



Εθνικόν και
Καποδιστριακόν
Πανεπιστήμιον
Αθηνών



Κολιστίνη / φωσφομυκίνη

Παραδείγματα αναγέννησης παλαιών αντιβιοτικών για νοσοκομειακή χρήση

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Any role for old antibiotics?

Reintroduced old antibiotics

- **Colistin**
- **Fosfomycin**
- Minocycline
- Temocillin
- Isepamicin
- Mecillinam
- Nitrofurantoin
- Chloramphenicol
- Trimethoprim-sulfamethoxazole



Any role for old antibiotics?

Colistin: Rapidly Desired Plasma Concentrations

Concentration-dependent with time-dependence

- $fAUC/MIC$
- Post-antibiotic effect
- With a CMS loading dose of 480 mg (6 MU) it may take several hours to achieve effective plasma colistin concentrations
- **Increase LD to 9 MU**

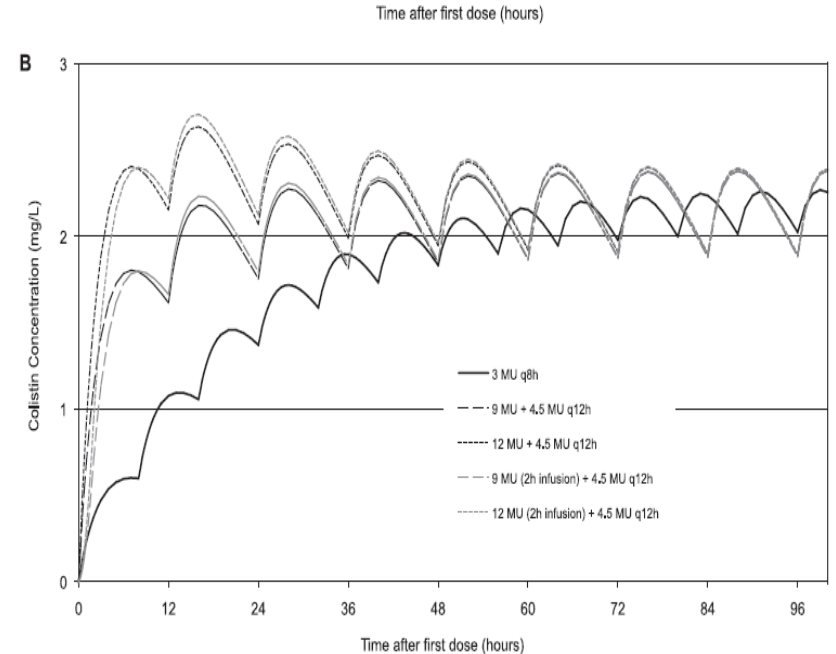


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).



Any role for old antibiotics?

Recently Updated EMA & US FDA

Creatinine Clearance (mL/min)	EMA Daily Dose ^a	US FDA Daily Dose ^b
≥80	9 MIU ^c (~ 300 mg CBA)	2.5–5 mg CBA/kg
50 to <80	9 MIU ^c (~ 300 mg CBA)	2.5–3.8 mg CBA/kg
30 to <50	5.5–7.5 MIU (~183–250 mg CBA)	2.5 mg CBA/kg
10 to <30	4.5–5.5 MIU (~150–183 mg CBA)	1 mg CBA/kg ^d
<10	3.5 MIU (~117 mg CBA)	Not stated

CBA, colistin base activity; MIU, million international units.

^aThe European Medicines Agency (EMA) expressed doses in terms of MIU.

The EMA doses have been converted to approximately equivalent doses expressed as milligrams of CBA, and these are shown in parentheses

^bThe US Food and Drug Administration (FDA)–approved product label indicates that in obese individuals

The dosage should be based on ideal body weight.

^cThe EMA-approved product label indicates that daily doses up to 12 MIU (approximately 400 mg CBA) may be required in patients with good renal function in some cases.

^dThe FDA-approved product label states 1.5 mg CBA/kg every 36 hours, which has been converted in the table to the corresponding daily rate.



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Any role for old antibiotics?

Colistin Dosing in CRRT

1. Colistin is substantially removed from the circulation in critically ill patients undergoing CVVHDF

Markou N, et al. J Antimicrob Chemother 2012; 67: 2459–62

2. Challenge for higher colistin dosage in critically ill patients receiving CVVHDF → LD of 12 MU CMS appears more appropriate, whilst a CMS maintenance dosage of at least 6.5-7.5 MU q12h

Karaiskos I et al. Int J Antimicrob Agents 2016;48(3):337-41

3. Polymyxin B unknown pharmacokinetic profile



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Any role for old antibiotics?

Fosfomycin

Phosphonic antibiotic

- Hydrophilic, MW 138 Da, Broad spectrum
- 50% excreted in urine unchanged
- T_{1/2} – 4-8h in plasma (renal failure >50h)
- Inhibition of enzyme involved in peptidoglycan synthesis
- Negligible protein binding
- Available in 2 dose forms
 - ✓ Oral : fosfomycin tromethamine (trometamol)
 - ✓ Parenteral : fosfomycin disodium penetrates most tissues well including CSF (although reduced activity), lungs, abscesses
- Dose
 - ✓ Oral : a single dose of 3 grs (Additional doses may be used in difficult eradication of infection)
 - ✓ IV : wide variation for CRE infections ranging 12- 24 g daily (3 or 4 times/d)



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Any role for old antibiotics?

Fosfomycin properties and safety

Registration : IV not registered in many countries

Susceptible pathogens

- *Staphylococci (incl MRSA), Enterococci, Haemophilus spp, Enterobacteriaceae (Klebsiella spp, Enterobacter, Serratia spp.)*
- *Acinetobacter spp. and Pseudomonas spp. ?????*
- Highly variable MICs
- EUCAST Resistant breakpoint 32 mg/L

PDs : Optimal PDs are unclear

- a time-dependent agent ?, **fAUC/MIC** is most predictive of efficacy
- may differ by species

Resistance to fosfomycin

- is suppressed by combining fosfomycin with other agents

SAFETY

- Not nephrotoxic
- IV → each 1g contains **330mg** (14.4 mEq) sodium
- IV → hypokalaemia (26%)



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Any role for old antibiotics?

Fosfomycin

Extracellular concentrations in lung tissue of septic patients

Microdialysis technique/probe into healthy and infected lung tissue

A single intravenous dose of 4 g of **fosfomycin** was administered

Healthy lungs		Infected lungs	
Mean C(max)	131.6 +/- 110.6 mg/L	Mean C(max)	107.5 +/- 60.2 mg/L
T(max)	1.1 +/- 0.4 h	T(max)	1.4 +/- 0.5 h
AUC(0-4)	242.4 +/- 101.6 mgxh/L	AUC(0-4)	203.5 +/- 118.4 mgxh/L
AUC(0-infinity)	367.6 +/- 111.9 mgxh/L	AUC(0-infinity)	315.1 +/- 151.2 mgxh/L.
AUC(0-infinity) L / AUC(0-infinity) PI		0.63 +/- 0.31	0.53 +/- 0.31



Any role for old antibiotics?

Fosfomycin : Dosing and Creatinine Clearance

CrCL (ml/min)	Dose	Interval
>40	6 g	q 6h
40-20	4 g	q 12h
20-10	4 g	q 24h
≤10	4 g	q 48h

Fosfomycin is actively eliminated by hemodialysis and largely retained between sessions.

IV administration **of 2-4 g after dialysis** is proposed.

Bouchet JL Clin Nephrol 1985; 23: 218

A regimen of 8.0 g of fosfomycin every 12 h is proposed for patients undergoing CVVH.

Gattringe R et al. JAC 2006; 58: 367



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Any role for old antibiotics?

Fosfomycin : How we start consider it ?

A randomly selected sample from septic ICU patients

- 30 *Klebsiella pneumoniae*
- 30 *Pseudomonas aeruginosa*
- 30 *Acinetobacter baumannii*

Fosfomycin MIC for each isolate

- was determined by the agar dilution method

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-007-0456-4

ARTICLE

Provisional susceptibility breakpoint ≤ 64 $\mu\text{g/ml}$ (2008)

Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin

M. E. Falagas · M. D. Kanellopoulou ·
D. E. Karageorgopoulos · G. Dimopoulos ·
P. I. Rafailidis · N. D. Skarmoutsou · E. A. Papafrangas



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Any role for old antibiotics?

Fosfomycin : How we start to consider it ?

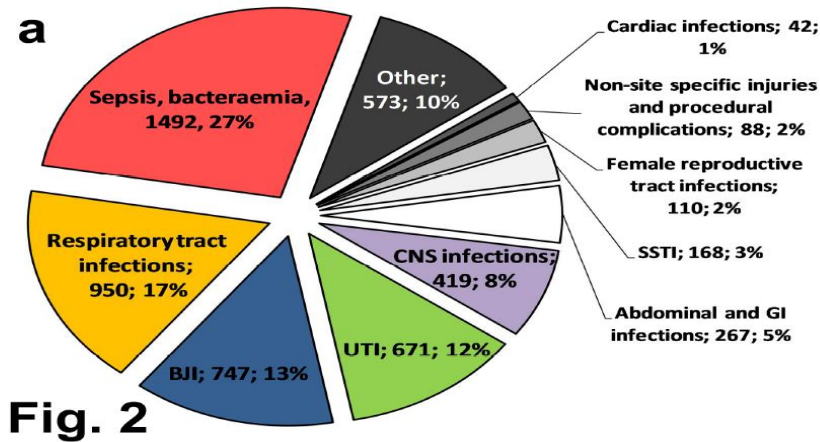
Fosfomycin : *in vitro* activity

<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>A. baumannii</i>
All isolates were ESBL and MBL (<i>bla_{VIM-1}</i>) producers	All isolates were ESBL producers	
MIC : 8-64 µg/ml	MIC:4 ->512 µg/ml	MIC: 64->512 µg/ml
MIC : 8-64 µg/ml MIC ₅₀ 16 µg/ml MIC ₉₀ 32 µg/ml	MIC ₅₀ 32 µg/ml MIC ₉₀ 128 µg/ml	MIC ₅₀ 256 µg/ml MIC ₉₀ >512 µg/ml
None of the isolates was resistant	20% of the isolates were resistant to fosfomycin	Non active

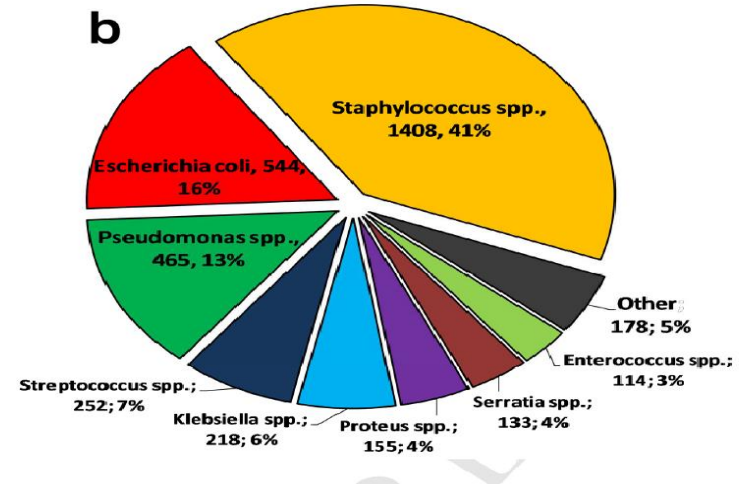


Any role for old antibiotics?

Fosfomycin IV by treatment indication and pathogen



IV fosfomycin by treatment indication



Numbers of microbiological isolates reported by pathogen.



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Any role for old antibiotics?

Fosfomycin : FOREST STUDY

Bacteraemic UTIs by ESBL producing *Escherichia coli*

Multicentre, open-label, phase III RCT

- IV fosfomycin (4 g/6 h) vs meropenem (1 g/8 h)
- a change to oral therapy is permitted after 5 days in both arms, in accordance with predetermined options
- The main objective is to demonstrate **clinical non-inferiority** of IV fosfomycin with regard to meropenem for treating bacteraemic UTIs caused by ESBL-EC
- Secondary objectives include the study of fosfomycin concentrations in plasma and the impact of both drugs on intestinal colonisation by multidrug-resistant Gram- negative bacilli.



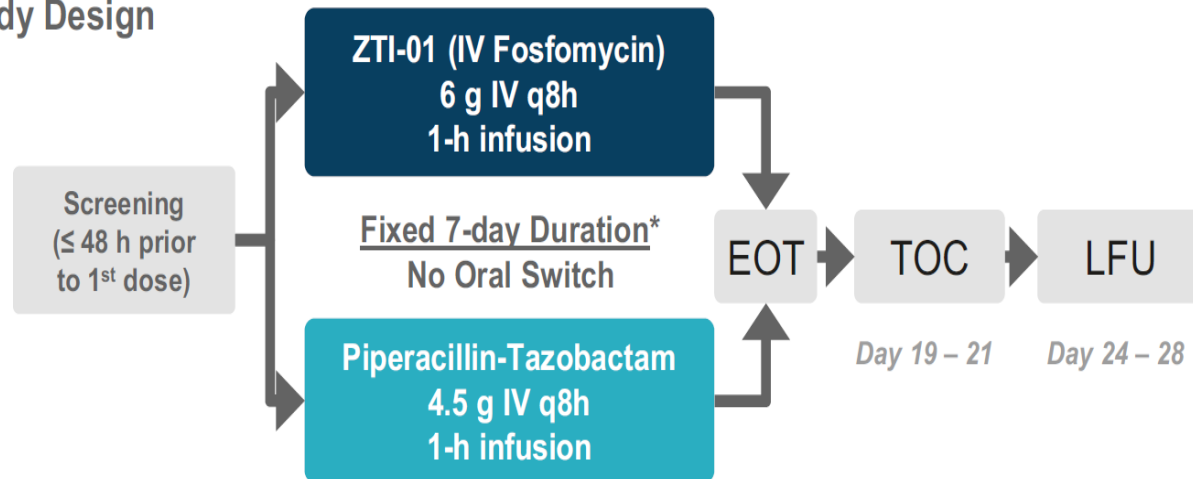
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Any role for old antibiotics?

Fosfomycin : ZEUS STUDY

Hospitalized patients with documented or suspected cUTI or Acute Pyelonephritis (> 2 signs/symptoms of UTI, evidence of pyuria and >1 associated risk factor)

Figure 1. Study Design



EOT: end-of-treatment; LFU: late follow-up visit; TOC: test-of-cure.

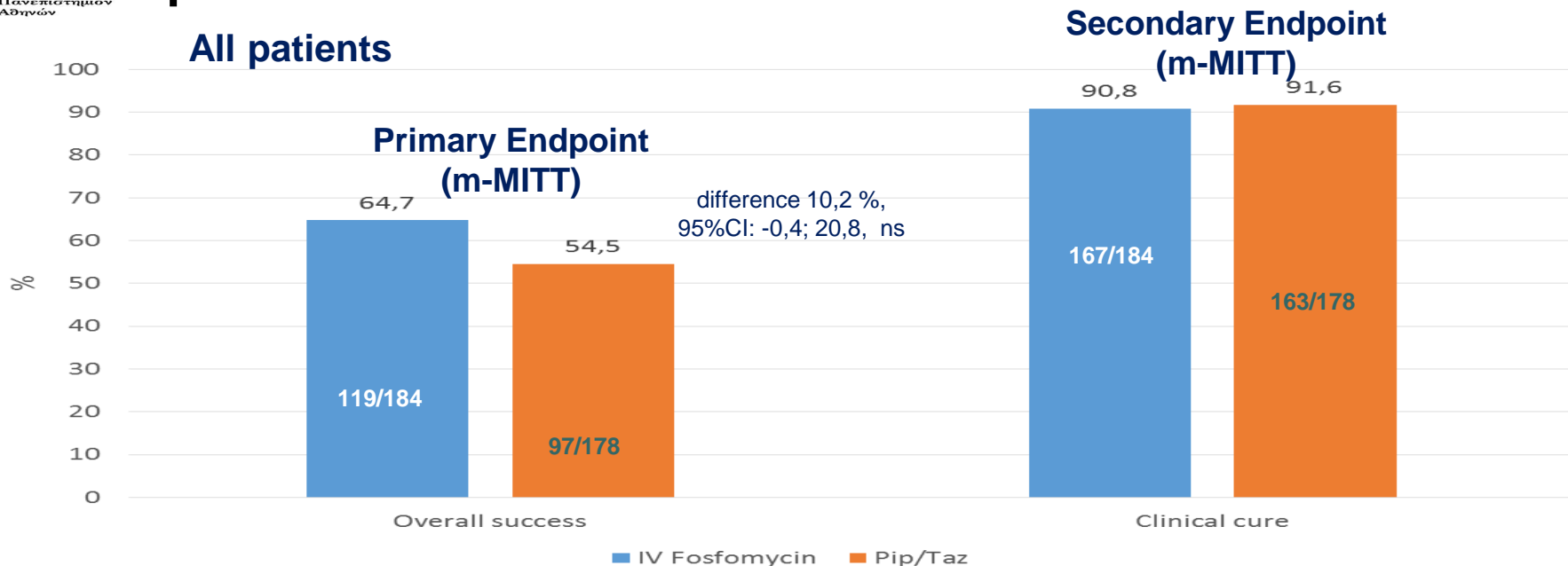
**Treatment extension up to 14 days if baseline bacteremia*



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Any role for old antibiotics?

Fosfomycin : ZEUS STUDY



Microbiological eradication (m-MITT)

IV Fosfomycin: 65,8% (121/184)

Pip/Taz: 56,2% (100/178)

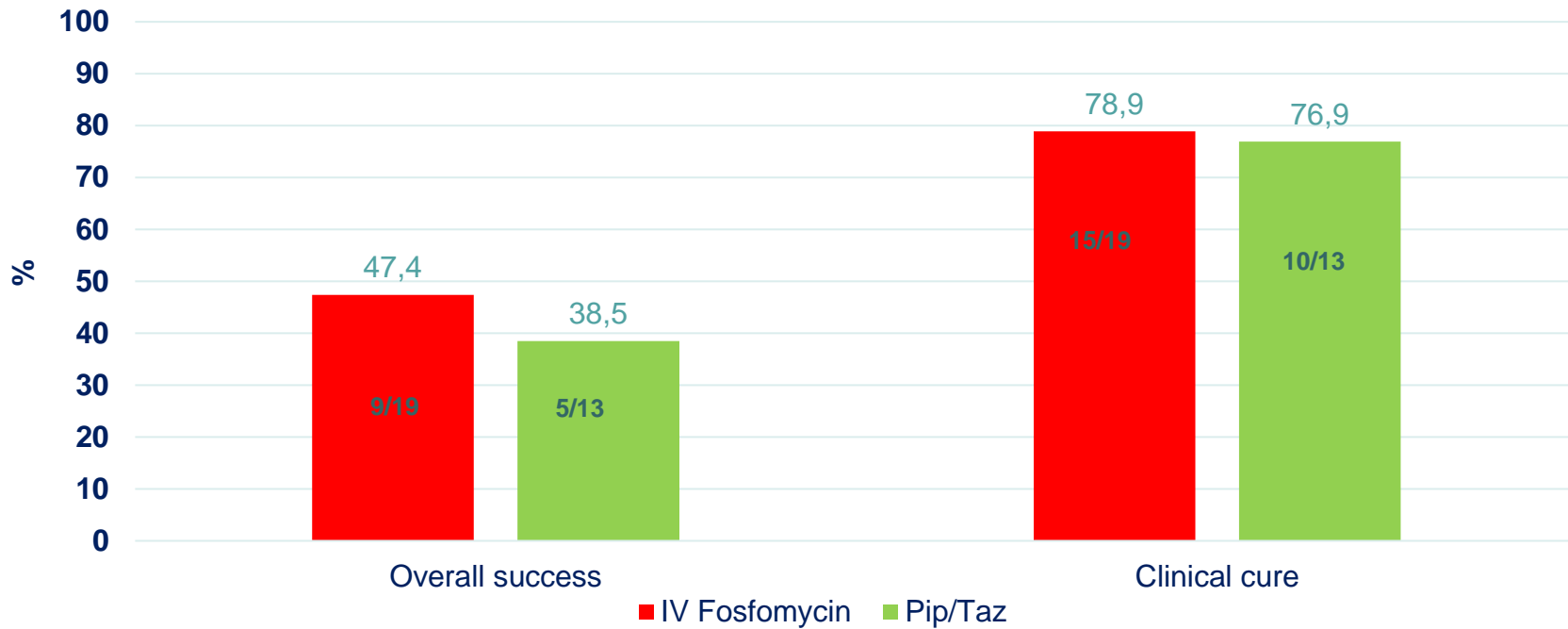
9,6 % difference, 95% CI -1,0, 20,1



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Any role for old antibiotics?

Fosfomycin : ZEUS STUDY - patients with bacteremia



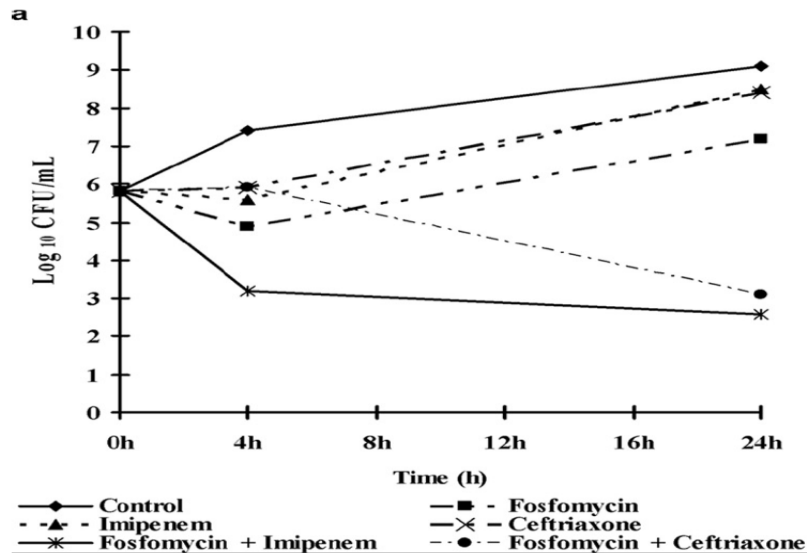


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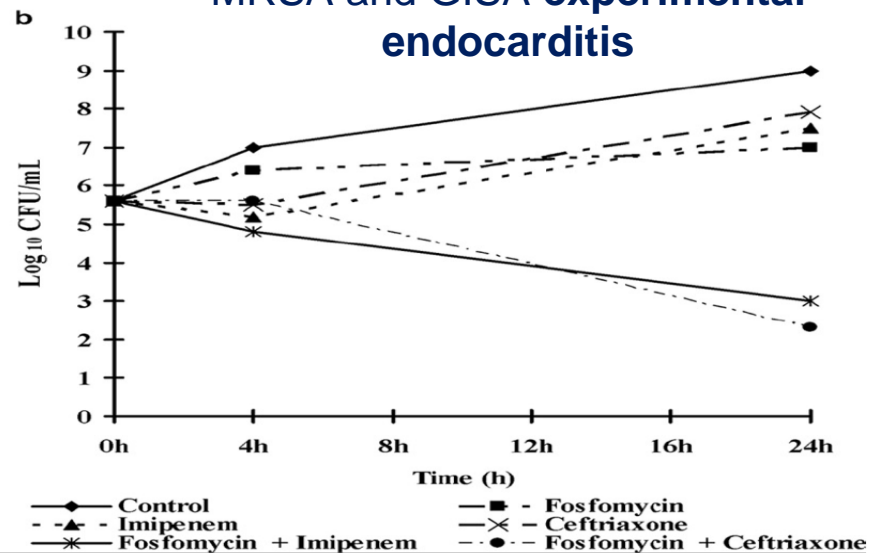
Any role for old antibiotics?

Fosfomycin against endocarditis

Synergistic bactericidal combinations for
MRSA and GISA **experimental**
endocarditis



MRSA strain (MRSA-277H) incubated with fosfomycin and imipenem or ceftriaxone (alone or in combination) at the MIC. Fosfomycin (4 g/ml), imipenem (16 g/ml), and ceftriaxone (64 g/ml) were used at the indicated concentrations.



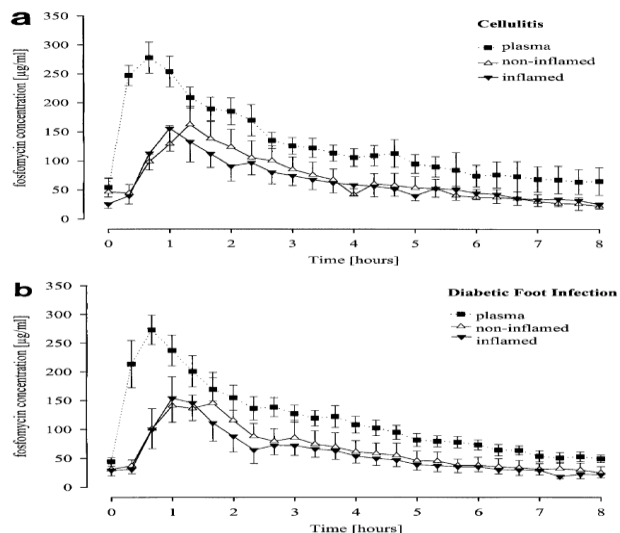
GISA-ATCC 700788 incubated with fosfomycin and imipenem or ceftriaxone (alone or in combination) at the MIC. Fosfomycin (16 g/ml), imipenem (1 g/ml), and ceftriaxone (128 g/ml) were used at the indicated concentrations.



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Any role for old antibiotics?

Fosfomycin against Cellulitis or Diabetic Foot



Daily dosage

- 200 mg/kg of body weight divided into three equal i.v. doses over 30 min every 8 h

Fosfomycin pharmacokinetic parameters^b

Fluid ^a	Patients with cellulitis				Patients with diabetic foot infection			
	C_{max} (µg/ml)	C_{8h} (µg/ml)	T_{max} (h)	AUC_{0-8} (µg · h/ml)	C_{max} (µg/ml)	C_{8h} (µg/ml)	T_{max} (h)	AUC_{0-8} (µg · h/ml)
Plasma	344 ± 53.6	65.0 ± 58.4		1,050 ± 139	320 ± 67.4	49.2 ± 15.9		1,331 ± 429
s.c. tissue fluid								
Noninflamed	141 ± 68.6	22.0 ± 15.1	1.13 ± 0.29	742 ± 483	136 ± 106.6	24.8 ± 26.2	1.15 ± 0.47	937 ± 848
Inflamed	150 ± 70.6	25.2 ± 19.2	0.78 ± 0.31	757 ± 492	139 ± 76.7	21.7 ± 13.7	0.90 ± 0.22	782 ± 524



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Any role for old antibiotics? Fosfomycin against CNS infections

Therapy group (dose in mg/ kg/day)	HUB 2349 strain				ATCC 51916 strain			
	initial titres (log cfu/mL)	bacterial decreases (Δ log cfu/mL) at 24 h	no. of animals with sterile CSF cultures at 24 h/total	PD parameter related to MIC ^a	initial titres (log cfu/mL)	bacterial decreases (Δ log cfu/mL) at 24 h	no. of animals with sterile CSF cultures at 24 h/total	PD parameter related to MIC ^a
FOF 1200	4.55 ± 0.40	-2.46 ± 1.77	5/9	3.65	5.16 ± 0.89	-4.29 ± 0.86 [†]	9/9	11.96
CRO 100	4.55 ± 0.47	-3.38 ± 1.38	8/9	5.94%	5.23 ± 0.88	-0.75 ± 1.72	0/8	0%
VAN 30	4.45 ± 0.55	-3.85 ± 0.73	10/10	37.82 h	5.00 ± 0.76	-3.44 ± 1.47 [†]	6/8	37.82 h
FOF + CRO	4.89 ± 1.02	-4.52 ± 0.84*	8/8		4.91 ± 0.78	-4.78 ± 0.73 [†]	8/8	
FOF + VAN	4.59 ± 0.66	-4.30 ± 0.97*	8/8		4.85 ± 0.59	-4.23 ± 0.63 [†]	8/8	
CRO + VAN	4.48 ± 0.57	-4.24 ± 0.74*	8/8		5.17 ± 1.14	-4.25 ± 1.17 [†]	8/8	
Control	4.59 ± 1.04	0.97 ± 1.94	0/10		4.78 ± 0.84	1.12 ± 2.09	0/12	

FOF, fosfomycin; CRO, ceftriaxone; VAN, vancomycin.

Data are expressed as means ± SD.

^aPD parameters were C_{max}/MIC for fosfomycin; $t > MIC$ for ceftriaxone; and AUC/MIC for vancomycin.

* $P < 0.05$ against FOF monotherapy (ANOVA test).

[†] $P < 0.05$ against CRO monotherapy (ANOVA test).

- Fosfomycin, alone and in combination with ceftriaxone or vancomycin, against 2 strains of *Streptococcus pneumoniae* HUB 2349 (fosfomycin and ceftriaxone, MICs 16 and 2 mg/L), ATCC 51916 (MICs 4 and 32 mg/L)
- Fosfomycin 1200 mg/kg/day, ceftriaxone 100 mg/kg/day and vancomycin 30 mg/kg/day, over 26 h.

Therapy group (dose in mg/kg/day)	HUB 2349 strain		ATCC 51916 strain	
	CSF lactate levels	CSF protein levels	CSF lactate levels	CSF protein levels
FOF 1200	4.37 ± 1.17	1.92 ± 0.87	4.41 ± 2.63	1.79 ± 0.68
CRO 100	3.20 ± 0.50	1.98 ± 1.17	6.87 ± 2.73	2.60 ± 1.00
VAN 30	3.37 ± 0.82	2.24 ± 0.99	3.64 ± 2.81 [†]	1.94 ± 1.12
FOF + CRO	3.15 ± 0.73	1.67 ± 0.71	3.93 ± 2.70 [†]	1.98 ± 1.30
FOF + VAN	2.92 ± 0.93	1.55 ± 0.85	2.56 ± 0.72** [†]	1.59 ± 0.87
CRO + VAN	2.93 ± 0.99	1.94 ± 0.80	2.39 ± 1.14** [†]	1.73 ± 0.94
Control	6.90 ± 5.84	2.53 ± 1.08	11.74 ± 10.34	3.45 ± 3.09



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Any role for old antibiotics?

Fosfomycin against MDR

45 pts /12 ICUs with PDR/XDR

infections [PDR 15, XDR 30]

- Mean (age 55.6 years, APACHE II 19.8, SOFA 8.6)
- Bacteremia (16 /6), CVCBSIs (8), VAP (14), IAIs(7)
- Sepsis, Severe Sepsis, Septic Shock (21.4%, 7.1%, 21.4%)
- Microbiologically documented infections (*K. pneumoniae* KPC (+) 83.7%, *P. aeruginosa* 35.7%)
- **IV 6gr x 4/ d for a mean of 12d**
Plus Colistin (28 pts) and/or

○ Clinical Outcome

- Successful by day 14 in 55.8% (10 pts) with PDR strains
- Failure in 27.9%
- Relapse in 4.7%
- Superinfection in 4.7%.

○ Microbiological Outcome

- Bacterial eradication in 54.8%
- Resistance development in 4 cases.

○ Main adverse event

Reversible hypokalemia (6 pts)



International Journal of Antimicrobial Agents 53 (2014) 52–59

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

Journal homepage: www.elsevier.com/locate/ijaa



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

Konstantinos Pontikis^{a,*}, Ilias Karaiskos^b, Styliani Bastani^c, George Dimopoulos^d, Michalis Kalogirou^e, Maria Katsiari^f, Angelos Oikonomou^g, Garyphalia Poulakou^g, Emmanuel Roilides^h, Helen Giamarellou^h

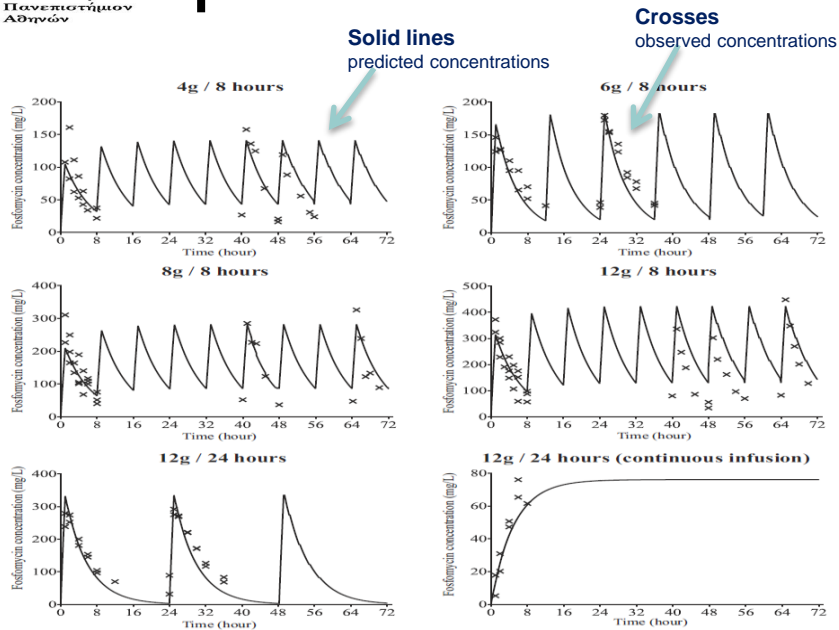




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Any role for old antibiotics?

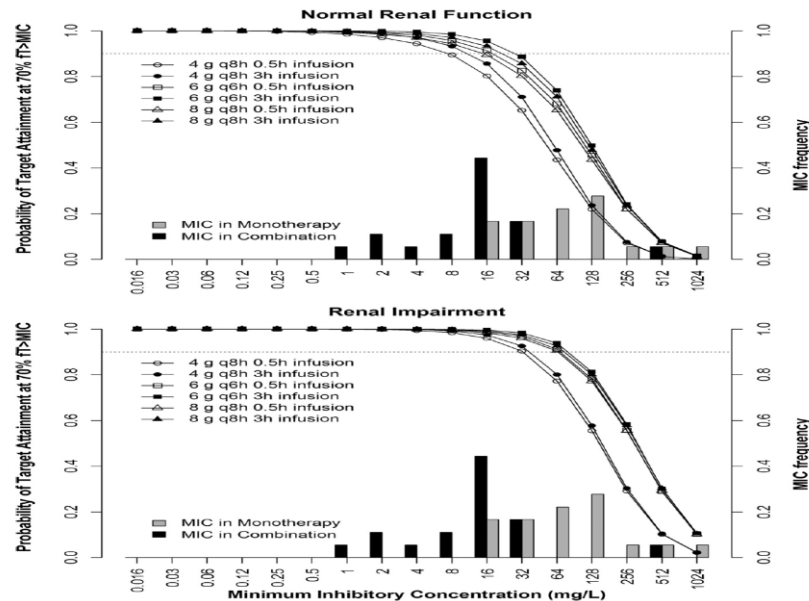
Fosfomycin : the right dose ?



Dose of 8 g/q8h

For strains with MIC of 1 mg/liter, the time above the MIC (T_{MIC}) covered the entire interval between doses

Docobo-Pérez et al, *Antimicrobial Agents and Chemotherapy* September 2015 Volume 59 Number 9



Monotherapy and combination with meropenem and probability of target attainment of 70% fT_{MIC} for the fosfomycin dosing regimens of 4 g q8h, 6 g q6h, and 8 g q8h in critically ill virtual patients.

Albiero J et al, *Antimicrob Agents Chemother.* 2016 Jun 20;60(7):4128-39

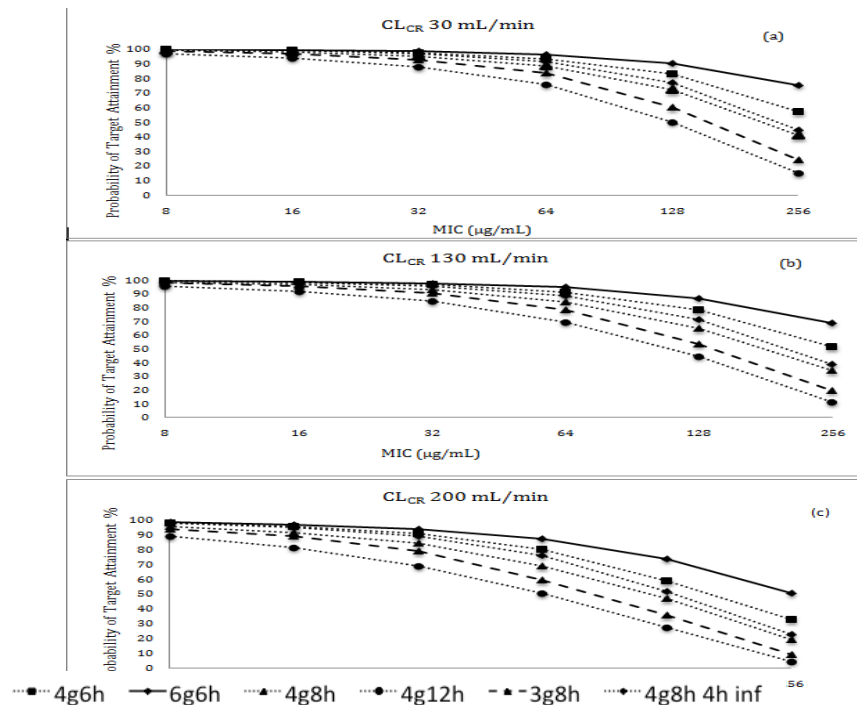


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Any role for old antibiotics?

Fosfomycin : 24g/day is enough for MDR ?

- **12 patients : CL_{CR} 30-300 mL/min**
 - Fosfomycin : dose 3 or 4 g x 3 IV
 - Infusion in 30 minutes
- Adequate concentrations in MIC >32 mg/L but insufficient in patients with CL_{CR} >200 mL/min
- Variations in PK/PDs
- Currently used doses (4g x 6) probably are insufficient in patients with \uparrow CrCl
- Dose of 6 g x 6 ?





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Any role for old antibiotics?

Fosfomycin : How to use it against MDR ?

- 1. Always in combination**
 - a. With at least another active agent
- 2. Monitor for emergence of resistance**
 - a. During treatment
- 3. Dosage adjustment**
 - a. Is required in renal failure
- 4. Monitor of**
 - a. sodium levels, especially in heart failure
 - b. potassium levels



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Any role for old antibiotics?

Minocycline

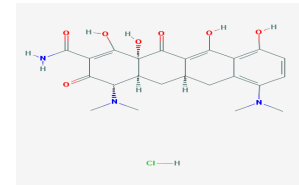
- Semisynthetic tetracycline derivative introduced in the 1960s
 - Available in both oral and intravenous dosage forms
- Currently approved FDA for treatment of **minocycline-susceptible *Acinetobacter* species infections**
- CLSI susceptibility breakpoints for *Acinetobacter*
 - ≤ 4 $\mu\text{g/mL}$ for susceptibility
 - 8 $\mu\text{g/mL}$ for intermediate and
 - ≥ 16 $\mu\text{g/mL}$ for resistance



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Any role for old antibiotics?

Minocycline



Activity : Inhibits bacterial protein synthesis

- through binding with the 30S subunit of the bacterial ribosome
- bacteriostatic effect
- synergistic and bactericidal activity against MDR *Acinetobacter* in combination with colistin or carbapenems**

Dosing

- IV 200-mg load, followed by 100 mg / 12 h (not >400 mg / 24 h)
- Renal dosing : Not required

Mechanisms of *Acinetobacter* resistance to minocycline

- tet(B) efflux gene
- plasmid- mediated ISCR2 mobile element



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Any role for old antibiotics?

PKs of Minocycline

Characteristic	Value
PKs	
Peak C (200-mg load)	Mean, 4.18 (2.52- 6.63 μ g/mL)
Trough C (100-mg/12h)	1.4–1.8 μ g/mL
AUC	67–85 mg · h/L (200-mg IV)
Vd	1.3 L/kg
Plasma protein binding	76%
Metabolism	Up to 6 hepatic metabolites; some active
Half-life	15–23 h



Any role for old antibiotics?

PDs of Minocycline

Characteristic	Value
PDs	
Microbiologic activity	<ol style="list-style-type: none">1. Primarily bacteriostatic2. Bactericidal in combination with carbapenems or colistin against <i>Acinetobacter baumannii</i>3. Time dependent
Primary PD index	AUC/MIC
MPC	1 µg/mL



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Any role for old antibiotics?

Clinical experience with Minocycline

- Retrospective small studies → *Acinetobacter* spp infections
- Dose → 100 mg x 2 after a loading dose of 200 mg
- Monotherapy → in S to tetracycline species
- In combination → MDR

- **VAP^{1,2,3,4}**
 - ✓ Critically ill
 - ✓ Successful outcomes → 70-100% (clinical and microbiological)
- **Skin / soft tissue infections with/ no osteomyelitis^{3,4,5}**
- **Bacteremia³**

✓ Trauma patients

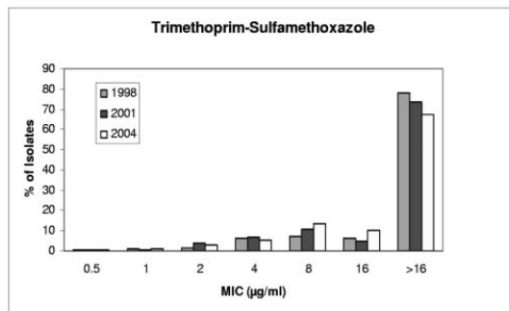
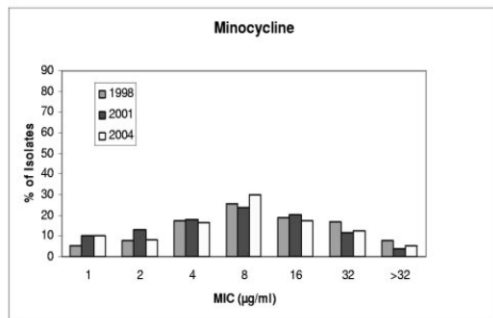
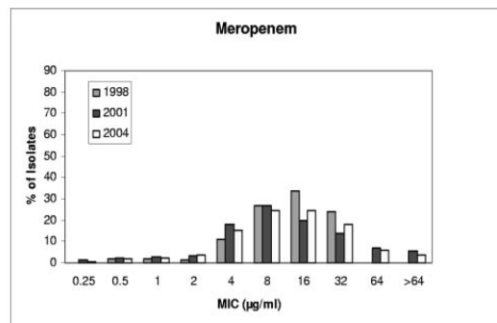
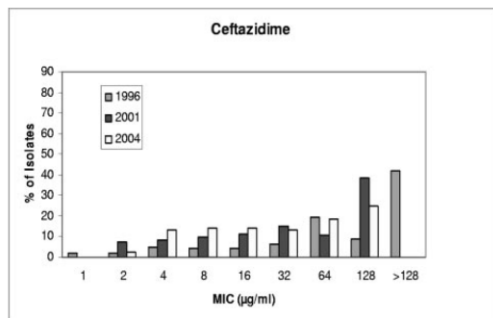
¹Wood GC et al, Intensive Care Med 2003; 29:2072–6, ²Chan JD et al J Intensive Care Med 2010; 25:343–8, ³Jankowski CA, et al, Infect Dis Clin Pract 2012; 20:184–7, ⁴Bishburg E et al Infect Dis Clin Pract 2014; 22:26–31, ⁵Griffith ME, et al, Infect Dis Clin Pract 2008; 16:16–9.



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Any role for old antibiotics?

Minocycline *in vitro* against *Burkholderia cepacia*



- 2,621 *Burkholderia cepacia* complex strains
- 1,257 CF patients.
- Susceptibility of 18 antimicrobial agents and synergy (23 combinations)
- **Minocycline, meropenem, and ceftazidime**
 - ❖ the most active, inhibiting 38%, 26%, and 23% of strains, respectively

❖ synergy was rarely noted

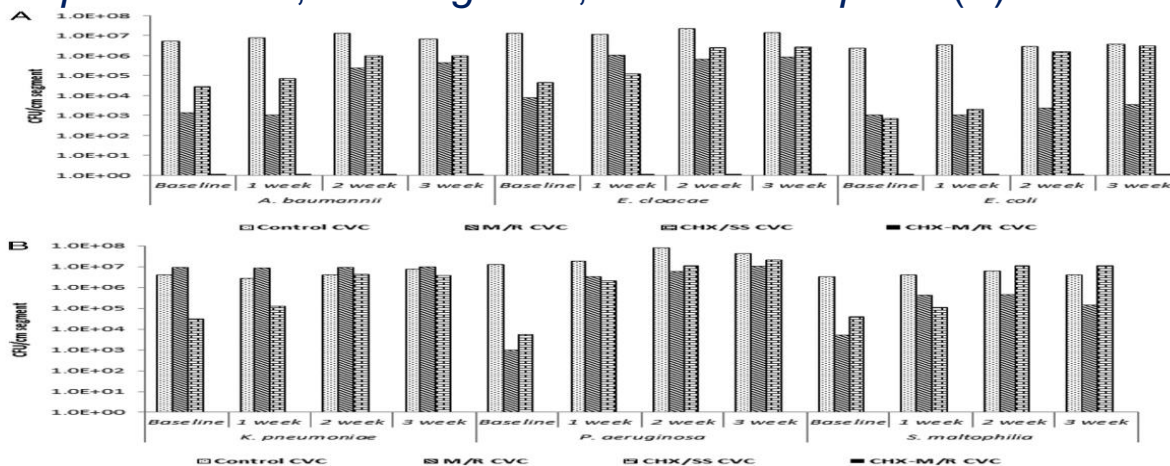


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Any role for old antibiotics?

Minocycline against *biofilm*

In vitro antimicrobial activity for 24 h (baseline) and durability for up to 3 weeks of different antimicrobial-coated catheters against *A. baumannii*, *E. cloacae*, and *E. coli* (A) and *K. pneumoniae*, *P. aeruginosa*, and *S. maltophilia* (B).



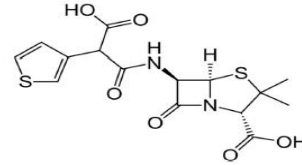
M/R : minocycline-rifampin, CHX/SS : chlorhexidine silver sulfadiazine
CHX-M/R : chlorhexidine-minocycline- rifampin



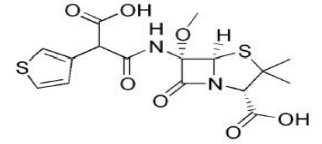
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Any role for old antibiotics?

Temocillin



Ticarcillin



Temocillin

- 6- α -methoxy derivative of ticarcillin
- In vitro spectrum restricted to *Enterobacteriaceae*
- No activity against Gram-positives and anaerobes
 - No affinity to PBP-1,-2,-3
 - Tightly binds PBP5 and PBP6
- No activity against Class B metalloenzymes or some Class D enzymes (OXA-48)
- No breakpoints from EUCAST or CLSI



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Any role for old antibiotics?

Temocillin Susceptibility and PKs

Country temocillin marketed	Sensitive	Resistant
Belgium	≤ 16	> 16
UK-BSAC systemic infection	≤ 8	> 8
UK-BSAC, uncomplicated UTI	≤ 32	> 32
France	≤ 8	> 8

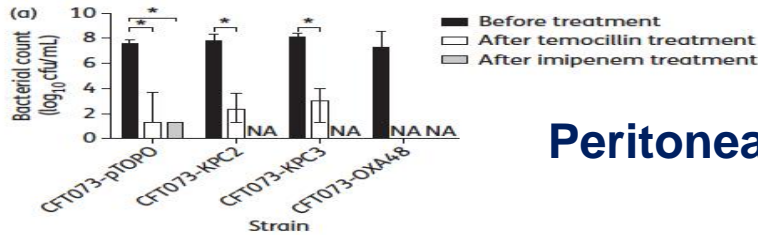
MIC (mg/L)

- IM or IV 1-2 g every 2-3 times daily
- 80% protein binding
- **Urinary recovery of unmetabolized temocillin after 24h is 72-82%**
 - 500 mg/L after 500 mg bid
- Elimination half life 5 h
- Low CSF penetration
- Remains un-degraded for several days in aqueous solutions

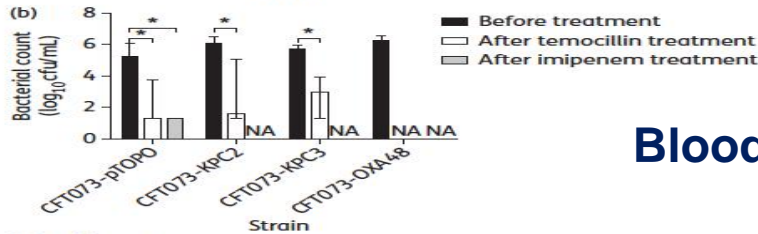


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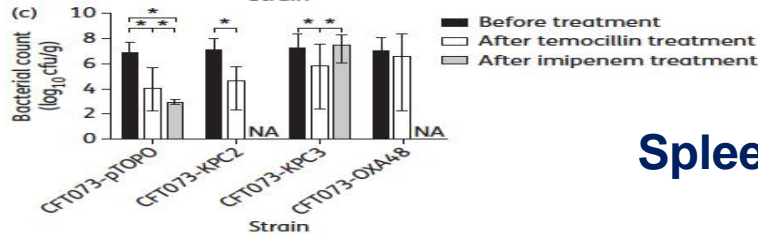
Any role for old antibiotics? Temocillin



Peritoneal fluid

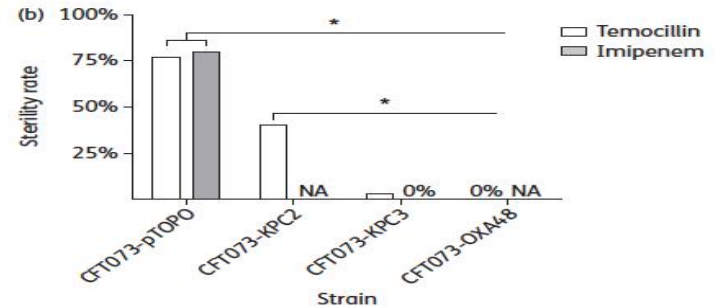
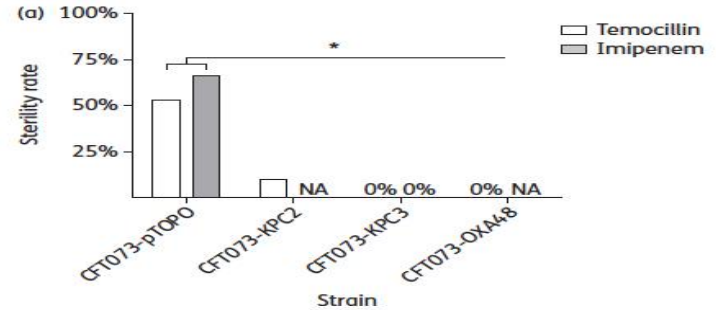


Blood



Spleen

Colony Counts

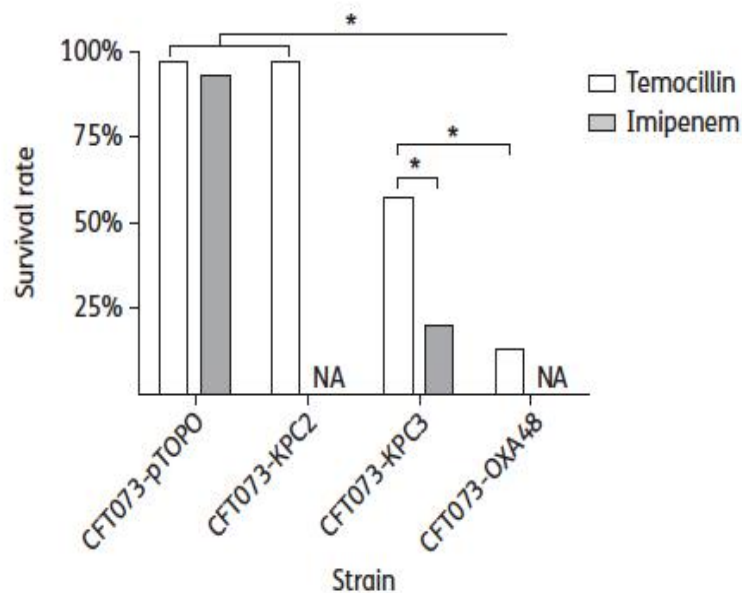


Sterility rates



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Any role for old antibiotics? Temocillin



Survival

- Temocillin is stable against KPC enzymes
 - For success, determining factor may only be the MIC irrespective of KPC production
- Could be a therapeutic option for UTI
 - Peritoneal infection may also be another target
- As its parent ticarcillin can be used up to 18 g/d, higher doses of temocillin may be tested for safety



Εθνικόν και
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Any role for old antibiotics?

Isepamicin

Belongs to the aminoglycoside group

- Is derived from gentamicin B

- theoretically, has better activity than amikacin against strains producing type 1 6'-*N*-acetyltransferase, which has been reported to be responsible for approximately 30% of the total resistance to aminoglycosides in the USA and west Europe, particularly among Enterobacteriaceae

- Antibacterial spectrum → Gram -) and (+) bacteria

- anaerobes, Neisseriaceae and streptococci → to Isepamicin

Available for clinical use in Taiwan, Korea, China, India, Japan, Hong Kong, Indonesia, Malaysia, Philippines, Vietnam, Singapore, Thailand, Bahrain, Turkey, Belgium and Italy

Relevant clinical data are limited

Livermore DM, et al *J. Antimicrob. Chemother.* 66(1), 48–53 (2011).



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Any role for old antibiotics?

Isepamicin

- Systematic review, 14 studies
- Microbiological and clinical studies
 - 4901 isolates tested
 - Isepamicin → higher *in vitro* activity compared with amikacin or active as amikacin
 - In MDR bacteria, isepamicin appeared superior to amikacin or active as to amikacin
 - Isepamicin might be active *in vitro* against Gram-negative bacteria with resistance to amikacin and other aminoglycosides.



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Any role for old antibiotics?

Pivmecillinam / Mecillinam

A penicillin derivative : since the early 1980s for UTIs

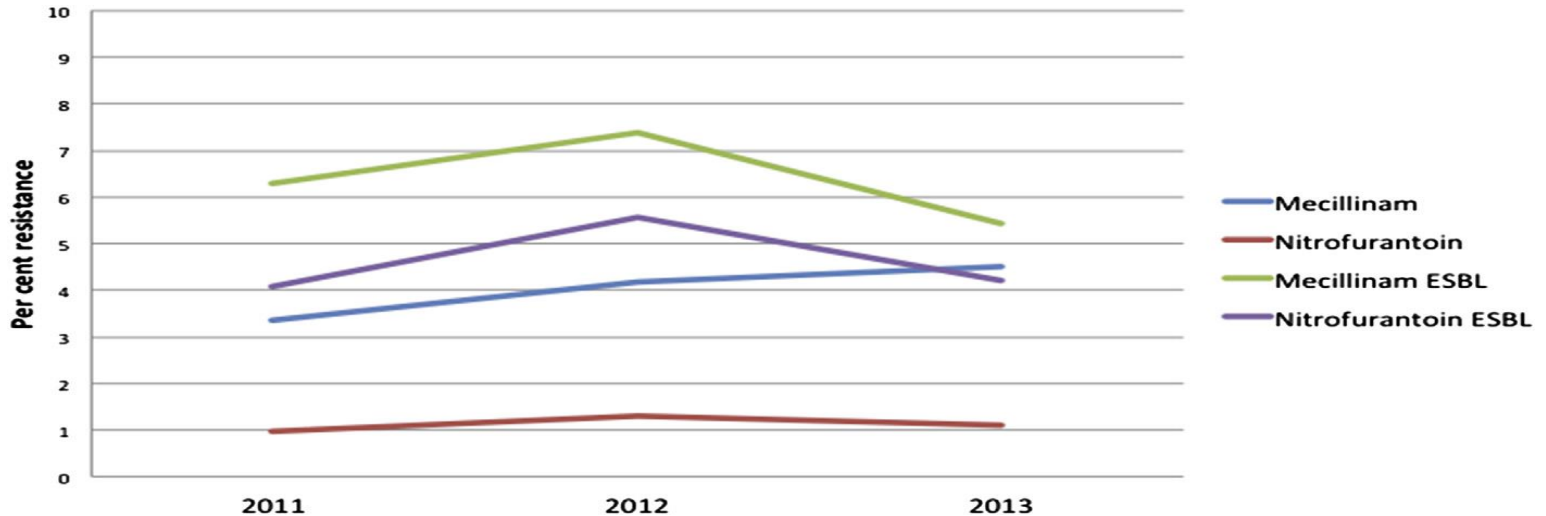
- high concentration in the urine
- low impact on the intestinal microbiota
- inhibition of penicillin-binding protein 2 (PBP2)
- mechanisms of resistance are poorly understood

- ESBL-producing Enterobacteriaceae
- NDM and IMP producers : frequently *in vitro* susceptible to mecillinam while KPC and VIM producers are resistant
- Unpublished data also suggest that mecillinam is highly *in vitro* active against OXA-48 producers



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Any role for old antibiotics? Mecillinam



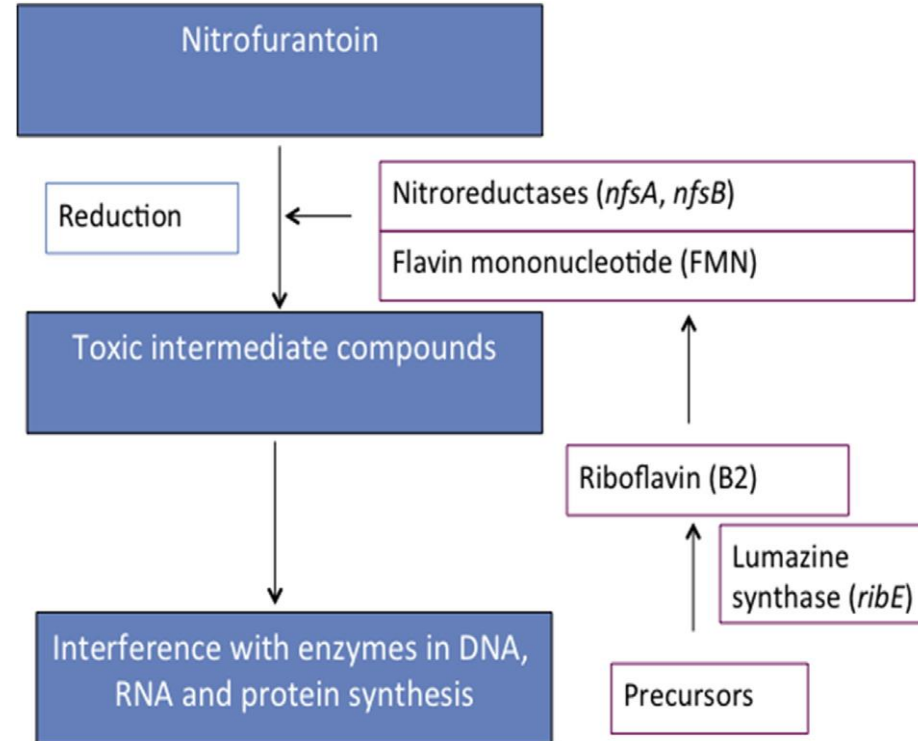
- *E. coli* resistance levels to mecillinam (Swedish university hospital), 2011–2013.
- Range of tested *E. coli* per year: 22.142 to 23.951
- Number of ESBL-producing *E. coli*: range 637–830.



Any role for old antibiotics?

Nitrofurantoin

- Nitrofurans family → nitrofurantoin
- PO → high urinary concentrations
- Metagenomic analysis → very low impact on the faecal microbiota
- Mode of action → ↓ nitrofurans to toxic compounds that can interfere with enzymes in DNA, RNA and protein synthesis
- Mechanism of resistance : mutations in *nfsA* or *nfsB*
- Low occurrence of resistance despite





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Any role for old antibiotics?

Chloramphenicol

Activity against Gram (+) and (-) bacteria

- ❖ bacteriostatic
- ❖ bactericidal in high concentrations or when used against *Streptococcus pneumoniae*, *Neisseria meningitidis* or *Haemophilus influenzae*
- ❖ excellent tissue penetration
- ❖ achieves 30%–50% of the serum concentration in the CSF and therapeutic levels are also achieved in pleural, ascitic and synovial fluids
- ❖ dose adjustment is required in cases of hepatic insufficiency but not with renal insufficiency.



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Any role for old antibiotics?

Chloramphenicol

Chloramphenicol may be a useful antimicrobial agent for MDR organisms such as VRE, MRSA or MDR Gram-negative bacteria

- 3051 MSSA and MRSA isolates → 96% of MSSA and 83% of MRSA isolates were susceptible to chloramphenicol.
- 413 Enterobacteriaceae isolates,
 - 182 (44.1%) R to amoxicillin/clavulanate
 - 76 (18.4%) R to chloramphenicol
- 78 VRE bacteraemias
 - 51 patients (65.4%) received chloramphenicol.
 - ✓ Chloramphenicol treatment led to a favourable clinical (61.1%) and microbiological (79.1%) response
- Nosocomial VRE infections in 16 liver transplant recipients
 - 93% were susceptible to chloramphenicol and resistance



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Any role for old antibiotics?

Trimethoprim-sulfamethoxazole (TMP-SMX)

1. Inhibits bacterial DNA synthesis through inhibition of the dihydrofolate pathway
2. Antibacterial activity against Gram (+) and bacteria
3. First-line treatment for
 - ✓ uncomplicated UTIs
 - ✓ skin and soft-tissue infections (SSTIs)
 - ✓ CA-MRSA infections
4. In combination with daptomycin, clindamycin or vancomycin and rifampicin → successful treatments for MRSA endocarditis



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Any role for old antibiotics?

Trimethoprim-sulfamethoxazole (TMP-SMX)

TMP-SMX against MDR *Acinetobacter* isolates

- Non-susceptibility for *Acinetobacter* spp (4% to 98.2%)
- Non-susceptibility for MDR *Acinetobacter* spp, (5.9% to 100%)
- Resistance of Extensively drug-resistant *Acinetobacter baumannii* complex (100%)
- Carbapenem-R *Acinetobacter* spp.had non-susceptibility rates to TMP-SMX of >80%
- Polymyxin-resistant *A. baumannii* showed a susceptibility rate of 54.2%
- TMP-SMX for *Acinetobacter* spp. infections in combination with other agents

Although TMP-SMX is not usually active against *Acinetobacter* spp., it might be considered in cases



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Any role for old antibiotics?

Conclusions

Old antibiotics

- a. Are reconsidered in clinical practice
 - mainly for severe infections
 - as salvage treatment (MDR)
- b. Small studies with heterogeneity support their use
- c. Unclear PK/PDs
 - Unclear the right dose mainly in MDR treatment
- d. Safety
 - Well tolerated