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Microbiology Section

Susceptibility Profile of Beta-lactam/ Beta-lactamase Inhibitor Combinations against Multidrug Resistant Gram-negative and Positive Bacteria at a Tertiary Care Centre in Northern India: A Retrospective Study

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ABSTRACT

Introduction: Currently, Antimicrobial Resistance (AMR) is a major global public health concern. Infections caused by resistant microorganisms are more difficult to treat in humans and animals, leading to longer illnesses, higher mortality rates, and increased medical expenses.

Aim: To determine the susceptibility profile of five beta-lactam/beta-lactamase inhibitor combinations for gram-negative and gram-positive bacteria.

Materials and Methods: This was a retrospective study conducted in the Department of Microbiology at SGPGIMS, Lucknow, Uttar Pradesh, India, from January 2022 to January 2023. The analysis evaluated the susceptibility of Ceftazidime-Avibactam (CZA), Tazobactam-Piperacillin (TZP), Ticarcillin-Clavulanic Acid (TCC), Ampicillin-Sulbactam (SAM), and Cefoperazone-Sulbactam (SCF). These combinations were used for gram-negative and gram-positive bacteria isolated from various specimens. A total of 1,648 samples were tested for these combinations. The isolates were identified using conventional methods and Matrix-Assisted Laser Desorption/ Ionisation Time-of-Flight (MALDI-TOF). Antibiotic Susceptibility Testing (AST) was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar (MHA).

Results: Out of the 1,648 samples (756 urine, 382 pus, 322 blood, and 188 sputum), the beta-lactam/beta-lactamase inhibitor combinations were tested. The most susceptible combination found in this study was CZA (76%), followed by TZP (60.7%), TCC (50%), SAM (38.2%), and SCF (31%).

Conclusion: CZA demonstrated better susceptibility compared to other beta-lactam/beta-lactamase inhibitor combinations. Recently discovered beta-lactam/beta-lactamase inhibitor combinations can be utilised as carbapenem-sparing agents for treating ESBL-producing Enterobacteriaceae (ESBL-PE), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

Keywords: Antimicrobial susceptibility test, Gram negative bacteria, Multidrug resistant, Susceptibility

INTRODUCTION

Globally, AMR presents a serious public health concern, and its growth rate is alarming [1]. Factors contributing to AMR include the misuse and overuse of antibiotics in both humans and animals, poor infection control practices in healthcare settings, and the increased mobility of people worldwide, which has facilitated the spread of Multidrug-Resistant (MDR) pathogens [2]. Infections caused by drug-resistant Gram-Negative Bacilli (GNB) result in significant morbidity and mortality [3]. Among the GNB, Enterobacteriaceae *(Escherichia coli, Klebsiella pneumoniae)* and non fermenters *(Pseudomonas aeruginosa, Acinetobacter baumannii)* are commonly encountered MDR pathogens [1].

Beta-lactams (BL) are the most frequently used bactericidal drugs for treating infections caused by both gram-positive and gram-negative microorganisms. They work by binding to Penicillin-Binding Proteins (PBPs) and inhibiting cell wall synthesis, leading to cell death [4]. Resistance to BL antibiotics in bacteria may result from modifications in the target site, activation of efflux pumps, or the production of beta-lactam enzymes [5]. In gram-negative bacteria, the predominant mechanism of beta-lactam resistance is the production of enzymes that hydrolyse the amide bond of the β-lactam ring, inactivating the antibiotic [6].

Beta-lactamases are classified into four groups based on their tertiary structures according to Ambler's classification (classes A, B, C, and D) [7]. Classes A, C, and D contain a serine residue for catalytic activity, while class B Metallo-Beta-Lactamases (MBL) utilise zinc for their activity [6]. An increasing number of beta-lactamases have been identified that can inactivate beta-lactam antibiotics. These enzymes are diverse, numerous, and spreading rapidly across the globe [1]. The most challenging and difficult-to-treat GNB include Extended-Spectrum Beta-Lactamase producing Enterobacteriaceae (ESBL-PE), Carbapenem-Resistant Enterobacteriaceae (CRE) that produce KPC or OXA-48-like carbapenemases, *Pseudomonas aeruginosa*, and *Acinetobacter* species [8].

The ESBL rates reported are approximately 70% in *E. coli* and *K. pneumoniae*, with significant variability in carbapenem resistance rates among organisms. *E. coli*, *K. pneumoniae, P. aeruginosa*, and *A. baumannii* exhibit resistance rates of 10%, 40%, 25%, and 70%, respectively. This wide variation in carbapenem resistance complicates the selection of empirical therapy [9].

Broad-spectrum Beta-Lactamase Inhibitors (BLI) have been developed to preserve the efficacy of beta-lactam antibiotics against pathogens capable of producing beta-lactamases (BL) [4]. Most BLIs do not have antibacterial activity on their own; hence, they are

used in combination with beta-lactam antibiotics and are referred to as β-lactam combination drugs by the Clinical Laboratory Standards Institute (CLSI) [6].

The first BLIs approved for use were clavulanic acid, sulbactam, and tazobactam (such as amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam). Structurally, they have a beta-lactam ring and act through a competitive inhibition mechanism. Their spectrum of activity is limited to class A beta-lactamases (e.g., TEM-1, SHV-1) and extended-spectrum beta-lactamases (ESBLs, e.g., CTX-M-15), as well as some class C and D beta-lactamases (e.g., AmpC and OXA-1) [10].

Most of the currently available BL inhibitors are effective against Class A beta-lactamases but not against MBL and bacteria that produce blaOXA-48 [1]. Research in antibiotic development continues to focus on finding and developing effective inhibitors for various beta-lactamases, including MBL and blaOXA-48-like producers, to overcome antibiotic resistance.

Based on their chemical properties, BLIs are represented in approved and developing beta-lactam/beta-lactamase inhibitor combinations, including sulfones and oxapenems. Non-beta-lactam-based BLIs derived from boronic acid (e.g., vaborbactam and taniborbactam) and diazabicyclooctane (DBO) BLIs (e.g., avibactam, relebactam, zidebactam, and durlobactam) are also under investigation [6].

Beta-lactam/BLI combinations approved by the Food and Drug Administration (FDA) for clinical use include ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, CZA, Ceftolozane-Tazobactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam. Many BL/BLI combinations are currently at different stages of development and approval [11].

Nowadays, various BL/BLI combinations are approved to treat infections caused by MDR bacteria. These combinations are available as carbapenem-sparing regimens. This was the first study in our region to determine the susceptibility profile of different BL/BLI combinations used against multidrug-resistant bacteria. The aim of this study was to evaluate the susceptibility profile of different BL/BLI combinations used for infections caused by gram-positive and GNB in a hospital setting, and to compare the susceptibility profiles of microorganisms isolated from different specimens.

MATERIALS AND METHODS

This was a retrospective study conducted in the Department of Microbiology at SGPGIMS, Lucknow, Uttar Pradesh, India. The study duration was one year, from January 2022 to January 2023. Data were collected, and samples were processed simultaneously during the study period. This study was approved by the Institutional Ethics Committee, with the ethical number PGI/BE/274/2020.

Inclusion criteria: During the study period, all gram-negative and gram-positive microorganisms isolated from different samples, such as blood, respiratory secretions, urine, pus, body fluids, and wound swabs, were included in the study.

Exclusion criteria: Samples with mixed growth were excluded from the study.

Study Procedure

For sample processing, HiChrome® media was used for urine samples, and blood agar (5% sheep blood) and MacConkey agar were used for other samples. Identification of isolates was performed using routine biochemical tests and MALDI-TOF. AST was conducted by the Kirby-Bauer disc diffusion method on MHA. This study evaluated the susceptibility of five BL/BLI combinations: CZA, TZP, TCC, SAM, and SCF. MHA plates were incubated at 35°C in an O_2 incubator for overnight incubation [Table/Fig-1]. AST results were interpreted by measuring the zone of inhibition manually using the CLSI breakpoints [12].

[Table/Fig-1]: Muller Hinton Agar (MHA) showing Antimicrobial susceptibility test by Kirby Bauer disc diffusion.

STATISTICAL ANALYSIS

Categorical variables are expressed as a number (%).

RESULTS

Analysis of Beta-Lactam/Beta-Lactamase Inhibitor (BL-BLI) Combinations

The five BL-BLI combinations (CZA, TZP, TCC, SAM, SCF) were tested in a total of 1,648 positive samples. Out of these, 756 samples were from urine, 382 from pus, 322 from blood, and 188 from sputum. In this study, the most susceptible combination was CZA, showing susceptibility in 56 isolates (76%), followed by TZP with 490 isolates (60.7%), TCC with 55 isolates (50%), SAM with 130 isolates (38.2%), and SCF with 99 isolates (31%).

Ceftazidime-avibactam (CZA)

This combination was tested in a total of 74 isolates from various samples, with 56 isolates showing susceptibility. In urine samples, *Pseudomonas* spp. exhibited a high sensitivity of 87.5%, followed by *E. coli*. In pus samples, *Pseudomonas* spp. showed 80% sensitivity, followed by *E. coli* and *Enterococcus* spp. In blood samples, *Ralstonia* and *Morganella* species demonstrated 100% sensitivity, followed by *Pseudomonas* spp. [Table/Fig-2].

Sample	Organism name	Total isolates N=74	Sensitive N=56	Resistant N=18
Urine	*Pseudomonas* spp.	8	7 (87.5%)	1
	E. coli	7	5 (71%)	2
Pus	*Pseudomonas* spp.	10	8 (80%)	2
	Enterococcus species	3	1 (33%)	2
	E. coli	7	5 (71%)	2
Sputum	*E. coli*	14	11 (78.5%)	3
Blood	*Serratia* spp.	2	1 (50%)	1
	Morganella spp.	3	3 (100%)	0
	Pseudomonas spp.	9	7 (78%)	2
	Ralstonia spp.	1	1 (100%)	0
	Klebsiella pneumoniae	10	7 (70%)	3

[Table/Fig-2]: Sensitivity pattern of CZA for different microorganisms isolated from different sample.
CZA: Ceftazidime avibactam

Ticarcillin-clavulanic acid (TCC)

A total of 110 isolates from different samples were tested for the TCC combination, with 55 isolates being susceptible. In urine samples, *Klebsiella pneumoniae* showed 45% susceptibility, followed by Pseudomonas spp. From pus samples, *Klebsiella pneumoniae*

and *Pseudomonas* spp. each demonstrated 20% sensitivity. In blood samples, *Stenotrophomonas maltophilia* had the highest susceptibility at 94%, followed by *Klebsiella pneumoniae* (37%). In sputum samples, *Pseudomonas* spp. showed 50% susceptibility, followed by *Klebsiella pneumoniae* [Table/Fig-3].

Sample	Organism name	Total isolates N=110	Sensitive N=55 (%)	Resistant N=55
Urine	*Pseudomonas* spp.	10	2 (20%)	8
	Klebsiella pneumoniae	22	10 (45%)	12
Pus	*Pseudomonas* spp.	5	1 (20%)	4
	Klebsiella pneumoniae	15	3 (20%)	12
Blood	*Stenotrophomonas maltopia*	33	31 (94%)	2
	Pseudomonas spp.	5	1 (20%)	4
	Klebsiella pneumoniae	8	3 (37%)	5
	Burkhulderia spp.	5	1 (20%)	4
Sputum	*Pseudomonas* spp.	2	1 (50%)	1
	Klebsiella pneumoniae	5	2 (40%)	3

[Table/Fig-3]: Sensitivity pattern of TCC for different microorganisms isolated from different samples.
TCC: Ticarcillin clavulanic acid

Piperacillin-Tazobactam (TZP)

TZP was against all pathogenic microorganisms isolated from urine samples and specifically for *Pseudomonas* spp. *i*solated from pus, blood, and sputum samples. A total of 807 isolates were tested for this combination, with 490 isolates showing susceptibility. In urine samples, *E. coli* had the highest susceptibility at 77%, followed by *Pseudomonas* spp. (51%) and *Klebsiella pneumoniae* (48%). For *Pseudomonas* spp. isolated from pus, blood, and sputum samples, the susceptibilities were 45%, 63%, and 39%, respectively [Table/Fig-4].

Sample	Organisms name	Total isolates N=807	Sensitive N=490 (%)	Resistant N=317
Urine	*E.coli*	383	295 (77%)	88
	Klebsiella pneumoniae	141	68 (48%)	73
	Pseudomonas spp.	85	44 (51%)	41
Pus	*Pseudomonas* spp.	108	47 (45%)	61
Blood	*Chryseobacter* spp.	6	1 (16%)	5
	Pseudomonas spp.	22	14 (63%)	8
Sputum	*Pseudomonas* spp.	62	21 (39%)	41

[Table/Fig-4]: Sensitivity pattern of TZP for different microorganisms isolated from different samples.
TZP: Tazobactam piperacillin

Ampicillin-Sulbactam (SAM)

This combination was used for gram-positive microorganisms isolated from various samples. *Staphylococcus* spp. 35.2% susceptibility, while *Streptococcus* spp. demonstrated 50% susceptibility [Table/Fig-5].

Sample	Organisms name	Total isolates N=340	Sensitive N=130 (%)	Resistant N=210
Urine	*Staphylococcus* spp.	40	14 (47%)	26
Pus	*Staphylococcus* spp.	100	50 (49%)	50
	Enterococcus spp.	40	14 (35%)	26
Blood	*Staphylococcus* spp.	132	32 (23%)	100
	Non-haemolytic streptococci.	28	20 (67%)	8

[Table/Fig-5]: Sensitivity pattern of SAM for gram-positive microorganisms isolated from different samples.
SAM: Ampicillin sulbactam

Cefoperazone-sulbactam (SCF)

Of the total 312 isolates tested, 99 were susceptible to the SCF combination. In urine samples, *Pseudomonas* spp. showed 41% susceptibility. For blood and pus samples, *Pseudomonas* spp. exhibited 67% susceptibility, followed by *Acinetobacter baumannii* (50%) and *Klebsiella pneumoniae* (25%). In sputum samples, *Pseudomonas* spp. showed 28% susceptibility [Table/Fig-6].

Sample	Organisms name	Total isolates N=312	Sensitive N=99 (%)	Resistant N=213
Urine	*Pseudomonas* spp.	68	29 (41%)	39
Pus	*Klebsiella pneumoniae*	20	5 (25%)	15
	Pseudomonas spp.	15	10 (67%)	5
	E.coli	56	11 (19%)	45
Blood	*Klebsiella pneumoniae*	20	5 (25%)	15
	Pseudomonas spp.	15	10 (67%)	5
	Acinetobacter baumannii	16	8 (50%)	8
Sputum	*Acinetobacter baumannii*	26	5 (16%)	21
	Pseudomonas spp.	29	8 (28%)	21
	Klebsiella pneumoniae	47	8 (21%)	39

[Table/Fig-6]: Sensitivity pattern of SCF for different microorganisms isolated from different samples.
SCF: Cefoperazone sulbactam

DISCUSSION

As the burden of AMR increases in Indian settings, empirical therapy becomes highly challenging due to resistance against third-generation cephalosporins. In this context, the choice between BL-BLI and carbapenem therapies varies [1]. Carbapenem remains the last therapeutic option for treating MDR pathogens. Recently, it has become a serious concern that Enterobacteriaceae exhibit high levels of resistance to carbapenem.

Nosocomial infections caused by carbapenem-resistant pathogens are associated with high morbidity and mortality in critically ill patients [13]. Therefore, there is an urgent need to develop antimicrobial agents that can effectively target carbapenem-resistant pathogens.

BL-BLI combinations serve as alternative therapies to treat less severe infections, while carbapenems can be reserved for more severe cases. These combinations are effective against ESBL-producing organisms, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, helping to preserve the efficacy of higher-level antibiotics such as colistin, tigecycline, and carbapenem. They can also be utilised as carbapenem-sparing agents for these infections [1].

Ceftazidime-Avibactam (CZA) and Other Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Avibactam is a novel broad-spectrum beta-lactamase (BL) inhibitor that has minimal antibacterial activity on its own. When added to ceftazidime, it extends the spectrum of activity to include most Enterobacteriaceae, including those that produce AmpC beta-lactamases, ESBLs, and some OXA-type carbapenemases.

Based on a surveillance study, ceftazidime/avibactam exhibits potent antimicrobial activity against ESBLs, AmpC, and carbapenemases (e.g., bla_{KPC}, bla_{GES}, and $bla_{OXA-48-like}$) in Enterobacteriaceae but is not active against MBL [14]. In a recent in vitro-study, CZA showed high activity against the carbapenem-resistant epidemic clone ST11 in *Klebsiella pneumoniae* [15]. Furthermore, in the absence of ESBL co-production, CZA demonstrated potent in-vitro activity against OXA-48 producers [16]. CZA remains effective against hyperproducing AmpC (chromosomal) *Pseudomonas aeruginosa* with altered OprD or drug efflux mechanisms [14].

Among the tested BL-BLI combinations, CZA (76%) was the most susceptible combination for multidrug-resistant microorganisms. It showed 80-90% susceptibility to *Pseudomonas* spp. isolated from different samples. *Ralstonia* and *Morganella* species isolated from blood samples exhibited 100% susceptibility. This combination has good susceptibility for non fermenters. *Yahav D et al.,* reported

that CZA inhibited 99.9% of all Enterobacteriaceae isolates and was highly active against MDR isolates, with 99.2% susceptibility, extensively drug-resistant (XDR) isolates with 97.8% susceptibility, and carbapenem-resistant Enterobacteriaceae (CRE) isolates with 97.5% susceptibility [4]. *Veeraraghavan B et al.,* demonstrated that CZA is a more potent agent against *Pseudomonas* spp. [1]. According to this study, the CZA combination could be an effective alternative therapy for treating bacteremia caused by *Morganella* and *Ralstonia* spp.

TTC showed varied susceptibility (40-63%) for *Pseudomonas* spp. isolated from different samples. *E. coli* and *Klebsiella pneumoniae* isolated from urine samples showed 77% and 48% susceptibility, respectively. Ghafur A et al., from South India reported an overall sensitivity of TZP for gram-negative bacteria at 60.5% and 77.8% for *Pseudomonas* spp. This combination is active against about half of the *Enterobacteriaceae* [17].

The majority of Enterobacteriaceae are resistant to ticarcillin; however, its activity is enhanced by adding beta-lactamase inhibitors like clavulanic acid. In this study, TCC showed varied susceptibility for *Pseudomonas* spp.: 50% from sputum samples, 20% from blood, and 20% from pus samples. Very limited data are available on this combination; one study from Turkey showed 64% susceptibility to *Pseudomonas* spp., attributed to variations in resistance genes across different geographic regions [18]. In this study, *Stenotrophomonas maltophilia* showed maximum susceptibility at 94%, isolated from blood. Cho et al., reported 40.7% susceptibility [19]. While cotrimoxazole is the drug of choice for *Stenotrophomonas maltophilia*, this combination can be considered as an alternative therapy in our region due to the limited data available on its efficacy.

Cefoperazone and Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Cefoperazone is a third-generation cephalosporin with activity against gram-positive and gram-negative microorganisms, including Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. It is inactivated by beta-lactamases (BL), so BL inhibitors like sulbactam are added to enhance its activity.

Sader HS et al. reported that this combination showed a susceptibility rate of 91.5% (82-94.4%) in *Enterobacterales. Pseudomonas aeruginosa* and *Acinetobacter* spp. exhibited susceptibility rates of 77.8% and 53.2%, respectively [11]. In this study, antimicrobial susceptibility profiles varied widely across geographic regions. *Pseudomonas* spp. showed 67% susceptibility when isolated from pus and blood, and 41% when isolated from urine. *Acinetobacter* spp. isolated from blood and sputum samples showed 50% and 16% susceptibility, similar to the findings reported by Sader HS et al., [11].

Ampicillin and Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Ampicillin belongs to a group of penicillin antibiotics, and its broad spectrum is enhanced by adding BL inhibitors like sulbactam. It has activity against gram-positive, gram-negative, and anaerobic bacteria. This study showed a susceptibility rate of 35.2% for *Staphylococcus* spp. and 50% for *Streptococcus* spp. Combinations were only tested for gram-positive bacteria; for gram-negative bacteria, other combinations such as TZP were used. Sader HS et al., reported a susceptibility rate of 39.5% for this combination in Enterobacterales [11]. Sultana Q et al., reported a susceptibility rate of 66.2% for gram-positive bacteria and 39.1% for gram-negative bacteria with SAM [20].

Reasons for Lower Susceptibility

Several factors contribute to the lower susceptibility of BL-BLI combinations:

1. Co-production of AmpC can mask ESBL effectiveness.
2. In severe infections with high bacterial populations, the inoculum effect may overwhelm the inhibitor's activity.
3. The presence of resistant mechanisms, such as TEM-IRT inhibitors [1].

New Recognitions and Recommendations

The newer BL-BLI combinations approved by the FDA are effective against Class A and C beta-lactamase-producing organisms but are not as effective against Class B and D (e.g., blaNDM, blaOXA-48), which are more prevalent in some regions [1]. It is essential to determine the Minimum Inhibitory Concentration (MIC) and identify the classes of beta-lactamases produced by the infecting organism. This strategy helps initiate targeted therapy, thereby minimising the inappropriate use of available antimicrobials. Such an approach significantly aids in our collective effort to combat drug-resistant infections.

Limitation(s)

Molecular determination of classes of beta-lactamases (ESBLs, AmpCs, carbapenemases) and non enzymatic mechanisms (porin and efflux) was not done, which hinders the initiation of targeted antimicrobial therapy.

CONCLUSION(S)

Recently discovered BL-BLI combinations represent new treatment options for MDR pathogens. These carbapenem-sparing agents can be used to treat ESBL-*producing* Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii*. According to this study, CZA showed the highest susceptibility rate of 76% for all microorganisms isolated from various specimens, including urine, pus, blood, and respiratory samples. TZP had a susceptibility rate of 60.7%. Based on these findings, these combinations can serve as carbapenem-sparing regimens for treating less severe infections. In the future, we plan to work on the molecular characterisation of beta-lactamases.

REFERENCES

[1] Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Anandan S, Ramasubramanian V, Swaminathan S, et al. Newer β-Lactam/β-Lactamase inhibitor for multidrug-resistant gram-negative infections: Challenges, implications and surveillance strategy for India. Indian J Med Microbiol. 2018;36(3):334-43.

[2] Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): A randomised, pathogen-directed, phase 3 study. Lancet Infect Dis. 2016;16(6):661-73.

[3] Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. J Infect Dis. 2008;197(8):1079-81.

[4] Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase inhibitor combinations. Clin Microbiol Rev. 2020;34(1): Doi: 10.1128/cmr.00115-20.

[5] Khalifa SM, El-Aziz AMA, Hassan R, Abdelmegeed ES. β-lactam resistance associated with β-lactamase production and porin alteration in clinical isolates of *E. coli* and *K. pneumoniae.* PLOS ONE. 2021;16(5):e0251594.

[6] Papp-Wallace KM. The latest advances in β-lactam/β-lactamase inhibitor combinations for the treatment of Gram-negative bacterial infections. Expert Opin Pharmacother. 2019;20(17):2169-84.

[7] Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, et al. Carbapenemase-producing organisms: A global scourge. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018;66(8):1290-97.

[8] Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen VHA, Takebayashi Y, et al. β-Lactamases and β-Lactamase inhibitors in the 21st century. J Mol Biol. 2019;431(18):3472-500.

[9] Gandra S, Singh SK, Jinka DR, Kanithi R, Chikkappa AK, Sharma A, et al. Point prevalence surveys of antimicrobial use among hospitalized children in six hospitals in India in 2016. Antibiotics. 2017;6(3):19.

[10] Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. Clin Microbiol Rev. 2010;23(1):160-201.

[11] Sader HS, Carvalhaes CG, Streit JM, Castanheira M, Flamm RK. Antimicrobial activity of cefoperazone-sulbactam tested against Gram-Negative organisms from Europe, Asia-Pacific, and Latin America. Int J Infect Dis 2020;91:32-37.

[12] CLSI. Clinical and Laboratory Standards Institute (CLSI) report 2020. Available from: https://www.nih.org.pk/wp-content/uploads/2021/02/CLSI-2020.pdf.

[13] Palombo M, Bovo F, Amadesi S, Gaibani P. Synergistic activity of Cefiderocol in combination with Piperacillin-Tazobactam, Fosfomycin, Ampicillin-sulbactam, Imipenem-Relebactam and Ceftazidime-avibactam against Carbapenem-resistant gram-negative bacteria. Antibiotics. 2023;12(5):858.
[14] Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF. In-vitro activity of ceftazidime/avibactam against isolates of *Pseudomonas aeruginosa* collected in European countries: INFORM global surveillance 2012-15. J Antimicrob Chemother. 2018;73(10):2777-81.
[15] Yu F, Lv J, Niu S, Du H, Tang YW, Bonomo RA, et al. In vitro activity of ceftazidime-avibactam against carbapenem-resistant and hypervirulent *Klebsiella pneumoniae* isolates. Antimicrob Agents Chemother. 2018;62(8):e01031-18.
[16] Stewart A, Harris P, Henderson A, Paterson D. Treatment of infections by OXA-48-producing enterobacteriaceae. Antimicrob Agents Chemother. 2018;62(11):e01195-18.
[17] Ghafur A, Pushparaju R, Rajkumar K, Sureshkumar D. Sensitivity pattern of Gram negative bacteria to the new β-lactam/ β-lactamase inhibitor combination: Cefepime/tazobactam. J Microbiol Infect Dis. 2012;2(01):05-08.
[18] Direke S, Uzunoglu E, Uzalp C, Findik E, Tontak S, Ahmadli C. Determination of *piperacillin/tazobactam* and ticarcillin/clavulanate susceptibilities in Pseudomonas aeruginosa isolates in hospitalised patients by E-test gradient method and comparison of results with disk diffusion tests . Clin Microbiol. 2017;6(1):1000273. | Semantic Scholar. Available from: https://www.semanticscholar.org/paper/Determination-of-Piperacillin-Tazobactam-and-in-in-Direkel-Uzuno%C4%9Flu/b3e174eec2cb6fde55c5fef0fa21195a6060bfc5.
[19] Cho SY, Lee DG, Choi SM, Park C, Chun HS, Park YJ, et al. *Stenotrophomonas maltophilia* bloodstream infection in patients with hematologic malignancies: A retrospective study and in vitro activities of antimicrobial combinations. BMC Infect Dis. 2015;15:69.
[20] Sultana Q, Ansari H, Ansari MAW. Bacteriological profile and antimicrobial susceptibility patterns of organisms responsible for blood stream infections. Indian J Microbiol Res. 2021;3(2):113-17.

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