ORIGINAL ARTICLE

Evaluation of resistance rates of enterobacterales to beta-lactam drugs and interpretation of their minimum inhibitory concentrations relative to clinical breakpoints

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Abstract

Background: Beta lactam group of antibiotics are one among the most widely used against enterobacterales. There has been an escalation of resistance among cephalosporins, and carbapenems in the recent days. Evaluation of resistance rates and careful selection of drugs based on Minimum Inhibitory Concentration (MIC) aids in effective therapy of infections caused by these resistant strains. *Aim and Objectives*: To determine the resistance rates of beta lactam antibiotics among enterobacterales, to analyse the relative extent of resistance and susceptibility based on their MIC, relative to their breakpoints, and also to determine MIC 50 and 90. *Material and Methods:* Study was conducted in a tertiary care hospital in rural Bengaluru from June 2022 to May 2023. A total of 733 clinical isolates from all samples were included in the study. Identification and antimicrobial susceptibility testing was done by VITEK-2 Compact automated system. *Results*: Based on analysis of MIC among urine samples, resistance rates of 88% for ampicillin, 71% for cefixime and 69% for ceftriaxone was seen. Among other samples 71%,61% and 57% resistance was seen to cefuroxime, ceftriaxone and amoxclav respectively. Least resistance was seen to meropenem (13%) cefoperazone sulbactam (17%) and imipenem (19%). Cefoperazone sulbactam and carbapenems had better susceptibility with MIC 50 less than the susceptible breakpoint. MIC 90 of piperacillin tazobactum and ceftazidime were well above the resistant breakpoint. *Conclusion*: Understanding the MIC and analysis of susceptibility and resistance of antibiotics will help in rational selection of antibiotics, which may serve as an aid in abating the development of resistant strains. It would be prudent to spare the drugs with MIC 90 above the resistant breakpoint from being included in the empirical panel and should be watchful while using third generation cephalosporins for uncomplicated infections.

Keywords: Beta lactams, Enterobacterales, Minimum Inhibitory Concentration, Breakpoint

Introduction

The family Enterobacterales are a large, ubiquitous, heterogeneous group of gram-negative bacilli whose natural habitat is the intestinal tract of humans and animals. These organisms, because of their high durability, pathogenicity and resistant mechanisms for antibiotics both intrinsic and acquired, are often described as a conspicuous part of hospital acquired infections. The World Health Organization (WHO) published the global list of priority pathogens in 2017 in which Enterobacterales appear among the highest critical category, due to development of resistance to antibiotics. India, being the largest consumer of antibiotics, is facing the brunt of antibiotic resistance due to lack of regulations over the availability of these drugs over the counter, which has led to over use and

misuse [1]. The emergence of antibiotic resistance leads to changes in consumption patterns, as more expensive and broad-spectrum antibiotics become inevitable to manage even common conditions [2]. Currently, it is estimated that 1.27 million global deaths annually are attributable to Antimicrobial Resistance (AMR), and it is projected that, by 2050, global annual deaths attributable to AMR will reach 10 million [3]. This threat, moreover, has higher mortality and morbidity rates than those of HIV, prostate and breast cancers combined [4]. Among other parameters, developing awareness about AMR through surveillance and data collection such as by developing an antibiogram at the institution level, could play a major role in circumventing the problem [5]. Beta lactams and their formulations with a combination of beta lactamase inhibitors are the most frequently prescribed antibiotics against Enterobacterales, which are one of the commonly implicated bacteria in all infections. Not many studies which delve into the importance of Minimum Inhibitory Concentration (MIC) interpretation of these drugs and their application are available to the best of our knowledge in this region. Hence this study was taken up in a tertiary care teaching hospital, with the objective of determining the resistance and susceptibility rates of enterobacterales to beta lactams based on their MIC relative to their breakpoints and also to determine MIC 50 and 90.

Material and Methods

This was a prospective study conducted at MVJ Medical College and Hospital, a tertiary care centre in rural Bengaluru, Karnataka from June 2022 to May 2023. A total of 733 clinical isolates from samples like blood, urine, exudate, pus, body fluid, sputum, Endotracheal Tube (ET) aspirate etc. were included in the study. Ethical committee approval was obtained from the Institutional Ethics Committee (IEC) and informed verbal consent was taken from study group subjects. Breakpoints, interpretation and methodology were according to CLSI 2023 M100 document 33rd edition. MIC_{50} and MIC_{90} were calculated using the formula, number of isolates (n)*0.5 and number of isolates (n)*0.9, respectively [6].

Inclusion criterion: Only isolates belonging to Enterobacterales family were considered.

Exclusion criterion: All other isolates were excluded. Repeat isolates from same patient were also excluded.

Clinical samples, collected in appropriate containers, under aseptic precautions, were received in Microbiology laboratory of MVJ hospital. All samples except urine, blood and body fluids were inoculated on blood agar and MacConkey agar. Urine samples were inoculated on CLED agar. Blood and body fluids were inoculated in blood culture bottles which were immediately loaded into automated BacT alert system followed by culture of flagged bottles on 5% sheep blood agar and MacConkey agar. Preliminary identification was done using basic tests like Gram's staining, catalase, and oxidase. Further identification was done in VITEK 2 compact automated system using identification cards. For antibiotic susceptibility, VITEK cards with number N 235 was used for lactose fermenting and non-lactose fermenting colonies from urine samples and N405 for similar isolates from other samples. McFarland matching with turbidometer was done before loading the isolate into the VITEK cards. AST interpretation, MIC_{50} and MIC_{90} of beta lactam group of drugs, namely, penicillin group, penicillinase resistant penicillins, cephalosporins and carbapenems were calculated.

Results

Urine and exudate/pus samples were received in highest number among others. Total of 733 isolates belonging to family Enterobacterales was included in the study. *E. coli* and *Klebsiella* were the most common organisms (Figure 1). Figure 2 depicts the resistance rates of Enterobacterales isolated from urine and other samples. Among urine isolates maximum resistance was seen for ampicillin at 88%, cefixime at 71% and ceftriaxone at 69%. Among isolates from other samples, resistance to cefuroxime was 71%, ceftriaxone resistance was 61% and 57% resistance was seen to Amoxicillin Clavulanate (AMC). Least resistance among urine isolates were to Piperacillin Tazobactam (PIT/TZP) and ertapenem, whereas among other isolates it was to cefoperazone sulbactam and carbapenems. Resistance rates of Enterobacterales was analysed organism-wise. Resistance rates in *E. coli* for ampicillin was 89%, for cefixime 84% and ceftriaxone 81%. Resistance rates among *Klebsiella* was also found to be 84%, 78% and 64% to cefixime, ceftriaxone and ertapenem, respectively.

Citrobacter koseri showed 72% resistance to ceftriaxone whereas *Citrobacter freundii* had only 20% resistance. *Enterobacter* in our study did not show significant resistance to any of these antibiotics. *Proteus sp* was found to be 79% resistant to cefuroxime and ceftriaxone and 76% resistant to AMC (Table 1).

MIC of Enterobacterales was also analysed (Table 2). 53.5% and 88% isolates were at resistance breakpoint MIC for AMC and ampicillin respectively. For PIT/TZP, 33.4% isolates were at 2 dilutions higher MIC than resistance breakpoint. Among cephalosporins, 71.3% isolates were 'at' the resistance breakpoint for cefixime. For cefoxitin and cefuroxime 64.9% and 47.5% isolates were at 1 dilution higher MIC than resistance breakpoint. For ceftazidime and ceftriaxone, 27.8% and 40% isolates were having a MIC of 3 and 5 dilutions higher than resistance breakpoint, respectively. Among carbapenems 51.2% and 56.9%% isolates were at 3 dilutions lower to susceptible MIC breakpoint. Entrapenem has the lowest MIC at 4 dilutions away (Table 2). Table 4 depicts MIC_{50} and MIC_{90} of Enterobacterales to different antibiotics.

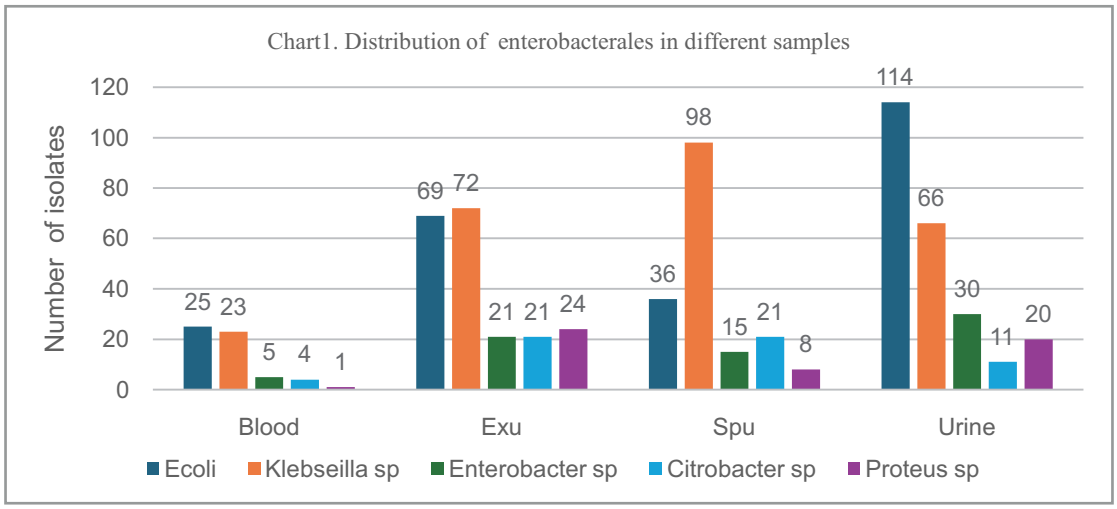

Figure 1: Distribution of Enterobacterales among different samples

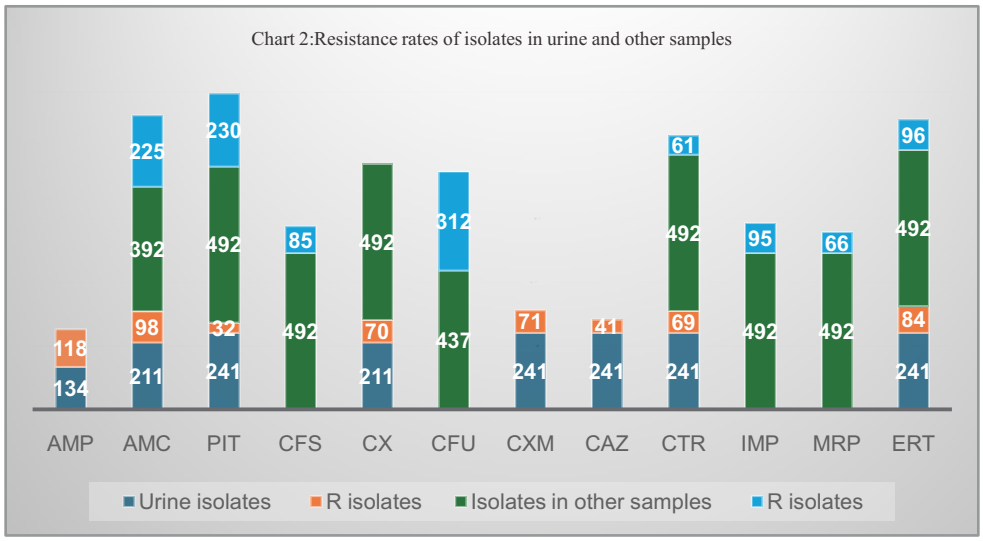

Figure 2: Depicts number of isolates tested and number of resistant isolates in urine and other samples. *AMP- Ampicillin, AMC- Amoxclav, PIT- Piperacillin tazobactum, CFS- Cefoperazonesulbactum, CX- Cefoxitin, CFU- Cefuroxime, CXM- Cefixime, CAZ- Ceftazidime, CTR- Ceftriaxone, IMP- Imipinem, MRP- Meropenem, ERT- Ertapenem.*

Table 1: Organism wise resistance rate among Enterobacterales in percentage

MIC Br. Pt.	*E. coli* (271)		*Kleb sp* (263)		*C. freundii* (55)		*C. koseri* (16)		*Enterobacter sp* (75)		*Proteus sp* (53)	
N=	U 114	O 157	U 66	O 197	U 0	O 55	U 11	O 5	U 30	O 45	U 20	O 33
AMP	89	NA	IR		IR		IR		IR		80	NA
AMC	38	80	70	38	IR		36	0	IR		20	76
PIT	32	86	57	3	0	20	18	2	0	22	0	6
CFS	NA	17	NA	26	NA	11	NA	0	NA	4	NA	0
CX	75	NA	70	NA	0	NA	54	NA	IR		55	NA
CFU	NA	78	NA	74	IR		NA	0	NA	38	NA	79
CXM	84	NA	84	NA	0	NA	36	NA	33	NA	30	NA
CAZ	33	NA	70	NA	0	NA	0	NA	33	NA	30	NA
CTR	81	80	78	6	0	20	72	0	33	33	20	79
IMP	NA	11	NA	24	NA	20	NA	0	NA	22	NA	30
MRP	NA	11	NA	10	NA	20	NA	20	NA	22	NA	22
ERT	26	13	64	25	0	20	18	20	33	17	0	18

IR- Intrinsic resistance. NA- Not applicable N- No of isolates. U- Urine, O- Other samples. AMP- Ampicillin, AMC- Amox clav, PIT- Piperacillin tazobactum, CFS- Cefoperazone sulbactam, CXM- Cefixime, CX- Cefoxitin, CAZ- Ceftazidime, CTR- Ceftriaxone, IMP- Impipenem, MRP- Meropenem, ERT- Ertapenem.

Table 2: Percentage of isolates having MIC values of different antibiotics

MIC Br. Pt.	<=0.12	0.25	0.5	1	2	4	8	16	32	64	>=128
AMP (n=134)	-	-	-	-	6% (8)	3% (4)	2.2% (2)	0.7% (1)	88% (118)	-	-
AMC (n=603)	-	-	-	-	19.9% (120)	6.6% (40)	6.6% (40)	13.2% (80)	53.5% (323)	-	-
PIT (n=733)	-	-	-	-	-	27.8% (204)	27.01% (198)	3.1% (23)	4.3% (32)	3.8% (28)	33.8% (248)
CFS (n=492)	-	-	-	-	-		66.6% (328)	12.6% (62)	3.4% (17)	17.27% (85)	-
CX (n=211)	-	-	-	-	-	18% (38)	9.47% (20)	1.8% (4)	5.6% (15)	64.9% (134)	-
CFU (n=437)		-		3.2% (14)	8.9% (39)	6.4% (28)	2.7% (12)	7.3% (32)	23.7% (104)	47.59% (208)	-
CXM (n=241)		9.1% (22)	8.2% (20)	4.5% (11)	6.6% (16)	71.3% (172)					-
CAZ (n=241)		9.95% (24)	7.05% (17)	5.4% (13)	6.6% (16)	17.8% (43)	11.6% (28)	14% (34)	5.8% (14)	27.8% (52)	-
CTR (n=733)	-	16.9% (124)	6% (44)	13.3% (98)	0	3.2% (24)	6.1% (45)	4.9% (36)	9.2% (68)	40% (294)	-
IMP (n=492)	-	51.2% (252)	15.4% (76)	7.7% (38)	6.3% (31)	4.2% (21)	7.9% (39)	7.1% (35)	-	-	-
MRP (n=492)	-	56.9% (280)	21.3% (105)	5.6% (28)	2.6% (13)	1.6% (8)	1.8% (9)	9.9% (49)	-	-	-
ERT (n=733)	24.8% (182)	3.8% (28)	42% (309)	4.6% (34)	6.2% (46)	7.3% (54)	10.9% (80)	-	-	-	-

First row indicates the MIC breakpoint values. MIC breakpoint values corresponding to green colour indicates Intermediate Breakpoint (IBP). Values to the left of IBP are susceptible BP and to the right of it are resistant BP. AMP- Ampicillin, AMC- Amox clav, PIT- Piperacillin tazobactum, CFS- Cefoperazone sulbactam, CXM- Cefixime, CX- Cefoxitin, CAZ- Ceftazidime, CTR- Ceftriaxone, IMP- Impipenem, MRP- Meropenem, ERT- Ertapenem.

Table 3: Depicts MIC_{50} and MIC_{90} of different antibiotics

Drug	S Breakpoint	Intermediate Breakpoint	R Breakpoint	Breakpoint of MIC_{50} of test isolates	Breakpoint of MIC_{90} of test isolates
AMP	<=8	16	>=32	32	32
AMC	<=8	16	>=32	32	32
PIT	<=8	16	>=32	8	128
CFS	<=16	32	>=64	8	64
CX	<=8	16	>=32	64	64
CFU	<=8	8-16	>=32	32	64
CXM	<=1	2	>=4	4	4
CAZ	<=4	8	>=16	8	64
CTR	<=1	2	>=4	16	64
IMP	<=1	2	>=4	0.25	8
MRP	<=1	2	>=4	0.25	8
ERT	<=0.5	1	>=2	0.5	8

AMP- Ampicillin, AMC- Amox clav, PIT- Piperacillin tazobactum, CFS- Cefoperazone sulbactam, CXM- Cefixime, CX- Cefoxitin, CAZ- Ceftazidime, CTR- Ceftriaxone, IMP- Impipenem, MRP- Meropenem, ERT- Ertapenem.

Discussion

Family of Enterobacterales is one of the largest group of gram negative bacteria, which includes organisms of clinical interest, implicated in various infections ranging from skin and soft tissue, to abdominal, urinary, chest and blood stream infections. Out of the total number of organisms isolated in our study, 40% were Enterobacterales. *E. coli* (37%) and *Klebseilla* (36%) were the most common isolates among them followed by *Enterobacter* (10%), *Citrobacter* (9.6%), *and Proteus* (7.2%), which is similar to study by Shivali *et al*. [7]. We had 32% of Enterobacterales from urine, 28% from pus, 24% from sputum, 8% from blood, and 6% from body fluids.

Beta lactams are preferred and most widely used antibiotics because of their clinical efficacy and safety by virtue of their highly selective toxicity. It has been calculated that the annual expenditure for these antibiotics makes up 65% of the total antibiotics market [8]. Beta lactams comprise of four main groups, three of which share a bicyclic structure (i.e., penicillins, cephalosporins, and carbapenems) and the fourth group has a monocyclic structure (i.e., monobactams).

Few Enterobacterales like *Klebsiella, Citrobacter sp and Enterobacter* possess intrinsic resistance to some of the cephalosporins (Table 1). Apart from this, three mechanisms of resistance to β-lactams are commonly exhibited by Enterobacterales, which include the production of enzymes like metallo-β-lactamases, AmpC beta-lactamases and cephalosporinases that catalyse the hydrolysis of β-lactam ring leading to prevention of action of cell wall active antimicrobials, others being porin defects, and efflux pump overexpression [8]. In order to circumvent resistance, novel broad-spectrum β-lactamase inhibitors like clavulanic acid, sulbactam, and tazobactam and the newer, avibactam and vaborbactam that are active against carbapenemases have been developed that work against many problematic β-lactamases. But of late, resistance has been observed to these drugs also. These resistant organisms can survive in hospital settings leading to Hospital-Acquired Infections (HAIs) with higher rates of morbidity and mortality [9]. These bacteria are present in human and animal gastrointestinal tracts and cause diseases in immunocompromised individuals, burn patients, and patients in intensive care units [10]. In the present study, we tried to interpret MIC of each drug for different isolates with respect to their breakpoint. MIC, by definition, is the lowest concentration of an antibacterial agent expressed in μg/ml which, under strictly controlled in vitro conditions, completely prevent visible growth of the test strain of an organism [11].

Ampicillin resistance in our study was 88%, and all these isolates had MIC >32. Santos *et al.* have reported 74.28% resistance for ampicillin and 62.85% for AMC [12]. Among beta lactam beta lactamase inhibitors, 53.5% isolates were resistant and also had an MIC higher than the resistant breakpoint.33.8% isolates had resistance to PIT/TZP with highest resistant MIC of > = 128 which means a much higher concentration of drug will be required to inhibit the organism. Whereas, cefoperazone sulbactam with resistance rate of only 17% had 66.6% isolates below the susceptible breakpoint which means a good susceptibility at a lower concentration of drug (Table 2). A high MIC for AMCand PIT/TZPcould be explained by the fact that according to Indian statistics, 655 million Daily Drug Doses (DDD) which amounts to 72.7% of penicillins came from fixed drug combination, predominantly as penicillin-beta-lactamase inhibitor combinations [13]. Resistance rates of 2nd generation cephalosporins, cefuroxime and cefoxitin was almost the same (70%) with 18% and 2.7% isolates below susceptible breakpoint respectively. Among 3rd generation drugs, resistance rate of ceftazidime was 41% which was less compared to ceftriaxone (63.7%) and cefixime (71%).

Ceftazidime also had 29% isolates below the susceptible breakpoint compared to 22% for ceftriaxone and 17.4% for cefixime. Among the main WHO's Priority Pathogen List 2021 of organisms identified, 72% of *E. coli* and 63%of *Klebsiella* spp. were resistant to 3rd generation cephalosporins due to Extended-spectrum βeta-Lactamase (ESBL) production [14].

Resistance of *Enterobacter spp* to third-generation cephalosporins is most typically caused by over-production of AmpC beta-lactamases, and treatment with third-generation cephalosporins may be selective for AmpC-overproducing mutants [15]. Organisms like *E. coli, Klebseilla and Proteus* also acquire plasmids containing genes that encode for ESBLs and other resistance genes. Transmissible

plasmids acquire genes for AmpC enzymes, which consequently appear in bacteria lacking or poorly expressing a chromosomal bla_{AmpC} gene, such as *Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis* [16]. This could be the reason for high resistance to third generation cephalosporins among *E. coli, Klebsiella* and *Proteus* (70-78%) although *Enterobacter* had a relatively low resistance (33%), in our study.

Among clinical isolates of *Klebsiella pneumoniae* and *E.coli,* a phenotype that has been classified as PIT/TZP non-susceptible but susceptible to 3rd generation cephalosporins and carbapenems has been described. The resistance mechanism associated with this phenotype has been identified as hyperproduction of the β-lactamase TEM [17-18]. We had 6 isolates in our study which were resistant to PIT/TZP, susceptible to carbapenems and third generation cephalosporins, among which 4 were susceptible to ceftriaxone and 2 to cefotaxime.

Among carbapenems, we found overall susceptibility to meropenem (86%) was better than imipenem (80.6%) and ertapenem (75%). Similar results were seen in studies by Mirzei *et al.* and Bahman *et al*. with susceptibility rates of 69.9% and 65% to imipenem and 71% and 65% to meropenem [19-20]. Results contrasting our findings were seen in studies by Hariharan *et al*. who reported resistance of only 1.7% to meropenem [21]. Gill *et al.* [22] reported ertapenem resistance of 89%. In our study, 78% isolates were having MIC below the susceptible breakpoint, for meropenem, 66% isolates for imipenem and only 28% isolates for ertapenem (Table 2). That means meropenem was effective at a much lower concentration compared to the other two. Resistance to ertapenem (64%) in *Klebsiella* was more compared to other species (Table 2). Studies have shown that OXA 2 beta lactamase plays a significant role in providing a high resistant MIC > 32 for ertapenem, with little or no effect on other carbapenems [23]. In our study we didn't have any isolates with MIC > 16.

Resistance to multiple drugs of different classes are on the rise. According to the European Centre for Disease Prevention and Control (ECDC) and the Centres for Disease Control and Prevention (CDC), Multi Drug Resistance (MDR) is defined as non-susceptibility to ⩾ 1 agent in ⩾ 3 antimicrobial categories; and Extreme Drug Resistance (XDR) as non-susceptibility to ⩾ 1 agent in all but ⩽ 2 categories. In our study we found around 23% carbapenem resistant Enterobacterales and 5.6% MDR. Among 22 MDR *Klebsiella* isolates, 7 were from urine and95% of these were sensitive to tigecycline and fosfomycin. Study by Gupta *et al*. found that 72% of MDR isolates were *K. pneumoniae* followed by *E. coli* (67.1%) [24].

Epidemiological cut off (ECOFF) of a strain, (as given in the EUCAST guidelines) is the highest MIC typical for wild-type strains. ECOFF distinguishes between bacterial strains without any phenotypically established acquired antibiotic resistance mechanism (wild strains) from those displaying such mechanisms [25]. The more susceptible the strain to the antibiotic, the greater the likelihood that it's MIC is below the ECOFF and therefore the strain does not develop any drug-resistant subpopulation [26]. According to study by Lowman *et al*. [27], MIC values derived by Vitek®- can be reliably used as a correlate for an ECOFF, thereby differentiating between wild- type strains from non-wild-type strains. In critically ill patients, where dosing could be difficult due to host related factors, selecting the antibiotic just based on

susceptibility may not be sufficient. Chances of clinical failure due to failure to attain pharmaco-kinetic/pharmacodynamic target, can be minimised by selecting a drug which is below ECOFF [27].

MIC for a particular drug at which 50% and 90% of the isolates are inhibited is called MIC_{50} and MIC_{90}, respectively. Table 3 explains these two values. We observed that for cefoperazone sulbactam, imipenem and meropenem, MIC_{50} was less than susceptible breakpoint and 50% isolates were inhibited at susceptible breakpoint of PIT (Table 3). These drugs possess a very good inhibitory effect at a lesser concentration of drug. On the other hand, for cefoxitin and ceftriaxone MIC_{50} and MIC_{90} were well above the resistance breakpoint which means very high concentration of drug was needed to inhibit the organism (Table 3). Centrally unapproved formulations account for 47.1% (2408 million) of total DDD among which cephalo-sporins contribute 917 million DDD (38.1%), and penicillins 247 million (10.3%) in India [13]. This could be the reason for increased resistance rates and a need to use higher dose of these drugs for treatment. It would be better to not include the antibiotics in the empirical drugs panel, whose MIC_{90} is close to the breakpoint because, although an isolate is susceptible to the drug (but with a higher MIC), there are chances of the isolate to eventually fall into resistant category [26]. During treatment, chances of drug reaching therapeutic concertation increases if antibiotic with an MIC lesser than susceptible range is chosen for a parti-cular isolate. This also helps in the effective eradication of the pathogen using standard dosage regimen [28]. Despite all the applications of MIC during selection of antibiotic, there are a few drawbacks. As MICs are determined for a specific standardised bacterial inoculum the results may not be generalised. If the bacterial inoculum at the infection site is greater, susceptibility determined in vitro may not be applicable for *in vivo* conditions and they may be therapeutically ineffective [25]. On the other hand, with a low inoculum, the antibiotic may prove effective despite the fact that the strain has been determined to be resistant to it [30]. The effectiveness of therapy may also depend on the strain's virulence, which is not reflected in the determined MIC value [31].

Conclusion

Judicious selection of antibiotics remains critical in the era of persistent rise in antibiotic resistance. Resistance patterns differ in each country and region wise due to alterations in the genetic pattern and irrational use of antibiotics. Antibiograms help in framing and updating antibiotic policy according to the trend of susceptibility of the isolates. We concluded that Enterobacterales have better susceptibility rates to cefoperazone sulbactam, ceftazidime and carbapenems compared to other beta lactams in this tertiary care centre. While selecting the antibiotic for treatment, emphasis should be given not only to the susceptibility and resistance pattern of the drugs but also to interpretation of MIC, with reference to their breakpoint values.

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