SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina
12° CONGRESSO NAZIONALE
CATANIA | 17-18 novembre 2022

Fosfomicina: Place in Therapy

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CENTRE FOR MACH
MultidisciplinAry ResearCh in Health Science

UNIVERSITA DEGLI ST
DIPARTIMENTO DI FIS
MEDICO-CHIRURGICA

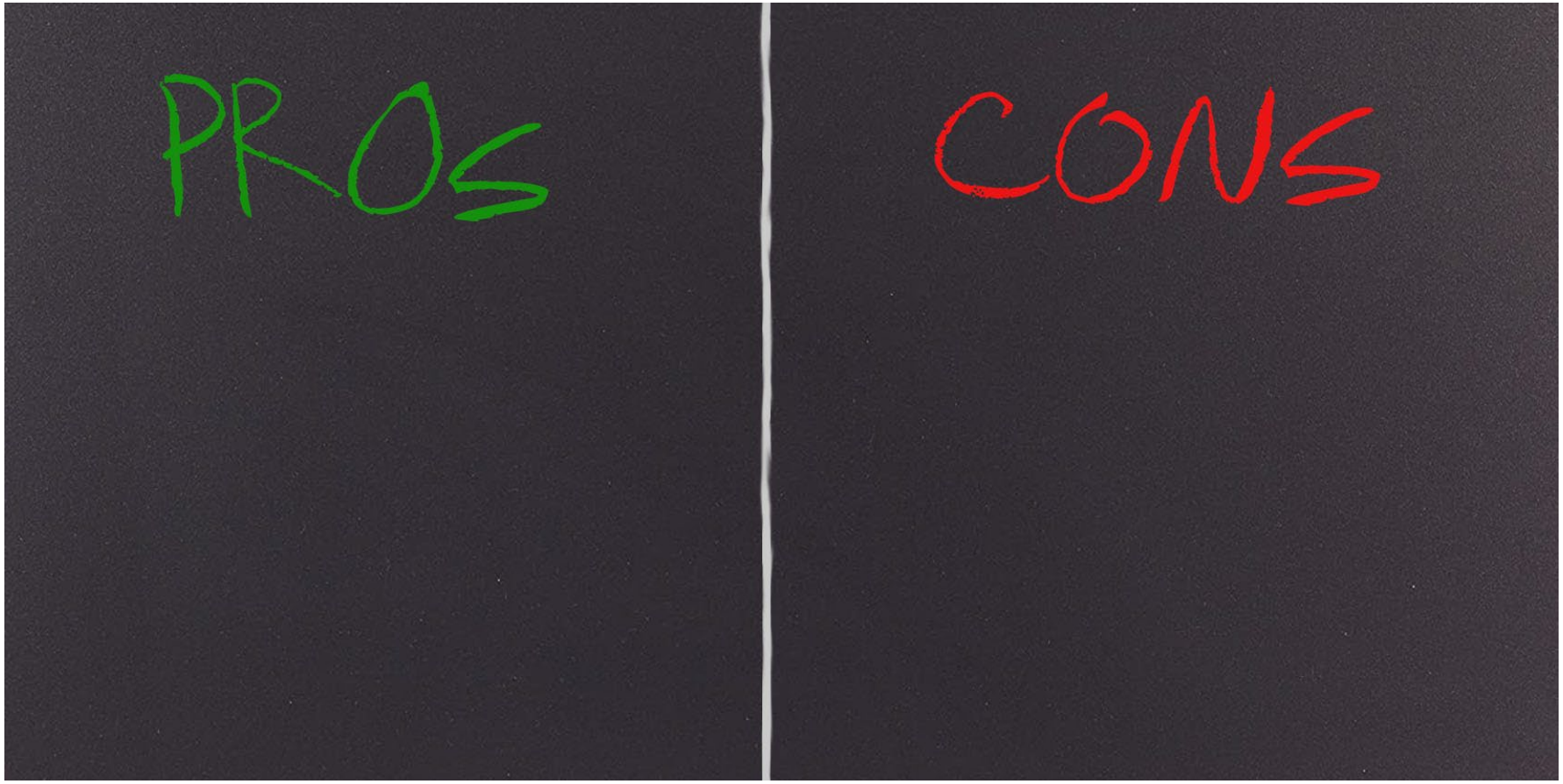
Conflitto di interessi

- AG received speaker’s honoraria and fees for attending advisory boards from ViiV Healthcare, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer and Novartis

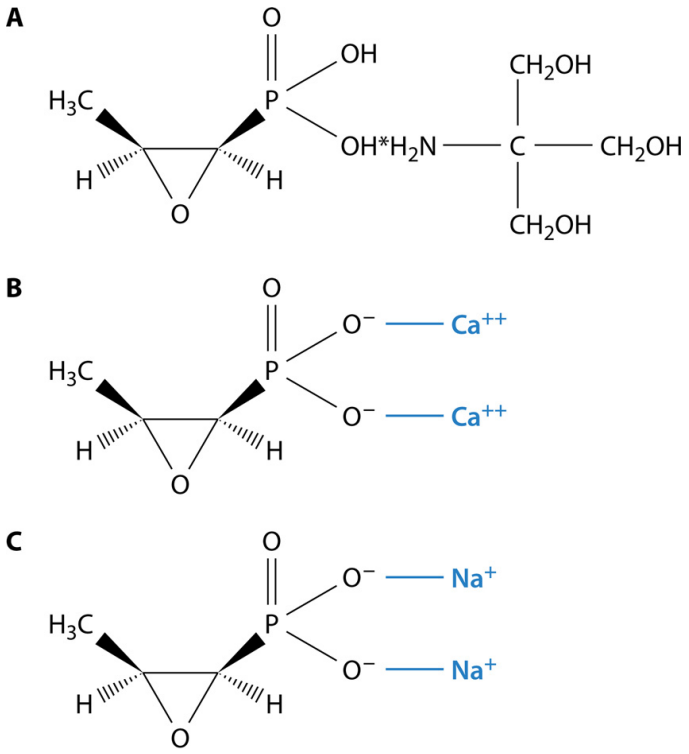
Fosfomicina: Place in Therapy

1. Profiling della molecola: Pros & Cons
2. Place in therapy
3. Real life experience

1. Caratteristiche della molecola: Pros & Cons (da parte del Clinico)



Caratteristiche della molecola: Pros & Cons (da parte del Clinico)



Fosfomycin trometamol

Fosfomycin calcium

Oral formulations

Fosfomycin disodium

Intravenous formulations

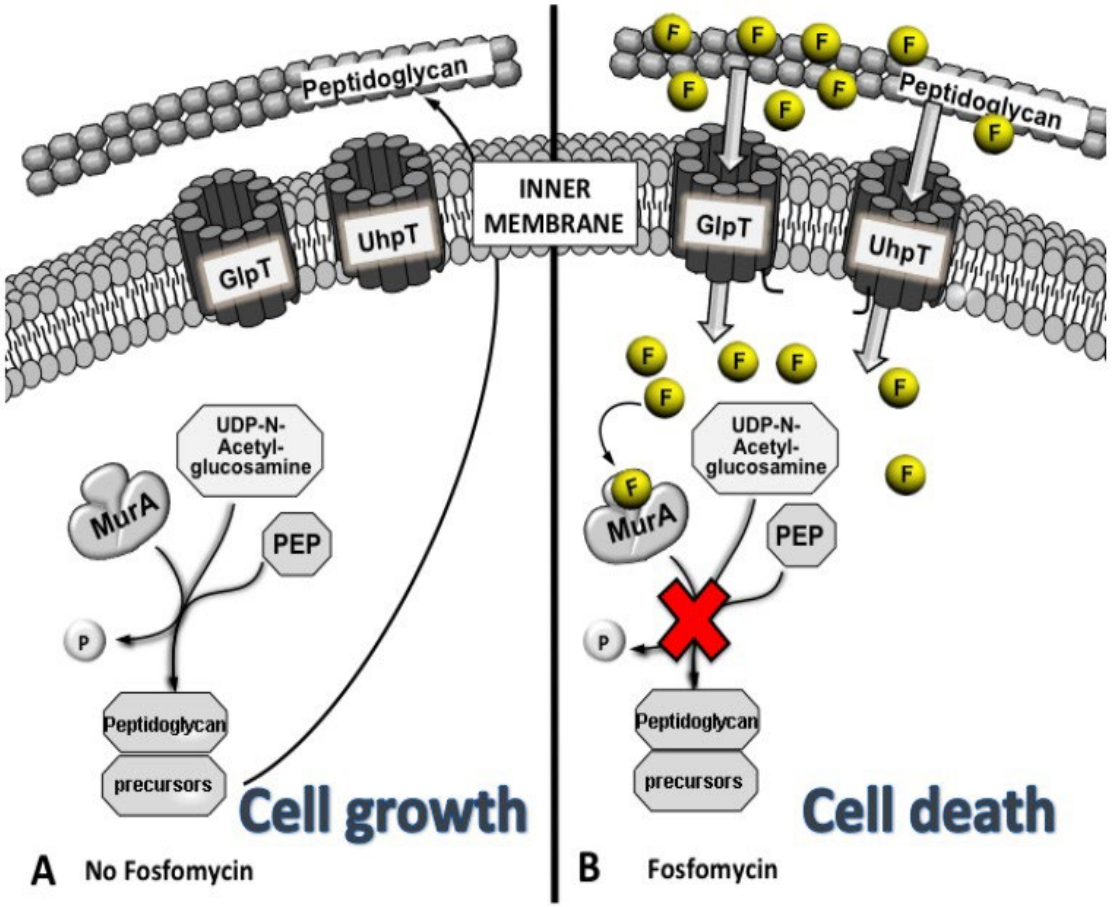
PK

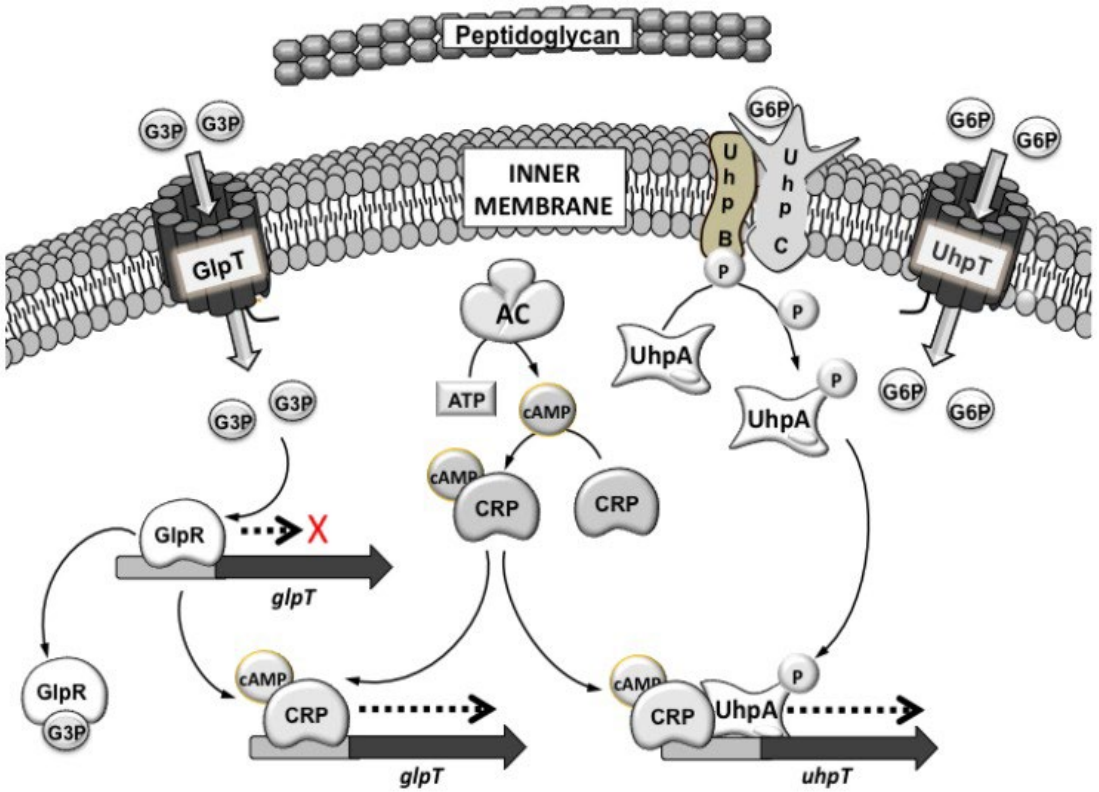
- Piccola molecola Idrofila
- Basso peso molecolare
- Basso legame con le proteine plasmatiche

PD

- Meccanismo di azione unico

Pros: meccanismo d'azione





Castañeda-García et al. Antibiotics (Basel), 2013

Pros: meccanismo d'azione

Meccanismi di resistenza

- **Target modifications:** MurA (point. mutations or overexpression)
- **Peptidoglycan recycling pathway**
- **Alterations in the permeability:**
  - Membrane transporters (GlpT, UhpT)
  - Regulation (UhpABC, CRP, CyaA, Ptsl… CpxAR….)
- **Fosfomycin-modifying enzimes:** FosA, FosB, FosX, FosC, FomA, FomB, FosK…

Castañeda-García et al. Antibiotics (Basel), 2013

Pros: spettro antimicrobico

	Organism	Susceptibility
Gram positive	*Staphylococcus* spp.	
	Enterococcus faecalis	
	Enterococcus faecium	
Gram negative	*Escherichia coli*	
	Klebsiella spp.	
	Acinetobacter spp.	
	Pseudomonas aeruginosa	
	Citrobacter species	
	Proteus spp.	
	Providencia spp.	
	Bacteroides fragilis	

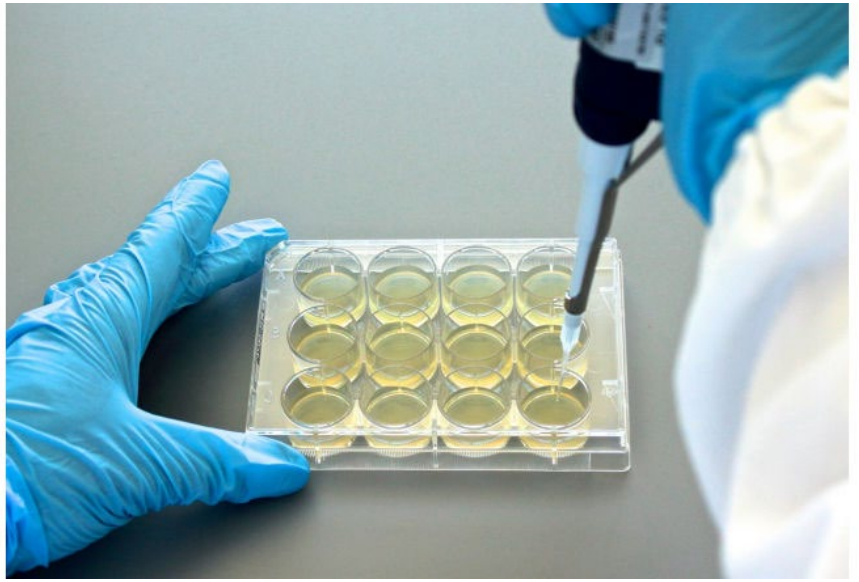
Highly susceptible (■

MDR GRAM-POSITIVES
• Methycillin-resistant S.aureus (MRSA) • Methycillin-resistant S.epidermidis (MRSE) • Vancomycin-resistant S.aureus (MRSA)
MDR GRAM-NEGATIVES
• Amber Class A: Penicillinases (TEM, SHV, CTX-M (ESBL), KPC-Carbapenemases • Amber Class B: Metallo-β-lactamases (NDM, VIM, IMP) • Amber Class C: Cephalosporinases (AmpC) • Amber Class D: Oxacillinases (OXA-48)

Falagas et al. Clin Microbiol Rev, 2016
Vardakas et al. Int J Antimicrob Agents. 2016
Avent et al. Intern Med J. 2018

Cons: test resistenza in vitro

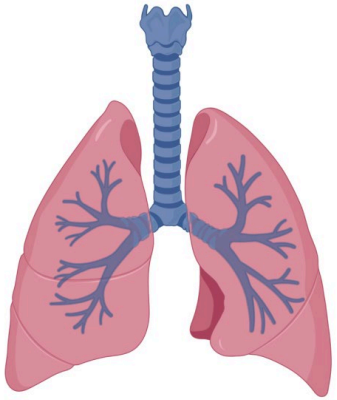
Agar diluizione (metodica di riferimento)

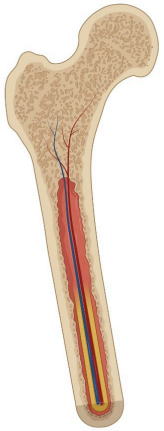


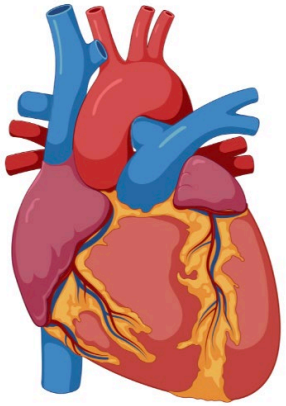
In vitro susceptibility testing with fosfomycin requires the addition of glucose-6-phosphate either to the medium or to the disk or gradient strip. For agar or broth microdilution MIC determination the medium should be supplemented with 25 mg/L of glucose-6-phosphate. In addition to fosfomycin, disks for diffusion susceptibility testing should contain 50µg of glucose-6-phosphate and gradient MIC strips should contain 25µg of glucose-6-phosphate.

EUCAST, Fosfomycin: Rationale for the EUCAST clinical breakpoints, version 1.0

Pros: caratteristiche farmacocinetiche



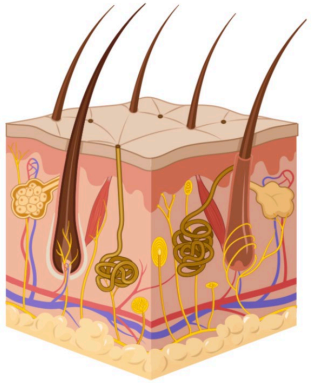


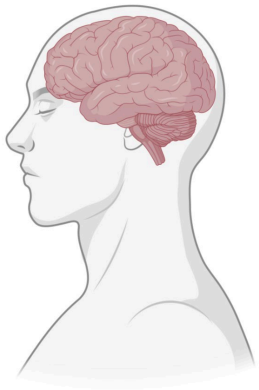


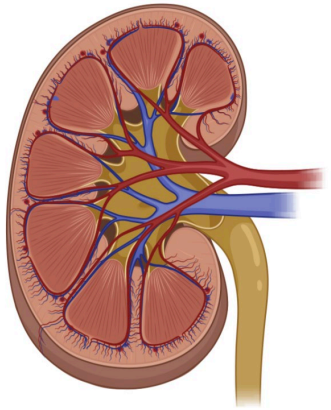
Piccola molecola Idrofila

Basso peso molecolare

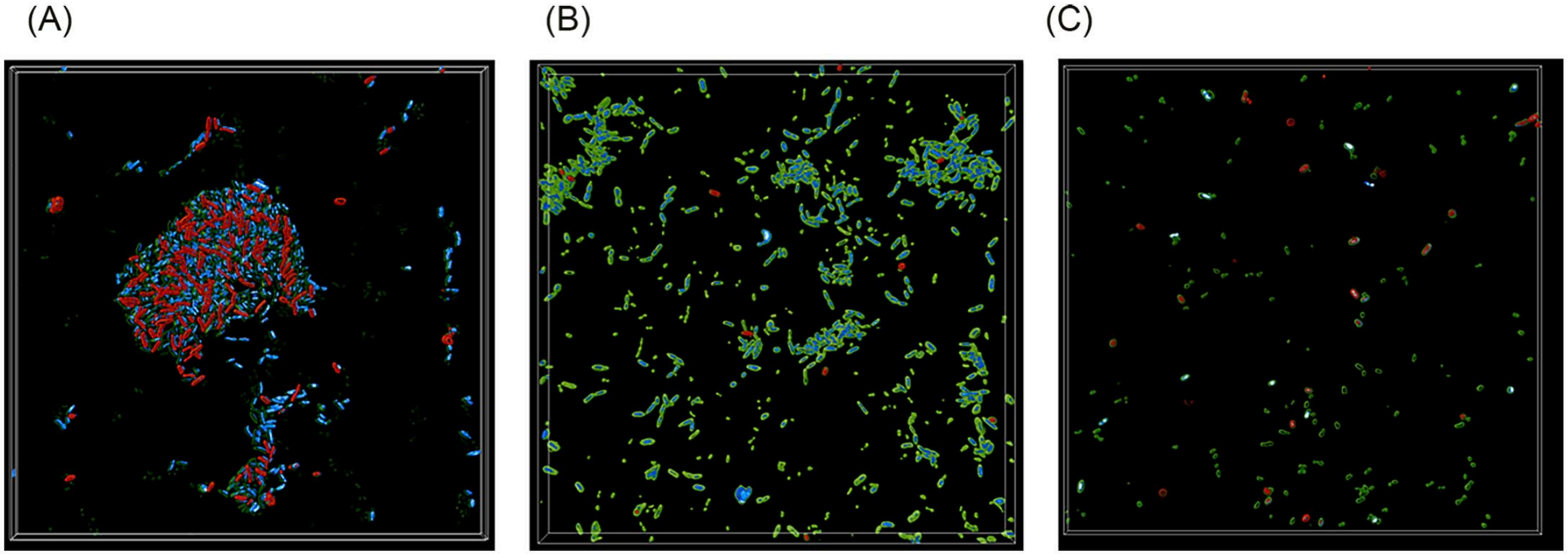
Scarso legame con proteine plasmatiche







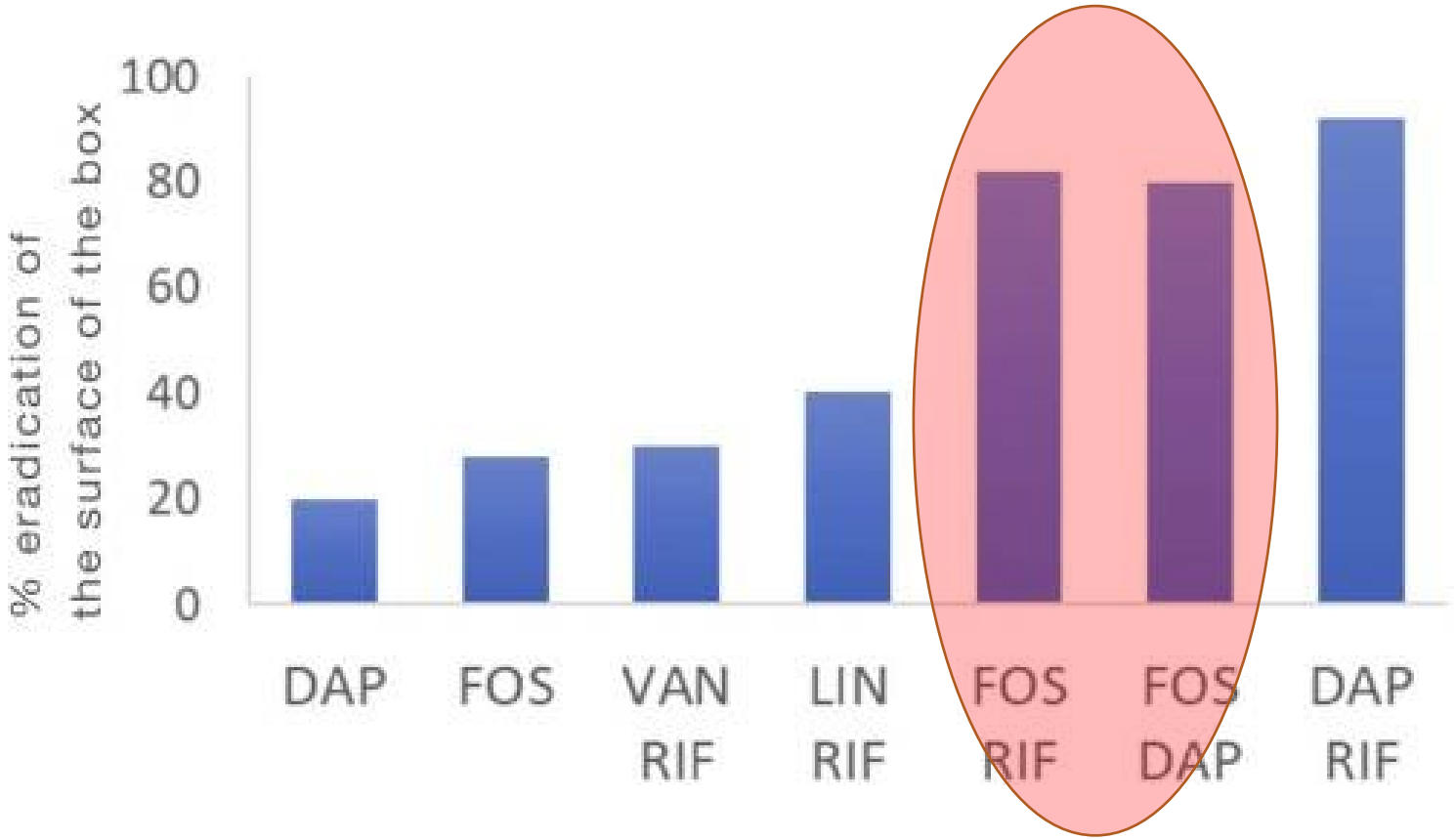
Pros: attività anti biofilm



Effect of different concentrations of fosfomycin on bacterial biofilm of uropathogenic *Escherichia coli* using 300 µg/ml (B) and 1500 µg/ml (C) of fosfomycin tromethamine compared with no fosfomycin tromethamine (A)

Gonzalez et al., Pathogens and Disease 2019

Pros: attività anti biofilm



Percentage eradication of a methicillin-resistant *Staphylococcus aureus* biofilm in the animal model of foreign body infection

Morata et al., Rev Esp Quimioter. 2019

Pros: sinergismo

TABLE 1 MICs of meropenem and fosfomycin alone or in combination against non-MBL and MBL-producing *Pseudomonas aeruginosa* clinical isolates by FICI and Loewe additivity index analysis[a]

	Mero			Fosfo						
	MIC (μg/ml)			MIC (μg/ml)			Synergism analysis			
P. aeruginosa isolate	Mero alone	Mero in combination	Fold reduction in Mero MIC	Fosfo alone	Fosfo in combination	Fold reduction in Fosfo MIC	FICI	S or I based on FICI	Loewe additivity index	S or A based on Loewe additivity index
PA-73	4	0.5	8	128	16	8	0.25	S	0.75	S
PA-87	4	2	2	128	32	4	0.75	I	0.25	S
PA-116	16	1	16	64	8	8	0.19	S	0.81	S
PA-106	16	4	4	64	4	16	0.50	S	0.69	S
PA-146	16	4	4	32	8	4	0.50	S	0.50	S
PA-149	128	64	2	128	16	8	0.62	I	0.38	S
PA-114	0.50	0.25	2	64	8	8	0.62	I	0.38	S
PA-64	0.25	0.06	4	32	8	4	0.49	S	0.51	S
PA-69	0.50	0.50		128	128		2.00	I	−1	A
PA-30[b]	16	4	4	512	8	64	0.26	S	0.73	S
PA-43[b]	4	0.25	8	512	1	512	0.06	S	0.90	S
PA-314[b]	8	2	4	128	4	32	0.28	S	0.72	S
PA-524[b]	8	1	8	64	16	4	0.37	S	0.62	S
PA-13[b]	512	128	4	64	16	4	0.50	S	0.50	S
PA-525[b]	1,024	32	32	128	16	8	0.16	S	0.85	S
PA-573[b]	128	8	16	512	64	8	0.19	S	0.81	S
PA-377[b]	256	32	8	128	32	4	0.37	S	0.63	S
PA-170[b]	8	1	8	128	32	4	0.37	S	0.63	S
PA-GIM[b]	512	64	8	256	16	16	0.19	S	0.81	S
MIC_{50}	16	2		128	16					
MIC_{90}	512	64		512	64					

[a]Mero, meropenem; Fosfo, fosfomycin; FICI, fractional inhibitory concentration index; S, synergy; I, indifferent; A, antagonistic.
[b]Metallo-β-lactamase-producing isolate.

Albiero et al., Antimicrob Agents Chemother. 2019

Cons: Tossicità

Tabulated list of common and uncommon adverse reactions

System Organ Class	Frequency Category	Adverse Drug Reactions
Metabolism and nutrition disorders	Common	Hypernatremia and/or hypokalaemia
	Uncommon	Decreased appetite, edema
Gastrointestinal disorders	Common	Retching, stomach ache
	Uncommon	Nausea, vomiting, diarrhea
Skin and subcutaneous tissue disorders	Common	Erythematous eruption
	Uncommon	Rash
Nervous system disorders	Uncommon	Dysgeusia, headache
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Fatigue

2. Place in therapy & new place in therapy

Systematic review

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

B. Grabein [1], W. Graninger [2], J. Rodríguez Baño [3, 4], A. Dinh [5], D.B. Liesenfeld [6, *]

Clinical Infectious Diseases

MAJOR ARTICLE

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Keith S. Kaye,[1] Louis B. Rice,[2] Aaron L. Dane,[3] Viktor Stus,[4] Olexiy Sagan,[5] Elena Fedosiuk,[6] Anita F. Das,[7] David Skarinsky,[8] Paul B. Eckburg,[8] and Evelyn J. Ellis-Grosse[8]

[1]Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor; [2]Department of Medicine, Warren Alpert Medical School of Brown University and Rhode Island Hospital and The Miriam Hospital, Providence; [3]DaneStat Consulting, Alderly Edge, United Kingdom; [4]Municipal Institution Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro; [5]Municipal Institution Zaporizhzhia Regional Clinical Hospital of Zaporizhzhia, Regional Council Department of Urology, State Institution Zaporizhzhia Medical Academy of Postgraduate Education under the Ministry of Health of Ukraine; [6]Brest Regional Hospital, Belarus; [7]Das Statistical Consulting, Guerneville, and [8]Zavante Therapeutics, Inc., San Diego, California

JAMA Network Open

Original Investigation | Infectious Diseases

Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections
A Randomized Clinical Trial

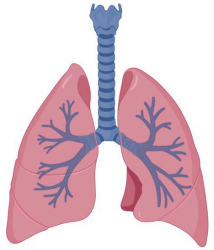
Jesús Sojo-Dorado, MD, PhD; Inmaculada López-Hernández, MD, PhD; Clara Rosso-Fernandez, MD, PhD; Isabel M. Morales, MD, PhD; Zaira R. Palacios-Baena, MD, PhD; Alicia Hernández-Torres, MD, PhD; Esperanza Merino de Lucas, MD, PhD; Laura Escolà-Vergé, MD, PhD; Elena Bereciartua, MD; Elisa García-Vázquez, MD, PhD; Vicente Pintado, MD, PhD; Lucía Boix-Palop, MD; Clara Natera-Kindelán, MD, PhD; Luisa Sorlí, MD, PhD; Nuria Borrell, MD, PhD; Livia Giner-Oncina, PharmD, PhD; Concha Amador-Prous, MD, PhD; Evelyn Shaw, MD, PhD; Alfredo Jover-Saenz, MD; Jose Molina, MD; Rosa M. Martínez-Alvarez, MD; Carlos J. Dueñas, MD; Jorge Calvo-Montes, MD; Jose T. Silva, MD, PhD; Miguel A. Cárdenes, MD; María Lecuona, MD, PhD; Virginia Pomar, MD, PhD; Lucía Valiente de Santis, MD; Genoveva Yagüe-Guirao, MD, PhD; María Angeles Lobo-Acosta, MD; Vicente Merino-Bohórquez, PharmD; Alvaro Pascual, MD, PhD; Jesús Rodríguez-Baño, MD, PhD; and the REIPI-GEIRAS-FOREST group

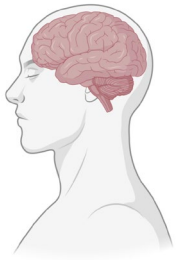
Place in therapy

Therapeutic indications (EMA)

- Osteomyelitis
- CNS infection (meningitis, encephalitis, abscess of the brain)
- Urinary tract infections
- Nosocomial lower respiratory tract infections
- Peri-operative infections
- Skin and soft tissue infections
- Burn infections
- Biliary tract infections
- Sepsis
- Endocarditis
- Oto-rhino-laryngological infections
- Ophthalmological infections
- Complicated urinary tract infections
- Bacteremia that occurs in association with or is suspected to be associated with any of the infections listed above
- Severe infections of other organ systems due to fosfomycin-susceptible Gram-negative pathogens with limited therapeutic options

Place in therapy





Infection (2019) 47:827–836
https://doi.org/10.1007/s15010-019-01323-4

ORIGINAL PAPER

Current clinical use of intravenous fosfomycin in ICU patients in two European countries

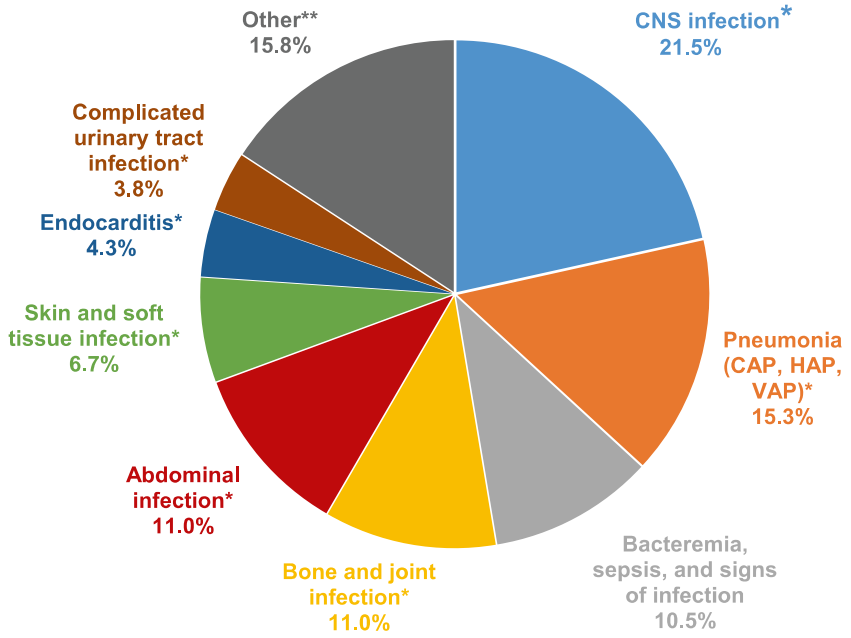


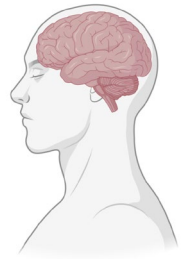
Fig. 1 Types of infection ($n = 209$); *± bacteremia or sepsis; **multiple infections or infections that could not be assigned to one of the other categories

Table 2 Microbiological spectrum (data from mono- and polybacterial infections)

Pathogen	*n* (%)
Staphylococcus aureus	58 (22.3)
Staphylococcus epidermidis/coagulase-negative staphylococci	37 (14.2)
Escherichia coli	32 (12.3)
Enterococcus spp.	28 (10.8)
Klebsiella spp.	20 (7.7)
Enterobacter/*Citrobacter* spp.	17 (6.5)
Pseudomonas aeruginosa	12 (4.6)
Streptococcus spp.	9 (3.5)
Proteus spp.	6 (2.3)
Serratia spp.	4 (1.5)
Other Gram-negative pathogens	19 (7.3)
Other Gram-positive pathogens	9 (3.6)
Anaerobes	9 (3.5)

Putensen et al., Infection 2019

Place in therapy



REVIEW

Intravenous fosfomycin for the treatment of patients with central nervous system infections: evaluation of the published evidence

Katerina G Tsegka[a,b], Georgios L Voulgaris[a,c], Margarita Kyriakidou[a,d] and Matthew E Falagas[a,b,e]

ABSTRACT

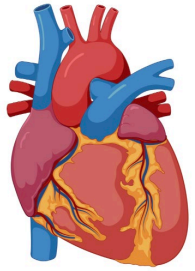
Introduction: Central nervous system (CNS) infections have considerable morbidity and mortality. Fosfomycin is a broad spectrum bactericidal antibiotic with favorable pharmacokinetic properties and low toxicity, satisfactory penetration in the cerebrospinal fluid and is authorized for the treatment of bacterial meningitis.

Areas covered: The objective of this analysis was to evaluate the available data regarding the effectiveness and safety of intravenous fosfomycin for the treatment of CNS infections. Thirty-two relevant publications were identified. Data from 224 patients who received intravenous fosfomycin as treatment for CNS infections were evaluated. Overall, 93.8% of patients were cured from the infection. *Staphylococcus* was the most frequent pathogen; *Streptococcus pneumoniae, Neisseria meningitidis,* and several other microbial agents, including multi-drug resistant and extensively drug-resistant bacteria, were also implicated. Fosfomycin was given as part of a combination treatment in the vast majority of the patients. The dosage of fosfomycin ranged between 4 g and 24 g per day; a regimen with 14–16 g per day was used in the majority of the cases. Fosfomycin was generally well tolerated.

Expert opinion: The evaluation of the published evidence suggests that fosfomycin may be beneficial in the treatment of patients with CNS infections.

Tsegka et al., Expert Rev Anti Infect Ther 2020

Place in therapy



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Table 2. Primary and Secondary Outcomes

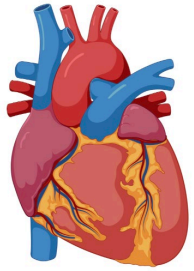
Outcome	Daptomycin Plus Fosfomycin, No. of Patients/Total (%)	Daptomycin Alone, No. of Patients/Total (%)	Relative Risk (95% CI)
Primary endpoint			
Treatment success at TOC	40/74 (54.1)	34/81 (42.0)	1.29 (.93–1.8)
Secondary endpoints			
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)	0.15 (.04–.63)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)	−6.2 (−11.4 to −.9)[a]
Positive blood cultures at TOC	0/74 (0.0)	4/81 (4.9)	−4.9 (−9.7 to −.2)[a]
Microbiological failure at TOC	0/74 (0.0)	9/81 (11.1)	−11.1 (−18.0 to −4.3)[a]
No. of episodes of complicated bacteremia at TOC	12/74 (16.2)	26/81 (32.1)	0.51 (.28–.94)
Any AE leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)	3.56 (1.21–10.44)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)	0.55 (.14–2.12)
Overall mortality at TOC	18/74 (24.3)	22/81 (27.2)	0.9 (.53–1.54)

Abbreviations: AE, adverse event; CI, confidence interval; TOC, test of cure.

[a]Proportion difference, as it was not possible to estimate the relative risk.

Pujol et al., Clin Inf Dis2021

Place in therapy



Clinical Infectious Diseases

MAJOR ARTICLE

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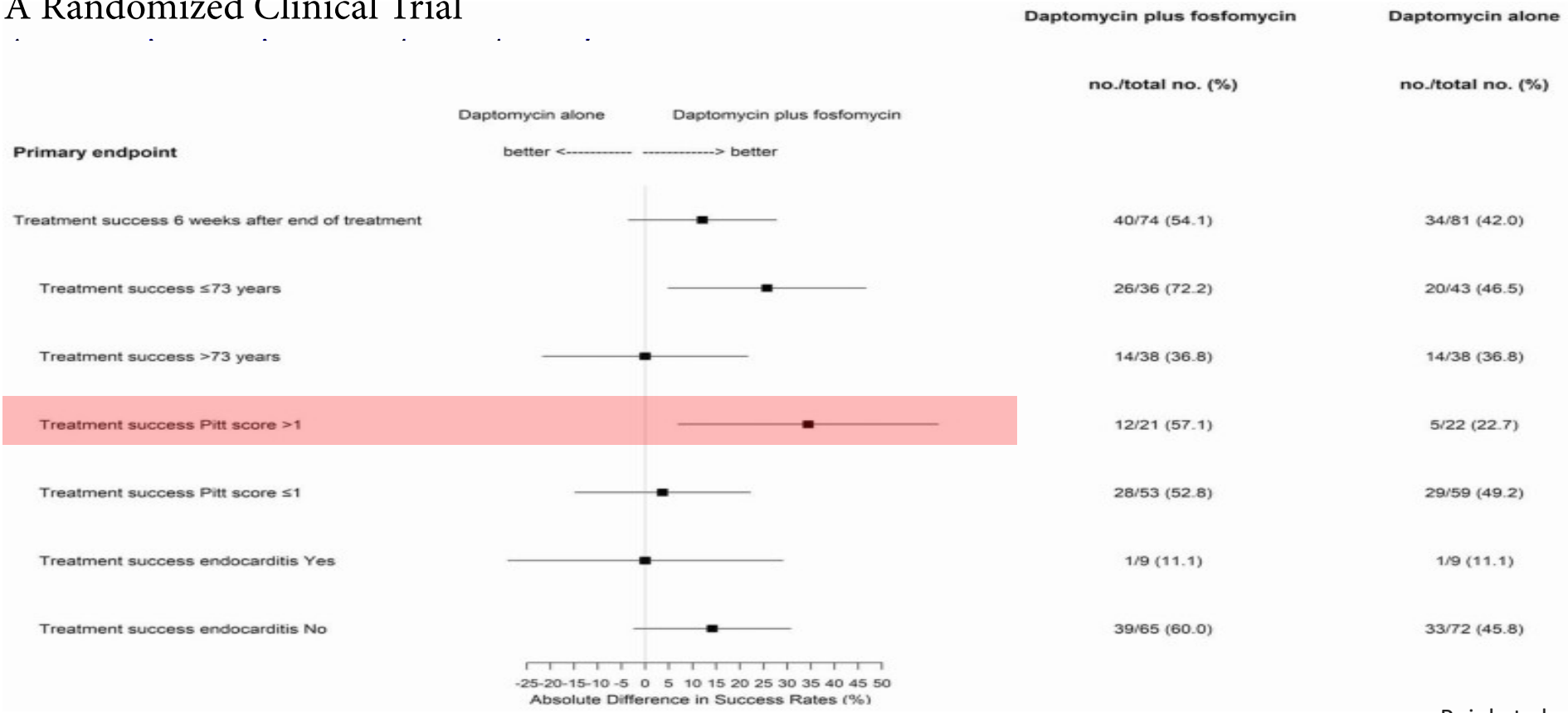
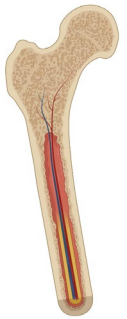
Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial



Pujol et al., Clin Inf Dis2021

Place in therapy



EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
2022, VOL. 20, NO. 1, 33–43
https://doi.org/10.1080/14787210.2021.1932463

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REVIEW

OPEN ACCESS Check for updates

Intravenous fosfomycin for the treatment of patients with bone and joint infections: a review

Katerina G. Tsegka, Georgios L. Voulgaris, Margarita Kyriakidou, Anastasios Kapaskelis and Matthew E. Falagas

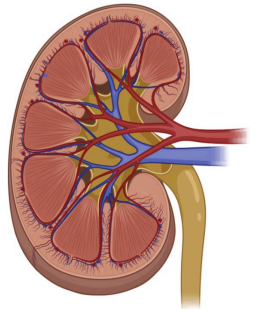
ABSTRACT

Introduction: Fosfomycin is a wide spectrum bactericidal antibiotic with a unique mode of action, low toxicity, and good penetration in tissues with deep-seated infections, including bone and joint infections.

Areas covered: Data were extracted from 19 published articles. Three hundred and sixty-five patients, with broad age range, received intravenous fosfomycin for the treatment of bone and joint infections (including arthritis, acute and chronic osteomyelitis, discitis, periprosthetic joint infection). Fosfomycin was given as part of a combination antimicrobial therapy in the majority of patients (93.7%). The dosage of fosfomycin ranged from 4 g/day (in one case) to 24 g/day. The dosage of fosfomycin, in some cases, mostly pediatric, was calculated based on body weight, ranging from 50 mg/kg/day to 250 mg/kg/day. The duration of fosfomycin treatment ranged from a couple of days up to 3 months. The most common isolated pathogen was *Staphylococcus aureus* (38.9%). Three hundred patients (82.2%) were successfully treated. Fosfomycin was well tolerated, as few patients developed mild adverse events, mostly gastrointestinal discomfort, hypernatremia, skin rash, and neutropenia.

Expert opinion: The available data suggests that intravenous fosfomycin may be beneficial for the treatment of patients with bone and joint infections, especially when used as part of a combination antibiotic regimen.

New place in therapy: monotherapy in UTI?



Clinical Infectious Diseases

MAJOR ARTICLE

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Keith S. Kaye,| Louis B. Rice,| Aaron L. Dane,| Viktor Stus,| Olexiy Sagan,| Elena Fedosiuk,| Anita F. Das,| David Skarinsky,†| Paul B. Eckburg,†| and Evelyn J. Ellis-Grosse†|

Background. ZTI-01 (fosfomycin for injection) is an epoxide antibiotic with a differentiated mechanism of action (MOA) inhibiting an early step in bacterial cell wall synthesis. ZTI-01 has broad in vitro spectrum of activity, including multidrug-resistant Gram-negative pathogens, and is being developed for treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) in the United States.

Methods. Hospitalized adults with suspected or microbiologically confirmed cUTI/AP were randomized 1:1 to 6 g ZTI-01 q8h or 4.5 g intravenous (IV) piperacillin-tazobactam (PIP-TAZ) q8h for a fixed 7-day course (no oral switch); patients with concomitant bacteremia could receive up to 14 days.

Results. Of 465 randomized patients, 233 and 231 were treated with ZTI-01 and PIP-TAZ, respectively. In the microbiologic modified intent-to-treat (m-MITT) population, ZTI-01 met the primary objective of noninferiority compared with PIP-TAZ with overall success rates of 64.7% (119/184 patients) vs 54.5% (97/178 patients), respectively; treatment difference was 10.2% (95% confidence interval [CI]: −0.4, 20.8). Clinical cure rates at test of cure (TOC, day 19–21) were high and similar between treatments (90.8% [167/184] vs 91.6% [163/178], respectively). In post hoc analysis using unique pathogens typed by pulsed-field gel electrophoresis, overall success rates at TOC in m-MITT were 69.0% (127/184) for ZTI-01 versus 57.3% (102/178) for PIP-TAZ (difference 11.7% 95% CI: 1.3, 22.1). ZTI-01 was well tolerated. Most treatment-emergent adverse events, including hypokalemia and elevated serum aminotransferases, were mild and transient.

Conclusions. ZTI-01 was effective for treatment of cUTI including AP and offers a new IV therapeutic option with a differentiated MOA for patients with serious Gram-negative infections.

Kaye et al., Clin Inf Dis 2019

New place in therapy: monotherapy in UTI?

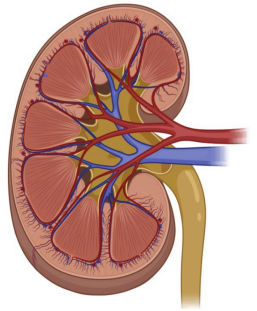


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Table 4. Clinical and Microbiologic Outcomes Among Patients With Baseline Pathogens Demonstrating Phenotypic Resistance Characteristics (Test of Cure, Microbiologic Modified Intent-to-Treat) [9]

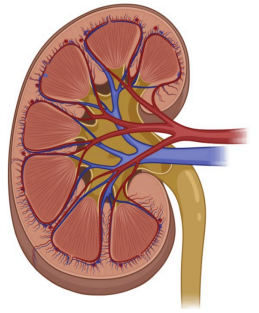
	ESBL		Amino-R		CRE		MDR	
	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)	Cure, % (n/N)	Eradication, % (n/N)
ZTI-01	93 (52/56)	55 (32/58)	97 (29/30)	67 (20/30)	100 (9/9)	56 (5/9)	92 (34/37)	54 (20/37)
PIP-TAZ	93 (51/55)	47 (27/57)	94 (29/31)	38 (12/32)	85 (11/13)	31 (4/13)	90 (28/31)	36 (12/33)

Using minimum inhibitory concentrations from an accompanying antibiotic panel or agar dilution supplemented with glucose 6-phosphate for fosfomycin, blood or urine isolates were identified to assess patient and microbiologic outcome. The following definitions were used for this assessment—ESBL: ≥2 μg/mL MIC for aztreonam, ceftazidime, or ceftriaxone; CRE: ≥4 μg/mL imipenem or meropenem; Amino-R: gentamicin ≥8 μg/mL or amikacin ≥32 μg/mL; MDR: nonsusceptibility ≥3 classes, using definitions above plus levofloxacin ≥4 μg/mL and trimethoprim/sulfamethoxazole ≥32 g/mL. Patients could have more than 1 isolate from blood and/or urine sources, and all organisms are presented for completeness. Patients with multiple organisms were counted only once per resistance grouping. If the same species was identified from a different source, the isolate was counted once for microbiological outcome.

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; ZTI-01, fosfomycin for injection.

Kaye et al., Clin Inf Dis 2019

New place in therapy – Monotherapy?



JAMA Network Open

Original Investigation | Infectious Diseases

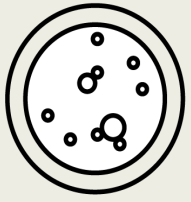
Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections
A Randomized Clinical Trial

comparators:
CEFTRIAXONE (1 g every 24 hours intravenously in 2-4 minutes) or if ceftriaxone resistant, MEROPENEM (1 g every 8 hours intravenously in 15-30 minutes)

JAMA Network Open

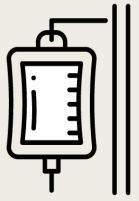
RCT: Effectiveness of Fosfomycin for Multidrug-Resistant Urinary Tract Infections From *Escherichia coli*

POPULATION
70 Men, 73 Women



Adults with bacteremic urinary tract infection due to multidrug-resistant *Escherichia coli*
Median age, 72 y

INTERVENTION
143 Participants randomized and analyzed

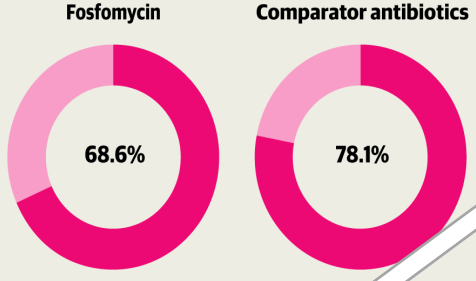


70 Fosfomycin
Intravenous (IV) fosfomycin 4 g every 6 h with option to switch to oral active agent after 4 d

73 Comparator antibiotics
IV ceftriaxone 1 g daily or meropenem 1 g every 8 h; could switch to oral agent or IV ertapenem after 4 d

FINDINGS
Fosfomycin did not demonstrate noninferiority to comparator antibiotics, with risk difference (−9.4 percentage points; 1-sided 95% CI, −21.5 to ∞ percentage points) < 7% noninferiority margin

Proportion of participants who reached clinical and microbiological cure



Adverse event discontinuations:
fosfomycin, 8.5%; comparators, 0%

SETTINGS / LOCATIONS

22 Hospitals in Spain

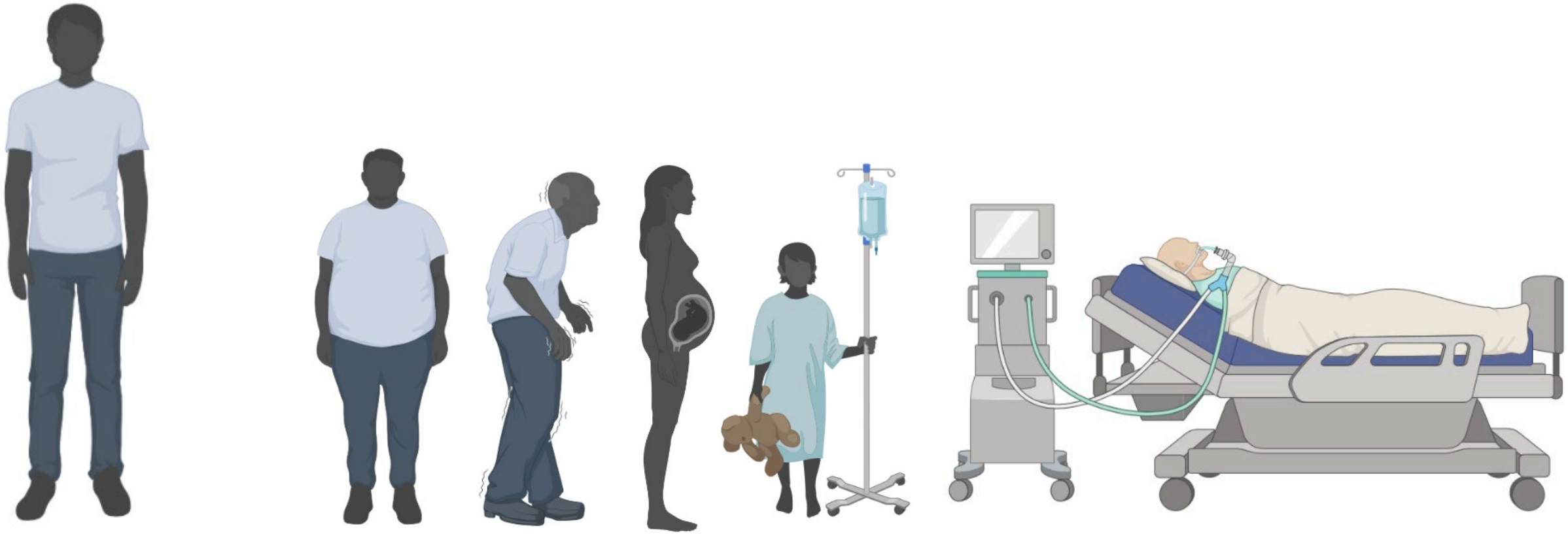
PRIMARY OUTCOME
Clinical and microbiological cure at 5-7 d posttreatment, with clinical cure defined as resolution of signs and symptoms and microbiological cure as no isolation of the causative *E coli* strain in blood or urine culture

conclusions:
i) possible use as carbapenem-sparing strategy

ii) use with caution, or avoid in older patients and patients with predisposing risk factors associated with heart failure

Sojo-Dorado et al., JAMA Netw Open 2022

3. Real life experience



RCT

real world

Infusione Continua o Intermittente?

Population Pharmacokinetics and Monte Carlo Simulation for Dosage Optimization of Fosfomycin in the Treatment of Osteoarticular Infections in Patients without Renal Dysfunction

Matteo Rinaldi,[a,b] Pier Giorgio Cojutti,[c,d] Eleonora Zamparini,[b] Sara Tedeschi,[a,b] Nicolò Rossi,[b] Matteo Conti,[a] Maddalena Giannella,[a,b]

Strong rationale for considering fosfomycin dosages of 8 to 16 g daily by CI in several clinical scenarios for osteoarticular infections patients

→ OPAT

Optimal PTAs and CFRs (≥90%) can be achieved administering a daily dosage of:

- 2 g every 6 h (q6h) by II against *Staphylococcus aureus*, *Escherichia coli*, expanded-spectrum beta-lactamase (ESBL)-producing *E. coli*, and methicillin-resistant *S. aureus*;
- 8 g by CI against coagulase-negative *staphylococci*, *K. pneumoniae*, and ESBL-producing *K. pneumoniae*;
- 12 g by CI against *P. aeruginosa*;
- 16 g by CI against KPC-producing *K. pneumoniae*

Rinaldi et al., AAC 2021

Impiego del Therapeutic drug monitoring (TDM)?

infectious disease reports

MDPI

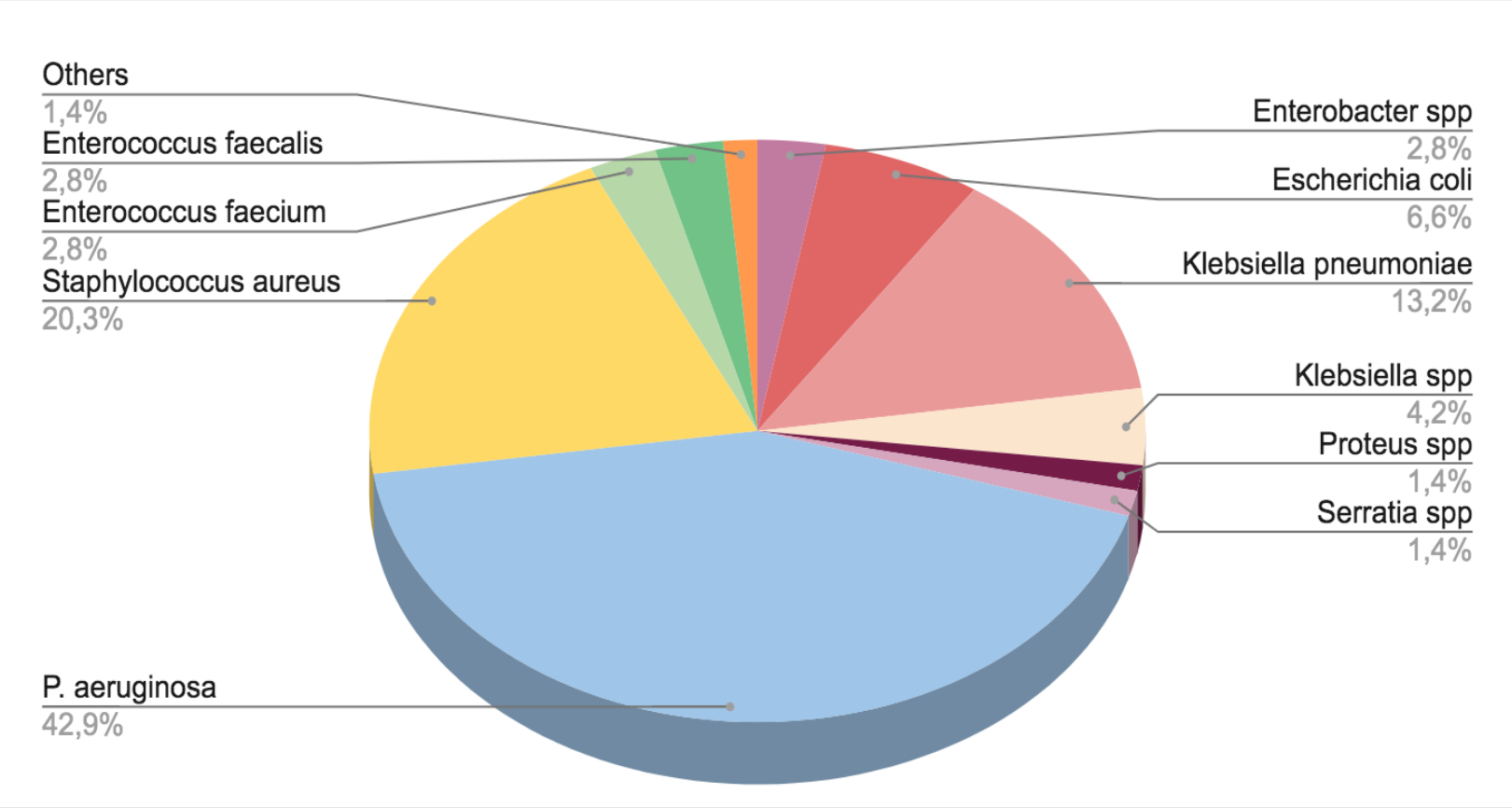
microorganisms

MDPI

Real world data: impiego in Policlinico

212 bacterial isolates
- 154 GNB (72.6%)
- 58 GPB (24.4%)

MDROs in 107/212 (50.5%) of total isolates
- 85/154 of GNB (55.2%)
- 22/58 of GPB (37.9%)



Biscarini et al., (submitted)

Real world data: impiego in Policlinico

187 pazients treated with IV fosfomicina ev >48h from 1 JAN 2019 to 1 JUL 2022

	n=187
Demographics and anamnestic data	
Age, years	64.0 [50.5-71.0]
Gender, female	65 (34.8)
Comorbidities	
• At least 1 comorbidity	119 (63.6)
• Myocardial infarction	18 (9.6)
• Chronic pulmonary disease	32 (17.1)
• Mild or severe liver disease	19 (10.1)
• Diabetes Mellitus	58 (31.0)
• Moderate to severe Chronic Kidney Disease	16 (8.6)
• Solid tumor	12 (6.4)
• Leukemia/Lymphoma	15 (8.0)
Clinical data at the time of starting fosfomyicin	
Patient's ward	
• ICU	82 (43.9)
• Medical Unit	87 (46.5)
• Surgical Unit	18 (9.6)
Infection site	
• BSI	62 (33.2)
○ Primary BSI	19/62 (30.1)
○ Secondary BSI	36/62 (58.1)
○ Not specified	7/62 (11.3)
• Lower respiratory tract infection	111 (59.4)
○ VAP	71/111 (63.9)
• Surgical site infection	9 (4.8)
• Urinary tract infection	11 (5.9)
• Skin and soft tissue infection	7 (3.7)
• Cardiovascular infection	12 (6.4)
• Osteoarticular infection	14 (7.5)
• Others	8 (4.3)
Septic shock with need of vasopressors	32/185 (17.3)
Estimate glomerular filtration rate, ml/min/1.73m^2	86.9 [52.2-107.5]

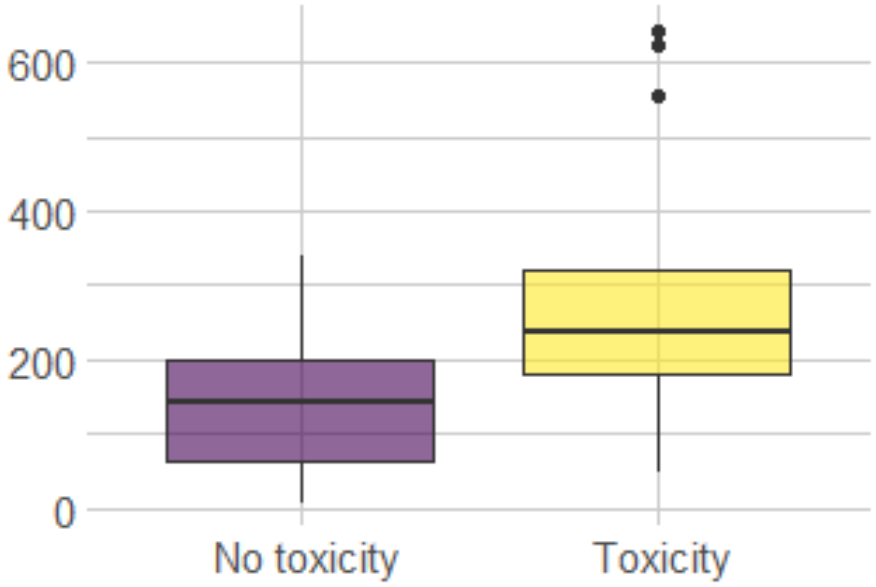
	n=187
Microbiological data at baseline	
Microbiologically defined infection (pathogen identified)	169 (90.4)
• Monomicrobial	123/169 (72.8)
• Polimicrobial	46/169 (27.2)
Infection sustained by MDR pathogens	83 (44.4)
Treatment data	
Daily dose of fosfomycin, grams	18.0 [12.0-24.0]
Time between identification of pathogens and fosfomycin start, days	3.0 [1.0-6.0]
Fosfomycin mode of administration	
• Intermittent	43 (23.0)
• Intermittent prolonged infusion*	123 (65.8)
• Continuous infusion	21 (11.2)
TDM assessment	49 (26.2)
Length of treatment with fosfomycin, days	10.0 [7.0-16.5]
Outcome data	
Adverse events CTCAE grade ≥ II	
• ≥ 1 adverse event	81 (43.3)
• Diarrhoea	18 (9.6)
• Nausea	6 (3.2)
• Hypernatremia	47 (25.1)
• Hypertransaminasemia	10 (5.3)
• Hypokalemia	15 (8)
• Hypercreatininemia	22 (11.8)
Length of hospital stay, days	44.0 [27.0-77.5]
Time between fosfomycin start and hospital discharge, days	25 [15.0-40.0]
In-hospital death	51 (27.3)
Death at 28 days from starting fosfomycin	43/180 (23.9)

Biscarini et al., (submitted)

Real world data: impiego in Policlinico

TDM levels (not IV fosfomycin daily dose) resulted associated with AEs

31 patients treated with intermittent IV fosfomycin underwent TDM:
Cmin 237.6 (180-320) mg/L in patients with AEs vs Cmin 140.6 (62-200) mg/L in patients with no-AEs (p=0.018)



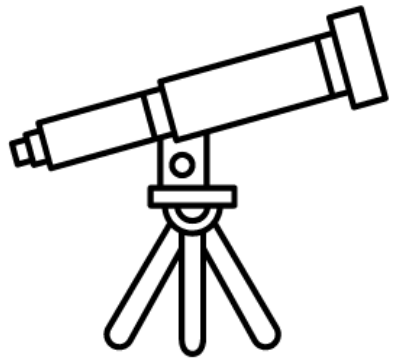
Outcome	≥1 AEs	Hypernatremia
Cmin cut-off (mg/L)	191	191
Sensitivity	0.73	0.9
Specificity	0.75	0.71
AUROC	0.75	0.80
PPV	0.73	0.6
NPV	0.75	0.94

Biscarini et al., (submitted)

Conclusioni

Fosfomicina EV ragionevole opzione nelle infezioni gravi
da Gram positivi e Gram negativi,
in particolare in terapia di combinazione

- Ampio spettro antimicrobico e di indicazioni terapeutiche
- Sinergismo con molti antibiotici
- Necessari ulteriori studi per stabilirne il ruolo in monoterapia
- Keep fosfomycin active! ⇨ ottimizzazione PK/PD



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