Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

"Η ΣΩΤΗΡΙΑ"

Κολιστίνη / φωσφομυκίνη

Παραδείγματα αναγέννησης παλαιών αντιβιοτικών για νοσοκομειακή χρήση

Καθηγητής Γιώργος Θ. Δημόπουλος

Α΄ Πανεπιστημιακή Πνευμονολογική Κλινική ΝΝΘΑ «ΣΩΤΗΡΙΑ»

Ιατρική Σχολή Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

gdimop@med.uoa.gr

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Reintroduced old antibiotics

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Colistin: Rapidly Desired Plasma Concentrations

Concentration-dependent with time-dependence

- ƒAUC/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**

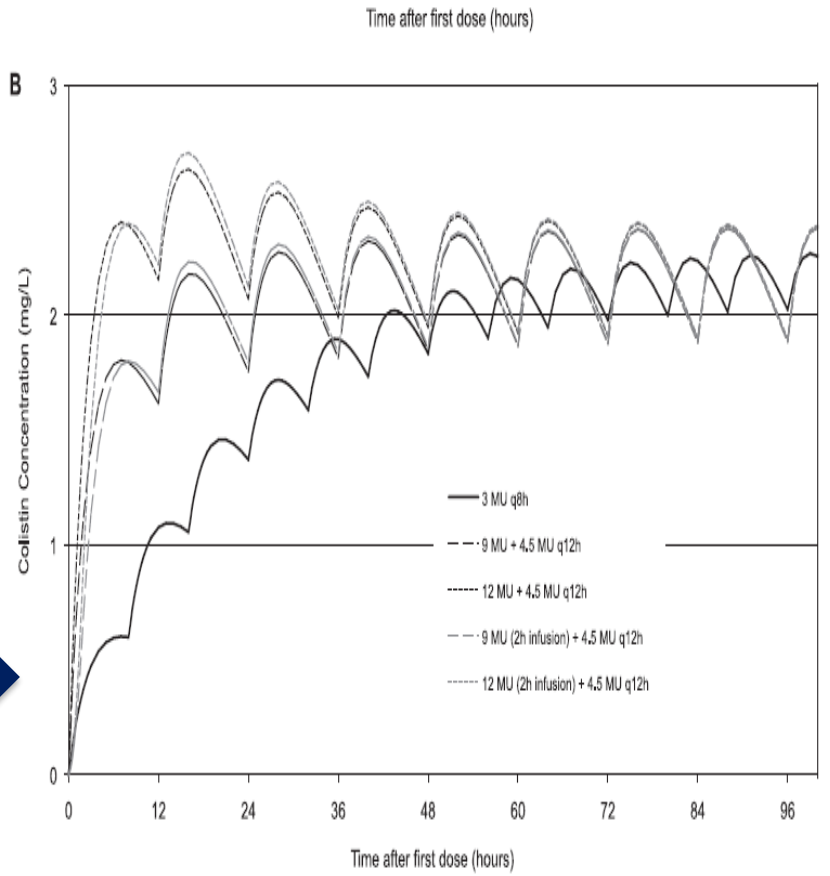


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance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

Mohamed et al. Antimicrob Agents Chemother 2012; 56:4241–9.

Plachouras et al. AAC 2009

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

[a]The 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

[b]The US Food and Drug Administration (FDA)–approved product label indicates that in obese individuals
The dosage should be based on ideal body weight.

[c]The 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.

[d]The 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.

Nation RL et al. Clin Infect Dis. 2016;62:552-558

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin

Phosphonic antibiotic

- Hydrophilic, MW 138 Da, Broad spectrum
- 50% excreted in urine unchanged
- T1/2 – 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)

Matthews et al. BMC Infectious Diseases (2016) 16:556
Dimopoulos G et al Expert Rev Infect Dis 2018 (in press)

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin properties and safety

Registration : IV not registered in many countries

Susceptible pathogens

- *Staphylococci (incl MRSA) and Enterococci, Heamophilus 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%)

Ribes et al JAC 2006; 57: 931-6,
Nau et al JAC 1995; 36: 997-1004), Drugs 1997; 53: 637-56

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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) Pl		**0.63 +/- 0.31**	**0.53 +/- 0.31**

Matzi V, J Antimicrob Chemother. 2010 May;65(5):995-8

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

Provisional susceptibility breakpoint ≤ 64 μg/ml (2008)

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

ARTICLE

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin : How we start to consider it ?

Fosfomycin : *in vitro* activity

K. pneumoniae	*P. aeruginosa*	*A. baumannii*
All isolates were ESBL and MBL (bla_{VIM-1}) 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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin IV by treatment indication and pathogen

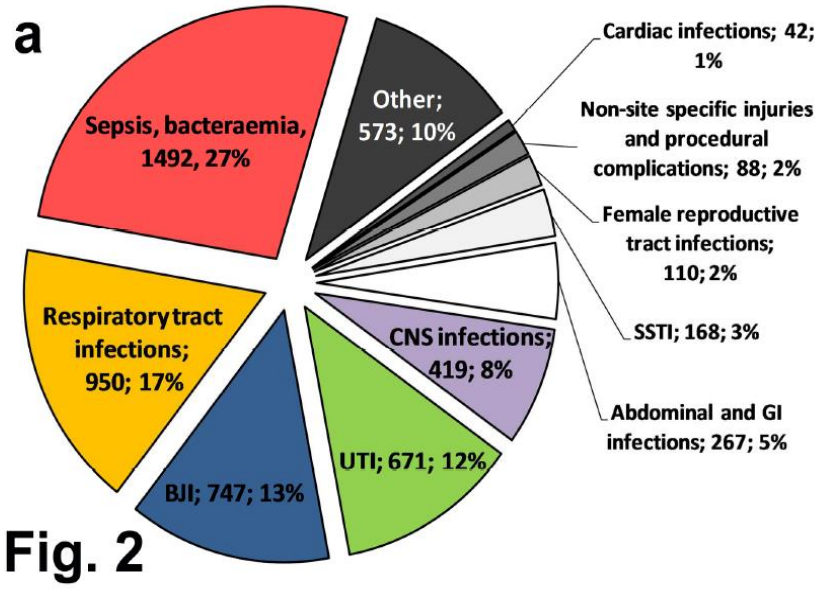
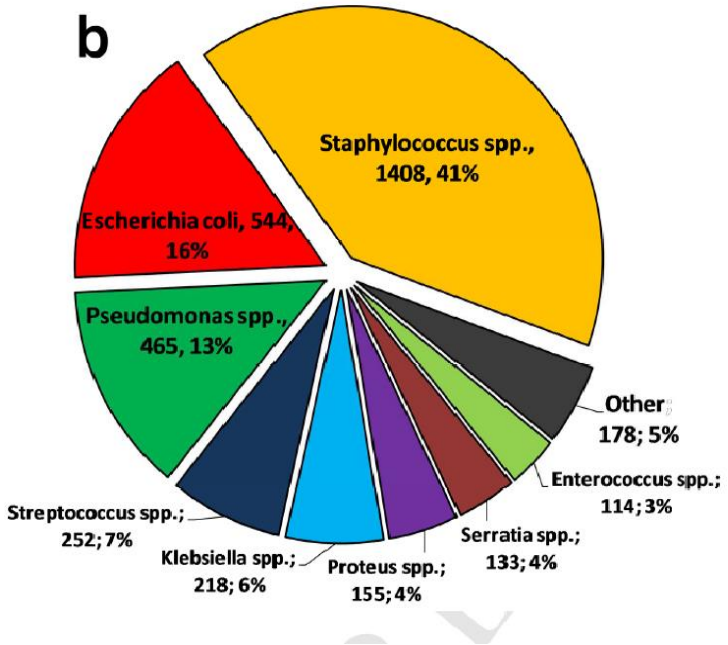


Fig. 2

IV fosfomycin by treatment indication



Numbers of microbiological isolates reported by pathogen.

Grabein, B et al , Clin Microb Infect 2016; Dec 9. pii: S1198-743X(16)30610-3.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

Clara Rosso-Fernández et al, BMJ Open 2015;5:e007363. doi:10.1136/bmjopen-2014- 007363

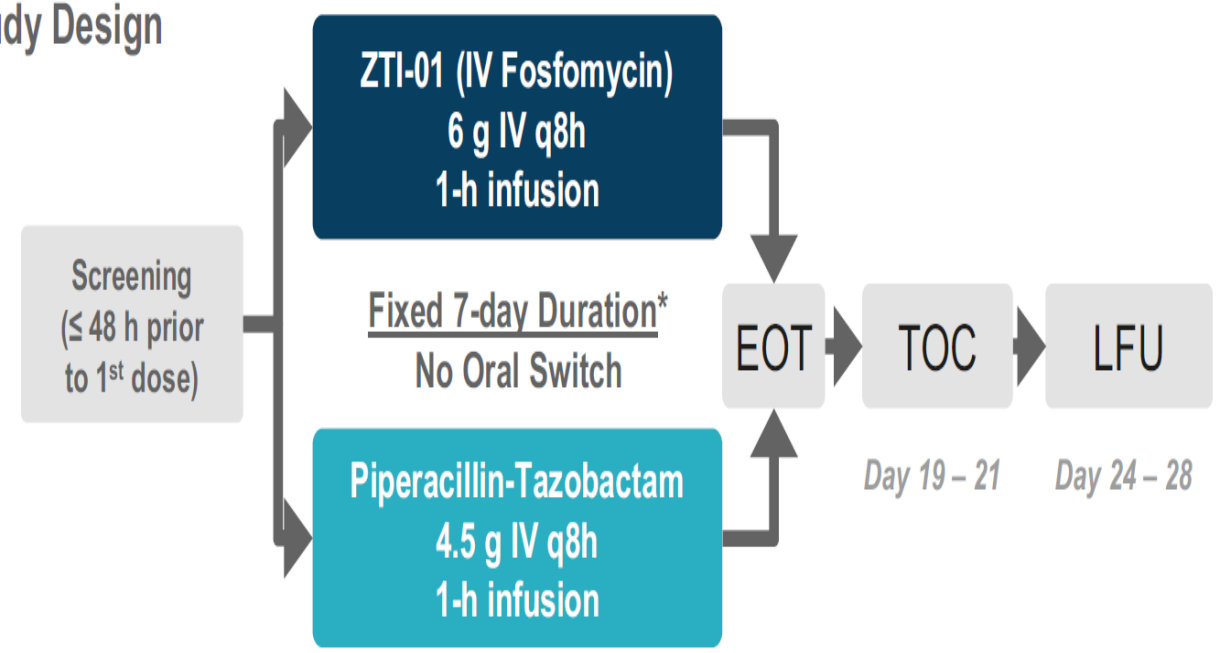
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

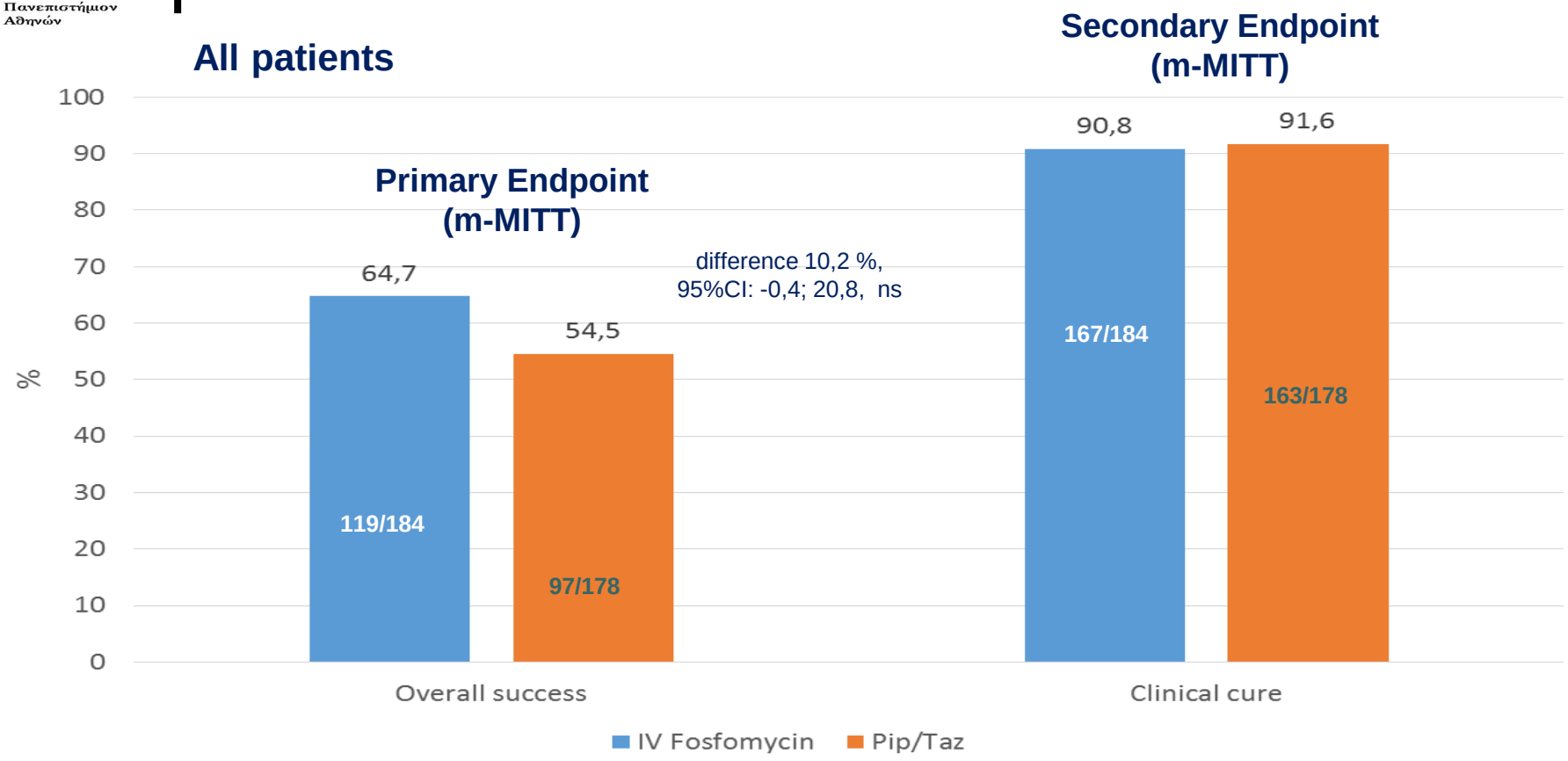
*Treatment extension up to 14 days if baseline bacteremia

Kaye KS et al. Poster 1845, presented at ID Week 2017

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin : ZEUS STUDY



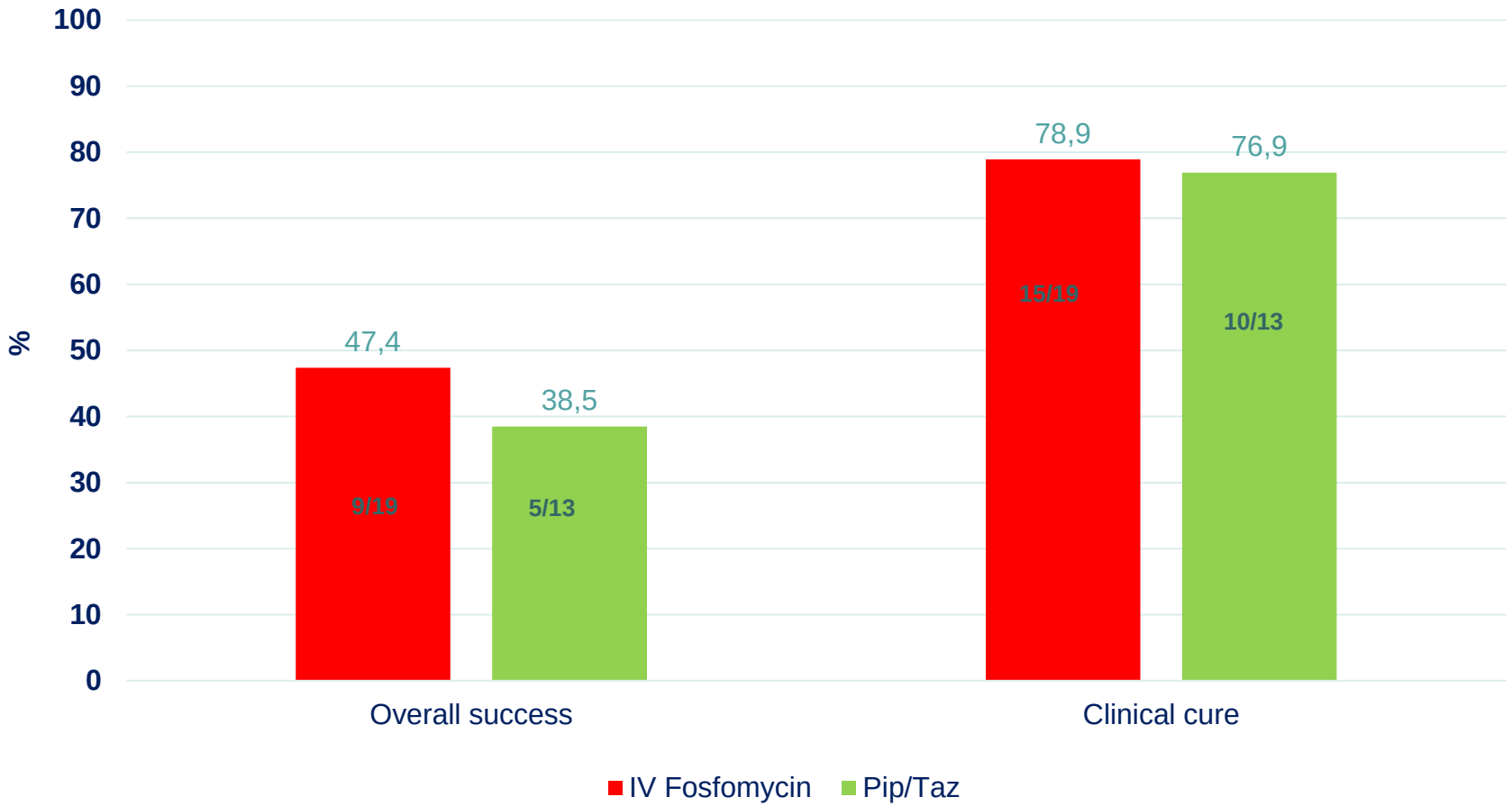
Microbiological eradication (m-MITT)
IV Fosfomycin: 65,8% (121/184)
Pip/Taz: 56,2% (100/178)
9,6 % difference, 95% CI -1,0, 20,1

Kaye KS et al. Poster 1845, presented at ID Week 2017

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin : ZEUS STUDY - patients with bacteremia



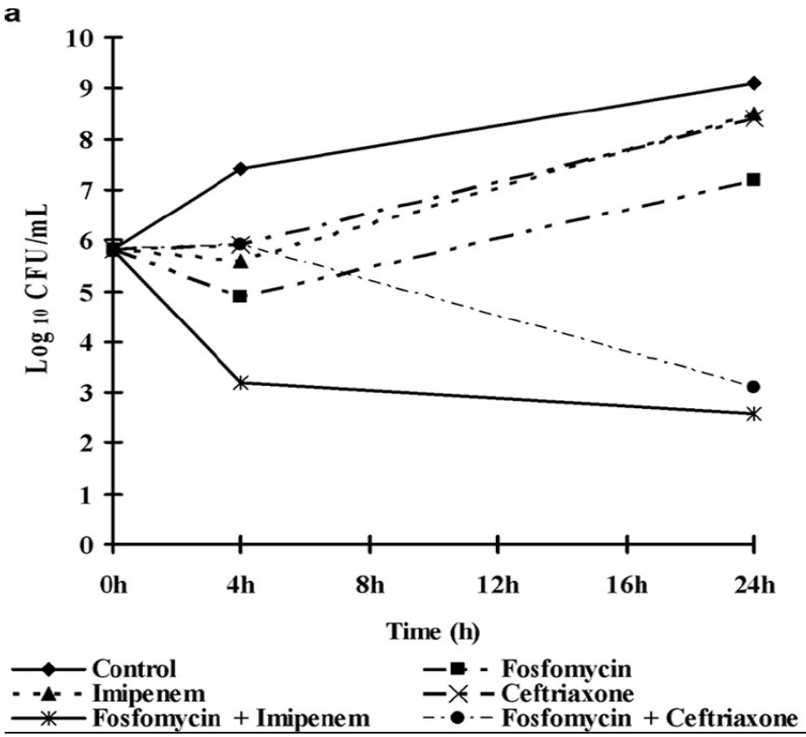
Kaye KS et al. Poster 1845, presented at ID Week 2017

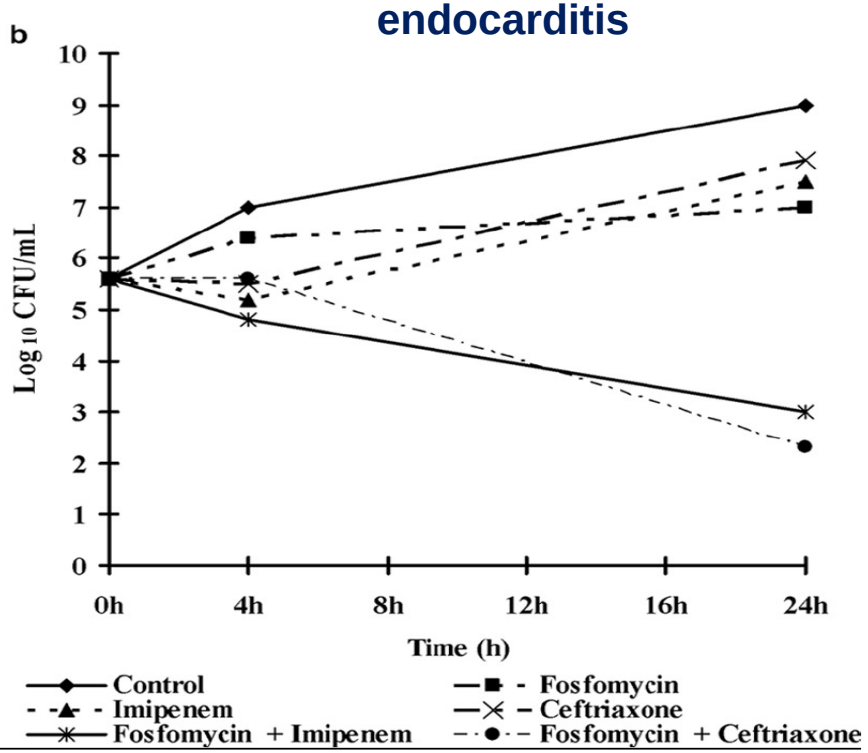
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

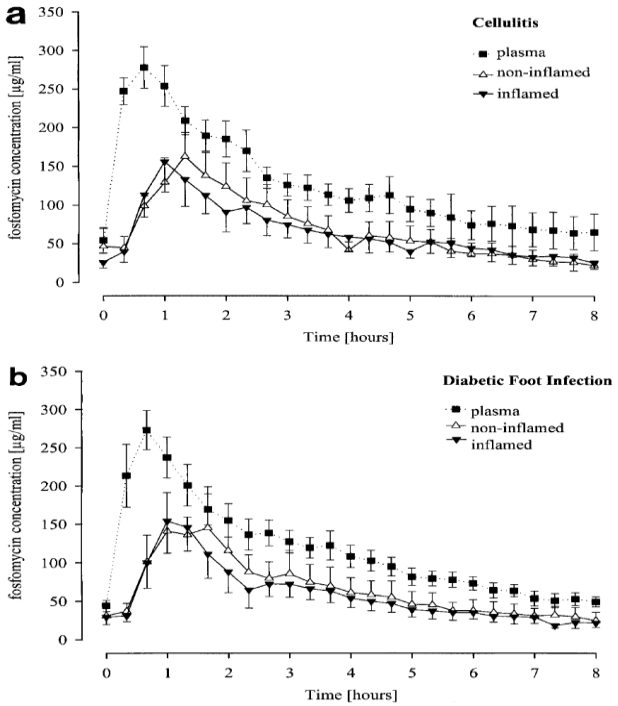
GISA-ATCC 700788 incubated with fosfomycin and imipenem or ceftriaxone (alone or in combination) at the MIC. Fosfomycin (16 g/ml), imipenem (1 g/ml), and ceftriaxone (128 g/ml) were used at the indicated concentrations.

A. del Rio et al Antimicrob Agents Chemother. 2015 Nov 2;60(1):478-86.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

Legat FJ, et al Antimicrob Agents Chemother. 2003 Jan;47(1):371-4.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Fosfomycin against CNS infections

Therapy group (dose in mg/kg/day)	HUB 2349 strain: initial titres (log cfu/mL)	HUB 2349 strain: bacterial decreases (Δlog cfu/mL) at 24 h	HUB 2349 strain: no. of animals with sterile CSF cultures at 24 h/total	HUB 2349 strain: PD parameter related to MIC[a]	ATCC 51916 strain: initial titres (log cfu/mL)	ATCC 51916 strain: bacterial decreases (Δlog cfu/mL) at 24 h	ATCC 51916 strain: no. of animals with sterile CSF cultures at 24 h/total	ATCC 51916 strain: 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.
[a]PD 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 ceftriaxoneor 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: CSF lactate levels	HUB 2349 strain: CSF protein levels	ATCC 51916 strain: CSF lactate levels	ATCC 51916 strain: 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

Ribes S, et al, J Antimicrob Chemother. 2006 May;57(5):931-6.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 Tigecycline (17 pts)

- **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 43 (2014) 52–59

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

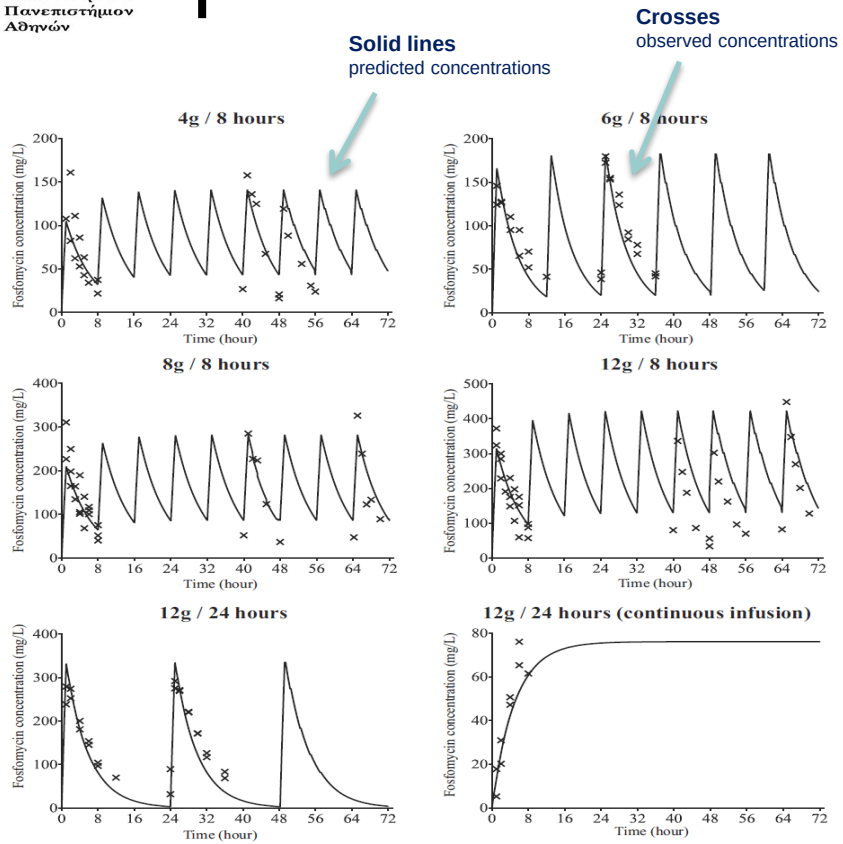
Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

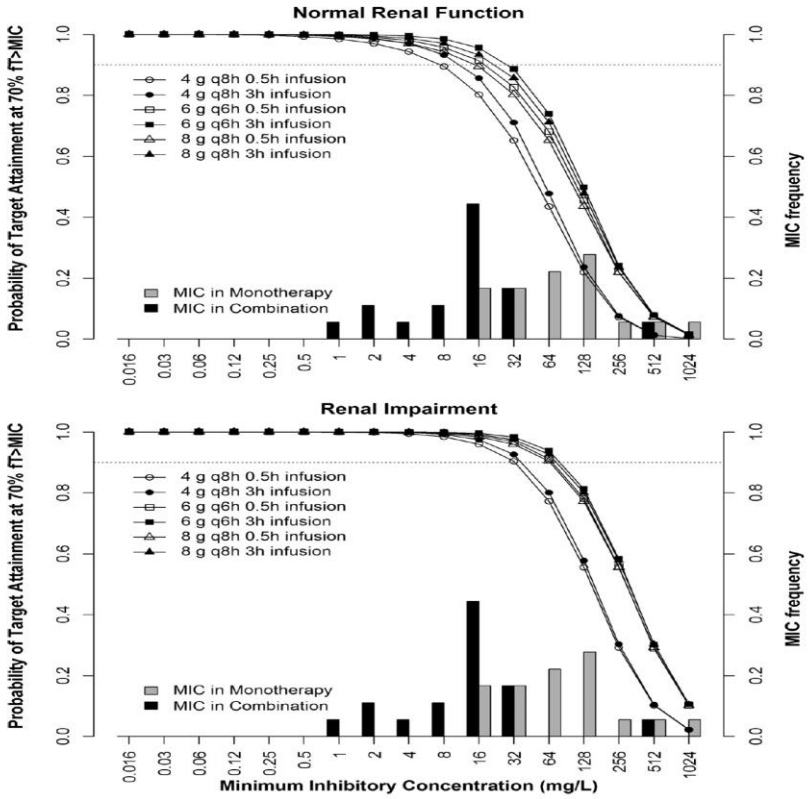
Fosfomycin : the right dose ?



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% *f*TMIC for the fosfomycin dosing regimens of 4 g q8h, 6 g q6h, and 8 g q8h in critically ill virtual patients.

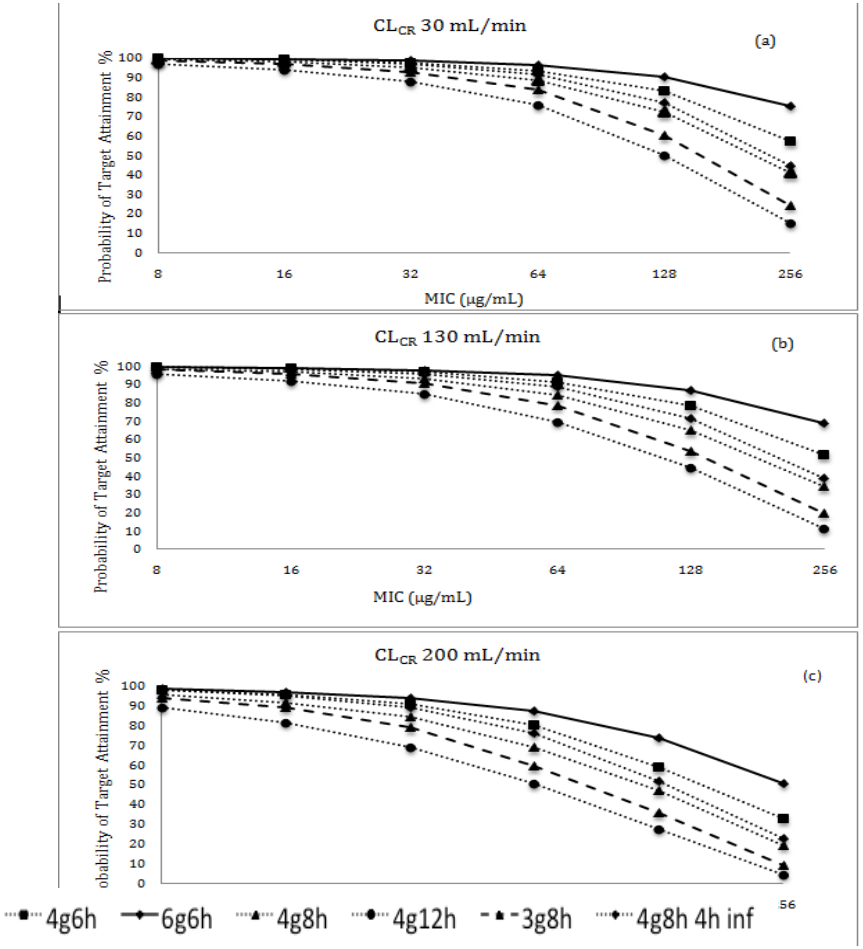
Albiero J et al, Antimicrob Agents Chemother. 2016 Jun 20;60(7):4128-39

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 concentartions in MIC >32 mg/L but insufficient in patients with CL_{CR} >200 mL/min
- Variations in PK/PDs
- Currently used doses (4gx6) probably are insufficient in patients with ↑CrCl
- Dose of 6 g x 6 ?



Parker S, Frantzeskaki F, Wallis S, Diakaki C, Giamarellou H, Karaiskos E, Lipman J, Dimopoulos G AAC (2015)

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Minocycline

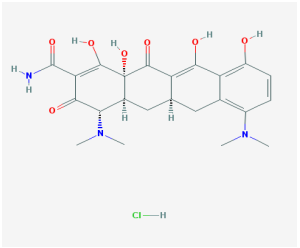
- Semisynthetic tetracycline derivative introduced in the 1960s
  - Available in both oral and intravenous dosage forms
- Currently approved FDA for treatment of **minocycline-susceptible Acinetobacter species infections**
- CLSI susceptibility breakpoints for *Acinetobacter*
  - ≤4 μg/mL for susceptibility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

Minocin [package insert]. San Diego, CA: Rempex Pharmaceuticals, 2013.
Ritchie DJ et al, CID 2014:59 (Suppl 6): S374-80

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Minocycline



Activity : Inhibits bacterial protein synthesis

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

Dosing

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

Mechanisms of *Acinetobacter* resistance to minocycline

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

Ritchie DJ et al, CID 2014:59 (Suppl 6): S374-80

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

PKs of Minocycline

Characteristic	Value
PKs	
Peak C (200-mg load)	Mean, 4.18 (2.52- 6.63μg/mL)
Trough C (100-mg/12h)	1.4–1.8 μg/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

Minocin [package insert]. San Diego, CA: Rempex Pharmaceuticals, 2013.
Ritchie DJ et al, CID 2014:59 (Suppl 6): S374-80

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

PDs of Minocycline

Characteristic	Value
PDs	
Microbiologic activity	1. Primarily **bacteriostatic** **2. Bactericidal in combination with carbapenems or colistin against *Acinetobacter baumannii*** **3. Time dependent**
Primary PD index	AUC/MIC
MPC	1 μg/mL

Liang W et al BMC Infect Dis 2011; 11:109, Lomovskaya O et al Abstracts of the 53rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, 10–13 September 2013.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

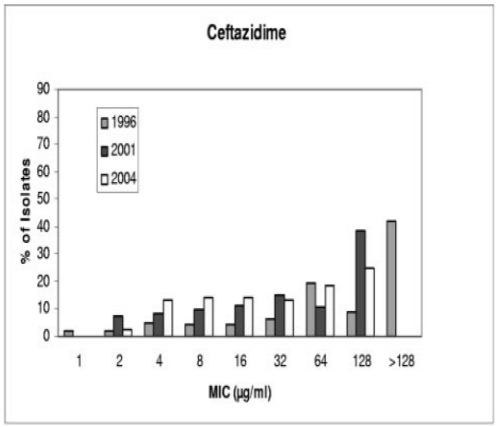
- **VAP[1,2,3,4]**
  - ✓ Critically ill
  - ✓ Successful outcomes ➔ 70-100% (clinical and microbiological)
- **Skin / soft tissue infections with/ no osteomyelitis[3,4,5]**
- **Bacteremia[3]**
  - ✓ Trauma patients

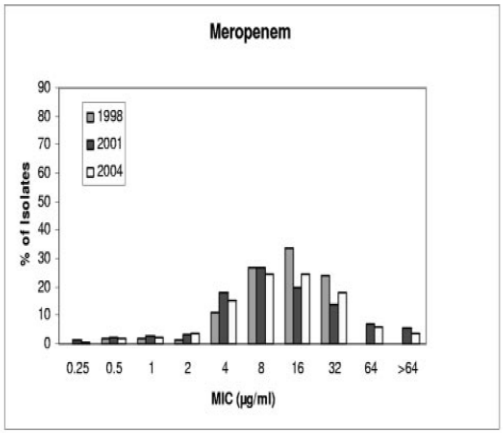
[1,]Wood GC et al, Intensive Care Med 2003; 29:2072–6, [2]Chan JD et al J Intensive Care Med 2010; 25:343–8, [3]Jankowski CA, et al, Infect Dis Clin Pract 2012; 20:184–7, [4]Bishburg E et al Infect Dis Clin Pract 2014; 22:26–31, [5]Griffith ME, et al, Infect Dis Clin Pract 2008; 16:16–9.

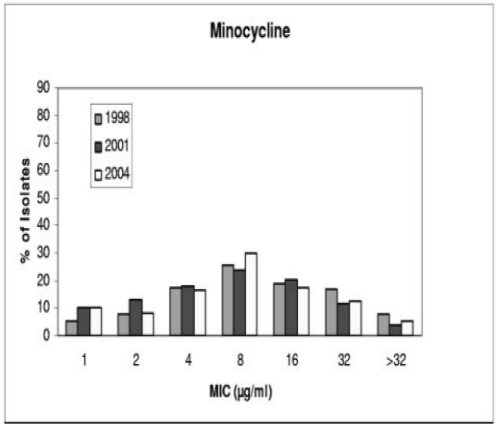
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

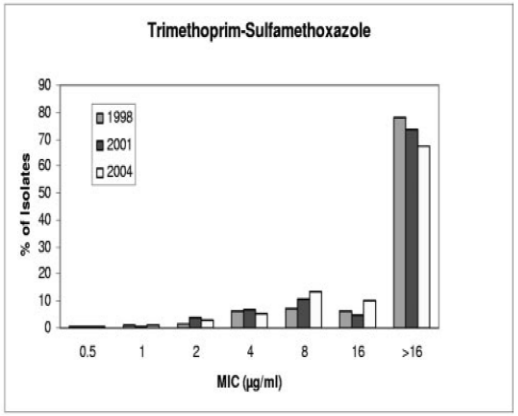
Any role for old antibiotics?

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 (range, 1% to 15% of strains per antibiotic combination).

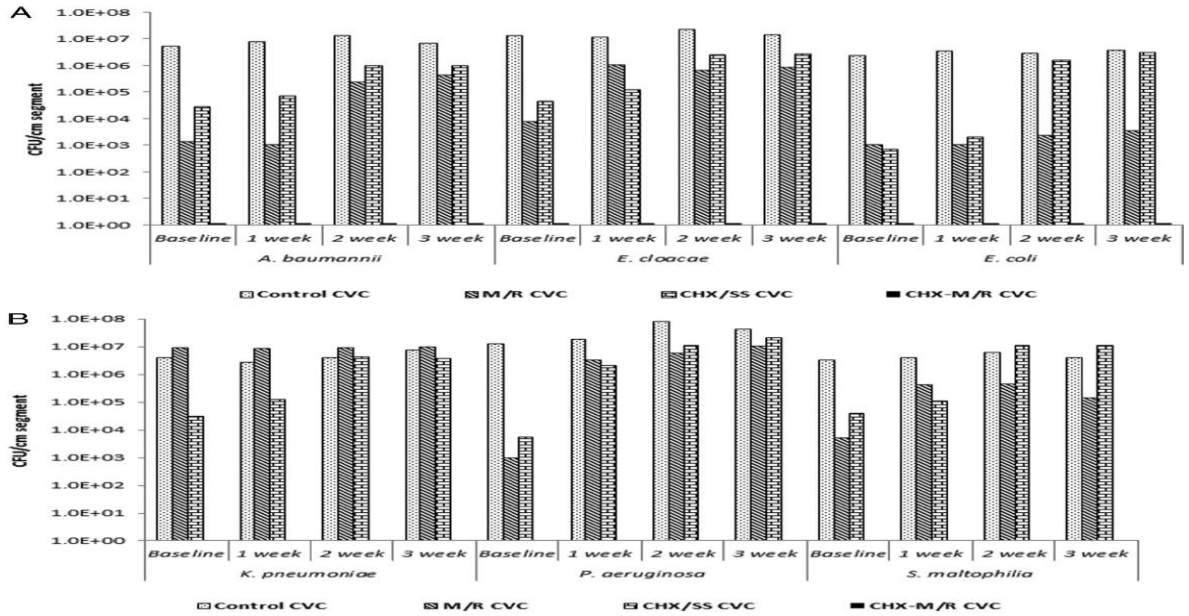
Zhou J et al Antimicrobial Agents and Chemotherapy, 2007; Mar. 2007, p. 1085–1088

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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).



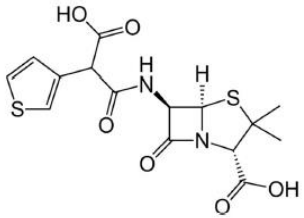
M/R : minocycline-rifampin, CHX/SS : chlorhexidine silver sulfadiazine
CHX-M/R : chlorhexidine-minocycline- rifampin

Jamal MA et al. AAC 2014;58(2):1179–1182

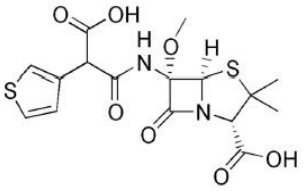
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 enyzmes (OXA-48)
- No breakpoints from EUCAST or CLSI

Woodford N, et al. JAC 2014;69:564
Alexandre K, Fantin B. Clin Pharmacokinet August 28, 2017 DOI 10.1007/s40262-017-0584-7

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

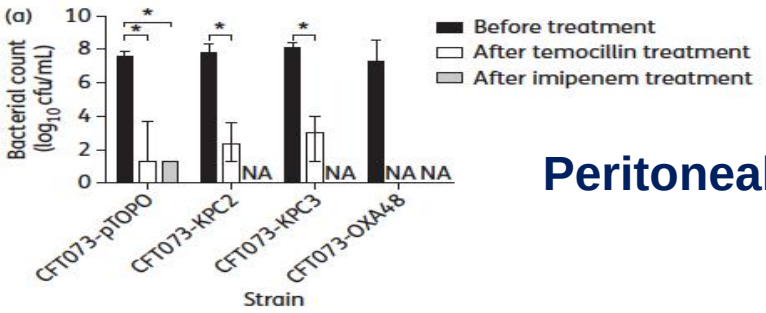
MIC (mg/L)

- 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

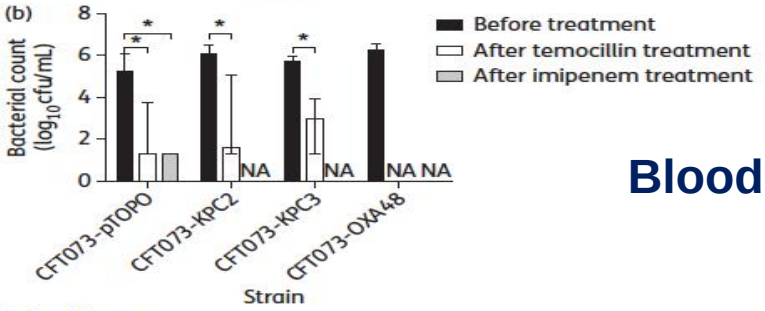
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

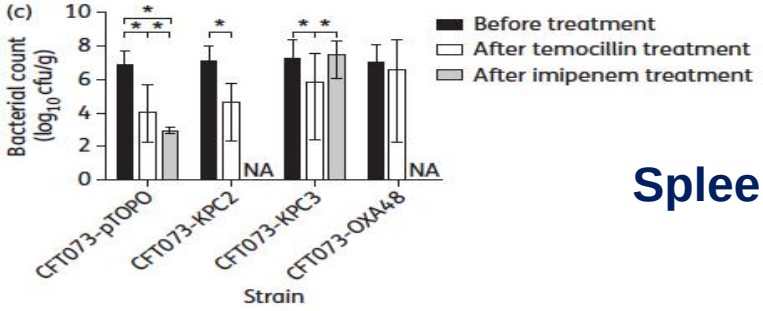
Temocillin



Peritoneal fluid

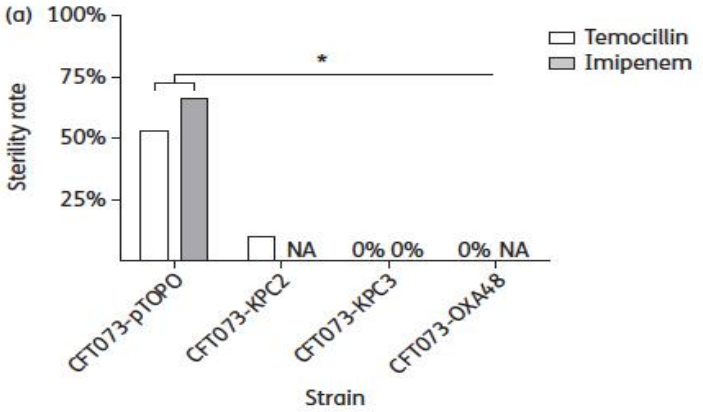


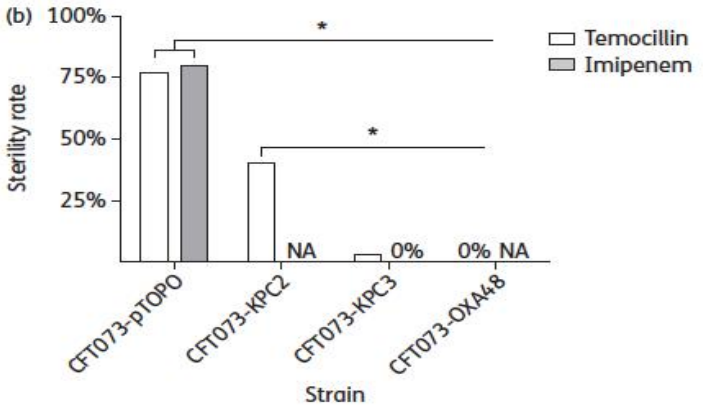
Blood



Spleen

Colony Counts





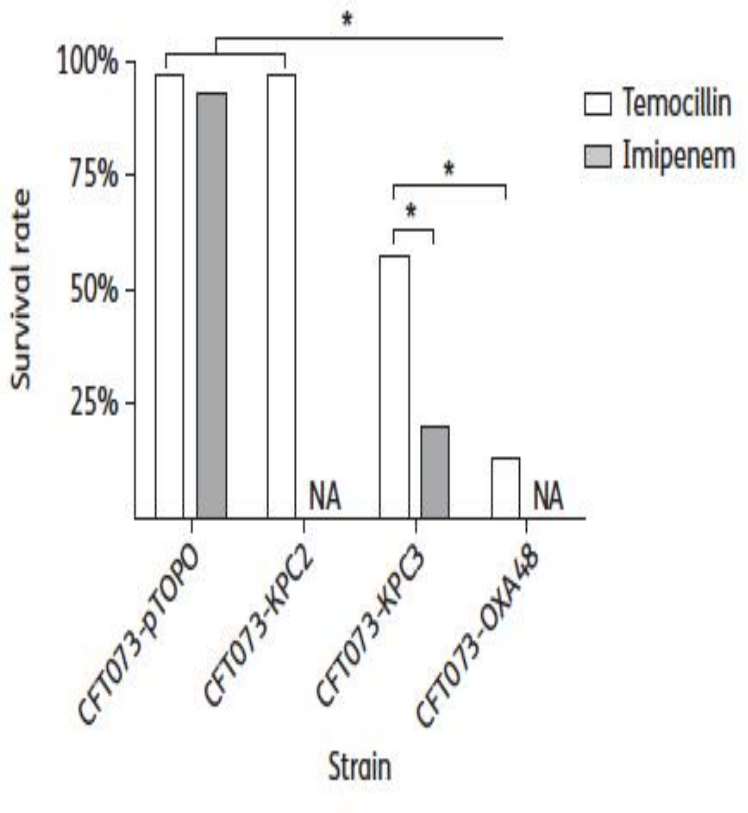
Sterility rates

Alexandre K, et al. JAC 2016; 71:1899

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 therapetic 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 Καποδιστριακόν Πανεπιστήμιον Αθηνών

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).

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

Falagas ME et al, *Expert Rev. Anti Infect. T* 208 *her.* 10(2), (2012)

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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

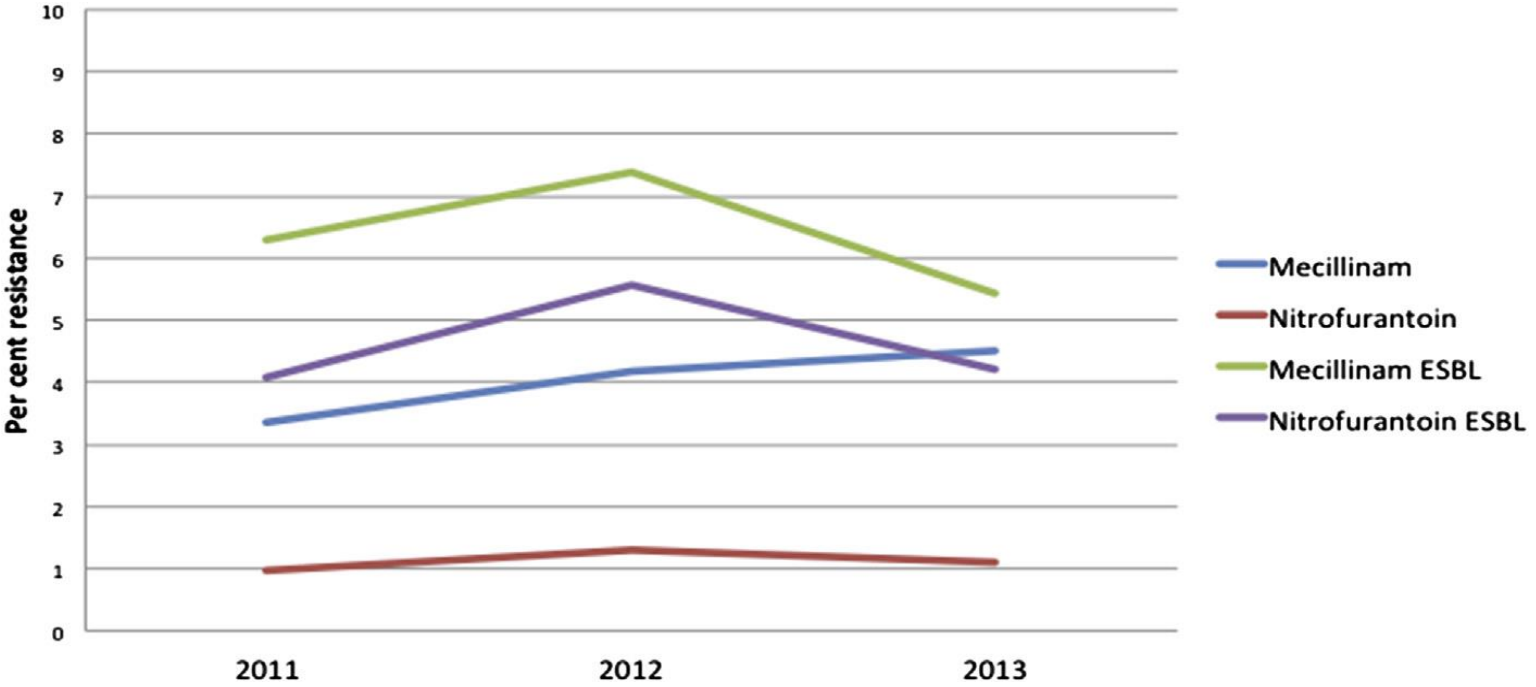
- ESBL-producing Enterobacteriaceae
- NDM and IMP producers : frequently *in vitro* susceptible to mecillinam while KPC and VIM producers are resistant
- Unpublished data also suggest that mecillinam is highly *in vitro* active against OXA-48 producers

Giske CG et al Clin Microbiol Infect 2015; 21: 899–905

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

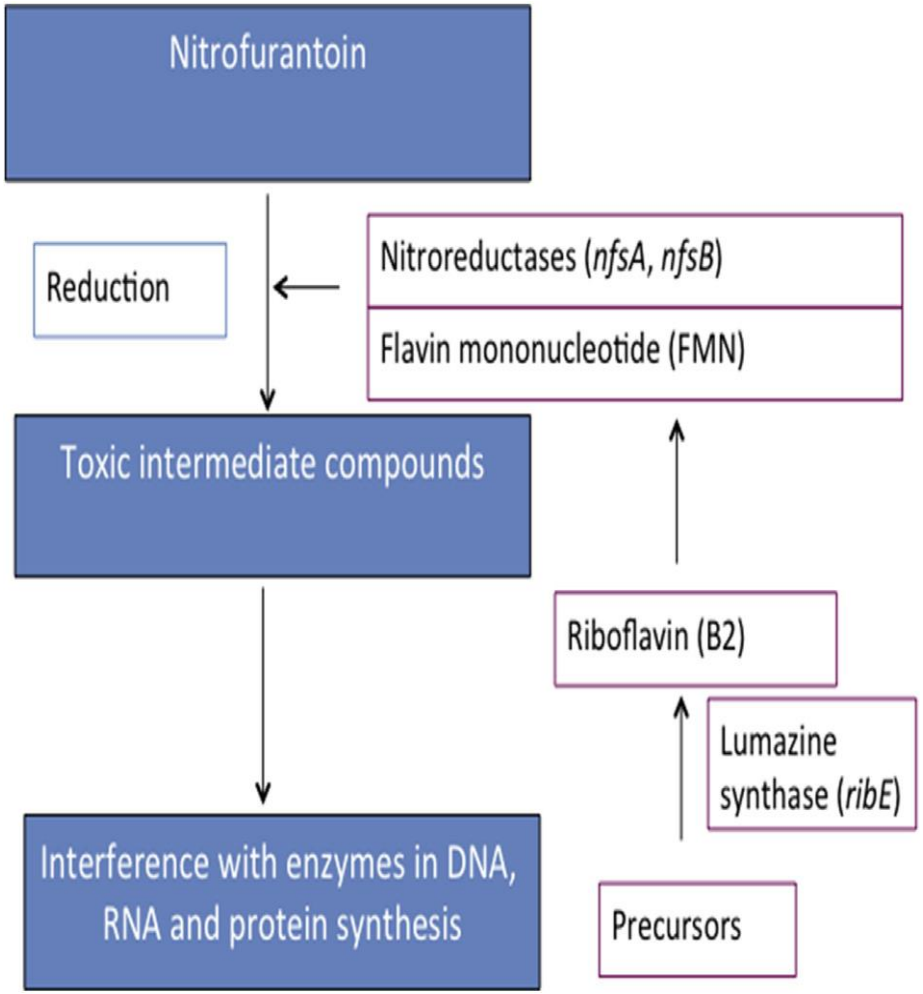
Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala, Sweden: SWEDRES-SVARM; 2013

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 high usage ☛ low fitness nfsA/nfsB mutants



Vervoort J et al J Antimicrob Chemother 2015.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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.

Raz et al J Antimicrob Chemother 2015; 70: 979–996.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 did not occur in recurrent VRE isolates.

Nitzan O, Isr Med Assoc J 2010; 12: 371–4.

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

Any role for old antibiotics?

Trimethoprim-sulfamethoxazole (TMP-SMX)

1. Inhibitis 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

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 where there are no other options.

Falagas ME et al International Journal of Antimicrobial Agents 46 (2015) 231–241

Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών

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 heterogenity support their use

c. Unclear PK/PDs
   - Unclear the right dose mainly in MDR treatment

d. Safety
   - Well tolerated