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CEFTAZIDIME- AVIBACTAM A CHOICE OF ANTIBIOTIC AND COST OF TREATMENT IN ENTEROBACTERALES PRODUCING ESBL AND MBL IN BLOOD CULTURE ISOLATES

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ABSTRACT **BACKGROUND:** Enterobacterales are common pathogens responsible for community and hospital associated infections. Of late they have developed resistance to most of the antibiotics , with the need to use Reserve group of antibiotics. These Reserved antibiotics increase the cost burden on patients used to treat such infections.

OBJECTIVE :

- To determine the drug susceptibility of
- ESBL isolates for piperacillin- tazobactam, imipenem, ceftazidime-avibactam
- MBL isolates for tegicycline, colistin, ceftazidime- avibactam +aztreonam
- To determine the total cost of antibiotic therapy

MATERIALS AND METHODS : Total 30 ESBL and MBL Enterobacteriaceae isolates from blood culture were taken, 15 were ESBL isolates and 14 MBL isolates and one ESBL + MBL. The isolates were tested for the Access and Reserve group of antibiotics. Information regarding the drug's dosage, duration and cost was obtained and compared. **RESULTS:** ESBL producing enterobacterales showed 56% susceptibility to Imipenem and Ceftazidime-avibactam with a therapeutic cost range of Rs.30,000 to 1 lakh and Rs.50,000 to 1.6 lakhs respectively. MBL producing enterobacterales were 100% sensitive to ceftazidime- avibactam + aztreonam and colistin with their cost ranging from Rs. 42,000 to 1.5 lakhs and Rs.73,000 to 2.4 lakhs respectively. **CONCLUSION:** There is a need to carefully choose the antibiotic in treatment of the patient, keepin in mind the patient's age, co-morbidites, antibiotic susceptibility report and socio-economic status.

KEYWORDS :

INTRODUCTION:

Antimicrobial resistance (AMR) is a serious global public health threat, which makes infections difficult or even impossible to treat. Resistant bacteria can cause severe illnesses, prolonged hospital stays, and increased medical costs. Currently, medications account for a significant portion (72%) of out-of-pocket healthcare expenses for many families.[1,2]

Research conducted in India reveals that a significant portion of Enterobacterales bacteria are capable of producing beta-lactamases. This alarming trend has necessitated the increased use of Access group (antibiotics that are first or second choice and have low potential for resistance) of drugs like carbapenems. The overuse of carbapenems has inadvertently led to the development of carbapenem-resistant Enterobacteriaceae, significantly limiting our therapeutic options.[3] To address this growing challenge of multi-drug resistant organisms (MDROs), it is imperative to employ antibiotics from the Reserved group (antibiotics that should only be used to treat MDROs) , such as polymyxins, tigecycline, and combination therapies.

Ceftazidime-avibactam is a combination drug that comprises a cephalosporin antibiotic and a novel non-beta-lactam beta-lactamase inhibitor (BL-BLI). This drug is effective against various bacteria, including Enterobacteriaceae and Pseudomonas aeruginosa, which produce certain enzymes like class A (ESBLs and KPCs) and class C (AmpCs) beta-lactamases. It also works against some Enterobacteriaceae producing class D (OXAs) beta-lactamases. However, it is less effective against class B carbapenemases and anaerobic bacteria compared to other BL-BLI combinations.[4] Combining ceftazidime-avibactam with aztreonam offers a potential treatment option for infections caused by bacteria producing MBL enzymes. However, it's important to note that this combination therapy is primarily effective against MBL-producing Enterobacteriaceae. Ceftazidime has no effect in this triple combination because it is easily hydrolyzed by MBL. Aztreonam MICs would suffice in the presence of avibactam.Aztreonam, a monobactam antibiotic, is highly resistant to all metallo-beta-lactamases, including New Delhi metallo beta-lactamases(NDM), Imipenemases(IMP), and Verona integron-mediated metallo-lactamase VIM. This makes it a suitable choice for treating infections caused by MBL-producing bacteria. However, it's important to note that aztreonam can be broken down by ESBLs and AmpC beta-lactamases, which are often co-produced with MBLs.[5]One of the biggest problems faced following treatment with these antibiotics is the high cost of the drugs.

The consequences of antibiotic resistance are far-reaching and severe. Patients face limited treatment options, extended hospital stays, and the need for constant medication. This can lead to significant financial burdens, including loss of income and medical debt, potentially pushing individuals and families into poverty, which is depicted by the WHO campaign slogan for AMR week 2024 as "AMR is invisible, but I am not".[6]

Therefore, this study was undertaken due to the paucity of information on available treatment options and their associated costs for resistant Enterobacterales infections, particularly in sepsis cases in India.

MATERIALS AND METHODS

The study was conducted in the Department of Microbiology on 30 ESBL and MBL isolates isolated from pediatric and adult blood culture samples from ICU. The samples were collected over a period of 2months. The objective of the study was;

- To determine the drug susceptibility of
- ESBL isolates for piperacillin- tazobactam, imipenem, ceftazidime-avibactam
- MBL isolates for tegicycline, colistin, ceftazidime- avibactam +aztreonam
- To determine the total cost of antibiotic therapy.

Antibiotic susceptibility test was done by Kirby bauer disc diffusion method and screened for ESBL and MBL production using ceftazidime(30µg)/ cefotaxime(30µg) and Imipenem(10µg) discs respectively as per CLSI.

CONFIRMATORY TEST FOR ESBL DETECTION:

ESBLs are enzymes that break down extended-spectrum cephalosporins (like ceftazidime, cefotaxime, and ceftriaxone) and monobactams (like aztreonam). However, they don't affect cephamycins (cefoxitin and cefotetan) or carbapenems (imipenem and meropenem)[7].

To confirm ESBL production, double-disc synergy test was used. Mueller Hinton (MH) agar plates were lawned with the suspected ESBL isolate, to which Ceftazidime/cefotaxime alone and Ceftazidime/cefotaxime with clavulinic acid was placed on the agar at a distance of 20mm from each other (center to center) and incubated . A ≥5mm increase in a zone diameter for either antimicrobial agent tested in combination with clavulanate versus the zone diameter of the agent when tested alone, indicated ESBL production.

CONFIRMATORY TEST FOR THE DETECTION OF MBL:

MBL's have a broad substrate spectrum and can catalyze the hydrolysis of all ß-lactam antibiotics with the exception of monobactams. They are not inhibited by clavulanate, sulbactam or tazobactam that are effective against serine based class A ß-lactamases.

Double disc synergy test was used to confirm the presence of MBL production:A lawn culture of test isolate (0.5 McFarland opacity standard) was done on MH agar. Two 10 µg imipenem discs were placed on inoculated plates. To one of the Imipenem discs, 10 µl of 0.5 M EDTA solution was added. After overnight incubation, if the zone of inhibition of imipenem + EDTA discs compared to imipenem alone is >7 mm, the test was considered as positive.

The ESBL positive isolates were tested for the drugs piperacillin-tazobactam(100/10µg), imipenem(10µg) and ceftazidime-avibactam(30/20µg) and the MBL positive isolates were tested for tegicycline(15µg), colistin (broth microdilution method) and ceftazidime-avibactam(30/20µg) + aztreonam(30µg). The zone sizewas interpreted as per CLSI guidelines, except for tigecycline it was interpreted according to the FDA criteria(susceptible (≥19 mm), intermediate (15-18 mm), or resistant (≤14 mm)).[9]

TESTING FOR CEFTAZIDIME-AVIBACTAM + AZTREONAM SYNERGY (DISC REPLACEMENT METHOD):

In this method, ceftazidime-avibactam disks (30 µg /20 µg) antibiotic disks were initially applied onto MHA plates inoculated with the test organism and incubated at 35 ± 2 °C for a period of one hour. Later, these disks were removed and replaced with aztreonam disks on the same site. After disk inoculation, plates were re-incubated overnight and then observed for a zone of inhibition on the next day and interpreted as per standard CLSI recommendations for disk diffusion testing of aztreonam.[10,11]

Following the susceptibility test of these drugs, information regarding the dosage and duration was collected from standard medical books[23,24,25] and the cost of drugs were obtained from the retail and online pharmacies, following which an average cost for each antibiotic was calculated. The drugs were then compared with each other based on the antibiotic susceptibility pattern and cost benefit.

RESULTS:

Total number of isolates in this study was 30. Out of which 15 were ESBL producers, 14 isolates were MBL positive and 1 was both ESBL and MBL positive. Of the 15 ESBL isolates 7 were *Klebsiella spp*(46.6%), 3 *E.coli*(20%), 5 *Enterobacter spp(*33.3%). Among the 14 MBL positive isolates 9 were *Klebsiella spp*(64.3%%), 4 *E.coli*(28.5%), 1*Enterobacter spp*(7.14%) and one isolate was both ESBL and MBL positive (Klebsiella species).All the ESBL positive isolates were tested for the susceptibility to the drugs Piperacillin-tazobactam (100/10µg), Imipenem(10µg) and Ceftazidime-avibactam(30/20µg).

Sensitivity pattern of the drugs used for the treatment of ESBL is summarized in Table 1.

25% of the ESBL isolates were susceptible to piperacillin-tazobactam and 56% of the isolates showed sensitivity for Imipenem and Ceftazidime-Avibactam.

TABLE 1: Table showing the susceptibility pattern of the ESBL isolates

	Klebsiella spp		E.coli		Enterobacter spp.	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Piperacillin-tazobactam (100/10µg)	3 (19%)	5 (31%)	1 (6%)	2 (12%)	0	5 (31%)
Imipenem (10µg)	4 (25%)	4 (25%)	3 (19%)	0	2 (12%)	3 (19%)
Ceftazidime-Avibactam (30/20)µg	4 (25%)	4 (25%)	3 (19%)	0	2 (12%)	3 (19%)

All the MBL isolates were tested for the susceptibility to the drugs tegicycline(15µg), colistin(broth microdilution) and ceftazidime-avibactam(30/20µg) + aztreonam(30µg).

Table 2 summarizes the susceptibility pattern of the different MBL isolates

Tigecycline was sensitive in 46.6% of the isolates, 93.3% of the isolates showed resistance to ceftazidime- avibactam , 100% sensitivity was observed for the drugs colistin and ceftazidime-avibactam+aztreonam.

TABLE 2: Table showing the susceptibility pattern of the MBL isolates

	Klebsiella. Spp		E.Coli		Enterobacter. spp	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Tigecycline (15µg)	5 (33%)	5 (33%)	2 (13%)	2 (13%)	0	1 (7%)
Colistin (BMD)	10 (67%)	0	4 (27%)	0	1 (7%)	0
Ceftazidime - avibactam (30/20µg)	1 (7%)	9 (60%)	0	4 (27%)	0	1 (7%)
Ceftazidime - avibactam + aztreonam (30µg)	10 (67%)	0	4 (27%)	0	1 (7%)	0

COST BENEFIT ANALYSIS OF THE DRUGS

DOSAGE OF THE DRUGS

Piperacillin-tazobactam commonly administered dose is 3.375g to 4.5g every 6hourly for 14 days. For Meropenem the dosage varies from 1g to 2g which can be given every 8hourly or 12hourly.The recommended dosage for tigecycline is initial dose of 100mg followed by 50mg every 12 hours for 5-14days. Colistin is given as 9 million units loading dose followed by 4.5 million units IV every 12th hour . Ceftazidime- avibactam dosage is 2.5mg (2g/0.5mg) iv infused over 2-3hours every 8hours and aztreonam 2g IV every 8 hours for 7-14days. The cost of each of these drugs are summarized in Table 3. Most of these drugs have only minor side effects like nausea, vomiting and diarrheaexcept for colistin which can lead to neurotoxicity and nephrotoxicity and should be used with caution. With a few and expensive antibiotics left to treat these MDR organism we have to choose a cost effective and beneficial antibiotic for the treatment of patients infected with these resistant organisms as all these drugs are at a risk of developing resistance too.

In our study most of the ESBL isolates are sensitive to Imipenem and ceftazidime avibactam with a therapeutic cost range of Rs.30,000 to 1 lakh and Rs.50,000 to 1.6 lakhs respectively. In case of MBL isolates most of them were sensitive to both colistin and ceftazidime –avibactam+ aztreonam, with their cost ranging from Rs. 42,000 to 1.5 lakhs and Rs.73,000 to 2.4 lakhs respectively.

TABLE 3: Estimated cost of the higher antibiotics used in treatment of ESBL and MBL

DRUG	COST PER DAY	COST FOR DURATION
Piperacillin tazobactam	Rs.2500- 3000	Rs.10,000-50,000
Meropenem	Rs.3,000- 9,000	Rs. 30000- 1lakh
Tegicycline	Rs. 6,000- 9,000	Rs. 30,000- 1.2lakhs
Colistin	Rs. 6,000-10,000	Rs. 42,000-1.5 lakhs
Ceftazidime-avibactam	Rs. 10,000-12,000 + aztreonam RS.2,500-6,400	Rs. 50,000-1.6lakhs + aztreonam Rs.12,500-80,000

DISCUSSION:

Multidrug-resistant Enterobacterales are becoming increasingly common, limiting our treatment options. To ensure effective and affordable therapy for patients with these resistant infections, accurate microbiological testing (culture and sensitivity) is crucial for selecting the right antibiotic.

The prevalence of ESBLs in India reported from various other studies ranges from 60% to 80%(12,13), with carbapenem being the first

choice of drug in the treatment of ESBL producing Enterobacterales. The injudicious use of this drug has led to a rise in carbapenem resistance,therefore carbapenem sparing strategies include the administration of non-carbapenem β-lactams (ceftolozane–tazobactam, ceftazidime–avibactam, temocillin, cephamycins, and cefepime) and non-β-lactams (aminoglycosides, quinolones, tigecycline, eravacycline, and fosfomycin).(14) In our study the susceptibility of the ESBL producing Enterobacterales for Piperacillin-tazobactam was only 25%, whereas in a study done by D Pierard et al(15) the sensitivity for Imipenem and ceftazidime – avibactam was >94.4% for ESBL positive isolates. In another study done by Benoit Pilmis et al(16) the sensitivity of piperacillin tazobactam against ESBL producing Enterobacterales was 80%. The low rate of sensitivity in our study could be due to the organisms harbouring multiples resistance mechanisms like ESBL and Amp C betalactamses which can reduce the effect of tazobactam and through activation of efflux pumps and porin mutations. Tazobactam and avibactam are also influenced by inoculum effect. (14)

In our study Imipenem and ceftazidime-avibactam showed 56.2% sensitivity. In a study done by Yuhang Wang et al(17) the overall resistance rate of Enterobacteriaceae to CAZ-AVI is <0.6%, with a minimum inhibitory concentration (MIC) of 50% (MIC50) ≤2 mg/L, an MIC of 90% (MIC90) ≤8 mg/L, and an MIC range from ≤0.015 to >128 mg/L. Even for strains that are positive for KPC, OXA-1, OXA-48, cefotaximase (CTX-M), original spectrum β-lactamase (OSBL), ESBL or AmpC, the resistance rates are less than 2.8% . However, when the strains are carbapenem-resistant, some reports indicate a sharp increase in CAZ-AVI resistance, reaching as high as 24.7%.

The prevalence of MBL in India varies from 7.5%-71%(18) and the current treatment options for these isolates are co-administration of ATM and CAZ-AVI, cefiderocol, colistin and tigecycline.(19) The susceptibility of MBL producers in our study for tigecycline was 46.6%, 100% sensitive for colistin and ceftazidime-avibactam + aztreonam and only one isolate was sensitive for ceftazidime avibactam which is almost similar to the results obtained by D Pierard et al.(15) Therefore, colistin and other combination drugs must be reserved for the treatment of MDR organisms. Tigecycline resistance in Enterobacterales is mainly due to the efflux pump like AcrAB and AcrEF and tet (X) gene.(20)

Most of the above-mentioned antibiotics are available in different brands with varying costs. A significant portion of healthcare expenses, ranging from 60% to 90%, is allocated to medications.(21) In our study we found that piperacillin- tazobactam was cost effective but only 25% of the ESBL isolates were sensitive to the drug while Imipenem and ceftazidime- avibactam showed better sensitivity pattern but were expensive for the patients. In case of MBL isolates, Tigecycline showed only 46.6% sensitivity while colistin and ceftazidime-avibactam + aztreonam showed 100% sensitivity, but increased cost of treatment in these cases makes it difficult for the patients to remain compliant to the treatment. Colistin needs to be used in patients with caution as it associated with adverse effects like neurotoxicity and nephrotoxicty. In a study done by lavanya et al(22) the mean of direct cost on empirical treatment in resistant cases was INR. 17349 which is expensive for a developing country like India which correlates with our study. Increase in antibiotic resistance has lead to prescription of Reserve group of antibiotics which are expensive, leading to decrease compliance to treatment and increased morbidity and mortality. Therefore the choice of antibiotics needs to be made based on the in vitro susceptibility test, patient's socioeconomic status and patient's underlying disease condition.

LIMITATIONS:

The study was conducted on only 30 isolates, there is need to conduct the study on a larger sample. The in vitro susceptibility test needs to be correlated with the clinical outcome.

CONCLUSION:

CAZ-AVI and CAZ-AVI+ATM combination offers a good therapeutic advantage compared to other alternative antibiotics for patients with BSI's due to ESBL and MBL producing Enterobacterales respectively. But cost factor also needs to be taken into concern in a developing country like India. So, there is need to choose the antibiotics wisely keeping in mind the patient's age, co-morbidites, antibiotic susceptibility report and socio-economic status.

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