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Activity of fosfomycin when tested against US contemporary bacterial isolates

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ABSTRACT

Fosfomycin and comparators were susceptibility tested against over 2200 contemporary clinical isolates from US medical centers. Fosfomycin was active against *Enterobacterales* ($MIC_{50/90}$, 4/16 μg/mL), including multidrug-resistant isolates. Potent activity was exhibited against gram-positive organisms, including *Staphylococcus aureus* ($MIC_{50/90}$, 4/8 μg/mL). Fosfomycin may provide a promising alternative option for treatment of infections where resistant bacteria may occur.

Fosfomycin is an epoxide antibiotic that inhibits bacterial cell wall production at an early stage and is unique from other bacterial cell wall inhibitors by blocking the first step in cell wall synthesis (Kahan et al., 1974). Cross-resistance with other cell-wall active agents does not occur due to the unique mode of action; however, resistance to fosfomycin has been described both in vitro and in vivo (e.g., Falagas et al., 2016; Karageorgopoulos et al., 2012a, 2012b; Nilsson et al., 2003; Popovic et al., 2010). Fosfomycin has a broad spectrum of in vitro activity that includes many gram-positive and gram-negative bacteria (Boyanova, 2015; Falagas et al., 2010c; Livermore et al., 2011; Michalopoulos et al., 2010; Patel et al., 1997; Popovic et al., 2010; Raz, 2012; Reffert and Smith, 2014). Potent activity has been shown against staphylococci, including methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (Falagas et al., 2010b; Popovic et al., 2010; Welte and Pletz, 2010). Additionally, due to its unique mode of action, fosfomycin is active against multidrug-resistant gram-negative bacteria, including *Enterobacterales* resistant to extended-spectrum cephalosporins and carbapenems (Albur et al., 2015; Falagas et al., 2010a; Hirsch et al., 2015; Livermore et al., 2011; Michalopoulos et al., 2010; Neuner et al., 2012; Reffert and Smith, 2014).

Although there are data in the literature describing the in vitro activity of fosfomycin, there are limited data concerning its in vitro activity against contemporary bacterial isolates in the United States (US), partly because of the oral tromethamine formulation's use in uncomplicated urinary tract infections (UTIs) where culture is rarely done and partly due to the fact that the reference method for fosfomycin susceptibility testing is agar dilution, which is costly and difficult to perform (CLSI, 2012, 2015, 2017; EUCAST, 2017). In the in vitro study presented herein, contemporary susceptibility information for fosfomycin against current bacterial isolates in the United States is provided as baseline susceptibility information to support newer fosfomycin regimens and/or uses with differing forms, such as the intravenous formulation (e.g. ZTI-01, currently under development for USA registration; NCT02753946, https://www.clinicaltrials.gov/ct2/show/NCT02753946?cond=zti&rank=3).

A total of 2254 gram-negative and gram-positive isolates collected in the United States as part of the SENTRY global surveillance program were tested. Isolates were from 2015 except 76 *Staphylococcus saprophyticus* isolates from 2012 to 2014 and 13 *Proteus* spp. isolates from 2014. The older organisms were included so that at least 100 organisms per organism group could be tested. Additionally, 6 *Escherichia coli* from 2014 were included in a carbapenem-resistant *Enterobacterales* (CRE) subset. Isolates were selected randomly (susceptibility information was not used in the selection process) from among isolates collected at various medical centers in the United States (109 medical centers across the US census divisions) except for specific subsets of gram-negative isolates chosen for their resistant phenotypes. The random isolates were chosen to provide an estimate of activity for fosfomycin against "routinely encountered" bacteria. As limited numbers of anaerobes are collected in the SENTRY Program, a small collection of 49 anaerobic gram-positive and gram-negative bacteria were randomly selected from the Jones Microbiology Institute (JMI) culture collection. The isolates were collected from 1992 to 2015; the majority

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were from 2013 to 2015. They were chosen to represent a number of common anaerobe species and were chosen without regard/bias for phenotypic drug resistance.

Fosfomycin susceptibility testing for aerobic organisms was performed by agar dilution using Mueller-Hinton agar supplemented with 25 μg/mL glucose-6-phosphate (CLSI, 2015). Comparator agents were tested in cation-adjusted Mueller-Hinton broth in frozen-form panels produced by JMI Laboratories (North Liberty, IA). Anaerobic susceptibility testing was performed following the Clinical and Laboratory Standards Institute (CLSI) agar dilution method; 25 μg/mL glucose-6-phosphate was added to the agar when testing fosfomycin (CLSI, 2012). Categorical interpretation criteria were those of CLSI (CLSI, 2012, 2015, 2017). CLSI interpretive criteria for fosfomycin apply only to *Escherichia coli* and *Enterococcus faecalis* from urinary tract infections; however, these interpretive criteria of susceptible (S)/intermediate (I)/resistant (R), ≤64/128/≥256 μg/mL were applied to all other organism groups for analytical purposes. Notably, the intravenous fosfomycin would not have the bioavailability constraints of an oral formulation, and thus the use of the current oral interpretative criteria may be a conservative estimate of susceptibility for an intravenous formulation.

Fosfomycin was active against *Enterobacterales* ($n = 1088$) with 97.7% of minimal inhibitory concentration (MIC) values at ≤64 μg/mL (Table 1). Fosfomycin exhibited activity against meropenem-nonsusceptible *Enterobacterales* with 90.3% at ≤64 μg/mL (data not shown).

All randomly selected *E. coli* were susceptible to fosfomycin (MIC_{50}, 0.5 μg/mL and MIC_{90}, 1 μg/mL; Supplemental Table 1). For the 11 selected CRE-phenotype isolates, fosfomycin (81.8% susceptible; MIC_{50}, 1 μg/mL and MIC_{90}, >256 μg/mL) was the most active agent (Supplemental Table 1). Levofloxacin susceptibility was 27.3% (MIC_{50}, >8 μg/mL and MIC_{90}, >8 μg/mL) and amikacin susceptibility was 72.7% (MIC_{50}, 2 μg/mL and MIC_{90}, >32 μg/mL; Supplemental Table 1). Susceptibilities for aztreonam, ceftriaxone, ceftazidime, meropenem, imipenem, and piperacillin-tazobactam were all at 0.0% (Supplemental Table 1; data not shown). All 22 selected extended-spectrum β-lactamase (ESBL) screen-positive phenotype isolates were susceptible to fosfomycin (MIC_{50}, 0.5 μg/mL and MIC_{90}, 2 μg/mL), amikacin, and meropenem (Supplemental Table 1). Aztreonam susceptibility was 9.1% (MIC_{50}, >16 μg/mL and MIC_{90}, >16 μg/mL), and piperacillin-tazobactam susceptibility was 81.8% (MIC_{50}, 4 μg/mL and MIC_{90}, 64 μg/mL; Supplemental Table 1).

A total of 97.0% of the randomly selected *Klebsiella pneumoniae* isolates exhibited fosfomycin MIC values at ≤64 μg/mL (Table 1 and Supplemental Table 1). Fosfomycin was active against 11 of 12 selected CRE-phenotype isolates (fosfomycin, 91.7% at ≤64 μg/mL; Table 1). Only 1 isolate (8.3%) was susceptible to levofloxacin (Supplemental Table 1). All 21 selected ESBL screen-positive phenotype isolates were susceptible to fosfomycin (MIC_{50}, 4 μg/mL and MIC_{90}, 8 μg/mL) and meropenem (Supplemental Table 1). Fosfomycin was active against *Klebsiella oxytoca* with 99.0% of MIC values at ≤64 μg/mL (MIC_{50}, 8 μg/mL and MIC_{90}, 16 μg/mL; Table 1).

There were 141 isolates of *Pseudomonas aeruginosa*, 100 of which were selected without regard to phenotypic MIC, 21 that were specifically selected for their ceftazidime-nonsusceptible and meropenem-susceptible phenotypes, and 20 that were specifically selected for their meropenem-nonsusceptible and ceftazidime-susceptible phenotypes (Table 1). A total of 80.0% of the randomly selected *P. aeruginosa* fosfomycin MIC values were ≤64 μg/mL (95.0% at ≤128 μg/mL; MIC_{50}, 64 μg/mL and MIC_{90}, 128 μg/mL; Table 1 and Supplemental Table 1). The activity of fosfomycin against the ceftazidime-nonsusceptible and the meropenem-nonsusceptible subgroups was similar to that shown for the random collection of *P. aeruginosa* (Table 1 and Supplemental Table 1).

Fosfomycin exhibited limited activity against *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* (Supplemental Table 1). Colistin was the only agent that exhibited >90% susceptibility against *A. baumannii* (96.0%; Supplemental Table 1), and trimethoprim-sulfamethoxazole was the only agent with >90% susceptibility (95.1%) against *S. maltophilia* (Supplemental Table 1).

Fosfomycin MIC values were all ≤64 μg/mL (Table 1 and Supplemental Table 2) when tested against *S. aureus*. Activity against methicillin-susceptible *S. aureus* (MSSA) and MRSA was similar. Activity against coagulase-negative staphylococci was slightly less than for *S. aureus* (Table 1). As expected, fosfomycin activity was compromised against *Staphylococcus saprophyticus* (23.5% of fosfomycin MIC values at ≤64 μg/mL; Table 1).

Fosfomycin was active against all streptococci (MIC values at ≤64 μg/mL; Table 1; *S. pyogenes* MIC_{50}, 32 μg/mL and MIC_{90}, 64 μg/mL). Among the *Enterococcus faecalis* isolates, 99.0% exhibited fosfomycin MIC values at ≤64 μg/mL (Table 1; 99.0% susceptible; MIC_{50}, 64 μg/mL and MIC_{90}, 64 μg/mL), while only 79.8% of *Enterococccus faecium* isolates exhibited fosfomycin MIC values at ≤64 μg/mL (Table 1; MIC_{50}, 64 μg/mL and MIC_{90}, 128 μg/mL). For *E. faecium*, a total of 77.8% of vancomycin-nonsusceptible isolates exhibited a fosfomycin MIC value of ≤64 μg/mL, whereas the fosfomycin MIC value for all vancomycin-susceptible *E. faecium* isolates was ≤64 μg/mL. The fosfomycin MIC value for 3 vancomycin-resistant *E. faecalis* isolates was 32 μg/mL.

Activity against the anaerobes varied by species (Table 1). The most potent activity was against *Veillonella* spp. (MIC values ranged from ≤0.03 to 0.06 μg/mL), *Finegoldia magna* (MIC values ranged from 0.5–1 μg/mL), and *Clostridium* spp., (MIC for 1 isolate was 4 μg/mL and for the other 4 isolates the MIC was 32 μg/mL).

Falagas et al. in a 2016 review indicated that there were no major differences in susceptibility to fosfomycin for gram-negative bacteria and *S. aureus* when comparing studies before 2010 with later studies (Falagas et al., 2016). They did note, however, that fosfomycin susceptibility for vancomycin-resistant enterococci appeared higher in more current studies. Our results for this US-based study were consistent with the Falagas review in that fosfomycin exhibited a high level of activity against gram-negative *Enterobacterales*, including multidrug-resistant isolates, and against *S. aureus*. Also, fosfomycin susceptibility was higher against vancomycin-resistant enterococci (78.6%, ≤64 μg/mL) as reported for later studies. The enterococcal fosfomycin susceptibility data in this report were similar to the US-based studies reported by Pogue et al. (isolates from 2008 to 2010), Descourouez et al. (isolates from 2007 to 2010), and Hirsch et al. (isolates from 2013 to 2014) (Descourouez et al., 2013; Hirsch et al., 2015; Pogue et al., 2013).

With broad-spectrum activity, including activity against multidrug-resistant gram-negative bacteria, fosfomycin merits further study in infections where resistant organisms may occur. It is encouraging that this agent is under numerous investigations globally to evaluate its utility in severe adult and pediatric patients as indicated in ClinTrials.gov. The current US Food and Drug Administration breakpoints and CLSI breakpoints for fosfomycin are based on oral administration for UTIs. With the potential introduction of an intravenous form for treatment of complicated urinary tract infections in the United States, and given that up to 18 grams a day are being administered intravenously compared to the oral dosage form (3 g and 37% bioavailability), determining whether existing breakpoints are appropriate for the intravenous formulation will be important to ensure that appropriate laboratory testing and guidance can be provided (CLSI, 2017; Monurol, 2014).

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Table 1
Antimicrobial activity of fosfomycin when tested against main organisms and organism groups.

Organisms/organism groups (no. of isolates)[a]	No. of isolates at MIC (μg/mL; cumulative %)													MIC_{50}	MIC_{90}
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256		
Enterobacterales (1088)	6 (0.6)	31 (3.4)	226 (24.2)	154 (38.3)	73 (45.0)	189 (62.4)	207 (81.4)	113 (91.8)	34 (94.9)	30 (97.7)	5 (98.2)	8 (98.9)	12 (100.0)	4	16
Escherichia coli (135)		2 (1.5)	80 (60.7)	41 (91.1)	2 (92.6)	1 (93.3)	2 (94.8)	1 (95.6)	3 (97.8)	1 (98.5)	0 (98.5)	0 (98.5)	2 (100.0)	0.5	1
Random *E. coli* (102)		2 (2.0)	64 (64.7)	30 (94.1)	0 (94.1)	1 (95.1)	2 (97.1)	1 (98.0)	1 (99.0)	1 (100.0)				0.5	1
Selected *E. coli* CRE-phenotype (11)			5 (45.5)	3 (72.7)	0 (72.7)	0 (72.7)	0 (72.7)	0 (72.7)	1 (81.8)	0 (81.8)	0 (81.8)	0 (81.8)	2 (100.0)	1	>256
Selected *E. coli* ESBL-phenotype (22)			11 (50.0)	8 (86.4)	2 (95.5)	0 (95.5)	0 (95.5)	0 (95.5)	1 (100.0)					0.5	2
Klebsiella pneumoniae (133)					4 (3.0)	62 (49.6)	45 (83.5)	13 (93.2)	3 (95.5)	2 (97.0)	0 (97.0)	0 (97.0)	4 (100.0)	8	16
Random *K. pneumoniae* (100)					2 (2.0)	48 (50.0)	35 (85.0)	9 (94.0)	2 (96.0)	1 (97.0)	0 (97.0)	0 (97.0)	3 (100.0)	4	16
Selected *K. pneumoniae* CRE-phenotype (12)					1 (8.3)	2 (25.0)	4 (58.3)	3 (83.3)	0 (83.3)	1 (91.7)	0 (91.7)	0 (91.7)	1 (100.0)	8	64
Selected *K. pneumoniae* ESBL-phenotype (21)					1 (4.8)	12 (61.9)	6 (90.5)	1 (95.2)	1 (100.0)					4	8
Klebsiella oxytoca (102)				3 (2.9)	8 (10.8)	39 (49.0)	35 (83.3)	11 (94.1)	4 (98.0)	1 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)	8	16
Enterobacter aerogenes (104)		1 (1.0)	1 1.9	0 (1.9)	3 (4.8)	30 (33.7)	46 (77.9)	18 (95.2)	1 (96.2)	3 (99.0)	0 (99.0)	1 (100.0)		8	16
Enterobacter cloacae species complex (104)			7 (6.7)	8 (14.4)	7 (21.2)	13 (33.7)	26 (58.7)	23 (80.8)	9 (89.4)	5 (94.2)	3 (97.1)	0 (97.1)	3 (100.0)	8	64
Serratia marcescens (101)			1 (1.0)	4 (5.0)	8 (12.9)	24 (36.6)	35 (71.3)	22 (93.1)	4 (97.0)	3 (100.0)				8	16
Proteus mirabilis (103)	5 (4.9)	10 (14.6)	14 (28.2)	35 (62.1)	19 (80.6)	7 (87.4)	4 (91.3)	3 (94.2)	1 (95.1)	4 (99.0)	0 (99.0)	1 (100.0)		1	8
P. vulgaris group (100)			8 (8.0)	7 (15.0)	9 (24.0)	11 (35.0)	14 (49.0)	21 (70.0)	9 (79.0)	11 (90.0)	2 (92.0)	6 (98.0)	2 (100.0)	16	64
Citrobacter koseri (102)		1 (1.0)	41 (41.2)	50 (90.2)	9 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)						1	1
Citrobacter freundii species complex (104)	1 (1.0)	17 (17.3)	74 (88.5)	6 (94.2)	4 (98.1)	2 (100.0)								0.5	1
Pseudomonas aeruginosa (141)					3 (2.1)	8 (7.8)	3 (9.9)	10 (17.0)	32 (39.7)	57 (80.1)	21 (95.0)	3 (97.2)	4 (100.0)	64	128
Random *P. aeruginosa* (100)					2 (2.0)	7 (9.0)	3 (12.0)	6 (18.0)	17 (35.0)	45 (80.0)	15 (95.0)	3 (98.0)	2 (100.0)	64	128
Selected *P. aeruginosa* CAZ-NS (21)					1 (4.8)	0 (4.8)	0 (4.8)	3 (19.0)	7 (52.4)	7 (85.7)	2 (95.2)	0 (95.2)	1 (100.0)	32	128
Selected *P. aeruginosa* MER-NS (20)						1 (5.0)	0 (5.0)	1 (10.0)	8 (50.0)	5 (75.0)	4 (95.0)	0 (95.0)	1 (100.0)	32	128
Acinetobacter baumannii-calcoaceticus species complex (101)										2 (2.0)	80 (81.2)	18 (99.0)	1 (100.0)	128	256
Stenotrophomonas maltophilia (102)								1 (1.0)	2 (2.9)	36 (38.2)	53 (90.2)	10 (100.0)		128	128
Staphylococcus aureus (204)			2 (1.0)	9 (5.4)	51 (30.4)	109 (83.8)	28 (97.5)	3 (99.0)	1 (99.5)	1 (100.0)				4	8
MSSA (103)			2 (1.9)	8 (9.7)	38 (46.6)	46 (91.3)	7 (98.1)	2 (100.0)						4	4
MRSA (101)				1 (1.0)	13 (13.9)	63 (76.2)	21 (97.0)	1 (98.0)	1 (99.0)	1 (100.0)				4	8
Coagulase-negative staphylococci excluding *S. saprophyticus* (105)		1 (1.0)	4 (4.8)	11 (15.2)	17 (31.4)	15 (45.7)	13 (58.1)	11 (68.6)	16 (83.8)	8 (91.4)	2 (93.3)	1 (94.3)	6 (100.0)	8	64
Staphylococcus saprophyticus (102)					1 (1.0)	1 (2.0)	0 (2.0)	1 (2.9)	3 (5.9)	18 (23.5)	35 (57.8)	5 (62.7)	38 (100.0)	128	>256
Streptococcus pyogenes (100)							1 (1.0)	30 (31.0)	58 (89.0)	11 (100.0)				32	64
Streptococcus agalactiae (104)				5 (4.8)	13 (17.3)	23 (39.4)	25 (63.5)	20 (82.7)	2 (84.6)	16 (100.0)				8	64
Enterococcus spp. (207)								1 (0.5)	53 (26.1)	131 (89.4)	21 (99.5)	0 (99.5)	1 (100.0)	64	128
Enterococcus faecalis (103)								1 (1.0)	44 (43.7)	57 (99.0)	1 (100.0)			64	64
Enterococcus faecium (104)									9 (8.7)	74 (79.8)	20 (99.0)	0 (99.0)	1 (100.0)	64	128
Anaerobes (49)															
Clostridium spp. (5)						1 (20.0)	0 (20.0)	0 (20.0)	4 (100.0)					32	
Finegoldia magna (5)			3 (60.0)	2 (100.0)										0.5	
Peptostreptococcus spp. (5)				1 (20.0)	0 (20.0)	0 (20.0)	0 (20.0)	3 (80.0)	1 (100.0)					16	
Propionibacterium spp. (5)													5 (100.0)	>256	
Bacteroides fragilis group (9)								1 (11.1)	0 (11.1)	0 (11.1)	0 (11.1)	0 (11.1)	8 (100.0)	>256	
Fusobacterium spp. (5)					1 (20.0)	1 (40.0)	1 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	1 (80.0)	0 (80.0)	1 (100.0)	8	
Prevotella spp. (5)													5 (100.0)	>256	
Porphyromonas spp. (5)													5 (100.0)	>256	
Veillonella spp. (5)	5 (100.0)														

[a] CRE = carbapenem-resistant *Enterobacterales*; ESBL = extended-spectrum beta-lactamase; CAZ-NS = ceftazidime-nonsusceptible; MEM-NS = meropenem-nonsusceptible; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*.

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Appendix A. Supplementary data

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