IMPIEGO TERAPEUTICO DELLA FOSFOMICINA NELLE INFEZIONI DA BATTERI MULTIRESISTENTI

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TERAPIA DELLE INFEZIONI DA ENTEROBATTERI PRODUTTORI DI ESBL (betalattamasi a spettro esteso)

1. **IMIPENEM**
   MEROPENEM
   ERTAPENEM

2. (TIGECICLINA) **(non attiva su Proteus mirabilis e Proteus indolo**

4. FOSFOMICINA EV *(sempre in associazione)*

5. FOSFOMICINA os NITROFURANTOINA os (UTI)

6. CEFTOLOZANE/TAZOBACTAM

7. CEFTAZIDIME/AVIBACTAM

TERAPIE DELLE SEPSI DA KPC

- COLIMICINA + MEROPENEM + TIGECICLINA
- COLIMICINA + MEROPENEM + FOSFOMICINA

- GENTAMICINA + MEROPENEM + TIGECICLINA
- GENTAMICINA + MEROPENEM + FOSFOMICINA

- COLIMICINA o GENTAMICINA + TIGECICLINA
- COLIMICINA o GENTAMICINA + FOSFOMICINA

- CEFTAZIDIME/AVIBACTAM
- CEFTAZIDIME/AVIBACTAM + GENTAMICINA
- CEFTAZIDIME/AVIBACTAM + FOSFOMICINA

FOSFOMICINA

- Derivato dell'acido fosfonico isolato nel 1969 da colture di *Streptomyces spp*., attualmente prodotta in forma sintetica
  - fosfomicina-trometamina o fosfomicina sale calcico: **formulazione orale**
  - fosfomicina di-sodica: **formulazione parenterale**

- **Battericida**, inibisce la sintesi di peptidoglicano ad uno stadio più precoce rispetto alle β-lattamine

- **Ampio spettro d'azione**
  - Gram positivi: *S.aureus* anche *MR, S. epidermidis, S.pneumoniae, E.faecalis anche VR*
  - Gram negativi: *E.coli, Proteus spp, K.pneumoniae, Enterobacter spp, Serratia marcescens, Salmonella typhi*
  INATTIVA: *L. monocytogenes, Bacteroides fragilis.*
  Acinetobacter baumannii e *P.aeruginosa* tendenzialmente resistenti, ma se associata ad altre classi antibiotiche può manifestare effetto sinergico

- Meccanismo d'azione **concentrazione-dipendente o tempo-dipendente non chiaro**, secondo alcuni studi
  - concentrazione-dip. per *E.coli, Proteus mirabilis* (vitro) e *S.pneumoniae* (vivo)
  - tempo-dip per *S.aureus* (vitro)

CID 2008;46:1069-77
Int J Antimicrob Agents 2009;34:506-15

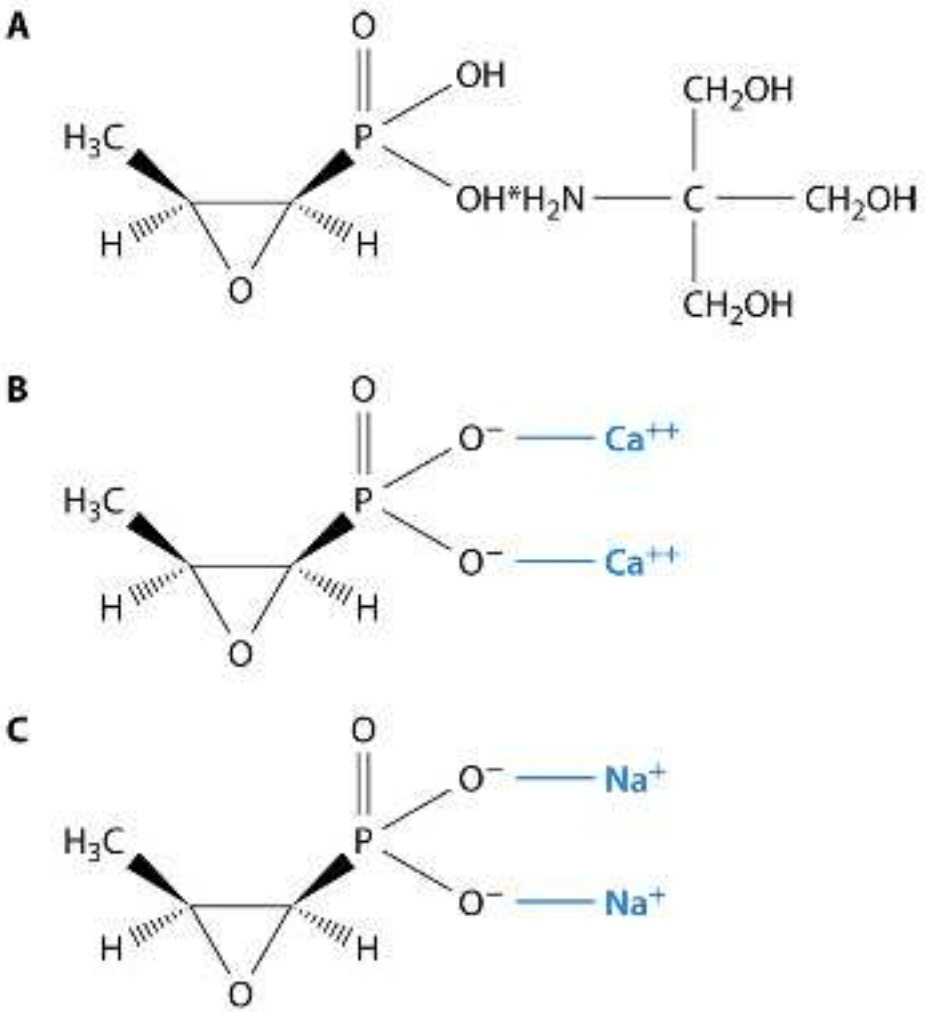


FIG 1 (A) Molecular structure of fosfomycin trometamol. (B) Molecular structure of fosfomycin calcium. (C) Molecular structure of fosfomycin disodium.

Origin and Chemical Structure

Fosfomycin is an old antibiotic agent, discovered in 1969 (1). It is a phosphoenolpyruvate (PEP) analogue that is produced by *Streptomyces* spp., namely, *Streptomyces fradiae* (ATCC 21096), *S. viridochromogenes* (ATCC 21240), and *S. wedmorensis* (ATCC 21239) (1). It may also be produced synthetically (2).

Fosfomycin is a molecule with a low molecular weight (MW) (138) (3). The molecular structure of fosfomycin differs in regard to the available drug formulations. Specifically, fosfomycin is available in two oral formulations, fosfomycin trometh-amine (or fosfomycin trometamol) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$) Fig. 1A) and fosfomycin calcium ($C_3H_5CaO_4P$) (Fig. 1B), and one intravenous (i.v.) formulation, fosfomycin disodium ($C_3H_5Na_2O_4P$) (Fig. 1C).

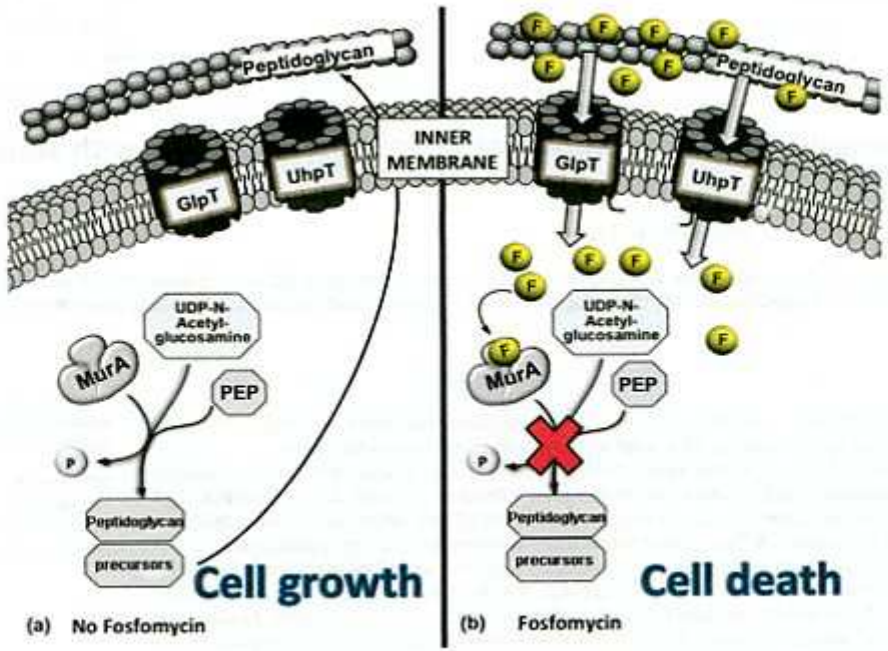
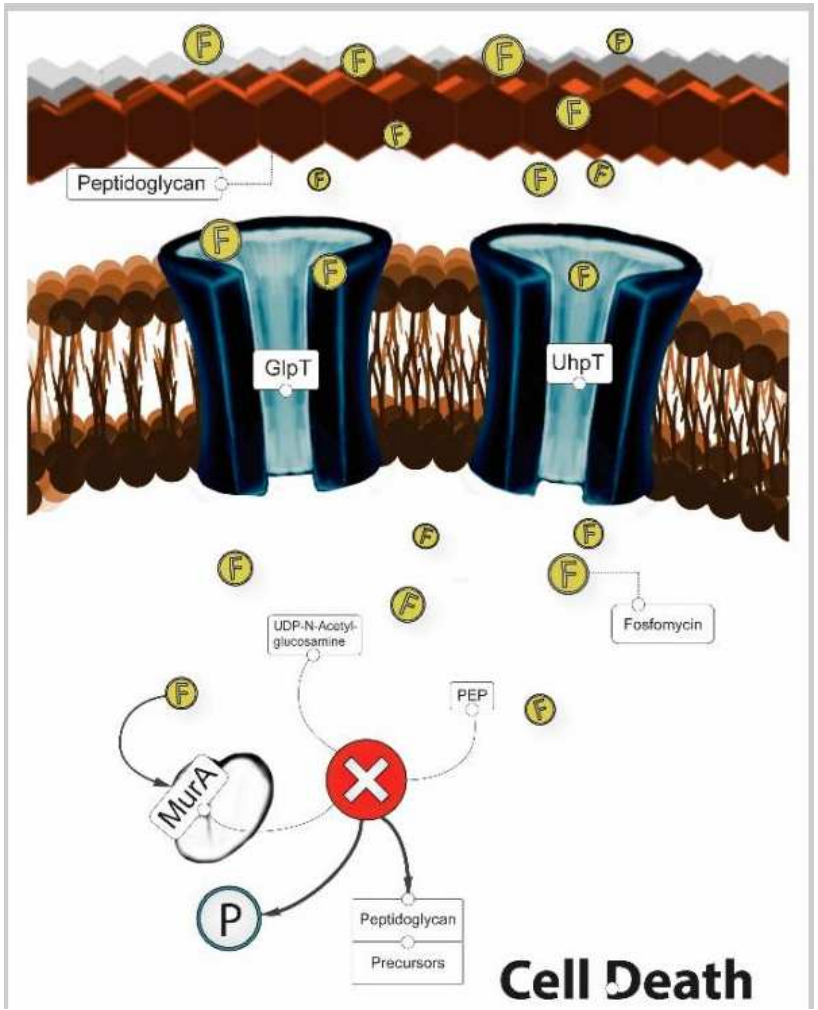


Figure 1. Mechanism of action of fosfomycin [5].

MECHANISM OF ACTION



Fosfomycin is an inhibitor of the MurA enzyme that catalyzes the first committed step in peptidoglycan synthesis.

A.C. Dijkmans 2017

Fosfomycin: susceptible species

Commonly susceptible species

Aerobic Gram positive microorganisms

Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae

Aerobic Gram negative microorganisms

Citrobacter spp.
Edwardsiella spp.
Enterobacter cancerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Neisseria spp.
Proteus mirabilis
Proteus penneri

Anaerobic microorganisms

Peptococcus spp.
Peptostreptococcus spp.

Species in which acquired resistance may be a problem

Gram positive microorganisms

Enterococcus faecalis
Staphylococcus epidermidis

Gram negative microorganisms

Enterobacter cloacae
Klebsiella pneumoniae
Proteus inconstans
Pseudomonas aeruginosa
Acinetobacter baumanii

Inherently resistant species

Gram negative microorganisms

Morganella morganii

Anaerobic microorganisms

Bacteroides spp.

Apathogenic anaerobic microorganisms

Lactobacillus spp.
Bifidobacterium spp.

Spectrum of Activity

In vitro susceptibility data suggest that fosfomycin is considerably active against both Gram-negative and Gram-positive pathogens. Specifically, fosfomycin is considered active against *Enterococcus* spp. (including *Enterococcus faecalis* and *E. faecium* irrespective of vancomycin resistance), *Staphylococcus aureus* (irrespective of methicillin resistance), and *S. epidermidis* (37, 38). Fosfomycin also exhibits considerable activity against Gram-negative pathogens, including *Salmonella* spp., *Shigella* spp., *E. coli*, *Klebsiella* and *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., and *Proteus mirabilis* (37–41). Fosfomycin has been also found to be active against *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Aerococcus urinae*, and *Helicobacter pylori* (42–45). Fosfomycin is not active against anaerobes, such as *Bacteroides* spp., but it is active against *Peptococcus* spp. and *Peptostreptococcus* spp. (46, 47). *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Staphylococcus capitis*, *Staphylococcus saprophyticus*, and *Mycobacterium tuberculosis* are intrinsically resistant to fosfomycin (48, 49). *Morganella morganii* is also resistant to fosfomycin (50).

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The majority of the recently published studies evaluated the *in vitro* activity of fosfomycin against ESBL-producing *Enterobacteriaceae*, particularly *E. coli* and *K. pneumoniae* (68–71, 73, 74, 77–81, 84–86, 89). Although studies evaluating the susceptibility of isolates recovered from blood or respiratory specimens have been published, the great majority of these studies focused on urine samples. In general, fosfomycin was more active against *E. coli* (range, 82% to 100%) than against *K. pneumoniae* (15% to 100%). Community-acquired strains were in general more susceptible than nosocomial strains. Susceptibility of other *Enterobacteriaceae* was less frequently reported, but fosfomycin remained active against a significant proportion (72% to 97.5%); *P. mirabilis* was reported as the least susceptible of them. Finally, fosfomycin was found to be active against 90.5% to 100% of MDR *Enterobacteriaceae* (57, 76).

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Fosfomycin was also evaluated against carbapenem-resistant (CR) or carbapenemase-producing Gram-negative bacteria (57, 76, 93). Most of the data refer to KPC-producing *K. pneumoniae* strains or, to a lesser extent, to other *Enterobacteriaceae*. MIC_{50} and MIC_{90} values were usually one dilution lower in ESBL-producing *K. pneumoniae* strains than in CR/KPC-producing *K. pneumoniae* strains. All CR *A. baumannii* strains were also resistant to fosfomycin (94), while 80.6% of CR *P. aeruginosa* strains were reported to be susceptible in one study (61).

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TABLE 2 Data on *in vitro* susceptibility of MDR or XDR bacteria to fosfomycin and relevant antibiotics from the larger studies published from 2010 onwards[a]

Category	First author, yr (reference)	Country, period	Method(s)	Source of infection	Resistance profile[b]	Organism(s)	No. of isolates	Susceptibility to fosfomycin (%)	Fosfomycin MIC_{50}, MIC_{90} (mg/liter)
Carbapenem-resistant or carbapenemase-producing Gram-negative bacteria	Jiang, 2015 (75)	China, 2010–2013	AD	NR	KPC	*K. pneumoniae*	278	39.2	64, >256
	Diaz-Aguilar, 2013 (61)	NR	AD, BMD	NR	CR (28.2)	*P. aeruginosa*	206	80.6	64, 256/512[d]
	Tuon, 2013 (88)	Brazil, 2010–2011	DD	Various	KPC-2	*K. pneumoniae*	311	99	NR
ESBL-producing *Enterobacteriaceae*	Cho, 2015 (73)	South Korea, 2008–2013	Microscan	UTI	ESBL	*E. coli*, *K. pneumoniae*	277	87.7 (*E. coli*, 94.9; *K. pneumoniae*, 61.7)	NR
	Sultan, 2015 (86)	India	DD	UTI	ESBL, AmpC	*Enterobacteriaceae* (*E. coli*, 90%)	372	98.9 (ESBL, 100; AmpC, 95.7)	NR
	Asencio, 2014 (69)	Spain, 2010–2012	Vitek II	Various	ESBL	*E. coli*	824	95 (ESBL, 82)	NR
						K. pneumoniae	136	88 (ESBL, 91)	
	Khan, 2014 (78)	Pakistan, NR	DD	UTI	ESBL	*Enterobacteriaceae*	381	Total, 84; *E. coli*, 93; *Klebsiella* spp., 64; *Proteus* spp., 50	NR
	Cagan Aktas, 2014 (71)	Turkey, 2011–2012	DD, Etest	UTI	ESBL (48.4)	*E. coli*	244	99 (ESBL, 97)	0.5, 3
	Sorlozano, 2014 (85)	Spain, 2006–2012	Wider, Microscan	UTI	ESBL (4.4–31.8)[c]	*K. pneumoniae*	3,271	40–78	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*E. coli*	374	97.6 (ESBL, 98.2)	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*K. pneumoniae*	94	94.7	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*P. mirabilis*	50	72	NR
	Lai, 2014 (79)	China, 2004–2012	AD	UTI	ESBL (58.1)	*E. coli*	908	98.4 (ESBL, 93.8)	NR
	Karlowsky, 2014 (77)	Canada, 2007–2013	AD	Various non-UTI	ESBL	*E. coli*	254	94.9	2, 4
					AmpC		119	96.6	2, 16
	Morfin-Otero, 2013 (81)	Mexico, 2010–2011	BMD	NR	ESBL (16)	*E. coli*	75	96.9	≤32, ≤32
						K. pneumoniae	21		≤32, ≤32
	Sahni, 2012 (84)	India, 2009–2010	DD	UTI	ESBL (47.6)	*E. coli*	2,416	83 (ESBL, 81)	NR
	Araj, 2012 (68)	Lebanon	DD	UTI	ESBL	*E. coli*	374	86	NR
						K. pneumoniae	168	62	
	Briongos-Figuero, 2012 (70)	Spain, 2009	Vitek II, Etest	UTI	ESBL	*E. coli*	372	88.7	NR
						Klebsiella spp.	28	46	

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Original article

Alternatives to carbapenems in ESBL-producing *Escherichia coli* infections

Alternatives aux carbapénèmes dans les infections à Escherichia coli producteurs de BLSE

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Abstract

Objectives. – The authors had for objective to assess the activity of a wide panel of antibiotics on extended-spectrum-β-lactamase producing *Escherichia coli* isolates (ESBL-Ec), because of the sharp increase of their frequency, leading to an increased use of carbapenems.

Material and methods. – We selected 100 ESBL-Ec in which ESBLs were identified by PCR and sequencing, between 2009 and 2010. We determined the MICs of amoxicillin-clavulanate, piperacillin-tazobactam, temocillin, mecillinam, cefoxitin, cefotaxime, ceftazidime, aztreonam, tigecycline, nitrofurantoin, and fosfomycin using reference methods. The susceptibility profiles were defined according to EUCAST 2012 recommendations.

Results. – Fosfomycin, nitrofurantoin, and pivmecillinam were active against more than 90% of isolates and remain excellent choices for the oral treatment of urinary tract infections (UTIs). Temocillin and piperacillin-tazobactam are also good candidates for the treatment of pyelonephritis or bloodstream infections. Only 27, 23, and 8% of isolates were susceptible to ceftazidime, cefepime, and cefotaxime, respectively.

Conclusion. – Our study results prove that in many cases, there are non-carbapenem alternatives for the treatment of ESBL-Ec infections.

Keywords: *Escherichia coli*; ESBL; Antibiotic resistance

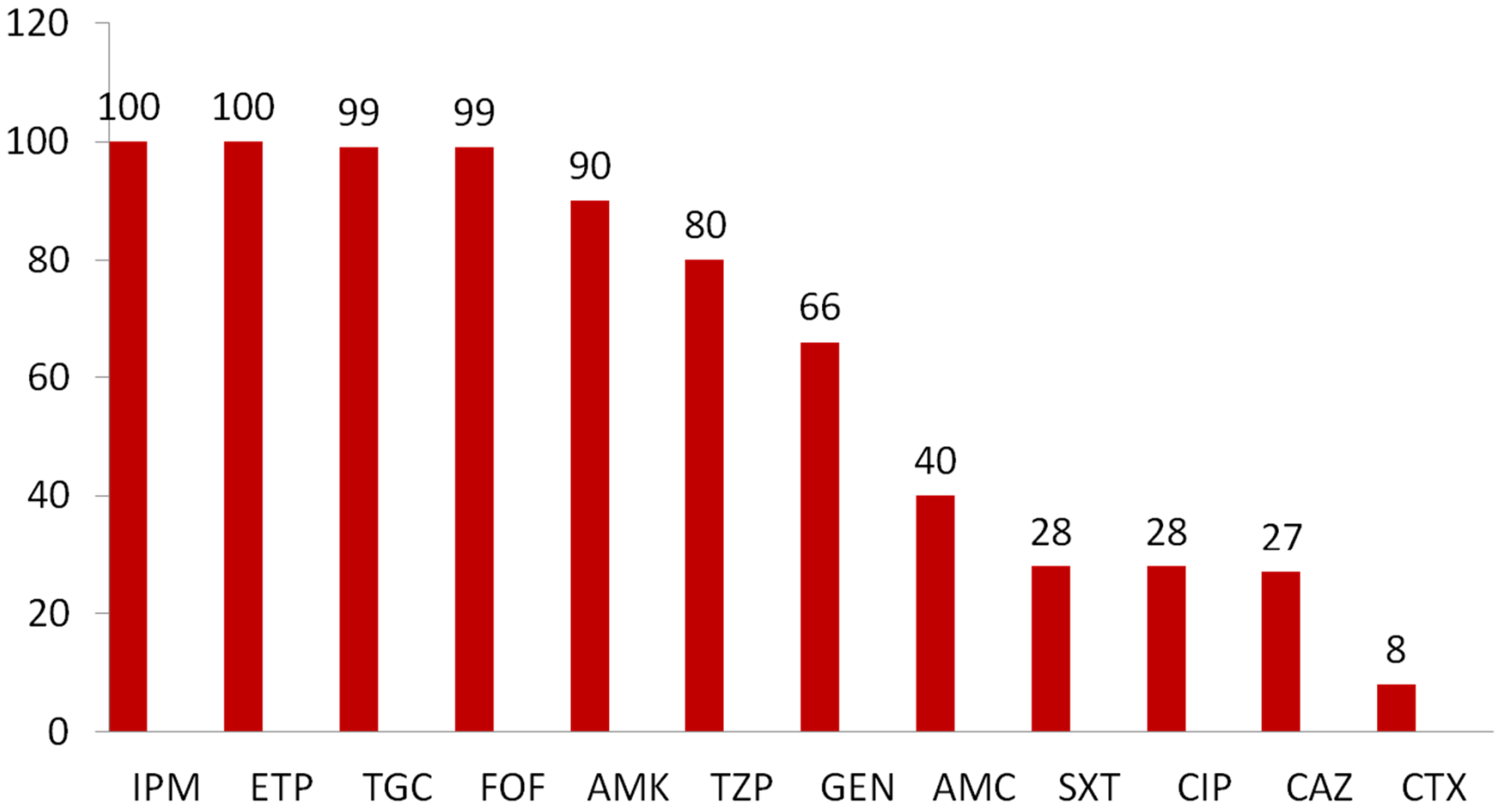
Table: In vitro activity of fosfomycin and 12 other antibacterial agents against the 499 isolates tested

Antibacterial agent	MIC (mg/l)														MIC_{50} (mg/l)	MIC_{90} (mg/l)	%S	%I	%R
	≤0.063	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512					
Fosfomycin					**293**	129	39	13	14	5	4	1	*1*		≤1	4	98.8	-	1.2
Amoxicillin				**2**	18	114	144	7	5	5	*204*				4	≥64	57.1	-	42.9
Amoxicillin-clavulanic acid					**29**	171	90	46	77	33	26	11	*16*		4	64	67.3	-	32.7
Cefuroxime				2	10	80	262	95	13	*37*					4	8	90.0	-	10.0
Cefixime	**27**	77	213	113	28	5	3	*33*							0.25	1	91.8	-	8.2
Cefpodoxime	**6**	36	242	144	28	3	3	*37*							0.25	1	91.4	-	8.6
Ciprofloxacin	**353**	9	25	9	4	1	6	9	*83*						≤0.063	≥16	79.4	0.8	19.8
Levofloxacin	**348**	8	24	16	5		12	43	*43*						≤0.063	8	80.4	0	19.6
Ofloxacin		**353**	7	19	19	3		12	*86*						≤0.125	≥16	76.0	3.8	20.2
Norfloxacin		**352**	13	28	5	2		2	*97*						≤0.125	≥16	78.8	1.0	20.2
Trimethoprim			**288**	39	7		2	2	4	*157*					≤0.25	≥32	66.9	0.4	32.7
Trimethoprim-sulfmethoxazole			**328**	8	4	3	2		2	*152*					≤0.25	≥32	68.7	0.4	30.9
Nitrofurantoin									**443**	48	4	3	1		≤16	32	99.2	-	0.8

Abbreviations: %-S, % susceptible; %-I, % intermediate; %-R, % resistant; numbers in bold include isolates with MIC < value shown; numbers in italic include isolates with MIC > the highest concentration tested.

M. Kresken, B. Körber-Irrgang – 22°ECCMID 2012

Susceptibility (%) of extended-spectrum-β-lactamase (ESBL) producing Escherichia coli to various antibiotics



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Antimicrobial susceptibility of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Enterobacteriaceae isolates to fosfomycin

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ABSTRACT

The advancing antimicrobial drug resistance among Enterobacteriaceae renders the evaluation of potential novel therapeutic options necessary. We sought to evaluate the in vitro antimicrobial activity of fosfomycin against multidrug-resistant (MDR) Enterobacteriaceae isolates. Antimicrobial susceptibility to fosfomycin and 12 additional antibiotics of MDR Enterobacteriaceae isolates collected between November 2007 and April 2009 at the University Hospital of Heraklion, Crete, Greece, was examined using the Etest method. A total of 152 MDR Enterobacteriaceae isolates were studied, including *Klebsiella pneumoniae* (76.3%), *Escherichia coli* (17.1%), *Proteus mirabilis* (4.6%) and other species (2.0%). Antimicrobial susceptibility rates were highest for fosfomycin (92.8%), tigecycline (92.1%) and colistin (73.0%) followed by imipenem (35.5%), tetracycline (20.4%), gentamicin (19.7%), trimethoprim/sulfamethoxazole (12.5%) and ciprofloxacin (10.5%). Of the 152 isolates, 85 (55.9%) were extensively drug-resistant (XDR), of which 78 (91.8%) remained susceptible to fosfomycin. Susceptibility to fosfomycin of the 79 carbapenemase-producing, 34 extended-spectrum β-lactamase-producing and 24 metallo-β-lactamase-producing isolates was 94.9%, 94.1% and 83.3%, respectively. In conclusion, in this study fosfomycin exhibited good in vitro antimicrobial activity against MDR and XDR Enterobacteriaceae. We suggest further evaluation of the potential clinical utility of fosfomycin against infections caused by these pathogens.

TABLE 1 Available fosfomycin MICs and zone diameter breakpoints according to the latest EUCAST and CLSI criteria[a]

Criteria[b]	Organism(s) and delivery route	MIC (mg/liter)			Zone diameter (mm)		
		S	I	R	S	I	R
EUCAST	*Enterobacteriaceae*						
	Intravenous	≤32		>32	NR		NR
	Oral[c]	≤32		>32	NR		NR
	Pseudomonas spp.						
	Intravenous[d]						
	Oral	NR		NR	NR		NR
	Staphylococcus spp.						
	Intravenous	≤32		>32	—[e]		—
	Oral	NR		NR	NR		NR
CLSI[f]	*E. coli*[g]	≤64	128	≥256	≥16	13–15	≤12
	E. faecalis[h]	≤64	128	≥256	≥16	13–15	≤12

[a] S, susceptible, I, intermediate, R, resistant; NR, not reported.

[b] EUCAST criteria are from version 5.0, 2015 (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf); CLSI criteria are from 2015 (48).

[c] For uncomplicated urinary tract infections.

[d] Epidemiological cutoff for wild-type isolates, ≤128 mg/liter.

[e] —, MICs are recommended.

[f] *Pseudomonas* spp., *Acinetobacter* spp., *B. cepacia* complex, *S. maltophilia*, *S. saprophyticus*, and *S. capitis* are considered to have intrinsic resistance, defined as inherent or innate (not acquired) antimicrobial resistance, which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary.

[g] Testing and reporting only for *E. coli* urinary isolates.

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EUCAST

Enterobacteriaceae (new taxonomy: Enterobacterales*)

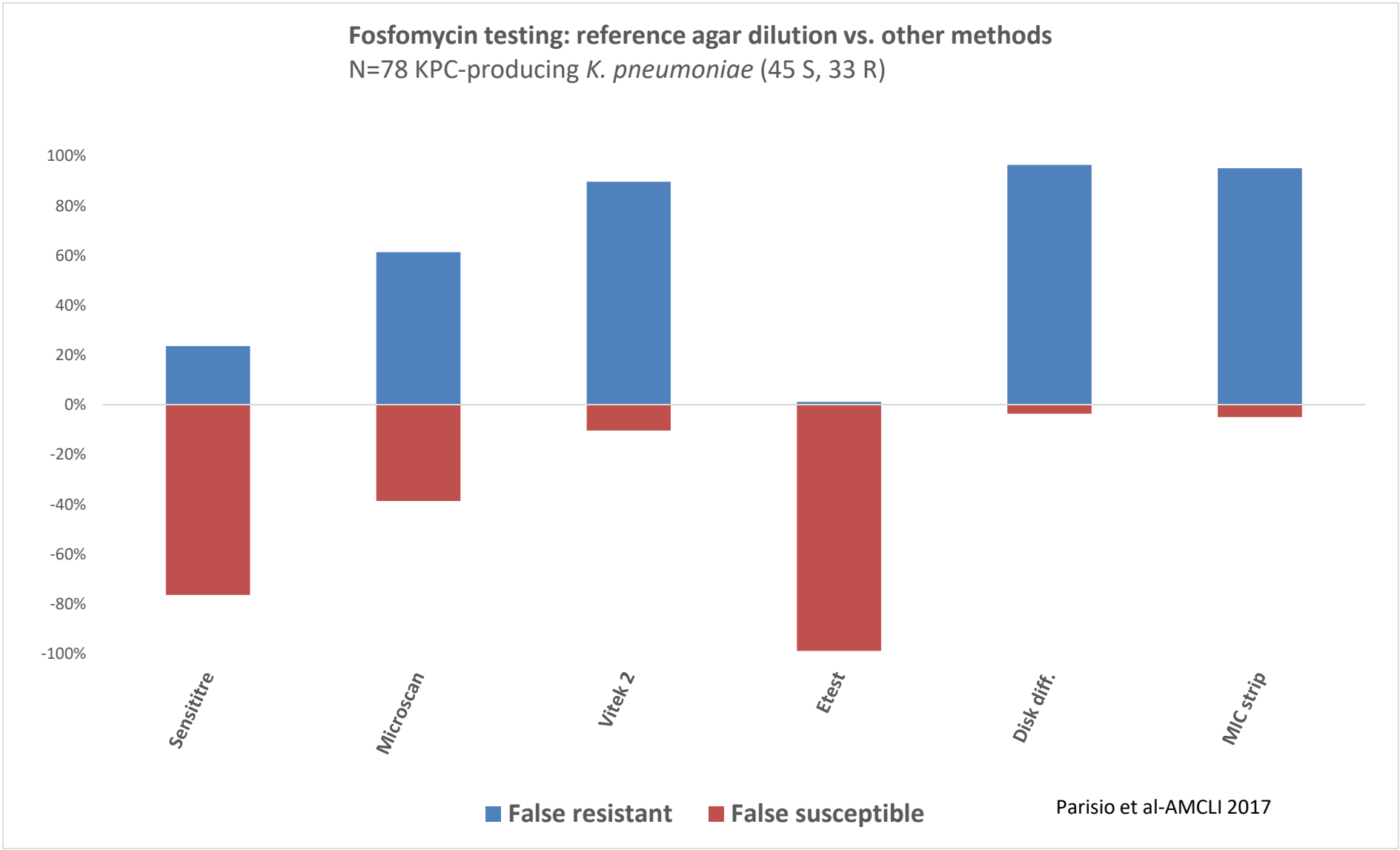
EUCAST Clinical Breakpoint Tables v. 8.0, valid from 2018-01-01

Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Chloramphenicol	8	8	30	17	17	1. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).
Colistin[1]	2	2		Note[A]	Note[A]	
Daptomycin	-	-		-	-	
Fosfomycin iv	32[2]	32[2]	200[B]	24[C,D]	24[C,D]	2. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.
Fosfomycin oral (uncomplicated UTI only)	32[2]	32[2]	200[B]	24[C,D]	24[C,D]	3. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.
Fusidic acid	-	-		-	-	
Metronidazole	-	-		-	-	A. Use an MIC method (broth microdilution only).
Nitrofurantoin (uncomplicated UTI only), *E. coli*	64	64	100	11	11	B. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate.
Nitroxoline (uncomplicated UTI only), *E. coli*	16	16	30	15	15	C. Zone diameter breakpoints apply to *E. coli* only. For other Enterobacteriaceae, use an MIC method.
Rifampicin	-	-		-	-	D. Ignore isolated colonies within the inhibition zone (see pictures below).
Spectinomycin	-	-		-	-	
Trimethoprim (uncomplicated UTI only)	2	4	5	18	15	
Trimethoprim-sulfamethoxazole[3]	2	4	1.25-23.75	14	11	

Examples of inhibition zones for *Escherichia coli* with fosfomycin.

a-c) Ignore all colonies and read the outer zone edge.

d) Record as no inhibition zone.


Fosfomycin testing: reference agar dilution vs. other methods
N=78 KPC-producing K. pneumoniae (45 S, 33 R)
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
-100%
Sensititre
Microscan
Vitek 2
Etest
Disk diff.
MIC strip
False resistant
False susceptible
Parisio et al-AMCLI 2017

TERAPIA ANTIBIOTICA DI ASSOCIAZIONE CON FOSFOMICINA:

GRAM NEGATIVI

A) **Synergy of fosfomycin with carbapenems, colistin, netilmicin and tigecyclin against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa***

Antibiotic in combination with fosfomycin	*K. pneumoniae* KPC (N=50)	*P. aeruginosa* MDR (N=15)	*E. coli* ESBL (N=20)	*K. pneumoniae* ESBL (N=14)	*K. pneumoniae* (KPC+MBL+ESBL) (N=65)
Isolates exhibiting synergy, n (%)					
IMP	37 (74,0)	7 (46,7)	11 (55,0)	11 (78,6)	4 (75,4)
MPM	35 (70,0)	8 (53,3)	5 (25,0)	6 (42,9)	41 (63,1)
DPM	37 (74,0)	11 (73,3)	6 (30,0)	6 (42,9)	43 (66,2)
TIGECICLINA	15 (30,0)	2 (13,3)	5 (25,0)	3 (21,4)	18 (27,7)
COLISTINA	18 (36,0)	2 (13,3)	3 (15,0)	1 (7,1)	19 (29,2)
AG (netilmicina)	21 (42,0)	2 (13,3)	5 (25,0)	6 (42,9)	27 (41,5)

[Samonis G, et al. Eur J Clin Microbiol, Infect Dis 2012, 31:695-701]

Synergistic activity of fosfomycin

TABLE 3 Synergistic activity of fosfomycin in combination with other antibiotics against several clinically relevant bacteria

Organism(s)	Antibiotics with activity in combination with fosfomycin (reference[s])		
	Synergy	Indifference	Antagonism
MSSA	Linezolid (174), ciprofloxacin (24), ceftriaxone (137), ciprofloxacin (137), rifampin (137)	Vancomycin (137), ceftriaxone (137), gentamicin (137)	
MRSA	Cefamandole (138, 139, 268), cefazolin (138, 139, 268), vancomycin (29, 137, 229), rifampin (29, 90, 142, 147), carbapenems (13, 152), cefmetazole (13), cefoperazone-sulbactam (13), linezolid (161), quinupistin-dalfopristin (162), fusidic acid (90), minocycline (163), tigecycline (29), daptomycin (29, 165)	Aminoglycosides (268), fusidic acid (268), trimethoprim (268), vancomycin (137)	Rifampin (139)
Glycopeptide-intermediate *S. aureus*	Imipenem (166), vancomycin (166), linezolid (166)		
CoNS	Ciprofloxacin (137), imipenem (137), rifampin (137)	Vancomycin (137)	
MR *S. epidermidis*		Vancomycin (167)	
Enterococcus VRE	Cefotaxime (137), daptomycin (137),[a] imipenem (137)[a]		
	Daptomycin (36), teicoplanin (92), amoxicillin (36), linezolid (36, 92),[b] ampicillin (92),[b] vancomycin (92),[a] tigecycline (92),[a] rifampin (92)[a]	Nitrofurantoin (92), minocycline (92)	Ampicillin (92)
Streptococcus spp.	Penicillin (137),[a] cefminox (137),[a] cefotaxime (137)[a]	Vancomycin (137), imipenem (137), ceftriaxone (137), cefepime (137)	
[illegible]	[illegible]		
ESBL-producing *E. coli*	Carbapenems (84),[a] aztreonam (153),colistin (84),[b] aminoglycosides (28, 84),[a] tigecycline (28, 84),[a] colistin (28)		
ESBL-producing *K. pneumoniae*	Carbapenems (84), colistin (84),[b] netilmicin (84),[a] tigecycline (84)[a]		
K. pneumoniae	Gentamicin (137)[a]		
MDR *K. pneumoniae*	Carbapenem (152), aztreonam (153)		
CR *K. pneumoniae*	Carbapenems (84, 164, 179), colistin (84, 164, 179),[a] tigecycline (84),[a] netilmicin (84)[a]	Gentamicin (179)	Colistin (156), (OXA-48-producing strain)
NDM-1-producing *Enterobacteriaceae*		Colistin (158), tigecycline (158)	
[illegible]	[illegible]		
P. aeruginosa	Aztreonam (137),[a] levofloxacin (137),[a] ciprofloxacin (137),[a] cefepime (137),[a] gentamicin (137),[a] piperacillin (137),[a] ceftazidime (137),[a] imipenem (137)[a]	Imipenem (137), ceftazidime (137), ciprofloxacin (137), gentamicin (137)	
CR *P. aeruginosa*	Colistin (149),[a] carbapenems (149, 150),[a] aminoglycosides (27, 40), piperacillin-tazobactam (40), ceftazidime (40), cefepime (40), ciprofloxacin (40)		
MDR *P. aeruginosa*	Carbapenems (84), colistin (189),[b] tigecycline (84),[b] netilmicin (84)[b]	Carbapenems (152), aminoglycosides (168)	
Acinetobacter	Amikacin (137)[a]	Imipenem (137), ceftazidime (137), ciprofloxacin (137)	
OXA-23-producing *Acinetobacter*	Colistin (59, 89),[a,b] sulbactam (89)		
Pan-drug-resistant *Acinetobacter*	Polymyxin B (90),[b] minocycline (90)[b]		
N. gonorrhoeae	Ceftriaxone (44)	Cefixime (159, 253), ceftriaxone (159, 253), azithromycin (253), colistin (253), ertapenem (253), gentamicin (253), minocycline (253), oxifloxacin (253)	

[a] Synergy was observed in ≤50% of tested strains.
[b] Synergy was observed in <20% of tested strains.

M.E. Falagas 2016

Table 2

Fractional inhibitory concentration indices (FICIs) of fosfomycin (FM) combined with other agents against 136 KPC-producing *Klebsiella pneumoniae* isolates.

FM plus	Synergistic (FICI ≤ 0.5)			Additive (0.5 < FICI ≤ 1)			Indifferent (1 < FICI ≤ 2)			Antagonistic (FICI > 2)		
	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)
IMP	21 (15.4%)	20.7	11.5	114 (83.8%)	77.6	88.5	1 (0.7%)	1.7	0	0	0	0
ETP	30 (22.1%)	34.5	12.8	104 (76.5%)	62.0	87.2	2 (1.5%)	3.5	0	0	0	0
TGC	2 (1.5%)	1.7	1.3	113 (83.1%)	74.1	89.7	19 (14.0%)	24.2	6.4	2 (1.5%)	0	2.6
COL	5 (3.7%)	3.5	3.9	109 (80.1%)	79.3	80.8	22 (16.2%)	17.2	15.3	0	0	0
AMK	7 (5.1%)	5.2	5.1	109 (80.1%)	87.9	74.4	20 (14.7%)	6.9	20.5	0	0	0

IMP, imipenem; ETP, ertapenem; TGC, tigecycline; COL, colistin; AMK, amikacin; S, susceptible; R, resistant.

Wei Yu 2017

3. Pharmacodynamic characteristics of fosfomycin

Fosfomycin exerts bactericidal antimicrobial activity against susceptible pathogens by blocking the early stage of bacterial cell wall synthesis [36]. Specifically, fosfomycin binds to and inhibits the cytoplasmic enzyme uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc) enolpyruvyl transferase (MurA). This enzyme is responsible for the synthesis of UDP-*N*-acetylenolpyruvylglucosamine, which is a metabolic pentapeptide intermediate in the biosynthesis of the peptidoglycan layer of the bacterial cell wall [37]. To exert its action, fosfomycin needs to penetrate the bacterial cell membrane. This is accomplished by means of two distinct membrane uptake systems, namely the L-α-glycerophosphate and the hexose phosphate systems. Of note, the activity of the latter system is induced by glucose-6-phosphate.

Whether fosfomycin exhibits concentration-dependent or time-dependent bactericidal activity has not been accurately established. In this respect, some studies have found that fosfomycin demonstrates concentration-dependent killing activity against strains of *Escherichia coli* and *Proteus mirabilis* in vitro as well as strains of *S. pneumoniae* in vivo [38,39]. However, other studies have noted time-dependent bactericidal activity of fosfomycin against *S. aureus* strains in vitro [32,40].

Fosfomycin has also exhibited a rather prolonged post-antibiotic effect (PAE) in vitro against strains of *E. coli* and *P. mirabilis*, varying between 3.4 h and 4.7 h depending on the drug concentration applied [38]. However, against strains of *S. aureus* a relatively shorter PAE has been observed (0.5–1.4 h) [41].

regimens described in the limited reports of intravenous fosfomycin for CRE infections, ranging up to 24 g of drug daily divided 3 or 4 times a day.[74,75] Optimal pharmacodynamic targets for fosfomycin are unclear; historically it has been considered a time-dependent agent, but some recent pharmacodynamic studies with fosfomycin against *E. coli* have shown the fAUC/MIC ratio to be most predictive of efficacy.[76,77] The pharmacodynamics of fosfomycin may differ by species.[76-78]

E.A. Neuner 2017

Table 1. Optimal PK-PD parameter for CRE treatment options.

CRE Treatment Option	Optimal PK-PD Parameter
Carbapenems	T > MIC
Polymixins	AUC/MIC
Fosfomycin	AUC/MIC
Tigecycline	AUC/MIC
Aminoglycosides	Cmax: MIC
Ceftazidime-avibactam	T > MIC

E. A. Neuner 2017

Table 2
The maximum of %PTA for fosfomycin (FOF) achive more than 70% time above MIC_{90} and carbapenem (doripenem (DOM), imipenem (IPM), meropenem (MEM)) 40% time above MIC_{90} of non MDR-PA* when combinations.

%PTA of combinations	IPM 1 g q 8 h	IPM 1 g in 3 h q 8 h	DOM 1 g q 8 h	DOM 1 g in 4 h q 8 h	MEM 1 g q 8 h	MEM 1 g in 3 h q 8 h	MEM 2 g q 8 h	MEM 2 g in 3 h q 8 h
FOF 4 g q 12 h	0	0	0	0	0	0	0	0
FOF 8 g q 12 h	0	0	0	0	0	0	0	0
FOF 4 g q 8 h	1	2	2	3	3	3	3	3
FOF 4 g q 6 h	11	23	23	24	24	24	24	24
FOF 8 g q 8 h	30	30	49	49	49	49	50	50
FOF 16 g continuous infusion	32	33	77	80	80	80	80	80
FOF 8 g in 6 h q 8 h	34	35	93	95	95	96	96	96

* fosfomycin combined with carbapenems had MIC_{90} 12 μg/ml for imipenem combined with fosfomycin, 3 μg/ml for meropenem combined with fosfomycin and 2 μg/ml for doripenem combined with fosfomycin and 128 μg/ml for fosfomycin combined with carbapenems
# The PTA ≥ 90% was considered optimal against a bacterial population, whereas a PTA between 80% and 90% was associated with moderate probabilities of success.

O. Asuphon 2016

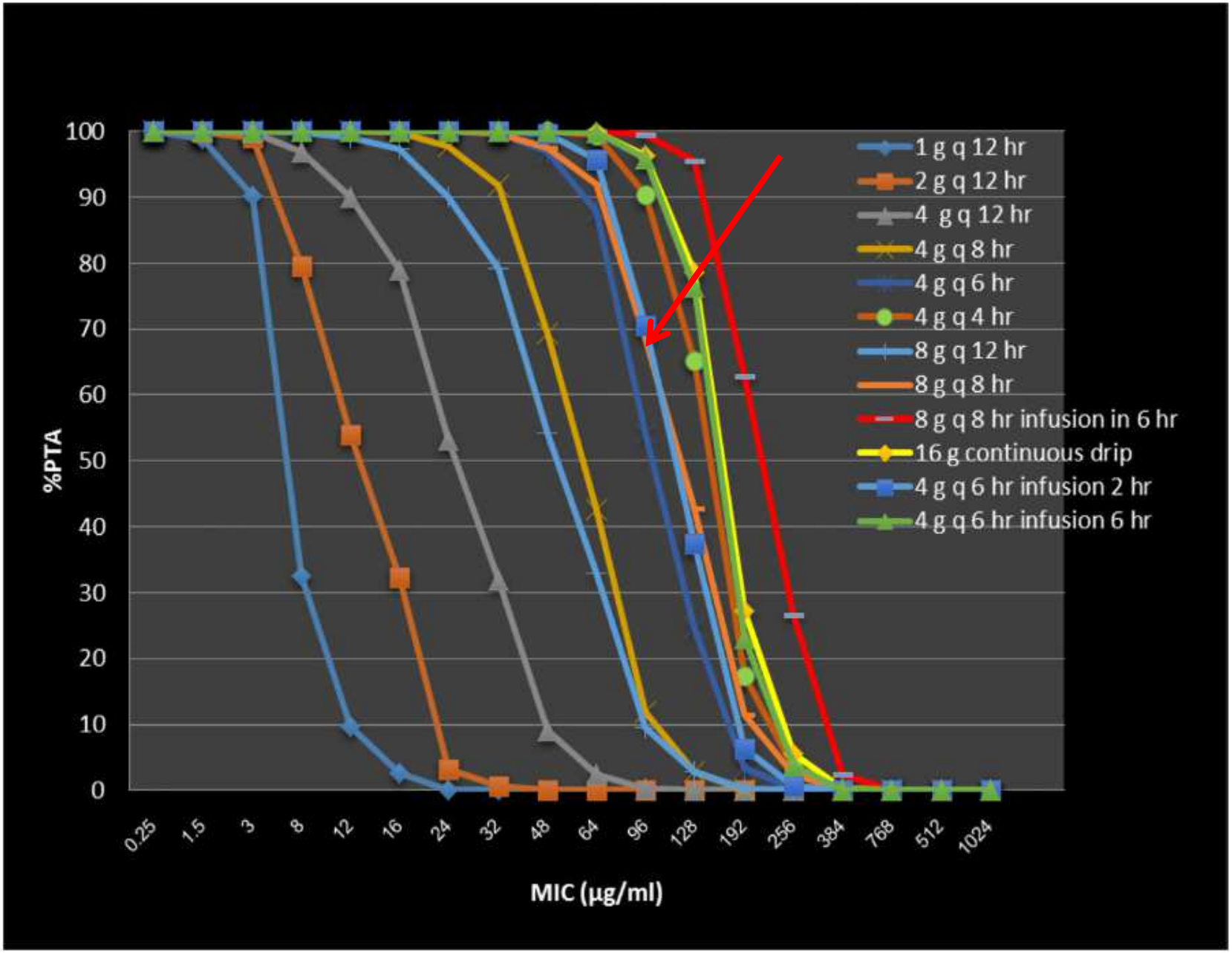


Figure 2. The probability of target attainment (%PTA) of fosfomycin monotherapy achieve more than 70% time above MIC.

O. Asuphon 2016

Pharmacokinetics of intravenous Fosfomycin

- Fosfomycin is a **highly hydropilic** molecule
- **Serum protein binding** around 3 %
- **Good tissue availability** while lower molecular mass
- **Volume of distribution** at steady state is reported between 18 and 27 L.
- A **4 gram ev** infusion achieves C max of 200 to 250 mcg/ml and **8 gram ev** 260 to 450 mcg/ml
- Around 93 % is **excreted** unchanged in urine through glomerular filtration

Fosfomicina: farmacocinetica e farmacodinamica

Autore	Dose	T 1/2	C max
Berthelot	4 g	NR	120 +/ 36
Forestier	4 g	2,98	252 +/- 97
Frossard	4 g	NR	202 +/- 20
Brunner	4 g	NR	244
Joukhadar	8 g	3,9	357 +/- 28
Gattringer	8 g	12,1 (anurici)	442 +/- 124
Sauuermann	8 g	3,7	446 +/- 128

N Roussos Int. J Antimicob Agents 2009

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2017
VOL. 15, NO. 10, 935–945
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REVIEW

Intravenous fosfomycin for the treatment of hospitalized patients with serious infections

Andrew F. Shorr[a], Jason M. Pogue[b] and John F. Mohr[c]

Table 1. Intravenous fosfomycin pharmacokinetics in critically ill patients [5].

	Healthy	Critically ill
C_{max} (mg/L)	4 g: 202 ± 20 8 g: 395 ± 46	4 g: 243.3 ± 58.5 8 g: 260 + 85 to 357 ± 28
V_d (L)	22[a]	48.8
Clearance (L/h)	7.2[a]	2.06

C_{max} = maximum concentration; V_d = volume of distribution; IV: intravenous.
[a]4 g IV q 6 h

Table 2. Non-compartmental analysis of fosfomycin parameters after administration of a single dose of 4 g IV in septic patients (adapted from Matzi et al. [29]).

PK Parameter	Plasma (n = 7)	Healthy lung (n = 7)	Infected lung (n = 5)
C_{max} (mg/L)	243.3 ± 58.5	131.6 ± 110.6	107.5 ± 60.2
AUC_{0-4} (mg h/L)	453.0 ± 113.4	242.4 ± 101.6	203.5 ± 118.4
$AUC_{0-\infty}$ (mg h/L)	665.9 ± 179.5	367.6 ± 111.9	315.1 ± 151.2
$t_{1/2}$ (h)	2.5 ± 0.5	2.2 ± 0.8	2.7 ± 1.5

C_{max} = maximum concentration; AUC = area under the time–concentration curve; $t_{1/2}$ = half-life; IV: intravenous.

Distribution and Tissue Penetration

4.2.2. Distribution and Tissue Penetration Fosfomycin binds to plasma proteins at only negligible levels [31] and is distributed widely into a variety of tissues; in addition to serum, biologically relevant concentrations of fosfomycin have been measured in the kidneys, bladder, prostate, lungs, bone, and cerebrospinal fluid, as well as in inflamed tissues and abscess fluid [32,33,34,35,36,37,38,39,40].

The apparent volume of distribution (V_d/F) following oral administration of fosfomycin tromethamine is approximately 100–170 L for a 70-kg individual [29,30]. In contrast, because of its higher bioavailability, IV-administered fosfomycin disodium has a reported V_d of 9–30 L at steady state, and values of 3–12 L have been reported for both the central (Vc) and peripheral (Vp) compartments [25,27,28,32,36,41,42].

A.C. Dijkmans 2017

Following intravenous administration, variable peak, mean, and trough fosfomycin levels have been reported in humans. In general, peak concentrations were high (up to 606 mg/liter) (174). Nonrenal elimination of intravenous fosfomycin is negligible, with 93 to 99% excreted unchanged in the urine (22, 175, 181).

With regard to patients with impaired renal function, currently it is not clear if dose adjustment is required for an estimated creatinine clearance of 40 to 80 ml/min. For patients with estimated creatinine clearances of 40, 30, 20, and 10 ml/min, a reduction to 70%, 60%, 40%, and 20% of the daily recommended dose, respectively, is proposed. In patients undergoing intermittent dialysis (every 48 h), 2 g after each session is recommended (https://www.medicines.org.uk/emc/medicine/28971). There are no data for dose reduction in patients with hepatic impairment or for elderly patients without renal impairment.

M. Falagas 2016

Table 1
Review of literature for pharmacokinetic (PK) data on intensive care unit (ICU) patients receiving fosfomycin.

Reference	Study population	No. of patients	Fosfomycin dose	PK parameter					
				V_d (L)	$t_{1/2}$ (h)	CL (L/h)	C_{max} (mg/L)	T_{max} (h)	AUC (mg h/L)
Bergan et al. [13]	Healthy volunteers	12	3 g i.v.	20.6[a]	2.1 ± 0.1	6.8[b]	370.6 ± 92	0.02 ± 0	443.6 ± 48.9
Frossard et al. [4]	Healthy volunteers	6	4 g i.v., once	nd	nd	9.0[b] (serum)	97 ± 13 (muscle) 144 ± 1 (subcutis) 202 ± 20 (serum)		201.7 ± 56.7 (muscle) 313.3 ± 43.3 (subcutis) AUC_{0-8}, 443.3 ± 41.7 (serum)
			8 g i.v., once	nd	nd	9.0[b] (serum)	156 ± 16 (muscle) 209 ± 30 (subcutis) 395 ± 46 (serum)		460 ± 40 (muscle) 596.7 ± 48.3 (subcutis) 886.7 ± 70 (serum)
Gattringer et al. [33]	Anuric ICU patients (CVVH)	12	8 g (CVC)	33.7 ± 12.7	12.1 ± 5.2	6.4 ± 7.6 (total) 1.1 ± 0.2 (HF)[c]	442.8 ± 124.0	0.4 ± 0.1	AUC_{0-12}, 2159.4 ± 609.8
Joukhadar et al. [23]	Sepsis	9	8 g i.v.	31.5 ± 4.5	3.9 ± 0.9 4.1 ± 0.6 (muscle)	7.2 ± 1.3	357 ± 28 (plasma) 247 ± 38 (muscle)	0.4 ± 0.1 (plasma) 1.2 ± 0.2 (muscle)	AUC_{0-4}, 721 ± 66 (plasma) AUC_{0-4}, 501 ± 69 (muscle)
Pfausler et al. [14]	Bacterial ventriculitis	6	8 g i.v.	30.8 ± 10.2	3.0 ± 1.0	7.4 ± 2.3	260 ± 85 (plasma) 43 ± 20 (CSF)	1.2 ± 0.4 (plasma) 3.8 ± 1.8 (CSF)	929 ± 280 (plasma) 225 ± 131 (CSF)
			8 g t.i.d.	26.3 ± 9.7	4.0 ± 0.5	5.0 ± 2.0	307 ± 101 (plasma) 62 ± 38 (CSF)	1.5 ± 1.2 (plasma) 4.5 ± 2.7 (CSF)	1035 ± 383 (plasma) 295 ± 179 (CSF)
Pfeifer et al. [26]	Perioperative neurosurgical patients	39	5 g i.v.	15.4	2	7.2	253 ± 108 9–10 (CSF)	0.25 3–6	
			10 g i.v.	nd	nd	nd	14–17 (CSF)	2–6	
			5 g i.v. t.i.d.	nd	nd	nd	32 (CSF)	Between 2 days and 5 days	
Matzi et al. [19]	Sepsis	7	4 g i.v.	31.7[a]	2.5 ± 0.5 (plasma)	8.8[b]	243.3 ± 58.5 (plasma)	0.3 ± 0 (plasma)	AUC_{0-4}, 453.0 ± 113.4 (plasma)
		n = 7 healthy lung		nd	2.2 ± 0.8[d]	nd	131.6 ± 110.6[d]	1.1 ± 0.4[d]	AUC_{0-4}, 242.4 ± 101.6[d]
		n = 5 infected lung		nd	2.7 ± 1.5[e]	nd	107.5 ± 60.2[e]	1.4 ± 0.5[e]	AUC_{0-4}, 203.5 ± 118.4[e]

V_d, volume of distribution; $t_{1/2}$, terminal elimination half-life; CL, clearance; C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC, area under the concentration–time curve; i.v., intravenous; nd, not described; AUC_{0-x}, AUC from time 0–*x* h; CVVH, continuous venovenous haemofiltration; CVC, central venous catheter; HF, haemofiltration; t.i.d., three times daily; CSF, cerebral spinal fluid.

[a] Calculated based on the approximation that $k_e = 0.693/t_{1/2} = CL/V_d$.

[b] Calculated based on the approximation CL = dose/AUC.

[c] The clearance of haemofiltration (CL_{HF}) was calculated with the formula $CL_{HF} = (UFR \times C_{UF})/C_A$, where UFR refers to the ultrafiltration rate and C_{UF} and C_A refer to the ultrafiltrate and arterial (dialyser inlet) serum fosfomycin concentrations, respectively.

[d] Healthy lung.

[e] Infected lung.

FOSFOMICINA

VIA DI SOMMINISTRAZIONE :	E.V.
DOSE UNITARIA :	4 gr.
PICCO SERICO :	223 ± 16 mg/l
POSOLOGIA:	16-24 gr. in 4 dosi
METABOLIZZAZIONE:	assente
LEGAME PROTEICO:	< 10
VOLUME DISTRIBUZIONE:	0,3 l/kg
ESCREZIONE URINARIA:	> 85 %
ELIMINAZIONE BILIARE:	modesta
DIFFUSIONE NEL LCR :	20% dei valori serici
DIFFUSIONE NEL POLMONE	50 % dei valori serici

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Systematic review

Intravenous fosfomycind back to the future. Systematic review and meta-analysis of the clinical literature

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abstract

Objectives: We conducted a systematic review and meta-analysis to summarize the clinical evidence and usage patterns of intravenous fosfomycin from its development to the present time.

Methods: PubMed, the Cochrane Library and local journals were searched for relevant studies reporting aggregated data of intravenous fosfomycin use in adults and children, with no restrictions regarding study design. Single case reports were excluded. Data were systematically abstracted for all included studies. Clinical and microbiological efficacy from randomized controlled and comparative observational studies were synthesized using meta-analysis to calculate pooled effect sizes.

Results: In all, 128 studies on intravenous fosfomycin in 5527 patients were evaluated. Fosfomycin was predominantly used for sepsis/bacteraemia, urinary tract, respiratory tract, bone and joint, and central nervous system infections. No difference in clinical (OR 1.44, 95%CI 0.96e2.15) or microbiological (OR 1.28, 95%CI 0.82e2.01) efficacy between fosfomycin and other antibiotics was observed in comparative trials. The pooled estimate for resistance development during fosfomycin monotherapy was 3.4%(95%CI 1.8%e5.1%). Fosfomycin showed a favourable safety profile, with generally mild adverse events not requiring discontinuation of treatment. Included studies explored intravenous fosfomycin as an anti-staphylococcal agent in monotherapy and combination therapy, whereas studies from 1990 focused on combination therapy (fosfoymcin þ b-lactams or aminoglycosides) for challenging infections frequently caused by multidrug-resistant organisms.

Conclusion: Intravenous fosfomycin can play a vital role in the antibiotic armamentarium, given its long history of effective and safe use. However, well-designed randomized controlled trials are still desired.

B. Grabein, Clin Microbiol Infect 2017;23:363

ABSTRACT

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B. Grabein, Clin Microbiol Infect 2017;23:363

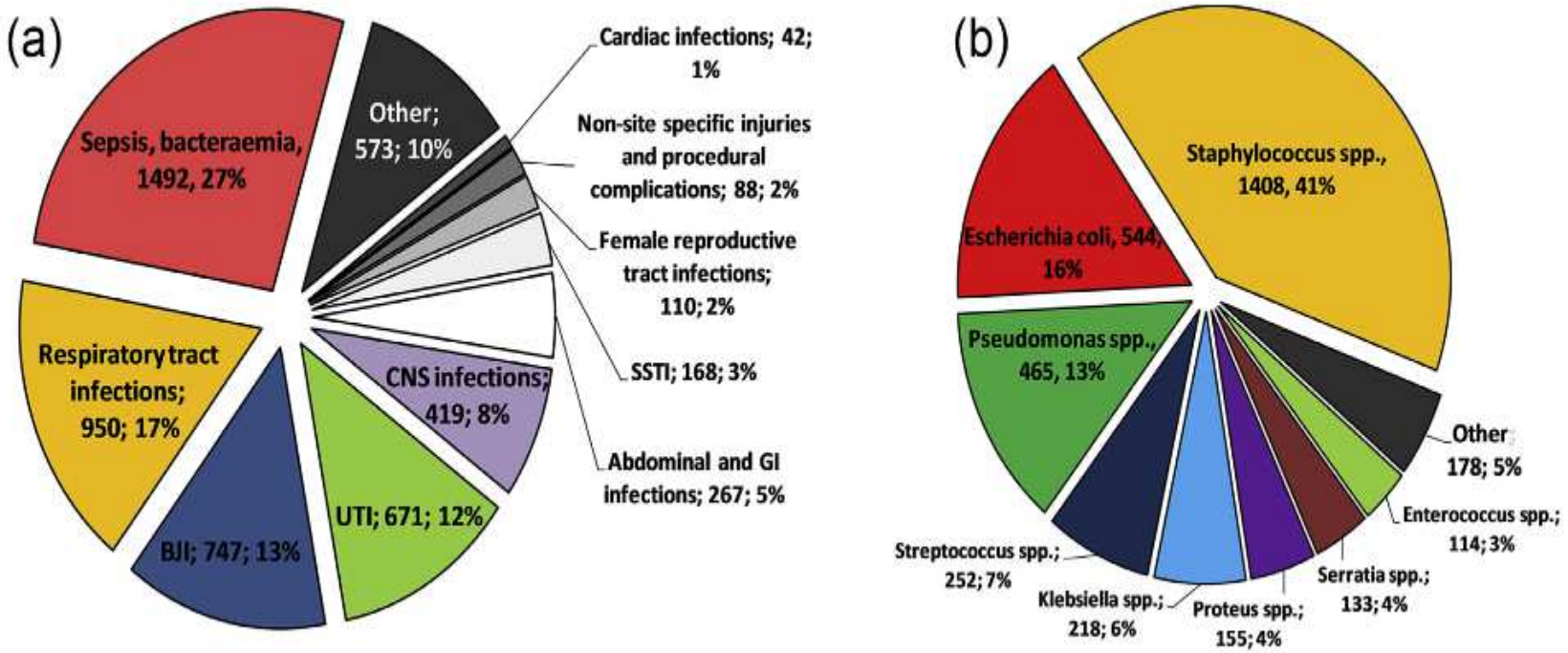
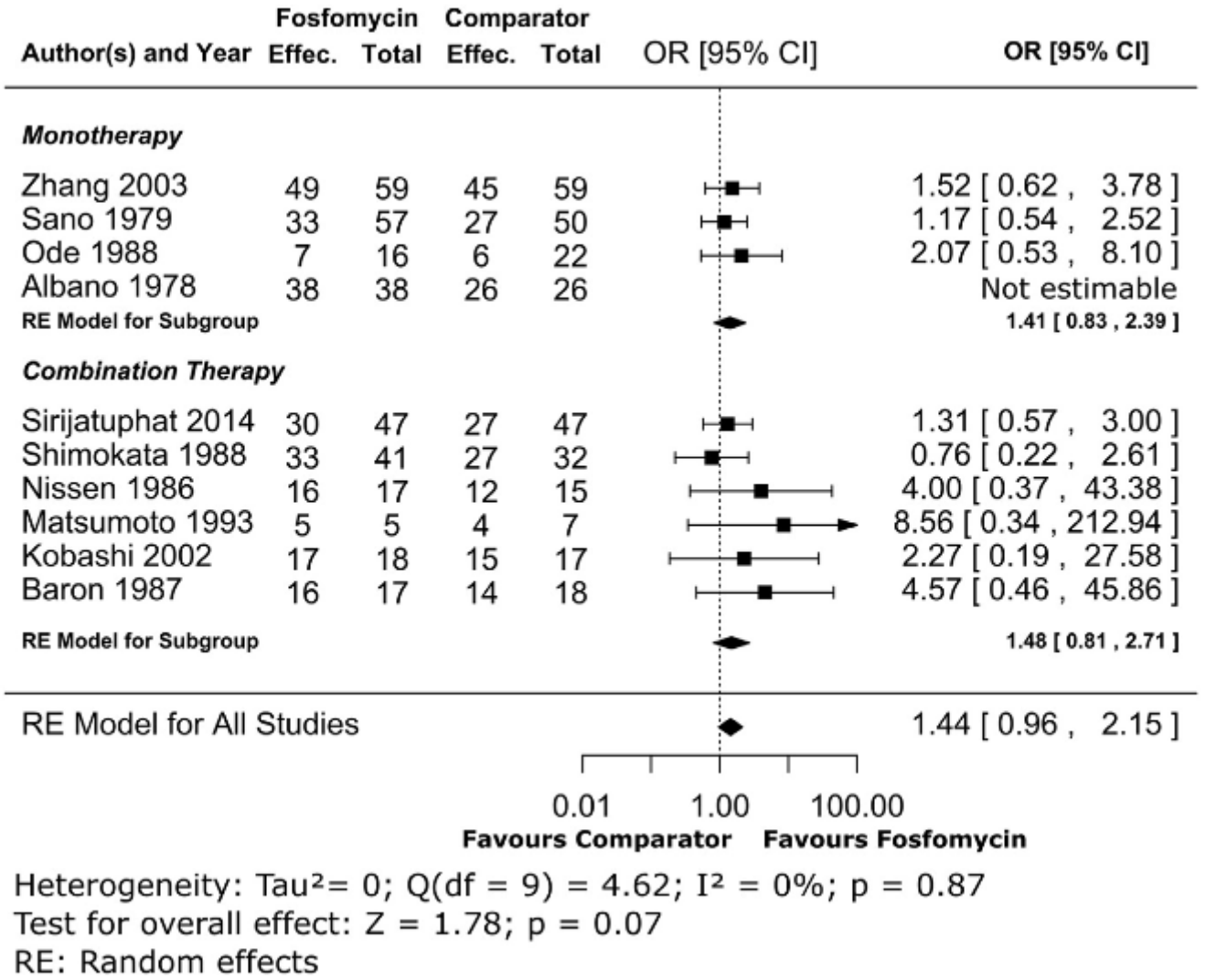


Fig. 2. Descriptive summary of the studies reviewed here. (a) Numbers of patients treated with intravenous fosfomycin by treatment indication as per MedDRA version 19.0. BJI, bone and joint infections; UTI, urinary tract infections; CNS, central nervous system infections; SSTI, skin and soft-tissue infections. (b) Absolute numbers of microbiological isolates reported by pathogen.

B. Grabein 2017



Heterogeneity: $Tau^2 = 0$; $Q(df = 9) = 4.62$; $I^2 = 0\%$; $p = 0.87$
Test for overall effect: $Z = 1.78$; $p = 0.07$
RE: Random effects

B. Grabein 2017

TABLE 5 Studies with clinical outcomes after fosfomycin administration for non-urinary tract infections published from 2010 onwards[a]

First author, yr of publication (reference)	Study place, yr	Design	Patients, *n*	Infections (*n*)	Bacteria	Fosfomycin	Comparator	Mortality	Clinical cure	Microbiological cure
Michalopoulos, 2010 (220)	Greece, 2008	Prospective	Adults, 11	ICU infections	CR *K. pneumoniae*	i.v. 4 g q6h plus other antibiotics	NA	2/11 (18.2%)	NR	NR
Apisarnthanarak, 2010 (219)	Thailand, 2009–2010	Retrospective	Adults, 8	HAP/VAP	CR *P. aeruginosa*	i.v. 2 g q8h plus i.v. doripenem (1 g q8h, extended infusion)	NA	2/8 (25%)	6/8 (75%)	6/7 (86%)
Florent, 2011 (243)	France, 2005–2010	Retrospective arm, prospective arm	Adults, 72	BJI (33), CNS infections (11), EaS infections (9), UTI (9), BSI (5), SSTI (4), pneumonia (1)	*Enterobacteriaceae* (24 including 5 ESBL- and 4 AmpC-producing strains) *P. aeruginosa* (13, including 5 MDR strains), staphylococci (12, including 6 MRSA strains); overall, MDR, 28%	i.v. 4 g q8h plus other antibiotics	NA	NR	63/72 (87%)	NR
Kusachi, 2011 (244)	Japan, NA	NA	Adults, 114	Intra-abdominal abscess	NA	i.v. added on previously failing antibiotic	NA	NR	91/104 (87.5%)	NA
Dihn, 2012 (242)	France, 2007	Prospective	Adults and children 116	Lung infections (33), BJI (32), UTI (16), BSI (9), IAI, endocarditis, CNS infections (7)	*P. aeruginosa* (43), *Enterobacteriaceae* (29), MRCNS (23 MRSA (15), *Streptococcus* spp (6), MDR (83), ESBL (49)	i.v. 4 g q6h–q8h plus other antibiotics	NA	30/116 (25.9%)	77/99 (77%)	66/83 (79.5%)
Apisarnthanarak, 2012 (240)	Thailand, 2007–2011	Retrospective	49	HAP/VAP	CR *P. aeruginosa*	i.v. for ≥2 days plus doripenem (1 g q8h) or colistin (5 mg/kg/day in 2 divided doses)	NA	20/49 (40.8%)	29/49 (59.2%)	33/49 (67.3%)
Navarro-San Francisco, 2013 (245)	Spain, 2010–2012	Prospective	5	Bacteremia	OXA-48-producing *pneumoniae*	i.v. plus either tigecycline or colistin	Combinations of tigecycline, colistin, carbapenems, aminoglycosides	2/5 (40%) vs 24/ (68.6%)	NR	NR
Pontikis, 2014 (246)	Greece 2010–2012	Prospective	ICU, 66	Primary BSI, VAI CR-BSI, IAI	KPC-producing *K. pneumoniae* (41), *aeruginosa* (17)	i.v. 16–24 g in divided doses plus other antibiotics	NA	18/48 (37.5%)	26/48 (54.2%)	27/48 (56.3%)
Del Rio, 2014 (241)	Spain, 2001–2010	Prospective	16	BSI (75% endocarditis)	MRSA	i.v. 2 g q6h plus imipenem (1 g q6h)	NA	5/16 (31%)	NR	NR

[a] Abbreviations: BJI, bone and joint infections; BSI, bloodstream infections; CNS, central nervous system; CR, carbapenem resistant; CR-BSI, catheter-related bloodstream infections; EaS, ear and sinus infections; ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infections, i.v., intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MRCNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; NA, not available; SSTI, skin and soft tissue infections; UTI, urinary tract infections; VAP, ventilator-associated pneumonia.

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Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

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ABSTRACT

Fosfomycin is active in vitro against extensively drug-resistant (XDR) and pandrug-resistant (PDR) *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* carbapenemase-producing strains; however, the in vivo effectiveness against such pathogens is almost unknown. A multicentre, observational, prospective case-series study was performed in 11 ICUs. All consecutive fosfomycin-treated patients suffering from XDR or PDR fosfomycin-susceptible, microbiologically documented infections were recorded. Clinical and microbiological outcomes were assessed. A safety analysis was performed. In total, 68 patients received fosfomycin during the study period, 48 of whom were considered suitable for effectiveness analysis based on predefined criteria. Bacteraemia and ventilator-associated pneumonia were the main infections. Carbapenemase-producing *K. pneumoniae* and *P. aeruginosa* were isolated in 41 and 17 cases, respectively. All isolates exhibited an XDR or PDR profile, being fosfomycin-susceptible by definition. Fosfomycin was administered intravenously at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Clinical outcome at Day 14 was successful in 54.2% of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively. All-cause mortality at Day 28 was 37.5%. Bacterial eradication was observed in 56.3% of cases. Fosfomycin resistance developed in three cases. The main adverse event was reversible hypokalaemia. In conclusion, fosfomycin could have a place in the armamentarium against XDR and PDR Gram-negative infections in the critically ill. Resistance development during therapy, which has been a matter of concern in previous studies, did not occur frequently. The necessity of combination with other antibiotics requires further investigation.

15 patients with PDE K.pneumoniae

Table 6
Detailed analysis of 15 patients with pandrug-resistant (PDR) *Klebsiella pneumoniae* strains treated with fosfomycin in combination with other antibiotic(s).

	Sex/age (years)	Admission type	ICU day[a]	Days from infection onset[b]	Sepsis classification	APACHE II score	SOFA score	Type of infection	Co-infection	Combination therapy	Clinical/microbiological outcome	Fosfomycin duration (days)	Status	
													Day 14	Day 28
1	M/75	Medical	28	2	Septic shock	19	10	IAI + secondary bacteraemia		COL, TGC, TZP	Failure/failure	21	Alive	Death
2	M/53	Emergent surgery	46	7	Sepsis	14	15	IAI + secondary bacteraemia		COL, GEN	Successful/eradication	15	Alive	Death
3	M/63	Medical	34	2	Severe sepsis	14	3	UTI		COL, MER	Successful/indeterminate	14	Alive	Alive
4	M/79	Medical	45	0	Septic shock	26	9	CR-BSI	XDR *Pseudomonas aeruginosa*	COL	Failure/indeterminate	4	Death	Death
5	M/30	Emergent surgery	34	0	Sepsis	11	6	CR-BSI		COL, MER	Superinfection/eradication	17	Alive	Alive
6	M/52	Medical	92	0	Septic shock	14	6	VAP		COL, TGC	Successful/eradication	15	Alive	Alive
7	F/35	Medical	38	7	Sepsis	15	6	Primary bacteraemia		TGC	Successful/eradication	11	Alive	Alive
8	M/63	Medical	32	1	Severe sepsis	22	11	CR-BSI		COL, TGC	Indeterminate/indeterminate	10	Death	Death
9	M/43	Medical	63	3	Severe sepsis	14	8	Primary bacteraemia		COL	Successful/eradication	18	Alive	Alive
10	M/82	Medical	29	1	Septic shock	33	10	VAP		GEN	Successful/eradication	10	Alive	Death
11	F/18	Emergent surgery	27	19	Sepsis	16	6	Meningitis	*Candida* sp.	COL, TZP	Failure/eradication	>28	Alive	Alive
12	M/27	Medical	6	3	Sepsis	10	6	Primary bacteraemia		GEN	Successful/eradication	14	Alive	Alive
13	M/58	Emergent surgery	53	0	Severe sepsis	17	5	VAP + empyema	XDR *P. aeruginosa*	TGC	Successful/failure	14	Alive	Alive
14	F/73	Medical	54	5	Sepsis	14	7	Primary bacteraemia		TGC, GEN	Successful/eradication	7	Alive	Alive
15	M/72	Planned surgery	3	0	Septic shock	33	14	VAP	XDR *P. aeruginosa*	COL, MER	Failure/failure	14	Alive	Death

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IAI, intra-abdominal infection; UTI, urinary tract infection; CR-BSI, catheter-related bloodstream infection; VAP, ventilator-associated pneumonia; COL, colistin; TGC, tigecycline; TZP, piperacillin/tazobactam; GEN, gentamicin; MER, meropenem; XDR, extensively drug-resistant.

[a] Day of ICU hospitalisation that fosfomycin was initiated on.

[b] Days between infection onset and fosfomycin initiation.

Sensibilità alla fosfomicina di Enterobacteriacee ESBL + isolate in corso di infezioni diverse da UTI e tratto gastro-enetrico

	Studies showing susceptibility to fosfomycin of 90% or more compared with total number of studies	Cumulative susceptibility of isolates according to the CLSI criteria†
All Enterobacteriaceae isolates		
Any advanced antimicrobial drug resistance profile	11 of 17 (64·7%)[18-34]	3891 of 4478 (86·9%)[18-25,27,29,31]
ESBL-producing	11 of 17 (64·7%)[18-34]	3569 of 3911 (91·3%)[18-25,27,29,31]
Isolates from urinary tract	8 of 10 (80·0%)[19-21,23-28,30]	2061 of 2227 (92·5%)[19-21,23-25,27]
Isolates from mixed sites‡	5 of 8 (62·5%)[18,22,25,29,31-34]	1508 of 1684 (89·5%)[18,22,25,29,31]
Isolates from outpatients	3 of 3 (100·0%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 8 (50·0%)[21,22,25,28,29,31,33,34]	1344 of 1519 (88·5%)[21,22,25,29,31]
***Escherichia coli* isolates**		
Any advanced antimicrobial drug resistance profile	11 of 12 (91·7%)[18,20,21,24-32]	1672 of 1725 (96·9%)[18,20-21,24,25,27,29,31]
ESBL-producing	11 of 12 (91·7%)[18,20,21,24-32]	1604 of 1657 (96·8%)[18,20,21,24,25,27,29,31]
Isolates from urinary tract	6 of 7 (85·7%)[20,21,24-28]	704 of 721 (97·6%)[20,21,24,25,27]
Isolates from mixed sites‡	5 of 6 (83·3%)[18,25,29-32]	900 of 936 (96·2%)[18,25,29,31]
Isolates from outpatients	3 of 3 (100%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 5 (80·0%)[21,25,28,29,31]	864 of 909 (95·0%)[21,25,29,31]
***Klebsiella pneumoniae* isolates**		
Any advanced antimicrobial drug resistance profile	3 of 6 (50·0%)[18,21,29-31,33]	608 of 748 (81·3%)[18,22,29,31]
ESBL-producing	3 of 6 (50·0%)[18,21,29-31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from mixed sites‡	2 of 5 (40·0%)[18,21,29,31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from hospitalised patients	2 of 4 (50·0%)[21,29,31,33]	480 of 610 (78·7%)[22,29,31]

ESBL=extended-spectrum β-lactamase. CLSI=Clinical and Laboratory Standards Institute. *Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. †CLSI fosfomycin susceptibility criteria refer specifically to urinary isolates of *Escherichia coli*. ‡Urinary tract isolates are potentially included.

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Lancet Inf Dis 2010;10:43-50

FOSFOMICINA

S. Felice, 9 maggio 2016

Oggetto: InfectoFos® - Fosfomicina disodica ora autorizzata e disponibile in Italia

Gent.le Dottoressa / Egr. Dottore,

Nordic Pharma è lieta di annunciare la disponibilità di InfectoFos® (Fosfomicina disodica) e.v. fiale da 2 g e 4 g in Italia.
InfectoFos® e.v. fiale da 2 g e 4 g è indicato per il trattamento delle seguenti infezioni negli adulti e nei bambini inclusi i neonati:

- **Osteomielite**
- **Infezioni complicate delle vie urinarie**
- **Infezioni nosocomiali delle vie respiratorie inferiori**
- **Meningite batterica**
- **Batteriemia che si manifesta in associazione o che si ritiene eventualmente associata ad una qualsiasi delle infezioni sopracitate**

La Fosfomicina deve essere utilizzata esclusivamente quando l'uso degli antibatterici comunemente raccomandati per il trattamento iniziale delle infezioni sopracitate non è considerato opportuno o quando tali antibatterici alternativi non sono stati efficaci.[1]
InfectoFos® è particolarmente efficace nelle infezioni batteriche difficili da trattare grazie a specifiche peculiarità:

Terapia degli Enterobatteri produttori di ESBL

1. Imipenem 500 mg x 4 , 1 gr x 3
2. Meropenem 1 gr x 3-4, 2 gr x 3
3. Ertapenem 1 gr / die
4. Tigeciclina (solo per infezioni cute e tessuti molli complicate e per infezioni intraddominali) 100 mg poi 50 mg x 2, nelle sepsi occorre raddoppiare la dose
5. Ceftolozane/Tazobactam 1,5 g x 3 (3 g x 3 nelle HAP)
6. Ceftazidime/Avibactam 2,5 g x 3
7. Fosfomicina ev (in associazione) 16-24 g/die
8. Fosfomicina os e Nitrofurantoina nelle UTI

K. pneumoniae KPC: typical XDR phenotype

Antibiotic	MIC mg/L (S/I/R)
Amp/Sulb	>32 R
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Fosfomycin	32 S
Tigecycline	1.5 I
Colistin	0.4 S

Treatment options:

- Colistin
- Carbapenem (especially if MIC relatively low)
- Tigecycline (HD)
- Gentamicin
- Fosfomycin HD
- Rifampin (test synergy)

Combination regimens (open issues)

Hirsch & Tam – JAC 2010
Qureshi *et al* – AAC 2012
Tumbarello *et al* - CID 2012

Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study

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Summary

Background Gaps in the diagnostic capacity and heterogeneity of national surveillance and reporting standards in Europe make it difficult to contain carbapenemase-producing Enterobacteriaceae. We report the development of a consistent sampling framework and the results of the first structured survey on the occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in European hospitals.

Methods National expert laboratories recruited hospitals with diagnostic capacities, who collected the first ten carbapenem non-susceptible clinical isolates of *K pneumoniae* or *E coli* and ten susceptible same-species comparator isolates and pertinent patient and hospital information. Isolates and data were relayed back to national expert laboratories, which made laboratory-substantiated information available for central analysis.

Findings Between Nov 1, 2013, and April 30, 2014, 455 sentinel hospitals in 36 countries submitted 2703 clinical isolates (2301 [85%] *K pneumoniae* and 402 (15%) *E coli*). 850 (37%) of 2301 *K pneumoniae* samples and 77 (19%) of 402 *E coli* samples were carbapenemase (KPC, NDM, OXA-48-like, or VIM) producers. The ratio of *K pneumoniae* to *E coli* was 11:1. 1·3 patients per 10000 hospital admissions had positive clinical specimens. Prevalence differed greatly, with the highest rates in Mediterranean and Balkan countries. Carbapenemase-producing *K pneumoniae* isolates showed high resistance to last-line antibiotics.

Interpretation This initiative shows an encouraging commitment by all participants, and suggests that challenges in the establishment of a continent-wide enhanced sentinel surveillance for carbapenemase-producing Enterobacteriaceae can be overcome. Strengthening infection control efforts in hospitals is crucial for controlling spread through local and national health care networks.

Funding European Centre for Disease Prevention and Control.

Lancet Inf. Dis
Feb. 2017

	Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n)	Number of submitted carbapenem non-susceptible *K pneumoniae* isolates	Confirmed carbapenemase-producing *K pneumoniae* isolates					Other (n, %)*
			KPC (n, %)	NDM (n,%)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
Albania	3	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Austria	6	15	6 (40·0)	2 (13·3)	2 (13·3)	0 (0)	10 (66·7)	5 (33·3)
Belgium	11	48	13 (27·1)	2 (4·2)	18 (37·5)	0 (0)	33 (68·8)	15 (31·3)
Bulgaria	3	4	0 (0)	2 (50·0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)
Croatia	14	48	1 (2·1)	0 (0)	1 (2·1)	5 (10·4)	7 (14·6)	41 (85·4)
Cyprus	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Czech Republic	5	26	0 (0)	1 (3·8)	1 (3·8)	0 (0)	2 (7·7)	24 (92·3)
Denmark	3	8	1 (12·5)	3 (37·5)	2 (25·0)	0 (0)	6 (75·0)	2 (25·0)
Estonia	1	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100)
Finland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
France	11	27	1 (3·7)	0 (0)	10 (37·0)	0 (0)	11 (40·7)	16 (59·3)
Germany	13	36	8 (22·2)	2 (5·6)	12 (33·3)	0 (0)	22 (61·1)	14 (38·9)
Greece	10	86	56 (65·1)	12 (14·0)	2 (2·3)	9 (10·5)	79 (91·9)	7 (8·1)
Hungary	7	36	0 (0)	0 (0)	0 (0)	26 (72·2)	26 (72·2)	10 (27·8)
Ireland	7	12	2 (16·7)	2 (16·7)	2 (16·7)	0 (0)	6 (50·0)	6 (50·0)
Israel	7	39	31 (79·5)	2 (5·1)	1 (2·6)	0 (0)	34 (87·2)	5 (12·8)
Italy	22	195	187 (95·9)	1 (0·5)	1 (0·5)	3 (1·5)	192 (98·5)	3 (1·5)
Latvia	1	4	0 (0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)	2 (50·0)
Lithuania	4	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)
Luxembourg	3	10	4 (40·0)	0 (0)	2 (20·0)	2 (20·0)	8 (80·0)	2 (20·0)
Malta	1	9	0 (0)	0 (0)	9 (100)	0 (0)	9 (100)	0 (0)
Montenegro	1	10	0 (0)	10 (100)	0 (0)	0 (0)	10 (100)	0 (0)
Norway	4	5	0 (0)	1 (20·0)	0 (0)	0 (0)	1 (20·0)	4 (80·0)
Poland	10	34	2 (5·9)	2 (5·9)	0 (0)	0 (0)	4 (11·8)	30 (88·2)
Portugal	17	61	36 (59·0)	0 (0)	0 (0)	0 (0)	36 (59·0)	25 (40·9)
Romania	8	68	4 (5·9)	5 (7·4)	50 (73·5)	2 (2·9)	61 (89·7)	7 (10·3)
Serbia	11	67	1 (·5)	33 (49·3)	9 (13·4)	0 (0)	43 (64·2)	24 (35·8)
Slovakia	5	22	1 (4·5)	0 (0)	0 (0)	0 (0)	1 (4·5)	21 (95·5)
Slovenia	4	12	0 (0)	1 (8·3)	1 (8·3)	1 (8·3)	3 (25·0)	9 (75·0)
Spain	20	116	9 (7·8)	0 (0)	81 (69·8)	12 (10·3)	102 (87·9)	14 (12·1)
Macedonia	1	3	2 (66·7)	0 (0)	0 (0)	0 (0)	2 (66·7)	1 (33·3)
Turkey	17	124	0 (0)	9 (7·3)	98 (79·0)	5 (4·0)	112 (90·3)	12 (9·7)
UK-England and Northern Ireland	15	47	14 (29·8)	3 (6·4)	7 (14·9)	1 (2·1)	25 (53·2)	22 (46·8)
UK-Scotland	4	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Total	251	1203	379 (31·5)	93 (7·7)	310 (25·8)	68 (5·7)	850 (70·7)	353 (29·3)

Iceland, Kosovo, and Sweden did not find any *K pneumonia* isolates that were suspected non-susceptible to carbapenems during the study period. *Other mechanism of carbapenem non-susceptibility, since none of the genes coding for the four major types of carbapenemases (KPC, NDM, OXA-48-like and VIM) were detected. All data are n, except where otherwise indicated.

***Table 2: Klebsiella pneumoniae* clinical isolates submitted as non-susceptible to carbapenems, confirmed as producing a carbapenemase and type of carbapenemase, by country**

	Number of confirmed carbapenemase-producing *K pneumoniae* isolates	Colistin		Fosfomycin		Tigecycline		Total antibiotics tested*	Isolates resistant to all tested antibiotics (%)
		Tested	Resistant (%)	Tested	Resistant (%)	Tested	Resistant (%)		
Austria	10	10	3 (30·0)	10	2 (20·0)	0	–	17	1 (10·0)
Belgium	33	0	–	0	–	0	–	12	5 (15·2)
Bulgaria	2	2	0	2	0	2	0	18	0 (0)
Croatia	7	0	–	0	–	0	–	11	2 (28·6)
Cyprus	1	0	–	0	–	0	–	13	0 (0)
Czech Republic	2	2	1 (50·0)	2	0	2	0	18	0 (0)
Denmark	6	0	–	0	–	0	–	–	–
Estonia	0	0	–	0	–	0	–	18	–
Finland	0	0	–	0	–	0	–	18	–
France	11	11	2 (18·2)	11	2 (18·2)	11	1 (9·1)	18	0 (0)
Germany	22	22	8 (36·4)	16	7 (43·8)	22	2 (9·1)	17	0 (0)
Greece	79	21	4 (19·0)	0	–	21	4 (19·0)	13	15 (19·0)
Hungary	26	26	1 (3·8)	26	5 (19·2)	26	2 (7·7)	18	0 (0)
Ireland	6	6	1 (16·7)	6	1 (16·7)	6	1 (16·7)	18	0 (0)
Israel	34	34	4 (11·8)	34	3 (8·8)	0	–	17	0 (0)
Italy	192	192	77 (40·1)	149	99 (66·4)	192	2 (1·0)	16	11 (5·7)
Latvia	2	0	–	0	–	0	–	11	0 (0)
Lithuania	0	0	–	0	–	0	–	18	–
Luxembourg	8	4	1 (25·0)	1	1 (100)	1	0	15	0 (0)
Malta	9	9	0	9	2 (22·2)	9	1 (11·1)	18	0 (0)
Montenegro	10	0	–	9	5 (55·6)	1	0	12	1 (10·0)
Norway	1	1	0	1	0	1	0	16	0 (0)
Poland	4	3	1 (33·3)	0	–	4	0	16	0 (0)
Portugal	36	0	–	0	–	0	–	15	8 (22·2)
Romania	61	61	43 (70·5)	61	61 (100)	61	11 (18·0)	18	8 (13·1)
Serbia	43	43	6 (14·0)	41	5 (12·2)	38	11 (13·2)	17	2 (4·6)
Slovakia	1	1	0	0	–	1	0	15	0 (0)
Slovenia	3	3	0	3	3 (100)	3	0	18	0 (0)
Spain	102	102	10 (9·8)	102	70 (68·6)	102	19 (18·6)	18	1 (0·9)
Macedonia	2	2	0	0	–	0	–	12	1 (50·0)
Turkey	112	66	19 (28·8)	17	4 (23·5)	27	7 (25·9)	11	24 (21·4)
UK-England and Northern Ireland	25	25	2 (8·0)	0	–	25	3 (12·0)	16	0 (0)
UK-Scotland	0	0	–	0	–	0	–	14	–
Total	850	646	183 (28·3)	500	270 (54·0)	555	29 (5·2)	162	79 (9·3)

Albania, Iceland, Kosovo and Sweden did not find any K pneumoniae isolates that were suspected non-susceptible to carbapenems during the study period. *Mean number of antibiotics tested.

Table 4: Resistance of confirmed carbapenemase-producing *Klebsiella pneumoniae* to last-line antibiotics and to all tested antibiotics

Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•COLIMICINA dose da carico 9 milioni poi

4,5 milioni x 2 /die

+

MEROPENEM* 2 gr x 3 /die

oppure

IMIPENEM* 1 gr x 3/die

•COLIMICINA dose come sopra

+

MEROPENEM* 2 gr x 3 /die

IMIPENEM* 1 gr x 3 /die

+

FOSFOMICINA 4 gr x 4-6/die

Oppure

TIGECICLINA 100 o 150 mg x 2 / die

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* Scelta basata sul valore della CMI ; il carbapenemico deve essere utilizzato anche nei casi in cui le CMI superino, non di molto, il breakpoint di resistenza

Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•COLIMICINA dose da carico 9 milioni poi

4,5 milioni x 2 /die

+

TIGECICLINA 100 o 150 mg x 2/die

oppure

FOSFOMICINA 4 g x 4-6/die

Ceftazidime avibactam (uso compassionevole)

CEFTAZIDIME AVIBACTAM 2,5 g (2 g ceftazidime, 0,5 avibactam) ogni 8 ore (2 h di infusione)

monoterapia ?
associazione ?
con quali farmaci ? (gentamicina
fosfomicina
……..)

DOSE 2,5 x 3 ? (HAP,VAP, Osteomieliti…….)

Terapia solo delle KPC o anche ESBL, Pseudomonas

Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•Ceftazidime/avibactam 2,5 g x 3

*Ceftazidime/avibactam 2,5 g x 3 + Gentamicina 5 mg/Kg/die

•Ceftazidime/avibactam 2,5 g x 3 + Fosfomicina ev 16-24 g/die

•Ceftazidime/avibactam 2,5 g x 3 + Colimicina 9 milioni poi 4,5/die

N.B. non esistono ancora studi sulle associazioni, né sulle posologie in corso di infezioni localizzate

TERAPIE DELLE SEPSI DA KPC

- COLIMICINA + MEROPENEM + TIGECICLINA
- COLIMICINA + MEROPENEM + FOSFOMICINA

- GENTAMICINA + MEROPENEM + TIGECICLINA
- GENTAMICINA + MEROPENEM + FOSFOMICINA

- COLIMICINA o GENTAMICINA + TIGECICLINA
- COLIMICINA o GENTAMICINA + FOSFOMICINA

- CEFTAZIDIME/AVIBACTAM
- CEFTAZIDIME/AVIBACTAM + GENTAMICINA
- CEFTAZIDIME/AVIBACTAM + FOSFOMICINA
- CEFTAZIDIME/AVIBACTAM + COLIMICINA

Terapia delle infezioni da Pseudomonas aeruginosa MDR

1. CEFTOLOZANE/TAZOBACTAM 1,5 g x 3/die (3 g x 3 nelle HAP)

2. COLIMICINA (9 milioni dose da carico poi 4,5 milioni x 2 / die) +
   RIFAMPICINA 600 -900 mg /die (l'uso prescinde dalla sensibilità in vitro)

3. COLIMICINA (dose come sopra) +
   FOSFOMICINA (4 gr x 4-6 / die) (solo se è dimostrata una sensibilità in vitro)

Important safety consideration for parenteral fosfomycin is its high sodium content which may result in sodium overload and heart failure [23, 70]. Thus, each gram of fosfomycin contains 14.35 mEq (330 mg) of sodium. Considering that an average dose of fosfomycin is about 12 g, the sodium load associated with its use may be significant, especially for patients with underlying heart failure. In comparison, piperacillin and tazobactam, the antibacterial drug that is considered to have high sodium content contains 2.36 mEq (54.28 mg) of sodium per gram of piperacillin. A pooled analysis of comparative trials in our review did not demonstrate a higher rate of heart failure in fosfomycin-treated patients.

D. Iarikov 2015

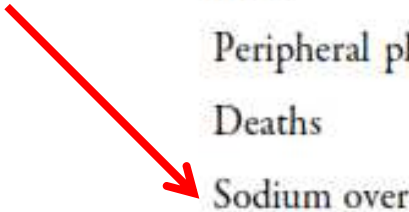
5570 pazienti

Table 2
List of adverse events reported with intravenous fosfomycin use, categorized by their MedDRA preferred and high level terms

Adverse event	No. occurrence	Relative occurrence (%)
Gastrointestinal disorders	140	5.24
Gastrointestinal disorders (unspecified)	69	2.56
Diarrhoea	16	0.60
Nausea	13	0.49
Dysgeusia	31	1.16
Vomiting	9	0.34
Abdominal pain	1	0.04
Retching	1	0.04
Metabolism and nutrition disorders	99	3.71
Hypokalaemia	78	2.92
Hypernatraemia	18	0.68
Decreased appetite	1	0.04
Skin and subcutaneous tissue disorders	23	0.86
Rash	19	0.71
Rash morbilliform	2	0.07
Urticaria	1	0.04
Erythema multiforme	1	0.04
Injury, poisoning and procedural complications	27	1.01
(Thrombo)phlebitis	16	0.60
Venous intolerance	11	0.41
Altered laboratory parameters	103	3.85
Hepatic enzyme increased (unspecified)	59	2.21
Transaminases increased (unspecified)	20	0.75
Alanine aminotransferase increased	5	0.19
Laboratory test abnormal (unspecified)	5	0.19
Blood alkaline phosphatase increased	5	0.19
Aspartate aminotransferase increased	3	0.11
Blood bilirubin increased	2	0.07
Blood urea increased	2	0.07
Blood creatinine increased	1	0.04
Respiratory rate increased	1	0.04
Blood and lymphatic system disorders	19	0.71
Leukopenia*	6	0.22
Anaemia	5	0.19
Thrombocytopenia	4	0.15
Neutropenia*	3	0.11
Eosinophilia	1	0.04
General disorders and administration site conditions	19	0.71
Oedema	6	0.22
Asthenia	4	0.15
Hyperhydrosis	3	0.11
Injection site pain	3	0.11
Pyrexia	1	0.04
Nicolau syndrome*,[a]	1	0.04
Flush	1	0.04
Infections and infestations	6	0.22
Systemic candidiasis*	2	0.07
Fungal infection	2	0.07
Herpes simplex infection	2	0.07
Nervous system disorders	16	0.60
Headache	14	0.52
Vertigo	1	0.04
Hyperosmolar coma* + hyperglycaemia	1	0.04
Vascular disorders	5	0.19
Hypertension	2	0.07
Vascular pain	2	0.07
Shock*	1	0.04
Cardiac disorders	9	0.34
Tachycardia	3	0.11
Cardiac failure*,[a]	2	0.07
Pain in the heart*	2	0.07
Cardiac disorders (unspecified)	2	0.07
Other	16	0.60
Worsening of pulmonary oedema* in patients with heart insufficiency and endocarditis	2	0.07
Cough	1	0.04

Table 5 Adverse events associated with parenteral administration of fosfomycin in 15 non-comparative trials [18–32]

Adverse event	Fosfomycin *N* = 578 *n* (%)
Hypokalemia	28 (5%)
Transaminase elevation	10 (2%)
GI disorders	12 (2%)
Rash	11(2%)
Peripheral phlebitis	7 (1%)
Deaths	5 (1%)
Sodium overload and heart failure	5 (1%)
Neutropenia (not defined)	5 (1%)
Injection site pain	4 (1%)
Thrombocytopenia	4 (1%)
Renal toxicity	3 (<1%)
Heart failure	2 (<1%)
Hypertension	2 (<1%)



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