

# Fosfomycin intravenous: Rationale for EUCAST Clinical Breakpoints

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## Introduction

Fosfomycin is an organic phosphonate agent. It is rapidly bactericidal and inhibits cell wall synthesis by irreversibly inhibiting enol-pyruvyl transferase, which catalyses the first step in the biosynthesis of peptidoglycan.

Fosfomycin is a broad-spectrum agent which is particularly active against *Escherichia coli* and some other *Enterobacterales*. It also shows good activity against *Staphylococcus aureus*, including methicillin resistant *S. aureus* and most coagulase-negative staphylococci. It is less active against *Enterococcus* spp. and *Pseudomonas aeruginosa*, which show a wide range of MIC values among isolates. There are three mechanisms of intrinsic (i and ii) or acquired (iii) resistance: i) inactivation of fosfomycin by cleavage of the molecule by bacterial enzyme FosA, ii) modification of the bacterial enzyme MurA to which fosfomycin must bind in order to exhibit its antibacterial effect, and iii) mutation of the gene responsible for the expression of the fosfomycin transporter, resulting in reduced uptake of fosfomycin by the pathogen. The majority of *Klebsiella pneumoniae*, *Klebsiella aerogenes*, *Pseudomonas aeruginosa* and *Enterobacter* spp. have FosA enzymes. *Escherichia coli* isolates with MICs of more than 8 mg/L harbour the *fosA* gene. Although the emergence of resistance occurs rapidly in vitro, resistance rates in clinical isolates are still relatively low. In vitro, resistant mutants arise at a frequency of  $10^4$  to  $10^5$ . In vivo resistance is increasingly recognised, particularly in ESBL-producing *E. coli*. In critically ill patients.

Fosfomycin iv is most commonly used in combination therapy. This rationale document provides the rational for fosfomycin iv used as **monotherapy**.

## Dosages related to clinical breakpoints

**Standard dosage:** 4g x 4 iv or 6g x 3 iv

**High dosage:** None

## MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

## Pharmacokinetics

PK parameter	Non-critically ill (N=11) Sauerman et al., 2005	Non-critically ill (N=6) Pfausler et al., 2004		Non-critically ill (N=16) Merino-Bohórquez et. al., 2018	Non-critically ill (N=14) Dorn et al., 2019	Healthy (n=27) Wenzler et al., 2017	Critically ill Parker et al., 2015	
	8 g (single dose)	8g q8h (single dose)	8g q8h (multiple doses)	4g q6h (steady state)	8g (single dose)	8g (single dose)	6g q6h (first dose)	6g q6h (2 <sup>nd</sup> day)
C <sub>max</sub> (mg/L)	446 ± 128	260 ± 85	307 ± 101	422.6 ± 86.8	594 ± 149	370 ± 61.9		
	0.47 ± 0.12	1.2 ± 0.4	1.5 ± 1.2			1.08 ± 0.01		
C <sub>min</sub> (mg/L) (range)				178.7 (106.11-246.93)			84.3 (41-172)	250 (76-684)
Total body clearance (L/h)	7.56 ± 4.08	7.4 ± 2.3	5.0 ± 2.0	2.43 ± 1.64	5.55 ± 1.19	7.8 ± 1.4	2.06	5.57
Elimination T <sub>½</sub> (h), mean (range)	3.7 ± 2.2	3.0 ± 1.0	5.0 ± 2.0		2.74 ± 0.47	2.8 ± 0.6		
AUC <sub>0-8</sub> (mg.h/L)	1,029 ± 398	929 ± 280	1,035 ± 383					
AUC <sub>0-24</sub> (mg.h/L)				5,215.08 ± 1972.27				
AUC <sub>0-∞</sub> (mg.h/L)					1,515 ± 352	1,060 ± 192		
Volume of distribution <sub>ss</sub> (L)	28.6 ± 9.9	30.8 ± 10.2	26.3 ± 9.7		19.0 ± 3.1	31.5 ± 10.4	49.5	48.8

Protein binding of fosfomicin is effectively 0%

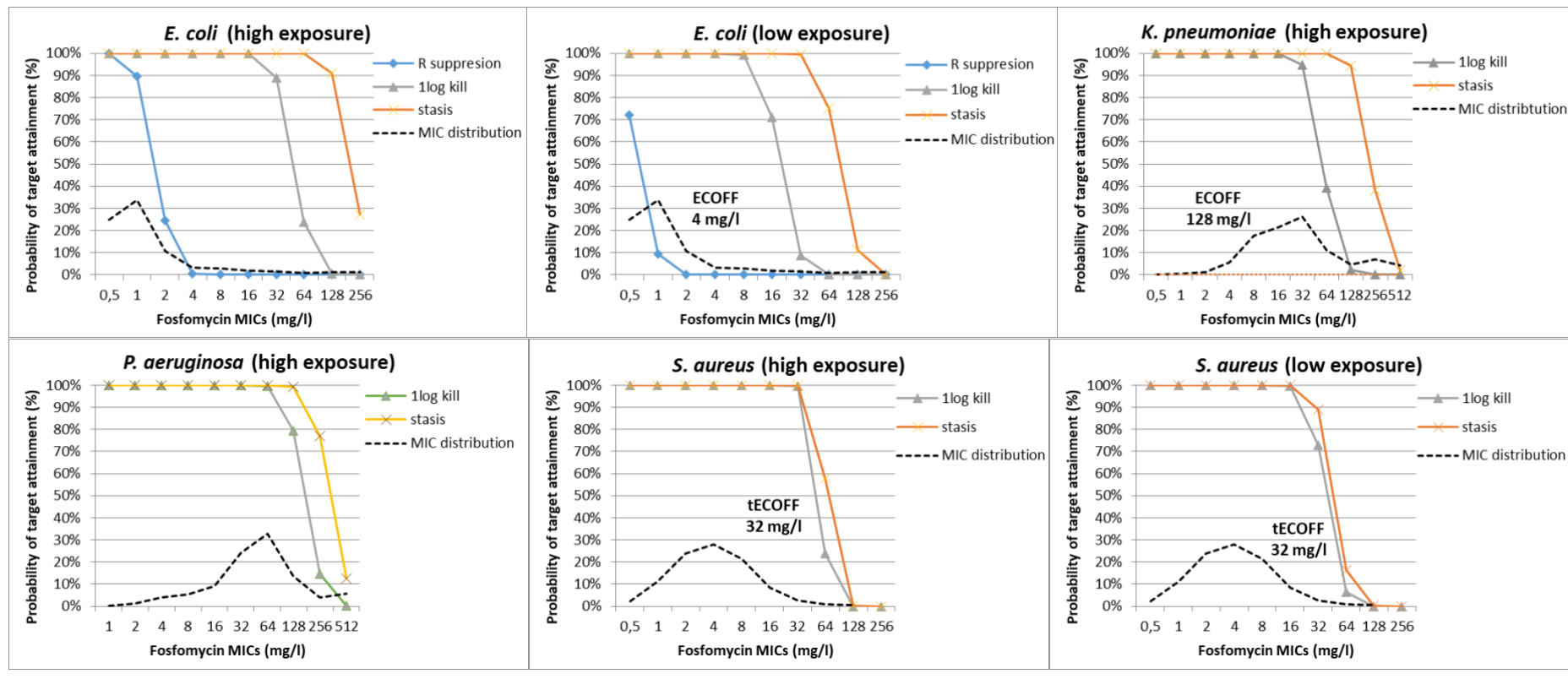
## Pharmacodynamics

Index*	Neutropenic thigh infection model Lepak et al., 2017			In vitro hollow fibre model		
	<i>E. coli</i> (N=5)	<i>K. pneumoniae</i> (N=3)	<i>P. aeruginosa</i> (N=2)	<i>E. coli</i> (N=1) Docobo-Peréz et al., 2015	<i>E. coli</i> (N=3) Van Scoy et al., 2015	<i>S. aureus</i> (N=5) Noel et al., 2020
<i>f</i> AUC <sub>0-24</sub> /MIC bacteriostasis	23.7±15.3	21.1±19.5	11.3/17.9			
<i>f</i> AUC <sub>0-24</sub> /MIC for 1-log <sub>10</sub> kill	98.9±78.4 <sup>1</sup>	21.6 (1 strain) <sup>1</sup>	15.6/40.8 <sup>1</sup>			
<i>f</i> AUC <sub>0-24</sub> /MIC resistance suppression,				3136		
<i>f</i> Cmax/MIC for stasis					11.9 x ~20	6.2±2.4
<i>f</i> Cmax/MIC for 1-log <sub>10</sub> kill					20.9 x ~20	7.5±2.4
<i>f</i> Cmax/MIC for 2-log <sub>10</sub> kill					32.8 x ~20	9.2±3.4

## Monte Carlo simulations

Probability of target attainment for *E. coli*, *K. pneumoniae* and *P. aeruginosa* and for PK/PD targets for stasis, 1-log<sub>10</sub> kill and resistance suppression at each fosfomycin MIC for the 16g per day dose based on high and low exposure described by Merino-Bohorquez et al. 2018 (AUC<sub>24</sub> 5,215.08±1972.27 mg.h/L, C<sub>max</sub>=423±86.8) and Pfausler et al. 2004 (AUC<sub>0-24</sub>=2070±766 mg.h/L, C<sub>max</sub>=307±101 mg/l), respectively. As the 1 log kill effect was reached only in 1 animal, the *Enterobacteriales* PK/PD target of 83.3 fAUC/MIC was used for *K. pneumoniae*.

Probability of target attainment for *S. aureus* for static, 1-log and 2-log kill effects (fC<sub>max</sub>/MIC 6.2, 7.5, 9.2, Noel et al. 2020) at each fosfomycin MIC based on the population pharmacokinetic models of Merino-Bohórquez et al. (2018). Based on low exposure Monte Carlo simulations, a PK/PD cut-off of 8 mg/l was determined for *E. coli*. For the other species, PK/PD cut-offs split the WT population even with high exposure.



## Clinical studies

Data relating susceptibility to outcome for intravenous fosfomycin used alone are available for only one study ZEUS trial (Kaye et al., 2019). There is a wide range of other clinical studies where intravenous fosfomycin has been used in combination with other active antimicrobial agents (Falagas et al., 2016).

The ZEUS trial was a multi-center, randomized, double-blind, study of fosfomycin iv (6g every 8 h) compared to piperacillin/tazobactam (4,5g/8h) in the treatment of complicated urinary tract infections, including acute pyelonephritis (54%), by MDR gram-negative pathogens in hospitalized adults. Outcomes were assessed at day 19. Clinical cure was achieved in 90.8% of the fosfomycin group compared to 91.6% in the piperacillin-tazobactam group). Microbiological eradication was observed in 64.7% of the fosfomycin group versus 54.5% of the piperacillin/tazobactam group (10,2% difference, 95% CI: -0.4, 20.8), respectively. For *E. coli* isolates in the study, few had MICs above 2 mg/L. For *Klebsiella pneumoniae* there did not appear to be a relationship between MIC and outcome. Clinical and Microbiological Outcomes by Baseline Pathogen and MIC at Test of Cure are shown below.

Baseline Pathogen	Clinical Cure		Microbiologic Eradication	
	ZTI-01, n/N (%)	PIP-TAZ, n/N (%)	ZTI-01, n/N (%)	PIP-TAZ, n/N (%)
<i>Escherichia coli</i>	120/133 (90.2)	120/133 (90.2)	97/133 (72.9)	84/133 (63.2)
<i>Klebsiella pneumoniae</i>	25/27 (92.6)	25/25 (100)	18/27 (66.7)	14/25 (56.0)
<i>Proteus mirabilis</i>	8/9 (88.9)	3/5 (60.0)	8/9 (88.9)	1/5 (20.0)
<i>Enterobacter cloacae</i> species complex	8/9 (88.9)	3/3 (100)	6/9 (66.7)	3/3 (100)
<i>Klebsiella oxytoca</i>	2/3 (66.7)	2/2 (100)	2/3 (66.7)	2/2 (100)
<i>Raoultella ornithinolytica</i>	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
<i>Serratia marcescens</i>	1/1 (100)	1/1 (100)	1/1 (100)	0/1 (0)
<i>Morganella morganii</i>	0/0 (...)	1/1 (100)	0/0 (...)	1/1 (100)
<i>Citrobacter amalonaticus/farmer</i>	1/1 (100)	0/0 (...)	1/1 (100)	0/0 (...)
<i>Pseudomonas aeruginosa</i>	8/8 (100)	9/9 (100)	3/8 (37.5)	4/9 (44.4)
<i>Acinetobacter baumannii-calcoaceticus</i> species complex	2/2 (100)	0/0 (...)	2/2 (100)	0/0 (...)
<i>Enterococcus faecalis</i>	2/3 (66.7)	6/7 (85.7)	1/3 (33.3)	4/7 (57.1)
<i>Staphylococcus aureus</i>	1/1 (100)	0/0 (...)	1/1 (100)	0/0 (...)
<i>Staphylococcus saprophyticus</i>	0/0 (...)	1/1 (100)	0/0 (...)	1/1 (100)

Baseline Pathogen	ZTI-01		Piperacillin/Tazobactam	
	MIC (µg/mL)	(N=184) n/N1 (%)	MIC (µg/mL)	(N=178) 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)

	ESBL		Amino-R		CRE		MDR	
	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)
ZTI-01	93 (52/56)	55 (32/58)	97 (29/30)	67 (20/30)	100 (9/9)	56 (5/9)	92 (34/37)	54 (20/37)
PIP-TAZ	93 (51/55)	47 (27/57)	94 (29/31)	38 (12/32)	85 (11/13)	31 (4/13)	90 (28/31)	36 (12/33)

Abbreviations: ZTI-01 = fosfomycin iv; PIP-TAZ = piperacillin-tazobactam

## Clinical breakpoints

The clinical breakpoints for **fosfomycin intravenous** can be found in the most recent version of the Breakpoint tables: [https://www.eucast.org/clinical\\_breakpoints](https://www.eucast.org/clinical_breakpoints)

**Note: Published breakpoints for fosfomycin intravenous apply only situations where the agent is used as monotherapy.**

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