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Antimicrobial susceptibility of multi-drug and extensively-drug-resistant *Escherichia coli* to ceftolozane-tazobactam and ceftazidime-avibactam: An *in vitro* study*

Wrażliwość wielolekoopornych szczepów *Escherichia coli* na ceftolozan z tazobaktamem i ceftazydym z awibaktamem – badanie *in vitro*

Patrycja Zalas-Więcek[A,B,C,D,E,F,G], **Eugenia Gospodarek-Komkowska**[E,G]

Department of Microbiology, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Dr. Antoni Jurasz University Hospital No. 1, Bydgoszcz, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Aim: *Escherichia coli* is one of the Gram-negative bacteria, known to cause many nosocomial infections. Multi-drug (MDR) and extensively-drug resistant (XDR) *E. coli* are of particular note, due to significant limitations in antibiotic therapy. Ceftolozane-tazobactam and ceftazidime-avibactam are novel therapeutic options against Gram-negative bacteria; hence the aim of this study was to evaluate and compare the *in vitro* activity of ceftolozane-tazobactam and ceftazidime-avibactam against MDR and XDR clinical *E. coli* isolates.

Material/Methods: The study included 100 non-replicate *E. coli* isolates derived from clinical samples of patients hospitalized in teaching hospitals. Bacteria were identified by applying mass spectrometry in the MALDI Biotyper system (Bruker). ESBL ($bla_{\text{CTX-M-1group}}$, $bla_{\text{CTX-M-9group}}$) and carbapenemase ($bla_{\text{KPC}}$, bla_{VIM}, bla_{NDM}, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-181}}$) genes were detected using the eazyplex® SuperBug CRE test, based on a loop-mediated isothermal amplification (LAMP). The *in vitro* susceptibility to ceftolozane-tazobactam and ceftazidime-avibactam was tested using validated MIC Test strips (Liofilchem).

Results: All 84 extended-spectrum β-lactamase-producing (ESBL) *E. coli* isolates were susceptible to ceftazidime-avibactam and 83 to ceftolozane-tazobactam. Among 17 *E. coli* isolates with resistance to at least one of the carbapenems, three (17.6%) were susceptible to ceftolozane-tazobactam and ceftazidime-avibactam. All 14 bla_{VIM} gene-positive *E. coli* isolates were resistant to both ceftolozane-tazobactam and ceftazidime-avibactam. Both antibiotics were active against $bla_{\text{CTX-M-9group}}$ and $bla_{\text{OXA-48}}$ gene-positive *E. coli* isolates, but they were not active against $bla_{\text{CTX-M-1group}}$ and bla_{VIM} gene-positive isolates.

Conclusions: Ceftolozane-tazobactam and ceftazidime-avibactam are alternative, non-carbapenem therapeutic options for ESBL-positive *E. coli* strains, and they are promising in the treatment of carbapenem-resistant *E. coli* strains, but not for those carrying the metallo-β-lactamase enzymes. Both drug combinations have comparable activity against ESBL, however, lower MIC values were found for ceftazidime-avibactam.

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Keywords: ceftazidime-avibactam • ceftolozane-tazobactam • *Escherichia coli* • extensively-drug resistance • multi-drug resistance

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Author's address: Patrycja Zalas-Więcek, PhD, ORCID: 0000-0003-2063-6850; Department of Microbiology, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Dr Antoni Jurasz University Hospital No. 1, 9 M. Skłodowska-Curie Str., PL-85-094 Bydgoszcz, Poland; e-mail: patrycjazalas@go2.pl

INTRODUCTION

Escherichia coli is an *Enterobacteriaceae* family member known to cause many nosocomial infections, such as: urinary tract infections, wound infections, intra-abdominal infections, pneumonia, bacteremia, sepsis and neonatal meningitis [17]. Of particular note are multi-drug (MDR) and extensively-drug resistant (XDR), extended spectrum β-lactamase-producing (ESBL), and/or carbapenem-resistant *E. coli* strains, due to significant limitations in antibiotic therapy, and thus, morbidity and mortality. The prevalence of these strains has dramatically increased over the past few years, becoming a serious public health concern worldwide [9]. However, recently, new antibiotics have been developed to combat these resistant strains [8].

Ceftolozane is a novel combination of third-generation cephalosporin with tazobactam, a β-lactamase inhibitor. This antibiotic is active against many Gram-negative bacteria, including the *Enterobacteriaceae* family. Ceftolozane, a new oxyimino-cephalosporin, structurally similar to the third-generation cephalosporin – ceftazidime, works by binding to penicillin-binding proteins, resulting in an inhibition of bacterial cell wall biosynthesis. Tazobactam has little antimicrobial activity, while it restores ceftolozane activity in the presence of most class A and some of class C and D β-lactamases [1, 8]. Ceftolozane-tazobactam (Zerbaxa; Merck & Co., Kenilworth, NJ, USA) was approved by the Food and Drug Administration (FDA) (2014) and the European Medicines Agency (EMA). It is indicated for the treatment of patients with complicated intra-abdominal infections, combined with metronidazole, and complicated urinary tract infections, including pyelonephritis [8]. A phase 3 clinical trial of ceftolozane-tazobactam for the treatment of hospital-acquired and ventilator-associated pneumonia is in progress (ClinicalTrials.gov).

Ceftazidime is a third-generation cephalosporin combined with the novel non-β-lactam β-lactamase inhibitor – avibactam. Avibactam lacks clinically significant antibacterial activity; however, it inhibits a broad spectrum of β-lactamases, with high affinity towards class A, C, and some D enzymes, restoring the *in vitro* activity of ceftazidime. Ceftazidime-avibactam (Avycaz; Allergan, Inc., Irvine, CA, USA) was approved by the FDA (2015) for the same clinical indications as ceftolozane-tazobactam [1, 8]. Ceftazidime-avibactam can also be used for the treatment of hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), and for the treatment of aerobic Gram-negative infections in patients who have limited treatment options.

Both ceftolozane-tazobactam and ceftazidime-avibactam are available only as an intravenous formulation [8].

In Poland, a high prevalence of β-lactamase-producing and carbapenem-resistant Gram-negative bacteria is observed. The predominant type of ESBL enzyme is CTX-M-1. It can be found mainly in *E. coli* and *Klebsiella pneumoniae*, while the most common carbapenemases are VIM, NDM and KPC [9, 12, 14, 15]. According to EARS-Net data from 2017 [5], Poland is among countries with a higher than the European average percentage of *E. coli* strains resistant to: aminopenicillins (EU/EEA average 58.7%), fluoroquinolones (EU/EEA average 25.7%), third generation cephalosporins (EU/EEA average 14.9%), aminoglycosides (EU/EEA average 11.4%), and higher than the European average 6.3% share of MDR strains. A statistically significant increase in the resistance of *E. coli* compared with the isolates from 2015 is of great concern. The share of strains resistant to aminopenicillins increased from 64.7% to 69.5%, resistant to fluoroquinolones from 27.9% to 35.9%, resistant to third generation cephalosporins from 11.9% to 16.7%, resistant to aminoglycosides from 11.2% to 14.0%, and MDR strains from 6.1% to 8.2%. Moreover, Poland, along with Slovakia and Portugal, is among the countries in which a statistically significant increase in carbapenem resistance has been recorded over the last few years.

Ceftolozane-tazobactam and ceftazidime-avibactam may be an alternative in the treatment of patients with infections caused by MDR and XDR, but also ESBL-pro-

ducing and carbapenem-resistant *E. coli*. There are no Polish articles describing the susceptibility of *E. coli* strains to ceftolozane-tazobactam and ceftazidime-avibactam, and comparing ceftolozane-tazobactam and ceftazidime-avibactam activity against *E. coli* isolates. Therefore, in this study, the susceptibility of ESBL-producing and carbapenem-resistant *E. coli* isolates to ceftolozane-tazobactam and ceftazidime-avibactam was evaluated and compared.

MATERIALS AND METHODS

Bacterial isolates and identification

The study included 100 *E. coli* isolates derived from the collection of the Department of Microbiology Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. All of them were isolated from clinical samples of patients (one isolate per patient) hospitalized in different clinical departments from January 2016 to December 2018 in two Polish Teaching Hospitals. *E. coli* isolates were identified by applying mass spectrometry in the MALDI Biotyper system (Bruker), according to the manufacturer's instruction, and compared with the pulsed-field gel electrophoresis as described previously [18]. Only non-replicate isolates were included in the study. Bacteria were isolated from the following clinical specimens: 46 (46.0%) from urine, 19 (19.0%) from rectal swab and stool, 17 (17.0%) from wound, 10 (10.0%) from abdominal fluid, 7 (7.0%) from blood and one from pleural fluid.

Antimicrobial susceptibility tests

E. coli isolates were tested for susceptibility to ceftolozane-tazobactam and ceftazidime-avibactam using validated MIC Test strips (Liofilchem) following the manufacturer's recommendations. The European Committee on Antimicrobial Susceptibility Testing (EUCAST version 9.0 2019) [6] breakpoints were used as follows: ≤1 µg/ml susceptible, >1 resistant to ceftolozane-tazobactam and ≤8 µg/ml susceptible, >8 resistant to ceftazidime-avibactam. Antimicrobial susceptibility testing of other drugs; i.e. amoxicillin-clavulanic acid, piperacillin-tazobactam, cefuroxime, cefotaxime, ceftazidime, cefepime, imipenem, meropenem, ertapenem, gentamicin, amikacin, tobramycin, ciprofloxacin, trimethoprim-sulfamethoxazole, tigecycline, and colistin; was performed using the NMIC-402 panels that were read out with Phoenix M50 automated system (Becton-Dickinson) and interpreted according to EUCAST (version 9.0 2019) [6] clinical breakpoints. MDR bacteria were defined as isolates non-susceptible to one or more agents in three or more antimicrobial classes, XDR bacteria: as isolates non-susceptible to one or more agents in all but two or fewer classes, and PDR bacteria: as non-susceptible to all antimicrobial classes tested [11]. To assess the effectiveness of ceftolozane-tazobactam and ceftazidime-avibactam against *E. coli* strains, on the basis of the MIC values of ceftolozane-tazobactam and ceftazidime-avibactam obtained for all *E. coli* isolates, the MIC_{50} (Minimum Inhibitory Concentration required to inhibit the growth of 50% of bacteria) and MIC_{90} (Minimum Inhibitory Concentration required to inhibit the growth of 90% of bacteria) were determined.

Phenotypic screening of ESBLs and carbapenemases

E. coli isolates were classified as ESBL-producers based on their resistance to penicillins and extended spectrum cephalosporins, positive Phoenix M50 ESBL testing, and DDST (double-disk synergy test), using the following disks: ceftazidime (30 µg), cefotaxime (30 µg), and amoxicillin/clavulanic acid (20/10 µg) (Oxoid). To increase the sensitivity of the test, disks containing cefepime (30 µg) (Oxoid) were added. In the absence of strain susceptibility to at least one of the carbapenems (i.e. imipenem, meropenem or ertapenem), the Carba NP test (B-PER II Buffer – Thermo Scientific; Tienam/imipenem 500 mg + cilastatin 500 mg/- Merck Sharp & Dohme; 0.5% Phenol-red solution – Sigma Aldrich; $ZnSO_4 \cdot 7H_2O$ –Merck) [13] was performed. To detect the type of carbapenemase, phenotypic tests; i.e. EDTA test for MBL (EDTA – Sigma-Aldrich; ceftazidime (30 µg) and imipenem (10 µg) – Oxoid) [10], boronic acid test for KPC (boronic acid – Sigma-Aldrich; meropenem (10 µg) – Oxoid) [4] and 30 µg temocillin test for OXA-48 (Oxoid) [7, 16]; were applied.

Loop-mediated isothermal amplification (LAMP) assay

Simultaneously with the phenotypic tests, ESBL ($bla_{CTX\text{-}M\text{-}1group}$, $bla_{CTX\text{-}M\text{-}9group}$) and carbapenemase ($bla_{KPC}$, bla_{VIM}, bla_{NDM}, $bla_{OXA\text{-}48}$, $bla_{OXA\text{-}181}$) genes were detected using the eazyplex® SuperBug CRE test (Amplex Biosystems GmbH, Giessen, Germany), based on LAMP, and read out with the Genie II device (Optigene, Horsham, UK), according to the manufacturer's instruction.

RESULTS

Among 100 *E. coli* isolates, 7 (7.0%) and 93 (93.0%) were defined as XDR and MDR, respectively. None of the isolates were PDR. The results of antibiotic susceptibility testing are shown in Tab. 1.

Eighty four (84.0%) isolates were positive for ESBLs according to DDST and Phoenix method. LAMP results indicated that 75 (75.0%), and 9 (9.0%) among 100 *E. coli* isolates were positive in terms of $bla_{CTX\text{-}M\text{-}1group}$ and $bla_{CTX\text{-}M\text{-}9group}$ genes, respectively. Seventeen (17.0%) isolates were positive for carbapenem resistance determining genes. The bla_{VIM} gene was detected in 14 (14.0%) of the *E. coli* isolates. The bla_{KPC}, bla_{NDM} and $bla_{OXA\text{-}181}$ genes were not detected in any of the isolates tested. Two *E. coli* isolates were positive for both ESBL and carbapenemase genes. One of them was positive for the $bla_{CTX\text{-}M\text{-}9group}$, and $bla_{OXA\text{-}48}$ genes, while the second one was positive for the $bla_{CTX\text{-}M\text{-}1group}$, and bla_{VIM} genes.

Table 1. Antimicrobial susceptibility of ESBL-positive and carbapenem-resistant *E. coli* isolates (n = 100)

Antimicrobial agent	No. (%)* of susceptible *E. coli* isolates
Amoxicillin-clavulanic acid	5 (5.0)*
Piperacillin-tazobactam	58 (58.0)
Cefuroxime	0 (0.0)
Cefotaxime	0 (0.0)
Ceftazidime	10 (10.0)
Cefepime	6 (6.0)
Ceftolozane-tazobactam	84 (84.0)
Ceftazidime-avibactam	85 (85.0)
Imipenem	85 (85.0)
Meropenem	86 (86.0)
Ertapenem	81 (81.0)
Gentamicin	48 (48.0)
Tobramycin	33 (33.0)
Amikacin	46 (46.0)
Ciprofloxacin	13 (13.0)
Trimethoprim-sulfamethoxazole	31 (31.0)
Tigecycline	97 (97.0)
Colistin	99 (99.0)

All but one ESBL-positive isolates were susceptible to ceftolozane-tazobactam (MIC range: 0.094–2 µg/ml, MIC_{50}: 0.38 µg/ml, MIC_{90}: 0.75 µg/ml) and ceftazidime-avibactam (MIC range: 0.047-0.75 µg/ml, MIC_{50}: 0.125 µg/ml, MIC_{90}: 0.38 µg/ml) (Tab. 2). MIC range, MIC_{50}, and MIC_{90} of 75 (75.0%) $bla_{CTX\text{-}M\text{-}1group}$ – and 9 (9.0%) $bla_{CTX\text{-}M\text{-}9group}$-gene-positive *E. coli* isolates are presented in Tab. 2. Ceftolozane-tazobactam and ceftazidime-avibactam were active against all AMG-resistant, CIP-resistant, and SXT-resistant ESBL-positive isolates.

Among 17 *E. coli* isolates resistant to at least one of the carbapenems (imipenem, meropenem or ertapenem), three (17.6%) were susceptible to ceftolozane-tazobactam (MIC range: 0.38 – >256 µg/ml, MIC_{50}: >256 µg/ml, MIC_{90}: >256 µg/ml) and ceftazidime-avibactam (MIC range: 0.023 – >256 µg/ml, MIC_{50}: >256 µg/ml, MIC_{90}: >256 µg/ml), respectively. All 14 bla_{VIM} gene-positive *E. coli* isolates were resistant to both ceftolozane-tazobactam (MIC range: 3 – >256 µg/ml, MIC_{50}: >256 µg/ml, MIC_{90}: >256 µg/ml) and ceftazidime-avibactam (MIC range: 12 – >256 µg/ml, MIC_{50}: >256 µg/ml, MIC_{90}: >256 µg/ml). Ceftolozane-tazobactam and ceftazidime-avibactam were active against $bla_{CTX\text{-}M\text{-}9group}$ and $bla_{OXA\text{-}48}$ gene-positive *E. coli* isolates, but not active against $bla_{CTX\text{-}M\text{-}1group}$ and bla_{VIM} gene-positive isolates, respectively.

DISCUSSION

The spread of MDR and XDR Gram-negative rods producing ESBLs and carbapenemases represents an emerging public-health concern with the attendant loss of many previously effective antimicrobial therapeutic agents. Infections caused by these strains are associated with the increased morbidity and mortality, and prolonged hospitalization; resulting in a significant burden on the healthcare systems [9]. Therefore, there is a strong need to introduce new antibiotics active against MDR and XDR bacteria. Ceftolozane-tazobactam and ceftazidime-avibactam are novel combinations of cephalosporins with β-lactamase-inhibitors that have some promising results against MDR and XDR Gram-negative bacteria, including *E. coli* [1, 8].

This study evaluated the antimicrobial activity of ceftolozane-tazobactam and ceftazidime-avibactam against 100 MDR and XDR *E. coli* isolates. These combined antibiotics had hight activity against the ESBL-positive *E. coli* isolates (98.8% *vs.* 100% susceptible strains, respectively) and also had a better activity against *E. coli* isolates than: amoxicillin-clavulanic acid, piperacillin-tazobactam, cefuroxime, cefotaxime, ceftazidime, cefepime, ertapenem, gentamicin, tobramycin, amikacin, ciprofloxacin or trimethoprim-sulfamethoxazole. Ceftolozane-tazobactam and ceftazidime-avibactam had a similar activity to imipenem, but less activity than meropenem, tigecycline or colistin (Tab. 1). These results are concordant with the other *in vitro* study [1], which shows an excellent and comparable activity of ceftolozane-tazobactam and ceftazidime-avibactam against ESBL-positive *E. coli* strains (97.0% vs. 100% susceptible strains, respectively),

Table 2. Antibacterial activity of ceftolozane-tazobactam and ceftazidime-avibactam against ESBL-positive and CR *E. coli* isolates (n = 100)

Resistance profile (n)	Ceftolozane-tazobactam				Ceftazidime-avibactam			
	MIC_{50}	MIC_{90}	MIC range	S No. (%)	MIC_{50}	MIC_{90}	MIC range	S No. (%)
ESBL-positive (84)	0.38	0.75	0.094–2	83 (98.8)	0.125	0.38	0.047–0.75	84 (100)
CTX-M1-group-positive (75)	0.38	1	0.094–2	74 (98.7)	0.125	0.38	0.047–0.75	75 (100)
CTX-M9-group-positive (9)	0.25	0.38	0.19–0.38	9 (100)	0.125	0.125	0.047–0.125	9 (100)
ESBL-positive, AMG-resistant (53)	0.38	0.75	0.094–1	53 (100)	0.125	0.25	0.047–0.75	53 (100)
ESBL-positive, CIP-resistant (73)	0.38	0.75	0.094–2	72 (98.6)	0.125	0.38	0.047–0.75	73 (100)
ESBL-positive, SXT-resistant (54)	0.38	0.75	0.094–2	53 (98.1)	0.125	0.38	0.047–0.75	54 (100)
CR (17)	>256	>256	0.38–>256	3 (17.6)	>256	>256	0.023–>256	3 (17.6)
VIM-positive (14)	>256	>256	3–>256	0 (0)	>256	>256	12–>256	0 (0)
	MIC value				MIC value			
CTX-M1 and VIM-positive (1)	>256			0 (0)	>256			0 (0)
CTX-M9 and OXA-48-positive (1)	0.38			1 (100)	0.023			1 (100)

AMG – aminoglycosides; CIP – ciprofloxacin; CR – carbapenem-resistant; ESBL – extended-spectrum beta-lactamase; MIC – minimum inhibitory concentration; MIC_{50} – Minimum Inhibitory Concentration required to inhibit the growth of 50% bacteria; MIC_{90} – Minimum Inhibitory Concentration required to inhibit the growth of 90% bacteria; n – number of isolates; S – susceptible; SXT – trimethoprim-sulfamethoxazole

making them superior to all other antimicrobials tested with ESBL-positive isolates. On the other hand, Bouxom et al. [2] reported a higher share of the ESBL-positive *E. coli* isolates susceptible to ceftazidime-avibactam, compared with ceftolozane-tazobactam (100% *vs.* 78.0% susceptible strains, respectively).

Ceftazidime-avibactam was active against all aminoglycosides-, ciprofloxacin-, and trimethoprim-sulfamethoxazole-resistant ESBL-positive *E. coli* isolates. Ceftolozane-tazobactam was also active against all aminoglycosides-resistant isolates, but not for all ciprofloxacin- and trimethoprim-sulfamethoxazole-resistant isolates. In the study by Alatoom et al. [1], ceftazidime-avibactam was active against all gentamicin-, amikacin-, ciprofloxacin-, and trimethoprim-sulfamethoxazole-resistant ESBL-positive *E. coli* isolates. Ceftolozane-tazobactam was also active against all of these isolates except for one ciprofloxacin- and one trimethoprim-sulfamethoxazole-resistant isolates.

This study showed that ceftazidime-avibactam had lower MIC values, compared with ceftolozane-tazobactam, against ESBL-positive *E. coli* isolates (MIC_{50}: 0.125 µg/ml *vs.* 0.38 µg/ml, respectively). This phenomenon was also reported by Alatoom et al. [1], who obtained lower MIC values of ceftazidime-avibactam compared with ceftolozane-tazobactam (MIC_{50}: 0.125 µg/ml *vs.* 0.38 µg/ml, respectively) for 29 ESBL-positive *E. coli* and *K. pneumoniae* isolates. The MIC_{90} of both drugs against *E. coli* were comparable with the results obtained in the previous report [1].

Ceftolozane-tazobactam and ceftazidime-avibactam did not show a good activity against carbapenemase-producing *E. coli* isolates. None of the 14 VIM-producing (bla_{VIM} gene-positive) *E. coli* isolates were susceptible to those combinations of antibiotics. Ceftazidime-avibactam and ceftolozane-tazobactam were active only against one carbapenemase-(OXA-48)-producing (bla_{OXA-48} gene-positive) *E. coli* isolate. Similar results were reported by other authors [1, 3]. Alatoom et al. [1] observed a good activity of ceftazidime-avibactam against OXA-48-producing *E. coli* and *K. pneumoniae* isolates (80.0% susceptible isolates), but a poor activity against NDM-1-, NDM-1/OXA-48-, and VIM-producing isolates (29.0%, 5.0%, and 0.0% susceptible isolates, respectively). Ceftolozane-tazobactam, on the other hand, had a poor activity against all these isolates (13.0%, 21.0%, and 0.0% susceptible isolates, respectively). de Jonge et al. [3] found that ceftazidime/avibactam was not active *in vitro* against 145 metallo-ß-lactamase-poducing *Enterobacteriaceae* with 96.6% resistant isolates, while isolates that carried KPC or OXA-48-like-lactamases, both alone and in combination with ESBLs and/or AmpC enzymes, were 98.7% and 98.5% susceptible to ceftazidime-avibactam, respectively. The prevalence and type of carbapenemase vary in different geographical regions, therefore, studies to evaluate the effect of new drugs on local MDR isolates are recommended.

In this study, two carbapenem-resistant and ESBL-positive *E. coli* isolates, which gave negative results in both the eazyplex® SuperBug CRE and Carba NP assays, were included. Ceftolozane-tazobactam and ceftazidime-avibactam were active against these isolates. Their resistance to β-lactam antibiotics, including carbapenems, may result from: 1) the hyperproduction of ESBL and/or AmpC enzymes combined with an impaired permeability of the outer membrane porins, which decrease the ability of the antibiotic to reach its bacterial target, or 2) the presence of other low-level resistance mechanisms, which cannot be detected by eazyplex® SuperBug CRE and/or Carba NP assays [1, 8]. Also in the study by de Jonge et al. [3], 207 meropenem-nonsusceptible, carbapenemase-negative *Enterobacteriaceae* isolates demonstrated 94.7% susceptibility to ceftazidime-avibactam. Ceftazidime-avibactam activity was compromised only in isolates for which carbapenem resistance was mediated by metallo-β-lactamases.

Ceftolozane-tazobactam and ceftazidime-avibactam are two new combinations of cephalosporin and β-lactamase inhibitors that have a high activity against the MDR and XDR ESBL-positive *E. coli* isolates. They are also a good alternative to other agents tested in this study, including carbapenems, which until now have been the antibiotics of choice in the treatment of infections caused by ESBL-positive strains. These antibiotics should be considered for patients as a definitive therapy in the setting of confirmed resistance to other β-lactam agents, particularly for institutions with increasing reports of carbapenem resistance.

CONCLUSION

Ceftolozane-tazobactam and ceftazidime-avibactam are an alternative, non-carbapenem therapeutic option for ESBL-positive *E. coli* strains. They are promising in the treatment of carbapenem-resistant *E. coli* strains, but not for those carrying the metallo-β-lactamases.

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