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Research Article

Impact of Susceptible-Dose-Dependent (SDD) Minimum Inhibitory Concentration (MIC) on Reporting and Prescribing Antibiotics

Kalpana T[1], Mugunthan M[2], Symphonia A[1], Haritha M[2], Deepashree R[3] and Apurba Sastry[4]*

[1]*Junior Resident, Department of Microbiology, JIPMER, Pondicherry, India*

[2]*Senior Resident, Department of Microbiology, JIPMER, Pondicherry, India*

[3]*Assistant Professor, Department of Microbiology, JSS Medical College, Mysore, India*

[4]*Associate Professor, Department of Microbiology, JIPMER, Pondicherry, India*

***Corresponding Author:** Apurba Sastry, Associate Professor, Department of Microbiology, JIPMER, Pondicherry, India.

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Abstract

Introduction: Clinical and Laboratory Standards Institute (CLSI) introduced susceptible dose dependent (SDD) in place of intermediate category for selected drug pathogen combinations such as *Enterobacteriaceae*-cefepime and *Enterococcus*-daptomycin. For SDD-isolates, the antimicrobial agent can be used in higher-than-normal doses, precluding the use of higher antimicrobials thereby preventing antibiotic resistance. Therefore, this study was undertaken.

Aim of the Study: To know the SDD pattern among *Enterobacteriaceae* and *Enterococcus* to cefepime and daptomycin respectively.

Settings and Design: The *Enterobacteriaceae* and *Enterococcus* isolates from blood cultures were included in this study between August 2019 to July 2020.

Materials and Methods: After excluding the repeat isolates, antimicrobial susceptibility test was carried out by VITEK 2 system (bioMérieux) and the MIC result obtained was interpreted by using CLSI guideline 2019. The *Enterobacteriaceae* and *Enterococcus* isolates showing SDD results for cefepime and daptomycin respectively were determined.

Statistical Analysis Used: Nil.

Results: Total of 545 *Enterobacteriaceae* and 115 *Enterococcus* isolates were included in the study. 15.1% of *Enterobacteriaceae* isolates were SDD to cefepime, majority of which were *Escherichia coli* and *Klebsiella* spp. Among the SDD-isolates, 36.6% were found to have MIC of 4 µg/mL and 63.4% exhibited a MIC of 8 µg/mL. Cefepime in increased dose is a better therapeutic option for the SDD isolates rather switching to higher antimicrobials like carbapenems. Among the *Enterococcus* isolates, 28.7% (all were *E. faecalis)* were found SDD to daptomycin.

Conclusion: We found there was an increase in isolation of *Enterobacteriaceae* and *Enterococcus* isolates that were SDD to cefepime and daptomycin respectively.

Keywords: SDD; MIC; Cefipime; Daptomycin; *Enterobacteriaceae*; *Enterococcus*

Introduction

Breakpoints commonly referred as antimicrobial susceptible test interpretive categories represent the antimicrobial concentration that separates the microbial population as susceptible, resistant or intermediate, according to Clinical and Laboratory Standards Institute (CLSI). Clinical breakpoints are derived by con-

sidering factors like microbiological profile, pharmacokinetic (PK) and pharmacodynamic (PD) of the antibiotics, clinical outcome achieved and the animal modeling data. Breakpoints differ across the globe due to different antimicrobials that are in practice, lack of standardized methods, and prevalence of varied resistance pattern of the microorganisms [1]. When a minimum inhibitory concentration (MIC) or zone diameter falls in the intermediate category (I), it creates ambiguity among the clinicians. There are many clinical interpretation of Intermediate category-(i) the response rates may be lower than for susceptible isolates (ii) increased dose may be clinically effective, but there is no validated studies available in support, (iii) may represent a buffer zone between S and R category; results from a technical error, (iv) should be avoided for therapy if alternative drugs with susceptible breakpoints are available, (v) may be clinically effective in body sites where the antibiotic is physiologically concentrated. Therefore, clinicians may consider an antibiotic with intermediate breakpoint for therapy only when all other antibiotics are found resistant and in such case it should be administered in higher-than-normal dose for achieving clinical efficacy, which may warrant adverse side effects.

To combat the issues with intermediate category, CLSI has introduced another clinical interpretative category as susceptible dose dependent (SDD). For selected drug bug combinations CLSI has replaced the intermediate category with susceptible dose dependent (SDD) category where susceptibility can be predicted by increasing the dosage or frequency or infusion time [4]. However, these SDD category has been established based on PK, PD clinical outcome from adult population which may not be applicable for pediatric population [2]. Currently the SDD has been established for cefepime, daptomycin, ceftaroline for *Enterobacteriales*, *Enterococcus faecium*, *Staphylococcus aureus* respectively [4].

It is the responsibility of the microbiology laboratory to report SDD reports so that the clinicians can institute appropriate increased doses. However, there is paucity of data in the literature on studying the SDD pattern for cefepime and daptomycin. Therefore, this study was undertaken to find out the SDD pattern among *Enterobacteriaceae* to cefepime and *Enterococcus* to daptomycin and its clinical impact on prescribing appropriate antimicrobials.

Materials and Methods

The study was conducted in the department of Microbiology from August 2019 to July 2020. The blood cultures received in the laboratory were incubated in the BacT/Alert Virtuo (bioMérieux) automated blood culture system for 5 days. Once the blood culture system flagged positive, gram staining was performed and the subculture was done on to blood agar and MacConkey agar. Culture plates were incubated at 37°C overnight. Colonies grown were subjected to identification by the Matrix assisted laser desorption ionization time of flight (MALDI-TOF) VITEK-MS (bioMérieux), followed by antimicrobial susceptibility test (AST) by the automated MIC based detection, VITEK- 2 (bioMérieux). The MIC result was interpreted by using CLSI guideline 2019. The number of isolates of *Enterobacteriaceae* showing SDD results for cefepime and *Enterococcus* species showing SDD results for daptomycin were determined. As ceftaroline is not available in the VITEK panel as well as not used clinically in our hospital, testing of S. aureus of ceftaroline SDD is excluded from our study. The repeat isolates from same patient and organism with less than 30 isolates were excluded from analysis.

Results

A total of 14,892 blood culture samples were included in the study, out of which 3489 samples flagged positive. Among the flagged samples, 545 were identified as *Enterobacteriaceae* and 115 as *Enterococcus* species. The majority of the samples yielded *Enterobacteriaceae* isolates were received from the emergency service 292 (53.6%) followed by ward 203 (37.2%) and intensive care units 50 (9.2%) whereas the *Enterococcus faecium* isolates were received in higher frequency from ward (48.7%) followed by emergency service (41.7%) and the intensive care units (9.6%). The most common organism isolated among *Enterobacteriaceae* was *Escherichia coli* (243), *Klebsiella pneumoniae* (203), *Enterobacter* species (32) and *Proteus* tribe (31), *Serratia marcescens* (non-pigmented) (30). Table 1 depicts the AST result of *Enterobacteriaceae* for cefepime. About 15.1% (82/545) of *Enterobacteriaceae* isolates were SDD to cefepime, whereas 37.2% (203/545) isolates were found susceptible and 47.7% (260/545) isolates were tested resistant. *Escherichia coli, Klebsiella pneumoniae* and *Enterobacter* species were found SDD in 20.2%, 11.3% and 15.6% of isolates respectively.

Among the *Enterobacteriaceae* isolates tested SDD to cefepime, 36.6% (30/82) found to have MIC of 4 µg/mL and 63.4% (52/82) was found to have MIC of 8 µg/mL. The non-susceptibility to meropenem, piperacillin-tazobactam, cefoperazone-sulbactam and amikacin among the *Enterobacteriaceae* isolates tested SDD to cefepime were 28.1% (23/82), 39% (32/82) 31.7% (26/82) and

29.3% (24/82) respectively. 28.1% of the SDD isolates were susceptible to atleast one first line antibiotics.

Organisms	Total isolates	Cefepime AST(VITEK)		
		S	SDD	R
Escherichia coli	243	88(36.2%)	49 (20.2%)	106 (43.6%)
Klebsiella pneumoniae	203	62 (30.5%)	23 (11.3%)	118(58.1%)
Enterobacter species	32	17 (53.1%)	5 (15.6%)	10 (31.3%)
Proteus tribe	31	14 (45.2%)	2 (6.5%)	15 (48.4%)
Serratia marcescens	30	16 (53.3%)	3 (10%)	11 (36.7%)
Others	6	6	0	0
Total isolates	545	203 (37.2%)	82 (15.1%)	260 (47.7%)

Table 1: Antimicrobial susceptibility report of *Enterobacteriaceae* for cefepime.

MIC (µg/mL)	SDD isolates
4	30 (36.6%)
8	52 (63.4%)

Table 2: MIC values of *Enterobacteriaceae* isolates tested SDD to cefepime.

Antimicrobial agents		Percentage
Meropenem	Susceptible	72% (59/82)
	Non-susceptible	23/82(28.1%)
Piperacillin- tazobactam	Susceptible	50/82 (61%)
	Non-susceptible	32/82(39%)
Cefoperazone-sulbactam	Susceptible	56/82 (68.3%)
	Non-susceptible	26/82 (31.7%)
Amikacin	Susceptible	58/82 (71%)
	Non-susceptible	24/82 (29.3%)
Susceptible to at least one first line antibiotics (ceftriaxone, amoxyclav, ceftazidime, ciprofloxacin and cotrimoxazole)		23/82 (28.1%)

Table 3: AST results of other antimicrobial agents for the isolates that are SDD to cefepime.

As given in table 4, among the *Enterococcus* isolates, *Enterococcus faecium* was the most common species (58.3%, 67/115), followed by *Enterococcus faecalis* (34.8%, 40/115). By applying CLSI 2019 breakpoint guideline, 28.7% (33/115) isolates of *Enterococcus* species were found SDD to daptomycin and all the SDD isolates belonged to *E. faecalis* (82.5%, 33/40).

Organism	Total (115)	Daptomycin AST (VITEK)		
		S	SDD	R
Enterococcus faecalis	40	6 (15%)	33(82.5%)	1(2.5%)
Enterococcus faecium	67	0	0	0
Enterococcus species	8	0	0	0

Table 4: Antimicrobial susceptibility report of *Enterococcus* species for daptomycin.

It was also observed that among the *Enterococcus* isolates tested SDD to daptomycin, 27.3% (9/33) found to have MIC of 2 µg/mL and 72.7% (24/33) found to have MIC of 4 µg/mL (Table 5). All 33 daptomycin SDD isolates were susceptible to both vancomycin and linezolid. 65.4% of the SDD isolates were susceptible to atleast one first line antibiotics (Table 6).

MIC (µg/mL)	SDD isolates
2	9/33 (27.3%)
4	24/33 (72.7%)

Table 5: MIC values of *Enterococcus* isolates tested SDD to daptomycin.

Antimicrobial agents		Percentage
Vancomycin	Susceptible	33/33 (100%)
	Non-susceptible	0
Linezolid	Susceptible	33/33 (100%)
	Non-susceptible	0
Sensitive at least to 1 first line antibiotic (ampicillin, tetracycline and high level gentamicin)		65.4%

Table 6: AST results of other antimicrobial agents for the isolates that are SDD to daptomycin.

Discussion

In lieu of ambiguity of intermediate breakpoint, CLSI has introduced a new clinical interpretative category called 'susceptible-dose-dependent (SDD)' in order to help the physicians to use the SDD antimicrobial in increased dose in clinically indicated cases [2]. However, SDD breakpoints are available only for limited drug-

bug combinations-*Enterobacteriaceae* to cefepime and *Enterococcus* to daptomycin [4]. This study was undertaken to determine the SDD pattern among these isolates and its clinical impact on prescribing appropriate antimicrobials.

Extended spectrum beta lactamase (ESBL) producing organisms were initially considered to be resistant to all cephalosporins and hence there are increased chances that a physician may switch over to increased use of carbapenems, thereby increasing the selective pressure. A reclassification was made were it was found that ESBL producing organisms was found susceptible to certain cephalosporins based on their MIC [5]. One such novel cephalosporins is Cefepime, a fourth generation cephalosporin that and has broad spectrum activity against both gram positive and gram negative organisms and is highly useful in the treatment of infections like complicated urinary tract infection, intra-abdominal infections etc based on their MIC [6]. CLSI in 2014 revised the interpretive breakpoint among *Enterobacteriaceae* for cefepime susceptibility and they re-categorized them as susceptible dose-dependent if the zone diameter and MIC were 19 - 24 mm and 4 - 8 µg/mL respectively [4]. The recommended therapeutic dose of cefepime for susceptible isolates is 1g 12 hourly, which can be increased for SDD-isolates.

In the present study, 15.1% of the *Enterobacteriaceae* isolates were found to be SDD to cefepime; the majority of which were *Escherichia coli* followed by *Klebsiella pneumoniae*. In discordant to our study, lower SDD rates were reported from other studies-Rivera., *et al*. and Park., *et al*. documented that 1.6% and 11.8% of *Enterobacteriaceae* isolates were SDD to cefepime respectively [8,9].

In our study we also found that the majority (63.4%) of the SDD-cefepime isolates showed MIC of 8 µg/mL compared to 36.6% isolates exhibited a MIC of 4 µg/mL. This finding was in concordant with the study in USA where 57% and 43% of the isolates were having MIC of 8 µg/mL and 4 µg/mL respectively [8]. The distribution of MIC is of paramount importance since the therapeutic dose for isolates with SDD breakpoint is MIC dependent; 1 gram every 8 hourly or 2 gram every 12 hourly for MIC of 4 µg/ml and 2 gram every 8 hourly for an MIC of 8 µg/ml [7]. This also signifies the importance of MIC based method over disk diffusion test for performing cefepime susceptibility. Unlike MIC, the therapeutic dose is not dependent on zone diameter. This is because zone diameters do not correlate with specific MICs, therefore any zone diameter in the SDD range should be treated as equivalent to highest MIC of SDD range (8 µg/mL) and a therapeutic dose of 2 gram every 8 hourly is recommended.

We found that susceptibility to meropenem, piperacillin-tazobactam, cefoperazone-sulbactam and amikacin among the SDD *Enterobacteriaceae* isolates was 72%, 61%, 68.3% and 71% respectively. The clinicians should be educated that the cefepime (in increased dose) will be a better antibiotic of choice in these cases rather than switching over to carbapenem or beta lactam combination drugs. Similarly, the non-susceptibility to meropenem, piperacillin-tazobactam, cefoperazone-sulbactam and amikacin among the SDD *Enterobacteriaceae* isolates was found to be 28.1%, 39%, 31.7% and 29.3% respectively. In these isolates, cefepime increased dose will definitely have a therapeutic value rather switching over to other higher antimicrobials like colistin.

Daptomycin, a lipopeptide antibiotic is clinically indicated in treatment of multidrug resistant gram-positive organisms such as methicillin resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant *Enterococcus* (VRE). It acts in a concentration dependent manner against the above organisms [10]. In the present study, we found 28.7% of the *Enterococcus* isolates are SDD to daptomycin. All the SDD isolates belonged to the species *Enterococcus* faecalis. Most of the daptomycin SDD isolates were having MIC 4 µg/mL (72.7%) followed by with MIC 2 µg/mL (27.3%). All daptomycin SDD isolates were found to be susceptible to vancomycin and linezolid. When the MIC falls in the SDD range for daptomycin, then the recommended dosage for serious infection will be 8 - 12 mg/kg bodyweight. However, in CLSI guideline 2020, the SDD breakpoint is only available for *Enterococcus faecium*; whereas for other *Enterococcus* species including *E. faecalis* only an intermediate breakpoint is available.

Conclusion

In the present study, we found that about 15.1% of *Enterobacteriaceae* isolates are SDD to cefepime. Cefepime in increased dose is a safe therapeutic option in these cases rather switching to higher antimicrobial agents. 82.5% of *E. faecalis* isolates are SDD to daptomycin. It is important that the microbiologists should communicate the SDD breakpoint to the physicians and should routinely report SDD results in the antimicrobial susceptibility report, with footnote explaining the interpretation of SDD. The clinicians must have a basic understanding of the SDD breakpoint and should be able to use the antibiotics with SDD report therapeutically whenever clinically

indicated so that the usage of higher antimicrobials can be reduced and thereby preventing resistance. Antimicrobial stewardship team plays an important role in this aspect by providing basic education to the physicians about "susceptible dose dependent" which include the definition of SDD and recommended increased dose of antibiotic required to meet those pharmacodynamics level in the patient [3].

Key Messages

Routine reporting of these SDD drugs by the microbiologist and proper use of these drugs in therapy by physicians will help in combating the use of higher classes of antimicrobials.

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