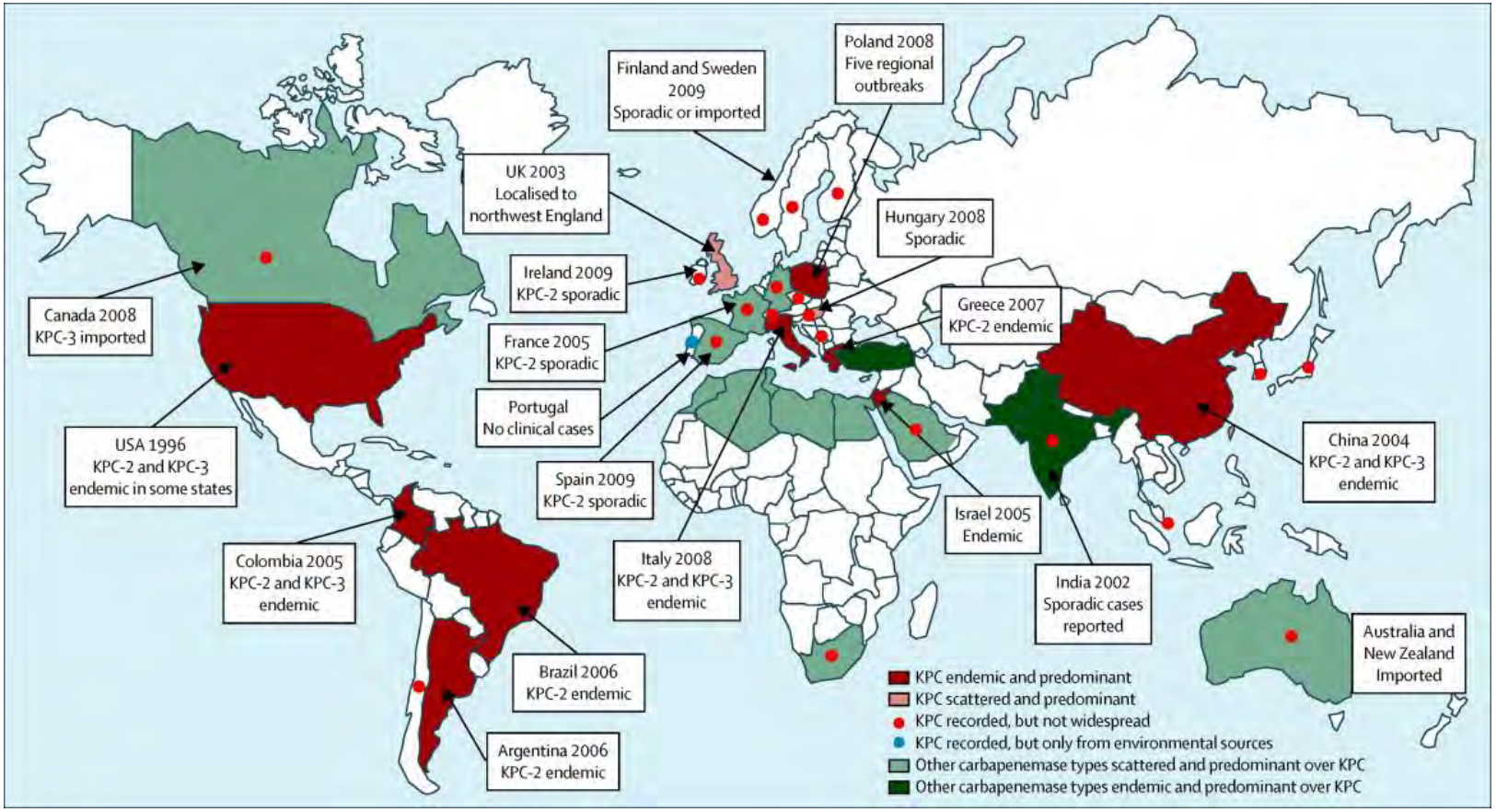
Τι νεώτερο στη θεραπεία λοιμώξεων από πολυανθεκτικούς οργανισμούς Gram-αρνητικά

Γιώργος Λ. Δαΐκος

Α΄ΠΠΚ Ιατρικής Σχολής ΕΚΠΑ, Λαϊκό Νοσοκομείο

7ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΕΛΕΓΧΟΥ ΛΟΙΜΩΞΕΩΝ. 6-7 ΝΟΕΜΒΡΙΟΥ 2014

Global expansion of *Klebsiella pneumoniae* carbapenemases

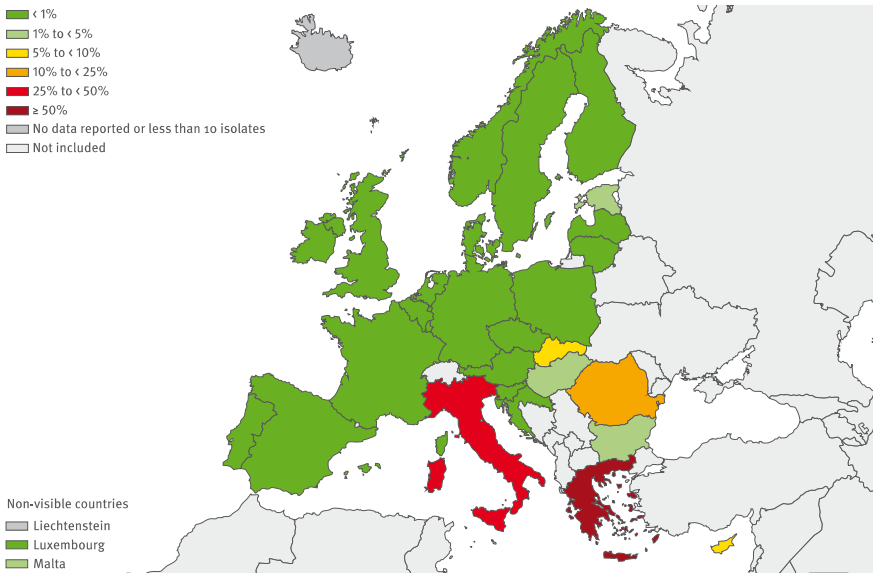


L Silvia Munoz-Price , Laurent Poirel , Robert A Bonomo , Mitchell J Schwaber , George L Daikos , Martin Cormican ...

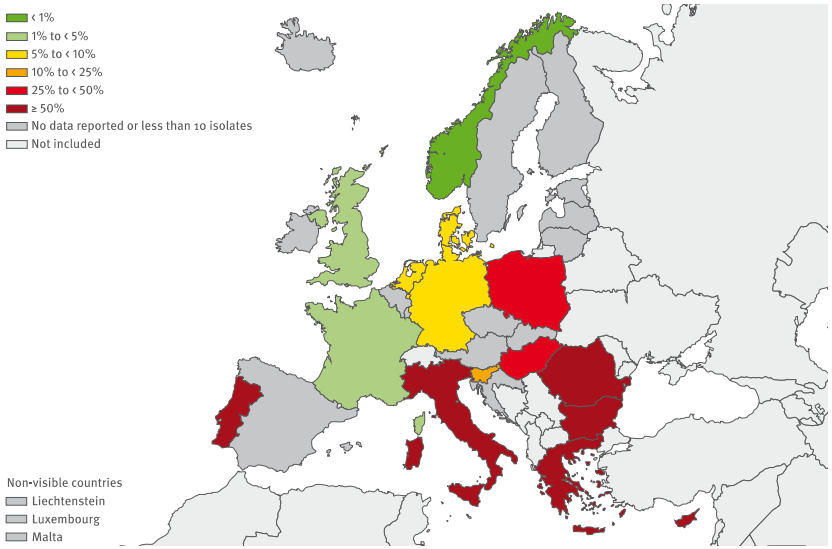
The Lancet Infectious Diseases, Volume 13, Issue 9, 2013, 785 - 796

Percentage (%) of invasive isolates with resistance to carbapenems, by countr, 2012

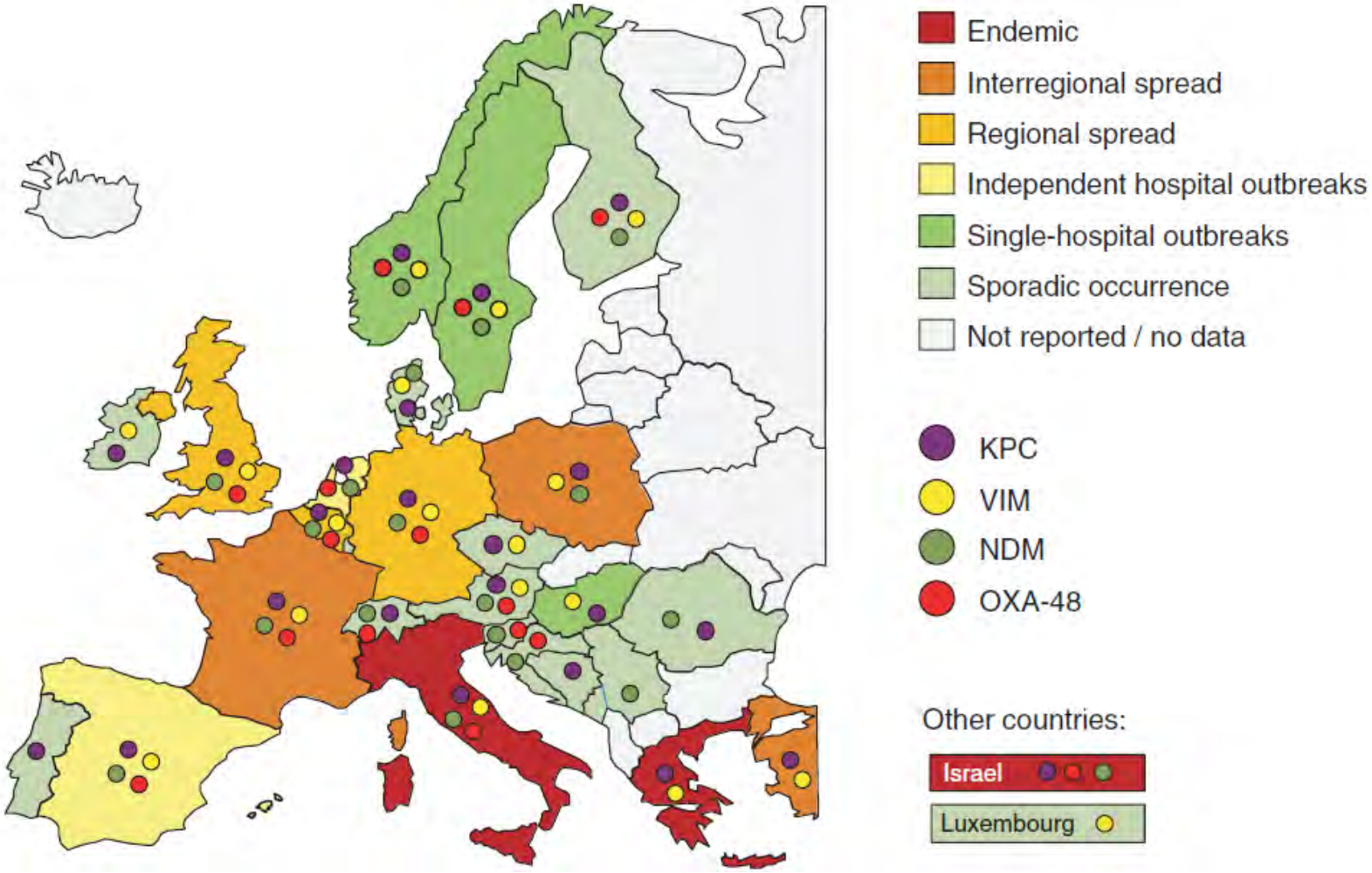
Klebsiella



Acinetobacter



Distribution of Carbapenemases in Europe



R Canton Clin Microbiol Infect 2012; 18: 413–431

Resistance Profile of Blood Cultures Isolates from Patients in Medical Wards (July-December 2013, WHONET)

Antibiotic	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*A.baumannii*
Amox/clav sulbactam	11.8%	42%	-	51%
Cefoxitin	3%	36.7%	-	-
Ceftazidine/CTX M	5%/15.7%	39/36%	25.4%	-
Imipenem	0.1%	33%	35%	82%
Gentamicin	9.2%	17%	22%	70%
Amikacin	0.6%	22.5%	24%	75.3%
Ciprofloxacin	30.7%	46.7%	?	87%
Co-trimoxazole	39.6%	45%	-	58%
Piperacillin/Tazo	5.1%	42%	22.4%	79%

Resistance Profile of Blood Cultures Isolates from ICU Patients 2013 (WHONET)

Antibiotic	***K. pneumoniae***	***P. aeruginosa***	***A.baumannii***
Ceftazidime	74.3%	26.4%	93%
Meropenem	67%	53%	92%
Gentamicin		27%	92%
Amikacin	35%	42%	85%
Ciprofloxacin	77%	22.6	92%
Piperacillin/Tazobactam	79%	48%	100%

KPC Infections from 114 Hospitals

National Action Plan (2010-2011)

Department

- ICU 51.6%
- Medicine 31.5%
- Surgery 16.9%

Source of Infection

- Pneumonia 32.5%
- Bacteremia 31.5%
- UTIs 23%
- SSI 12.9%

Hellenic Center for Disease Control and Prevention (KEELPNO)

IMMUNOCOMPROMISED HOSTS INVITED ARTICLE

David R. Snydman, Section Editor

The Global Challenge of Carbapenem-Resistant Enterobacteriaceae in Transplant Recipients and Patients With Hematologic Malignancies

Michael J. Satlin,[1,2] Stephen G. Jenkins,[2,3] and Thomas J. Walsh[1,2]

[1]Transplantation-Oncology Infectious Diseases Program, Division of Infectious Diseases, [2]New York-Presbyterian Hospital, and [3]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, New York

Clinical Infectious Diseases 2014; 58:1274

Therapeutic Options for Carbapenem-Resistant GNB

Pseudomonas aeruginosa

- Colistin
- Fosfomycin ?

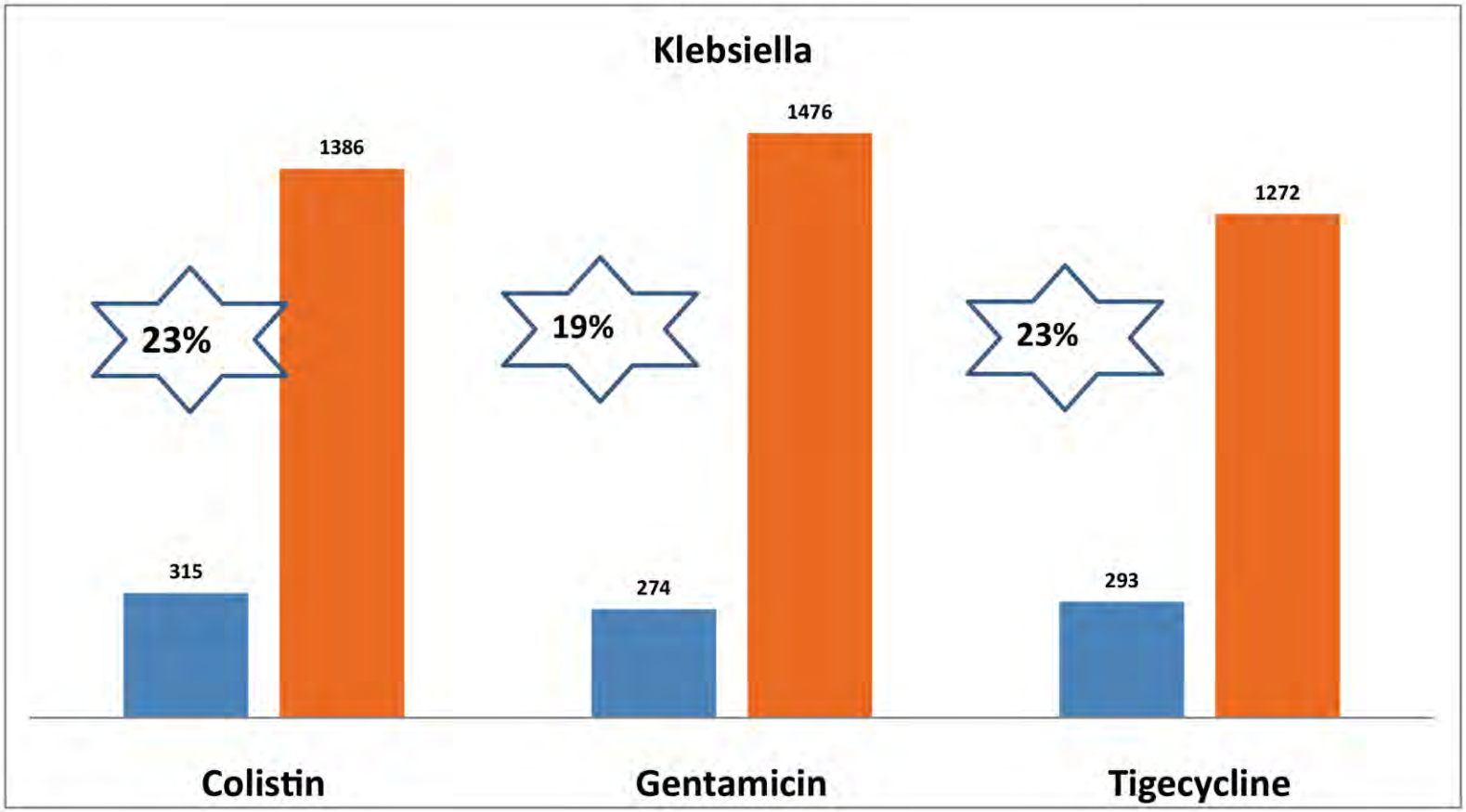
Klebsiella pneumoniae

- Colistin
- Tigecycline
- Aminoglycoside
- Fosfomycin?

Acinetobacter baumannii

- Colistin
- Tigecycline

Resistance Profile of CPKP

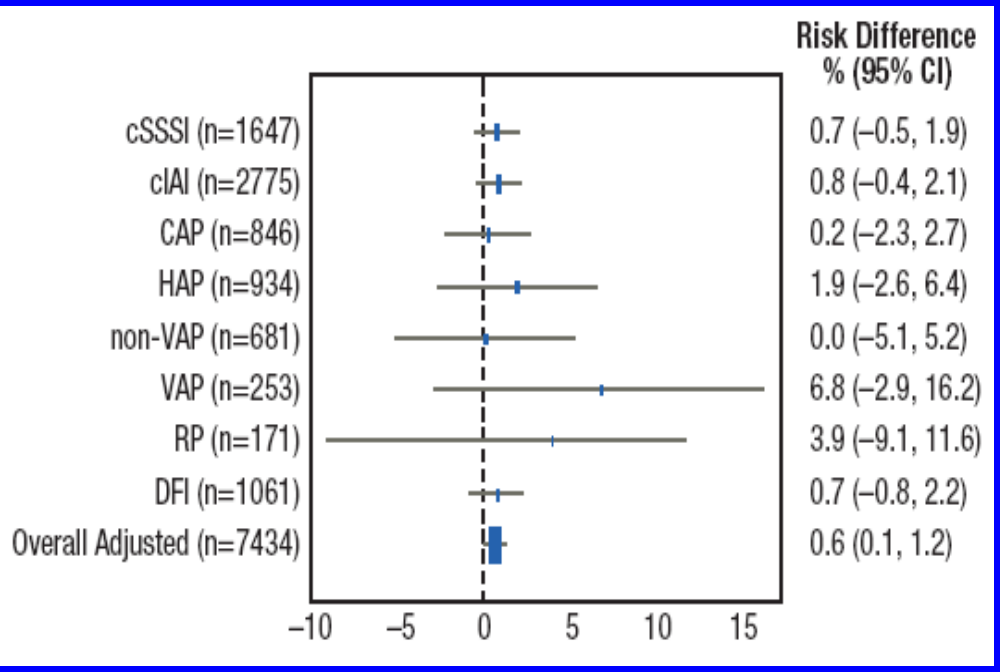


Hellenic Center for Disease Control and Prevention

Optimizing Colistin Dosing Regimens

- **Suboptimal dosing regimen of the drug.**
  - multivariate analysis of survival data showed that a lower total daily dosage of intravenous colistin was associated with increased mortality (Falagas et al. Int. J. Antimicrob. Agents 2010; 35:194 – 199.
- **Delay in attaining an efficacious drug concentration**
  - Necessity to give a loading dose (Plachouras et al. Antimicrob. Agents Chemother. 2009; 53:3430 –3436)
- **Optimal dosing regimen (gaps in our knowledge)**
  - Once daily, twice daily or three times daily?

Mortality imbalance in the Tigecycline Phase 3 and 4 Clinical Trials



- ✓Logistic regression modelling identified baseline bacteraemia as a predictor of mortality in the TGC treatment group
- ✓The mortality rate for TGC subjects with VAP and baseline bacteraemia was 50% (9/18 subjects) versus 7.7% (1/13 pts) in the COM group

CID 2012:54 (15 June) • Prasad et al

De Pascale *et al. Critical Care* 2014, **18**:R90
http://ccforum.com/content/18/3/R90

CRITICAL CARE

RESEARCH Open Access

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

Gennaro De Pascale[1*], Luca Montini[1], Mariano Alberto Pennisi[1], Valentina Bernini[1], Riccardo Maviglia[1], Giuseppe Bello[1], Teresa Spanu[3], Mario Tumbarello[2] and Massimo Antonelli[1]

Logistic regression analysis of factors associated with clinical cure in 63 patients with ventilator-associated pneumonia

Variable	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

Fosfomycin for the Treatment of 11 Critically-ill Patients infected with CR *K. pneomoniae*

Characteristic	
Mean age, years	67.5
APACHE II score	23.4
No. of organ dysfunction, median	3
VAP Primary bacteremia Other	5 2 4
All cause hospital mortality	18.2%

All patients received combination Rx Fosfomycin with CMS or GM or Pip/tazo

Michalopoulos A et. al Clin Microbiol Infect 2010; 16: 184-6

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]

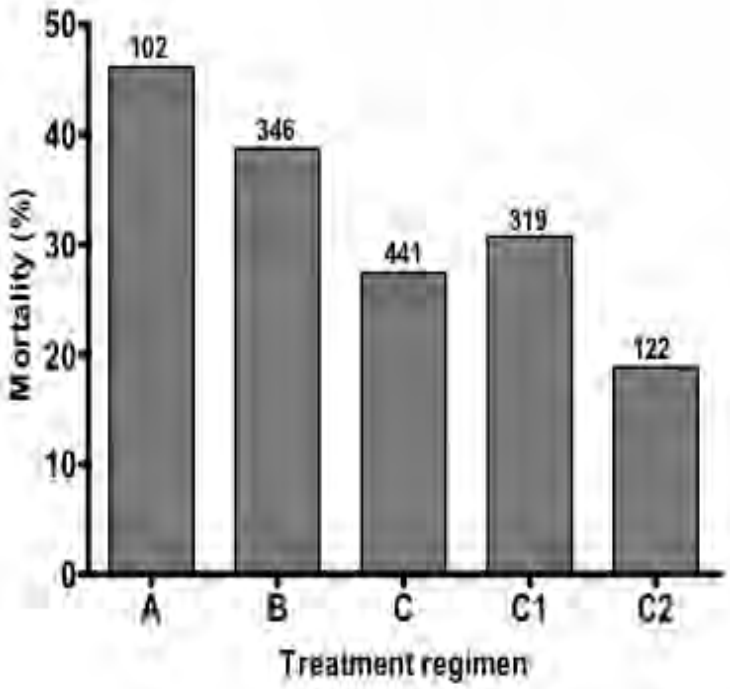
- 48 pts with XDR *K. pneumoniae, P. aeruginosa infections*
- 25 BSIs, 14 VAP, 11 other
- Fosfomycin in combination with CMS, Tigecycline, Meropenem, Gentamicin, PIP/Tazo

Outcome of 48 patients with serious infections caused by XDR Gram(-)

- Clinical success: 26/48 (54.2%)
- Microbiologic success: 27/48 (56.3%)
- 28-day mortality: 18/48 (37.5%)

Pontikis et al IJAA 2014; 43: 52–59

Outcomes of 889 Patients with Serious Infections Caused by CPKP According to Treatment



A Inappropriate Rx

B Monotherapy

C Combination therapy

C_1 Carbapenem-sparing combination

C_2 Carbapenem-containing combination

Tzouvelekis et al Clin Microb Infect 2014; 20: 862

J Antimicrob Chemother
doi:10.1093/jac/dks270

Emergence of resistance to fosfomycin used as adjunct therapy in KPC *Klebsiella pneumoniae* bacteraemia: report of three cases

Drosos E. Karageorgopoulos[1], Vivi Miriagou[2], Leonidas S. Tzouvelekis[3], Kalliopi Spyridopoulou[1] and George L. Daikos[1*]

Multivariate Analysis of Factors Associated with all-cause 30-day Mortality of Patients with KPC BSIs

Variable	P	OR(95% CI)
Septic shock	0.008	7.17 (1.65-31.03)
APACHE	<0.001	1.04 (1.02-1.07)
Inadequate empirical Rx	0.003	4.17 (1.61-10.76)
Definitive Rx Col+tigecl+merop	0.01	0.11 (0.02-0.69)

Tumbarello M et al. CID 2012; 55: 943

Cox proportional hazards model of factors associated with all-cause 28-day mortality in 175 patients with carbapenemase-producing *K. pneumoniae* bloodstream infections

(Daikos GL AAC 2014; 58: 2322–2328)

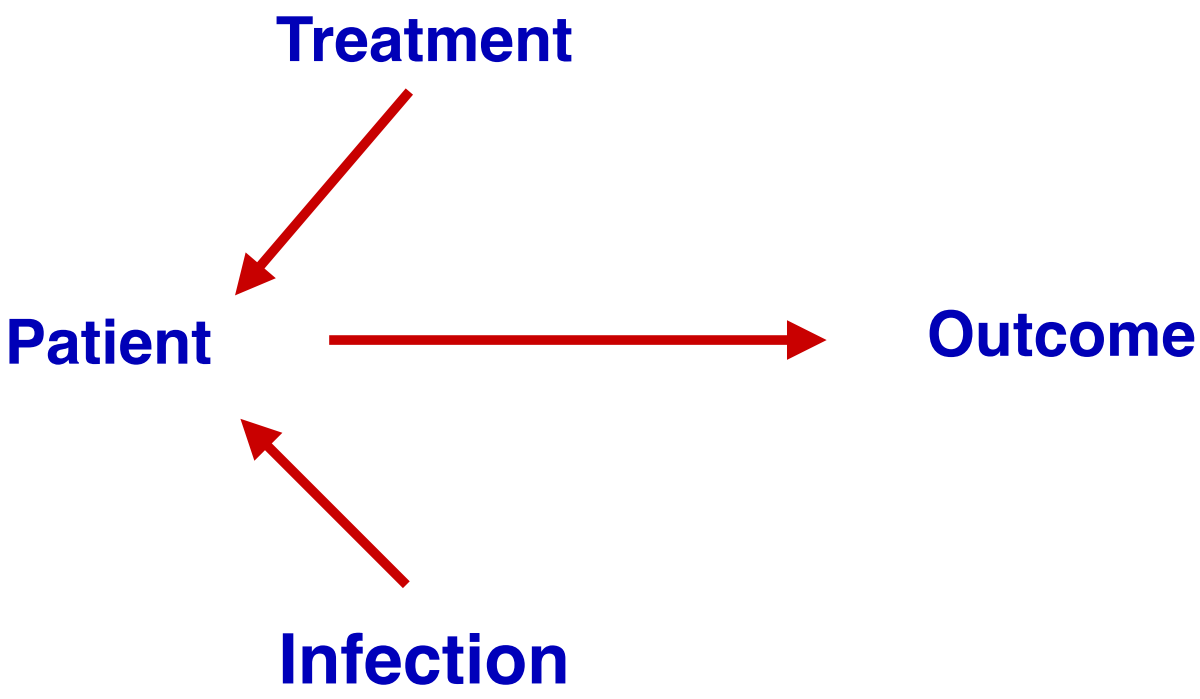
Variable	HR	P
Age	1.01(0.99-1.03)	0.37
Mc Cabe		
Ultimately fatal/non fatal	3.13(1.43-6.83)	0.004
Rapidly fatal/non fatal	4.23(2.19-8.16)	<0.001
Severity of sepsis		
Severe sepsis/sepsis	1.8(0.83-3.97)	0.14
Septic shock/sepsis	2.28 (1.22-4.27)	0.01
Time to initiation of active therapy		
≤48 h	1.44(0.79-2.62)	0.24
>48 h		
1 active vs >1 active	2.12(1.25-3.61)	0.006

Outcome of Patients with CPKP BSIs According to Treatment

Antimicrobial regimen	No. of patients		
	Survived	Died	% Died
Combination			
Carbapenem-containing regimen	25	6	19.3
Carbapenem-sparing regimen	50	22	30.5
Total[a]	**75**	**28**	**27.2**
Monotherapy			
Tigecycline	16	11	40.7
Colistin	10	12	54.5
Other	14	9	39.1
Total[a]	**40**	**32**	**44.4**

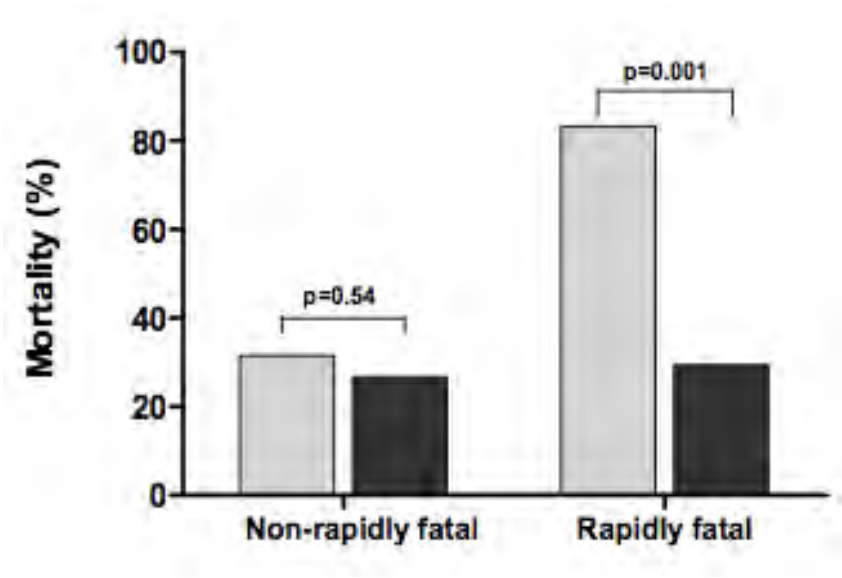
[a] $P=0.018$

Daikos GL Antimicrob Agents Chemother 2014; 58: 2322–2328

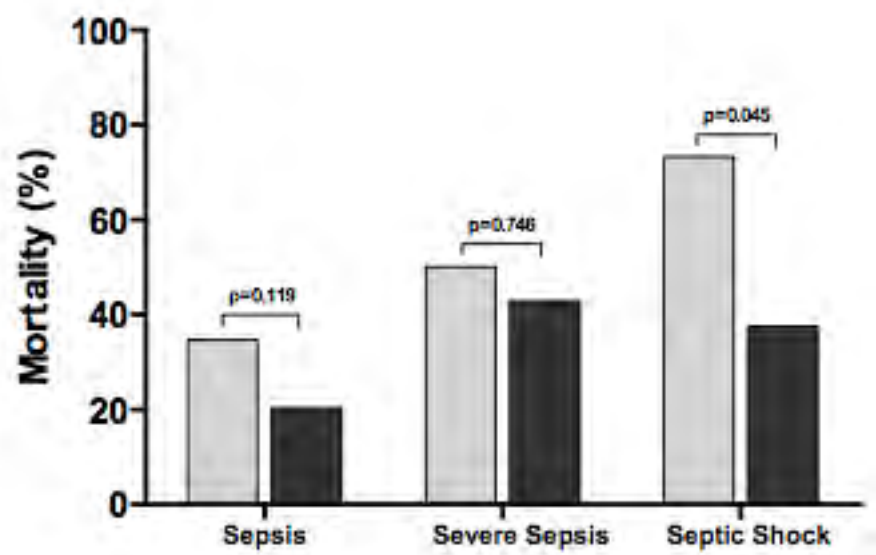

Treatment
Patient
Outcome
Infection

Effect of treatment against CPKP BSIs
(monotherapy vs combination therapy)

By severity of underlying disease



By severity of sepsis



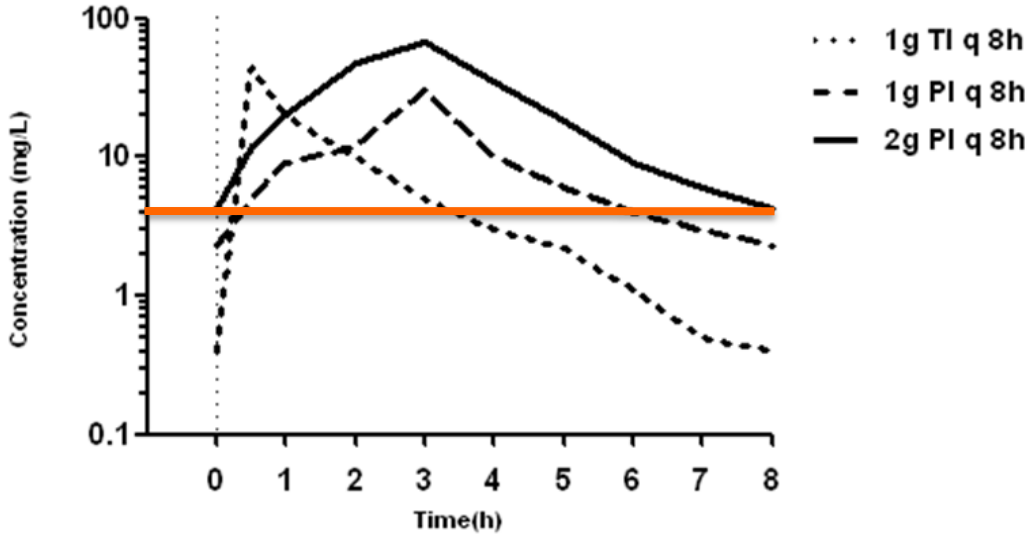
Daikos GL Antimicrob Agents Chemother 2014; 58: 2322–2328

Blood culture grew *K. pneumoniae*

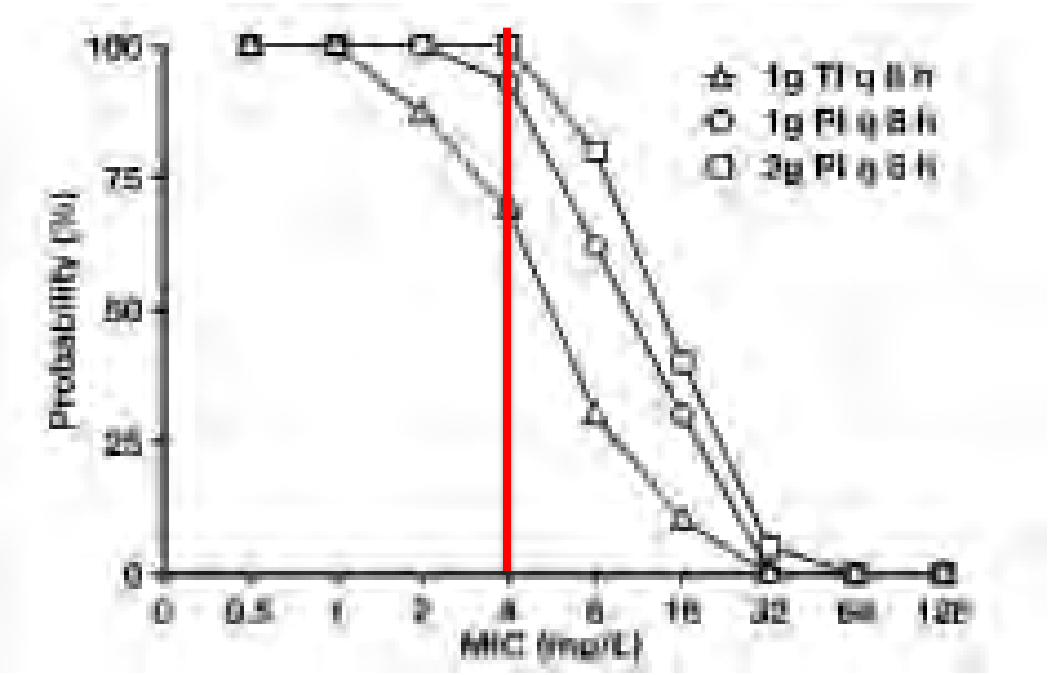
• Amoxicillin	\	R
• Co-amoxiclav		R
• Piperacillin+tazob		R
• Cefuroxime		R
• Ceftazidime		R
• Cefotaxime		R
• Aztreonam		R
• Cefepime		R
• Imipenem	4 mg/L	R by CLSI, I by EUCAST
• Meropenem	4 mg/L	R by CLSI, I by EUCAST
• Gentamicin	1 mg/L	S
• Amikacin		R
• Tigecycline	1 mg/L	S
• Colistin	1 mg/L	S

Μη έχοντας στη διάθεσή μας πιό αποτελεσματικά φάρμακα μπορούμε να χρησιμοποιήσουμε meropenem (MIC=4mg/L)

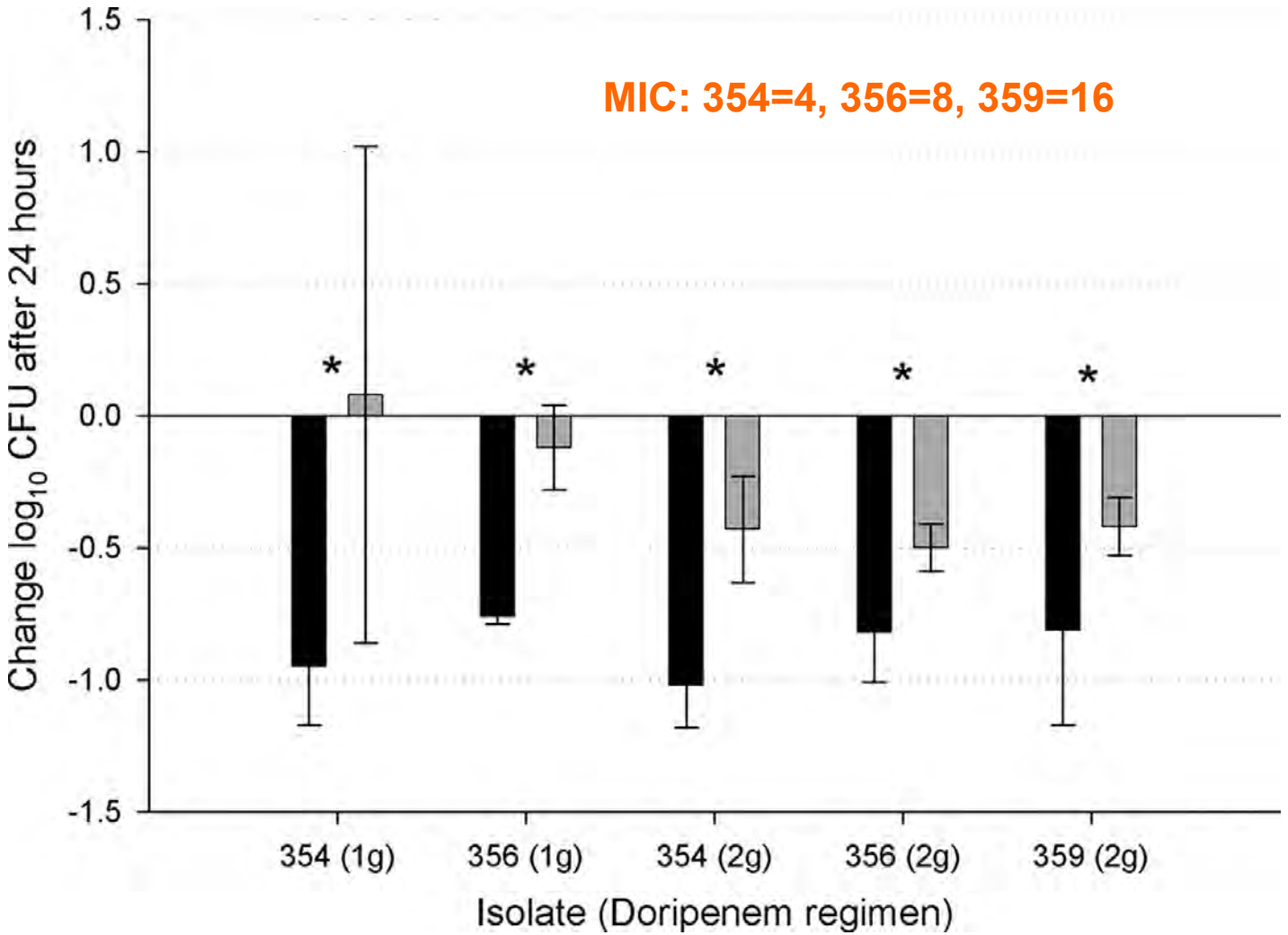
Pharmacokinetics of three different dosing regimens of meropenem



Simulated Target Attainment Probabilities for 50%T>MIC of three Different Dosing Regimens of Meropenem



Comparison of the efficacies of two different doses of doripenem against carbapenemase-producing K. pneumoniae isolates in immunocompromised and immunocompetent animals.



Bulik C C , Nicolau D P Antimicrob. Agents Chemother. 2010;54:4112-4115

Antimicrobial Agents and Chemotherapy

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Carbapenem Monotherapy in 50 Patients with Serious CPE Infections

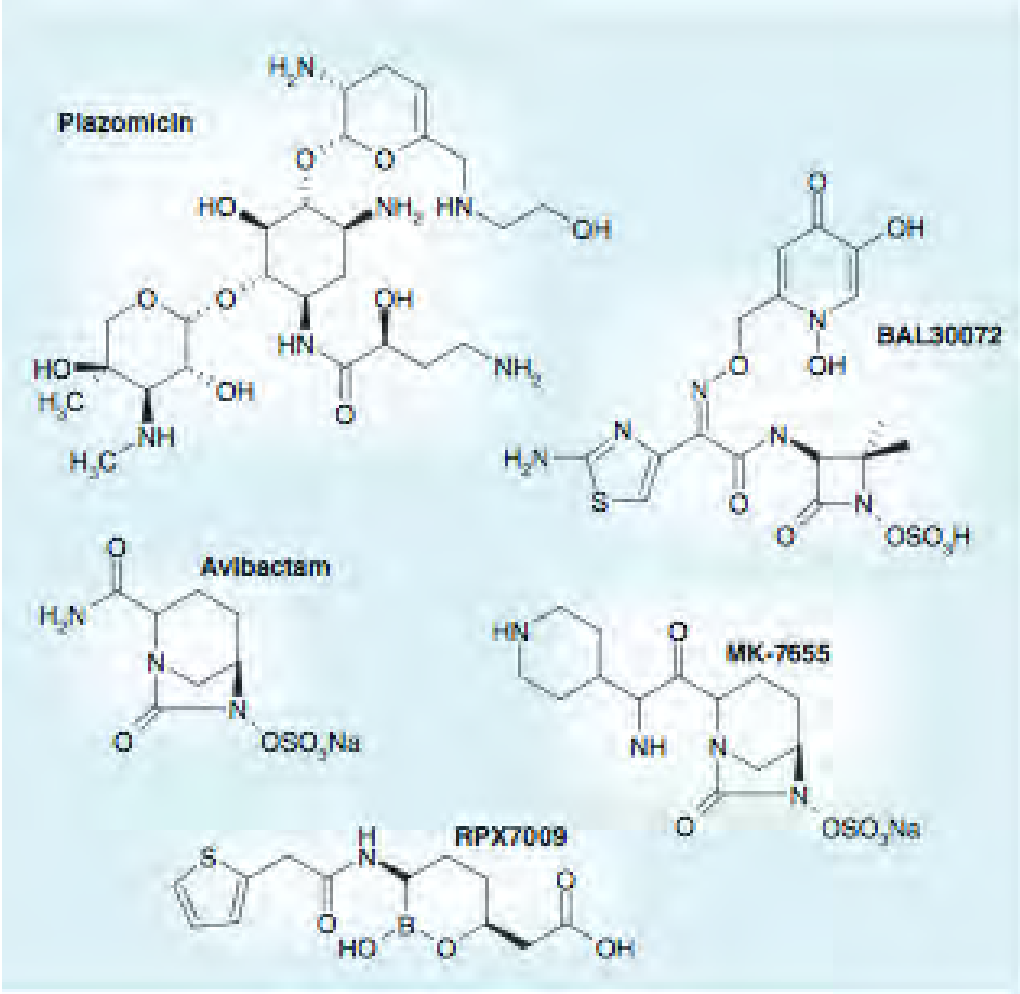
(*Results compiled from 15 studies*)

MIC (µg/ml)	No. of patients	No. of successes	No. of failures	% failure
≤ 1	17	12	5	29.4
2	12	9	3	25
4	7	5	2	28.6
8	6	4	2	33.3
> 8	**8**	**2**	**6**	**75**

Tzouvelekis et al CMR 2012; 25: 682-707

"Tell me...what IS in the pipeline?"

Νεότερα Φάρμακα με Δράση έναντι Πολυανθεκτικών Gram-αρνητικών



Markogiannakis et al. Future Microbiology 2013

Avibactam

- Νέος μη β-λακταμικός αναστολέας, χωρίς ενδογενή αντιμικροβιακή δράση
- Έχει δράση έναντι κλάσης A και C κατά Ambler β-λακταμάσες (ESBL,AmpC, KPC)
- Δεν είναι δραστική έναντι κλάσης B MBLs.
- Δεν είναι επαγωγέας β-λακταμασών

Συνδυασμοί Αναστολέων β-λακταμασών

- Ceftazidime/Avibactam (Cazavi)
- Aztreonam/Avibactam
- Imipenem/MK7655

Επίδραση του Συνδυασμού Ceftazidime/Avibactam στην MIC της Ceftazidime σε Στελέχη *K. pneumoniae*

Β-λακταμάση	Ceftazidime MIC	Ceftazidime/Avibactam MIC	Χ Ελάττωση
CTXM-15	>128	1	>128
SHV-5	64	0.5	128
KPC	>128	1	>128
VIM	256	256	1
AmpC	256	0.5	512

Μελέτες Φάσης ΙΙ με Ceftazidime/Avibactam (CAZAVI)

Είδος λοίμωξης	Αρ. Ασθενών	Δοσολογικό σχήμα	Μικροβιολογική ανταπόκριση	Κλινική ανταπόκριση
Επιπλεγμένες ουρολοιμώξεις	64	CAZ/AVB 500/125 mg q 8 h vs MP 1g q 8 h	93.4%	93.4%
Επιπλεγμένες ενδοκοιλιακες λοιμώξεις	144	CAZ/AVB + metro 2/0.5 +0.5g q 8 h vs MP 1g q 8 h	91.2%	91.2%

Δραστικότηα Aztreonam και Aztreonam/Avibactam έναντι διαφόρων Gram-αρνητικών.

- Ο συνδυασμός ATM-AVI είναι δραστικός έναντι Εντεροβακτηριακών που παράγουν MBL ανεξαρτήτως του είδους του μικροβίου και τον τύπο της MBL.

- Ενισχύει τη δράση της ATM και είναι δραστικός στο 94.1% των Εντεροβακτηριακών που παράγουν MBL ενώ η ATM στο 27.9%.

- Ο συνδυασμός ATM-AVI δεν ενισχύει τη δράση της ATM έναντι στελεχών Psp και Asp και αναεροβίων.

M CASTANHEIRA ECCMID 2013, Poster 1615

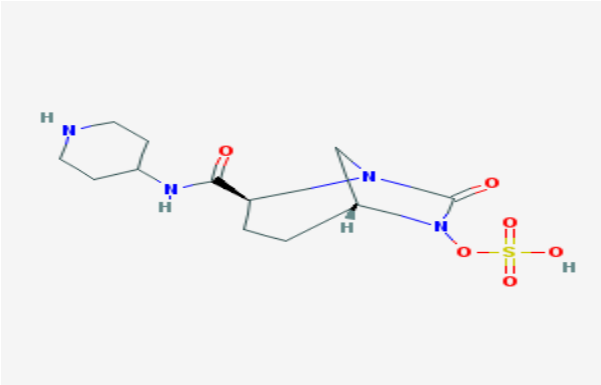
Δραστικότηα Aztreonam και Aztreonam/Avibactam έναντι διαφόρων Gram-αρνητικών.

M CASTANHEIRA ECCMID 2013, Poster 1615

	MIC50	
Είδος μικροβίου	**Aztreonam**	**Aztreonam/Avibactam**
Enterobacteriaceae	>64	<0.5
Pseudomonas	16	16
Acinetobacter	32	32

ΚΑΡΒΑΠΕΝΕΜΕΣ/ΑΝΑΣΤΟΛΕΙΣ

- Ιμιπενέμη+MK-7655:

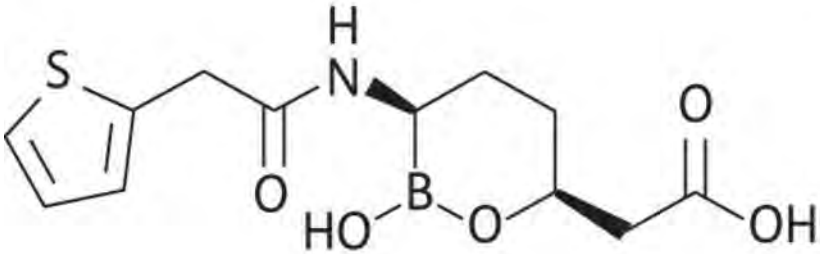


- Αναστολέας κλάσης A και C καρβαπενεμασών
- Έχει δράση και έναντι αναεροβίων

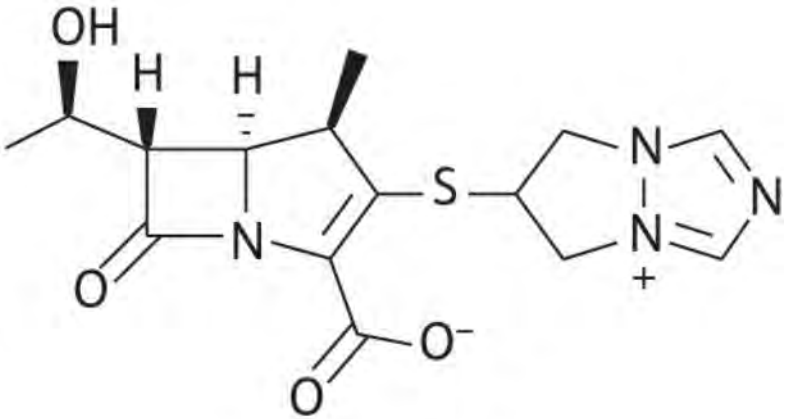
Μελέτες Imipenem/MK7655

- Μελέτη φαρμακοκινητικής (μία δόση)
- Επιπλεγμένες ουρολοιμώξεις
  - IM/MK7655 0.5/0.125g q 6h vs IM 0.5g q 6h
- Επιπλεγμένες ενδοκοιλιακές λοιμώξεις
  - IM/MK7655 0.5/0.125g ή 0.250g q 6h vs IM 0.5g q 6h

Structures of RPX7009 and biapenem.



RPX7009



Biapenem

Livermore D M , and Mushtaq S J. Antimicrob. Chemother. 2013;68:1825-1831

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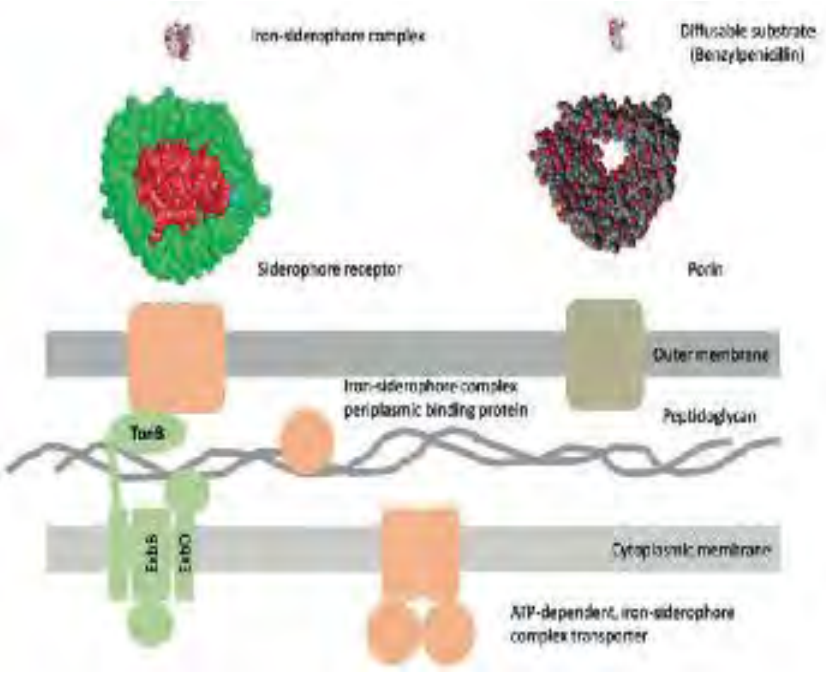
Journal of Antimicrobial Chemotherapy

Biapenem/RPX7009 (Carbavance)

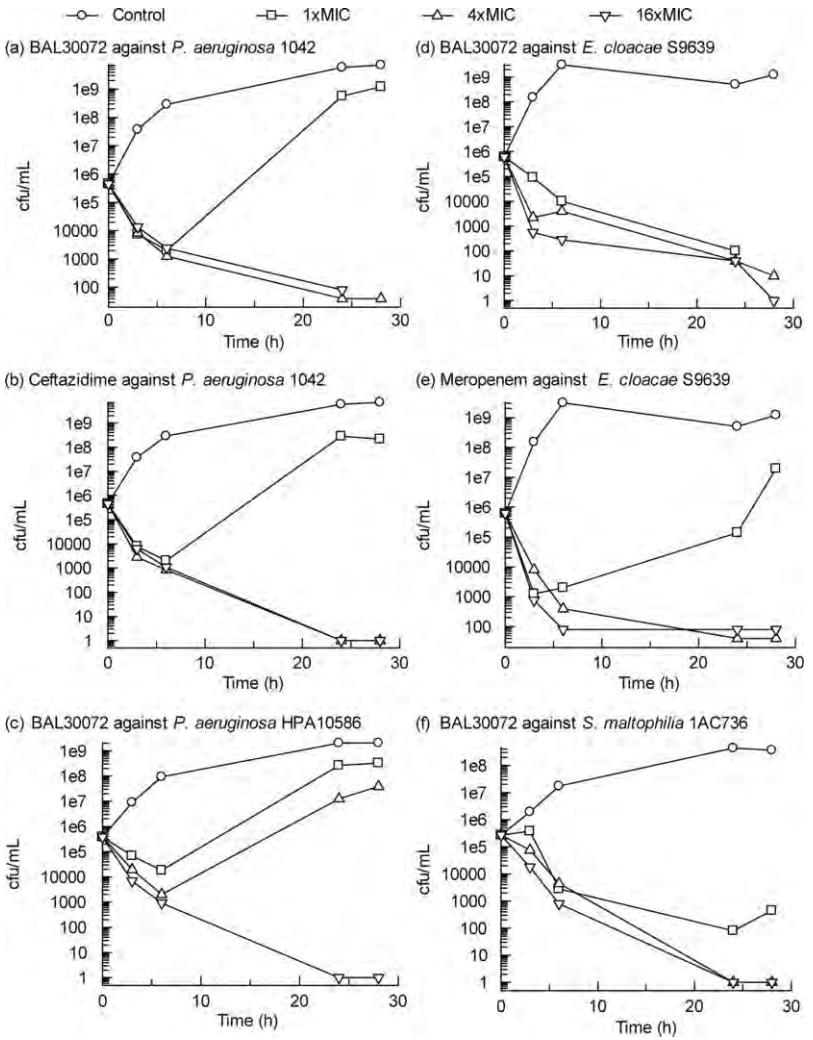
- Η biapenem επηρεάζεται λιγότερο από τις αντλίες εξόδου συγκριτικά με τις άλλες καρμπαπενέμες
- Η biapenem δεν υδρολύεται ικνοποιητικά από τις MBL και OXA-48, αλλά υδρολύεται από τις KPC καρμπαπενεμάσες
- Το RPX7009 δεν έχει αντιμικροβιακή δράση δεν αναστέλλει τις MBL και OXA αλλά αναστέλλει τις KPC καρμπαπενεμάσες

BAL30072

- Siderophore monocyclic β-lactam
- Χρησιμοποιεί το σύστημα μεταφοράς σιδήρου για την είσοδο στο κύτταρο
- Αναστέλλει περισσότερες από μία PBPs
- Δεν υδρολύεται από τις καρμπαπενεμάσες τύπου MBL, OXA-48, KPC, αλλά υδρολύεται από ESBL τύπου SHV
- Δεν έχουν αρχίσει κλινικές μελέτες, σε πειραματικές λοιμώξεις έχει συνδυασθεί με μεροπενέμη



Bactericidal action of BAL30072 and comparators against representative strains of P. aeruginosa, E. cloacae, and S. maltophilia.



Page M G P et al. Antimicrob. Agents Chemother. 2010;54:2291-2302

Antimicrobial Agents and Chemotherapy

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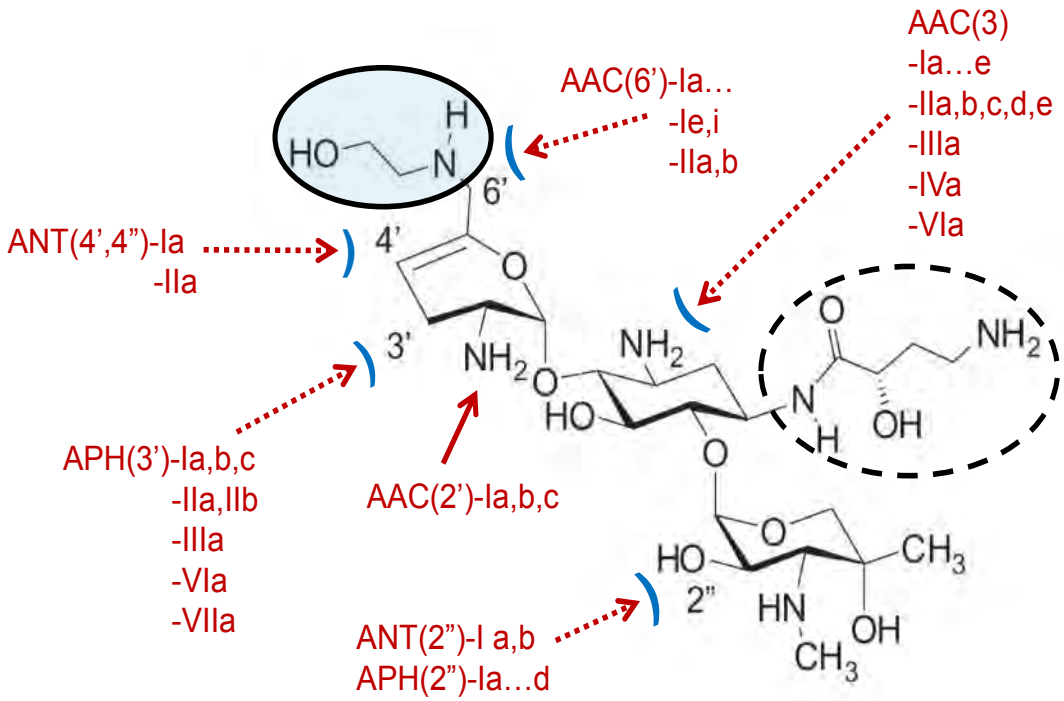
Plazomicin: Modification of Sisomicin Scaffold to Block Clinically Relevant Aminoglycoside Modifying Enzymes



- AMEs co-travel with other resistance mechanisms, including carbapenemases (eg., KPCs, MBLs)

Plazomicin retains potent activity vs. multi-drug resistant strains, including carbapenem and aminoglycoside-resistant strains

Plazomicin's Key Microbiological Advantage

Potent in vitro activity vs. carbapenemase producing Enterobacteriaceae

Compound	n	MIC 50 µg/ml	MIC 90 µg/ml	Range Min	Range Max
plazomicin	769	0.5	2	≤0.125	>128
gentamicin	769	4	128	≤0.25	>128
amikacin	768	32	64	≤0.5	>64
tigecycline	685	1	2	≤0.125	16
colistin/polymixin B	692	1	4	≤0.25	>16
ciprofloxacin	767	8	8	≤0.03	>128
ceftazidime	510	64	>128	≤0.25	>128
piperacillin/tazobactam	693	>128	>128	≤0.5	>128

Susceptible

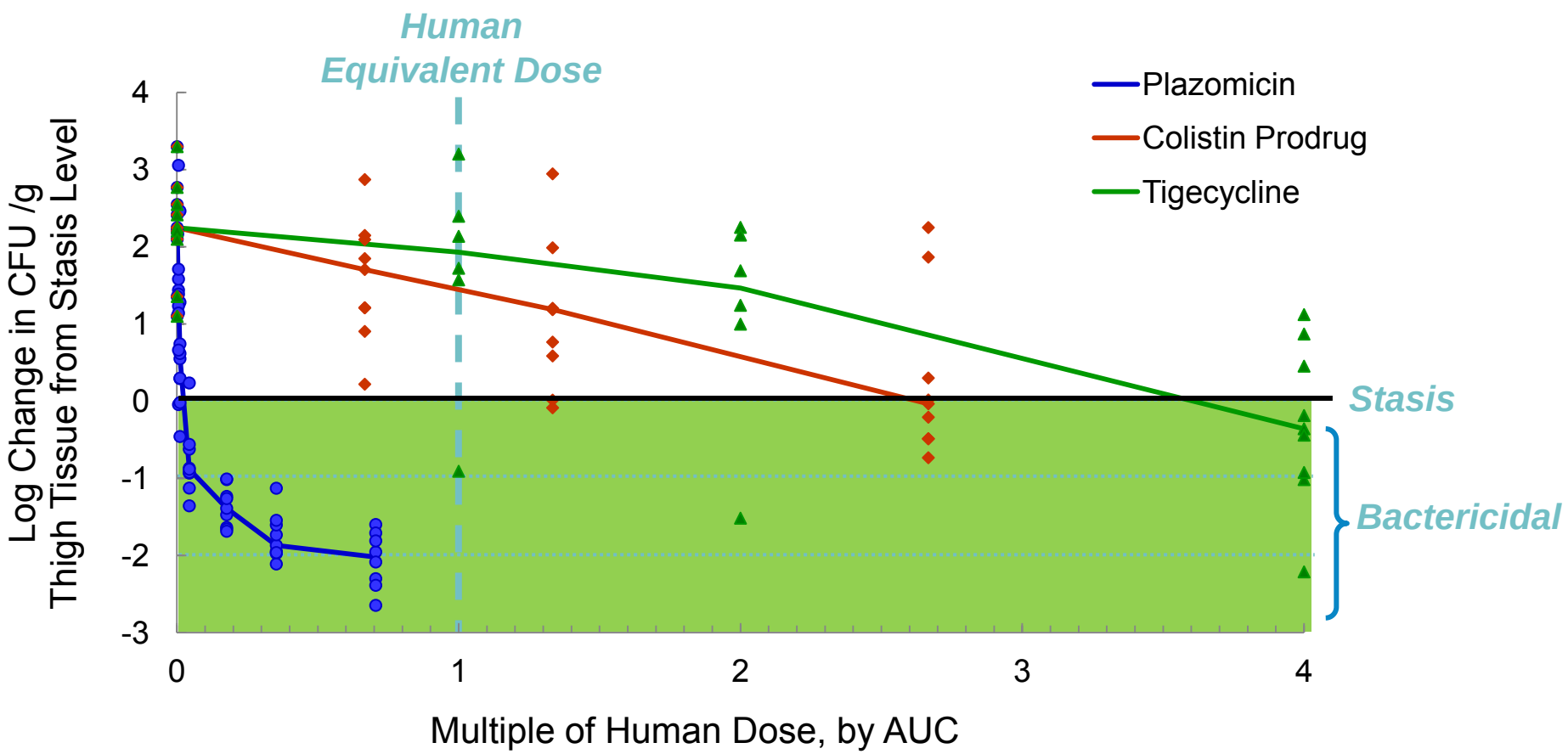
Intermediate

Resistant

CLSI 2012 breakpoint applied, except tigecycline and colistin (EUCAST breakpoint). CRE = MIC≥2 to any Type II carbapenem. Data includes clinical isolates from three studies: 1) J Chemother. 2012 Aug;24(4):191-4, 2) J Antimicrob Chemother. 2011 Jan;66(1):48-53, 3) J Antimicrob Chemother. 2010 Oct;65(10):2123-7

Plazomicin is Efficacious vs CRE in Mouse Model

Improved Efficacy Compared to Colistimethate Sodium and Tigecycline

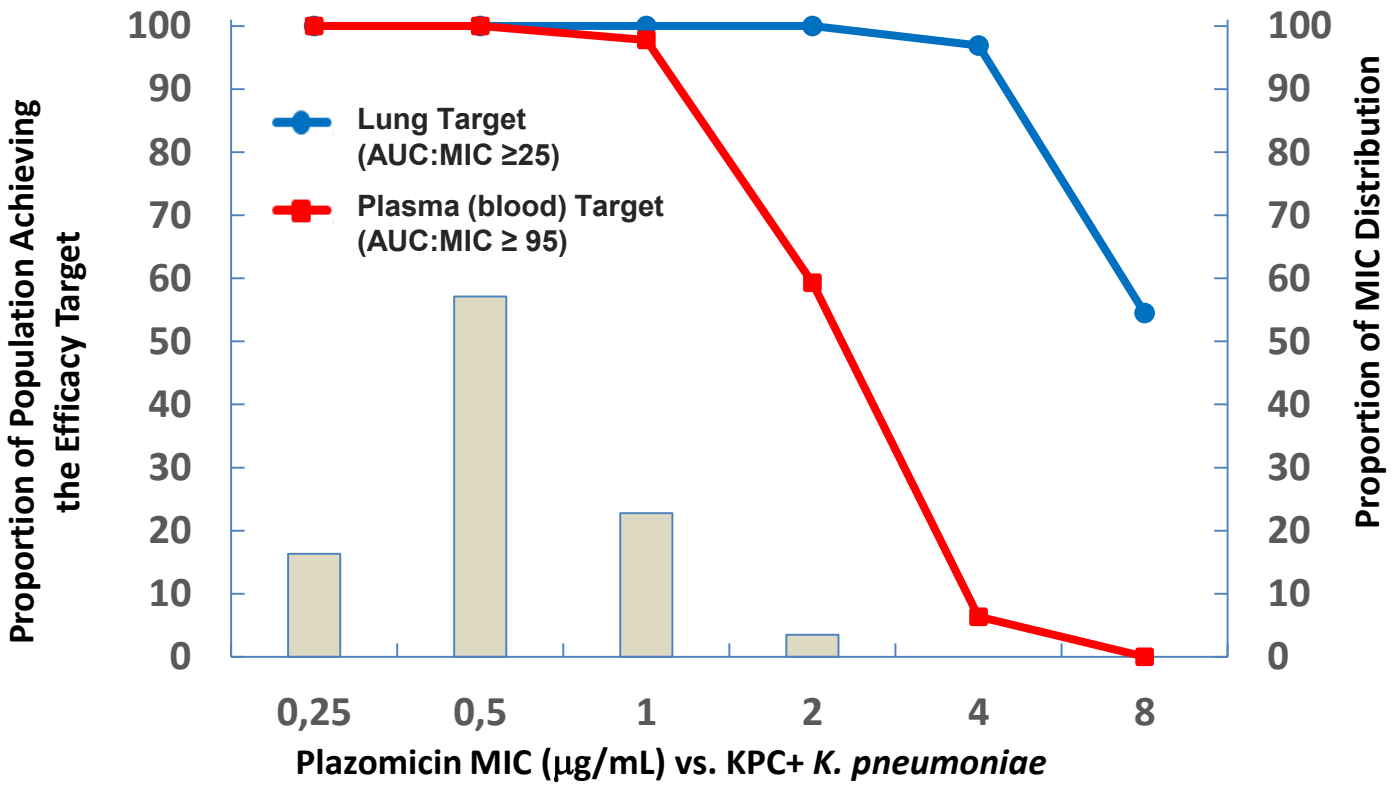


N=9 CRE clinical isolates

Source: Louie et al. Plazomicin demonstrates potent efficacy against carbapenem-resistant Enterobacteriaceae (CRE) in the neutropenic mouse thigh infection model. *ECCMID 2013*, Poster # LB 2961.

Projection of Plazomicin Clinical Efficacy

Clinical dose projected to effectively treat ≥98% of KPC+
K. pneumoniae *strains based on clinical PK and murine efficacy data*



Overall Proportion of KPC+ *K. pneumoniae* Covered		
	Plazomicin plasma AUC:MIC target of 95	Plazomicin ELF AUC:MIC target of 25
Plazomicin 15 mg/kg, KPC+ *Kpn* isolates (n=373)	98%	>99%

Summary of Plazomicin Clinical Safety Experience

Aminoglycoside Class Related Toxicities

Nephrotoxicity

- Phase 2: Mean serum creatinine values stable with minor elevations in a small number of patients

Ototoxicity

- Phase 1: mild, transient tinnitus (n=5)
- Phase 2: mild, permanent tinnitus (n=1)
  mild, transient vertigo (n=1)

Other Adverse Events

- Generally well tolerated
- Most common AEs were nausea, diarrhea, headache, hypo / paraesthesia & dizziness. These were typically mild and transient.
- Symptomatic hypotension reported in 1 patient in the Phase 2 study.
- Neutropenia reported in 1 subject in TQT study. Neutrophil count fell from a low pretreatment baseline count of 1010 to 940 cells / mm^3 on day 1.

Topline safety data as of 7/13/12

Plazomicin Phase 2 cUTI Trial

Similar efficacy to active comparator levofloxacin

Trial Design

- **Protocol:** Multi-national, randomized, double-blind study in complicated urinary tract infection and acute pyelonephritis (cUTI/AP)
- **Study Drugs:** Plazomicin (10 or 15 mg/kg) vs. levofloxacin (750 mg)
- **n:** 145

Primary Outcome*

Patient Population	Plazomicin	Levofloxacin
Modified intent-to-treat	n=63	n=29
(mITT)	58.7%	58.6%
95% CI	(45.6%, 71.0%)	(38.9%, 76.5%)
Microbiologically Evaluable	n=42	n=21
(ME)	88.1%	81.0%
95% CI	(74.4%, 96.0%)	(58.1%, 94.6%)

* Microbiological Eradication

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IDSA PUBLIC POLICY

10 × '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] Daniel K. Benjamin Jr,[3,4] John Bradley,[5,6] Robert J. Guidos,[7] Ronald N. Jones,[8,9] Barbara E. Murray,[10] Robert A. Bonomo,[11,12,13,14] and David Gilbert,[15,16] for the Infectious Diseases Society of America*

Συμπεράσματα

- Από τα προαναφερθέντα αντιμικροβιακά φάρμακα κανένα δεν έχει δράση έναντι όλων των πολυανθεκτικλων Gram-αρνητικών
- Κανένα νέο φάρμακο δεν φαίνεται να έχει αξιόπιστη δράση έναντι του *A. baumanii*
- Δεν αναμένεται να εγκριθούν και να κυκλοφορήσουν νορίτερα από 5 χρόνια

Prudent use of antibiotics

Enhanced infection control

Thanks for your attention