



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Fosfomycin

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Why do we change breakpoints?

- Data-driven decisions
- Patient safety in focus
- We always consider
 - Clinical data
 - Practical clinical implications

Revision of fosfomycin breakpoints

This is a general consultation on proposed breakpoints for fosfomycin. Breakpoints are proposed for systemic infections caused by *Enterobacterales* primarily *Escherichia coli* and *Staphylococcus aureus*. The fact that fosfomycin retains activity against the majority of extended-spectrum-beta-lactamase (ESBL) producing and other multidrug resistant (MDR) isolates has led to an increased interest in the drug. However, fosfomycin was administered mostly as combination therapy with β -lactams or aminoglycosides against CRE and other MDR pathogens.

The proposed species related breakpoints apply only for *E. coli* for a total daily dose 16-18 g.
S \leq 8 mg/L / R > 8 mg/L for *Escherichia coli*

The draft rationale document below outlines the reasons for the selection of proposed breakpoints.

Fosfomycin	Current MIC Breakpoint (mg/L)		Proposed MIC Breakpoint (mg/L)	
	S \leq	R >	S \leq	R >
<i>Enterobacterales</i>	32	32		
<i>E. coli</i>			8	8
<i>E. cloacae</i>			IE	IE
<i>E. faecium</i>			IE	IE
<i>E. faecalis</i>			IE	IE
<i>K. pneumoniae</i>			Note ¹	Note ¹
<i>P. aeruginosa</i>			-	-
<i>S. aureus</i>	32	32	Note ¹	Note ¹

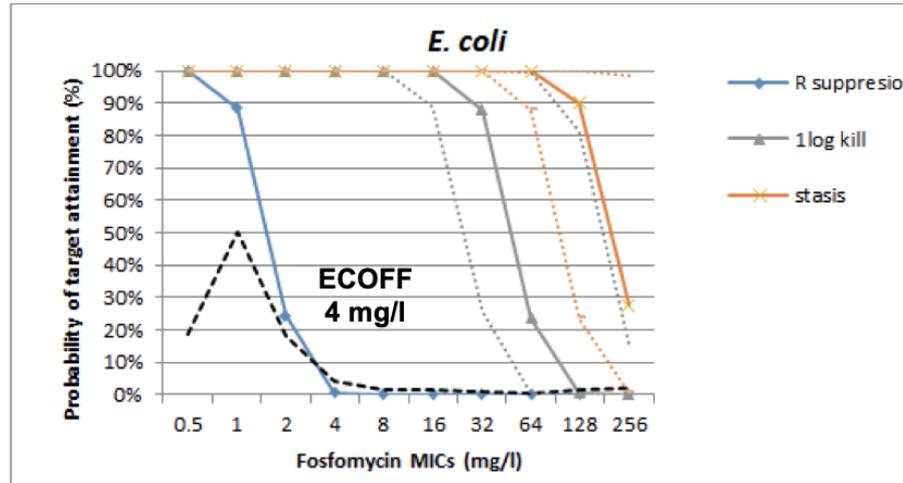
¹For *K. pneumoniae* and *S. aureus* there is clinical experience with use in combination therapy. The ECOFFs are 128 and 32 mg/L, respectively, and can be used to separate strains with and without acquired resistance mechanisms. It is not known whether the ECOFF can be used to predict efficacy in combination therapy.

Revision of fosfomycin breakpoints (II)

ZEUS Trial: Microbiological Eradication Including Molecular Microbiology Data at TOC Visit by Baseline Pathogen and MIC to Study Drug Received (Population: Microbiologic Modified Intent-to-Treat)

Baseline Pathogen	ZTI-01		Piperacillin/Tazobactam	
	MIC	(N=184)	MIC	(N=178)
	(µg/mL)	n/N1 (%)	(µg/mL)	n/N1 (%)
Gram-negative Enterobacteriaceae				
<i>Escherichia coli</i>	0.25	1/ 2 (50.0)	1	29/ 42 (69.0)
	0.5	42/ 59 (71.2)	2	41/ 67 (61.2)
	1	46/ 61 (75.4)	4	7/ 9 (77.8)
	2	8/ 8 (100.0)	8	5/ 7 (71.4)
	4	0/ 1 (0.0)	16	0/ 3 (0.0)
	32	0/ 1 (0.0)	32	1/ 1 (100.0)
			64	1/ 1 (100.0)
			>64	0/ 2 (0.0)
<i>Klebsiella pneumoniae</i>	4	0/ 3 (0.0)	1	2/ 3 (66.7)
	8	3/ 3 (100.0)	2	2/ 4 (50.0)
	16	6/ 8 (75.0)	4	3/ 4 (75.0)
	32	4/ 6 (66.7)	8	3/ 6 (50.0)
	128	3/ 3 (100.0)	16	1/ 1 (100.0)
	512	1/ 1 (100.0)	64	1/ 1 (100.0)
	>512	0/ 2 (0.0)	>64	2/ 5 (40.0)

Revision of fosfomycin breakpoints (IV)



- A BP of 16 mg/l for *E. coli* is supported by Monte Carlo simulation using the high 24h-drug exposure described by Merino-Bohorquez et al
- Fosfomycin plasma levels demonstrated high variability among studies, the PTA based on a lower 24-drug exposure described in other studies e.g. Pfausler et al JAC 2004 support 8 mg/L
- Isolates with MIC >4 mg/l may possess the *fosA* gene
- There are no clinical data showing efficacy for isolates with MIC >2 mg/l (no microbiological eradication was observed in two patients infected with isolates with MICs 4 and 32 mg/L in ZEUS trial),
- A BP of 16 mg/l would not work for the disk diffusion test.

Revision of fosfomycin breakpoints (III)

- The EUCAST breakpoints proposed for *E. coli* pertain to the use of intravenous fosfomycin in monotherapy for infections originating in the urinary tract.
- The proposed breakpoints do not contradict, fail to acknowledge, or discourage from the use of intravenous fosfomycin in combination therapy for other infections. However, the correlation between the in vitro susceptibility of a pathogen to fosfomycin and the efficacy of adding fosfomycin to combination therapy has not been formally studied. **Consequently, it is not possible to propose a breakpoint for use in any combination regimen.**
- ECOFFs can be used to determine if a strain belongs to the wild type, **although this information does not predict efficacy in combination therapy.** For *S. aureus* the ECOFF is 32 mg/L, for *K. pneumoniae* it is 128 mg/L, for *P. aeruginosa* it is 256 mg/L, and for *P. mirabilis* it is 8 mg/L. For other species: insufficient data

No indication for MIC-testing

Correlation of treatment success and MIC

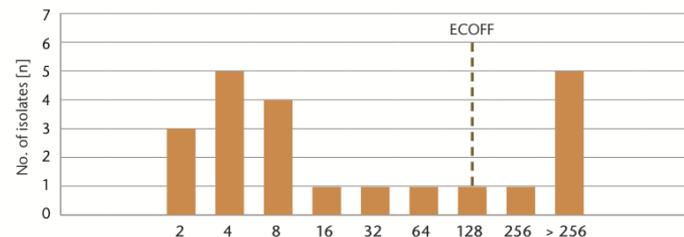
- MICs of isolated pathogens were correlated to patients with clinical success at EOT
- MICs of isolates were obtained by agar dilution (EUCAST reference method)

MICs of IV fosfomycin, MIC range, MIC₅₀ and MIC₉₀ against isolated *K. pneumoniae*

Pathogen	ECOFF (mg/L)	MIC range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	WT population [% of isolates with MIC ≤ ECOFF]
<i>K. pneumoniae</i> (n=22)	128 ¹	0.5–256	8	> 256	73

¹ EUCAST ECOFF; MIC, minimum inhibitory concentration; ECOFF, epidemiological cutoff value; MIC₅₀, MIC value at which growth was inhibited in 50% of isolates; MIC₉₀, MIC values at which growth was inhibited in 90% of isolates.

MIC distribution of *K. pneumoniae* isolates from 22 patients successfully treated with IV fosfomycin combination regimens



Bodmann KF et al. ESCMID Global 2024

Table 3. Multivariable analysis for risk factors for 30-d mortality

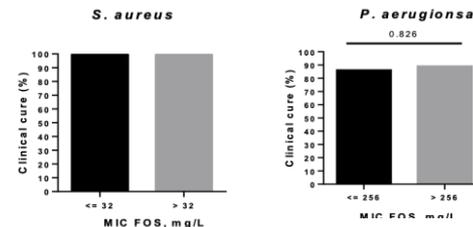
	OR (IC95%)	P-value
FOF MIC 128µg/mL	1.56 (0.26-9.41)	0.624
Septic shock	5.75 (1.05-31)	0.044
Therapy appropriateness	0.20 (0.02-1.81)	0.153
Source of BSI (lung vs other)	1.06 (0.14-7.79)	0.949

Oliva A et al. ESCMID Global 2024 (CAZ-AVI plus fosfomycin vs KPC-producers)

Clinical experience with intravenous (IV) fosfomycin for treatment of complex bone and implant-associated infections: prospective cohort

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Pathogen
<i>S. aureus</i> , n = 6
<i>E. faecium</i> , n = 17
<i>E. faecalis</i> , n = 37
<i>E. coli</i> , n = 40
<i>K. pneumoniae</i> , n = 39
<i>P. mirabilis</i> , n = 12
<i>S. marcescens</i> , n = 4
<i>P. aeruginosa</i> , n = 25



These interim real-world data emphasise that IV fosfomycin is a useful combination partner for the treatment of complex, deep-seated infections using a standardized treatment algorithm. Moreover, although there was no correlation between respective clinical breakpoints and treatment outcome, the data demonstrate that fosfomycin-based regimens can be effective up to very high MICs, highlighting the synergistic capacities of IV fosfomycin with other antibiotics.

Breakpoint tables v14.0 (2024)

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	Note ¹	Note ¹			Note ^A	Note ^A		<p>Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.</p> <p>1/A. Efficacy for <i>Enterobacterales</i> is uncertain. Screening cut-off values can be used to distinguish wild-type isolates from isolates with acquired resistance (MIC >16 mg/L; zone diameter <17 mm for the chloramphenicol 30 µg disk). For chloramphenicol treatment in meningitis, see table of dosages.</p> <p>2. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (<i>E. coli</i> ATCC 25922 or <i>P. aeruginosa</i> ATCC 27853) and the colistin resistant <i>E. coli</i> NCTC 13846 (<i>mcr-1</i> positive).</p> <p>3. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.</p> <p>4. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.</p> <p>5/E. <u>There is currently a lack of clinical evidence to support clinical breakpoints.</u></p> <p>6/F. <u>Antimicrobial susceptibility testing is discouraged. For information on the use of fosfomycin iv in combination therapy in other <i>Enterobacterales</i>, see https://www.eucast.org/eucastguidancedocuments/.</u></p> <p>7. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.</p> <p>B. Use an MIC method (broth microdilution only).</p> <p>C. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate.</p> <p>D. Zone diameter breakpoints apply to <i>E. coli</i> only. For other <i>Enterobacterales</i>, use an MIC method.</p> <p>D. Ignore isolated colonies within the inhibition zone (see pictures below).</p>
Colistin ²	(2) ³	(2) ³			Note ^B	Note ^B		
Daptomycin	-	-			-	-		
Fosfomycin iv (infections originating from the urinary tract), <i>E. coli</i>	8 ⁴	8 ⁴	200 ^C	24 ^D	24 ^D			
Fosfomycin iv (other indications), <i>E. coli</i>	Note ⁵	Note ⁵		Note ^E	Note ^E			
Fosfomycin iv, other <i>Enterobacterales</i>	Note ⁶	Note ⁶		Note ^F	Note ^F			
Fosfomycin oral (uncomplicated UTI only), <i>E. coli</i>	8 ⁴	8 ⁴	200 ^C	24 ^D	24 ^D			
Fusidic acid	-	-		-	-			
Lefamulin	-	-		-	-			
Metronidazole	-	-		-	-			
Nitrofurantoin (uncomplicated UTI only), <i>E. coli</i>	64	64	100	11	11			
Nitroxoline (uncomplicated UTI only), <i>E. coli</i>	16	16	30	15	15			

Thank you for your attention!



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