Ceftriaxone treatment of complicated urinary tract infections as a risk factor for enterococcal re-infection and prolonged hospitalization: A 6-year retrospective study

Kristian Karlović[1], Jadranka Nikolić[1,2], Jurica Arapović[1,2*]

[1]Faculty of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina, [2]Department of Infectious Diseases, University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina

ABSTRACT

A frequent complication during hospital stay of patients with urinary tract infections (UTIs) is a re-infection of the urinary tract after the initial improvement. In this study, we investigated the impact of two empirical antibiotic therapies on the outcomes of complicated bacterial UTIs. We retrospectively evaluated 325 adult patients hospitalized during 6 years period with a diagnosis of complicated bacterial UTIs. The patients were classified into two groups according to the antibiotic therapy: ceftriaxone- and co-amoxiclav+gentamicin-treated group. Clinical data were collected from the patient records into a designed form. Output data included information on the treatment outcome, length of stay (LOS), development of complications, and cause of re-infections. The patients treated with ceftriaxone had significantly longer LOS (p = 0.012), as well as higher occurrence of complications (p = 0.023) and urinary tract re-infections (p < 0.001), compared to co-amoxiclav+gentamicin-treated group. No significant difference was observed in the treatment outcome between the two groups (p = 0.137). The most common complication in both investigated groups were re-infections of the urinary tract, and *Enterococcus spp.* was detected as the cause of re-infections only in patients from ceftriaxone-treated group (40/69 patients). Out of the 40 ceftriaxone-treated patients with enterococcal urinary tract re-infections, 35 patients had one or more chronic diseases and 29 patients had urinary catheter inserted. Ceftriaxone therapy should be considered carefully in patients with complicated UTIs due to the possibility of enterococcal re-infection and consequent prolonged hospital stay.

KEY WORDS: Urinary tract infection; ceftriaxone; aminoglycosides; co-amoxiclav; re-infection; *Enterococcus spp.*

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INTRODUCTION

Urinary tract infections (UTIs) are among the most common infections in adults [1] and account for nearly 70% of all nosocomial infections [2,3]. Risk factors that make some people more susceptible to UTIs include: older age, female gender, promiscuity, anatomical abnormalities of the urinary tract, urinary tract obstructions, impaired immune response, urinary catheter inserted, and surgical procedures of the urinary tract [4-12].

According to the severity of clinical presentation, development of complications and antibiotic therapy, UTIs are classified into two groups, uncomplicated and complicated UTIs. Uncomplicated UTIs include: acute infection of the lower urinary tract in pre-menopausal, non-pregnant women, acute pyelonephritis and uncomplicated recurrent UTIs with no associated risk factors. Complicated UTIs include UTIs in: men, patients with a functional obstruction or anatomical abnormality of the urinary tract, patients with urinary catheter, pregnant women, postmenopausal women and nosocomial UTIs [13,14].

The empirical antibiotic therapy for complicated bacterial UTIs should be effective against the most common microbial causes of UTIs. Moreover, the antibiotic therapy can be adapted or completely changed based on the urine culture results [15]. According to the Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) of the Ministry of Health of the Republic of Croatia guidelines, co-amoxiclav in combination with aminoglycosides (gentamicin) should be used as the first-choice therapy for complicated bacterial UTIs

*Corresponding author: Jurica Arapović, Department of Infectious Diseases, University Clinical Hospital Mostar, Kralja Tvrtka b.b., 88000 Mostar, Bosnia and Herzegovina. Phone: +387 36 336 581, +387 36 336 577; Fax: +387 36 328 072. E-mail: jurica.arapovic@mef.sum.ba

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in adults, while the third generation cephalosporins are proposed as the alternative therapy [13]. In complicated cases of UTIs, co-amoxiclav and gentamicin should be administered together due to their synergistic activity, and injected intravenously [16]. Special caution is required when administering the therapy to patients with impaired renal function, since the combination of aminopenicillins and aminoglycosides may cause further damage to renal function [17,18].

One of the most common complications during hospital stay is a re-infection of the urinary tract, meaning that the patient developed a new UTI after the initial improvement, caused by a different pathogen. The re-infection can manifest with clinical signs and, in many cases, with a positive urine culture [19]. A common cause of re-infection of the urinary tract is *Enterococcus spp.*, which has been isolated more often from older patients and those with urinary catheter inserted [20-22]. In addition, considering the antimicrobial spectrum of third generation cephalosporins, *Enterococcus spp.* is expected to be more frequent in patients treated with ceftriaxone [23-26].

In this study, we investigated the impact of two empirical antibiotic therapies, ceftriaxone and co-amoxiclav+gentamicin, on the outcomes of complicated bacterial UTIs.

MATERIALS AND METHODS

This retrospective observational study included 325 adults hospitalized at the Department of Infectious Diseases of University Hospital Mostar in the period between 1st June 2011 and 31st May 2017. All patients were over 18 years old and diagnosed with a bacterial UTI, including the diagnoses of complicated UTIs and sepsis due to UTI. Patients with fungal UTIs were excluded from the study. The input data included information on the patient sex, age, comorbidities, mobility, urinary catheterization and inflammatory markers, i.e., C-reactive protein (CRP) and leukocyte count in the peripheral blood. The output data included information regarding the treatment outcome, length of stay (LOS), and development of complications with special emphasis on re-infections and their causative agents. According to different parameters, the patients were classified into several groups:

- Two groups of patients with respect to the antibiotic treatment (ceftriaxon-treated group and co-amoxiclav+gentamicine-treated group);
- Two groups of patients with respect to the treatment outcome (successfully treated patients and those with fatal outcome);
- Two groups of patients with respect to the LOS (patients who stayed less than 10 days in the hospital [including day 10] and those who stayed 11 or more days in the hospital);
- Two main groups (patients who developed complications and those who did not) and three subgroups with respect to the development of complications. Three types of complications included re-infection, organ complication, and other types of complications. A re-infection of the urinary tract was defined as a new UTI acquired after the initial clinical improvement. Organ complications included all complications that could be associated with a single organ system (e.g., renal failure, hepatic failure, anemia, stroke, embolism, etc.). If the patient developed a type of complication that could not be classified in one of the first two subgroups, it was designated as other type of complication.

The treatment outcome, LOS, and development of complications were compared between ceftriaxone-treated and co-amoxiclav+gentamicin-treated group as well as within each of the treated group.

All procedures followed were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. As this was a retrospective database analysis, informed consent was not required and any potentially identifying patient information was omitted.

Statistical analysis

We analyzed the results using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, NY) and Microsoft Excel (365). The results are presented as absolute numbers (n) and percentages (%). The relationship between variables was determined with Chi-squared test (χ^2 test). Categorical variables were tested with Fisher's exact test, while the Mann–Whitney *U* test was used for continuous variables. All tests were two-tailed and values of $p < 0.05$ were considered statistically significant.

RESULTS

This 6-year retrospective study included 325 patients with clinical presentation of a complicated bacterial UTI. With respect to the clinical characteristics, 271/325 patients (83.4%) had one or more chronic diseases ($p < 0.001$) and 221/325 patients (68%) had urinary catheter inserted ($p < 0.001$). No significant difference was observed with regard to the patient mobility between ceftriaxone-treated and co-amoxiclav+gentamicin-treated group [$p = 0.589$] (Table 1).

No significant differences were observed in CRP levels (Mann–Whitney *U*; $p = 0.094$) and leukocyte count (Mann–Whitney *U*; $p = 0.706$) between ceftriaxone-treated and co-amoxiclav+gentamicin-treated group. Similarly, significant differences were not observed between the two groups in the patient age (Mann–Whitney *U*; $p = 0.066$), comorbidities ($p = 0.692$), mobility ($p = 0.539$) and presence of urinary catheter ($p = 0.713$). With regard to the gender, in co-amoxiclav+-gentamicin-treated group, female patients 45/60 patients (75%) were more prevalent compared to males ($p = 0.039$).

TABLE 1. Socio-demographic and clinical characteristics of patients with complicated bacterial urinary tract infections and treated with ceftriaxone or co-amoxiclav+gentamicin therapy

Characteristic	Ceftriaxone (n=265)	Co-amoxiclav+gentamicin (n=60)	*p*
Age, median (IQR)	76 (17)	72 (21.5)	0.660*
Sex, n (%)			
Male	104 (39.2)	15 (25)	0.014**
Female	161 (60.8)	45 (75)	
Mobility, n (%)			
Mobile	143 (54)	35 (58.3)	0.589**
Immobile	122 (46)	25 (41.7)	
Urinary catheter, n (%)			
Inserted	179 (67.5)	42 (70)	0.713**
Missing	86 (32.5)	18 (30)	
Comorbidity, n (%)			
Yes	222 (83.8)	49 (81.7)	0.692**
No	43 (16.2)	11 (18.3)	
Leukocyte count, median (IQR)	13.1 (8.15)	13.1 (7.53)	0.094*
CRP, median (IQR)	185 (128.7)	156 (143.6)	0.706*

*Mann–Whitney *U* test was used. **χ^2 test was used. IQR: Interquartile range; CRP: C-reactive protein

TABLE 2. Clinical outcomes in patients with complicated bacterial urinary tract infections and treated with ceftriaxone or co-amoxiclav+gentamicin therapy

Outcomes of empirical therapy	Ceftriaxone (n=265)	Co-amoxiclav+gentamicin (n=60)	*p*
Treatment outcome, n (%)			
Successfully treated	207 (78.1)	52 (86.7)	0.137*
Death	58 (21.9)	8 (13.3)	
Length of stay, n (%)			
<10 days	172 (64.9)	49 (81.7)	0.012*
>10 days	93 (35.1)	11 (18.3)	
Complications, n (%)			
Yes	108 (40.8)	15 (25)	0.023*
No	157 (59.2)	45 (75)	

*χ^2 test was used.

Table 2 shows the analysis of the treatment outcome, LOS and development of complications in relation to the empirical antibiotic therapy. Complications were more common in ceftriaxone-treated group and patients in that group had significantly longer LOS compared to co-amoxiclav+gentamicin-treated group ($p = 0.023$ for complications and $p = 0.012$ for LOS). On the contrary, no significant difference was observed in the treatment outcome between the two groups ($p = 0.137$).

In each of the treated groups (ceftriaxone-treated and co-amoxiclav+gentamicin-treated group), the patients were classified into the three subgroups according to the types of complications. Re-infections were the most common complication in both treated groups, but this result was significant only in ceftriaxone-treated group [$p < 0.001$] (Table 3).

When analyzing the potential cause of the re-infections in the two treated groups, *Enterococcus spp.* was isolated from 40 patients (58%) in ceftriaxone-treated group, while this bacterium was not detected as the cause of re-infections in co-amoxiclav+gentamicin-treated group [Fisher's exact test; $p = 0.002$] (Table 4). Out of the 40 ceftriaxone-treated patients who developed enterococcal urinary tract re-infection, 26 patients (65%) were women ($p = 0.058$), 35 patients (87.5%) had one or more chronic diseases ($p < 0.001$), 23 patients (57.5%) were immobile ($p = 0.343$), and 29 of patients (72.5%) had urinary catheter inserted [$p = 0.004$] (Table 5).

TABLE 3. Different types of complications in patients with complicated bacterial urinary tract infections and treated with ceftriaxone or co-amoxiclav+gentamicin therapy

Type of complication, n (%)	Ceftriaxone (n=108)	Co-amoxiclav+gentamicin (n=15)
Re-infection	69 (63.9)	8 (53.3)
Organ	18 (16.7)	3 (20)
Other	21 (19.4)	4 (26.7)
p value	<0.001*	0.247*

*χ^2 test was used.

DISCUSSION

In this study, we showed that the patients with UTIs and treated with ceftriaxone developed complications more frequently compared to the patients treated with a combination of co-amoxiclav and gentamicin. The majority of the complications in ceftriaxone-treated group were urinary tract re-infections caused by *Enterococcus spp.* The increased use of cephalosporins in the hospitalized patients may explain, at least partially, the high occurrence of the enterococcal

TABLE 4. The most common cause of re-infection in ceftriaxone- and co-amoxiclav+gentamicin treated groups

The cause of re-infection, n (%)	Ceftriaxone (n=69)	Co-amoxiclav+gentamicin (n=8)	*p*
Enterococcus spp.	40 (58)	0 (0)	0.002*
Other	29 (42)	8 (100)	

*Fisher's exact test was used.

TABLE 5. Characteristics of ceftriaxone-treated patients who developed enterococcal re-infection

Characteristics	Re-infection with *Enterococcus* spp. (n=40)	*p*
Sex, n (%)		
Male	14 (35)	0.058*
Female	26 (65)	
Chronic diseases, n (%)		
Yes	35 (87.5)	<0.001*
No	5 (12.5)	
Mobility, n (%)		
Mobile	17 (42.5)	0.343*
Immobile	23 (57.5)	
Catheterization, n (%)		
Yes	29 (72.5)	0.004*
No	11 (27.5)	

*χ^2 test was used.

re-infections. It is important to note here that most of the patients included in this study were affected by one or more chronic diseases and had urinary catheter inserted. This may be due to the older age of participants, as most of the patients included in the study were elderly people. The aging process is characterized by metabolic as well as hormonal changes, and consequently results in a higher incidence of chronic diseases. This could also be associated with a higher incidence of UTIs in elderly population [4,5,21,27,28].

A large number of UTIs can be directly linked to uncomfortable catheter placement [29-31]. Our results showed that the immobility of patients was not significantly associated with the incidences of UTIs and enterococcal urinary tract re-infections. However, these findings are not in agreement with previously published results showing that immobile patients were more likely to be affected by UTIs and enterococcal urinary tract re-infections [32-34]. This could be explained by the burden of comorbidities.

In this study, most of the patients with a complicated UTI had been treated with third generation of cephalosporins as the first-choice therapy, although guidelines suggest a combination of co-amoxiclav and aminoglycosides as the primary therapy [13]. This may be related to the problems with the purchase of antibiotics on the national level in the last years.

Several studies have reported a possible correlation between an increased use of cephalosporins and enterococcal infections [24,25,35]. For example, Morrison et al. observed that a higher enterococcal UTI incidence was caused by cephalosporin treatment of nosocomial UTIs [36]. Moreover, Magnussen et al. concluded that not all generations of cephalosporins, but only the third generation, affected the incidence of enterococcal infections [26]. In their study, most of the enterococcal infections were also UTIs. A possible explanation for the increase in the incidence of enterococcal infections after the treatment with third generation cephalosporins might be the cephalosporin spectrum of action, where majority of cephalosporins are not effective against *Enterococcus spp.* [37] but, nevertheless, act against large part of normal bacterial flora of the gastrointestinal tract [26,38]. Furthermore, it might be possible that *Enterococcus* colonisation or infection following ceftriaxone treatment is due to the microbiome changes. One additional reason for the higher occurrence of enterococcal re-infections in our study, may be the emergence of antibiotic resistance, which is not rare in the cases of enterococcal infection treated with third generation of cephalosporins, as previously reported [39,40].

In addition to ceftriaxone as a risk factor of urinary tract re-infection, our study suggests that female sex, comorbidities, and presence of urinary catheter may significantly increase the risk of enterococcal infection.

In contrast to our results, several previous studies showed that the majority of patients with enterococcal infections were men [38,41,42]. Pinholt et al studied the incidence, clinical characteristics and 30-day mortality of enterococcal bacteremia in Denmark, and they found that most of the patients diagnosed with enterococcal bacteremia were men [38]. We also showed that patients treated with ceftriaxone had significantly longer LOS compared to the patients treated with the combination of co-amoxiclav and gentamicin. Reciprocally, this could be explained by the higher occurrence of complications and re-infections in ceftriaxone-treated group.

It is well known that patients with comorbidities have more frequently *Enterococcus spp.* as the agent of infection [38,41-43]. For example, McBride et al. showed that more than 85% of patients with vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* bacteremia had one or more comorbidities [42].

Gruber et al. investigated risk factors for the infections with multidrug resistant (MDR) bacteria among patients in geriatric clinics, nursing homes, and outpatient care centers. They concluded that the majority of patients with isolated MDR bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL) producing

Enterobacteriaceae, were immobile or had inserted urinary catheter [44].

Maki et al. observed that *Enterococcus spp.* was more commonly present in the urine sample of patients with urinary catheter placed compared to those without catheter [45]. In agreement with several other studies [4,21], our study also showed that the insertion of urinary catheter increases the risk for urinary tract re-infection, however, not to the extent shown by studies conducted on patients in intensive care units, where most of the isolates were MDRs [46].

Considering that, in our study, ceftriaxone therapy was associated with longer LOS and higher incidence of complications such as enterococcal re-infection, we suggest caution in using empirical therapy with such antibiotics.

Among the limitations of this study are its retrospective design and the fact that the study was conducted in a developing country, with a limited availability of new antibiotics and expected lower rate of antibiotic resistance. In addition, other Gram-negative bacteria, such as *Pseudomonas* and some resistant Gram-negative strains, together accounted for less than 10% of the isolates; therefore, we did not discuss the incidence of complications in these cases (data not shown). In this context, an additional limitation of our study might be that we only analyzed enterococcal re-infections of the urinary tract. Further studies should comprehensively investigate other causes of urinary tract re-infections.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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