

Introduction

- In North America, oral fosfomycin tromethamine is approved for the treatment of uncomplicated urinary tract infection (UTI) and intravenous (IV) fosfomycin sodium is indicated alone for complicated UTI, and in combination with other antimicrobials for the treatment of serious infections in adults and children.
- Fosfomycin inhibits susceptible bacteria by irreversibly inactivating the enzyme UDP-N-acetylglucosamine-3-enolpyruvyltransferase (MurA) which ligates phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-N-acetylglucosamine, an essential building block of peptidoglycan.
- Clinical laboratories do not routinely determine fosfomycin MICs using the CLSI reference method (agar dilution) because it is labor-intensive and impairs workflow.
- Susceptibility to fosfomycin may also be determined by Etest® (gradient strip) or by disk diffusion; however, the appearance of colonies within the zone of inhibition can complicate zone size reading.
- Broth dilution testing is not an acceptable method for fosfomycin (CLSI, EUCAST).
- Current CLSI, EUCAST, and FDA MIC/zone size breakpoints for fosfomycin are restricted to only a few bacterial species.

Methods

- 135 ertapenem-resistant (MIC $\geq 2\mu\text{g/ml}$) isolates of *Enterobacterales* collected by the annual CANWARD surveillance study (12–15 Canadian tertiary-care hospital clinical laboratories/year) from 2007 to 2023 were included in the study.
- Fosfomycin susceptibility testing was performed using the CLSI M07 reference agar dilution method (Mueller-Hinton agar supplemented with 25 $\mu\text{g/ml}$ of glucose-6-phosphate); all other antibacterial agents were tested by the CLSI reference broth microdilution method.

Results

Table 2. MIC₅₀, MIC₉₀, and percent susceptible data at MIC breakpoint concentrations for fosfomycin and percent susceptible data for comparators tested against ertapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* isolated in Canadian tertiary-care hospital clinical laboratories from 2007 to 2023

	MIC ₅₀ /MIC ₉₀ µg/ml	% Susceptible (MIC breakpoint concentration)			% Susceptible			
Isolate Phenotype (n)	Fosfomycin	Fosfomycin (≤64 µg/ml) ^a	Fosfomycin (≤32 µg/ml) ^b	Fosfomycin (≤8 µg/ml) ^c	CIP	SXT	GENT	MERO
<i>Klebsiella pneumoniae</i> (26)	128/512	NA	26.9	NA	11.5	23.1	57.7	30.8
<i>Escherichia coli</i> (23)	8/16	95.7	NA	65.2	13.0	30.4	65.2	65.2

Abbreviations: CIP, ciprofloxacin; SXT, trimethoprim-sulfamethoxazole; GENT, gentamicin; MERO, meropenem; NA, not applicable.

^a MICs interpreted using CLSI M100 (36th Edition, 2026) breakpoints (urine) for *E. coli* and *E. faecalis*.

^b MICs interpreted using FDA breakpoint for IV fosfomycin for *K. pneumoniae*.

^c MICs interpreted using EUCAST (Version 16.0, 2026) oral (uncomplicated UTI) and IV (infections originating from the urinary tract) breakpoints for *E. coli*, and the FDA breakpoint for IV fosfomycin for *E. coli*.

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Conclusions

- Fosfomycin inhibited 65.2% of ertapenem-resistant *E. coli* at ≤ 8 $\mu\text{g/ml}$ and 95.7% of ertapenem-resistant *E. coli* at 64 $\mu\text{g/ml}$.
- Fosfomycin inhibited 26.9% of ertapenem-resistant *K. pneumoniae* at 32 $\mu\text{g/ml}$.
- Clinicians should be aware of differences in fosfomycin formulations and their associated MIC breakpoints.
- The differences in CLSI, EUCAST, and FDA MIC breakpoints impacts the percentage of isolates *Enterobacterales* reported as susceptible.

Table 1. Currently published fosfomycin breakpoints

Breakpoint Setting Organization	Fosfomycin formulation	Specimen Source	Pathogen	Breakpoints					
				Susceptible		Intermediate		Resistant	
				MIC µg/ml	Zone Size mm	MIC µg/ml	Zone Size mm	MIC µg/ml	Zone Size mm
CLSI	Fosfomycin tromethamine (oral)	Urine	<i>E. coli</i>	≤64	≥16	128	13–15	≥256	≤12
	Fosfomycin tromethamine (oral)	Urine	<i>E. faecalis</i>	≤64	≥16	128	13–15	≥256	≤12
EUCAST	Fosfomycin sodium (IV)	Infections originating from the urinary tract	<i>E. coli</i>	≤8	≥24	NA	NA	>8	<24
	Fosfomycin tromethamine (oral)	Uncomplicated UTI only	<i>E. coli</i>	≤8	≥24	NA	NA	>8	<24
FDA ^a	Fosfomycin sodium (IV)	Systemic	<i>E. coli</i>	≤8	≥24	16	21–23	≥32	≤20
	Fosfomycin sodium (IV)	Systemic	<i>K. pneumoniae</i>	≤32	≥18	64	15–17	≥128	≤14

NA: not applicable.

Agar dilution: MICs determined using agar containing 25 µg/ml glucose-6-phosphate.

Disk diffusion: Zone sizes determined using a 200 µg fosfomycin disk containing 50 µg glucose-6-phosphate.

^a Susceptibility interpretive criteria are based on a dose of 6 grams fosfomycin every 8 hours by IV infusion over 1 hour in patients with an estimated creatinine clearance of 50 ml/minute.

Table 3. Cumulative MIC distributions for fosfomycin against ertapenem-resistant *Enterobacterales* species isolated in Canadian tertiary-care hospital clinical laboratories from 2007 to 2023

Ertapenem-resistant species (n)	MIC ₅₀ /MIC ₉₀ µg/ml	Fosfomycin MIC (µg/ml)									
		Cumulative % of isolates inhibited at MIC ^a									
		≤1	2	4	8 ^b	16	32 ^c	64 ^d	128	256	≥512
<i>Enterobacter cloacae</i> (59)	32/256	3.4	25.4	33.9	37.3	42.4	61.0	69.5	89.8	98.3	100
<i>Klebsiella pneumoniae</i> (26)	128/512	0	0	0	0	3.8	26.9	42.3	65.4	84.6	100
<i>Escherichia coli</i> (23)	8/16	0	17.4	43.5	65.2	95.7	95.7	95.7	95.7	100	
<i>Klebsiella aerogenes</i> (10)	64/128	0	0	10.0	10.0	10.0	20.0	60.0	90.0	90.0	100
<i>Serratia marcescens</i> (8)	16/>512	0	0	12.5	37.5	50.0	62.5	62.5	87.5	87.5	100
<i>Citrobacter freundii</i> (4)	4/256	25.0	25.0	50.0	50.0	75.0	75.0	75.0	75.0	100	
<i>Klebsiella oxytoca</i> (2)	16/32	0	0	0	0	50.0	100				
<i>Proteus mirabilis</i> (2)	4/4	0	0	100							
<i>Morganella morganii</i> (1)	>512/>512	0	0	0	0	0	0	0	0	0	100
All isolates (135)	32/256	2.2	14.8	26.7	33.3	43.7	58.5	68.1	85.2	94.1	100

^a MIC percentile only for organisms not listed in CLSI, EUCAST, or FDA MIC breakpoint references.

^b MICs interpreted using EUCAST (Version 16.0, 2026) oral (uncomplicated UTI) and IV (infections originating from the urinary tract) breakpoints for *E. coli*, and the FDA breakpoint for IV fosfomycin for *E. coli*.

^c MICs interpreted using FDA breakpoint for IV fosfomycin for *K. pneumoniae*.

^d MICs interpreted using CLSI M100 (36th Edition, 2026) breakpoints (urine) for *E. coli* and *E. faecalis*.

References

1. Monurol® package insert. 2019. Allergan, Inc.
2. Contempo package insert. 2025. Meitheal Pharmaceuticals Inc.
3. M07, 12th edition. 2024. CLSI.
4. M100, 36th edition. 2026. CLSI.
5. Clinical breakpoints – bacteria (v 16.0). 2026. EUCAST.
6. <https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria>

- Percent susceptible values for ciprofloxacin (11.5–13.0%) and trimethoprim-sulfamethoxazole (23.1–30.4%) were low for ertapenem-resistant *K. pneumoniae* and ertapenem-resistant *E. coli*.
- The meropenem percent susceptible value was considerably lower for *K. pneumoniae* (30.8%) than for *E. coli* (65.2%).
- Fosfomycin frequently demonstrated *in vitro* activity against some isolates of species of *Enterobacterales* other than *K. pneumoniae* and *E. coli*.