Fosfomycin susceptibility of carbapenem resistant Enterobacterales and Methicillin-Resistant S*taphylococcus Aureus* blood stream isolates in a tertiary care hospital, South India

Running title: *In-vitro* fosfomycin susceptibility

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Abstract

Background: The emergence of multi-drug resistant organisms has limited the choice of therapeutic options to treat infections. The lack of development of new antimicrobials paved the way for considering the reassessment of older antibiotics like fosfomycin. In this context, we assessed the *in vitro* effect of fosfomycin against carbapenem-resistant Enterobacterales and methicillin-resistant *Staphylococcus aureus* (MRSA) on bloodstream isolates by agar dilution, disk diffusion, and screen agar.

Methods: In this study, the 141 consecutive blood isolates that were resistant to carbapenem and 62 MRSA blood culture isolates were collected over a period of 8 months. The methods such as fosfomycin agar dilution (0.25 µg/ml to 512 µg/ml), Kirby-Bauer disk diffusion (150µg of fosfomycin + 50µg of glucose-6-phosphate), and fosfomycin screen agar (32 µg/ml, 48µg/ml & 64µg/ml) were performed. All three methods were interpreted using EUCAST guidelines. The agreement between the new method and the reference method was calculated.

Results: Among the tested isolates, 100 % of MRSA, followed by *E. coli* (86.4%), *K.pneumoniae* (65.2%) and *E.cloacae* (50%) were susceptible to fosfomycin. The MIC50 and MIC90 of fosfomycin were 0.5µg/ml and 2µg/ml for MRSA, 16µg/ml and 32µg/ml for *K.pneumoniae*, 4µg/ml and 16µg/ml for *E.coli*, 8µg/ml and 32µg/ml for *E.cloacae*, respectively.

Conclusion: Fosfomycin demonstrated a good *in-vitro* effect on most of the carbapenem resistant Enterobacterales and MRSA isolates tested.

Key words: Fosfomycin; Susceptibility testing; Antibiotic resistance; MRSA; Carbapenem resistant Enterobacterales; MIC

Introduction

Antimicrobial resistance (AMR) is an increasing concern for public health. The emergence of drug-resistant pathogens such as multi-drug resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant gram-negative organisms (PDR) remains a major threat all over the world, responsible for increasing mortality and morbidity (1,2,3). The emergence of drug-resistant organisms has limited the choice of therapeutic options to treat infections. Of particular concern is the spread of carbapenemases, because these beta-lactamases are resistant to almost all beta-lactam antibiotics
(4,5). Methicillin-resistant *Staphylococcus aureus* (MRSA), which is resistant to almost all available beta-lactam antimicrobial drugs (except 5th-generation cephalosporins), has been increasing over the last decades. In India, the MRSA rate is around 30-40% though it varies between years and places (6). The increasing resistance rates among both gram-positive and gram-negative pathogens necessitate the implementation of alternative treatment options. The lack of development of new antimicrobials paved the way for considering the reassessment of older antibiotics like fosfomycin.

One such promising agent is fosfomycin, a bactericidal antibiotic active against both gram-positive and gram-negative pathogens. It inhibits the initial step of cell wall synthesis involving phosphoenolpyruvate synthetase. The World Health Organization (WHO) classified fosfomycin in the category of a 'critically important' antimicrobial for investigation of efficacy against gram-negative infections (7). Fosfomycin was previously used as an oral treatment for uncomplicated urinary tract infections (UTIs) (8,9). It has a low level of existing resistance and also has activity in biofilms (8). Considering the potential utility of fosfomycin against multi-drug resistance bacteria, we have undertaken this study to determine the fosfomycin susceptibility of carbapenem-resistant Enterobacterales (CRE) and MRSA.

Very few studies on fosfomycin susceptibility are available for bloodstream isolates. According to the Clinical and Laboratory Standards Institute (CLSI) – and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, only agar dilution is a valid method for fosfomycin to determine the minimal inhibitory concentration (MIC) (10,11,12). This study aimed to detect fosfomycin susceptibility patterns against isolates of carbapenem-resistant Enterobacterales and MRSA from bloodstream infections to determine its therapeutic utility in our healthcare facility (4,13).

Methods

The study was conducted at Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), which is a tertiary care referral center and an Institution of National Importance under the Ministry of Health and Family Welfare, Government of India. This study was approved by JIPMER Institutional Ethics Committee (IEC) with the approval number JIP/IEC/2021/070. A certificate for waiver of informed consent was also obtained from the IEC as this study included the bacterial isolates that were routinely isolated in our hospital laboratory and did not involve human subjects directly. Therefore, informed consent was not taken from the patients as part of our institute's policy. The samples were collected from April 2021 to November 2021. During this study period, all the consecutive one forty-one CRE isolates, which include *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Morganella* species, and *Providencia* species, which were showing carbapenem resistance (meropenem, imipenem, ertapenem, doripenem) and MRSA isolates were collected over a period of 8 months. The carbapenem and methicillin resistance is confirmed by either disc diffusion or VITEK 2 ™. Subculture was done from stocked isolates. The identification of the isolated colonies was confirmed with VITEK MS ™ -

biomerieux (matrix-assisted laser desorption ionization time of flight - mass spectrometry technique).

The only approved minimum inhibitory concentration (MIC) method for fosfomycin testing is the agar dilution method (11). Fosfomycin (Sigma - Aldrich) (P5396) was obtained as powder and disk (200 µg). The agar dilution (AD) method was performed according to CLSI M100 guidelines. The MIC of fosfomycin was determined by the agar dilution method. The MIC >32 µg/ml is considered as resistant to fosfomycin according to EUCAST 2022 guidelines. A series of Mueller-Hinton agar (MHA) plates containing 25µg/ml of glucose-6-phosphate and fosfomycin in concentrations ranging from 0.25 µg/ml to 512 µg/ml were prepared, as this range covers all the current clinical breakpoints of fosfomycin for various organisms, plus two dilutions on either side, as the lowest susceptible and highest resistant breakpoints MICs being 8 µg/ml and 256 µg/ml respectively. The bacterial inoculum was prepared and matched to 0.5 McFarland (1-2 × 10^8 CFU/ml). The final inoculum on the agar needed was 10^4 CFU/ml, so 0.1µl of this inoculum was pipetted onto the agar surface. The plates were incubated overnight at 37°C and interpreted according to EUCAST guidelines (10). As per the literature, the recommended concentration of the drug in a fosfomycin screen agar plate is 32µg/ml. Because of variability in susceptible breakpoint, it was difficult to decide on which single concentration of the drug plate to be tested as a screen that can cover all organisms (10,11). In the present study, we tried to evaluate the utility of using three different concentrations of fosfomycin as screen agar, i.e., 32 µg/ml (to detect susceptible break point of 32µg/ml), 64µg/ml (to detect resistant break point of 128µg/ml) and 48µg/ml (in between both breakpoints). The interpretation of fosfomycin screen agar was done according to EUCAST guidelines (10). Kirby Bauer disk diffusion method was performed on only CRE isolates. The fosfomycin disk (150µg of fosfomycin + 50µg of glucose-6-phosphate) was placed onto an MHA plate and incubated at 37 °C for overnight and interpreted according to EUCAST guidelines. According to EUCAST guidelines, disk diffusion breakpoints are available only for *E. coli*. There are no disk diffusion breakpoints for other species of the family Enterobacterales. The results are interpreted using the *E. coli* disk diffusion breakpoints.

The statistical analysis performed by using Stata version 14 software and *the p-value* was calculated. The comparison of agar dilution and disk diffusion was analyzed by McNemar's chi-square test.

Results

In this study, a total of 203 isolates were included, consisting of 141 CRE isolates and 62 MRSA isolates. Among the 141 CRE isolates, *K.pneumoniae* was the most common (67.3%; 95/141), followed by *E.coli* (26.24%), *E.cloacae* (4.2%), *P.stuartii* (1.4%) *and M.morganii* (0.7%). All three methods were evaluated according to EUCAST guidelines. The MIC of quality control strains was within the limits, 0.5-2µg/ml for ATCC *Escherichia coli* 25922, and 0.5-4µg/ml for ATCC *Staphylococcus aureus* 25923 on all occasions. Out of the 203 isolates, MRSA (62/62), *E. coli* (32/37), *K.pneumoniae* (64/95), *E.cloacae* (3/6), and *P.stuartii* (2/2) were shown susceptible to fosfomycin (shown in the figure 1). The MIC of the test isolate done by fosfomycin screen agar was the same as that of the reference method. The test method is essentially agreed with the reference method. The essential agreement between fosfomycin screen agar and reference method was 100%.

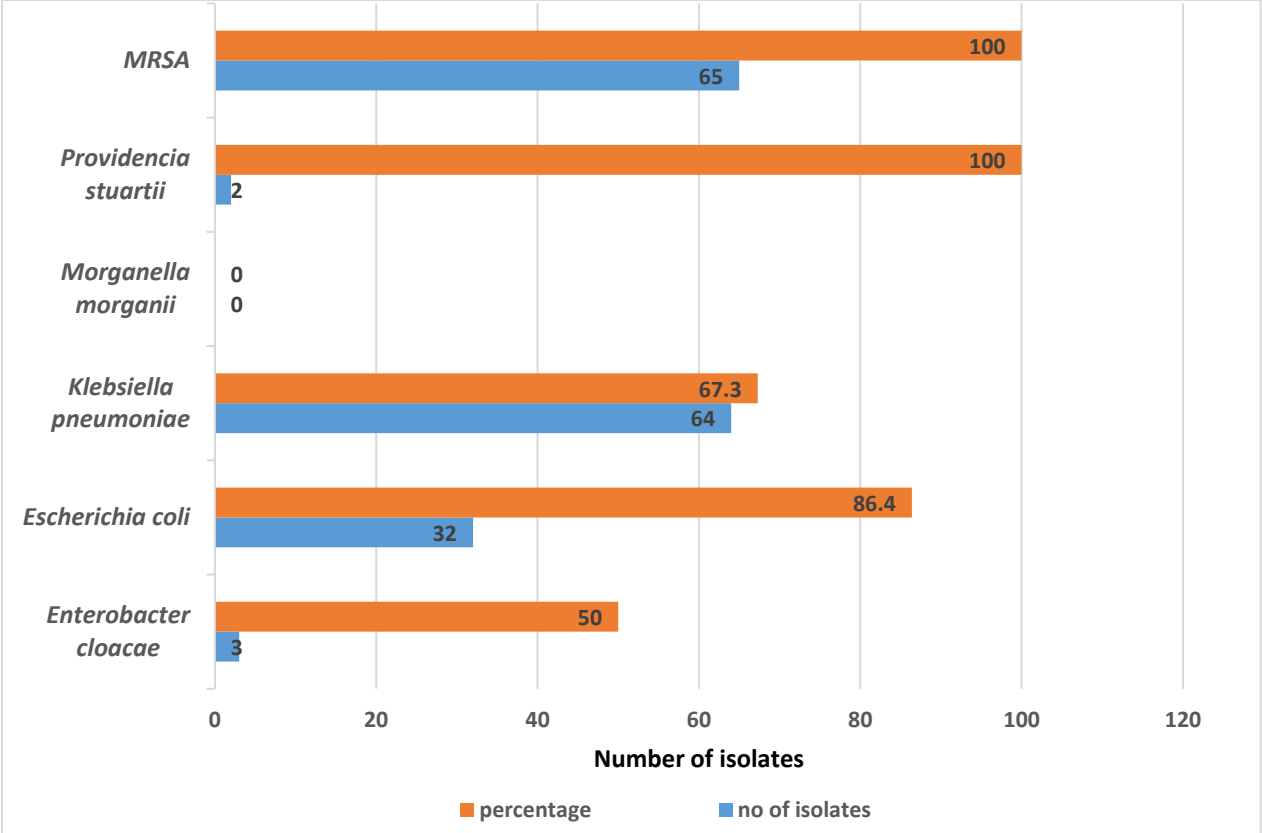

Figure 1. Column chart depicting isolates susceptible to Fosfomycin by agar dilution.
Abbreviation: MRSA- Methicillin-Resistant *Staphylococcus Aureus*

The categorical agreement of 141 CRE isolates for fosfomycin disc diffusion with reference method was 96%. The categorical disagreement of 141 CRE isolates for fosfomycin disc diffusion with reference method was found to be 4.2%, the majority of which were very major errors (VME, 5.0 %) followed by major errors (ME,4.0%) (Shown in table 1). There is high concordance between agar dilution MICs and disc diffusion breakpoints for *E. coli.* The p -value between the agar dilution and disk diffusion for *E. coli* was found to be <0.05 (significant) and others are not significant. According to EUCAST guidelines, the MIC of fosfomycin for Enterobacterales and *S.aureus* is (S≤32, R ≥64). The MIC50 and MIC90 of fosfomycin for MRSA were 0.5µg/ml and 2µg/ml, respectively. The MIC50 and MIC90 of fosfomycin for *K.pneumoniae* were 16µg/ml and 32µg/ml . For *E. coli*, the MIC 50 and MIC 90 of fosfomycin were 4µg/ml and 16µg/ml respectively. For *E.cloacae*, the MIC50 and MIC90 of fosfomycin were 8µg/ml and 32µg/ml respectively.

Table 1. Agreement between disk diffusion and agar dilution

Organism	Categorical agreement		Categorical disagreement		Major error		Very major error		Statistical analysis *(p value)*
	No. of isolates	Percentage	No. of isolates	Percentage	No. of isolates	Rate (%)	No. of isolates	Rate (%)	
Carbapenem resistant Enterobacterales	135/141	96	6/141	4.2	4/101	4.0	2/40	5	0.41
Enterobacter cloacae	6/6	100	0	0	0	0	0	0	0.08
Escherichia coli	37/37	100	0	0	0	0	0	0	0.03
Klebsiella pneumoniae	89/95	93.6	6/95	6.31	4/64	6.25	2/31	6.4	0.41
Morganella morganii	1/1	100	0	0	0	0	0	0	-
Providencia stuartii	2/2	100	0	0	0	0	0	0	-

Discussion

In the era of increasing drug resistance with the available antibiotics, gram-positive and gram-negative pathogens often cause difficult-to-treat infections. The outcome of patients infected with multi-drug resistant bacteria is worse than that of susceptible strains. The dramatic increase in drug resistance and limited availability of novel antibiotics necessitates the implementation of alternative treatment strategies. Fosfomycin has a significant role in carbapenem-sparing treatment strategy in MDR sepsis. But the susceptibility testing method for fosfomycin is challenging due to issues involved in the preparation and interpretation process. In this study, we tested isolates against fosfomycin by agar dilution, screen agar and disc diffusion methods.

A total of 203 non- repetitive CRE and MRSA isolated consecutively from blood stream infections were collected and subjected to fosfomycin susceptibility by various methods. *K.pneumoniae* was the most common isolate among all CRE isolates, followed by *E.coli, E.cloacae, P.stuartii* and *M.morganii.* The EUCAST breakpoints were used in this study. In the current CLSI M100, the zone diameter and MIC breakpoints are restricted only to urinary isolates of *E. faecalis* and *E. coli*, while the MIC values from the current EUCAST breakpoints are applicable to all isolates from Enterobacterales. Zone diameter breakpoints are available only for *E. coli* from all samples. In this study, disk diffusion breakpoints for Enterobacterales were interpreted using *E. coli* DD breakpoints.

We observed that most of the isolates obtained from bloodstream infections included in this study were sensitive to fosfomycin. Our study results demonstrate the potential activity of fosfomycin against MRSA isolates and this finding was similar to the previous study (13). Among all isolates, MRSA seemed to be the most susceptible (100%, 62/62) to fosfomycin, followed by *E. coli* (86.4%, 32/37), *K.pneumoniae* (67.3%, 64/95), and *E.cloacae* (50%, 3/6). In this study, *K.pneumoniae* exhibited the highest non-susceptibility (33%, 31/95) followed by *E.cloacae* (50%, 3/3) and *E.coli* (13.5%, 5/37) respectively.

In our study, MRSA (0.5µg/ml) strains had significantly lower fosfomycin MIC, followed by *E. coli* (4µg/ml), *E.cloacae* (8µg/ml) and *K.pneumoniae* (16µg/ml) which is in accordance with previous report (14,15,16,17). Williams PC et al. (18) studied 247 multi-drug resistance gram negative isolates from sepsis and analyzed *in-vitro* activity of these isolates against fosfomycin. The reference method used in this study was agar dilution. In this study, 90% (202/224) of Enterobacterales were highly susceptible to fosfomycin as per EUCAST (≤32µg/ml) criteria. Among these Enterobacterales, *K.pneumoniae* was found to be highly non-susceptible followed by *E.coli* and *E.cloacae,* which were matched with our study results. They found high concordance between agar dilution and disc diffusion for *E. coli,* which is similar to our study results.

In our study, we found 72% (101/141) of the CRE isolates were susceptible to fosfomycin. These data results are similar to those reported by Livermore et al. (17) where 66.7% of strains were sensitive to fosfomycin among Enterobacterales-producing carbapenemases, using the agar dilution method. In a study done by Falgas et al. (16) 84.8% of isolates of Enterobacterales were susceptible to fosfomycin by the E-strip test method but without characterized carbapenemases types. Endimiani et al. (19) found 75% (MIC ≤32µg/ml) of KPC-producing *K.pneumoniae* strains were susceptible to fosfomycin by agar dilution method. Pasteran F et al. (20) found 86.7% of strains were susceptible to fosfomycin, which comprises mostly KPC-producing Enterobacterales.

In the work of Behara et al. (21) on 137 non-urinary isolates (pus, tracheal aspirate and blood), 81 (59.12%) isolates were resistant to fosfomycin according to EUCAST breakpoints. By using CLSI breakpoints, among 142 urinary isolates, 129 were sensitive to fosfomycin. They found a slight high resistance rate in non-urinary isolates (57%) when compared to urinary isolates (9.2%). Maximum susceptibility was observed in *E. coli* (62%,

18/29) followed by *K.pneumoniae* (44.4%, 24/54). The study done by Chitra et al. showed increased resistance for *K.pneumoniae* isolates from blood / sterile body fluids when compared to urinary isolates. But *E.coli* is uniformly susceptible to fosfomycin in both urine and blood/sterile fluid isolates.

Gopichand P et al. evaluated the fosfomycin effect on multi-drug resistant gram-negative bacteria from urinary tract infections (22). In this study, AmpC beta-lactamases, beta-lactamases, and carbapenemase producing strains of *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp, and *Pseudomonas aeruginosa* were included. They also found a good inhibitory effect of fosfomycin on *K.pneumoniae* and *E. coli*. Sayantan Banerjee et al. included extended spectrum beta-lactamases, multidrug-resistant and beta lactamase producing uropathogens and found that 98.14% of *E. coli* and 95.52% K.pneumoniae were susceptible to fosfomycin .

Mittal et al. (23) found that fosfomycin was 100% susceptible to uropathogenic *E. coli*. In a study done by Rajenderan et al. (24), fosfomycin effectively inhibited 90% of the strains of *Klebsiella* and *E. coli* strains. Sahni et al. (25) found that fosfomycin susceptibility was 83% for *E. coli*, which was similar to our study also. *M.morganii* was resistant to fosfomycin as shown in this study. In the work of Floriana Campanile et al. (26), 99 isolates of Enterobacterales and 80 isolates of *S.aureus* were tested using agar dilution. According to EUCAST guidelines, 61% of *S.aureus* and 76% of Enterobacterales are inhibited by fosfomycin . These data results were similar to our present study.

Inclusion of a greater number of isolates is necessary to further validate the result. This study was purely laboratory based. The test results did not clinically correlate with patient outcome. Lack of molecular analysis is another limitation of this study in order to determine the mechanism of fosfomycin resistance.

Conclusion

In this study, we observed that fosfomycin has a positive *in-vitro* effect on most of the carbapenem resistant Enterobacterales and MRSA isolates tested. Therefore, we propose that fosfomycin could be considered as a therapeutic option for the treatment of extensively-drug resistant Enterobacterales where there are no alternative therapeutic options available. For MRSA isolates, fosfomycin can be considered as an alternative to vancomycin in scenarios such as raised renal parameters or when vancomycin MIC is >1µg/ml where a vancomycin sparing regimen is preferred.

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Ethics approvals

The study was approved by the institutional ethics committee of the JIPMER (JIP/IEC/2021/070). Informed consent was not taken from the patient as per institute policy.

Conflicts of interest

None

Author contributions

The authors contributed equally to the conception, design, analysis, and writing of this manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

Abbreviations

CLSI - Clinical and Laboratory Standards Institute; EUCAST - European Committee on Antimicrobial Testing; MIC - Minimum Inhibitory Concentration; MRSA - Methicillin Resistant *Staphylococcus Aureus*; CRE - Carbapenem Resistant Enterobacteriaceae; DD - Disk Diffusion; UTI - Urinary Tract Infection; G-6-P - Glucose 6 Phosphate; MALDI - Matrix Assisted Laser Desorption Ionisation - Time of flight

References

1. 1.E, Marcou M, Tofarides A. Antimicrobial Resistance in Bacteria: Mechanisms, Evolution, and Persistence. J Mol Evol. 2020 Jan;88(1):26-40. doi: 10.1007/s00239-019-09914-3. Epub 2019 Oct 28. PMID: 31659373.
2. Morrison L, Zembower TR. Antimicrobial Resistance. Gastrointest Endosc Clin N Am. 2020 Oct;30(4):619-635. doi: 10.1016/j.giec.2020.06.004. Epub 2020 Aug 1. PMID: 32891221.
3. Septimus EJ. Antimicrobial Resistance: An Antimicrobial/Diagnostic Stewardship and Infection Prevention Approach. Med Clin North Am. 2018 Sep;102(5):819-829. doi: 10.1016/j.mcna.2018.04.005. Epub 2018 Jun 27. PMID: 30126573.
4. Kaase M, Szabados F, Anders A, Gatermann SG. Fosfomycin susceptibility in carbapenem-resistant Enterobacterales from Germany. Journal of clinical microbiology. 2014 Jun 1;52(6):1893-7.
5. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacterales: an evolving crisis of global dimensions. Clinical microbiology reviews. 2012 Oct 1;25(4):682-707.\
6. Patil SS, Suresh KP, Shinduja R, Amachawadi RG, Chandrashekar S, Pradeep S, Kollur SP, Syed A, Sood R, Roy P, Shivamallu C. Prevalence of methicillin-resistant Staphylococcus aureus in India: a systematic review and meta-analysis. Oman Medical Journal. 2022 Jul;37(4):e440.
7. World Health Organization. Critically important antimicrobials for human medicine,6th Revision.
8. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clinical Microbiology Reviews. 2016 Apr 1;29(2):321-47.
9. Aprile A, Scalia G, Stefani S, Mezzatesta ML. In vitro fosfomycin study on concordance of susceptibility testing methods against ESBL and carbapenem-resistant Enterobacterales. J Glob Antimicrob Resist. 2020 Dec;23:286-289. doi: 10.1016/j.jgar.2020.09.022. Epub 2020 Oct 9. PMID: 33045444.
10. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpreters. Version 11.0, 2021. http://www.eucast.org
11. CLSI M100, 2022 Edition, February 2022 - Performance Standards for Antimicrobial Susceptibility Testing.
12. CLSI M02 Performance Standards for Antimicrobial Disk Susceptibility Tests, 13th Edition.
13. Falagas ME, Roussos N, Gkegkes ID, Rafailidis PI, Karageorgopoulos DE. Fosfomycin for the treatment of infections caused by Gram-positive cocci with advanced

antimicrobial drug resistance: a review of microbiological, animal and clinical studies. Expert opinion on investigational drugs. 2009 Jul 1;18(7):921-44.
14. De Cueto M, Lopez L, Hernandez JR, Morillo C, Pascual A. In vitro activity of fosfomycin against extended-spectrum-β-lactamase-producing *Escherichia coli* and Klebsiella pneumoniae: comparison of susceptibility testing procedures.
15. Li R, Tang H, Xu H, Ren Y, Li S, Shen J. Direct-on-target microdroplet growth assay applications for clinical antimicrobial susceptibility testing. Infection and Drug Resistance. 2021;14:1423.
16. Falagas ME, Maraki S, Karageorgopoulos DE, Kastoris AC, Mavromanolakis E, Samonis G. Antimicrobial susceptibility of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Enterobacteriaceae isolates to fosfomycin. International journal of antimicrobial agents. 2010 Mar 1;35(3):240-3.
17. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. International journal of antimicrobial agents. 2011 May 1;37(5):415-9.
18. Williams PC, Waichungo J, Gordon NC, Sharland M, Murunga S, Kamau A, Berkley JA. The potential of fosfomycin for multi-drug resistant sepsis: an analysis of in vitro activity against invasive paediatric Gram-negative bacteria. Journal of medical microbiology. 2019 May 1;68(5):711.
19. Endimiani A, Patel G, Hujer KM, Swaminathan M, Perez F, Rice LB, Jacobs MR, Bonomo RA. In vitro activity of fosfomycin against bla KPC-containing *Klebsiella pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin. Antimicrobial agents and chemotherapy. 2010 Jan;54(1):526-9.
20. Pasteran F, Lucero C, Rapoport M, Guerriero L, Barreiro I, Albornoz E, Veliz O, Corso A. Tigecycline and intravenous fosfomycin zone breakpoints equivalent to the EUCAST MIC criteria for Enterobacteriaceae. The Journal of Infection in Developing Countries. 2012 Feb 17;6(05):452-6.
21. Behera B, Mohanty S, Sahu S, Praharaj AK. In vitro activity of fosfomycin against multidrug-resistant urinary and nonurinary Gram-negative isolates. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine. 2018 Jul;22(7):533.
22. Gopichand P, Agarwal G, Natarajan M, Mandal J, Deepanjali S, Parameswaran S, Dorairajan LN. In vitro effect of fosfomycin on multi-drug resistant gram-negative bacteria causing urinary tract infections. Infection and drug resistance. 2019;12:2005.
23. Mittal S, Sharma M, Chaudhary U. Fosfomycin use in multi drug resistant uropathogenic *Escherichia coli.* Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders). 2015 Oct 1;15(3):196-201.
24. Rajenderan S, Balaji V, Anandan S, Sahni RD, Tansarli GS, Falagas ME. Determination of MIC distribution of arbekacin, cefminox, fosfomycin, biapenem and other antibiotics against gram-negative clinical isolates in South India: a prospective study. PLoS One. 2014 Jul 28;9(7):e103253.
25. Sahni RD, Balaji V, Varghese R, John J, Tansarli GS, Falagas ME. Evaluation of fosfomycin activity against uropathogens in a fosfomycin-naive population in South India: a prospective study. Future microbiology. 2013 May;8(5):675-80.
26. Campanile F, Wootton M, Davies L, Aprile A, Mirabile A, Pomponio S, Demetrio F, Bongiorno D, Walsh TR, Stefani S, Mezzatesta ML. Gold standard susceptibility testing of fosfomycin in Staphylococcus aureus and Enterobacterales using a new agar dilution panel®. Journal of Global Antimicrobial Resistance. 2020 Dec 1;23:334-7.