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Review Article

# Minimum Inhibitory Concentration and Susceptibility Patterns of Organisms to Fosfomycin as Determined by BD Phoenix M50

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## Abstract

**Objectives:** To compare the fosfomycin minimum inhibitory concentrations of *Enterobacterales* and non-*Enterobacterales*, as determined by the BD Phoenix M50, to EUCAST and CLSI clinical breakpoints.

**Methods:** 158 Gram-negative organisms isolated from clinical samples underwent susceptibility testing using the BD Phoenix M50, NMIC-404 panel. The fosfomycin MICs of both *Enterobacterales* and non-*Enterobacterales* were compared to EUCAST and CLSI clinical breakpoints.

**Results:** A total of 138 *Enterobacterales* were tested, including 81 *E. coli* isolates. 131 (95.0%) were considered susceptible using EUCAST breakpoints and 134 (97.1%) were considered susceptible using CLSI breakpoints. Of the 20 non-*Enterobacterales* tested, 5 isolates (25.0%) showed an MIC below ≤32 mg/L (EUCAST breakpoint for *Enterobacterales*), and 16 isolates (80.0%) had an MIC of ≤64 mg/L (CLSI breakpoint for *E. coli* isolates).

**Conclusions:** This study showed high susceptibility rates of most *Enterobacterales* to fosfomycin, even in the presence of resistance mechanisms (ESBL and CPO), while most of the non-*Enterobacterales* tested showed elevated MICs to fosfomycin.

**Keywords:** *E. coli; Enterobacterales;* EUCAST; Fosfomycin

## Introduction

Fosfomycin is a broad-spectrum antibiotic commonly used in UTIs. It has activity against most *Enterobacterales*, notably *Escherichia coli*, *Proteus mirabilis* and *Citrobacter* spp., while more varied activity has been described against non-*Enterobacterales* [1]. Mowlaboccus., *et al.* performed a study which showed low incidence of fosfomycin resistance in *Escherichia coli* urinary tract infection isolates in Australia (2 of 1033 isolates resistant) [2].

Fosfomycin acts by inhibiting the MurA enzyme, which catalyses the first stage in peptidoglycan synthesis [3]. EUCAST clinical breakpoints for *Enterobacterales* in uncomplicated urinary tract infection (UTI), are MIC of ≤32 mg/L (susceptible) and MIC of >32 mg/L (resistant), with no other MIC breakpoints or zone diameters set for non-*Enterobacterales* [4,5]. CLSI clinical breakpoints, which apply only to *E. coli* urinary tract isolates, are MIC of ≤64 mg/L (susceptible); MIC of 128 mg/L (intermediate); MIC of ≥256 mg/L (resistant) [8].

A previous study examined the accuracy of the Phoenix in detecting fosfomycin resistance compared to other methods (i.e. disc

diffusion, Etest, Vitek). Despite the current gold standard for susceptibility testing being agar dilution and disc diffusion, the Phoenix showed 99.5% categorical agreement for *E. coli*, and 93% for *K. pneumoniae*, with significantly lower major/very major errors compared to the other methods [7].

## Aim of the Study

This study was designed to compare the fosfomycin MICs of different *Enterobacterales* and non-*Enterobacterales* (consisting of *Pseudomonas* spp.), as determined by the BD Phoenix M50, NMIC-404 panel, to EUCAST and CLSI clinical breakpoints.

## Methods

Over a three-month period, a total of 158 Gram-negative organisms isolated from clinical samples, were collected. This included 23 extended-spectrum β-lactamase (ESBL) producing organisms and 5 carbapenemase-producing organisms (CPO) (IMP4: n = 2, KPC: n = 1, oxa48: n = 1, AIM: n = 1). Each isolate had susceptibility testing performed on a pure culture using the BD Phoenix M50, NMIC-404 panel. This data was correlated and fosfomycin MICs of both *Enterobacterales* and non-*Enterobacterales* were compared to EUCAST and CLSI clinical breakpoints.

## Results and Discussion

A total of 138 *Enterobacterales* were tested, 81 of which were *E. coli*. Of the *E. coli* isolates, 81 (100.0%) were classified as susceptible, including 18 ESBL positive isolates, when EUCAST and CLSI breakpoints were used.

Of the other *Enterobacterales* (n = 57), 50 (87.7%) were classified as susceptible (MIC of ≤ 32 mg/L) including 5 ESBL producing organisms and 4 CPO, while 7 (12.3%) were classified as resistant using EUCAST breakpoints (MIC of > 32 mg/L); the majority of these were *Morganella morganii.* Using CLSI breakpoints, 53 isolates (93.0%) were classified as susceptible (MIC of ≤64 mg/L), while 4 isolates (7.0%) showed an MIC of >64 mg/L, which were classified as either intermediate (MIC of 128 mg/L) or resistant (MIC of ≥256 µg/mL); all of which were *M. morganii* (Figure 1).

A total of 20 non-*Enterobacterales* were tested, comprised of *Pseudomonas aeruginosa* (n = 19) and *Pseudomonas putida* (n = 1). Using EUCAST breakpoints set for *Enterobacterales*, only 5 isolates (25.0%) showed an MIC below the breakpoint of ≤ 32 mg/L, while 15 isolates (75.0%) had an MIC > 32 mg/L. Using CLSI breakpoints,

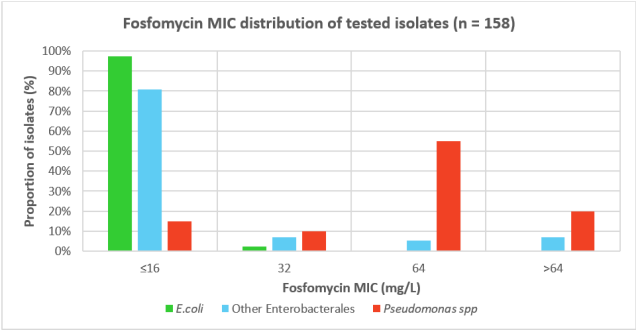


**Figure 1:** Fosfomycin MIC distribution of tested isolates.

16 isolates (80.0%) had an MIC of ≤ 64 mg/L, including 1 CPO, while 4 isolates (20.0%) had an MIC > 64 mg/L (Figure 1).

Of the 23 ESBL producing organisms tested, 23 (100.0%) had an MIC of ≤ 32 mg/L, classifying them as sensitive using both EUCAST and CLSI, with 22 (95.6%) having an MIC of ≤ 16 mg/L. Of the 4 CPO positive *Enterobacterales*, 4 (100.0%) had an MIC ≤ 32 mg/L classifying them as susceptible according to EUCAST and CLSI (Table 1).

Although 100% of the *Klebsiella* isolates which were tested had an MIC of ≤ 32 mg/L, indicating *in vitro* susceptibility, reduced clinical activity, emergence of resistance and failure in treatment has been shown to be significant among *Klebsiella* spp [6,7].

## Conclusion

The results of this study showed high susceptibility rates of most *Enterobacterales* to fosfomycin (excluding *Morganella* spp.), even in the presence of presumed resistance mechanisms, while most of the *Pseudomonas* spp. tested showed elevated MICs to fosfomycin. EUCAST and CLSI have not set clinical breakpoints for *Pseudomonas* spp. Fosfomycin may be a useful therapeutic option for most *Enterobacterales*, including ESBL and CPO positive isolates, however further study is required to ensure adequate clinical activity. Fosfomycin is unlikely to be beneficial in the treatment of non-*Enterobacterales*.

## Transparency Declarations

None to declare.

| | Organism Name/Genus | | n | Fosfomycin MIC (mg/L) | | | |
|---|---|---|---|---|---|---|---|
| | | | | ≤16 | 32 | 64 | >64 |
| *Enterobacterales* | *Citrobacter* spp. | | 5 | 5<br>*C. amalonaticus* (IMP4: n = 1) | 0 | 0 | 0 |
| | *Enterobacter* spp. | | 5 | 5<br>*E. cloacae* (ESBL: n = 2, IMP4: n = 1) | 0 | 0 | 0 |
| | *E. coli* | | 81 | 79<br>(ESBL: n = 18) | 2 | 0 | 0 |
| | *Klebsiella* spp. | | 22 | 21<br>*K. pneumoniae* (oxa48: n = 1, ESBL: n = 1) | 1<br>*K. pneumoniae* (KPC+ESBL: n = 1) | 0 | 0 |
| | *Morganella* spp. | | 4 | 0 | 0 | 0 | 4 |
| | *Proteus* spp. | *P. mirabilis* | 9 | 8 | 0 | 1 | 0 |
| | | Other | 2 | 2 | 0 | 0 | 0 |
| | *Providencia* spp. | | 2 | 0 | 0 | 0 | 0 |
| | *Raoutella* spp. | | 1 | 0 | 0 | 1 | 0 |
| | *Salmonella* spp. | | 3 | 3<br>*Salmonella* spp. (ESBL: n = 1) | 0 | 0 | 0 |
| | *Serratia* spp. | | 3 | 0 | 3 | 0 | 0 |
| | *Shigella* spp. | | 1 | 1 | 0 | 0 | 0 |
| | Total | | 138 | 125 | 6 | 3 | 4 |
| Non-enterobacterales | *Pseudomonas* spp. | *P. aeruginosa* | 19 | 3 | 2 | 11<br>(AIM: n = 1) | 3 |
| | | Other | 1 | 0 | 0 | 0 | 1 |
| | Total | | 20 | 3 | 2 | 11 | 4 |

**Table 1:** Breakdown of tested isolates and respective fosfomycin MIC distribution.

## Conflicts of Interest and Sources of Funding

The authors state that there are no conflicts of interest to disclose. No funding was received for this study.

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