In Vitro Activities of Ceftazidime-Avibactam and Comparator Antimicrobial Agents Tested against ESBL Producing Urinary E. coli Isolates

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ABSTRACT

Objectives: Urinary tract infections (UTIs) remain one of the most common infections for antibiotic prescription. Increased resistance to antibiotics currently used to treat these infections may lead to significant problems. Extended spectrum beta-lactamase (ESBL) production in organisms causing UTIs are often responsible for the increase in resistance. The aim of this study was to investigate the in vitro antimicrobial susceptibility of ESBL producing community acquired urinary E. coli isolates to Ceftazidime/Avibactam (CAZ/AVI) and other antimicrobial agents using disk diffusion method.

Methods: Between 2016 and 2017, a total of 100 ESBL producing E. coli urine isolates were collected from outpatients who had no history of hospitalization in the last three months in Akdeniz University Hospital. All isolates were tested for in vitro susceptibility to the CAZ/AVI and other antimicrobial agents using disk diffusion method.

Results: No CAZ/AVI and carbapenem resistance were observed. Resistance rates to other antimicrobial agents were as follows: ampicillin 100%, amoxicillin/clavulanate 85%, cefotaxime 98%, ceftazidime 89%, cefepime 82%, gentamicin 41%, ciprofloxacin 65%, levofloxacin 39%, fosfomycin 3%, nitrofurantoin 2%, trimethoprim/sulfamethoxazole 72% and Piperacillin/Tazobactam 41%.

Conclusions: Our results showed that ceftazidime / avibactam, carbapenems, nitrofurantoin and fosfomycin may be among the first line treatment options in the empirical therapy. In selected patients, CAZ/AVI could be an option for the treatment of UTI caused by ESBL producing E. coli which may reduce the use of carbapenems. J Microbiol Infect Dis 2019; 9(2):112-115.

Keywords: Ceftazidime-avibactam, ESBL, Urinary tract infections, in vitro susceptibility test

INTRODUCTION

Each year, 150 million people are affected by urinary tract infections (UTIs) worldwide. It is the most common infection for prescribing antibiotics. Although, the microbial spectrum of UTIs consists mainly of Escherichia coli (75%–95%), other species of Enterobacteriaceae, such as Proteus mirabilis and Klebsiella pneumoniae, and Staphylococcus saprophyticus occasionally cause UTIs [1,2]. Increased resistance to antibiotics currently used to treat these infections may lead to significant problems. Extended spectrum beta-lactamase (ESBL) production in organisms causing UTIs, particularly E. coli and Klebsiella spp. are often responsible for the increase in resistance [3].

ESBLs, generally encoded by plasmid-borne genes, are capable of hydrolyzing the beta-lactam antibiotics such as penicillins, broad-spectrum cephalosporins and monobactams. ESBL producing organisms often show multidrug-resistance phenotypes such as resistance to fluoroquinolones, aminoglycosides and co-trimoxazole. Most ESBLs belong to the Ambler class A of β-lactamases and are inhibited by β-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam and avibactam) [4,5].
ESBL producing gram-negative bacteria has been associated with increased mortality, length of hospitalization, and hospital costs compared to non ESBL producing bacterial infections.

ESBL-producing strains have increased the use of carbapenems which causes an increase in carbapenem resistance.

New beta-lactam/beta-lactamase inhibitor combinations may be useful for the prevention of carbapenem overuse [6]. CAZ/AVI has not yet been licensed for use in our country.

The aim of this study was to investigate the in vitro antimicrobial susceptibility of ESBL producing community acquired urinary E. coli isolates to CAZ/AVI and other antimicrobial agents using disk diffusion method.

METHODS

Between 2016 and 2017, a total of 100 ESBL producing E. coli urine isolates from outpatients with no history of hospitalization in the last three months in Akdeniz University Hospital were included in the study. E. coli strains were isolated from clean-voided midstream urine. Identification of the strains were performed using MALDI-TOF MS (Bruker Daltonics, Germany) according to the manufacturer's instructions. Detection of ESBL was performed using phenotyping confirmatory disk diffusion test according to EUCAST recommendation's [7]. Both cefotaxime and ceftazidime, alone and in combination with clavulanate were used for ESBL confirmatory test. A ≥5mm increase in a zone diameter of cefotaxime-clavulanic acid and/or ceftazidime/clavulanic acid, compared with zone diameters when the cefotaxime and ceftazidime were tested alone, was considered to be phenotypic confirmation of ESBL production. Antimicrobial susceptibility testing and interpretation of results were performed in accordance with EUCAST recommendation's [8]. All isolates were tested for in vitro susceptibility to CAZ/AVI, ampicillin, amoxicillin/clavulanic acid, cefotaxime, ceftazidime, cefepime, ertapenem, imipenem, meropenem, gentamicin, ciprofloxacin, levofloxacin, fosfomycin, nitrofurantoin and trimethoprim-sulfamethoxazole by disk diffusion method. Quality control was performed as recommended in EUCAST documents using Escherichia coli ATCC 25922 and Klebsiella pneumoniae ATCC 700603.

This study was approved by the Akdeniz University School of Medicine Ethical Committee of Clinical Research (Decision number: 70904504/65/91).

RESULTS

No CAZ/AVI and carbapenem resistance were observed in any of the isolates.

The least active agents were ampicillin, cefotaxime, ceftazidime and cefepime.

All isolates were resistant to ampicillin, whereas resistance to cefotaxime (98%), ceftazidime (89%) and cefepime (82%) all exceeded 80%.

Fluoroquinolone resistance to ciprofloxacin and levofloxacin was determined as 65% and 39%, respectively.

Amoxicillin/clavulanate has very poor activity with a resistance of 85%, while piperacillin/tazobactam was moderately active with 41% resistance to ESBL producing E. coli isolates.

Resistance rates to other antimicrobial agents were found to be as follows: gentamicin 41%, fosfomycin 3%, nitrofurantoin 2%, and trimethoprim-sulfamethoxazole 72% (Table 1).

Table 1. Antibiotic resistance in ESBL producing E. coli isolates

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Resistance n (%)</th>
</tr>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>85 (85)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>98 (98)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>89 (89)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>82 (82)</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>65 (65)</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>72 (72)</td>
</tr>
</tbody>
</table>
DISCUSSION
Antibiotic resistance has become an increasing problem worldwide, use and abuse of antibiotics in medicine and agriculture has amplified the resistance especially in bacteria known to cause community and hospital acquired infections. The CDC considers Gram-negative bacilli that produce ESBLs as serious threats [9,10].

In our study, CAZ/AVI and carbapenems possess excellent activity against ESBL producing E. coli isolates. CAZ/AVI has been approved by the Food and Drug Administration and European Medicines Agency for cUTI [11]. According the results from the INFORM global surveillance study conducted in 2012 to 2014, CAZ/AVI inhibited 99.9% of molecularly confirmed ESBL-producing isolates of E. coli, K. pneumoniae, K. oxytoca, and P. mirabilis [12]. The INFORM Global Surveillance Program results in Asia-Pacific countries, susceptibility to CAZ/AVI for Enterobacteriaceae isolates from each of the Asia-Pacific countries surveyed ranged from 99.1–100%, except China, Thailand, and Philippines. CAZ/AVI inhibited 99.6% of ESBL-positive isolates [13]. In a study conducted to determine the in vitro activity of avibactam in combination with beta-lactams against Gram-negative bacteria, all E. coli and K. pneumoniae isolates with CTX-M-15 - lactamase were susceptible to CAZ/AVI [14]. In one study from China, the susceptibility of E. coli to CAZ/AVI was found as 96.8%, but for carbapenem -resistant E. coli CAZ/AVI susceptibility to CAZ/AVI was reduced to 28.6%. The authors attributed this to the fact that 67.9% of carbapenem-resistant E. coli was blaNDM-Positive [15]. In addition to blaNDM gene, mechanisms of CAZ/AVI resistance in carbapenem-resistant Enterobacteriaceae include, but are not limited to, mutations in the blaKPC gene, differences in susceptibilities of KPC subtypes and other resistance determinants - e.g. outer membrane proteins (OMPs) such as ompK36 and ESBLs [16]. In our study, we think that the reason for not having resistance to CAZ/AVI was the lack of carbapenem resistance in our isolates.

Although the frequency of urinary multidrug resistant (MDR) E. coli among US outpatients increased between 2001 and 2010, nitrofurantoin demonstrated consistent antimicrobial activity against MDR E. coli [18]. In our study, ESBL producing E. coli isolates demonstrated high susceptibility for nitrofurantoin and fosfomycin. Resistance trimethoprim-sulfamethoxazole exceeded 20%, suggesting that these agent may not be reliable for use as empiric therapy.

In 2015, Detection and Monitoring of Antimicrobial Drug Susceptibility (ADSI) Working Group was performed laboratory-based resistance surveillance to determine the antimicrobial susceptibility to various antimicrobial agents for urinary E. coli isolates obtained from various geographic regions in Turkey. In this study, 37% of the isolates were found to be ESBL positive and antimicrobial resistance rates of ESBL producing strains were found as: 62.1% to norfloxacin, 68.3 % to trimethoprim-sulfamethoxazole, 12.1% to nitrofurantoin and 4 % to fosfomycin [19].

In our study, CAZ/AVI and carbapenems showed excellent in vitro activity against ESBL producing E. coli strains. High rates of resistance to trimethoprim/sulfamethoxazole and ciprofloxacin indicate that these antibiotics cannot be recommended for empirical treatment. Therapy of urinary tract infections with ESBL producing strains is problematic. An understanding of local antimicrobial resistance patterns of E. coli and other uropathogens is essential for the management of empirical antimicrobial treatment. Our result showed that CAZ/AVI, carbapenems, nitrofurantoin and fosfomycin may be among the first line treatment options in empirical therapy. In selected patients, CAZ/AVI could represent an option for the treatment UTI caused by ESBL producing E. coli which may reduce the use of carbapenems.

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REFERENCES


