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Fosfomycin Activity When Tested against Gram-Positive and Gram-Negative US Isolates Collected by the SENTRY Antimicrobial Surveillance Program

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Abstract

Background: ZTI-01 (fosfomycin, FOS, for injection) is under US development to treat complicated urinary tract infections. FOS is unique compared to other antimicrobials because it inhibits an early step in cell wall synthesis via covalent binding to MurA. FOS demonstrates broad *in vitro* activity against gram-negative (GN) and -positive (GP) bacteria, including multidrug-resistant (MDR) organisms.

Methods: FOS was tested against over 1,400 GN and 800 GP clinical isolates collected in US medical centers from the SENTRY Antimicrobial Surveillance Program (96% of isolates from 2015) and a selection of 29 GN and 20 GP anaerobes. Isolates were susceptibility (S) tested against FOS and comparators by reference agar dilution (25 µg/mL glucose-6-phosphate supplementation) using existing FDA breakpoints of the oral formulation for comparative assessments.

Results: FOS was very active against selected *Enterobacteriaceae* ($MIC_{50/90}$, 4/16 mg/L). For randomly selected *Escherichia coli*,100.0% were S to FOS ($MIC_{50/90}$, 0.5/1 mg/L), and the FOS $MIC_{50/90}$ for *Klebsiella pneumoniae* was 4/16 mg/L (97.0% ≤64 mg/L). The FOS $MIC_{50/90}$ for randomly selected *Enterobacter aerogenes*, *E. cloacae* complex, *Serratia marcescens*, *Proteus mirabilis*, *Citrobacter koseri*, and *C. freundii* complex was 8/16, 8/64, 8/16, 1/8, 1/1, and 0.5/1 mg/L, respectively. For *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* complex, higher FOS $MIC_{50/90}$ values were observed, 64/128 mg/L and 128/256 mg/L, respectively. FOS activity was limited against *Prevotella* and *Porphyromonas* spp. ($MIC_{50/90}$,>256 mg/L) with variable MICs for the *Bacteroides fragilis* group. FOS was very active against *Staphylococcus aureus* ($MIC_{50/90}$, 4/8 mg/L) and against coagulase-negative staphylococci, excluding *S. saprophyticus* ($MIC_{50/90}$, 8/64 mg/L). For *S. saprophyticus*, the FOS $MIC_{50/90}$ values were 128/>256 mg/L. No *E. faecalis* isolates were resistant to FOS (99.0%S; 1.0% intermediate). *E. faecium* MICs were generally higher to various antimicrobials, including 1 FOS isolate (19.2% intermediate; 79.8%S). FOS was active against β-haemolytic streptococci (*S. pyogenes;* $MIC_{50/90}$, 32/64 mg/L; *S. agalactiae*; $MIC_{50/90}$, 8/64 mg/L) and GP anaerobes.

Conclusions: FOS demonstrated broad-spectrum activity against a large collection of GN and GP bacteria. FOS merits further study in infections in which resistant GN and GP bacteria may occur. Potential introduction of an IV form will warrant a re-assessment of FDA breakpoints, given the bioavailability limitations of the current oral formulation.

Introduction

- Fosfomycin has been used in both an intravenous and oral form to treat a variety of infections, including urinary tract (UTI), respiratory tract, and skin and skin structure infections
- Fosfomycin exhibits a broad spectrum of activity that includes many gram-positive and gram-negative bacteria
- Due to its unique mode of action, fosfomycin is active against multidrug-resistant gram-negative bacteria, including *Enterobacteriaceae* resistant to extended-spectrum cephalosporins and carbapenems
- Current interpretative criteria established by the US Food and Drug Administration are based upon the approved oral formulation. Notably, the oral formulation is indicated for single-dose treatment of uncomplicated UTI and is only ~37% bioavailable to that of the intravenous formulation
- ZTI-01 (fosfomycin for injection) administered at 6 grams every 8 hours for 7–14 days is under development for treating complicated urinary tract infections (https://clinicaltrials.gov/ct2/show/NCT02753946)
- In the present study, the activity of fosfomycin was evaluated against a collection of over 2,000 contemporary bacterial clinical isolates from the US that included several select resistant groups (*Enterobacteriaceae* with an extended-spectrum β-lactamase screen phenotype and those exhibiting resistance to carbapenems)

Materials and Methods

- Greater than 2,000 gram-negative and gram-positive aerobic isolates collected during 2015 (except for 74 *Staphylococcus saprophyticus*, 13 *Proteus vulgaris* group, 6 *Escherichia coli*, and 2 *S. epidermidis* isolates) as part of the global SENTRY Antimicrobial Surveillance Program were tested
- Additionally, 49 anaerobic gram-positive and gram-negative bacteria were selected from the stock culture collection for testing
- Susceptibility testing for fosfomycin for aerobic organisms was performed by agar dilution using Mueller-Hinton agar supplemented with 25 mg/L glucose-6-phosphate, following CLSI recommendations
- Comparator agents were tested in cation-adjusted Mueller-Hinton broth in frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA)
- Anaerobic susceptibility testing was performed following the CLSI agar dilution method using supplemented Brucella agar with vitamin K, hemin, and lysed horse blood; 25 mg/L glucose-6-phosphate was added to the agar when testing fosfomycin
- Categorical interpretive criteria were those of CLSI (M100-S27 [2017]), EUCAST (2017), M11-A8, or US Food and Drug Administration when EUCAST or CLSI criteria were not available for comparative purposes

Results

- Activity against gram-negative aerobic bacteria
  - Fosfomycin was very active against *Enterobacteriaceae* exhibiting MIC_{50} and MIC_{90} at 4 and 16 mg/L (data not shown)
  - All *Escherichia coli* were susceptible to fosfomycin (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L; Tables 1 and 2)
  - A total of 97.0% of the *Klebsiella pneumoniae* isolates exhibited fosfomycin MIC values at ≤64 mg/L (96.0% susceptible [EUCAST criteria]; Tables 1 and 2)
  - A total of 80.0% of the *Pseudomonas aeruginosa* fosfomycin MIC values were ≤64 mg/L (no EUCAST species specific breakpoints; 95.0% at ≤128 mg/L; MIC_{50}, 64 mg/L and MIC_{90}, 128 mg/L; Tables 1 and 2)
  - A total of 38.2% of the *S. maltophilia* fosfomycin MIC values were ≤64 mg/L (no EUCAST species specific breakpoints; 90.2% at ≤128 mg/L; MIC_{50}, 128 mg/L and MIC_{90}, 128 mg/L; Tables 1 and 2)
- Activity against gram-positive aerobic bacteria
  - Fosfomycin MIC values were ≤64 mg/L (99.5% susceptible [EUCAST criteria]; Tables 1 and 3) when tested against *Staphylococcus aureus*
  - The fosfomycin MIC_{50} for methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) was 4 mg/L; however, the MIC_{90} values were 4 mg/L and 8 mg/L, respectively (Table 1)
  - A total of 91.4% of isolates of coagulase-negative staphylococci (except *S. saprophyticus*) exhibited fosfomycin MIC values at ≤64 mg/L (83.8% susceptible [EUCAST criteria]; MIC_{50}, 8 mg/L and MIC_{90}, 64 mg/L; Tables 1 and 3)
  - All *Streptococcus pyogenes* isolates exhibited fosfomycin MIC values at ≤64 mg/L (Table 1; MIC_{50}, 32 mg/L and MIC_{90}, 64 mg/L)
  - The 104 *S. agalactiae* isolates exhibited fosfomycin MIC values at ≤64 mg/L (Table 1; MIC_{50}, 8 mg/L and MIC_{90}, 64 mg/L)
  - Among the *Enterococcus faecalis* isolates, 99.0% exhibited fosfomycin MIC values at ≤64 mg/L (Tables 1 and 3; 99.0% susceptible; MIC_{50}, 64 mg/L and MIC_{90}, 64 mg/L)
  - A total of 79.8% of the 104 *E. faecium* isolates exhibited fosfomycin MIC values at ≤64 mg/L (Table 1; MIC_{50}, 64 mg/L and MIC_{90}, 128 mg/L)
- Activity against anaerobic gram-positive and gram-negative bacteria
  - When fosfomycin was tested against *Bacteroides fragilis* group isolates, 8 isolates exhibited MIC values >256 mg/L and 1 isolate was at 16 mg/L (Table 1)
  - Against *Prevotella* spp. and *Porphyromonas* spp., fosfomycin MIC values were all >256 mg/L
  - Against *Clostridium* spp., the MIC for 1 isolate was 4 mg/L and for 4 other isolates was 32 mg/L (Table 1)
  - For *Peptostreptococcus* spp., MIC values ranged from 1 to 32 mg/L (Table 1), and for *Finegoldia magna*, MIC values ranged from 0.5-1 mg/L (Table 1)

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

Organism (no.)	No. of isolates at MIC (mg/L; cumulative %)															MIC_{50}	MIC_{90}
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>				
Escherichia 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
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
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)	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 (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
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 *Staphylococcus 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)	2 (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)	39 (63.5)	20 (82.7)	16 (84.6)	2 (100.0)							8	64
Enterococcus spp. (207)						1 (0.5)	53 (26.1)	113 (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)	0 (20.0)	3 (80.0)	1 (100.0)							16	
Propionibacterium spp. (5)													5 (100.0)			>256	
Bacteroides fragilis (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)	0 (60.0)	1 (80.0)	1 (100.0)			8	
Prevotella spp. (5)													5 (100.0)			>256	
Porphyromonas spp. (5)													5 (100.0)			>256	

Table 2 Activity of fosfomycin and comparators when tested against gram-negative bacteria

Antimicrobial agent (no.)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[b] %S	EUCAST[b] %R
Escherichia coli (102)						
Fosfomycin	0.5	1	100.0	0.0	99.0	1.0
Levofloxacin	0.03	>8	69.6	30.4	69.6	30.4
Amikacin	2	4	100.0	0.0	99.0	0.0
Aztreonam	≤0.12	8	89.2	9.8	85.3	10.8
Cefepime	≤0.03	8	87.3	8.8	87.3	10.8
Ceftazidime	0.12	16	89.2	10.8	85.3	10.8
Ceftriaxone	≤0.06	>8	86.3	13.7	86.3	13.7
Gentamicin	0.5	>8	88.2	11.8	88.2	11.8
Imipenem	≤0.12	≤0.12	99.0	1.0	99.0	1.0
Meropenem	≤0.015	0.03	99.0	1.0	99.0	1.0
Piperacillin-tazobactam	1	8	95.1	2.9	93.1	4.9
Tetracycline	1	>8	67.6	32.4		
Trimethoprim-sulfamethoxazole	≤0.5	>4	70.6	29.4	70.6	29.4
Klebsiella pneumoniae (100)						
Fosfomycin	4	16			96.0	4.0
Levofloxacin	0.06	>8	86.0	2.0	84.0	14.0
Amikacin	1	2	100.0	0.0	97.0	0.0
Aztreonam	≤0.12	>16	85.0	0.0	85.0	15.0
Cefepime	≤0.03	16	88.0	2.0	85.0	12.0
Ceftazidime	0.12	32	85.0	1.0	83.0	15.0
Ceftriaxone	≤0.06	>8	85.0	0.0	85.0	15.0
Gentamicin	0.25	8	89.0	1.0	89.0	11.0
Imipenem	≤0.12	0.25	95.0	0.0	95.0	2.0
Meropenem	0.03	0.03	95.0	0.0	95.0	2.0
Piperacillin-tazobactam	2	16	91.0	2.0	87.0	9.0
Tetracycline	1	>16	85.0	1.0		
Trimethoprim-sulfamethoxazole	≤0.5	>4	82.0		82.0	18.0
K. oxytoca (102)						
Fosfomycin	8	16			98.0	2.0
Levofloxacin	0.06	0.06	99.0	1.0	97.1	1.0
Piperacillin-tazobactam	2	4	97.1	2.9	96.1	2.9
Enterobacter aerogenes (104)						
Fosfomycin	8	16			96.2	3.8
Levofloxacin	0.06	0.25	98.1	1.0	95.2	2.9
Piperacillin-tazobactam	2	32	88.5	1.0	80.8	11.5
***E. cloacae* complex** (104)						
Fosfomycin	8	64			89.4	10.6
Levofloxacin	0.03	0.5	96.2	3.8	90.4	4.8
Piperacillin-tazobactam	2	32	86.5	5.8	83.7	13.5
Serratia marcescens (101)						
Fosfomycin	8	16			97.0	3.0
Levofloxacin	0.12	0.5	98.0	1.0	93.1	4.0
Piperacillin-tazobactam	2	4	99.0	0.0	97.0	1.0
Proteus mirabilis (103)						
Fosfomycin	1	8			95.1	4.9
Levofloxacin	0.06	>8	70.9	23.3	62.1	31.1
Piperacillin-tazobactam	0.25	0.5	100.0	0.0	100.0	0.0
***P. vulgaris* group** (100)						
Fosfomycin	16	64			79.0	21.0
Levofloxacin	0.03	0.12	100.0	0.0	100.0	0.0
Piperacillin-tazobactam	≤0.5	≤0.5	99.0	0.0	99.0	1.0
Citrobacter koseri (102)						
Fosfomycin	1	1			100.0	0.0
Levofloxacin	0.03	0.06	99.0	0.0	97.1	2.0
Piperacillin-tazobactam	2	8	99.0	1.0	95.1	1.0
***C. freundii* complex** (104)						
Fosfomycin	0.5	1			100.0	0.0
Levofloxacin	0.06	1	92.3	6.7	82.7	9.6
Piperacillin-tazobactam	2	128	79.8	11.5	76.9	20.2
Pseudomonas aeruginosa (100)						
Fosfomycin	64	128			57.0	43.0
Levofloxacin	1	>8	64.0	27.0	57.0	43.0
Amikacin	2	8	97.0	1.0	95.0	3.0
Aztreonam	4	>16	71.0	19.0	4.0	19.0
Cefepime	2	16	87.0	3.0	87.0	13.0
Ceftazidime	2	16	83.0	9.0	83.0	17.0
Colistin	≤0.5	1	100.0	0.0	100.0	0.0
Gentamicin	2	4	90.0	7.0	90.0	10.0
Imipenem	1	>8	74.0	20.0	80.0	11.0
Meropenem	0.5	16	78.0	16.0	78.0	14.0
Piperacillin-tazobactam	4	64	73.0	9.0	73.0	27.0
***Acinetobacter baumannii-calcoaceticus* complex** (101)						
Fosfomycin	128	256				
Levofloxacin	2	>8	51.5	45.5	46.5	50.5
Piperacillin-tazobactam	64	>64	44.6	43.6		
Stenotrophomonas maltophilia (102)						
Fosfomycin	128	128				
Levofloxacin	1	8	80.4	12.7		
Piperacillin-tazobactam	>64	>64				
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	95.1	4.9	95.1	4.9

[a]Clinical and Laboratory Standards Institute (2017)
[b]EUCAST (2017)
MIC_{50}, mg/L, minimal inhibitory concentration to inhibit growth of 50% of isolates; MIC_{90} mg/L, minimal inhibitory concentration to inhibit growth of 90% of isolates

Table 3 Activity of fosfomycin and comparators when tested against gram-positive bacteria

Antimicrobial agent (no.)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[b] %S	EUCAST[b] %R
Staphylococcus aureus (204)						
Fosfomycin	4	8			99.5	0.5
Levofloxacin	0.25	>8	60.3	39.7	60.3	39.7
Clindamycin	≤0.25	>2	86.3	13.7	86.3	13.7
Daptomycin	0.25	0.5	100.0		100.0	0.0
Erythromycin	>8	>8	40.2	54.9	40.7	57.8
Gentamicin	≤1	≤1	97.5	2.5	97.1	2.9
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	2	>2	50.5	49.5	50.5	49.5
Penicillin	>2	>2	13.7	86.3	13.7	86.3
Tetracycline	≤0.5	≤0.5	94.1	5.9	93.6	5.9
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	98.5	1.5	98.5	1.5
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MRSA (101)						
Fosfomycin	4	8			99.0	1.0
Levofloxacin	4	>8	30.7	69.3	30.7	69.3
Clindamycin	≤0.25	>2	75.2	24.8	75.2	24.8
Erythromycin	>8	>8	9.9	86.1	9.9	90.1
Linezolid	1	1	100.0	0.0	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.0	3.0	97.0	3.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
Coagulase-negative staphylococci (excludes *S. saprophyticus*;105)						
Fosfomycin	8	64			83.8	16.2
Levofloxacin	0.25	>8	56.2	43.8	56.2	43.8
Clindamycin	≤0.25	>2	71.4	25.7	71.4	28.6
Erythromycin	>8	>8	38.1	58.1	38.1	61.0
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Oxacillin	1	>2	46.7	53.3	46.7	53.3
Trimethoprim-sulfamethoxazole	≤0.5	4	74.3	25.7	74.3	8.6
Vancomycin	1	2	100.0	0.0	100.0	0.0
S. saprophyticus (102)						
Fosfomycin	128	>256			5.9	94.1
Levofloxacin	0.5	0.5	100.0	0.0	100.0	0.0
Clindamycin	≤0.25	>2	81.4	18.6	80.4	18.6
Erythromycin	>8	>8	45.1	54.9	45.1	54.9
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	1	2	3.9	96.1	91.2	8.8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.1	2.9	97.1	2.0
Vancomycin	1	1	100.0	0.0	100.0	0.0
Streptococcus pyogenes (100)						
Fosfomycin	32	64				
Levofloxacin	0.5	1	100.0	0.0	100.0	0.0
Clindamycin	0.06	0.06	98.0	2.0	98.0	2.0
Erythromycin	≤0.03	>4	84.0	16.0	84.0	16.0
Penicillin	≤0.03	≤0.03	100.0		100.0	0.0
S. agalactiae (104)						
Fosfomycin	8	64				
Levofloxacin	0.5	1	99.0	1.0	99.0	1.0
Clindamycin	0.06	>2	62.5	36.5	63.5	36.5
Erythromycin	2	>4	42.3	56.7	42.3	56.7
Penicillin	0.06	0.06	100.0		100.0	0.0
Enterococcus faecalis (103)						
Fosfomycin	64	64	99.0	0.0		
Levofloxacin	1	>8	81.6	16.5	83.5	16.5
Linezolid	1	1	100.0	0.0	100.0	0.0
Tetracycline	>8	>8	21.4	76.7		
Vancomycin	1	2	97.1	2.9	97.1	2.9
E. faecium (104)						
Fosfomycin	64	128				
Levofloxacin	>8	>8	7.7	88.5	11.5	88.5
Linezolid	1	1	100.0	0.0	100.0	0.0
Tetracycline	>8	>8	23.1	71.2		
Vancomycin	>16	>16	22.1	76.9	22.1	77.9

[a]Clinical and Laboratory Standards Institute (2017)
[b]EUCAST (2017)
MIC_{50}, mg/L, minimal inhibitory concentration to inhibit growth of 50% of isolates; MIC_{90} mg/L, minimal inhibitory concentration to inhibit growth of 90% of isolates

Conclusions

- Fosfomycin was shown in this study to have potent activity against a broad range of gram-positive and gram-negative bacteria recently isolated from patients in US medical centers in 2015
- Activity included 99.5% of *S. aureus* and 94.9% of *Enterobacteriaceae* susceptible to fosfomycin (EUCAST criteria)
- Fosfomycin demonstrated potent activity against a wide range of *Enterobacteriaceae*, including isolates with an extended-spectrum beta-lactamase and carbapenem-resistant phenotype
- Against *P. aeruginosa,* including isolates selected as meropenem-nonsusceptible and ceftazidime-nonsusceptible; 80.0% of isolates exhibited fosfomycin MIC values ≤64 mg/L (95.0% at ≤128 mg/L)
- With broad-spectrum activity, including activity against multidrug-resistant gram-positive and gram-negative bacteria, fosfomycin merits further study in infections where resistant organisms may occur and a reassessment of US FDA susceptibility breakpoints for the intravenous formulation

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