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A Study on Ceftazidime/Avibactam and Aztreonam Synergy Among Aztreonam-resistant Metallo-β-lactamase Producing *Enterobacterales* in a Tertiary Care Hospital

Bir Üçüncü Basamak Hastanede Aztreonama Dirençli Metallo-β-laktamaz Üreten Enterobakterler Arasında Seftazidim/Avibaktam ve Aztreonam Sinerjisi Üzerine Bir Araştırma

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Abstract

Introduction: Global detection of bacteria harboring metallo-β-lactamase (MBL) genes has increased at an alarming rate. However, there is no concurrent increase in available antibiotics for treatment, which has turned these infections into a public health emergency. Newer antibiotics, such as ceftazidime/avibactam in combination with aztreonam and cefiderocol, constitute alternative options available for clinical use. While aztreonam remains stable against MBL-producing *Enterobacterales*, there is often concurrent production of other enzymes, such as extended-spectrum β-lactamases, AmpC β-lactamases, and serine carbapenemases, which can result in aztreonam resistance. The combination of ceftazidime/avibactam and aztreonam is an appealing alternative, as avibactam can deactivate other β-lactamases, thereby activating aztreonam.

Materials and Methods: The synergistic activity between ceftazidime/avibactam and aztreonam in aztreonam-resistant strains was investigated using the strip stacking method previously described. The findings are presented as numbers and percentages.

Results: Out of the 50 isolates, 43 (86%) demonstrated resistance to aztreonam, five (10%) were classified as intermediate, and two (4%) were sensitive to aztreonam. Aztreonam and ceftazidime/avibactam demonstrated a synergistic effect in all 43 (100%) isolates resistant to aztreonam. Synergistic action between aztreonam and ceftazidime/avibactam restores the activity of aztreonam against MBL. Avibactam, a novel β-lactam inhibitor, extends potent activity against class A β-lactamases and AmpC determinants.

Conclusion: This study demonstrated 100% synergistic activity between aztreonam and ceftazidime/avibactam among MBL-producing Enterobacterales.

Keywords: Carbapenemase, E-strip, MBL, strip stacking

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Öz

Giriş: Metalo-β-laktamaz (MBL) genlerini barındıran bakterilerin endişe verici bir hızla küresel olarak tespiti ve tedavi için antibiyotiklerin sayısının eş zamanlı olarak artırılmaması, bu tür enfeksiyonları halk sağlığı açısından acil bir durum haline getirmiştir. Daha yeni antibiyotiklerden seftazidim/avibaktam + aztreonam ile sefiderokol klinik kullanım için mevcut alternatif antibiyotiklerden bazılarıdır. Aztreonam, MBL üreten Enterobakterlere karşı stabil kalsa da, genellikle aztreonam direncine yol açabilen geniş spektrumlu β-laktamazlar, AmpC β-laktamazlar, serin β-laktamazlar gibi diğer enzimlerin birlikte üretimi söz konusudur. Seftazidim/avibaktam ve aztreonam kombinasyonu çekici bir alternatiftir çünkü avibaktam, aztreonamı aktif hale getirmek için diğer β-laktamazları etkisiz hale getirebilir.
Gereç ve Yöntem: Aztreonama dirençli suşlar arasında seftazidim/avibaktam ve aztreonamın sinerjistik aktivitesi, daha önce açıklanan strip istifleme yöntemiyle araştırıldı. Sonuçlar sayı ve yüzde olarak ifade edildi.
Bulgular: Elli izolattan 43'ünün (%86) aztreonama dirençli olduğu, beşinde (%10) orta derecede direnç olduğu ve ikisinin (%4) aztreonama duyarlı olduğu belirlendi. Aztreonam ile kombinasyon halinde seftazidim/avibaktam, aztreonama dirençli olan 43 (%100) izolatın tümünde sinerjistik etki göstermiştir. minimum inhibitör konsantrasyon değeri <0,016 ila 4 µg/ml arasında değişmektedir. Aztreonam ve seftazidim/avibaktam arasındaki sinerjistik etki, aztreonamın MBL'ye karşı aktivitesini geri kazandırır; çünkü yeni bir β-laktam inhibitörü olan avibaktam, A sınıfı β-laktamazlara ve AmpC belirleyicilerine karşı güçlü aktiviteye sahiptir.
Sonuç: Bu çalışma, MBL üreten Enterobakterler arasında aztreonam ve seftazidim/avibaktam arasında %100 sinerjistik aktivite olduğunu göstermiştir.
Anahtar Kelimeler: Karbapenemaz, E-strip, MBL, strip istifleme

Introduction

Carbapenem-resistant *Enterobacterales* (CRE) pose a growing threat to public health worldwide. They often exhibit resistance to multiple antibiotics, posing a challenge for effective treatment and resulting in elevated mortality and morbidity[1]. The resistance is primarily caused by the production of carbapenemase enzymes. Metallo-β-lactamases (MBL) are carbapenemases that hydrolyze almost all β-lactam antibiotics, except monobactams, such as aztreonam. They are not inhibited by β-lactamase inhibitors, such as clavulanic acid, tazobactam, or sulbactam[2].

The prevalence and types of enzymes produced by CRE vary in different geographical areas. Serine carbapenemases are commoner than MBLs in Western countries, whereas MBLs are the most common cause of carbapenem resistance among *Enterobacterales* in Southeast Asia[3]. In India, New Delhi Metallo-β-lactamase-1 (NDM-1) and Oxacillinases (OXA-48)-like enzymes are the most commonly identified carbapenemases. *Klebsiella pneumoniae* carbapenemases predominate in the United States, Greece, Italy, and Argentina. In Turkey, Malta, North Africa, and the Middle East OXA-48-like enzyme-producing CRE is endemic[4].

Although aztreonam remains stable against MBL-producing *Enterobacterales*, there is often coproduction of other enzymes, such as serine carbapenemases, extended-spectrum β-lactamases (ESBL) and AmpC β-lactamases, which can result in aztreonam resistance. The combination of ceftazidime/avibactam and aztreonam is an appealing alternative because avibactam can deactivate other β-lactamases, thereby activating aztreonam[5,6].

Currently, there is no Clinical and Laboratory Standards Institute (CLSI)-recommended method for assessing the efficacy of the ceftazidime–avibactam/aztreonam combination for routine diagnosis. Various *in vitro* susceptibility testing methods, such as broth disk elution disk stacking, gradient strip stacking, and strip crossing, are being employed[7]. We conducted this study to detect the synergy between ceftazidime/avibactam and aztreonam among aztreonam-resistant MBL-producing *Enterobacterales* isolated from various clinical samples using the strip stacking method.

Materials and Methods

This study was conducted over six months, from October 2021 to March 2022, in the department of microbiology of a 1,200-bed tertiary care hospital in Southern India. The study included 50 clinical isolates of MBL-producing *Enterobacterales*, detected using the CLSI-recommended modified carbapenem inactivation method in conjunction with the EDTA-modified carbapenem inactivation (mCIM/eCIM) method[8]. The data concerning age, gender, nature of the sample, and antibiotic susceptibility pattern tested by the Vitek-2 compact system, except for fosfomycin, which was tested by disk diffusion method, were obtained from the records maintained in the department of microbiology.

Susceptibility Testing of Isolates to Aztreonam

The susceptibility of the isolates to aztreonam was tested using the E-strip method. Aztreonam E strips (0.016-256 µg/ml) were obtained from HiMedia, Mumbai. A lawn culture of the test organism was prepared on Mueller-Hinton agar (MHA) plates. The E strips were placed on the lawn culture, and the MHA

plates were incubated at 37 °C for 18 h. The minimum inhibitory concentration (MIC) was read where the ellipse intersected the MIC scale. MIC values "in-between" twofold dilutions were rounded up to the next twofold dilution before categorization. Isolates with MIC of <4 µg/ml, 8 µg/ml, and ≥16 µg/ml were categorized as sensitive, intermediate, and resistant, respectively, following CLSI guidelines. *Escherichia coli* ATCC 25922 was used as the control[8].

Testing for the Synergistic Activity of Ceftazidime/avibactam and Aztreonam

The synergistic activity of ceftazidime/avibactam and aztreonam among aztreonam-resistant strains was studied by the strip stacking method previously described[9]. Briefly, to assess the synergistic activity, a lawn culture of the test organism was made on an MHA plate. The aztreonam E-strip was placed on the lawn culture, removed after 5 min, and subsequently replaced by the ceftazidime/avibactam E-strip at the same location, with the aztreonam strip positioned on top of the ceftazidime/avibactam E-strip. The MICs were determined by reading the point where the ellipse intersected the MIC scale on the aztreonam strip, positioned on top of the ceftazidime/avibactam strip. If there was a reduction in the MIC value of aztreonam in the presence of avibactam, it was interpreted as synergistic. The MIC breakpoints for aztreonam, as per CLSI guidelines, were utilized to interpret the results[8].

Ethical Clearance

Clearance for the study was obtained from the KS Hegde Medical Academy Institutional Ethics Committee before commencing the study (INST.EC/EC/133/2021-22, date: 22.01.2022). The study was funded through the university's student research fund.

Statistical Analysis

All the generated data were entered into Excel sheets for analysis. The results are expressed as numerical values and percentages.

Results

Among the 50 MBL-producing isolates of *Enterobacterales*, 34 (68%) were isolated from male patients and 16 (32%) from female patients. The age of the patients ranged from 21 to 78 years, with a mean age of 51.62±15.83 years.

The highest percentage of MBL-producing isolates was recovered from urine and wound swabs (36% each), followed by aspirated pus (8%), endotracheal (ET) aspirate (6%), sputum (6%), blood (6%), and biopsy tissue (2%). The sample distribution is illustrated in Figure 1.

Of the 50 MBL-producing *Enterobacterales* included in the study, there were 25 (50%) *Klebsiella pneumoniae*, 23 (46%) *Escherichia coli*, and two (4%) *Enterobacter* spp.

All 50 (100%) isolates were resistant to amoxicillin/clavulanic acid, piperacillin/tazobactam, ceftriaxone, imipenem, meropenem, and ertapenem. Among the 23 *E. coli* isolates, all 13 *E. coli* isolated from urine samples were susceptible to fosfomycin, while only six (46.1%) were susceptible to nitrofurantoin. All *K. pneumoniae* (4) and *Enterobacter* spp. (1) isolated from urine samples were resistant to nitrofurantoin. Table 1 demonstrates the antibiotic susceptibility pattern of the 50 MBL-producing *Enterobacterales* isolates.

Of the 50 isolates, 43 (86%) were resistant to aztreonam, while six (12%) were found to be intermediate, and one (2%) was sensitive to aztreonam. Aztreonam resistance was noted in all 25 (100%) *K. pneumoniae* isolates, two (100%) *Enterobacter* spp., and 16 (69.6%) *E. coli* isolates. Table 2 shows the aztreonam MIC of the isolates.

Ceftazidime/avibactam, in combination with aztreonam, showed a synergistic effect in all 43 (100%) isolates resistant to aztreonam. Table 3 shows the MIC of ceftazidime/avibactam and aztreonam synergy testing. Figure 2 illustrates the ceftazidime/avibactam and aztreonam synergy test using the strip stacking method.

Discussion

The increasing incidence and spread of MBL-producing *Enterobacterales* has posed a serious threat to public health worldwide. Beyond being resistant to carbapenems, these isolates often exhibit high resistance to other β-lactam antibiotics, including penicillins, cephalosporins, and β-lactam/β-lactam inhibitor combinations. Typically, these isolates are multidrug resistant (MDR) or pan-drug-resistant, which are attributed to associated non-β-lactam resistance determinants[10].

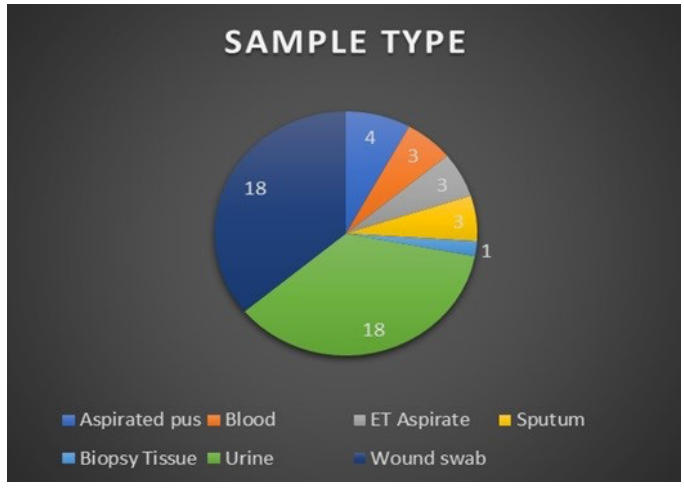

Figure 1. Distribution of different samples

Table 1. Antibiotic susceptibility pattern of the MBL-producing *Enterobacterales* isolates

Antibiotic	*K. pneumoniae* (n=25)		*E. coli* (n=23)		*Enterobacter* spp. (n=2)	
	Sensitive (%)	Resistant (%)	Sensitive (%)	Resistant (%)	Sensitive (%)	Resistant (%)
Amikacin	8 (32)	17 (68)	13 (56.5)	10 (43.5)	0	2 (100)
Amoxicillin/clavulanic acid	0	25 (100)	0	23 (100)	0	2 (100)
Ceftriaxone	0	25 (100)	0	23 (100)	0	2 (100)
Ciprofloxacin	0	25 (100)	1 (4.3)	22 (95.7)	0	2 (100)
Cotrimoxazole	4 (16)	21 (84)	02 (8.7)	21 (91.3)	1 (50)	1 (50)
Ertapenem	0	25 (100)	0	23 (100)	0	2 (100)
Fosfomycin*	Not tested	Not tested	13 (100)	0	Not tested	Not tested
Gentamicin	8 (32)	17 (68)	11 (47.8)	12 (52.2)	0	2 (100)
Imipenem	0	25 (100)	0	23 (100)	0	2 (100)
Meropenem	0	25 (100)	0	23 (100)	0	2 (100)
Nitrofurantoin†	0	4 (100)	06 (46.1)	7 (53.9)	0	1 (100)
Piperacillin/tazobactam	0	25 (100)	0	23 (100)	0	2 (100)

*For *E. coli* from urine samples only (n=13), tested by disc diffusion with oral formulation.

†For isolates from urine samples only.

MBL: Metallo-β-lactamase

Table 2. Aztreonam MIC for MBL-producing *Enterobacterales*

Aztreonam MIC (µg/ml)	*K. pneumoniae* (%)	*E. coli* (%)	*Enterobacter* spp. (%)
>256	13 (52)	11 (47.8)	0
128	0	0	0
64	6 (24)	0	2 (100)
32	4 (16)	2 (8.7)	0
16	2 (8)	3 (13.1)	0
8	0	6 (26.1)	0
2	0	1 (4.3)	0
Total	**25**	**23**	**2**

MBL: Metallo-β-lactamase, MIC: Minimum inhibitory concentration

Table 3. Aztreonam MIC on ceftazidime/avibactam and aztreonam strip stacking

Aztreonam MIC (µg/ml)	*K. pneumoniae* (%)	*E. coli* (%)	*Enterobacter* spp. (%)
<0.016	0	3 (18.8)	0
0.032	0	0	0
0.064	0	1 (6.2)	0
0.128	0	0	0
0.25	4 (16)	0	2 (100)
0.5	18 (72)	1 (6.2)	0
1	0	2 (12.6)	0
2	3 (12)	8 (50)	00
4	0	1 (6.2)	0
Total	**25**	**16**	**2**

MIC: Minimum inhibitory concentration

Figure 2. Ceftazidime/avibactam and aztreonam synergy test by strip stacking method

All 50 (100%) isolates in this study demonstrated resistance to amoxicillin/clavulanic acid, piperacillin/tazobactam, ceftriaxone, imipenem, meropenem, and ertapenem. The results of our study align with those of a study conducted at a tertiary care center in North India[11]. Another study from India revealed 100% resistance to all third-generation cephalosporins, imipenem, ertapenem, and amoxicillin/clavulanate in MBL-producing *K. pneumoniae*. Approximately 70% of *K. pneumoniae* isolates in this study demonstrated resistance to aminoglycosides, amikacin, and gentamicin. The percentage is slightly lower than the findings of a study from Jaipur, where 83% and 88% of the isolates were reported to be resistant to gentamicin and amikacin, respectively[12].

Aztreonam, approved by the FDA in 1986, is a monobactam antibiotic. It was used to treat various infections, including urinary tract infections, pelvic infections, and intra-abdominal infections caused by aerobic Gram-negative bacilli. With the emergence and spread of ESBLs and AmpC β-lactamases, the use of aztreonam has become limited. It is the only β-lactam antibiotic which is not destroyed by MBLs. However, the coproduction of other β-lactamases, such as ESBL, AmpC, and other serine carbapenemases with MBLs, can result in aztreonam resistance among MBL-producing isolates. In this study, 86% of the tested *Enterobacterales* were found to have aztreonam MIC in the resistant range. In a study evaluating the susceptibility of MBL producing MDR *Enterobacterales* and *Pseudomonas* to aztreonam and newer β- lactamase inhibitor combinations, the authors reported 17% of the MBL producing *Enterobacterales* were susceptible to aztreonam[13]. A study from Spain reported nearly 18% susceptibility to aztreonam among the 55 *Enterobacterales* isolates included in their study[14]. A study from North India revealed 100% resistance to aztreonam among the 60 MBL-producing Gram-negative bacilli included in the study[11].

Synergistic action between aztreonam and ceftazidime/avibactam restores the activity of aztreonam against MBL. Avibactam, a novel β-lactam inhibitor, exhibits potent activity against class A β-lactamases and AmpC determinants[15]. This study demonstrated 100% synergistic activity between aztreonam and ceftazidime/avibactam combination, with the MIC of aztreonam decreasing to the sensitive range in the presence of avibactam. The authors of a study conducted in North India also observed 100% susceptibility to the combination. In their study, the authors compared three different methods for the susceptibility testing of ceftazidime-avibactam along with aztreonam, namely the diffusion method, E-test agar synergy, and E-test fixed ratio method, and found 100% concordance among them[11]. Similar results were reported by several other studies from different parts of the world[16-18]. These results suggest that the combination of ceftazidime–avibactam and aztreonam is an alternative for treating infections caused by MDR carbapenemase-producing *Enterobacterales*.

Resistance to aztreonam/avibactam has been reported in Germany, not only in NDM carbapenemase-producing *E. coli* but also among OXA-48 producers, even before the combination became clinically available[19]. This serves as a reminder to use the available antibiotics judiciously.

Study Limitations

The primary limitation of this study is the small sample size. The study was performed on 50 isolates; therefore, the findings of this study may not be generalizable. Furthermore, the study was conducted on isolates identified as MBL producers using the modified carbapenem inactivation method in conjunction with the EDTA-modified carbapenem inactivation method, which is a phenotypic method. No genotypic methods were employed to identify MBLs or investigate the coproduction of serine carbapenemases, ESBLs, or AmpC β-lactamases. Additionally, there is no available data regarding the clinical utility of the combination in our setup.

Conclusion

This study demonstrated 100% synergistic activity between aztreonam and ceftazidime/avibactam among MBL-producing *Enterobacterales*. The combination of aztreonam and

ceftazidime/avibactam presents itself as a viable treatment option for serious infections caused by MBL-producing *Enterobacterales*.

Ethics

Ethics Committee Approval: Clearance for the study was obtained from the KS Hegde Medical Academy Institutional Ethics Committee before commencing the study (INST.EC/EC/133/2021-22, date: 22.01.2022).

Informed Consent: Patient consent is not required.

Authorship Contributions

Concept: A.P.KB., Design: A.P.KB., Data Collection or Processing: A.D'S., R.S., A.P.KB., Analysis or Interpretation: A.D'S., R.S., A.P.KB., Literature Search: A.D'S., R.S., A.P.KB., Writing: A.D'S., R.S., A.P.KB.

Conflict of Interest: No conflict of interest was declared by the authors.

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