

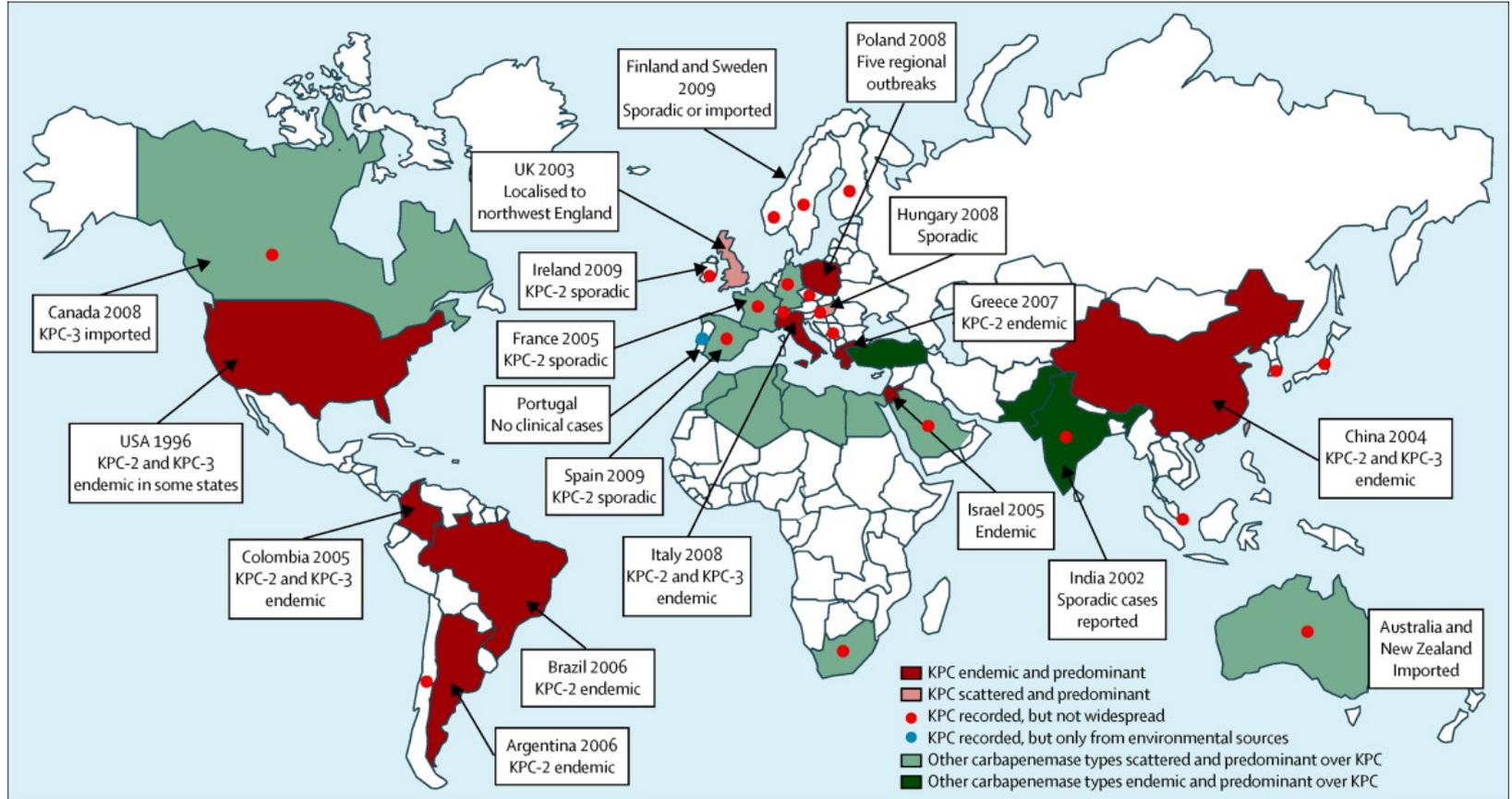
Treatment of Infections Caused by Carbapenemase - Producing Enterobacteriaceae

George L. Daikos, MD

University of Athens, Laiko General Hospital,
Athens, Greece

Goteborg, May 2016

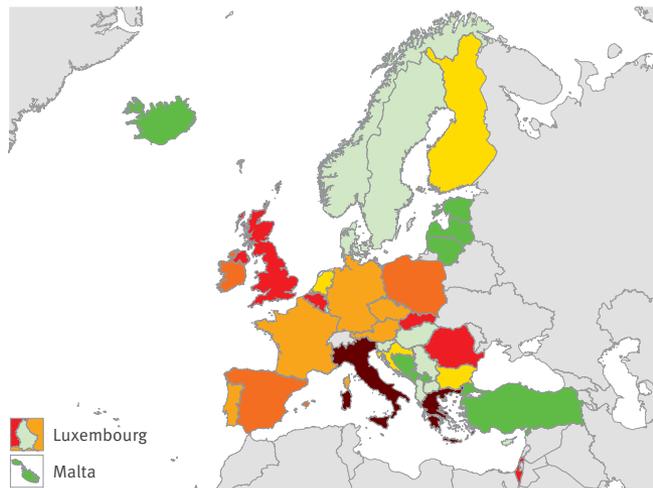
Global expansion of *Klebsiella pneumoniae* carbapenemases



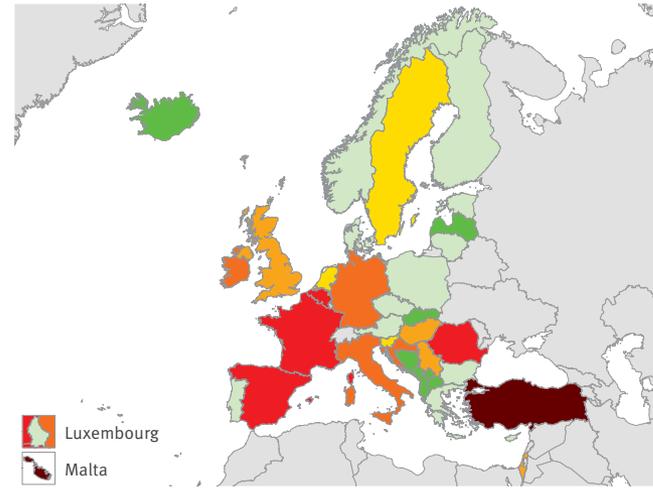
L Silvia Munoz-Price , Laurent Poirel , Robert A Bonomo , Mitchell J Schwaber , George L Daikos , Martin Cormican ...

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

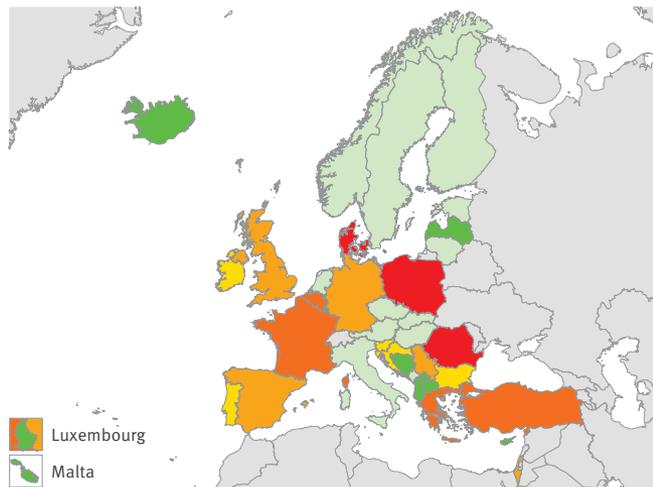
A. *Klebsiella pneumoniae* carbapenemase (KPC)



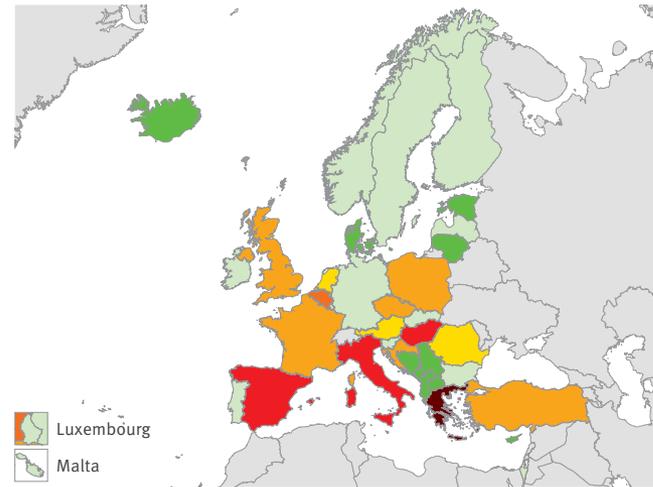
B. Oxacillinase-48 (OXA-48)



C. New Delhi metallo-beta-lactamase (NDM)



D. Verona integron-encoded metallo-beta-lactamase (VIM)



Epidemiological stages, 2014-2015

- Countries not participating
- No case reported (Stage 0)
- Sporadic occurrence (Stage 1)
- Single hospital outbreak (Stage 2a)
- Sporadic hospital outbreaks (Stage 2b)
- Regional spread (Stage 3)
- Inter-regional spread (Stage 4)
- Endemic situation (Stage 5)

Current Trends in Epidemiology of CPEs

Hospital setting

- Predominant bacterial host
 - *K. pneumoniae*
- Predominant enzymes
 - KPC
 - VIM
 - NDM
 - OXA-48

Community setting

- Predominant bacterial host
 - *E. coli*
- Predominant enzymes
 - NDM
 - OXA-48

Carbapenemase Producing Enterobacteriaceae (CPE). A major Public Health Threat

- High potential for spread
- Cause serious infections associated with increased mortality
- Limited treatment options

Therapeutic Options for CPE Infections

MBLs

(NDM, VIM, IMP)

- Aztreonam?

Carbapenemases

(VIM, KPC, NDM,
OXA-48)

- Colistin
- Aminoglycosides
- Tigecycline
- Fosfomycin
- Carbapenems?

Class D enzymes

(OXA-48)

- Cephalosporins?

Non-Susceptible KPC-Kp by Time Period

(Italian Study Group on Resistant Infections)

	2010	2013
Gentamicin	6%	21%
Colistin	11%	27%
Tigecycline	9%	25%

Tumbarello M J Antimicrob Chemother 2015; 70: 2133-43

EUCAST breakpoints: Gentamicin S ≤ 2mg/L, Colistin S ≤ 2mg/L, Tigecycline S ≤ 1mg/L

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco^{1,2}, T Giani^{2,3}, M Raffone^{1,4}, F Arena³, A Garcia-Fernandez¹, S Pollini³, Network EuSCAPE-Italy⁵, H Grundmann⁶, A Pantosti (annalisa.pantosti@iss.it)¹, G M Rossolini^{3,7,8}

Antimicrobial agent	No. of KPC-KP (% non-susceptible)
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Colistin	76 (43)
-----------------	----------------

Gentamicin	29 (16)
------------	---------

Tigecycline	11 (6)
-------------	--------

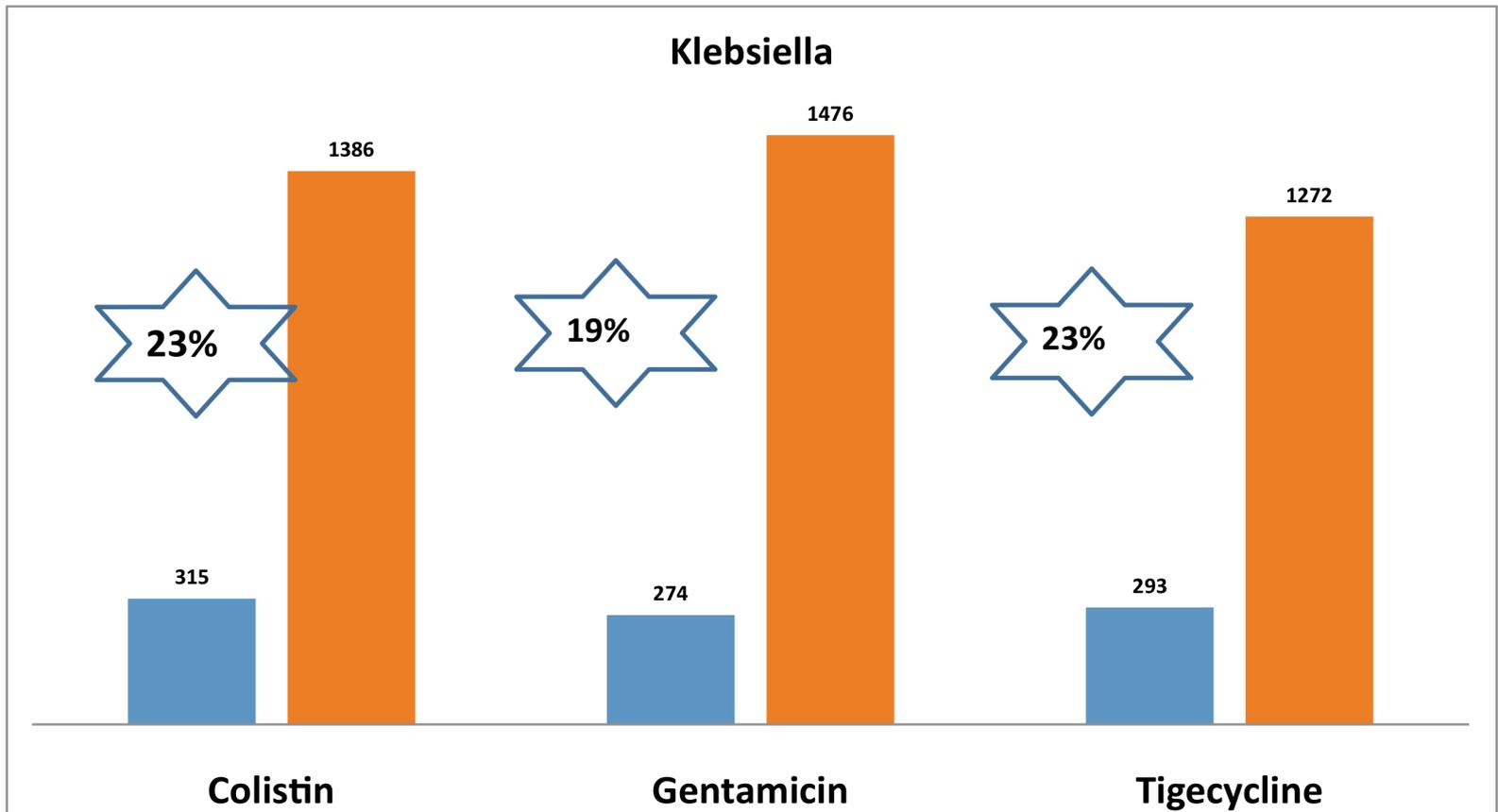


The New Superbug Gene (MCR-1) Has Reached at least 19 Countries



Graphic: NRDC, all-free-download.com, Source: The Lancet, Telegraph, Toronto Star, CIDRAP

Resistance Profile of CPKP



7477 Episodes of Infections Caused by Carbapenem Resistant Gram-negative Bacteria

Department

- ICU 51.7%
- Medicine 31.7%
- Surgery 16.6%

Source of Infection

- Pneumonia 34.0%
- Bacteremia 31.3%
- UTIs 22.8%
- SSI 11.9%

Hellenic Center for Disease Control and Prevention (KEELPNO)

Combination therapy for carbapenem-resistant Gram-negative bacteria

Mical Paul^{1*}, Yehuda Carmeli², Emanuele Durante-Mangoni³, Johan W. Mouton⁴, Evelina Tacconelli⁵,
Ursula Theuretzbacher⁶, Cristina Mussini⁷ and Leonard Leibovici^{8,9}

- No randomized control trial
- Observational studies
 - Small study size, selection bias
 - Different outcome definitions
 - Different definitions of combination therapy
 - Different breakpoints (EUCAST, CLSI, old, new)
 - Many treatment regimens

There is no evidence-based support for most combination therapies against CR-GNB

Randomized Control Trials in Progress

- Europe (AIDA, NCT01732250)
<http://clinicaltrials.gov/show/NCT01732250>)
– Colistin vs Colistin plus meropenem
- USA (NCT01597973)
<http://clinicaltrials.gov/show/NCT01597973>)
– Colistin vs Colistin plus meropenem

Patient 1

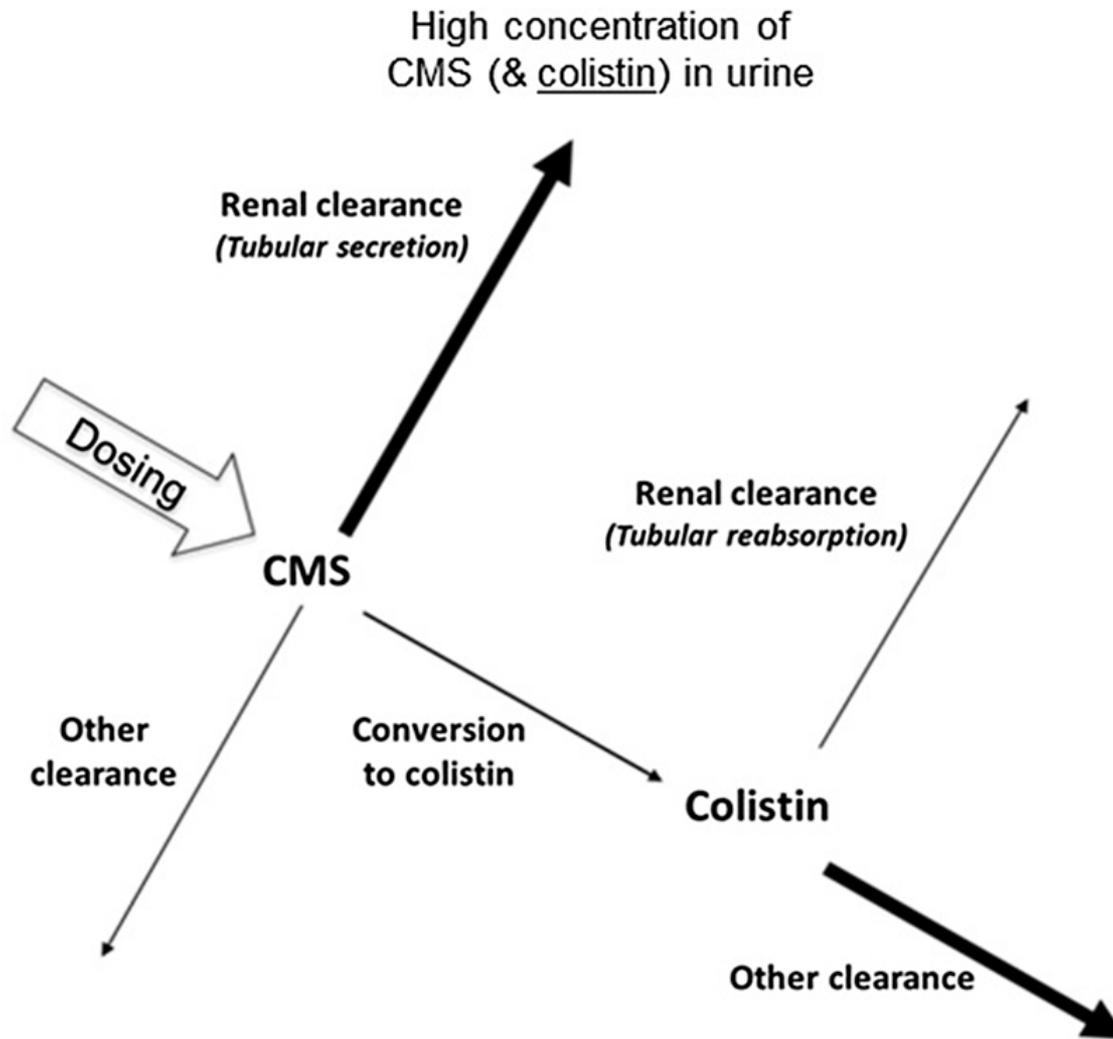
- 70 yo male complaining of urgency, pain during urination and fever up to 38° C. The symptoms started after removal of a foley catheter that was placed in his recent hospitalization for TURP.
- Empirical therapy with Pip/tazo was started

Patient 1 (*cont'd*)

- Blood and urine culture grew KPC Kp susceptible to **colistin** (MIC=0.5mg/L), **tigecycline** (MIC=1mg/L), **gentamicin** (MIC=2mg/L) and **fosfomycin** (MIC=16mg/L); and resistant to meropenem, MIC >256 mg/L

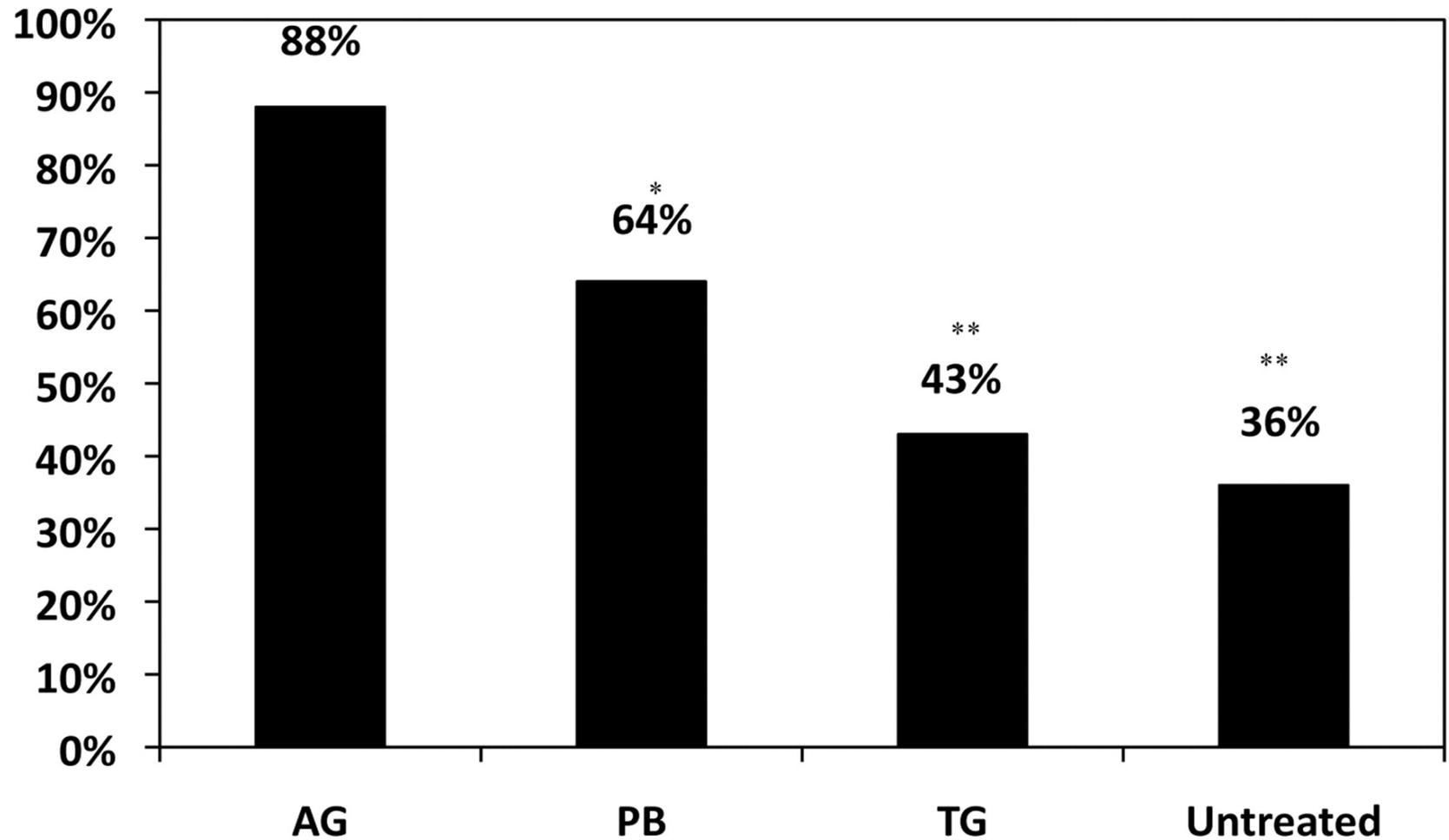
How would you treat this patient ?

1. Fosfomycin
2. Tigecycline
3. Gentamicin
4. Colistin



Li J et al. Lancet Infect Dis 2006; 6: 589–601

Microbiologic clearance rates of carbapenem-R-Kp by the antimicrobial treatment cohort.



Satlin M J et al. *Antimicrob. Agents Chemother.*
2011;55:5893-5899

Antimicrobial Agents and Chemotherapy

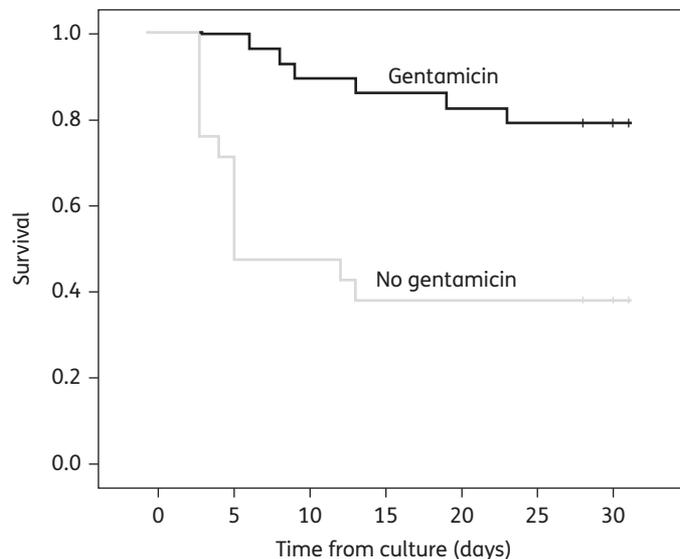
Treatment Regimen analysis Adjusted for Critical illness and presence of UTI

Active agent	Adjusted OR	95% CI	P
Aminoglycoside	0.34	0.15-0.73	0.005
Tigecycline	2.3	1.03-5.3	0.04

Patients treated with aminoglycosides were less likely to fail therapy, whereas patients treated with tigecycline were more likely to fail therapy

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Marcelino Gonzalez-Padilla^{1†}, Julián Torre-Cisneros^{1,2*†}, Francisco Rivera-Espinar³, Antonio Pontes-Moreno³, Lorena López-Cerero^{2,4,5}, Alvaro Pascual^{2,4,5}, Clara Natera¹, Marina Rodríguez³, Inmaculada Salcedo⁶, Fernando Rodríguez-López^{2,7}, Antonio Rivero¹ and Jesús Rodríguez-Baño^{2,4,5}



- 50 pts with KPC infections; 29 received gentamicin as monotherapy or combination
- Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9, $P=0.001$)

Aminoglycosides for Treatment of Bacteremia Due to Carbapenem-Resistant *Klebsiella pneumoniae*

Ryan K. Shields,^{a,b} Cornelius J. Clancy,^{a,b,c} Ellen G. Press,^a M. Hong Nguyen^{a,b}

Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA^a; XDR Pathogen Laboratory, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA^b; VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA^c

Aminoglycoside treatment of carbapenem-resistant (CR) *Klebsiella pneumoniae* bacteremia was associated with a 70% rate (23/33) of 30-day survival. Successful treatment was associated with sources of bacteremia amenable to reliable aminoglycoside pharmacokinetics ($P = 0.037$), acute physiology and chronic health evaluation II (APACHE II) scores of <20 ($P = 0.16$), and nonfatal underlying diseases ($P = 0.015$). Success rates were 78% and 100% if ≥ 2 and all 3 factors were present, respectively. Clinicians may consider the use of aminoglycosides against CR *K. pneumoniae* bacteremia if strains are susceptible and the sources of infection are amenable to reliable pharmacokinetics.

AAC 2016; 60: 3187

Expected Gentamicin Peak/MIC and AUC/MIC Values for Organisms with High MICs *(Craig W ESCMID Lecture Library)*

PK/PD Index	MIC	5mg/kg	7mg/kg	10mg/kg
Peak/MIC	1	14.7	20.5	29.3
AUC/MIC	1	55	77	110
	<u>EUCAST</u>			
Peak/MIC	2	7.3	10.2	14.7
AUC/MIC	2	28	38	55
	<u>CLSI</u>			
Peak/MIC	4	3.7	5.1	7.3
AUC/MIC	4	14	17	2.8

Fosfomycin susceptibility of Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs

Resistance profile	No. of isolates, susceptible/total, (%)
ESBL-producing	3569/3911 (91.3%)
Any advanced antimicrobial resistance profile	3891/4478 (86.9%)
OXA-48, VIM	182/379 (48%)

Falagas et al. Lancet Infect Dis 2010; 10: 43–50

Ote J et al. Antimicrob Ag Chemother 2015; 59:3406

Fosfomycin trometamol in a single dose vs seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women

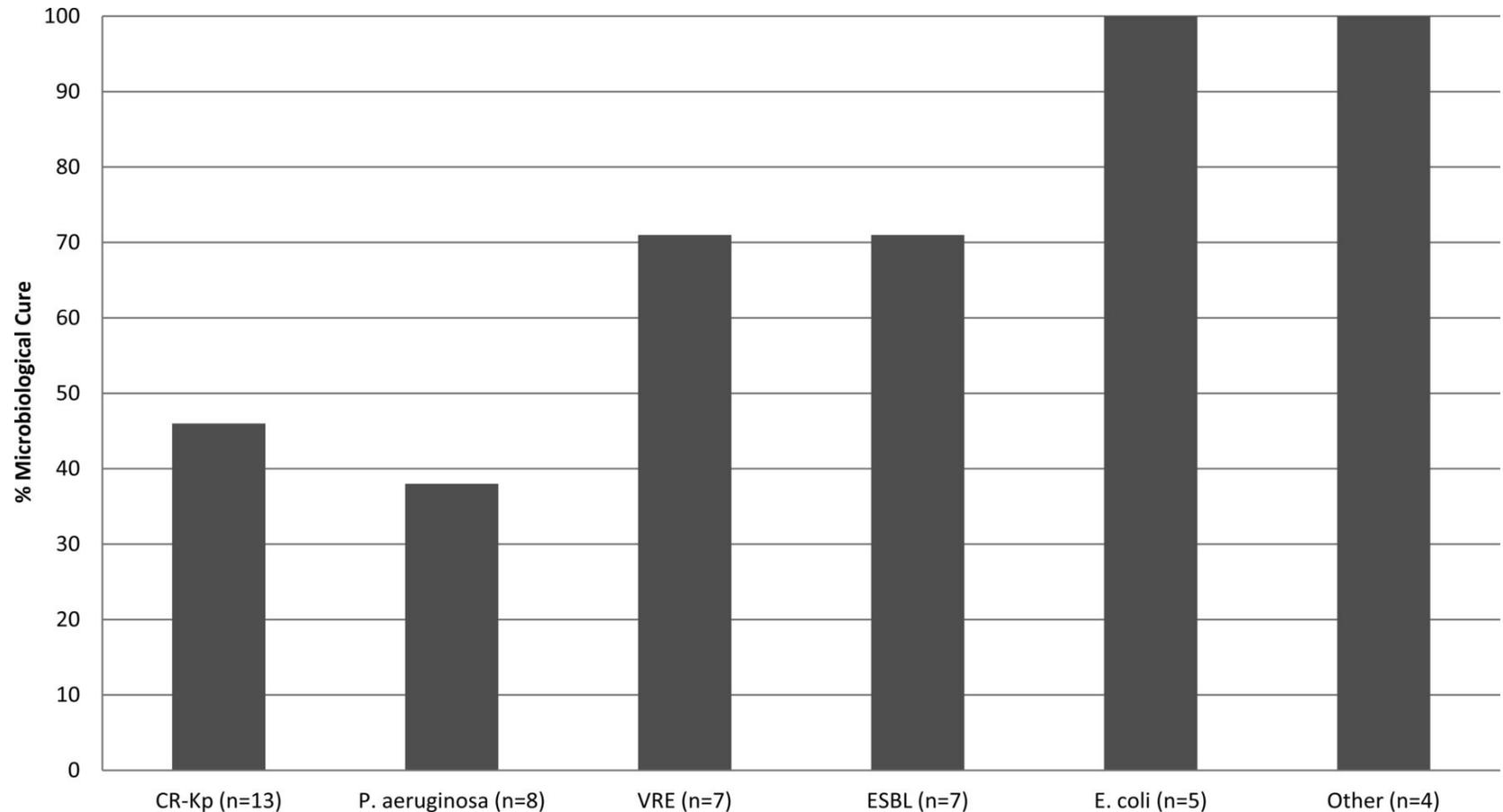
- Double blind randomized controlled trial in 31 general practices in the Netherlands
 - 231 women with lower UTI
 - Fosfomycin 3 g PO compared with nitrofurantoin 50 mg qid x 7 days
 - Clinical cure: Fosfomycin, 85%; Nitrofurantoin, 82%
 - Side effects: NS difference

Efficacy of fosfomycin trometamol for lower UTIs

- Double-blind RCT
- 1190 women with lower UTI

Outcome	Fosfomycin (N=771)	Co-trimoxazole (N=197)	Ciprofloxacin (N=222)
Microbiological eradication	82%	93%	93%
Clinical success	70%	94%	96%

Experience with Fosfomycin for Treatment of Urinary Tract Infections Due to Multidrug-Resistant Organisms



Elizabeth A. Neuner et al. *Antimicrob. Agents Chemother.*
2012;56:5744-5748

Antimicrobial Agents and Chemotherapy

**No experience with fosfomycin
monotherapy in bacteremic UTIs**

BMJ Open Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β -lactamase-producing *Escherichia coli* (FOREST): study protocol for an investigator-driven randomised controlled trial

Clara Rosso-Fernández,^{1,2} Jesús Sojo-Dorado,³ Angel Barriga,¹
Lucía Lavín-Alconero,¹ Zaira Palacios,^{3,4} Inmaculada López-Hernández,³
Vicente Merino,⁵ Manuel Camean,⁵ Alvaro Pascual,^{3,6} Jesús Rodríguez-Baño,^{3,7}
and the FOREST Study Group

Fosfomycin

- Elimination half life: 3.7h
- *C_{max}*
 - 4g IV: 105-120 mg/L
 - 8g IV: 240-440 mg/L
- Protein binding: negligible
- Excretion: primarily urine, unchanged
- Distribution favorable: soft tissue, lung, bone, CSF, heart, prostate
- PK/PD
 - Time dependent
 - PAE: 3.4-4.7 h for Enterobacteriaceae

Frossard M, et al. Antimicrob Agents Chemother 2000;44:2728-32

Roussos N et al. Int J Antimicrob Agents 2009;34:506-15

Sauermann R, et al. Antimicrob Agents Chemother 2005;49:4448-54



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 Karaikos^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/PDR infections caused by *K. pneumoniae* or *P. aeruginosa***
- **25 BSIs, 14 VAP, 11 other**
- **Fosfomycin in combination with CMS, Tigecycline, Meropenem, Gentamicin, PIP/Tazo**

Outcomes of 48 Patients with Serious Infections Caused by XDR/PDR Gram(-)

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

Fosfomycin How to Use

- For systemic infections 6 g IV q 6 h
- Always in combination with another active agent
- Dosage adjustment is required in renal failure

Dosing Fosfomycin According to 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*



Fosfomicin

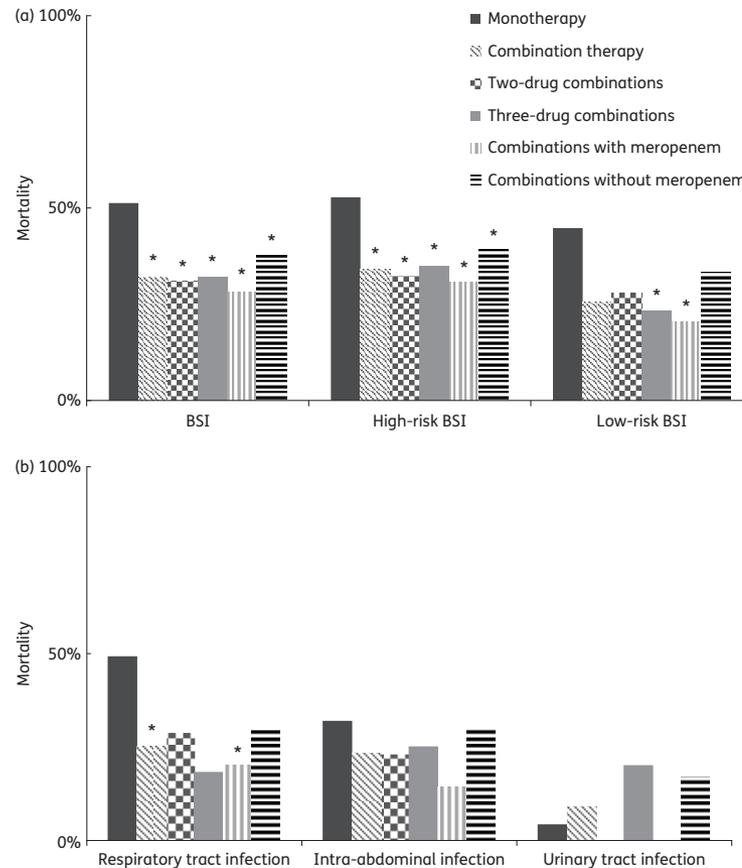
Matthew E. Falagas,^{a,b,c} Evidiki K. Vouloumanou,^a George Samonis,^d Konstantinos Z. Vardakas^{a,b}

Alfa Institute of Biomedical Sciences, Athens, Greece^a; Department of Internal Medicine-Infectious Diseases, Iaso General Hospital, Iaso Group, Athens, Greece^b;
Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA^c; Department of Internal Medicine, University of Crete School of Medicine,
Heraklion, Greece^d

What is the best treatment for patient 1

1. Monotherapy
2. Combination therapy
3. I do not know

Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs or non-bacteraemic infections



Tumbarello M et al JAC April 21 2015

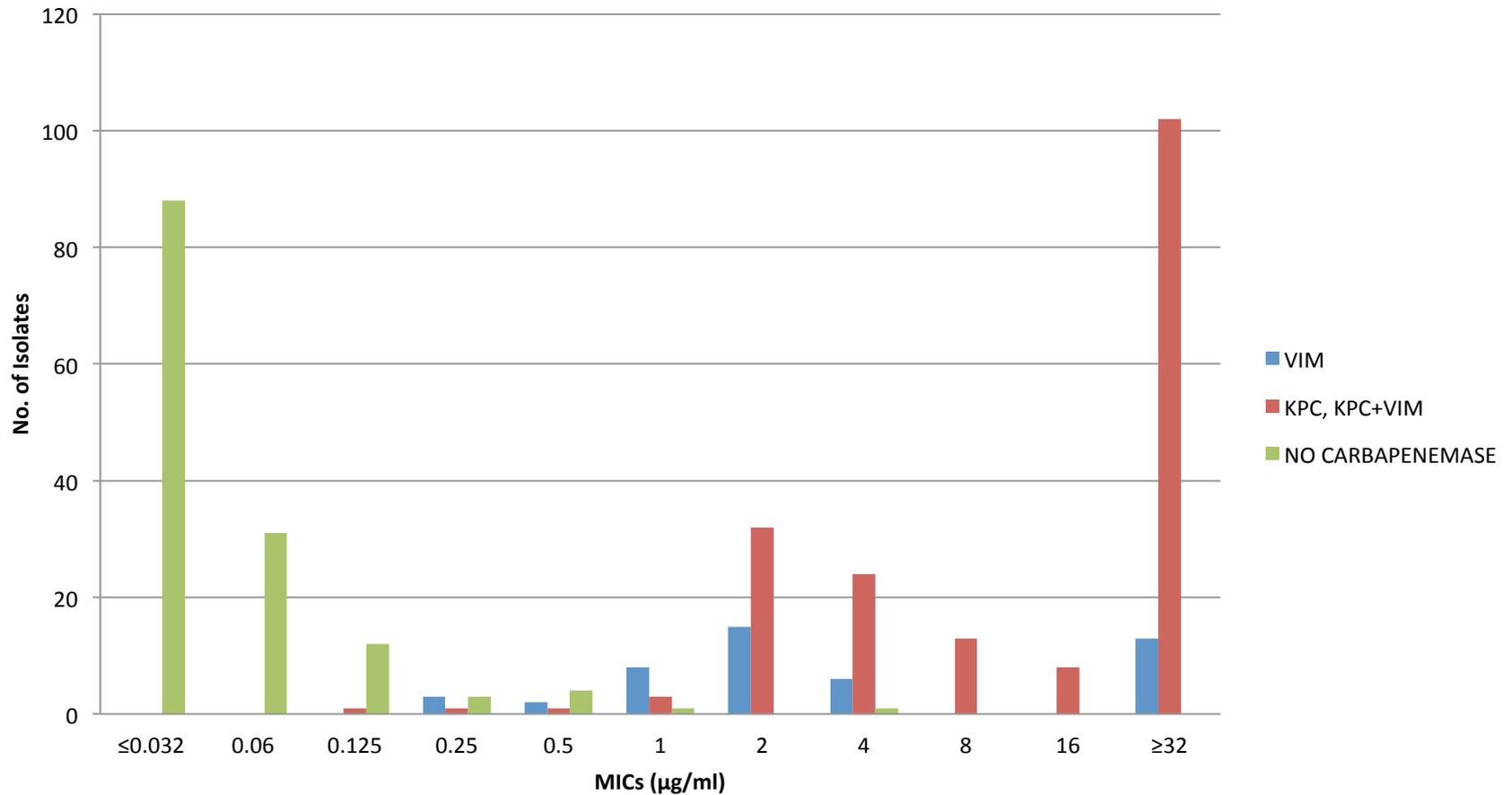
Questions

- Can we use carbapenems in the treatment of CPE infections?
- Is combination therapy superior to monotherapy?
- If so,
 - For all patients and all type of infections?

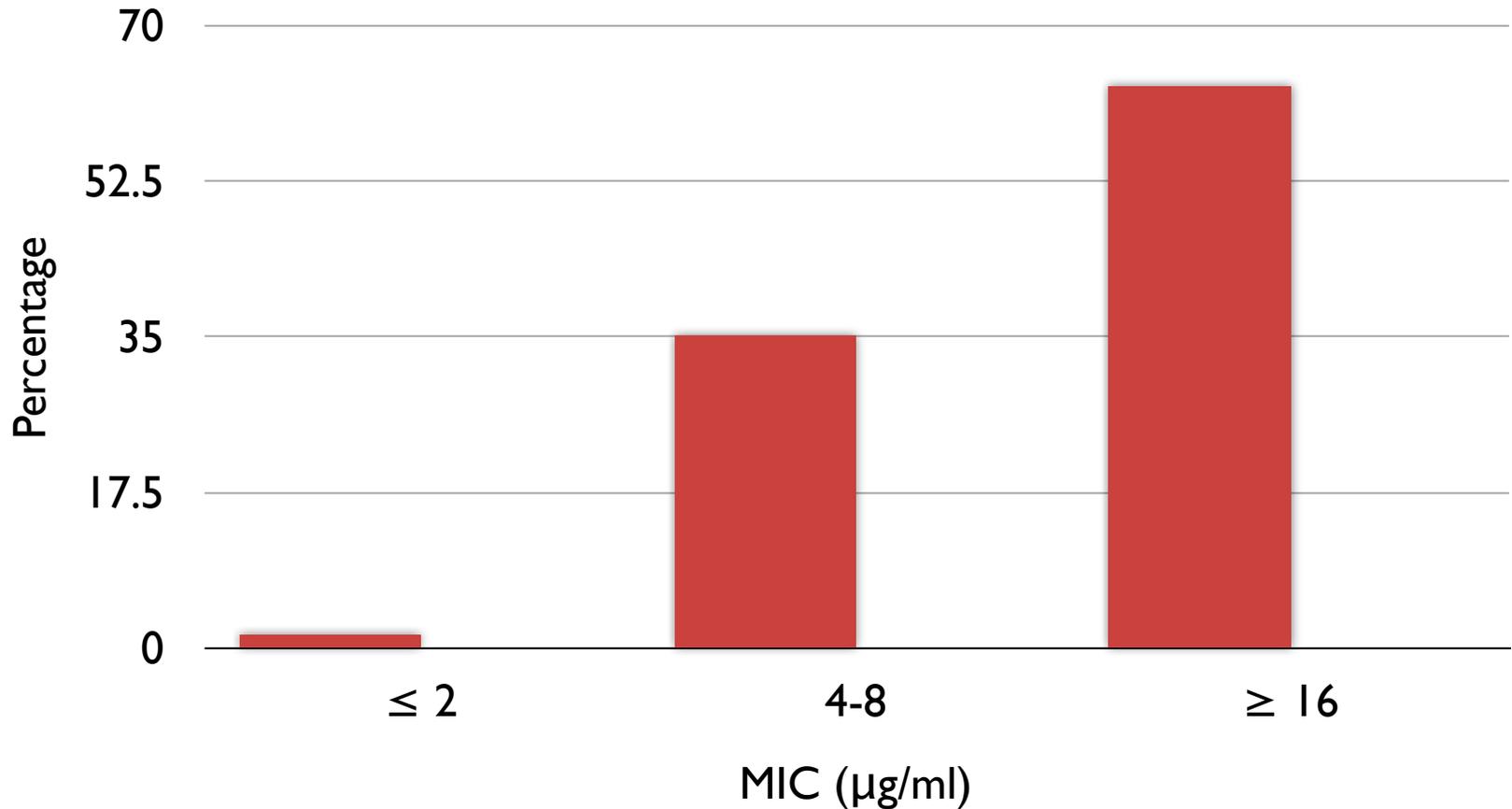
Can we use carbapenems against carbapenemase-producing organisms ?

- Experimental data
- PK/PD studies
- Human data

Distribution of Meropenem MICs for 372 Consecutive *K. pneumoniae* Blood Isolates

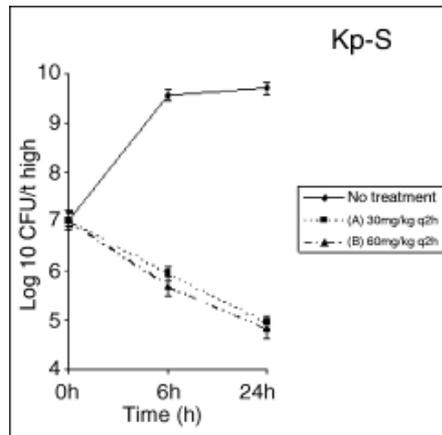


Distribution of Meropenem MICs of 661 KPC-Kp *(Italian Study Group on Resistant Infections)*

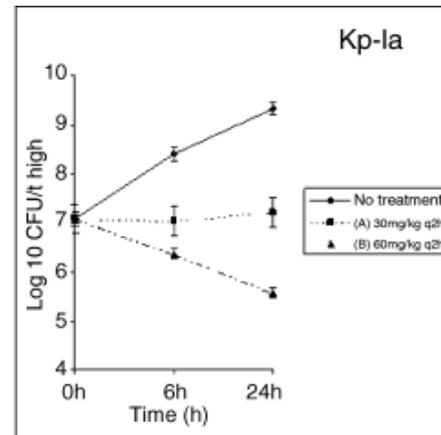


Activity of imipenem against VIM-1 metallo- β -lactamase-producing *Klebsiella pneumoniae* in the murine thigh infection model

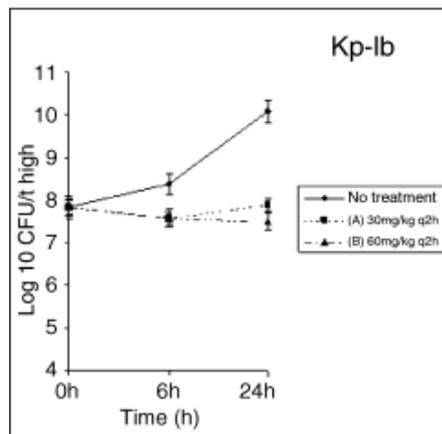
VIM-negative
MIC=0.12mg/L



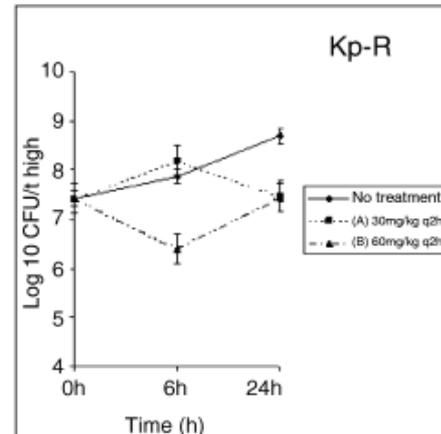
VIM-positive
MIC=2mg/L



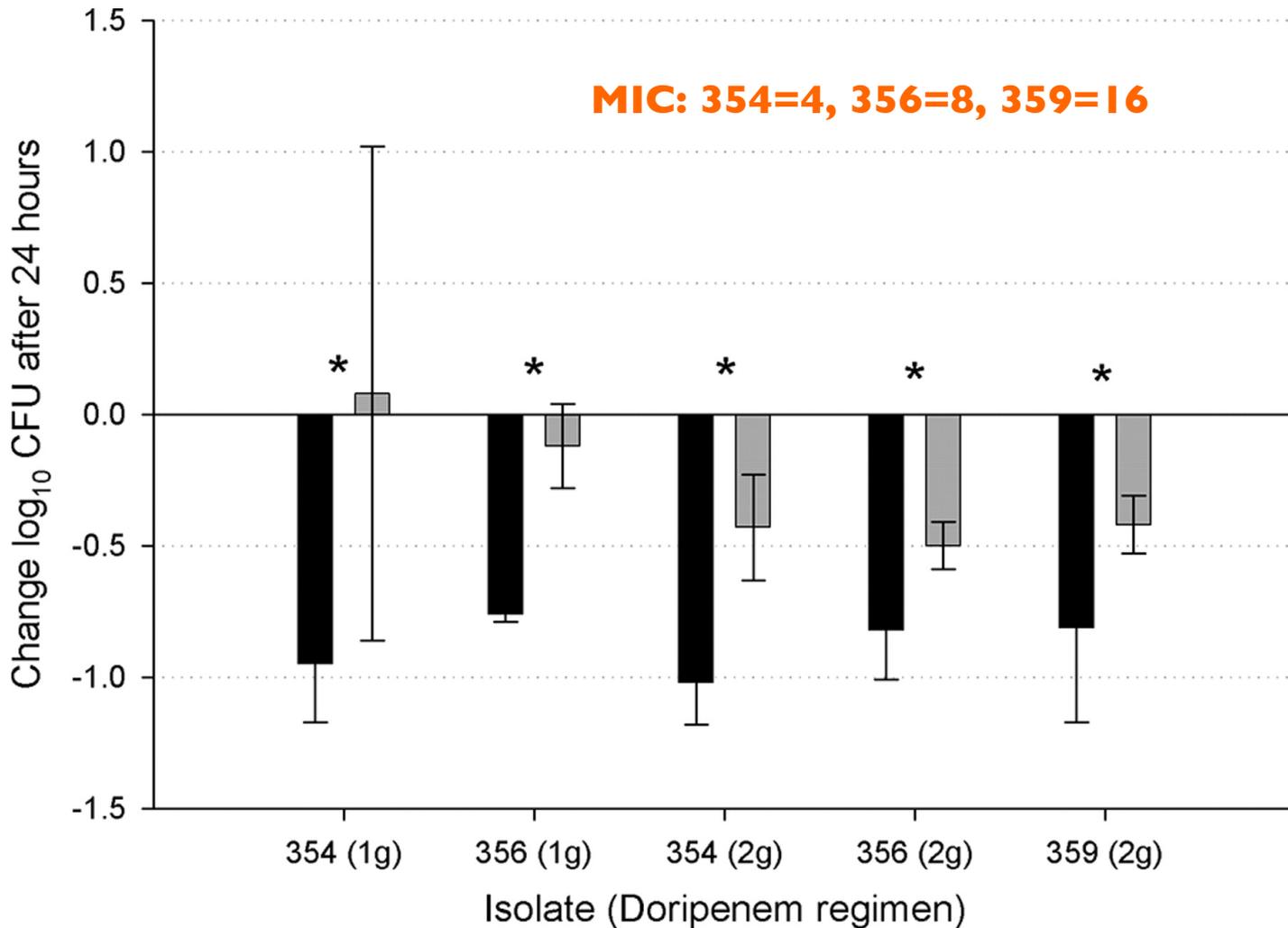
VIM-positive
MIC=4mg/L



VIM-positive
MIC=32mg/L



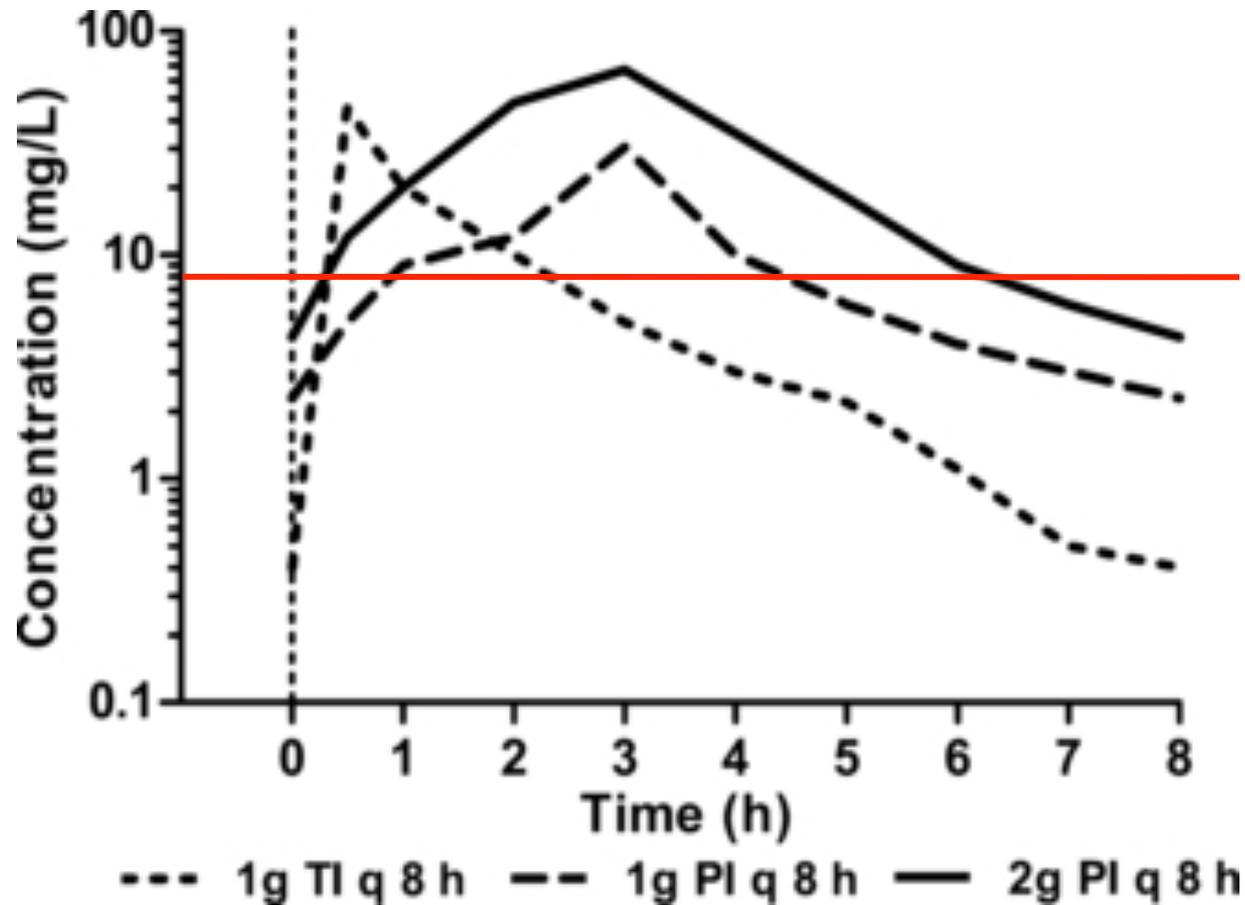
Comparison of the efficacies of two different doses of doripenem against carbapenemase-producing *K. pneumoniae* isolates in immunocompromised and immunocompetent animals.



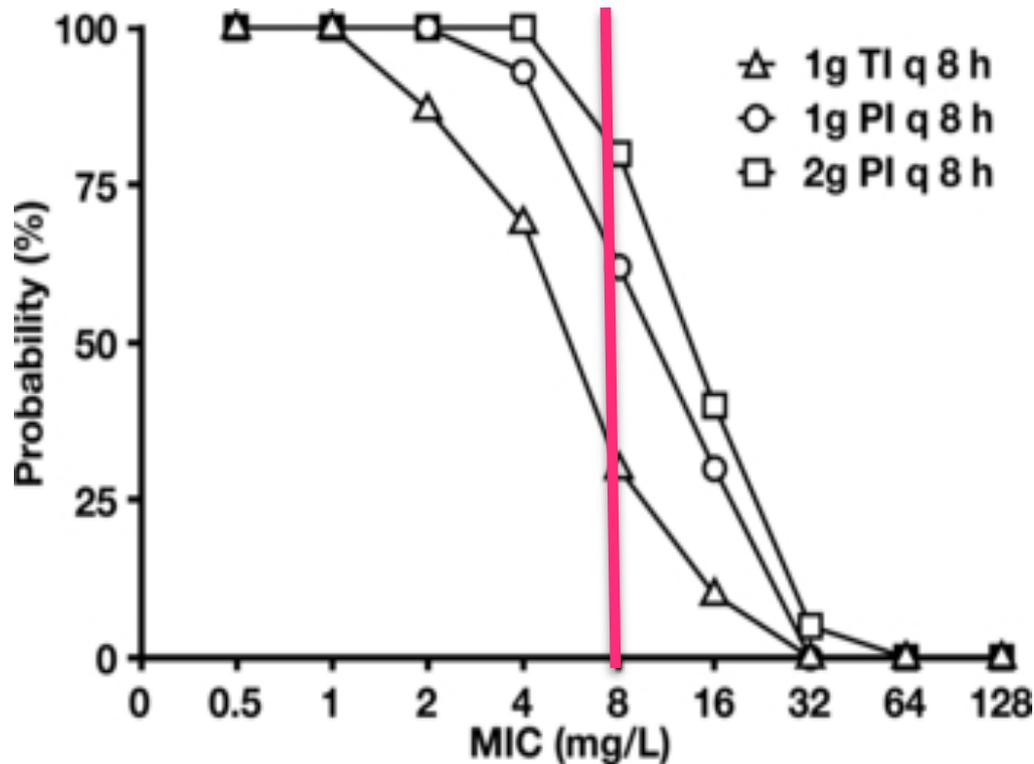
Bulik C C , Nicolau D P Antimicrob. Agents Chemother.
2010;54:4112-4115

Antimicrobial Agents and Chemotherapy

Pharmacokinetics of three different dosing regimens of meropenem



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



TA 50%T>MIC for meropenem:

✓ 30 min infusion of 1g, q8 h
For MIC of 4 mg/l → %69%

✓ 3 h infusion of 2g, q8 h
- For MIC of 4 mg/l → %100%
- For MIC of 8 mg/l → %85%

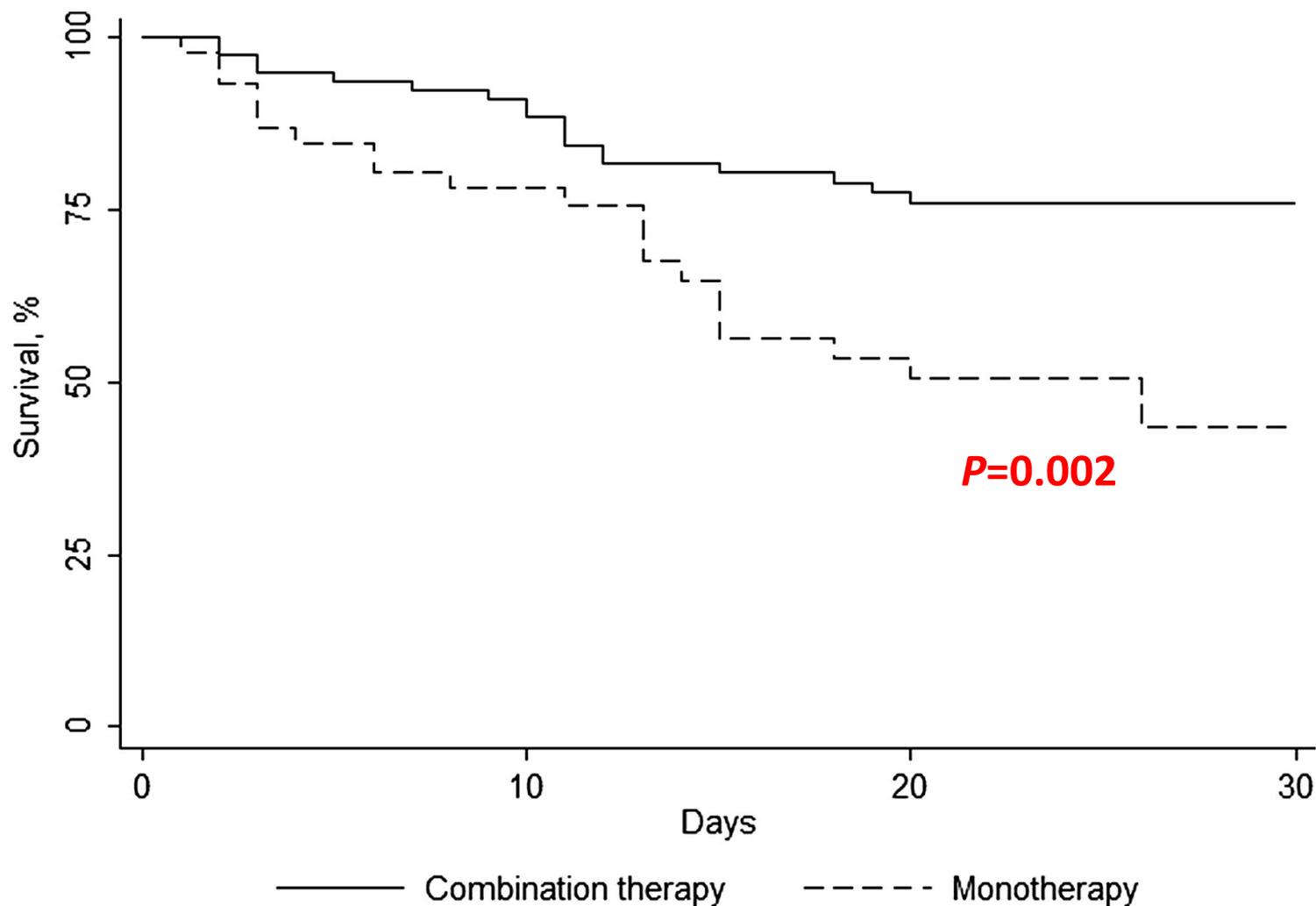
Carbapenem Monotherapy in 50 Patients with Serious CPE Infections

(Results compiled from 15 studies)

MIC ($\mu\text{g/ml}$)	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

Kaplan Meier Curves of Survival Propability of Patients with KPC BSIs According to Treatment



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)

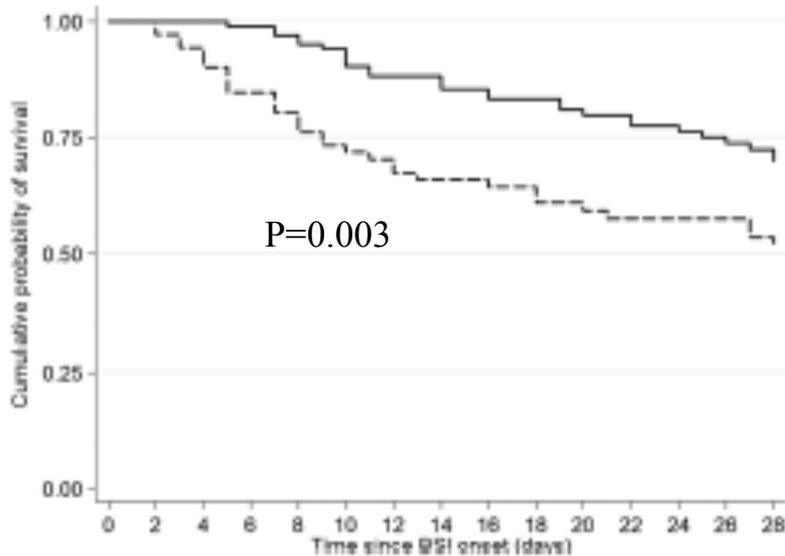
Variable	HR	P
Age	1.01(0.99-1.03)	0.37
Mc Cabe		
Ultimately fatal/non fatal	3.13(1.43-6.83)	0.004
Rapidly fatal/non fatal	4.23(2.19-8.16)	<0.001
Severity of sepsis		
Severe sepsis/sepsis	1.8(0.83-3.97)	0.14
Septic shock/sepsis	2.28 (1.22-4.27)	0.01
Time to initiation of active therapy		
≤48 h	1.44(0.79-2.62)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

Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

George L. Daikos,^a Sophia Tsaousi,^b Leonidas S. Tzouveleki,^c Ioannis Anyfantis,^a Mina Psychogiou,^a Athina Argyropoulou,^d Ioanna Stefanou,^e Vana Sypsa,^f Vivi Miriagou,^g Martha Nepka,^d Sarah Georgiadou,^a Antonis Markogiannakis,^h Dimitris Goukos,^a Athanasios Skoutelis^b

2014

205 patients with CP Kp bacteremia
Treatment with a combination: Independent predictor of survival!!



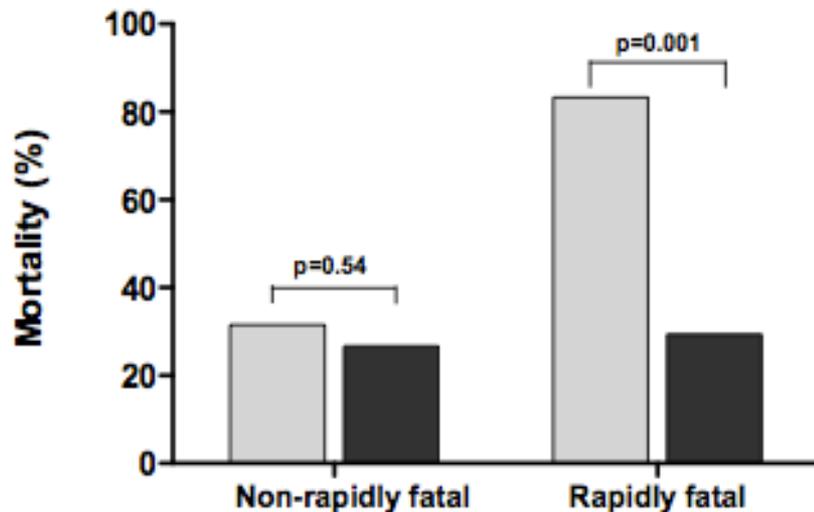
	Mortality %
No active drug	33.3
Monotherapy	44.4
Combination	27.2
without a carbapenem	30.6
with a carbapenem	19.3

P 0.018

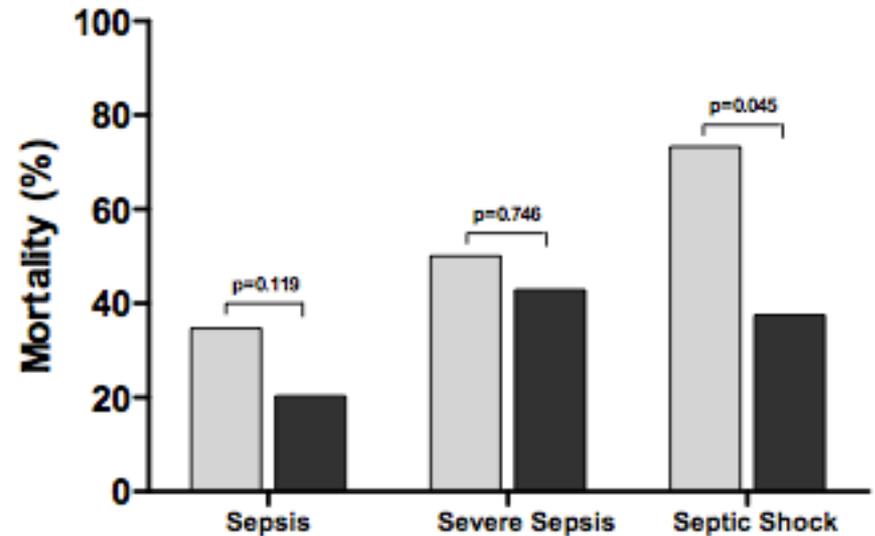
Effect of treatment against CP-Kp BSIs

(monotherapy vs combination therapy)

By severity of underlying disease



By severity of sepsis



Infections Caused by KPC-Kp: Differences in Therapy and Mortality in a Multicenter Study

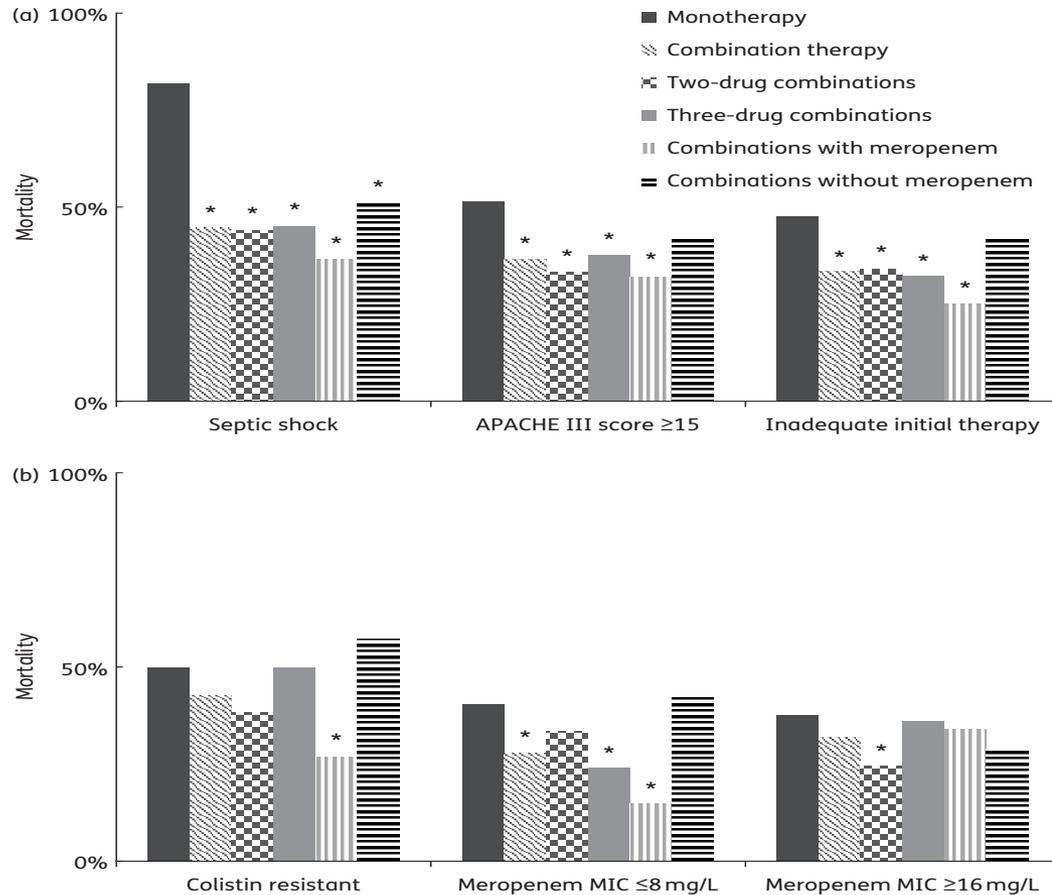


- 173 of 447 (38.7%) with BSI died
- 52/214 (24.3%) of non-bacteremic died

Risk factors for mortality

- BSI
- Septic shock
- Inadequate empiric Rx
- Chronic renal failure
- High APACHE III score
- Colistin-resistance
- Monotherapy

Mortality associated with different antimicrobial drug regimen categories in patients with different presenting features or in patients with different KPC-Kp isolate characteristics



Tumbarello M et al JAC advance access April 21 2015

Predictors of Outcome in ICU Patients with Septic Shock Caused by KPC Klebsiella

Variable	HR	95% CI	P
Colistin containing Regimen	0.21	0.05-0.72	<0.001
Combination Rx	0.08	0.02-0.21	<0.001
Infection Source control	0.14	0.04-0.25	<0.001
Colistin resistance	8.09	3.14-11.23	0.001
Intraabdominal source of infection	2.92	2.11-4.12	0.002

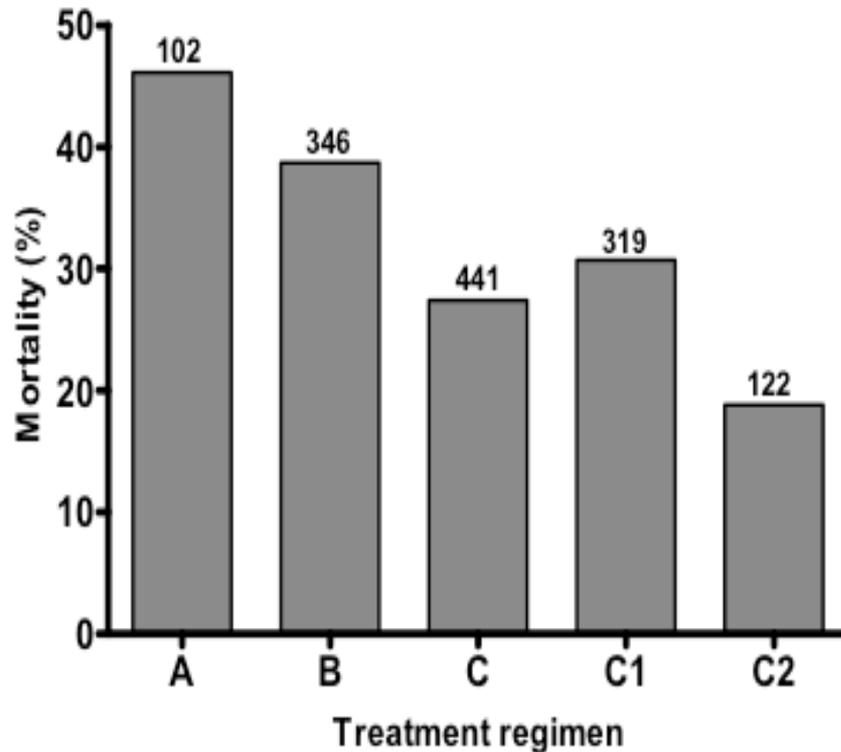
Systemic Review of Clinical Studies with CPE Infections

- Studies providing data for more than 10 patients
- Adequate information
 - Patient characteristics
 - Type of infection
 - In vitro susceptibilities of the infecting organism
 - Type of carbapenemase produced
 - Treatment schemes
 - Outcome

Systemic Review of Clinical Studies with CPE Infections (cont/d)

- 20 studies, 907 patients (70% ICU pts)
- 762 pts had BSIs
 - 339 primary
 - 288 secondary (HAP, cUTIs, cIAI)
 - 135 IV line related
- 145 non-bacteremic nosocomial infections (HAP, cUTIs, cIAIs)
- 75.3% KPC, 20.7% VIM, 4% OXA-48

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



A Inappropriate Rx

B Monotherapy

C Combination therapy

C₁ Carbapenem-sparing combination

C₂ Carbapenem-containing combination

Combination Regimens for the Treatment of Carbapenem Resistant Kp BSIs

- 141 CR BSIs
- 23% received monotherapy
- 26% received monotherapy + a β -lactam
- 28% received combination therapy
- 23% received combination + a β -lactam

Conclusion: In patients with CRKp BSIs caused by isolates with high carbapenem MICs the role of combination therapy remains unclear

Summary

- The positive impact of combination therapy on survival is more apparent for severe infections in critically ill patients.
- There are no adequate data to support combination therapy for patients with mild infections. For such infections, particularly for non-bacteremic UTIs, monotherapy appears to be adequate

Summary (cont/d)

- Carbapenems can be used against CPE infections, when:
 - the carbapenem MIC for the infecting organism is ≤ 8 mg/L
 - a high-dose prolonged-infusion regimen is administered to drive the PK/PD profile to acceptable exposures;
 - this class of agents is administered in combination with another active compound.

Patient 2

- 30 yo male patient with AML after induction chemotherapy developed fever 39⁰ C. RR: 30/min, HR: 110/min, BP: 90/60 mmHg. He was known to be colonized with CP-Kp
- CBC revealed pronounced neutropenia (<100 PMNs/ μ l).
- Two sets of blood cultures were drawn and he was started on empirical antimicrobial regimen

What empirical treatment would you start this patient pending culture results?

- 1 Colistin
- 2 Gentamicin
- 3 Tigecycline
- 4 Meropenem
- 5 Meropenem + Gentamicin \pm tigecycline
- 6 Meropenem + Colistin \pm tigecycline

- 50 to 60% of hematology patients with infections caused by ESBL-producers receive inappropriate initial therapy ([Gudio JAC 2010](#), [Ortega JAC 2009](#), [Tumbarello AAC 2006](#))
- Among 50 hematology pts, hospitalized in 3 tertiary care hospitals in Greece, with BSIs caused by CP-Kp 17 (34%) received inappropriate empirical therapy ([Tofas P IJAA 2016](#))

Studies with CRE BSI in Hematopoietic Stem Cell Transplant Recipients and Patients with Hematologic Malignancies

Geographic Location	Patients, No.	CRE Isolate(s) (No.)	Hematologic Malignancies (No.)	HSCT Recipients, No.	Neutropenic Patients, No.	In-Hospital Mortality Rate	CRE-Attributed Mortality Rate
NYC	18	<i>Klebsiella pneumoniae</i> (14) <i>Enterobacter cloacae</i> (3) Polymicrobial (1) ^a	Acute leukemia (11) Lymphoma (4) Multiple myeloma (2) Myelofibrosis (1)	6	13	56% ^b	56%
Israel	8	<i>K. pneumoniae</i>	Acute leukemia (3) Lymphoma (2) Aplastic anemia (2) Multiple myeloma (1)	5	7	50%	38%
Bethesda, Maryland	6	<i>K. pneumoniae</i>	Aplastic anemia (2) Lymphoma (2) Primary immunodeficiency (2)	4	NR	100%	67%
Israel	1	<i>K. pneumoniae</i>	Acute leukemia	0	1	1/1	1/1
Israel	1	<i>Escherichia coli</i>	Acute leukemia	1	0	NR	0/1
NYC	1	<i>Enterobacter gergoviae</i>	Acute leukemia	0	1	1/1	1/1

ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

De-escalation strategy

- De-escalation should be applied for patients
 - With complicated presentations
 - With individual risk factors for resistant pathogens
 - In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia

Initial therapy in patients colonized or previously infected by resistant Enterobacteriaceae

Resistance type	Treatment
ESBL	Carbapenems <i>BII</i>
Carbapenemase	Colistin <i>CIII</i> + β -lactam +/- one of: Tigecycline <i>CIII</i> or Aminoglycoside or fosfomycin <i>CIII</i>

Patient 2 (*cont'd*)

- The patient was started on meropenem and gentamicin and the blood cultures grew *K. pneumoniae*.
- He is hemodynamically stable but he remains neutropenic and febrile
- Within 48h we received the following results from microbiology lab

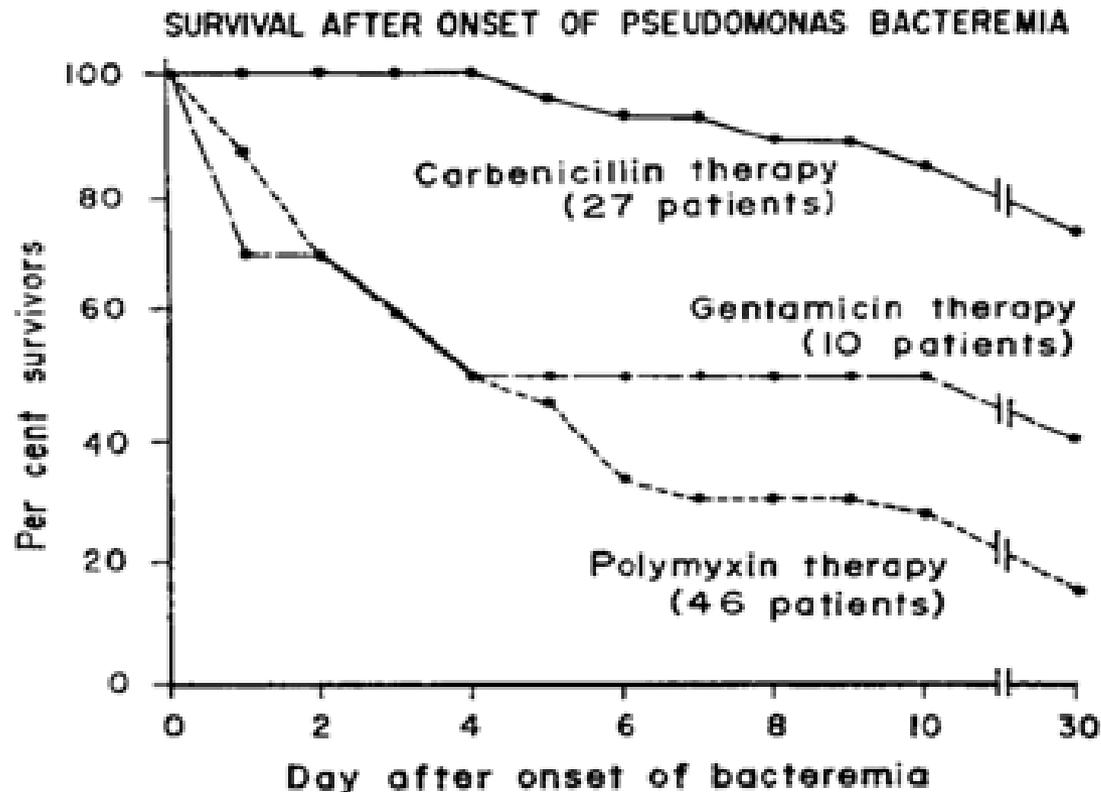
Blood culture grew *K. pneumoniae*

- 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 R
- Amikacin R
- Tigecycline 1 mg/L S
- Colistin 1 mg/L S

What would you choose for definite treatment?

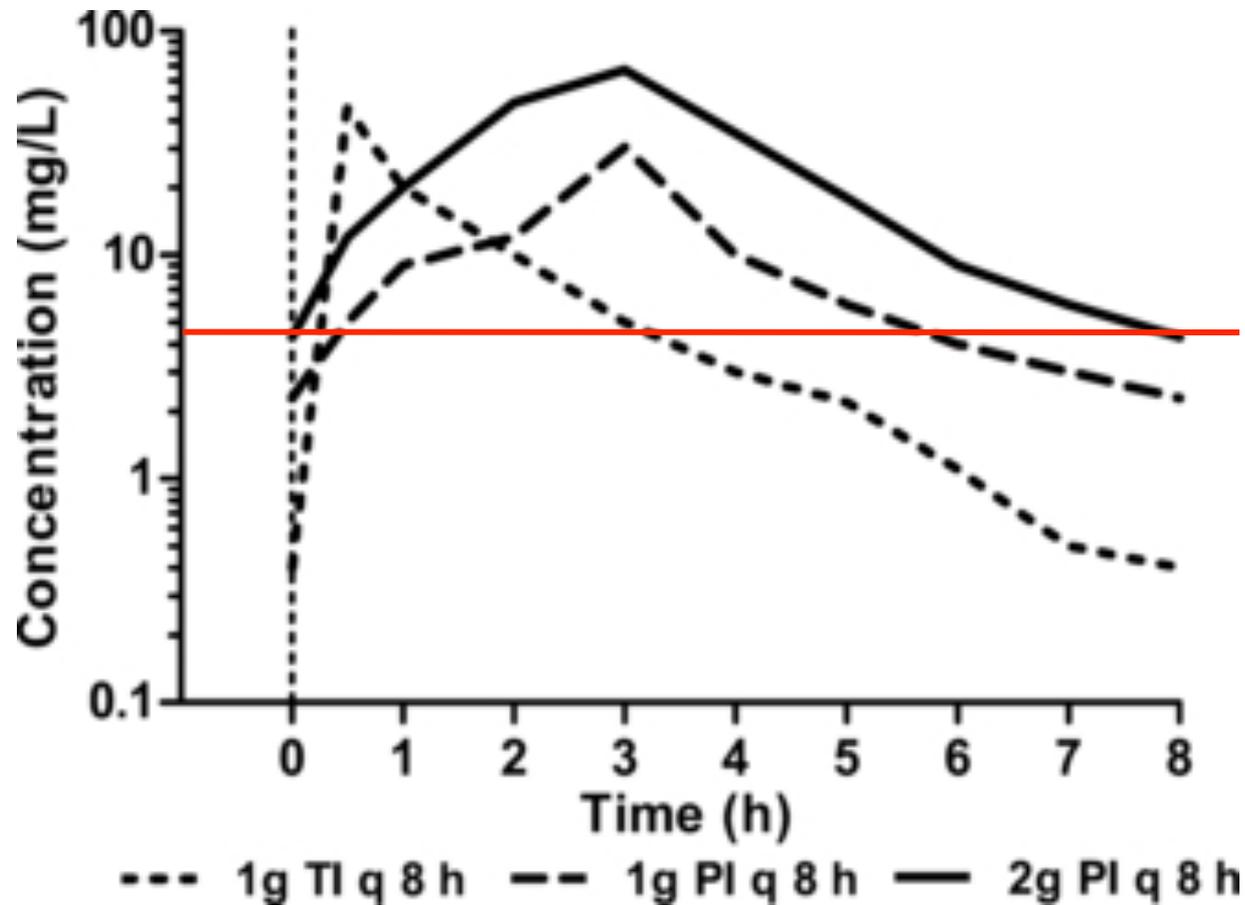
- 1 Colistin
- 2 Tigecycline
- 3 Meropenem
- 4 Meropenem + colistin
- 5 Meropenem + gentamicin

Comparison of β -lactams to Gentamicin and Polymyxin for *P. aeruginosa* bacteremia in Cancer Patients

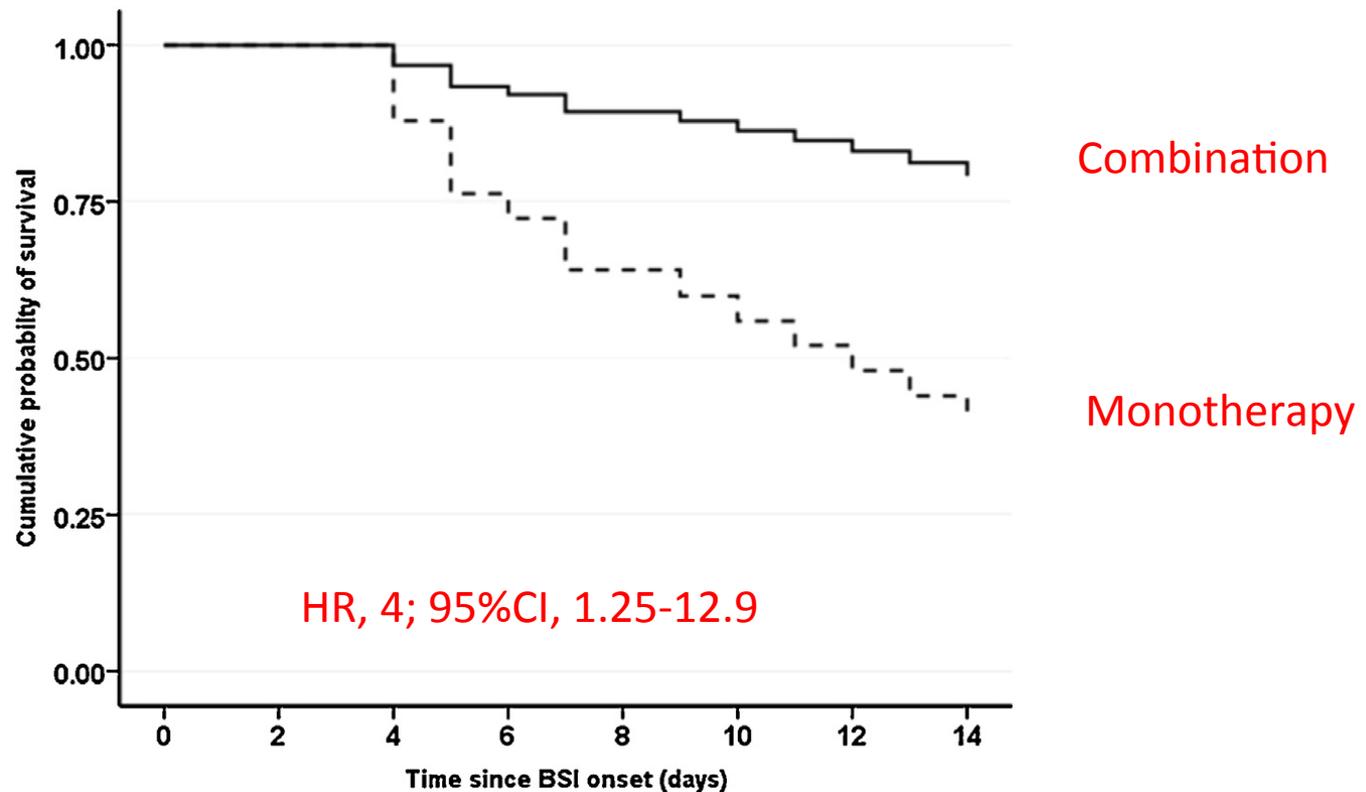


Bodey GP, et al. Eur J Cancer 1973 1972

Pharmacokinetics of three different dosing regimens of meropenem



Survival probability by in 40 neutropenic patients with CP-Kp BSI by treatment regimen after adjustment for septic shock, unresolved neutropenia and empirical therapy



Patient 3

- 28 yo male underwent neurosurgery for cerebellar hematoma after a car accident. Five days later he became confused and developed fever 39⁰ C.
- CSF revealed: WBC=2030/ μ l, glucose=25mg/dl, protein=125mg/dl
- Blood cultures and CSF cultures grew KPC-Kp

K. pneumoniae

- Co-amoxiclav R
- Piperacillin+tazob R
- Cefuroxime R
- Ceftazidime R
- Cefotaxime R
- Aztreonam R
- Cefepime R
- Imipenem > 256 mg/L
- Meropenem >256 mg/L
- Gentamicin R
- Amikacin R
- Tigecycline 1 mg/L
- Colistin 1 mg/L
- Fosfomycin 16 mg?L

Treatment?

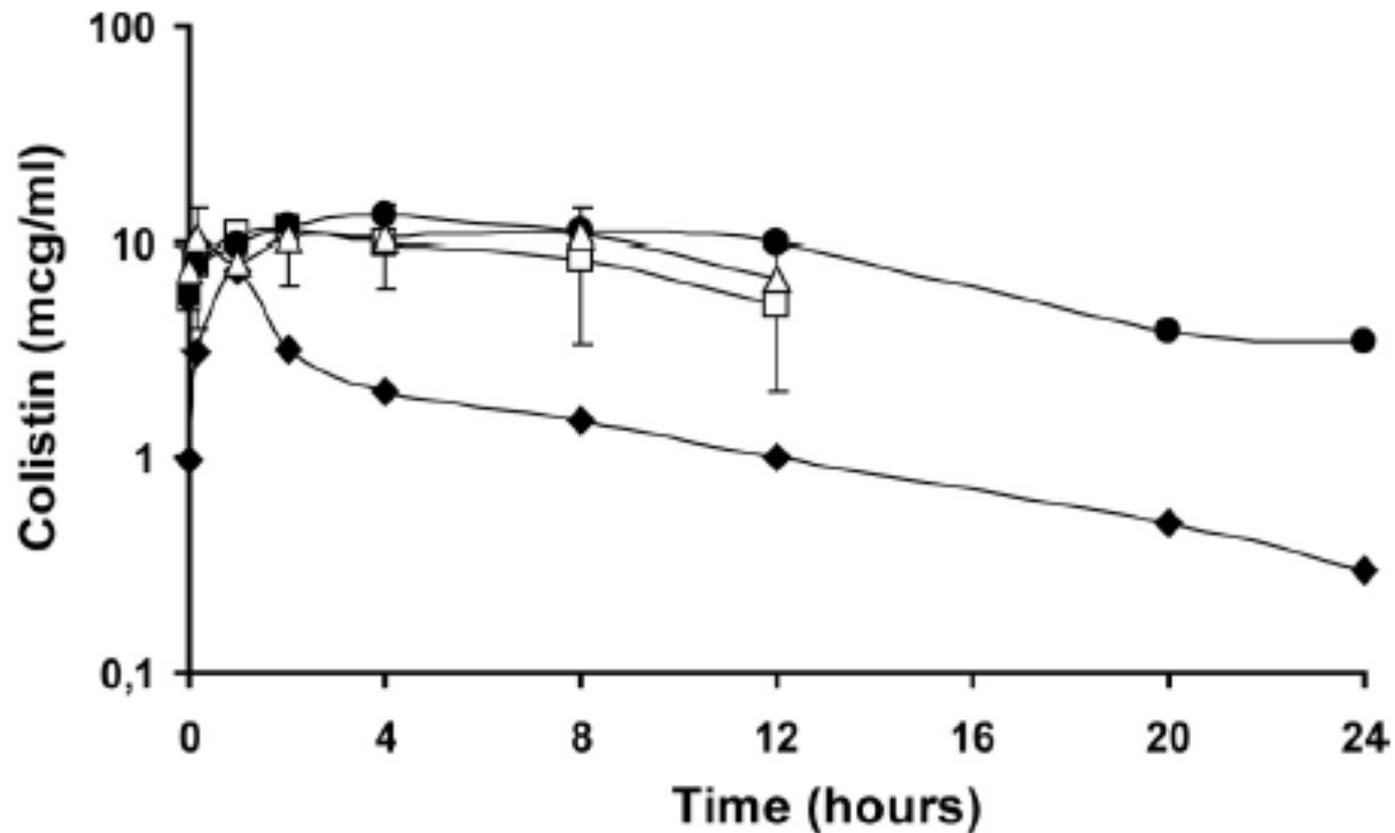
- 1 Colistin IV
- 2 Tigecycline IV
- 3 Colistin IV and intrathecally
- 4 Fosfomycin IV plus colistin IV and intrathecally

Penetration of Colistin into Cerebrospinal Fluid[∇]

S. L. Markantonis,^{1*} N. Markou,² M. Fousteri,¹ N. Sakellaridis,³ S. Karatzas,⁴
I. Alamanos,² E. Dimopoulou,² and G. Baltopoulos⁴

*University of Athens, Faculty of Pharmacy, Laboratory of Biopharmaceutics and Pharmacokinetics, 157.71 Athens, Greece¹;
ICU-B, KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece²; Department of Neurosurgery,
KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece³; and University of Athens School of
Nursing ICU, KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece⁴*

- 5 patients (age: 36 – 68 yrs)
- CMS administration for infections other than CNS
- Dosage : 2MU q12h or 3MU q8h
- Determination of colistin concentration by HPLC
- Colistin concentration CSF/serum : 0.05



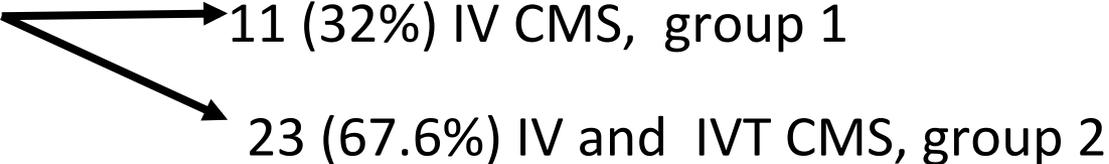
◆ 2.61 mg X 1 □ 2.61 mg x 2 ● 5.22 mg x 1 △ 5.22 mg x 2

FIG 3 Concentration-time profiles of colistin at steady state after intravenous administration of colistin methanesulfonate (CMS) at different dosage regimens. CMS was diluted in 3 ml of saline solution and administered as a bolus in 1 to 2 min. Data points represent the mean concentrations (\pm SD) of colistin, and symbols represent the dosage regimens as indicated in the key.

CLINICAL ARTICLE - VASCULAR

Outcomes in meningitis/ventriculitis treated with intravenous or intraventricular plus intravenous colistin

George Fotakopoulos^{1,3} • Demosthenes Makris² • Maria Chatzi² • Eleni Tsimitrea² •
Epaminondas Zakynthinos² • Kostas Fountas¹

- Retrospective study 2006 -2014
- Meningitis/ventriculitis MDR Gram-negative organisms
- 34 patients 
 - 11 (32%) IV CMS, group 1
 - 23 (67.6%) IV and IVT CMS, group 2
- IVT CMS: 170 000 IU
- In hospital mortality: 72.7% for group 1 vs 13% for group 2

Klebsiella Meningitis:

Intraventricular or Intrathecal Use of Polymyxins

- **15/19 episodes → Clinical Cure: 79 %**
- IVT/ITH administration: 15/4
- Cases of Colistin/Polymyxin B: 15/4
- Dose of polymyxin B → 20 000 IU – 50 000 IU
- Dose of colistin → 62 500 IU – 250 000 IU

Falagas M, et al. IJAA 2007; 29: 9-25

Ziaka M, et al. AAC 2013; 57: 1938-40

Nevrekar S, et al. Ann Pharmac. 2014;48:274-8

Imberti R, et al. AAC 2012; 56: 4416

Bargiacchi O, et al. Infection. 2014 ;42:801-9

Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant *Acinetobacter baumannii* ventriculitis and meningitis: a literature review

Ilias Karaiskos, Lambrini Galani, Fotini Baziaka, Helen Giamarellou*

- 83 episodes in 81 patients.
- Dose of colistin 125 000 IU
- Mean time of IVT/ITH administration of colistin was 18.5 days
- Mean time for CSF bacterial eradication was 4 days.
- **Clinical success rate 89%**

Adverse reactions

- **Chemical meningitis/ ventriculitis**
 - Similar to bacterial meningitis (fever, pleocytosis, low glucose, negative cultures)
 - D/C ITC/IVT for 2 days and continue if needed every 48h.
- **Seizures**

Optimizing treatment

Dosing Regimens of Colistin

Loading dose

For all patients

- $CBA \text{ (mg)} = C_{\text{target}} \times 2 \times BW$
- $MU = C_{\text{target}} \times 2 \times BW / 30$
- **Maximum dose 10 MU**

Maintenance dose

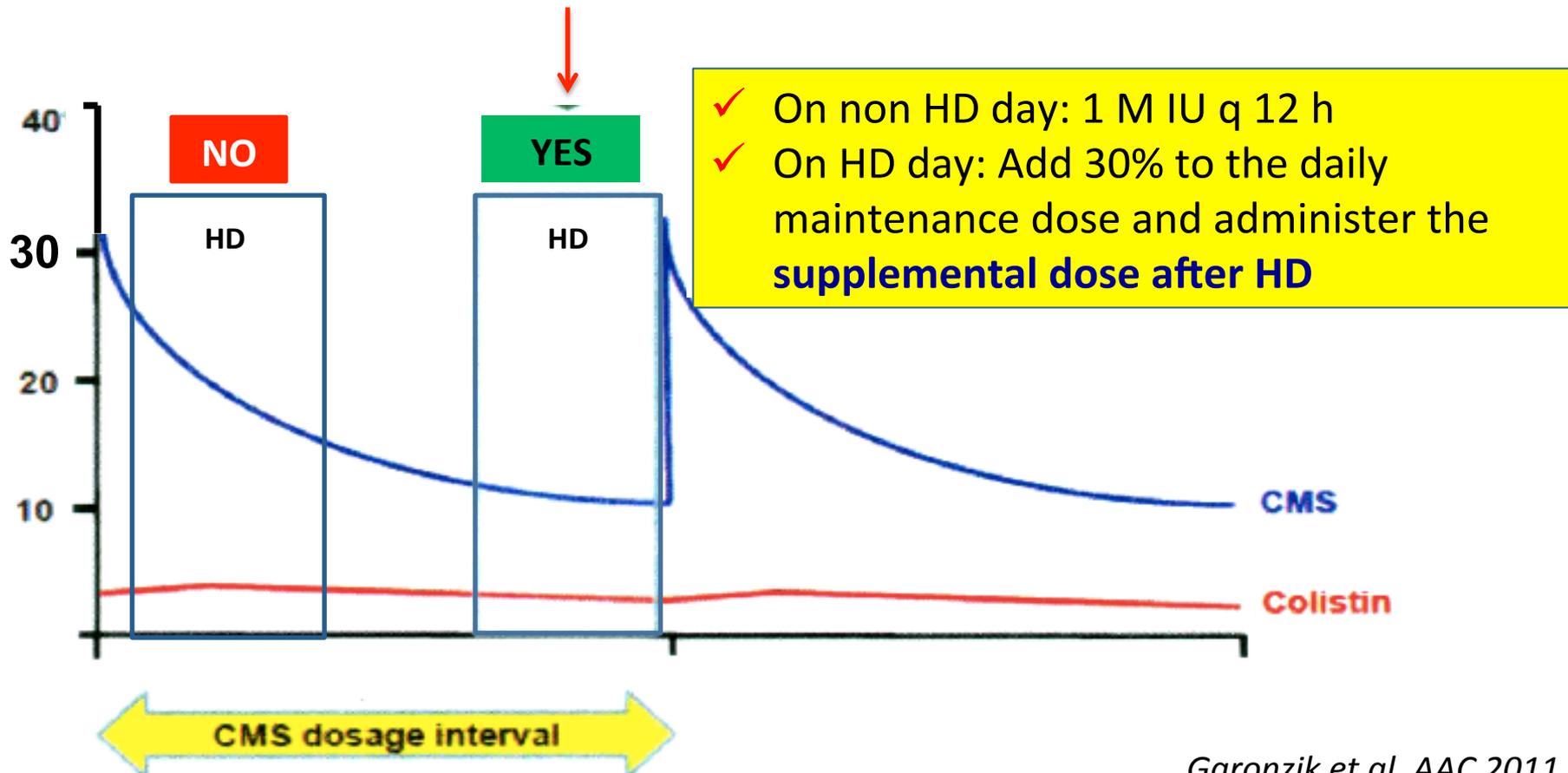
For patients
not on RRT

- $CBA \text{ (mg)} = C_{\text{target}} \times (1.5 \times CrCL + 30)$
- $MU = C_{\text{target}} \times [(1.5 \times CrCL + 30)] / 30$

Patients Receiving Intermittent HD

What is the optimal time to perform HD?

- CMS and Colistin are efficiently cleared by HD
- HD should occur towards the end of the CMS dosing interval
- Even then a supplemental dose should be given



Patients Receiving CRRT

Dose as in a patient with CrCL of 100 ml/min

For Colistin target of 2 mg/L

Dose = 6.4 M IU q 12 h or 192 mg CBA q 12 h

RESEARCH

Open Access

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

Gennaro De Pascale^{1*}, Luca Montini¹, Mariano Alberto Pennisi¹, Valentina Bernini¹, Riccardo Maviglia¹, Giuseppe Bello¹, Teresa Spanu³, Mario Tumbarello² and Massimo Antonelli¹

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

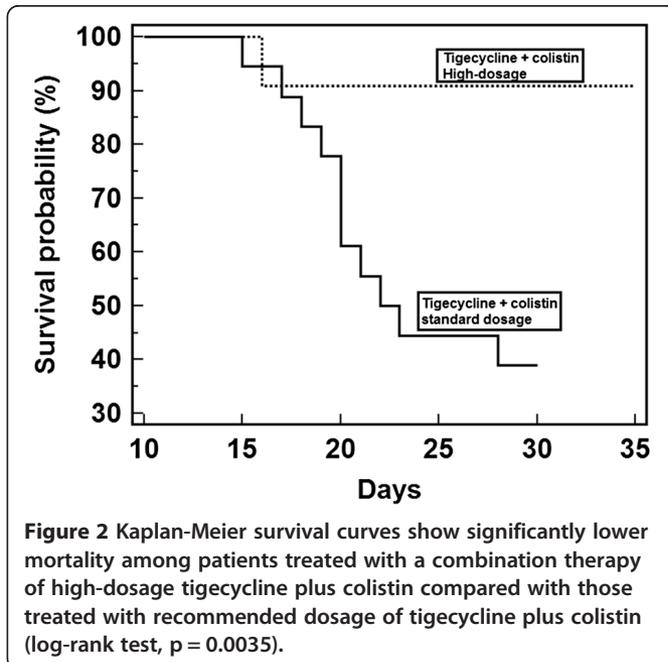
Variable	Multivariate analysis		
	Odds ratio	95% CI	P-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

RESEARCH ARTICLE

Open Access

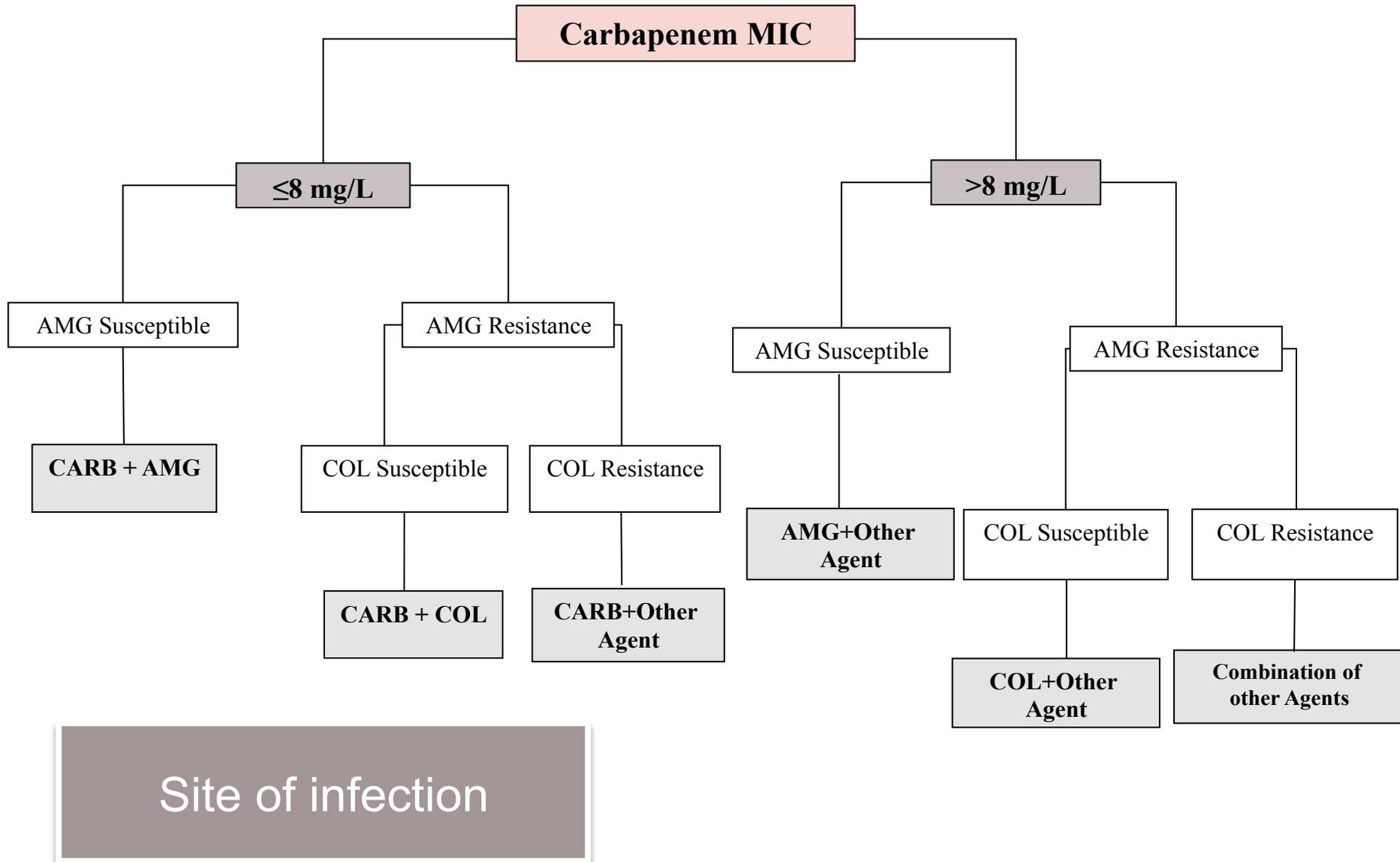
KPC - 3 *Klebsiella pneumoniae* ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients

Paola Di Carlo^{1*}, Gaspare Gulotta², Alessandra Casuccio³, Gianni Pantuso⁴, Maurizio Raineri⁵, Clizia Airò Farulla⁴, Sebastiano Bonventre², Giuliana Guadagnino¹, Daniela Ingrassia¹, Gianfranco Cocorullo², Caterina Mammina¹ and Antonino Giarratano⁵



- 30 patients with IAIs
- 12 received high-dose tigecycline in combination with colistin
- 18 received standard-dose of tigecycline in combination with colistin

Proposed Algorithm for Treatment of Serious CPE Infections



2015 May;33(5):337



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Consensus statement

Diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant *Enterobacteriaceae*. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology

Jesús Rodríguez-Baño^{a,b,*}, José Miguel Cisneros^{a,c}, Nazaret Cobos-Trigueros^d, Gema Fresco^e, Carolina Navarro-San Francisco^f, Carlota Gudiol^g, Juan Pablo Horcajada^h, Lorena López-Cerero^a, José Antonio Martínez^d, José Molina^a, Milagro Montero^h, José R. Paño-Pardo^f, Alvaro Pascual^{a,i}, Carmen Peña^g, Vicente Pintado^e, Pilar Retamar^a, María Tomás^j, Marcio Borges-Sa^k, José Garnacho-Montero^{c,l}, Germán Bou^j, for the Study Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases, Infectious Diseases (SEIMC)

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

New Agents against Gram-negative Organisms

- β -lactamase inhibitors

- Avibactam

- Relebactam (MK-7655)

- OPO595

- RPX7009



diazabicyclooctanes



boronate

- Siderophores

- LpxC inhibitors

- Plazomicin

β -lactamase inhibitors combinations

- Ceftazidime/Avibactam (Avycaz)
- Aztreonam/Avibactam
- Imipenem/Relebactam (MK-7655)
- Meropenem/RPX7009 (Carbavance)

Drug (Brand) Name/Company	Antibiotic Class	Development Phase	Activity Spectrum	Potential Indications
Ceftazidime+Avibactam (Avycaz)/AstraZeneca-Actavis	Cefalosporin + new BLI	FDA approved on Feb 2015, EMA not submitted yet	ESBL & KPC-producing strains	UTIs cIAIs
Meropenem+RPX7009 (Carbavance)/Rempex	Carbapenem+ new BLI	Phase III ongoing	ESBL & KPC-producing strains	cUTIs Pneumonia/VAP BSIs
Eravacycline/Tetraphase Pharmaceuticals	Tetracycline	Phase III ongoing	ESBL, MBL & KPC-producing strains	cUTIs cIAIs
Plazomicin /Achaogen	Aminoglycoside	Phase III ongoing	ESBL, MBL & KPC-producing strains	BSIs Pneumonia/VAP
Imipenem-cilastatin +Relebactam/ Merck	Carbapenem+ new BLI	Phase II completed	ESBL & KPC-producing strains	UTIs cIAIs Pneumonia/VAP
Ceftaroline+Avibactam/ AstraZeneca-Actavis	Cefalosporin + new BLI	Phase II completed	ESBL & KPC-producing strains	cUTIs
S-649266/Shionogi	Siderophore Cephalosporin	Phase II ongoing	ESBL, MBL & KPC-producing strains	cUTIs
Aztreonam+Avibactam/ AstraZeneca	Monobactam+ new BLI	Phase I completed	ESBL, MBL-producing strains	MDR Gram-negative bacterial infections
BAL30072/Basilea Pharmaceutical	Siderophore Monosulfactam	Phase I ongoing	MBL & KPC-producing strains, some ESBLs are not inhibited (e g SHV-5)	MDR Gram-negative bacterial infections



Prudent use of antibiotics
Enhanced infection control

Thanks for your attention