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Fosfomycin Activity against Gram-Negative Isolates from Eastern Europe Collected by the SENTRY Antimicrobial Surveillance Program

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Abstract

Background: ZTI-01 (fosfomycin, FOS, for injection) is an investigational antibiotic under US development to treat complicated urinary tract infections (cUTIs) and is different than other antimicrobials, as it is thought to inhibit an early step in cell wall synthesis. FOS demonstrates broad *in vitro* activity against gram-negative (GN) and -positive (GP) bacteria, including those containing extended-spectrum β-lactamases (ESBL). In this study, we investigated the activity of FOS against GN clinical isolates from 8 eastern European countries where FOS has been clinically available and extensively utilized (Belarus, Croatia, Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia) in 2016.

Methods: FOS was tested against 160 *Escherichia coli* (EC) and 160 *Klebsiella pneumoniae* (KPN). Isolates were susceptibility (S) tested against FOS by reference agar dilution (with 25 µg/mL glucose-6-phosphate) using FDA's existing oral formulation breakpoints. Comparators levofloxacin (LVX), piperacillin-tazobactam, ceftazidime (TAZ), meropenem (MEM), and amikacin (AMK) were tested by CLSI broth microdilution. ESBL-screen positive (ESBL-SP) and carbapenem-resistant (CRE) phenotypes were assigned according to CLSI (2017).

Results: FOS was very active against EC, 100.0%S to FOS ($MIC_{50/90}$, 0.5/1 mg/L); for KPN, FOS $MIC_{50/90}$ was 8/64 mg/L (90.6%S ≤64 mg/L). All other agents had lower %S for KPN, ranging from 85.0% (AMK) to 23.8% (CAZ) (Table 1). For EC, FOS and MEM were 100%S, AMK was 98.1%S, and LVX was least active. FOS activity was similar for ESBL-SP or CRE isolates.

Conclusions: FOS demonstrated excellent activity against EC and KPN from eastern Europe despite longevity of regional clinical use. FOS was more active than all agents tested for KPN and was as active as MEM for EC. FOS merits further US study in infections where resistant GN and GP may occur. Potentially introducing an IV form in the US will warrant reassessing FDA breakpoints, given the limited bioavailability of the current oral formulation.

Table 1. Comparison of activity of fosfomycin and comparators tested against *E. coli* and *K. pneumoniae* from eastern Europe

Antimicrobial agent	*E. coli* (n=160)			*K. pneumoniae* (n=160)		
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S
Fosfomycin	0.5	1	100.0	8	64	90.6[b]
Levofloxacin	1	>8	51.9	8	>8	35.2
Amikacin	2	8	98.1	4	>32	85.0
Meropenem	≤0.015	0.03	100.0	0.06	16	76.1
Ceftazidime	0.25	32	76.9	>32	>32	23.8
Piperacillin-tazobactam	2	16	90.6	32	>64	42.5

[a] Criteria as published by CLSI [2018]. CLSI oral formulation breakpoints are used for information.
[b] ≤64 µg/mL

Introduction

- ZTI-01 (fosfomycin, FOS, for injection) is under US development to treat complicated urinary tract infections (cUTIs) and is different than other antimicrobials as it is thought to inhibit an early step in cell wall synthesis
- FOS demonstrates broad *in vitro* activity against gram-negative (GN) and -positive (GP) bacteria, including those producing extended-spectrum β-lactamases (ESBL)
- FOS has been used for over 40 years to treat a variety of serious infections
- In this study, we investigated the activity of FOS against GN clinical isolates from 8 eastern European countries where FOS has been clinically available and extensively utilized (Belarus, Croatia, Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia)

Materials and Methods

- FOS was tested against 160 *Escherichia coli* and 160 *Klebsiella pneumoniae* collected in 2016 from patients hospitalized with various infection types in medical centers in the 8 selected eastern European countries
- Isolates were susceptibility (S) tested against FOS by reference agar dilution (with 25 µg/mL glucose-6-phosphate) using Food and Drug Administration's (FDA) existing oral formulation breakpoints
- Comparators levofloxacin (LVX), piperacillin-tazobactam (TZP), ceftazidime (CAZ), meropenem (MEM), and amikacin (AMK) were tested by CLSI broth microdilution
- ESBL-screen positive (ESBL-SP) and carbapenem-resistant *Enterobacteriaceae* (CRE) phenotypes were assigned according to CLSI (2018)

Results

- FOS was very active against *E. coli* (100%S; $MIC_{50/90}$, 0.5/1 mg/L); for *K. pneumoniae*, FOS $MIC_{50/90}$ was 8/64 mg/L (90.6% S; ≤64 mg/L) (Tables 1-3)
- For *E. coli*, FOS and MEM had 100%S, AMK was 98.1%S, and LVX was least active with 51.2%S (Table 1)
  - Susceptibilities for the comparators varied by country, with LVX S varying the most, from 20.7% in Poland to 75.0% in Romania (Table 4)
  - 100% of ESBL-SP *E. coli* were susceptible to FOS

Table 2 Antimicrobial activity of fosfomycin tested against main organisms and organism groups of *E. coli* isolates

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)									MIC_{50}	MIC_{90}
	≤0.12	0.25	0.5	1	2	4	8	16	32		
E. coli[a] (160)	0 0.0	14 8.8	106 75.0	27 91.9	8 96.9	4 99.4	0 99.4	0 99.4	1 100.0	0.5	1
ESBL-SP (58)	0 0.0	3 5.2	41 75.9	8 89.7	1 91.4	4 98.3	0 98.3	0 98.3	1 100.0	0.5	2
Belarus (21)		0 0.0	17 81.0	3 95.2	0 95.2	0 95.2	0 95.2	0 95.2	1 100.0	0.5	1
Croatia (21)	0 0.0	2 9.5	13 71.4	4 90.5	2 100.0					0.5	1
Czech Republic (30)	0 0.0	2 6.7	21 76.7	4 90.0	3 100.0					0.5	1
Hungary (33)	0 0.0	2 6.1	22 72.7	7 93.9	1 97.0	1 100.0				0.5	1
Poland (7)		0 0.0	3 42.9	3 85.7	1 100.0					1	N/A
Romania (4)	0 0.0	3 75.0	0 75.0	1 100.0						0.25	N/A
Russia (33)	0 0.0	5 15.2	22 81.8	3 90.9	0 90.9	3 100.0				0.5	1
Slovakia (11)		0 0.0	1 72.7	2 90.9	1 100.0					0.5	1

[a]CLSI (2018) oral formulation breakpoint ≤64 mg/L

Table 3 Antimicrobial activity of fosfomycin tested against main organisms and organism groups of *K. pneumoniae* isolates

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)									MIC_{50}	MIC_{90}
	≤1	2	4	8	16	32	64[a]	128	256	>[b]		
K. pneumoniae (160)	0 0.0	10 6.2	48 36.2	44 63.8	15 73.1	21 86.2	7 90.6	8 95.6	3 97.5	4 100.0	8	64
ESBL-SP (126)	0 0.0	7 5.6	40 37.3	29 60.3	12 69.8	18 84.1	6 88.9	8 95.2	3 97.6	3 100.0	8	128
CRE (36)		0 0.0	2 5.6	3 13.9	6 30.6	13 66.7	5 80.6	4 91.7	1 94.4	2 100.0	32	128
Belarus (30)	0 0.0	4 13.3	5 30.0	12 70.0	4 83.3	2 90.0	1 93.3	1 96.7	0 96.7	1 100.0	8	32
Croatia (13)		0 0.0	6 46.2	6 92.3	0 92.3	1 100.0					8	8
Czech Republic (11)		0 0.0	4 36.4	5 81.8	0 81.8	1 90.9	1 100.0				8	32
Hungary (18)	0 0.0	1 5.6	9 55.6	6 88.9	0 88.9	1 94.4	0 94.4	1 100.0			4	32
Poland (33)	0 0.0	3 9.1	8 33.3	7 54.5	2 60.6	2 66.7	5 81.8	3 90.9	1 93.9	2 100.0	8	128
Romania (4)		0 0.0	1 25.0	1 50.0	1 75.0	1 100.0					8	N/A
Russia (33)	0 0.0	1 3.0	6 21.2	4 33.3	7 54.5	10 84.8	0 84.8	3 93.9	2 100.0		16	128
Slovakia (18)	0 0.0	1 5.6	9 55.6	3 72.2	1 77.8	3 94.4	0 94.4	0 94.4	0 94.4	1 100.0	4	32

[a] CLSI (2018) oral formulation susceptible breakpoint shaded in darker blue, for information.
[b] Greater than the highest dilution tested.

Table 4 Susceptibilities of fosfomycin and comparators for *E. coli* for ESBL-SP and by country

Organism/organism group	n	% susceptible[a]					
		FOS	LVX	AMK	CAZ	TZP	MEM
E. coli	160	100.0	51.2	98.1	76.9	90.6	100.0
ESBL-SP	58	100.0	20.7	94.8	36.2	84.2	100.0
Belarus	21	100.0	33.3	95.2	52.4	90.5	100.0
Croatia	21	100.0	57.1	90.5	81.0	95.2	100.0
Czech Republic	30	100.0	66.7	100.0	93.3	93.3	100.0
Hungary	33	100.0	63.6	100.0	90.9	96.9	100.0
Poland	7	100.0	28.6	100.0	71.4	85.7	100.0
Romania	4	100.0	75.0	100.0	75.0	50.0	100.0
Russia	33	100.0	39.4	100.0	60.6	84.8	100.0
Slovakia	11	100.0	36.4	100.0	81.8	90.9	100.0

[a]CLSI 2018, fosfomycin oral formulation breakpoint used for information only.
Abbreviations: FOS, fosfomycin; LVX, levofloxacin; AMK, amikacin; CAZ, ceftazidime; TZP, piperacillin-tazobactam; MEM, meropenem

Table 5 Susceptibilities of fosfomycin and comparators for *K. pneumoniae*, for ESBL-SP and CRE phenotypes, and by country

Organism/organism group	n	% susceptible[a]					
		FOS	LVX	AMK	CAZ	TZP	MEM
K. pneumoniae	160	90.6	35.0	85.0	23.8	42.5	76.1
ESBL-SP	126	88.9	22.2	81.7	3.2	30.2	71.2
CRE	36	80.6	0.0	61.1	11.1	2.8	0.0
Belarus	30	93.3	46.7	83.3	46.7	56.7	86.2
Croatia	13	100.0	84.6	92.3	30.8	69.2	100.0
Czech Republic	11	100.0	90.9	100.0	54.5	63.6	100.0
Hungary	18	94.4	44.4	94.4	38.9	88.9	94.4
Poland	33	81.8	6.1	90.9	0.0	9.1	48.5
Romania	4	100.0	75.0	100.0	50.0	50.0	75.0
Russia	33	84.8	18.2	60.6	12.1	24.2	57.8
Slovakia	18	94.4	11.1	94.4	5.6	33.3	94.4

[a]CLSI (2018), fosfomycin oral formulation breakpoints used for information.
Abbreviations: FOS, fosfomycin; LVX, levofloxacin; AMK, amikacin; CAZ, ceftazidime; TZP, piperacillin-tazobactam; MEM, meropenem

- FOS was the most active agent tested against *K. pneumoniae* (90.6%S; Table 1)
  - All other agents had lower %S for *K. pneumoniae*, from 85.0% for AMK to 23.8% for CAZ (Tables 1 and 5)
  - 88.9% of ESBL-SP and 80.6% of CRE isolates were S to FOS
  - FOS %S ranged from 81.8% in Poland to 100.0% in Croatia, Czech Republic, and Romania (Table 5)
  - The comparator with the greatest variability in %S between countries was LVX with 6.1% in Poland to 90.9% in Czech Republic

Conclusions

- FOS demonstrated excellent *in vitro* activity against *E. coli* and *K. pneumoniae* from eastern European countries despite longevity of regional clinical use of FOS
- FOS was more active than all comparator agents tested for *K. pneumoniae* and was as active as MEM (100.0%) for *E. coli*
- FOS merits further US study in infections where resistant GN pathogens may occur
- Potentially introducing an IV formulation in the United States will warrant reassessing FDA breakpoints, given the limited bioavailability of the current oral formulation

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