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Original scientific paper

Ceftazidime/avibactam as a possible treatment option for carbapenem-resistant *Enterobacterales* infections

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Abstract

Carbapenem resistance (CR) in *Enterobacterales* is frequently determined by the production of enzymes, so called carbapenemases, (KPC, NDM, OXA-48 etc) or by porin deficiencies, combined with ESBLs. Several new agents with activity against certain carbapenem-resistant pathogens have been approved for clinical use, such as ceftazidime-avibactam (CAZ-AVI). The aim of this study is to detect the resistance of *Enterobacterales* to the new combination CAZ-AVI which were recently approved for the treatment of infections due to CRE.

In all 65 isolates the mechanisms of carbapenem resistance, i.e. the types of carbapenemases they produce, have been clearly defined by applying phenotypic and genotypic methods. New Vitek 2 susceptibility card (N-439) was used for determination of susceptibility to antimicrobial agents including CAZ/AVI. Most of the isolates produced NDM, followed by OXA-48 carbapenemases. The highest percentage of NDM-producing isolates showed susceptibility to colistin (74%), while all OXA-48-producers (100%) showed susceptibility to CAZ/AVI.

Many studies show that for bacteria with KPC, preferred treatment is the combination of βL-βLICs (Ceftazidime-avibactam, Meropenem-vaborbactam, and Imipenem-relebactam). For CRE producing metalo-beta-lactamases (NDM), preferred treatment is ceftazidime/avibactam in combination with aztreonam, and for those CRE which produce OXA-48, preferred treatment is ceftazidime/avibactam. Newly approved βL-βLICs are expected to offer many advantages, such as favorable safety profile and high activity against multi drug resistance gram-negative bacteria.

Key words: Ceftazidime–avibactam, resistance mechanisms, Beta-lactamases

Introduction

Antimicrobial resistance is globally recognized as one of the greatest threats to public health. Carbapenem resistance in Gram-negative bacteria has become a worldwide problem. The 2017 World Health Organization (WHO) global priority list of pathogens ranks carbapenem resistant *Enterobacterales* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CR-Pa), and carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) in the highest priority category (i.e. critical) (WHO, 2017).

For years, carbapenems have been used successfully to treat infections due to resistant *Enterobacterales*, such as *E. coli* and *K. pneumoniae*, including those producing extended spectrum-beta-lactamases (ESBLs), a subset of beta-lactamases that confer broad resistance to penicillins, cephalosporins, and the monobactams). However, recently CRE have emerged, which confer broad resistance to most beta-lactam antibiotics including last-line carbapenems (Nordmann, and Poirel, 2012).

Carbapenem resistance in *Enterobacterales* is frequently determined by the production of enzymes, so called carbapenemases, which are encoded mainly on

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plasmids and are highly transmissible (Nordmann, and Poirel, 2013). The Ambler classification system categorizes β-lactamase enzymes into 4 groups (ie, A, B, C, D) based on their central catalytic domain and substrate preference (Ambler, 1980). Of these, classes A, B, and D include carbapenemases, whereas class C enzymes hydrolyze primarily cephalosporins. Enzymes in classes A, C, and D have serine in the active catalytic site, whereas class B enzymes are metallo-βlactamases (MBLs) with zinc in the active site (Bush, 2010). Carbapenem resistance can also be conferred when porin deficiencies, which allow decreased entry of the beta-lactam into the cell membrane, are combined with ESBLs (Morrill et al., 2015).

CRE can cause a number of serious infection types, such as intra-abdominal infections, pneumonia, urinary tract infections, and device-associated infections, or asymptomatic colonization. Infections caused by CRE are extremely concerning, because CRE mortality rates are high and range from 18 to 48% depending on therapy. This result may be due to delayed time to active therapy, pharmacologic limitations of available treatment options, and the fact that patients with CRE infections tend to be critically ill (Akova et al., 2012).

Based on limited therapeutic options, various previously used drugs, such as fosfomycin and polymyxins have been reviewed for treatment of infections due to CRE. The use of older agents, such as tigecycline or colistin is frequently associated with unclear efficacy and/or toxicity issues (Chakhtoura et al., 2018).

Recently, WHO indicated a priority MDR pathogens list for which new antibiotics are urgently needed by guiding research, and promoted the development of new antibiotics (WHO, 2014). In this context, different β-lactam–β-lactamase inhibitor combinations (βL-βLICs) were recently developed and approved for the treatment of infections due to multidrug resistant microorganisms (MDR) (Yahav et al., 2020). These novel antimicrobial molecules are reported to be active against different MDR pathogens, including class A and D producing *Enterobacterales*, CR-Pa and CR-Ab. Ceftazidime–avibactam (CAZ-AVI) is the first member of this new generation of βL-βLICs. Avibactam is a non–β-lactam β-lactamase inhibitor that restores in vitro activity of a third-generation cephalosporin, ceftazidime, against Ambler class A, C, and some of class D carbapenemase (Falcone, and Paterson, 2016; Sharma et al., 2016). CAZ-AVI was the first βL-βLICs to be released and was approved for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) in 2015, and subsequently for the treatment of hospital-acquired and ventilator associated bacterial pneumonia (HABP/VABP) in 2018 (Levasseur et al., 2015; Sharma et al., 2016). CAZ-AVI is a novel association of ceftazidime, a third-generation cephalosporin with avibactam, a new reversible (nonsuicidal) beta-lactamase inhibitor belonging to the diazabicyclo octane class (DBOs). Avibactam (AVI) forms a covalent bond with the serine of the active center of the β-lactamase; however, unlike clavulanic acid and tazobactam, the molecule is not hydrolyzed, but is slowly separated and recovers its original structure. Avibactam is active against class A (ESBLs, KPCs), class C (Amp C, FOX, CMY-2, AAC-1), and class D (OXA-48) β-lactamases, while not active against MBL (e.g., NDM, VIM, IMP) due to the absence of active site serine residue and against *Acinetobacter* OXA-type carbapenemase. Reliable and rapid identification of carbapenemase type is essential for the establishment of therapies based on CAZ-AVI treatment (Ehmann et al., 2012; Lohans et al., 2017).

The aim of this study is to detect the resistance of *Enterobacterales* to the new combination CAZ-AVI which were recently approved for the treatment of infections due to carbapenem-resistant *Enterobacterales*.

Material and methods

All samples (urine, wound, blood, sputum, tracheal aspirate, tubus/canilla) during six-months period July-December 2024, obtained from patients hospitalized at the: University Clinics in "Mother Teresa" Clinical Campus, City hospital "8th September" and Special hospital for surgical diseases "St. Naum Ohridski", were processed at the Institute of Microbiology and Parasitology, Faculty of Medicine, UKIM, Skopje. For isolation and identification of the strains, standard microbiological techniques were used. Determination of the susceptibility to antimicrobial agents was done by standard disk diffusion method. Two additional tests were performed to all strains that showed smaller inhibition zones to carbapenems than the cut-offs recommended by EUCAST: CIM test- for carbapenemases (Carbapenem Inactivation Method) (Van der Zwaluw et al., 2015) and a phenotypic test for detection of carbapenemase group (Combination Disks Test, Mast Diagnostic, D70C) (Matuschek et al., 2014). Detection of β-lactamase genes was done by Eazyplex® SuperBug CRE (Amplex Biosystems GmbH, Giessen, Germany). Eazyplex® SuperBug CRE detects the most commonly described variants of metallo-beta lactamases (VIM-, NDM-), KPC-, OXA-48 family, OXA-181 as well as ESBLs (CTX-M-1 and the CTX-M-9 group). Loop-mediated isothermal amplification (LAMP) - products are visualized by measuring the fluorescence of double-stranded DNA-bound fluorescent dye using the GENIE II instrument (OptiGene, Hors) (Rodel et al., 2023).

New Vitek 2 cards for determination of susceptibility to antimicrobial agents including new combinations of beta-lactams with beta-lactamase inhibitors have been available at the Institute since July 2024. Therefore, we tested all resistant isolates on the Vitek 2 automated system (bioMerieux, France) using AST N-439 susceptibility card.

Results and discussion

A total of 65 isolates were included in the study, as

follows: *Klebsiella pneumoniae* (49 isolates), *Enterobacter cloacae* (9 isolates), *Serratia marcescens* (6 isolates), and *E. coli* (1 isolate). In all strains the mechanisms of carbapenem resistance, i.e. the types of carbapenemases they produce, have been clearly defined by applying phenotypic and genotypic methods. Results are shown in Table 2.

Carbapenemase production was detected in 49 isolates of *K. pneumoniae* (75%). Of these, NDM, OXA-48 and the combination of both NDM and OXA-48 were detected in 47%, 39%, and 12% of the isolates, respectively. In one isolate, although carbapenemase production was detected by phenotypic tests, the type of carbapenemase could not be determined. It is likely that it is a different type of carbapenemase that is not included in the appropriate test panel.

Carbapenemase production was detected in 9 isolates of *Enterobacter cloacae* (14%), and in 6 isolates of *Serratia marcescens* (9%). Production of NDM was confirmed in all isolates of *Enterobacter cloacae.* In 5 out of 6 isolates of *Serratia marcescens*, NDM production was detected, and in one isolate of *Serratia marcescens*, a combination of two carbapenemases (KPC and NDM) was detected. Only one *E. coli* strain (1.5%) was carbapenemase-producer, and that was NDM.

In total, 38 (58.5%) and 19 (29.2%) isolates produced NDM and OXA-48-type, respectively. In 6 (9.2%) and 1 (1.5%) isolate, two types of carbapenemases were detected (NDM and OXA-48; KPC and NDM), respectively. In 1 isolate (1.5%), no carbapenemase production gene was detected from the test panel.

All isolates that produced NDM showed resistance to most of the tested antimicrobial agents (Fig. 1). The highest percentage of isolates showed susceptibility to colistin (74%), while to MEM/VABOR, AK and G this percentage was 21, 24 and 26, respectively.

All isolates that produced OXA-48 showed resistance to most of the tested antimicrobial agents (Figure 2). The highest percentage of isolates showed susceptibility to CAZ/AVI (100%), while to colistin, MEM/VABOR, AK and G this percentage was 53,47, 26, and 21, respectively (Fig. 2).

Although the number of isolates producing two types of carbapenemases (NDM and OXA-48) was small, it can be noticed that the strains were resistant to all tested antimicrobial agents, except for colistin, to which 2 out of 6 isolates (67%) were susceptible (Fig. 3).

Table 1. Antimicrobial agents incorporated on AST N-439 susceptibility card for Vitek 2 automated system

Selected organism: *Klebsiella pneumoniae ssp pneumoniae*					
Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
Amoxicillin/Clavulanic acid	≥ 64	R	Meropenem/Vaborbactam	16	R
Piperacillin/Tazobactam	≥ 128	R	Amikacin	32	R
Ceftazidime	≥ 64	R	Gentamicin	≥ 16	R
Ceftazidime/Avibactam	0,5	S	Ciprofloxacin		
Ceftolozane/Tazobactam	≥ 32	R	Meningitis	≥ 4	R
Cefepime	≥ 32	R	Other	≥ 4	R
Meropenem			Tigecycline		
Meningitis	≥ 16	R	Fosfomycin		
Other	≥ 16	R	Colistin	0,5	S
Imipenem/Relebactam	4	R			

Table 2. Resistant strains in which genes for carbapenemase production have been detected

	NDM	OXA-48	NDM+OXA-48	KPC+NDM	Unidentified genes	Total
Klebsiella pneumoniae	23	19	6		1	49
Enterobacter cloacae	9					9
Serratia marcescens	5			1		6
Echerichia coli	1					1
Total	38 (58.5%)	19 (29.2%)	6 (9.2%)	1 (1.5%)	1 (1.5%)	65

Table 3. Susceptibility of carbapenem-resistant isolates to different antimicrobial agents

	NDM (38)		OXA-48 (19)		NDM+OXA-48 (6)	
	R	I/S	R	I/S	R	I/S
AMC	38		19		6	
PTZ	38		19		6	
CAZ	38		19		6	
CAZ/AVI	38		0	19	6	
Ceftolozane/TAZ	38		19		6	
FEP	38		19		6	
MEM	37	1	18	1	6	
IMI/RELE	38		18	1	6	
MEM/VABOR	30	8	10	9	6	
AK	29	9	14	5	6	
G	28	10	15	4	6	
CIP	36	2	19		6	
Colistin	10	28	9	10	2	4

AMC = Amoxicillin/Clavulanic Acid
PTZ = Piperacillin/Tazobactam
CAZ = Ceftazidime
CAZ/AVI = Ceftazidime/Avibactam
CEF/TAZ = Ceftolozane/Tazobactam
FEP = Cefepime
MEM = Meropenem
IMI/RELE = Imipenem/Relebactam
MEM/VABOR = Meropenem/Vaborbactam
AK = Amikacin
G = Gentamicin
CIP = Ciprofloxacin

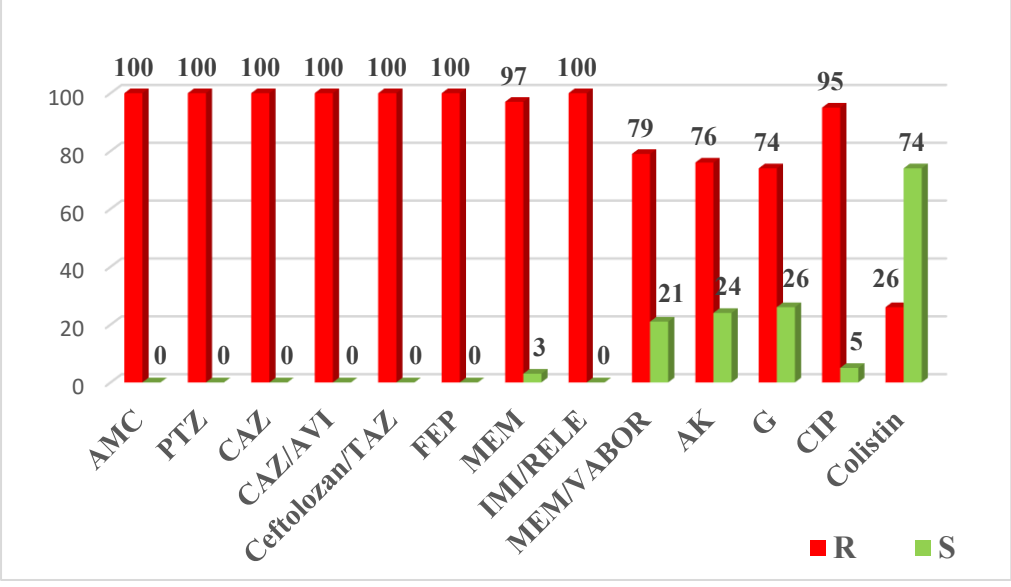

Fig. 1. Susceptibility of NDM-producing isolates.

Resistance to carbapenems is caused by the production of carbapenemases, which belong to different Ambler classes. Less frequently, carbapenem resistance stems from deficient outer-membrane protein expression. In Ambler class A, the main enzyme is KPC (*Klebsiella pneumoniae* carbapenemase) (Bassetti, and Peghin, 2020). Enzymes classified in Ambler class B are all carbapenemases belonging to the metallo beta-lactamase (MBL) group, due to their beta-lactamase activity through a metal ion (usually zinc) as cofactor. There are three main MBLs: imipenemase (IMP), Verona integron-encoded metallo beta-lactamase (VIM) and New Delhi metallo beta-lactamase (NDM). Encoded by plasmids or other mobile genetic elements, these MBLs are spreading rapidly all over the world and are now the mechanism of resistance of greatest concern; they are frequently associated with the expression of additional genes conferring resistance to other antimicrobial drug classes such as fluoroquinolones and aminoglycosides, and thus narrow the spectrum of therapeutic options. They are not inhibited by old beta-lactamases inhibitors (clavulanic acid or tazobactam) or by new ones (avibactam, relebactam or vaborbactam), but they remain susceptible to aztreonam (Shi et al., 2019). Class D enzymes pertain to the OXA-48 class, and have an unusual

mechanism of resistance; they are penicillinases (particularly oxacillinases) and carbapenamases, but they are susceptible to third generation cephalosporins, although they frequently co-produce as ESBL enzymes and thus confer resistance to all beta-lactams (Steward et al., 2018). From the epidemiological point of view, data from the latest ECDC report showed that several countries reported high percentages (above 10% or even 25%) of carbapenem-resistant *K. pneumoniae*, including Italy, France, Spain, Portugal and most Eastern European countries. Greece reported the highest levels of resistance with a prevalence of 50% (Bassetti et al., 2016). Carbapenem-resistant *Enterobacterales* (CRE) enzymes (except for OXA-48) are mainly encountered in the hospital setting in patients receiving prolonged antibiotic therapy, carrying indwelling devices, or undergoing long-term hospitalization or ICU admission (Bassetti et al., 2017).

In our study, more than half of the carbapenem-resistant isolates (58.5%) produced NDM, and 29% of the isolates produced OXA-48. A limitation of this study is that no isolate producing KPC was detected during the study period. Only one isolate which produced KPC was detected, but in combination with NDM, making the isolate resistant to the CAZ/AVI combination.

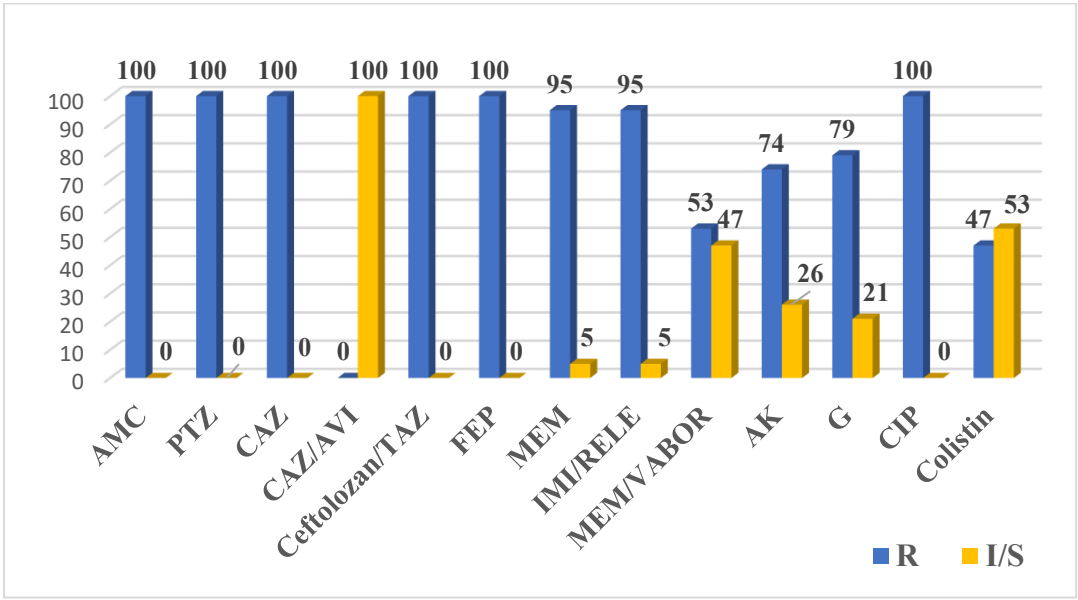

Fig. 2. Susceptibility of OXA-48-producing isolates.

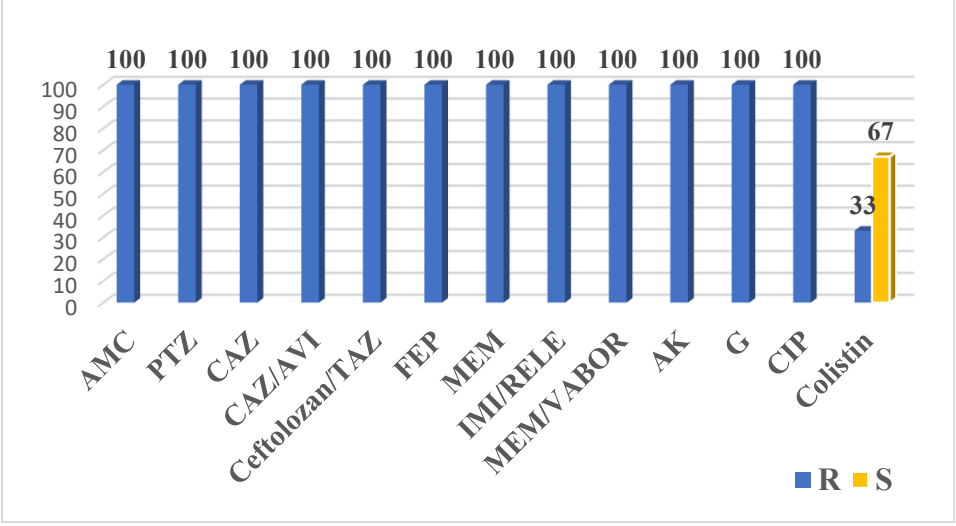

Fig. 3. Susceptibility of isolates producing two types of carbapenemases (NDM and OXA-48).

Ceftazidime/avibactam (CAZ/AVI) is a combination of an old cephalosporin (ceftazidime) with a new beta-lactamase inhibitor (avibactam). Avibactam is renally excreted, and its pharmacokinetics are similar to those of ceftazidime, allowing for coformulation. This combination shows activity against ESBLs, AmpC beta-lactamases (class C), class A (KPC) and class D (OXA). CAZ/AVI is highly active against KPC-producing CRE and has become the first line therapy for these infections in many hospitals. Its use has also been extended by the European medicines Agency (EMA) to infections due to aerobic Gram-negative bacteria with limited treatment options. Its use in real-life clinical situations has demonstrated its value in the treatment of other clinical syndromes such as primary blood stream infections (BSI) (Bassetti et al., 2020).

In real-life experience, high favorable response rates have been reported in patients with infections due to KPC-producing *Enterobacterales* treated with ceftazidime-avibactam, with an overall success rate around 70%. Among patients with KPC-KP BSI, 30-day mortality rates were significantly lower in the ceftazidime/avibactam group than in a matched group of patients receiving other treatments (36.5% versus 55.7%, $p = 0.005$). Ceftazidime/avibactam has shown promising results for salvage treatment of patients with severe infections due to OXA-48-producing *Enterobacterales* and with limited therapeutic options, with no evidence of the emergence of resistance to ceftazidime/avibactam (Dietl et al., 2020; Shields et al., 2017). Ceftazidime/avibactam has no activity against metallo-β-lactamase-producing *Enterobacterales*, but previous clinical studies including patients with BSI due to MBL-producing *Enterobacterales* have shown that combination therapy with CAZ-AVI plus aztreonam is an effective therapeutic option (Bassetti et al., 2020; Vena et al., 2019).

In our study, all isolates that produced NDM showed resistance to most of the tested antimicrobial agents. The highest percentage of bacterial isolates demonstrated susceptibility to colistin (74%), while susceptibility to MEM/VABOR, AK and G was confirmed in 21, 24 and 26% of the isolates, respectively. All isolates that produced OXA-48 demonstrated resistance to most of the tested antimicrobial agents. The highest percentage of isolates showed susceptibility to CAZ/AVI (100%), while susceptibility to colistin, MEM/VABOR, AK and G was confirmed in 53, 47, 26 and 21% of the isolates, respectively. Although the number of isolates producing two types of carbapenemases (NDM and OXA-48) was small, it can be noticed that the strains were resistant to all tested antimicrobial agents, except for colistin, to which 2 out of 6 isolates (67%) were susceptible.

Treatment of CRE infections with CAZ/AVI has been associated with higher rates of clinical success and survival, compared to colistin or aminoglycosides (Shields et al., 2017). Colistin (or polymyxin E) is a mixture of cyclic polypeptide antibiotics with activity against most species in the order *Enterobacterales* (except for *Serratia marcescens* and *Proteus, Providencia, Morganella*, and *Hafnia species*), *Pseudomonas aeruginosa, Acinetobacter baumannii*, and some *Stenotrophomonas maltophilia* strains. While prominent toxicity (both nephrotoxicity and neurotoxicity) has limited the clinical use of colistin, its broad-spectrum activity against carbapenem-resistant pathogens has led to its widespread use for the treatment of infections caused by such pathogens. Clinical observations suggest a less than optimal outcome of patients who received colistin monotherapy for these infections. In addition, colistin is administered as an inactive prodrug-colistin methanesulfonate-which results in a prolonged period of low plasma concentrations of the active drug and theoretically increases the risk for development of antimicrobial resistance. Because of these concerns, the standard practice over the past decade has proposed the use of colistin or polymyxin B in combination with at least one other agent of a different class when its use is warranted (Doi, 2019).

How do we achieve the best outcome for patients with CRE infection? Many studies show that preferred treatment for bacteria with KPC, is the combination of βL-βLICs (Meropenem-vaborbactam, Ceftazidime-avibactam, and Imipenem-relebactam). For CRE producing metalo-beta-lactamases (NDM) preferred treatment is ceftazidime/avibactam in combination with aztreonam, and ceftazidime/avibactam for those CRE which produce OXA-48. Alternative treatment for infections caused by CRE producing KPC or NDM or OXA-48 should include cefiderocol, tigecycline or eravacycline (Kanj, 2024).

Conclusion

Carbapenem-resistant Gram-negative pathogens have become a serious threat to global health due to their difficult-to-treat resistance phenotypes. Treatment options had been limited to agents such as colistin and tigecycline in combination with other antibiotics. Fortunately, several new agents with activity against carbapenem-resistant pathogens, such as novel βL-βLICs represent the key to overcoming this emerging scenario. These newer agents will become important additions to the currently limited treatment options and are expected to improve the outcome of patients affected by carbapenem resistant pathogens.

It is increasingly important to detect carbapenemase production in routine practice and wherever possible, to identify the enzyme family present. This information is often needed in selecting appropriate βL-βLICs agents that have class-specific activity. Thus, rapid diagnostic test should be integrated into antimicrobial stewardship programs to obtain more accurate susceptibility testing results to impact therapeutic choices.

References

Akova, M., Daikos, G.L., Tzouvelekis, L., Carmeli Y., 2012. Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria. Clin. Microbiol. Infect. 18, 439-48. https://doi.org/10.1111/j.1469-0691.2012.03823.x

Ambler, RP., 1980. The structure of beta-lactamases. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 16, 321-31. https://doi.org/10.1098/rstb.1980.0049

Bassetti, M., Carnelutti, A., Peghin, M., 2017. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. Expert Rev. AntiInfect. Ther. 15, 55-65. https://doi.org/10.1080/14787210.2017.1251840

Bassetti, M., Peghin, M., Pecori, D., 2016. The management of multidrug-resistant Enterobacteriaceae. Curr. Opin. Infect. Dis. 29, 583-594. https://doi.org/10.1097/QCO.0000000000000314

Bassetti, M., Peghin, M., 2020. How to manage KPC infections. Ther. Adv. Infect. Dis. 14(7), 2049936120912049. https://doi.org/10.1177/2049936120912049

Bassetti, M., Vena, A., Sepulcri, C., Giacobbe, D.R., Peghin, M., 2020. Treatment of Bloodstream Infections Due to Gram-Negative Bacteria with Difficult-to-Treat Resistance. Antibiotics (Basel) 22(9), 632. https://doi.org/10.3390/antibiotics9090632

Bush, K., Jacoby, G.A., 2010. Updated functional classification of beta-lactamases. Antimicrob. Agents Chemother. 54, 969-76. https://doi.org/10.1128/AAC.01009-09

Dietl, B., Martínez, L.M., Calbo, E., Garau, J., 2020. Update on the role of ceftazidime-avibactam in the management of carbapenemase-producing Enterobacterales. Future Microbiol. 15, 473-484. https://doi.org/10.2217/fmb-2020-0012

Doi, Y., 2019. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. Clin. Infect. Dis. 69, S565-S575. https://doi.org/10.1093/cid/ciz830

Dortet, L., Poirel, L., 2012. Carbapenem resistance in Enterobacteriaceae: here is the storm! Trends Mol. Med 18, 263-72. https://doi.org/10.1016/j.molmed.2012.03.003

Ehmann, D.E., Jahić, H., Ross, P.L., Gu, R.F., Hu, J., Kern, G., Walkup, G.K., Fisher, S.L., 2012. Avibactam is a covalent, reversible, non-β-lactam β-lactamase inhibitor. Proc. Natl. Acad. Sci. USA. 109, 11663-11668. https://doi.org/10.1073/pnas.1205073109

El Chakhtoura, N.G., Saade, E., Iovleva, A., Yasmin, M., Wilson, B., Perez, F., Bonomo, R.A., 2018. Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward 'molecularly targeted' therapy. Expert. Rev. AntiInfect. Ther. 16, 89-110. https://doi.org/10.1080/14787210.2018.1425139

Falcone, M., Paterson, D., 2016. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. J. Antimicrob. Chemother. 71, 2713-22. https://doi.org/10.1093/jac/dkw239Morrill, H.J., Pogue, J.M., Kaye, K.S., LaPlante, K.L., 2015. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect. Dis. 5, 2(2), ofv050. https://doi.org/10.1093/ofid/ofv050

Kanj, S., 2024. CRE treatment: do multinational observational studies help?, Oral presentation at the 33. International Congress of Antimicrobial Chemotherapy, Istanbul November 3-6.

Levasseur, P., Girard, AM., Miossec, C., Pace, J., Coleman, K., 2015. In vitro antibacterial activity of the ceftazidime-avibactam combination against enterobacteriaceae, including strains with well-characterized β-lactamases. Antimicrob. Agents Chemother. 59, 1931-1934. https://doi.org/10.1128/AAC.04218-14

Lohans, C.T., Brem, J., Schofield, C.J., 2017. New Delhi Metallo-β-Lactamase 1 Catalyzes Avibactam and Aztreonam Hydrolysis. Antimicrob. Agents Chemother. 61, e01224-17. https://doi.org/10.1128/AAC.01224-17

Matuschek, E., Brown, D.F., Kahlmeter, G., 2014. Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories. Clin. Microbiol .Infect. 20, O255-266. https://doi.org/10.1111/1469-0691.12373

Nordmann, P., Poirel, L., 2013. Strategies for identification of carbapenemase-producing Enterobacteriaceae. J. Antimicrob. Chemother. 68, 487-9. https://doi.org/10.1093/jac/dks426

Rödel, J., Pfeifer, Y., Fischer, M.A., Edel, B., Stoll, S., Pfister, W., Löffler, B., 2023. Screening of Klebsiella pneumoniae Isolates for Carbapenemase and Hypervirulence-Associated Genes by Combining the Eazyplex® Superbug CRE and hvKp Assays. Antibiotics (Basel) 25(12), 959. https://doi.org/10.3390/antibiotics12060959

Sharma, R., Park, T.E., Moy, S., 2016. Ceftazidime-Avibactam: A Novel Cephalosporin/β-Lactamase Inhibitor Combination for the Treatment of Resistant Gram-negative Organisms. Clin. Ther. 38, 431-44. https://doi.org/10.1016/j.clinthera.2016.01.018

Shi, C., Chen, J., Kang, X., Shen, X., Lao, X., Zheng, H., 2019. Approaches for the discovery of metallo-β-lactamase inhibitors: A review. Chem. Biol. Drug Des. 94, 1427-1440. https://doi.org/10.1111/cbdd.13526

Shields, R.K., Nguyen, M.H., Chen, L., Press, E.G., Potoski, B.A., Marini, R.V., Doi, Y., Kreiswirth, B.N., Clancy, C.J., 2017. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob. Agents Chemother. 25 - 61(8), e00883-17. https://doi.org/10.1128/AAC.00883-17

Stewart, A., Harris, P., Henderson, A., Paterson, D., 2018. Treatment of Infections by OXA-48-Producing Enterobacteriaceae. Antimicrob. Agents Chemother. 24 - 62(11), e01195-18. https://doi.org/10.1128/AAC.01195-18

Van der Zwaluw, K., de Haan, A., Pluister, G.N., Bootsma, H.J., de Neeling, A.J., 2015. The Carbapenem Inactivation Method (CIM), a Simple and Low-Cost Alternative for the Carba NP Test to Assess Phenotypic Carbapenemase Activity in Gram-Negative Rods. PLOS ONE 10(3), e0123690. https://doi.org/10.1371/journal.pone.0123690

Vena, A., Castaldo, N., Bassetti, M., 2019. The role of new β-lactamase inhibitors in gram-negative infections. Curr. Opin. Infect. Dis. 32, 638-646. https://doi.org/10.1097/QCO.0000000000000600

World Health Organization, 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Available at: http://www.who.int/medicines/publications/WHO

World Health Organization. Antimicrobial Resistance 2014. Global Report on Surveillance; World Health Organization: Geneva, Switzerland, p. 232. Available online: https://apps.who.int/iris/handle/10665/112642

Yahav, D., Giske, C.G., Grāmatniece, A., Abodakpi, H., Tam, V.H., Leibovici, L., 2020. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin. Microbiol. Rev. 3, e00115-20. https://doi.org/10.1128/CMR.00115-20

Резиме

Цефтазидим/авибактам како можна опција за третман на инфекции предизвикани од карбапенем-резистентни ентеробактерии

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Клучни зборови: цефтазидим-авибактам, механизми на резистенција, бета-лактамази

Причини за појава на резистенцијата на ентеробактериите кон карбапенеми се: продукција на ензими, ткн. карбапенемази, (KPC, NDM, OXA-48 итн.) или недостаток на порини, во комбинација со продукција на ESBL. Неколку нови агенси со активност кон карбапенем-резистентни микроорганизми се одобрени за клиничка употреба, како што е цефтазидим-авибактам (CAZ-AVI). Целта на оваа студија е да се детектира резистенцијата на *Enterobacterales* кон новата комбинација CAZ-AVI која неодамна беше одобрена за третман на инфекции предизвикани од CRE.

Во сите 65 изолати, механизмите на резистенција кон карбапенемите, т.е. типовите на карбапенемази што тие ги произведуваат, беа јасно дефинирани со примена на фенотипски и генотипски методи. Новата Vitek 2 картичка (N-439) беше употребена за одредување на осетливоста на изолираните ентеробактерии кон антимикробните агенси, вклучително и кон CAZ/AVI. Повеќето изолати продуцираа карбапенемази од типот NDM, а по нив следуваа изолатите со OXA-48. Највисокиот процент на изолати кои продуцираа NDM беа осетливи на колистин (74%), додека сите ентеробактерии, продуценти на OXA-48 (100%), беа осетливи на CAZ/AVI.

Многу студии покажуваат дека за бактериите со KPC, лек од избор е една од комбинациите на βL-βLICs (Ceftazidime-avibactam, Meropenem-vaborbactam, или Imipenem-reebactam). За CRE кои продуцираат метало-бета-лактамази (NDM) лек од избор е цефтазидим/авибактам во комбинација со азтреонам, а за оние CRE со OXA-48, лек од избор е цефтазидим/авибактам. Се очекува ново одобрените βL-βLICs да бидат побезбедни и да се поефикасни против мултирезистентните Грам-негативни бактерии.

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