lactamases (ESBL). ESBL-producing bacteria also typically show increased levels of resistance to other agents such as quinolones (Bazaz et al. 2010). Moreover, there are further problems in treating UTIs due to increasing antibiotic resistance rates as a result of inappropriate use of antibiotics, advanced age (>50), a history of previous invasive urological procedures, and the use of ciprofloxacin for complicated UTIs (Daza et al. 2001; Sobel et al. 2010; Wu et al. 2014). Resistant strains prolong the hospital stay duration and increase the frequency and cost of hospitalization by limiting the oral treatments available for UTIs.

The aim of this study was to assess the effect of ESBL-positivity and/or quinolone resistance on the hospital stay duration and the cost of hospitalization. Retrospective data of patients admitted to the Muðla Sitki Koçman University

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Training and Research Hospital with a diagnosis of UTI were used, together with cultures from which the causative agent was isolated.

MATERIAL AND METHODS

This study was conducted at the Muðla Sitki Koçman University Training and Research Hospital in Turkey, a third-grade general hospital with a capacity of 500 beds. Data of 112 patients admitted to the Infectious Diseases, Internal Medicine and Urology Department diagnosed with an UTI between 1st July 2012 and 30th June 2014, who had not been hospitalized previously and who had not undergone urological surgery within the last month, and/or for whom the blood culture samples tested positive for the causative pathogens, was analyzed retrospectively. Data was collected from the patient charts using a standard form, the patient's personal information, underlying disease, the antibiotics used, dosage, usage, duration, reason for antibiotic use and microbiological test results were recorded on the form.

Community-acquired infections were defined as infections diagnosed within the first 48 hours of hospitalization. It included the presence of one or more of the following: patient infection was classed as one associated with healthcare and these were excluded from the study. The criteria for inclusion were as follows: hospitalization for longer than 48 hours within the last 90 days, hemodialysis performance, use of intravenous medication or wound care within the last 30 days, and long-term residence in a nursing home. Patients who did not fulfill these criteria were classified as cases of community-acquired infections (Friedman et al. 2002). Eighty-eight patients who meet the above mentioned criteria were included in the study.

The total cost of all antibiotics used during hospitalization was calculated using the price list issued by the General Directorate of Pharmaceuticals of The Republic of Turkey on the 1st of July 2014. The cost was converted to US dollars (USD) based on the exchange rates of the Central Bank of The Republic of Turkey on the 1st of July 2014 (1 USD = 2.1 TL).

Microbiological Methods

Antimicrobial susceptibility was determined by the Kirby-Bauer disk diffusion method and confirmed using the criteria set by the ESBL Clinical and Laboratory Standards Institute (CLSI 2013).

Statistical Evaluation

Data was analyzed using the SPSS software version 20.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Distribution of the continuous variables was investigated by Kolmogorov-Simirnov and homogeneity tests. Numerical variables with a normal distribution were presented as means ± standard deviation (SD) and numerical variables not showing a normal distribution as medians (minimum-maximum). For numerical variables that did not show a normal distribution, such as age, cost and the duration of hospitalization, a logarithmic transformation was applied. The student's *t*-test was used for comparisons of averages of quantitative variables with a normal distribution, and for analysis of the data without a normal distribution, a Mann-Whitney U test was applied. A value of $p < 0.05$ was considered to indicate statistical significance.

The Ethics Board of Muðla Sitki Koçman University Clinical Research Hospital approved the study on 8th August 2014, under protocol number 59.

RESULTS

The median age of the 88 patients included in the study was 71 years (minimum 20, maximum 99 years), and comprised of 36 male (40.9%) and 52 female patients (59.1%). The median age of patients with ESBL and/or IBL positive bacteria was 69 years (minimum 23, maximum 99 years), the median age of negative patients was 77 years (minimum 20, maximum 97 years), and the difference was statistically insignificant ($p=0.425$). The median age of patients with infections caused by ciprofloxacin-susceptible bacteria was 74 years (minimum 20, maximum 99 years), and was 70.5 years (minimum 23, maximum 92 years) in cases involving ciprofloxacin-resistant bacteria; the difference was statistically insignificant ($p=0.903$). ESBL and/or IBL-positive bacteria accounted for 63.9 percent of cases in male patients, compared to only 42.3 percent in females; the difference was statistically significant ($p=0.038$). The rate of ciprofloxacin resistance was 63.9 percent and 48.1 percent in male and female patients, respectively; the dif-

ference was statistically insignificant (p=0.106). Of the 88 patients, 32 (36.3%) had used antibiotics within the last 3 months. Of the patients infected with ESBL and/or IBL-positive bacteria, 51.1 (23/45) had taken antibiotics in the previous 3 months; compared to 20.9 of those infected with ESBL and/or IBL-negative organisms; the difference was statistically significant (p=0.004). Of the patients infected with ciprofloxacin-sensitive bacteria, fifteen percent (6/40) had taken oral antibiotics within the last 3 months, compared to 54.2 (26/48) of those with resistant isolates; this difference was statistically significant (p=0.003).

Table 1 shows that the antibiotics most commonly used for the empiric treatment of patients admitted to hospital with UTIs were ceftriaxone (29.5%), ertapenem (22.7%), and ciprofloxacin (20.5%). Ciprofloxacin was prescribed for six patients, with five being administered ceftriaxone and one receiving ertapenem and gentamicin. Among the 4 of 13 patients prescribed different antibiotics due to their culture results, meropenem and piperacillin tazobactam were preferred. Two patients were given cefoperazone sulbactam, and ertapenem and tigecycline was administered to one patient.

Table 1: Antibiotics are preferred for empiric therapy in UTI

Antibiotics	*Frequency*	*Percent*
Ceftriaxone	26	29.5
Ertapenem	20	22.7
Ciprofloxacin	18	20.5
Sefaperazon/sulbactam	8	9.1
Piperacilin/tazobactam	8	9.1
Amikacin	2	2.3
Gentamicin	2	2.3
Moxifloxacin	1	1.1
Ampicilin/sulbactam	1	1.1
Imipenem	1	1.1
Meropenem	1	1.1
Total	88	100

Table 2 shows that the median duration of hospitalization of the 88 patients included in the study was 7 (2-24) days. The median duration of hospitalization of patients with ESBL and/or IBL-positive bacteria was 9 (3-24) days, compared to 5 (2-14) days for those with ESBL and/or IBL-negative bacteria; the difference was statistically significant (p=0.001). The median hospitalization duration of patients infected with ciprofloxacin-susceptible isolates was 4 (2-17) days, compared to 9 (3-24) days in those infected with ciprofloxacin-resistant organisms; the difference was statistically significant (p=0.001).

Table 3 shows that E. coli was isolated in 78.4 percent of the 88 patients included in the study. Enterobacteriaceae accounted for 93.2 percent of the causative agents. Of the isolated strains, 51.1 were ESBL- and/or IBL-positive and 54.5 were resistant to ciprofloxacin. Of the 45 ESBL- and/or IBL-positive strains, eighty percent were resistant to ciprofloxacin, compared to 27.9 of the 43 ESBL- and/or IBL-negative strains. Of the 48 ciprofloxacin-resistant strains, seventy-five percent were ESBL- and/or IBL-positive, compared to 22.5 percent of the ciprofloxacin-sensitive strains. This indicated a statistically significant correlation between ESBL- and/or IBL-positivity and ciprofloxacin resistance (p=0.001).

Table 3: Frequency of bacterial agents isolated from urine specimen in this study

Isolates	*Number of isolates*	*Percent*
Escherichia coli	69	78.4
Klebsiella pneumoniae	10	11.4
Pseudomonas aeruginosa	6	6.8
Enterobacter aerogenes	3	3.4
Total	88	100

Table 4 shows that antibiotic susceptibility analysis revealed that the most effective antibiotics for use against Enterobacteriaceae were imipenem, amikacin, tigecycline and ertapenem;

Table 2: The patients were followed with UTI, antibiotic costs and average length of stay

Isolates	*Average length of stay (Days)*	*P values*	*Costs($)*	*P values*
ESBL/IBL Positive (45)	9 (3-24)	P=0.001	110.6 (5.5-505.2)	P=0.001
ESBL/IBL Negative (43)	5 (2-14)		19.8 (6.5-384.2)	
Ciprofloxacin Resistant (48)	9 (3-24)	P=0.001	135.1 (5.5-505.2)	P=0.001
Ciprofloxacin Sensitive (40)	4 (2-17)		19.8 (6.56-234.6)	
Total (88)	7 (2-24)		37.5 (5.5-505.2)	

the rate of resistance to ciprofloxacin was 45.1 percent and that of ESBL- and/or IBL-positivity was 48.9. For *Pseudomonas* strains, 83.3 percent were IBL-positive; amikacin and colistin susceptibility were detected in all strains, but only fifty percent were susceptible to ciprofloxacin, ceftazidime and gentamicin.

Table 4: Antibiotics susceptibility patterns of Enterobacteriaceae species

Antibiotics	*Isolates*			
	E. coli (n:69) %	*K. pneumoniae (n:10) %*	*Enterobacter spp. (n:3) %*	*Total (n:82) %*
Gentamicin	49.3	50	66.7	50
Amikacin	98.6	100	100	98.6
Nitrofurantoin	72.5	70	33.3	70.7
TMP/SXT	42	50	33.3	42.7
Ciprofloxacin	44.9	50	33.3	45.1
Cefazolin	27.5	30	0	26.8
Cefuroxime axetil	42	40	0	40.2
Ceftriaxone	50.7	40	0	47.6
Ceftazidime	56.5	50	66.7	56.1
Piperacillin tazobactam	87	90	100	87.8
Cefoperazone sulbactam	79.7	80	66.7	79.2
Cefoxitin	66.7	50	0	62.2
Ertapenem	91.3	100	100	92.7
Imipenem	100	100	100	100
Tigecycline	95.7	90	100	95.1
Cefepime	52.2	60	0	51.2
Colistin	100	100	100	100

Table 2 shows that the median cost of antibiotics used during hospitalization of the 88 patients included in the study was USD37.51 (USD5.5-USD505.2). The median cost of antibiotics for patients with ESBL- and/or IBL-positive strains was USD110.6 (USD5.5-USD505.2), compared to USD19.8 (USD6.5-USD384.2) for patients with ESBL- and/or IBL-negative strains; the difference was statistically significant (p=0.001). The median cost of antibiotics for patients infected with ciprofloxacin-resistant strains was USD135.1 (USD5.5-USD505.2), compared to USD19.8 (USD6.5-USD234.6) for those infected with ciprofloxacin-susceptible bacteria; the difference was statistically significant (p=0.001).

DISCUSSION

The study has shown that resistance to ciprofloxacin and B-lactam antibiotics, which are the preferred empiric treatment, prolongs hospitalization and increases the cost of antibiotic treatment.

Treatments for UTIs are usually empirical and are prescribed by primary healthcare workers without the use of microbiological tests such as urine cultures and antibiotic-susceptibility assays. Rather they are based on the patient's clinical presentation and a basic urinalysis. However, the growing number of resistant strains over recent years has led to failure of empiric treatment and increases in hospitalization rates and treatment costs.

Similar to other infections, the earlier the treatment for UTIs is started, the higher the likelihood of recovery. Delaying treatment or prescribing inappropriate antibiotics during empirical treatment can result in a worsening clinical condition, increased duration of hospitalization and cost, or even death. Antibiotic resistance rates vary among countries because of epidemiological factors (Karaca et al. 2005). To establish the patterns of drug-resistance in community-acquired UTIs and to rapidly implement effective empiric treatment by defining a patient's risk factors, a wide range of microbiological diagnostic methods should be employed as a first step in healthcare institutions or upon hospitalization. Furthermore, to enable rapid identification of the ESBL-producing bacteria, routine use of ESBL NDP (Nordmann/Dortet/Poirel) tests and chromogenic media should be evaluated (Bayindir et al. 2010; Dortet et al. 2014).

The major risk factors for community-acquired UTIs are: female gender, sexual activity, use of contraception, menopause, urinary tract abnormalities or obstructions, diabetes mellitus, immunosuppressive diseases such as malignancy, and the use of urinary catheters. For UTIs caused by ESBL-producing bacteria, the known risk factors are: male gender, >60 years of age (Colodner et al. 2004), prior hospitalization history (Wu et al. 2014), use of antibiotics within the last 3 months (Kanafani et al. 2005; Osthoff et al. 2015), and a history of urological surgery performed within the last 6 months (Rodríguez-Baño et al. 2004).

Many risk factors are associated with infection by ESBL-producing bacteria, one of which is age. In numerous studies an age of above 60 years was recognized as a risk factor. As age increased, the number of underlying diseases, rates of hospitalization and ESBL-positivity also increased (Colodner et al. 2004; Rodríguez-Baño et al. 2004: Eshetie et al. 2015). In this study, no

statistically significant difference was found in age, ESBL production, and ciprofloxacin resistance. The study was conducted on patients hospitalized for treatment of UTIs, and advanced age was one of the most important factors influencing the rate of hospitalization. Because the median age of patients evaluated in this study was 71 years, most were aged >60 years, which is a recognized risk factor for infection with ESBL-producing bacteria.

Despite UTIs being more common in female patients, in male patients the course of the disease was usually more complicated and infections with resistant bacteria were more frequent (Ben-Ami et al. 2009). Despite a finding of greater numbers of female patients being hospitalized, infections with ESBL-producing strains were significantly more frequent in male patients. However, there was no difference between the genders in terms of the rate of isolation of ciprofloxacin-resistant bacteria.

As shown in this study and worldwide, gr (-) enteric bacilli, especially *E. Coli*, are the most common cause of UTIs (Gales et al. 2000; Kahlmeter 2003; Matute et al. 2004; Citil et al. 2006). Antibiotic resistance rates are increasing globally, including among the causative microorganisms of UTIs (Hooton et al. 2004; Sanchez et al. 2012; Miranda et al. 2014). The results showed resistance to most of the preferred empiric treatments; the rate of resistance to ceftriaxone was 51.1 percent and that to ciprofloxacin was 54.5 percent. These rates were higher than those reported by other studies because this study included a group of patients at a higher risk of resistant infection.

The increasing antibiotic resistance rate limits the options for treatment of community-acquired UTIs. Following the first report of ESBL in Europe, it rapidly spread globally (Shah et al. 1983). After 2000, factors such as horizontal gene transfer led to an expansion of antibiotic-resistant bacteria. Additionally, there has been a dramatic increase in community-acquired infections, the agents of which are antibiotic-resistant bacterial strains (Bonnet et al. 2004; Kojima et al. 2005; Carattoli et al. 2005). In Turkey, quinolones together with second- and third-generation cephalosporins are the preferred antimicrobial agents for the empiric treatment of UTIs. However, ESBL-producing Enterobacteriaceae species can show cross-resistance to non–b-lactam antibiotics, such as quinolones. The correlation between quinolone resistance and ESBL production has resulted in fewer antibiotics being available for the empiric treatment of UTIs (Colodner et al. 2004). This study showed that eighty percent of ESBL-producing bacteria were resistant to ciprofloxacin, whereas 27.9 percent of ESBL-negative strains were resistant to ciprofloxacin. The rate of quinolone resistance has increased worldwide independently of quinolone use, likely due to resistance gene transfer between gram-negative enteric bacteria (Sedlákova et al. 2014). Furthermore, fluoroquinolones, which are used widely in poultry farming, have influenced increases in the prevalence of quinolone resistance (Petersen et al. 2006).

As in similar studies, in this study, in terms of ESBL-positivity and resistance to ciprofloxacin, patients with a history of antibiotic use were at greater risk of infection than those who had not used antibiotics (Spadafino et al. 2014; de La Blanchardière et al. 2015). Whereas previous studies reported a tenfold increase in the ESBL rate after the use of second- and third- generation cephalosporins, quinolone use resulted in a fourfold increase; in addition, use of first-generation cephalosporins, macrolides, aminoglycosides, and TMP/SMX did not affect the ESBL rate (Colodner et al. 2004). In particular, the use of third-generation cephalosporins increased ESBL production by 28 times (Kanafani et al. 2005), whereas the use of ciprofloxacin increased ESBL production by twofold (Arslan et al. 2005).

This study found that ESBL-positivity and resistance to quinolone were associated with a significant increase in the duration of hospitalization and cost of antibiotic treatment. Other studies reported a similar finding, that is, ESBL-positivity was one of the major factors responsible for the increased duration of hospitalization and cost of treatment (Lee et al. 2006; Schwaber et al. 2006; Yang et al. 2010; MacVane et al. 2014).

Weaknesses of this study are retrospective and so is the number of samples. This study could be studied prospectively in a larger sample. Nevertheless, the results of this study show that ESBL production and ciprofloxacin resistance prolong the duration of hospitalization, which increases the cost of treatment in urinary tract infections.

CONCLUSION

The incidence of community-acquired UTIs caused by ESBL-producing bacteria is increasing. Being male and prior use of antibiotics within the last 3 months are independent risk factors

for infections with ESBL-producing gram-negative bacteria. Patients suffering from UTIs caused by ESBL-producing bacteria are hospitalized for longer and incur higher overall costs for antibiotics.

RECOMMENDATIONS

- In UTI's treatment, the antibiotics chosen for empiric treatment and the treatment initiation time are essential for a good clinical outcome.
- ESBL-producing bacteria should be identified rapidly by microbiological tests, and clinicians should have a detailed knowledge of the risk factors for infection with ESBL-producing bacteria.
- To decrease the cost of antibiotics and reduce the rate of treatment failure, the antibiotics should be selected carefully.
- Moreover, to overcome the problem represented by resistant organisms, awareness should be created in the community about the rational use of antibiotics and the need to limit their use (for example, in animal husbandry and farming) to essential cases.

LIMITATIONS OF THE STUDY

This study has several limitations. First, it is a retrospective study and a single center study, involving a relatively small sample size (88 subjects), which might not be representative of the overall patient population admitted to other hospitals in Turkey or elsewhere.

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