

# MDR Gram negatives

## Some clinical cases...

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Spanish Network for Research in Infectious Diseases

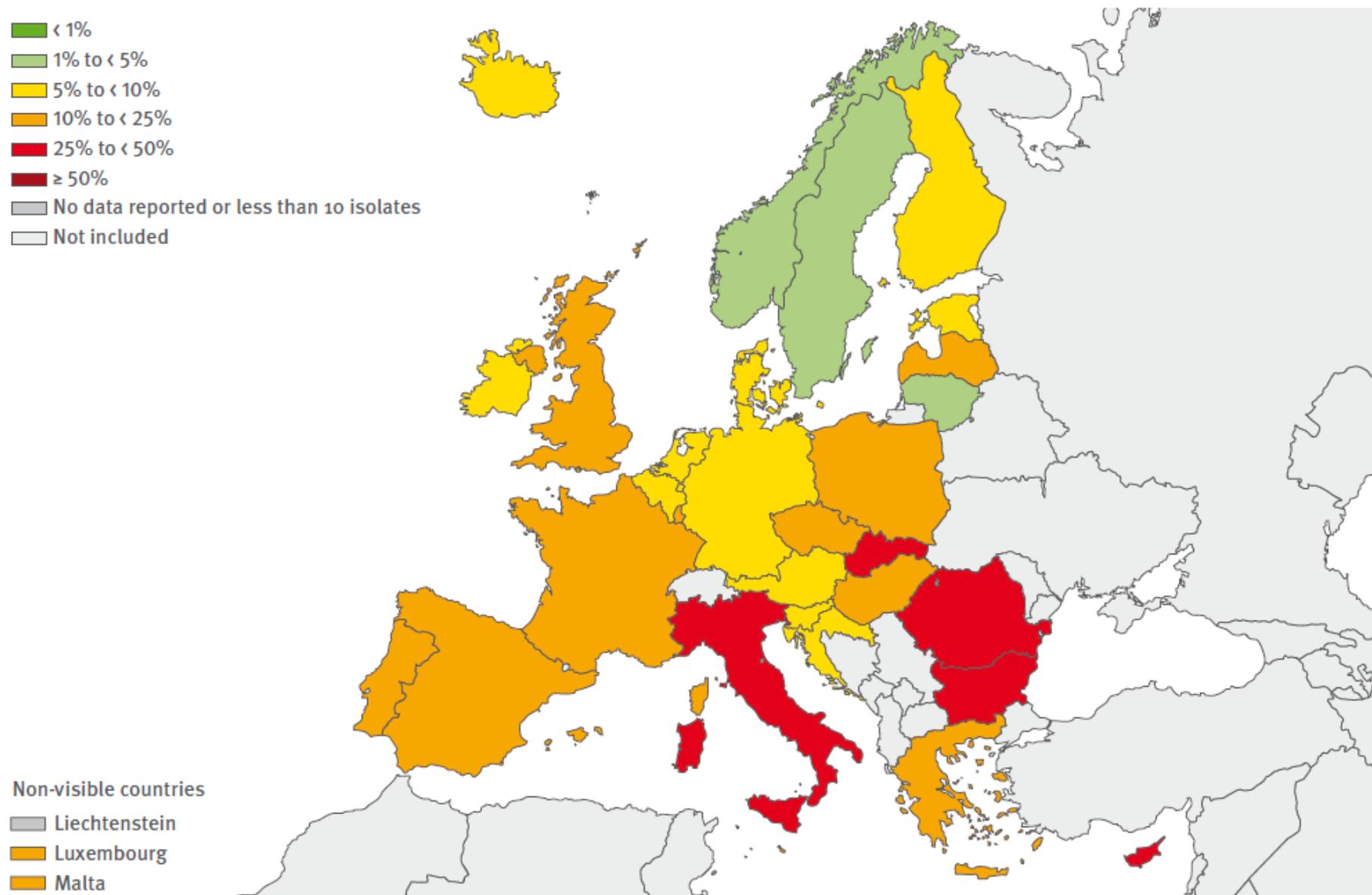
Hospital Universitario  
Virgen Macarena, Seville



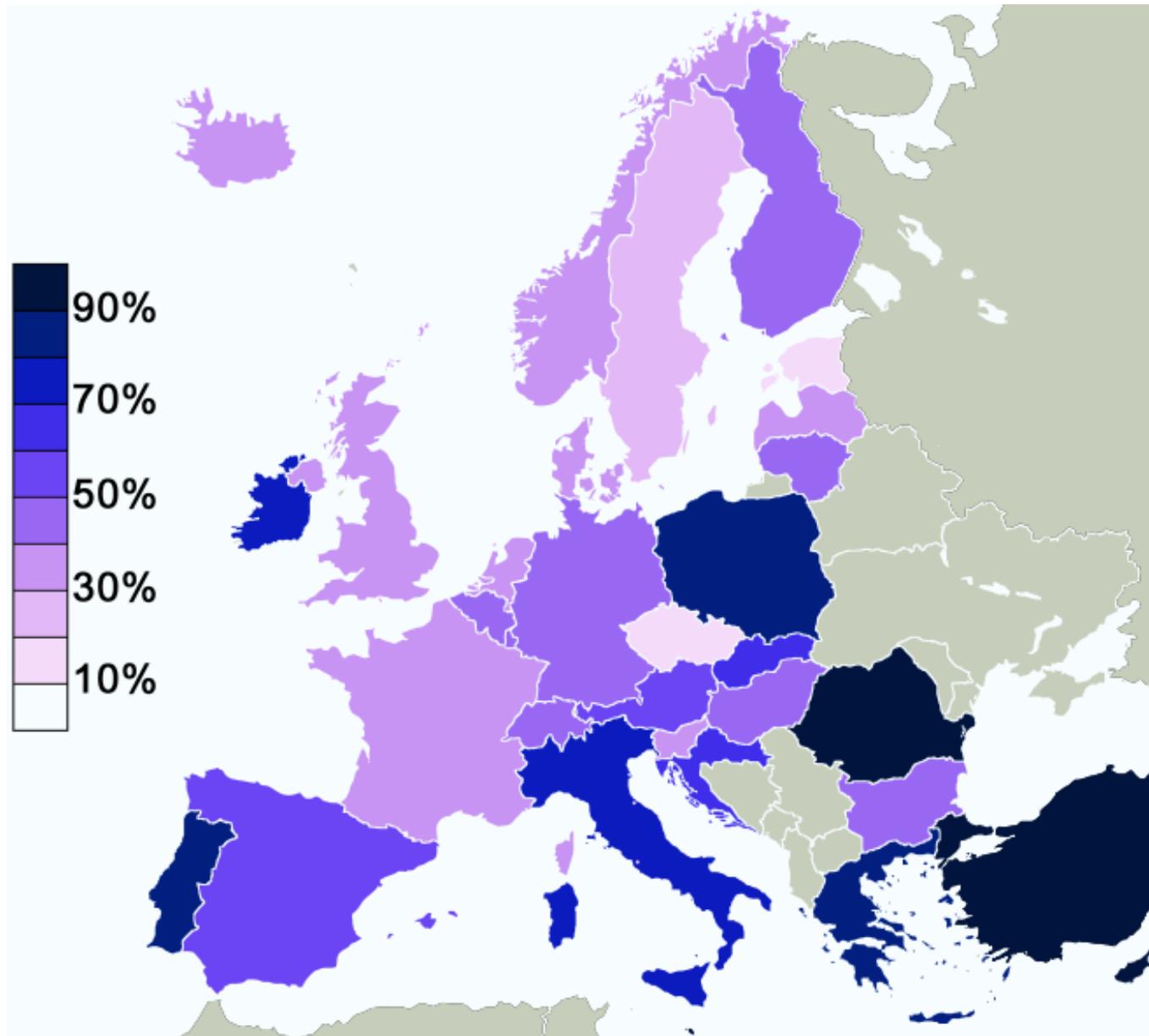
# Conflicts of interest

- Speaker: AstraZeneca, Astellas, Pfizer, Novartis, Merck
- Scientific advisory: Merck, AstraZeneca, Roche, Anchaogen
- Research grants:
  - Gilead, Novartis
  - Spanish Ministry of Economy, Andalusian Healthcare System
  - FP7, IMI (EU + EFPIA)

**Figure 3.1.** *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country, EU/EEA countries, 2012



# Percentage of responders "I believe there is a god"



Source: Eurobarometer, 2005

- 74 yo female. Fever, right flank pain, dysuria (48h)
- Diabetes mellitus. Admitted because of CAP 2 months before, received ceftriaxone. Cystitis 4 months ago treated with cipro.
- T<sup>a</sup> 39°C, BP: 110/65, pulse 88 bpm, rest unremarkable.
- 15.000 leucocytes (95% PMN), creatinine 1.9 mg/dL (calculated Cr Cl 40 mL/min), lactate normal, CRP 85 mg/L. Urine: leucocytes+++
- Urine and blood cultures performed
- Echography; mild right hydronephrosis due to ureter stone
- Nephrostomy planned for next morning



# Would you empirically cover...

- Fluorquinolone-resistant isolates
- Cephalosporin-resistant isolates (e.g., ESBL)
- Carbapenem-resistant isolates
- FQ and ceph-resistant isolates
- None of the above

# Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum $\beta$ -lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis

Wouter C. Rottier<sup>1\*</sup>, Heidi S. M. Ammerlaan<sup>1,2</sup> and Marc J. M. Bonten<sup>1,3</sup>

J Antimicrob Chemother 2012

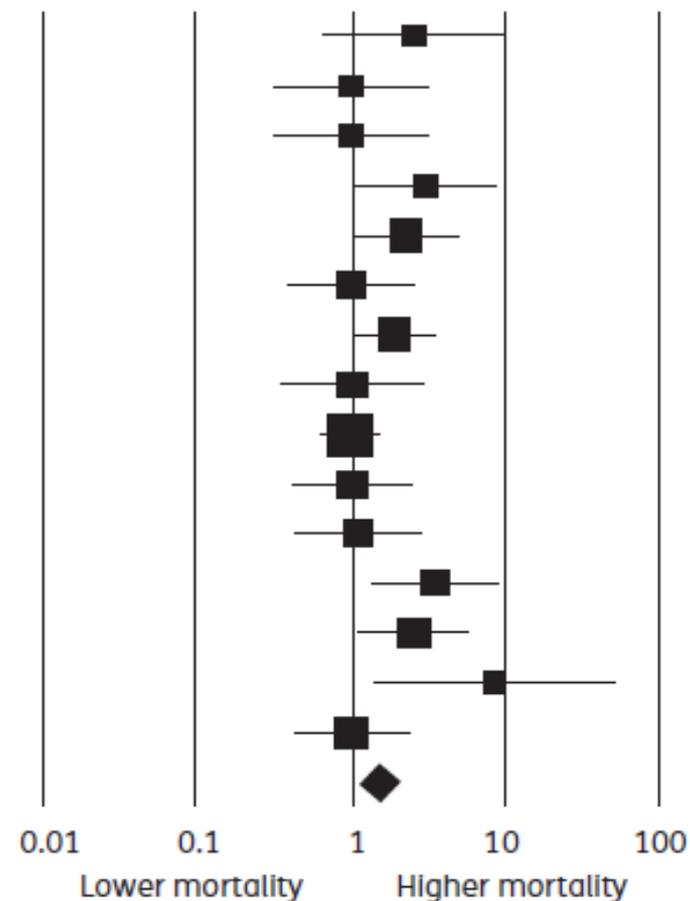
Study name

OR and 95% CI

aORs

Lower limit  
Upper limit

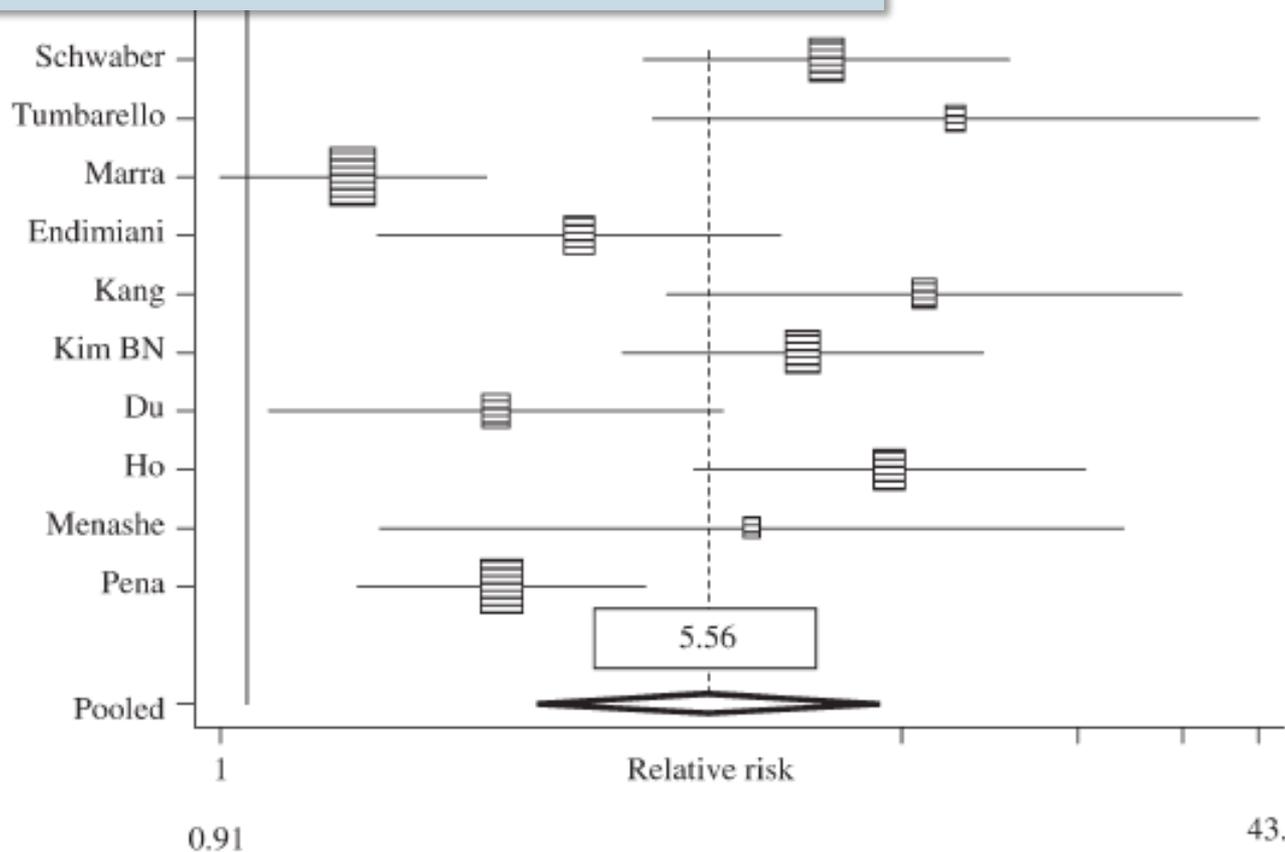
Study name	aORs	Lower limit	Upper limit
Cordery	2.55	0.64	10.15
Dalkos	1.00	0.31	3.18
Gudiol	1.00	0.33	3.00
Kang	2.99	1.01	8.85
Marchalm	2.30	1.09	4.87
Marra	1.00	0.39	2.56
Meizer	1.81	0.93	3.52
Menashe	1.00	0.34	2.94
Ortega	1.00	0.68	1.48
Peña	1.00	0.41	2.46
Rodríguez-Baño	1.08	0.43	2.69
Schwaber	3.60	1.38	9.38
Szilágyi	2.47	1.13	5.40
Trecarichi	8.84	1.48	52.86
Tsal	1.00	0.42	2.37
	1.52	1.15	2.01



# Mortality and delay in effective therapy associated with extended-spectrum $\beta$ -lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Mitchell J. Schwaber<sup>1\*</sup> and Yehuda Carmeli<sup>1,2</sup>

## ESBL producers: risk of appropriate treatment delay



# Community-Onset Bacteremia Due to Extended-Spectrum $\beta$ -Lactamase–Producing *Escherichia coli*: Risk Factors and Prognosis

Clin Infect Dis 2010

Jesús Rodríguez-Baño,<sup>1</sup> Encarnación Picón,<sup>2</sup> Paloma Gijón,<sup>4</sup> José Ramón Hernández,<sup>2</sup> Maite Ruíz,<sup>3</sup> Carmen Peña,<sup>6</sup> Manuel Almela,<sup>7</sup> Benito Almirante,<sup>8</sup> Fabio Grill,<sup>5,a</sup> Javier Colomina,<sup>10</sup> Monserrat Giménez,<sup>11</sup> Antonio Oliver,<sup>12</sup> Juan Pablo Horcajada,<sup>13,a</sup> Gemma Navarro,<sup>14</sup> Ana Coloma,<sup>9</sup> and Alvaro Pascual,<sup>2</sup> for the Spanish Network for Research in Infectious Diseases (REIPI)

**Table 4. Univariate and Multivariate Analysis of Variables Associated with Death among 282 Patients with Community-Onset Bacteremia Due to *Escherichia coli***

Variable	No. of patients who died/no. of patients in the category (%)	RR (95% CI)	<i>P</i>	Adjusted OR	<i>P</i>
Empirical treatment					
Inappropriate	17/77 (22)	3.3 (1.6–6.2)	<.001	3.0 (1.3–12.2)	.007
Appropriate	14/205 (7)				
ESBL producer					
Yes	16/95 (17)	2.1 (1.0–4.1)	.02	...	
No	15/187 (8)				

Adjusted by source and Pitt score

Hospital Universitario Virgen Macarena, Seville

ESCMID COLLABORATIVE CENTRE



# Antibiotic resistance—the need for global solutions

Ramanan Laxminarayan, Adriano Duse, Chand Wattal, Anita KM Zaidi, Heiman FL Wertheim, Nithima Sumpradit, Erika Vlieghe, Gabriel Levy Hara, Ian M Gould, Herman Goossens, Christina Greko, Anthony D So, Maryam Bigdeli, Göran Tomson, Will Woodhouse, Eva Ombaka, Arturo Quizhpe Peralta, Farah Naz Qamar, Fatima Mir, Sam Kariuki, Zulfiqar A Bhutta, Anthony Coates, Richard Bergstrom, Gerard D Wright, Eric D Brown, Otto Cars

## Carbapenems sales

Lancet Infect Dis 2013

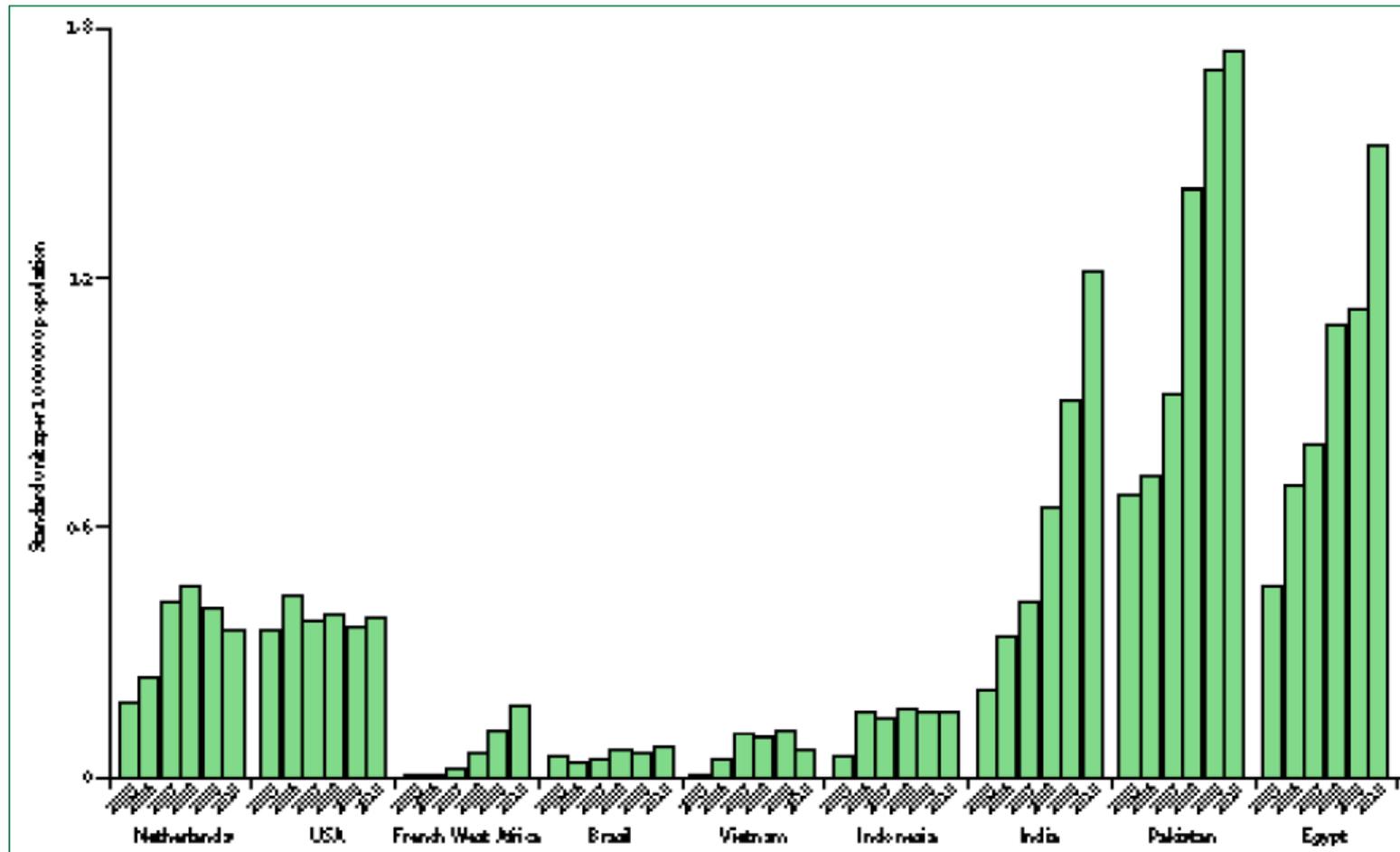
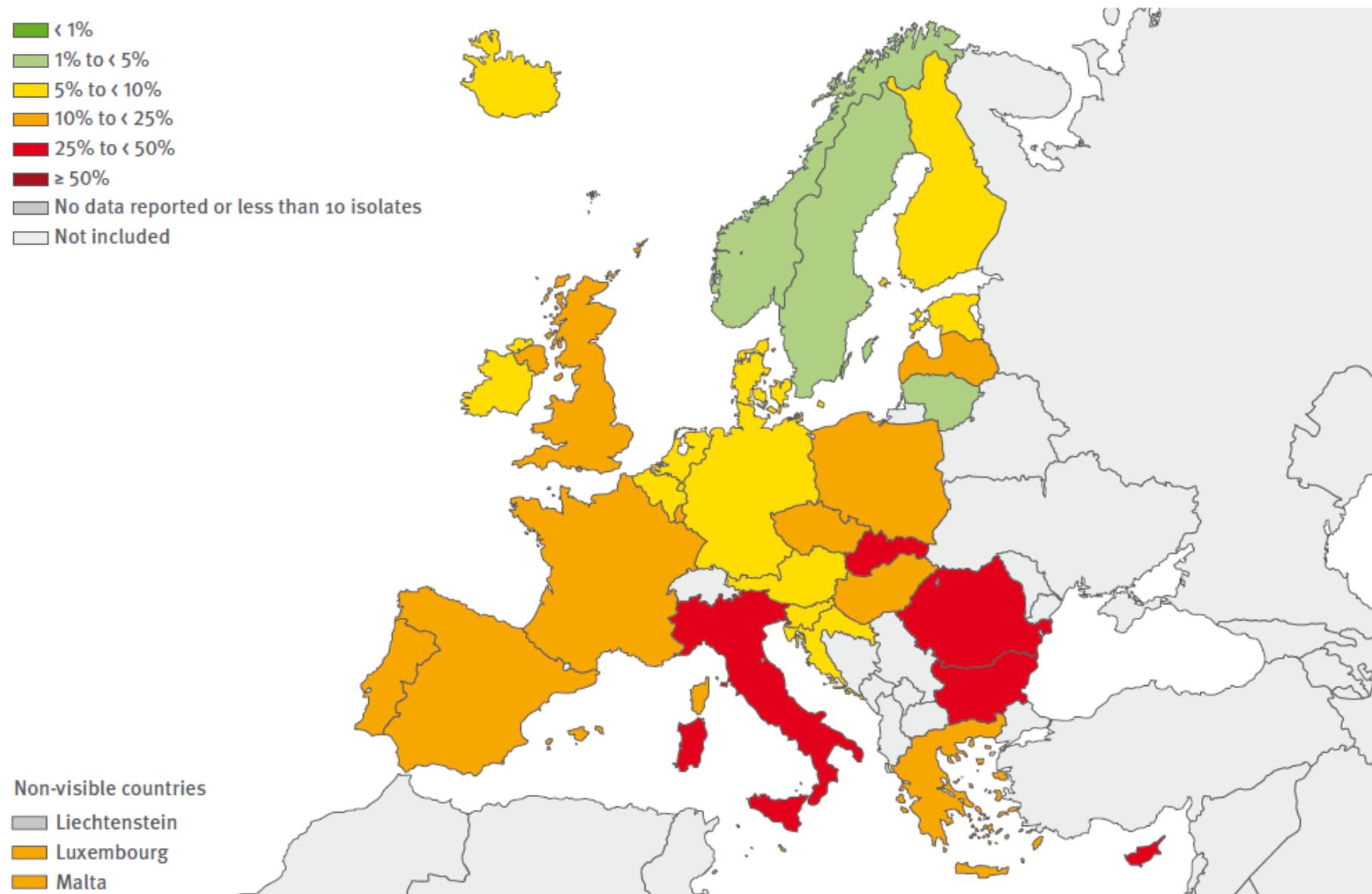


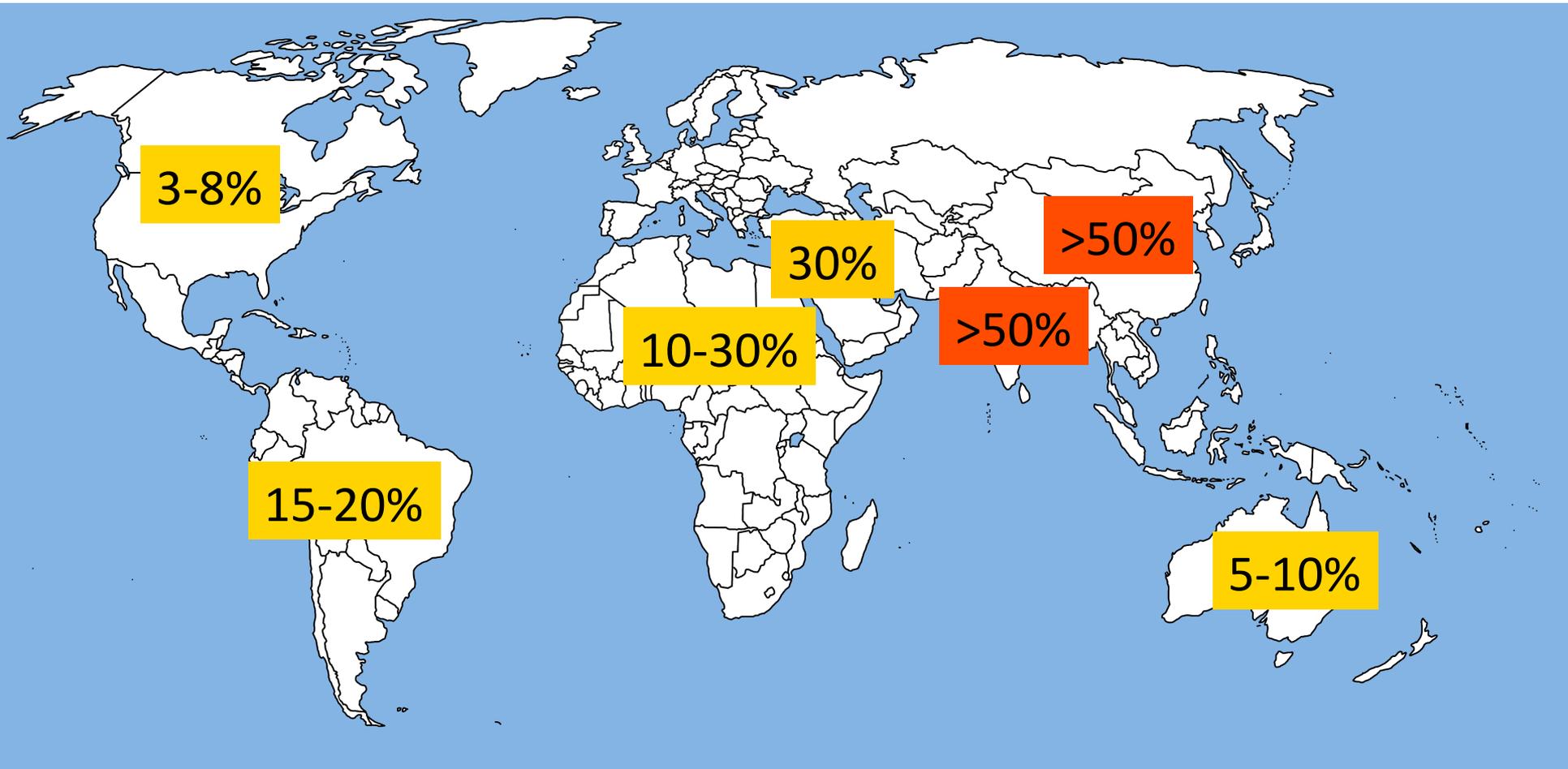
Figure 1: Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria

**Figure 3.1.** *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country, EU/EEA countries, 2012



Coming from abroad?

Prevalence of ESBL producers in other areas



Data from EARS-Net, SMART, SENTRY, MYSTIC, EARSS...

## Local prevalence at the time: 5-10%

TABLE 2. Multivariate logistic regression analysis of risk factors for ESBL-producing *Enterobacteriaceae* isolation within 48 h of hospital admission in the derivation set, with corresponding point values

Parameter	Regression coefficient	P	OR (95% CI)	Score
Recent hospitalization <sup>a</sup>	1.73	<0.001	5.69 (2.94–10.99)	3
Admission from another healthcare facility	1.72	0.006	5.61 (1.65–19.08)	3
Charlson comorbidity index $\geq 4$	1.33	<0.001	3.80 (1.90–7.59)	2
Previous therapy with $\beta$ -lactams and/or fluoroquinolones <sup>b</sup>	1.30	<0.001	3.68 (1.96–6.91)	2
History of urinary catheterization <sup>c</sup>	1.25	<0.001	3.52 (1.96–6.91)	2
Age $\geq 70$ years	1.16	<0.001	3.20 (1.79–5.70)	2

Score 7  $\rightarrow$  80% PPV

Tumbarello et al, AAC 2011

# Back to our case...

- Empirical therapy: amoxicillin/clavulanic acid (2 g/8h) + amikacin (one dose, adjusted to renal function)
- Day 1: Nephostomy catheter placed. Purulent urine obtained. Urine + blood cultures: Gram negative, *E. coli* (MALDI-TOF)
- Day 2. T<sup>a</sup> 37.7°C. Normal WBC count. Creatinine 1.3 mg/dl. CRP 15 g/L. Blood and urine cultures...

# ESBL-producing *E. coli*

CTX-M-14-producer

■ Ampicillin	R
■ Amoxicillin/clavulante	S (MIC=4 mg/L)
■ Piperacillin/tazobactam	S (MIC=2 mg/L)
■ Ceftazidime	S (MIC=1 mg/L)
■ Cefotaxime	R
■ Temocillin	S
■ Meropenem	S
■ Ertapenem	S
■ Ciprofloxacin	R
■ Co-trimoxazole	R
■ Gentamicin	R
■ Amikacin	S
■ Tigecycline	S (but UTI)
■ Fosfomycin	S

# Your choice for definitive therapy...

- Amox/clav
- Pip/taz
- Ceftazidime
- Ertapenem
- Imipenem or meropenem
- Amikacin
- Fosfomycin (IV)

# Aminoglycosides

- Meta-analysis for AG in monotherapy, compared to other drugs (mostly beta-lactams and quinolones)
  - Higher failure rate except in UTI
  - Higher rate of adverse events
    - Vidal et al, JAC 2007

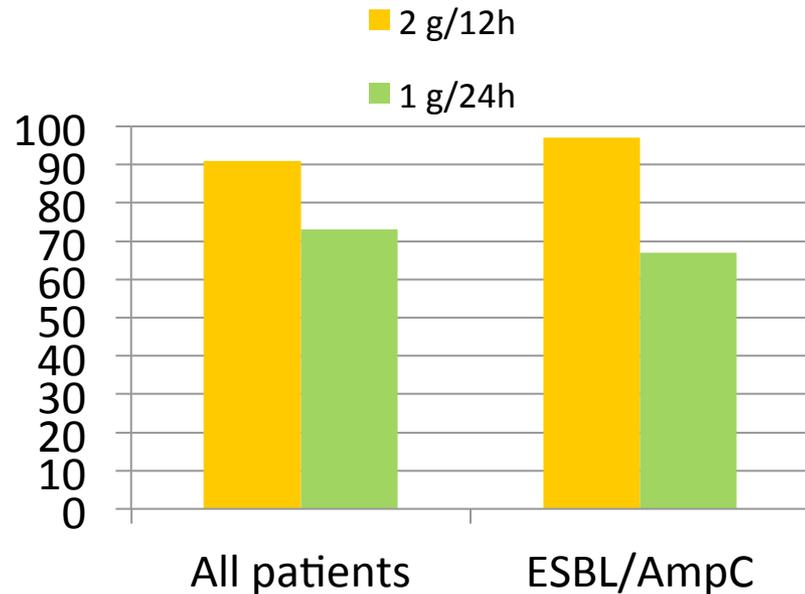
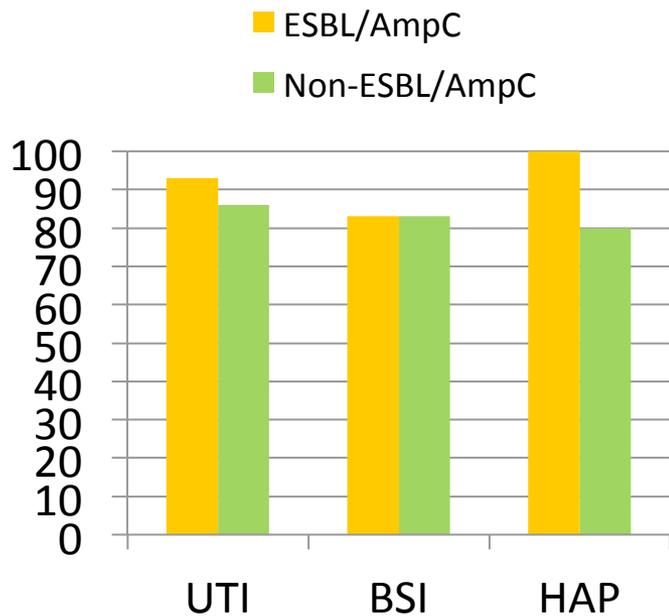
# Fosfomicin disodium (IV)

- Lack of adequate PK/PD data and dosing schedule (2-8 g / 6-8h)
  - Parker, IJAA 2013
- Risk of resistance development; probably lower for *E. coli*
  - Karageorgopoulos, JAC 2012
- Well tolerated (hypokaliemia; sodium overload)
- Limited clinical expedience, always in combination
  - Karageorgopoulos JAC 2012, Dihn, SJID 2012, Navarro-San Francisco, CMI 2013, Michalopoulos CMI 2010, Pontikis IJAA 2014
- Ongoing RCT
  - FOREST: fosfomicin vs meropenem in bacteraemic UTI due to ESBL-producing *E. coli*

# Temocillin

N=91 (43 UTI, 42 BSI, 8 HAP); 53 ESBL/AmpC producers

## CURE RATES:



Balakrishnan et al, JAC 2011C

# Oxy-imino-cephalosporins

- Cefotaxime, ceftriaxone, ceftazidime, cefepime
- Stochastic modelling suggest appropriate target attainment
  - MacGowan, CMI 2008, Nguyen, JAC 2014
- Doubts: inoculum effect, expression of beta-lactamases
- Breakpoints for susceptibility
  - EUCAST:  $\leq 1$  mg/L
- Scarce clinical data
  - Good results: Goethaert, CMI 2006 (n=21); Bin, DMID 2006 (n=7)
  - Not so good: Rodríguez-Baño, CMI 2012; Chopra, AAC 2012, Lee, CID 2013
- Interpretation
  - Probably safe for UTI if MIC  $\leq 1$  mg/L
  - Doubts for septic shock/non-UTI...

# Beta-lactam/beta-lactam inhibitors

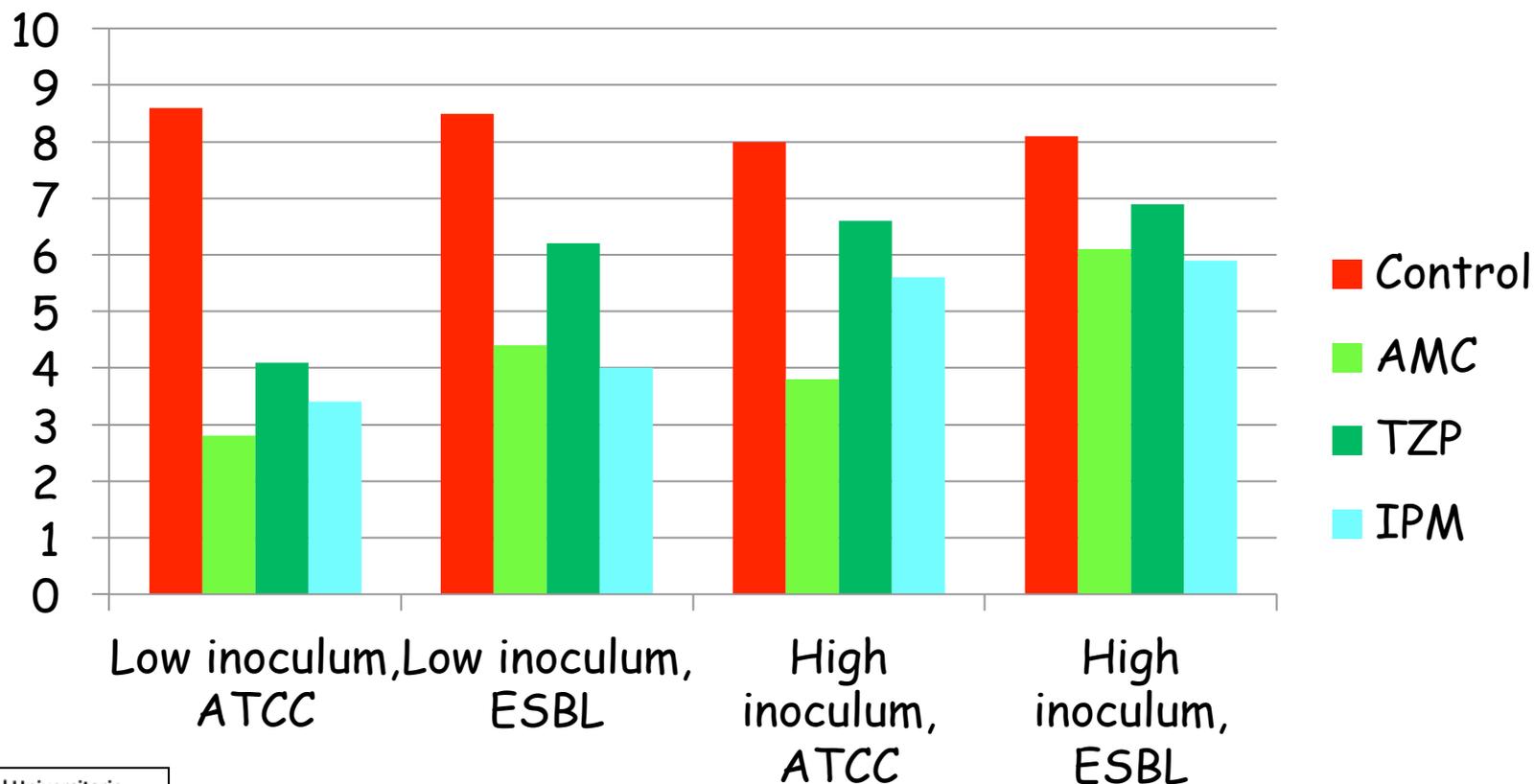
- Resistance due to ESBL overproduction, additional mechanisms (AmpC-type, OXA-1, porin loss, etc.)
- Inoculum effect: pit/taz but not amox/clav
  - López-Cerero, CMI 2010
- Animal models: exposure-dependent efficacy
  - Rice et al, AAC 1994, Thauvin-Eliopoulos et al, AAC 1997, Mentec et al, AAC 1992, Leleu et al, AAC 1994, Docobo et al AAC 2013
- Vitek® may fail to detect pip/taz R in *E. coli* producing CTX-M-15 + OXA-1
  - Pitout et al, Int J Antimicrob Agents 2008

# Inoculum Effect on the Efficacies of Amoxicillin-Clavulanate, Piperacillin-Tazobactam, and Imipenem against Extended-Spectrum $\beta$ -Lactamase (ESBL)-Producing and Non-ESBL-Producing *Escherichia coli* in an Experimental Murine Sepsis Model

F. Docobo-Pérez,<sup>a</sup> L. López-Cerero,<sup>b</sup> R. López-Rojas,<sup>a</sup> P. Egea,<sup>b</sup> J. Domínguez-Herrera,<sup>a</sup> J. Rodríguez-Baño,<sup>b</sup> A. Pascual,<sup>b,c</sup> J. Pachón<sup>a</sup>

AAC 2013

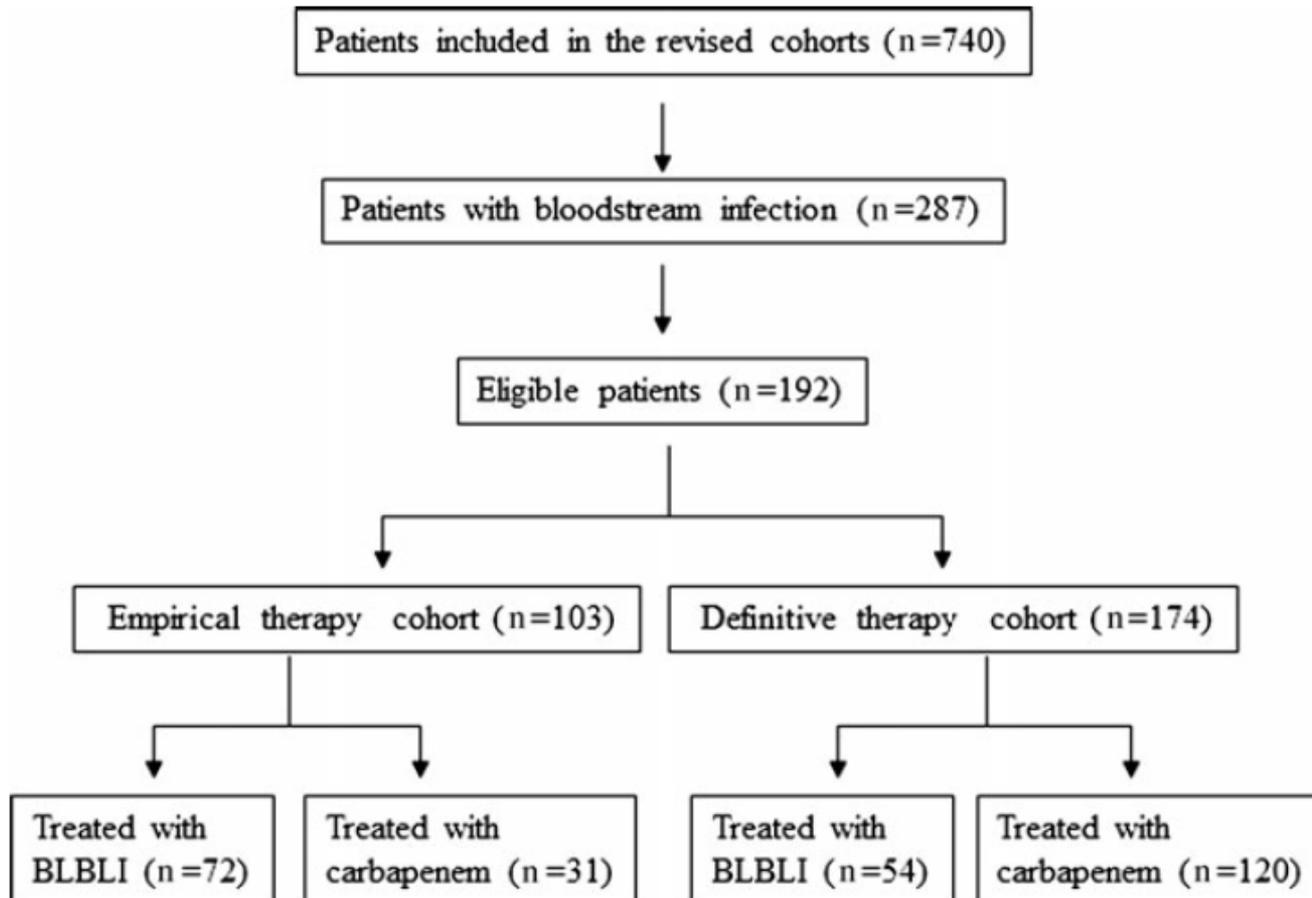
## Bacterial concentration in spleen (log<sub>10</sub> CFU/g)



# $\beta$ -Lactam/ $\beta$ -Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum $\beta$ -Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Clin Infect Dis 2012; 54: 167-74

Jesús Rodríguez-Baño,<sup>1,2</sup> María Dolores Navarro,<sup>1</sup> Pilar Retamar,<sup>1</sup> Encarnación Picón,<sup>1</sup> Álvaro Pascual,<sup>1,3</sup> and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group<sup>a</sup>



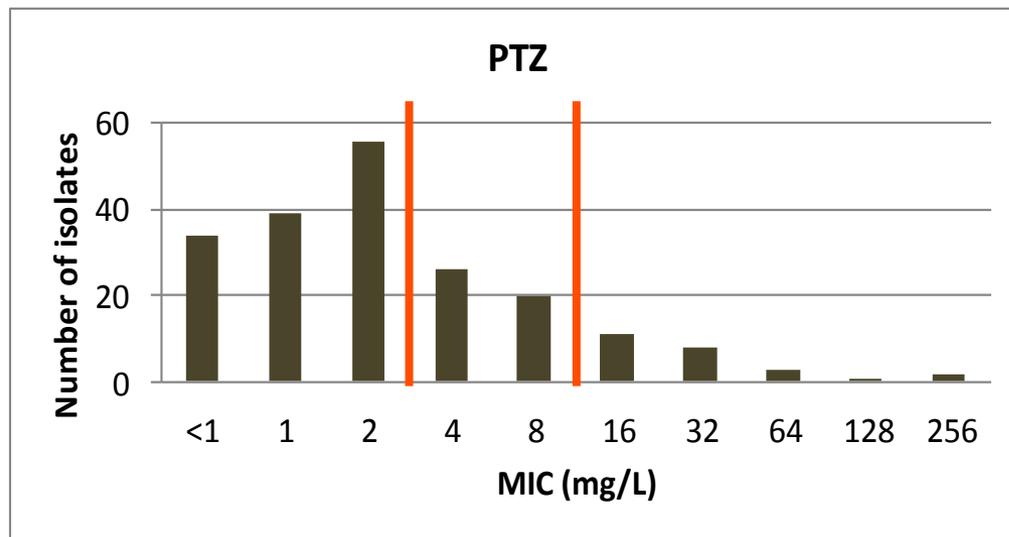
BLBLI vs carbapenems	Empirical therapy cohort	Definitive therapy cohort
Death (HR,adjusted)*	0.93 (0.25-3.51)	0.76 (0.28-2.07)
Hospital stay (HR, adjusted)*	1.07 (0.3-3.0)	1.32 (0.91-1.90)

\*Including propensity score

Community-onset BSI due to ESBL-*E. coli*  
60% urinary or biliary tract

Rodríguez-Baño et al, Clin Infect Dis 2012

# MIC distribution



Bacteraemia due to ESBLEC treated with PTZ  
N=39

Urinary tract  
N=11

Other source  
N=28

Low MIC  
Mortality 0/7<sup>a</sup>

Intermediate MIC  
Mortality 0/2

High MIC  
Mortality 0/2

Low MIC  
Mortality 0/11<sup>b</sup>

Intermediate MIC  
Mortality 3/8 (37.5%)<sup>c</sup>

High MIC  
Mortality 4/9 (44.4%)<sup>d</sup>

# Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum $\beta$ -lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas<sup>1,2</sup>, Giannoula S. Tansarli<sup>1</sup>, Petros I. Rafailidis<sup>1,2</sup> and Matthew E. Falagas<sup>1-3\*</sup>

JAC 2013

Carbapenems		Pooled RR (95% CI)
vs. non-BLBLI	Empirical	0.50 (0.33-0.77)
	Definitive	0.65 (0.47-0.91)
vs. BLBLI	Empirical	0.91 (0.66-1.25)
	Definitive	0.52 (0.23-1.13)

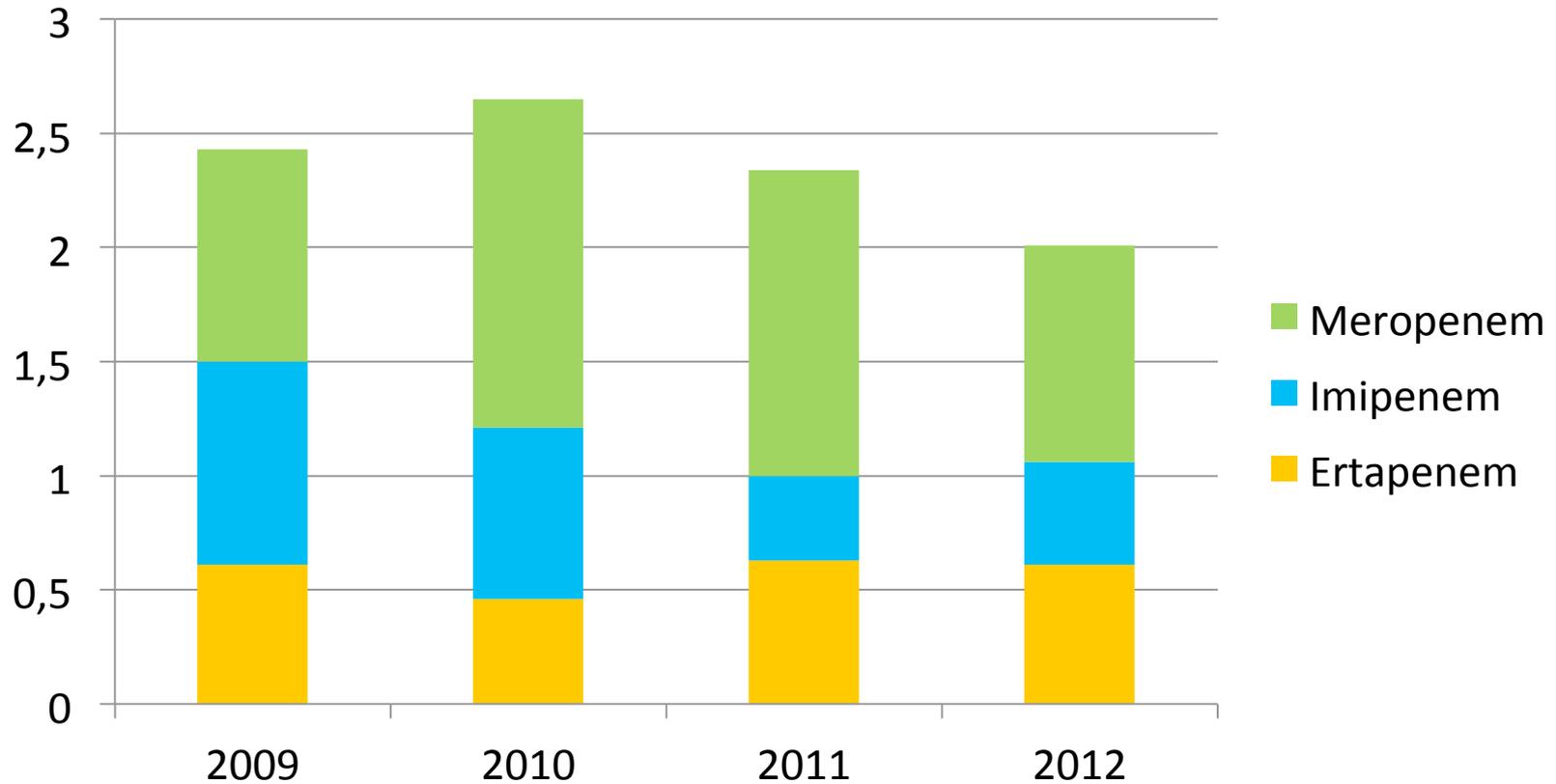
Merino trial ongoing in Australia/New Zealand!!

# Back to our case...

- Definitive therapy: amoxicillin/clavulanic acid (2 g/8h), switched to oral after 4 days
- Discharged day 8
- Follow-up culture negative on day 4 and thereafter
- 10 days total duration of therapy
- Lithotripsy performed 2 weeks later, nephrostomy catheter removed

# Hospital Universitario Virgen Macarena

Carbapenems, DDD / 100 patient-days



- 78 yo female, admitted because of stroke. Urinary catheter because of urinary retention.
- Day 5: UTI due to *Proteus mirabilis*, ciprofloxacin.
- Day 10: new fever, cough, dyspnoea. Aspiration 2 days before.
- T<sup>a</sup> 39°C, BP 95/65 mmHg, heart rate 90/min, rest unremarkable.
- 17.000 WBC (85% leucocytes), creatinine 0.9 mg/dl, lactate 2.5 mmol/L. O<sub>2</sub> sat 94%. Chest X-ray: new infiltrate
- Urine and blood cultures performed
- Oxygen, IV fluids and piperacillin/tazobactam (4/0.5 g bid, prolonged infusion) + amikacin (15 mg/Kg) administered.
- Blood cultures...



# ESBL-producing *K. pneumoniae*

■ Ampicillin	R	CTX-M-15
■ Amoxicillin/clavulante	R	SHV-1
■ Piperacillin/tazobactam	R	OXA-1
■ Ceftazidime	R	
■ Cefotaxime	R	
■ Cefoxitin	R	
■ Temocillin	R	
■ Meropenem	S ( $\leq 0.125$ mg/L)	
■ Ertapenem	S (0.5 mg/L)	
■ Ciprofloxacin	R	
■ Co-trimoxazole	R	
■ Gentamicin	R	
■ Amikacin	S	
■ Tigecycline	S (1 mg/L)	
■ Fosfomycin	S (8 mg/L)	
■ Colistin	S (1 mg/L)	

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy



Lower efficacy in  
non-UTI infections  
Paul et al, JAC 2007

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy



Lower efficacy in  
meta-analysis  
Tasina et al, Lancet ID 2011  
Yahav et al, JAC 2011  
Prased et al CID 2012

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy



Scarce experience,  
combination

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

Reserve for carba-R?

# Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomicin
- Colistin
- Combination therapy

No evidence for  
superiority

# Ertapenem

- Lower ecologic (or not higher) impact on *P. aeruginosa* compared to imipenem/meropenem
  - Sousa, JAC 2013; Carmeli, DMID 2011; Eagye, JAC 2011; Cook, AAC 2011; Nicoalu, IJAA 2012
- Evidence in ESBL: cohorts, case-series
  - VAP: Bassetti, JAC 2007
  - Bacteraemia: Lye, Ann Acad Med Singapore 2008; Collins, AAC 2012; Wu, IJID 2012; Lee, AAC 2012; Fong, Ann Pharmacother 2012
  - OPAT: Bazaz, JAC 2010

# Development of ertapenem resistance in a patient with mediastinitis caused by *Klebsiella pneumoniae* producing an extended-spectrum $\beta$ -lactamase

David Skurnik,<sup>1†</sup> Sigismond Lasocki,<sup>2</sup> Sylvie Bremont,<sup>3</sup>  
Claudette Muller-Serieys,<sup>1</sup> Marie Dominique Kitzis,<sup>4</sup> Patrice Courvalin,<sup>3</sup>  
Antoine Andreumont<sup>1</sup> and Philippe Montravers<sup>2</sup>

*Journal of Medical Microbiology* (2010), 59, 115–119

In Vivo Development of Ertapenem Resistance in a Patient with Pneumonia Caused by *Klebsiella pneumoniae* with an Extended-Spectrum  $\beta$ -Lactamase

CID 2006:42

Eugene Elliott,<sup>1</sup> Adrian J Brink,<sup>1</sup> Johan van Greune,<sup>2</sup> Zia Els,<sup>3</sup>  
Neil Woodford,<sup>4</sup> Jane Turton,<sup>5</sup> Marina Warner,<sup>4</sup> and David M Livermore<sup>4</sup>

## Case Report

# Refractory vertebral osteomyelitis due to CTX-M-14-producing *Escherichia coli* at ertapenem treatment in a patient with a coexisting urinary tract infection caused by the same pathogen

Int J Antimicrob Agents

Chen Hsiang Lee<sup>a,b</sup>, Lin-Hui Su<sup>c,d</sup>, Wei-Che Lin<sup>e</sup>, Yang-Fang Tang<sup>b</sup>, Jien-Wei Liu<sup>a,b,\*</sup>

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2006, p. 2833–2835  
0066-4804/06/\$08.00+0 doi:10.1128/AAC.01591-05  
Copyright © 2006, American Society for Microbiology. All Rights Reserved.

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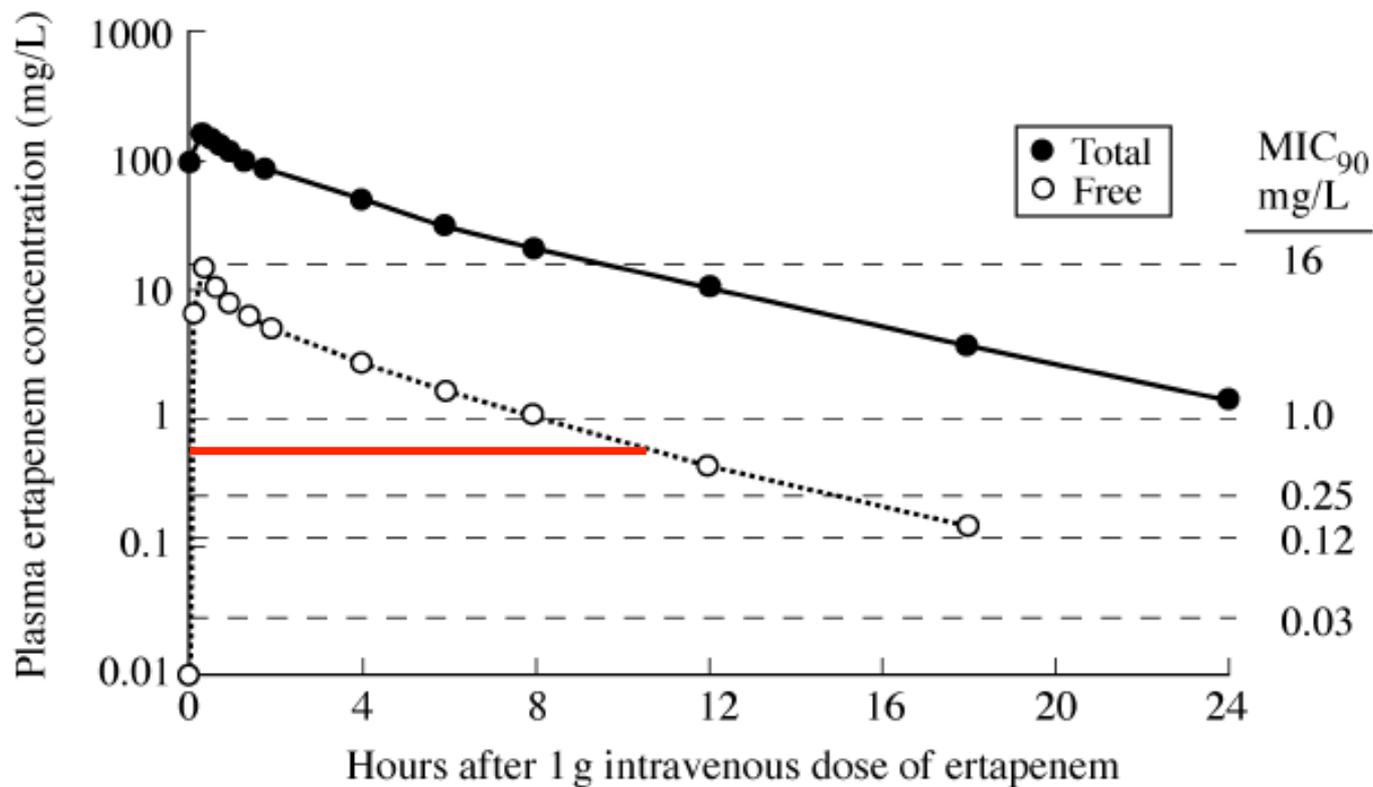
# Outer Membrane Protein Changes and Efflux Pump Expression Together May Confer Resistance to Ertapenem in *Enterobacter cloacae*

Dóra Szabó,<sup>1,2</sup> Fernanda Silveira,<sup>1</sup> Andrea M. Hujer,<sup>3</sup> Robert A. Bonomo,<sup>3</sup> Kristine M. Hujer,<sup>3</sup>  
Jane W. Marsh,<sup>1</sup> Christopher R. Bethel,<sup>3</sup> Yohei Doi,<sup>1</sup> Kathleen Deeley,<sup>1</sup>  
and David L. Paterson<sup>1\*</sup>

# Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians

David E. Nix<sup>1</sup>, Anup K. Majumdar<sup>2</sup> and Mark J. DiNubile<sup>2\*</sup>

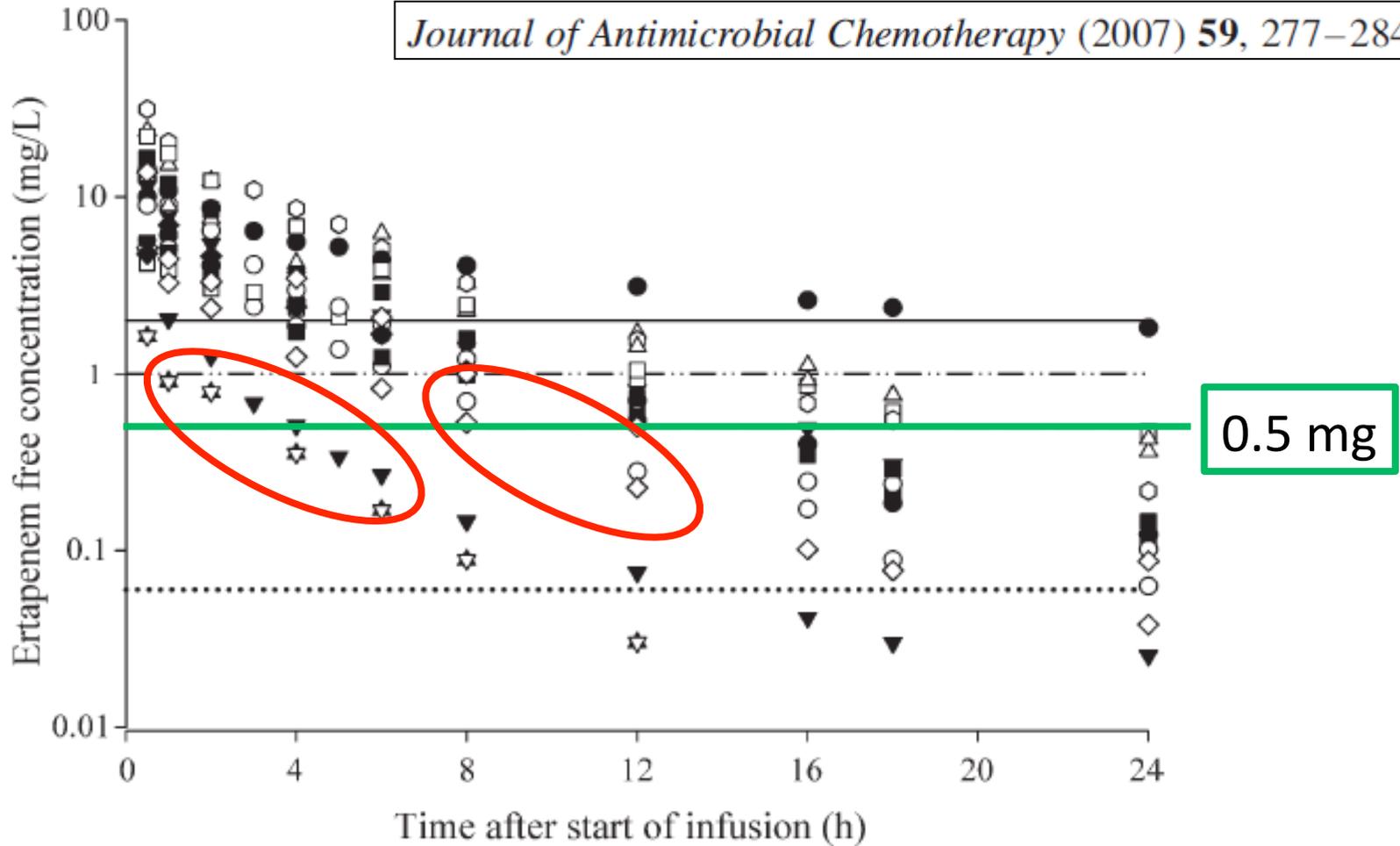
*Journal of Antimicrobial Chemotherapy* (2004) **53**, Suppl. S2, ii23–ii28



# Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration

Olaf Burkhardt<sup>1-3\*</sup>, Vipul Kumar<sup>1</sup>, Denise Katterwe<sup>3</sup>, Jolanta Majcher-Peszynska<sup>4</sup>,  
Bernd Drewelow<sup>4</sup>, Hartmut Derendorf<sup>1</sup> and Tobias Welte<sup>2,3</sup>

*Journal of Antimicrobial Chemotherapy* (2007) **59**, 277–284



# Back to our case...

- Contact precautions
- Day 3: Definitive therapy:
  - Discussion AMS team: ertapenem 1 gr/day, ertapenem 2 gr/day or meropenem 1 gr/8h
  - Meropenem was started (cheaper)
- Early response. Negative follow-up blood cultures
- Day 6: switched to ertapenem 1 gr/day and discharged (OPAT)
- Day 10: stop antibiotics (7 days, total duration with carbapenems)

# This is not a real case...

- 57 y, male, stroke
- Nosocomial pneumonia, severe sepsis, bacteraemic

<i>K. pneumoniae</i> MIC (mg/L)	Report	
– Ceftazidime	>32	R
– Meropenem	8	R
– Gentamicin	>32	R
– Cipro	>2	R
– Tigecycline	4	R
– Colistin	1	S
– Fosfomycin	16	S

# Select your choice...

- Meropenem (optimised)
- Colistin (optimised)
- Combination: meropenem + colistin
- Combination: meropenem + colistin + fosfo/tige
- Combination: colistin + fosfomycin
- Any other

# This is a real case...

- 57 y female, kidney stones
- ED: low grade fever, urinary complains. Urine + blood cultures. Discharged with oral amox/clav → ID outpatient clinic
- Urine and blood:

<i>K. pneumoniae</i>	MIC (mg/L)	Report
– Ceftazidime	>32	R
– Meropenem	0.5	S
– Ertapenem	2	R
– Gentamicin	0.5	S
– Cipro	>2	R
– Tigecycline	0.5	S
– Colistin	1	S
– Fosfomycin	16	S

# Select your choice...

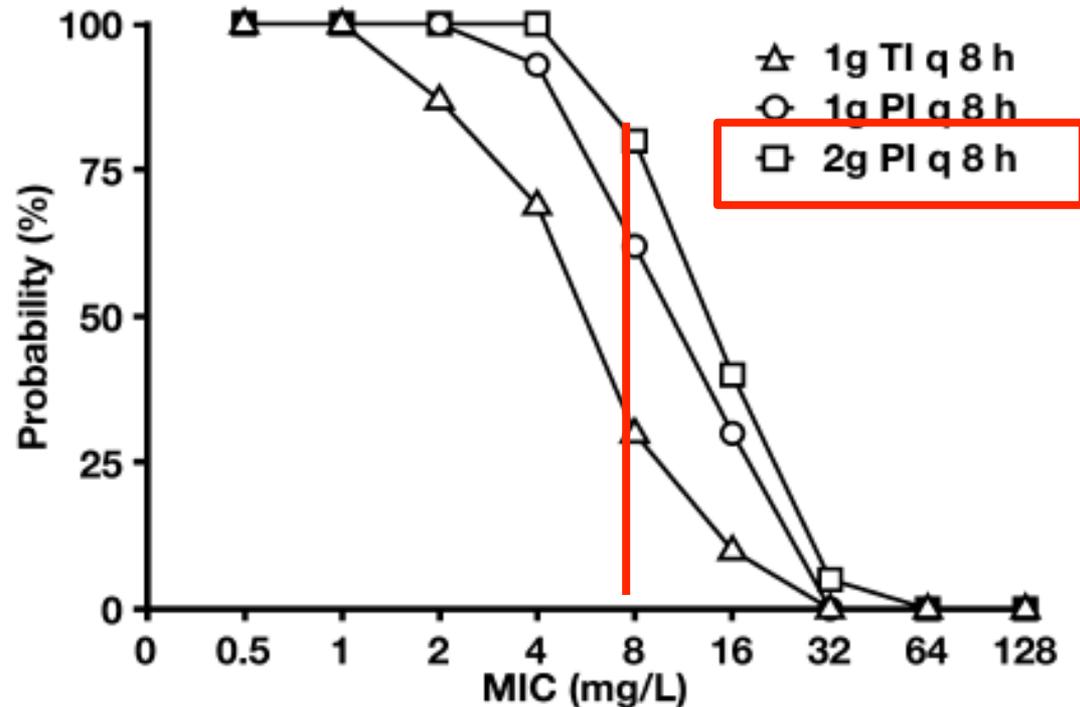
- Meropenem
- Colistin
- Combination: meropenem + colistin
- Combination: meropenem + colistin + fosfo/tige
- Combination: colistin + fosfomicin
- Any other



# Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems?

Clin Microbiol Infect 2011

G. L. Daikos<sup>1</sup> and A. Markogiannakis<sup>2</sup>

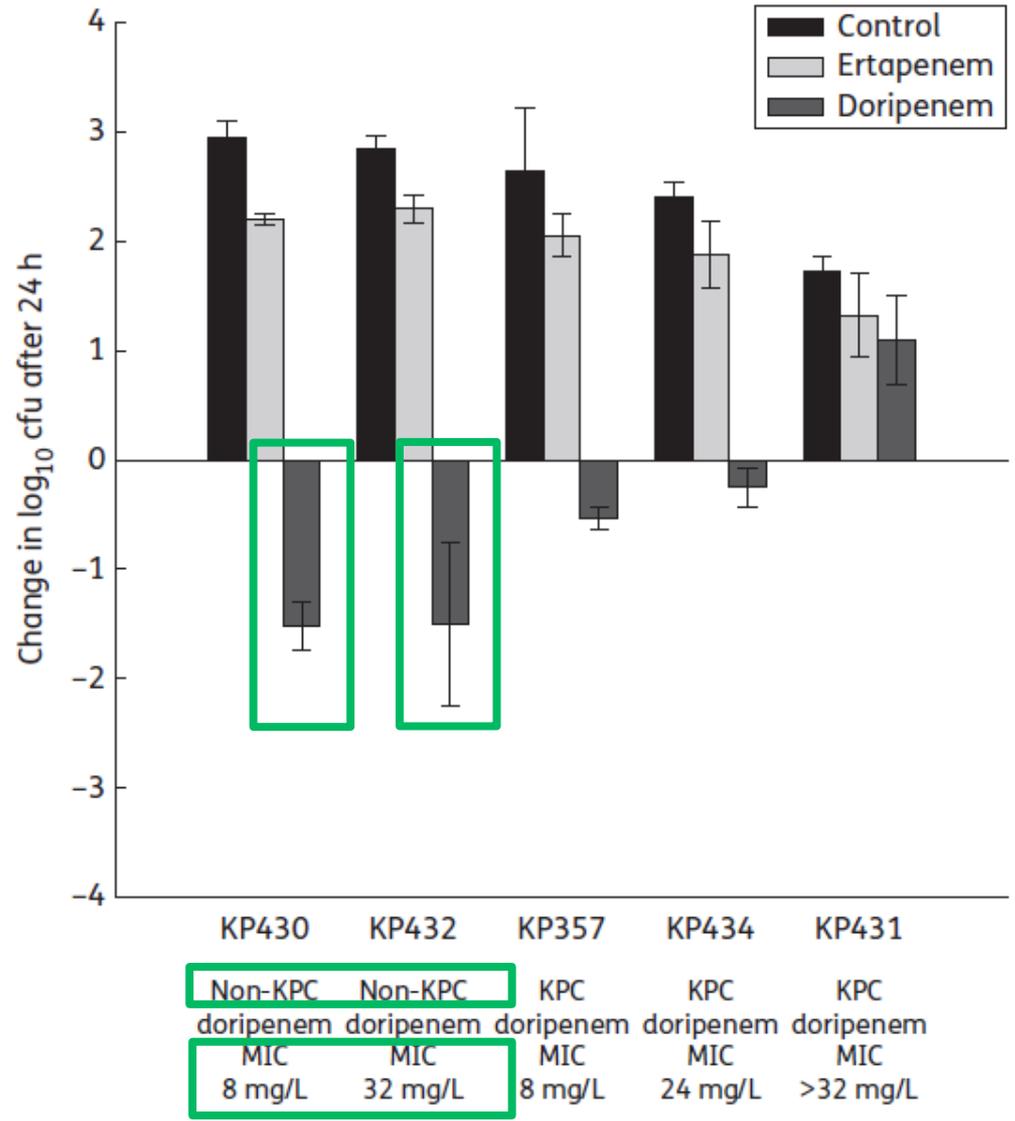


**FIG. 2.** Simulated target attainment probabilities for 50% time above the MIC (50%  $T > \text{MIC}$ ) of three different regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

# Efficacy of doripenem and ertapenem against KPC-2-producing and non-KPC-producing *Klebsiella pneumoniae* with similar MICs

Mao Hagihara<sup>1,2</sup>, Jared L. Crandon<sup>1</sup>, Carl Urban<sup>3</sup> and David P. Nicolau<sup>1\*</sup>

*J Antimicrob Chemother* 2013; **68**: 1616–1618



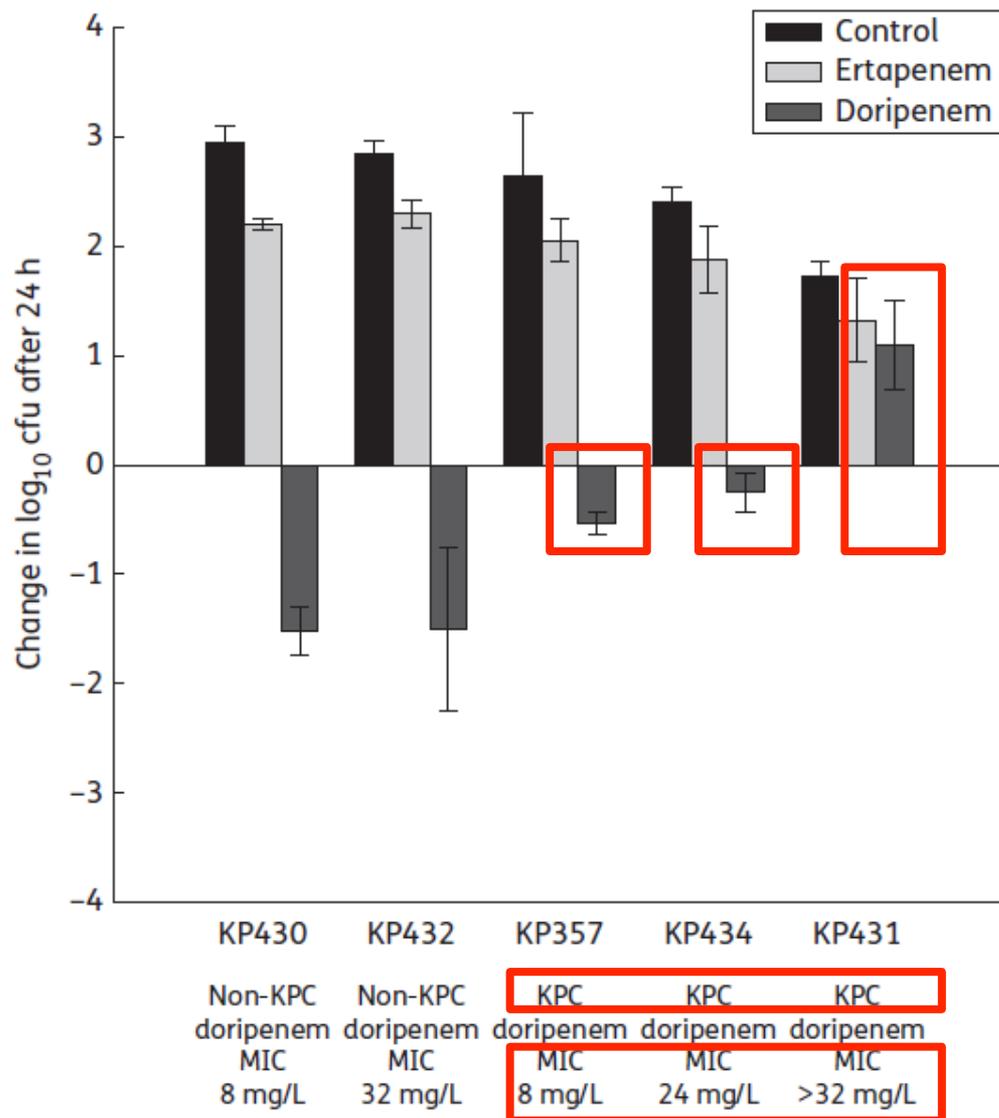
Isolate	MIC(mg/L)		Genotype
	doripenem	ertapenem	
KP430	8	>32	porin+ ACT-1
KP432	32	>32	porin+ ACT-1
KP357	8	>64	KPC-2 producing
KP434	24	>32	KPC-2 producing
KP431	>32	>32	KPC-2 producing

Non-KPC	Non-KPC	KPC	KPC	KPC
doripenem	doripenem	doripenem	doripenem	doripenem
MIC	MIC	MIC	MIC	MIC
8 mg/L	32 mg/L	8 mg/L	24 mg/L	>32 mg/L

# Efficacy of doripenem and ertapenem against KPC-2-producing and non-KPC-producing *Klebsiella pneumoniae* with similar MICs

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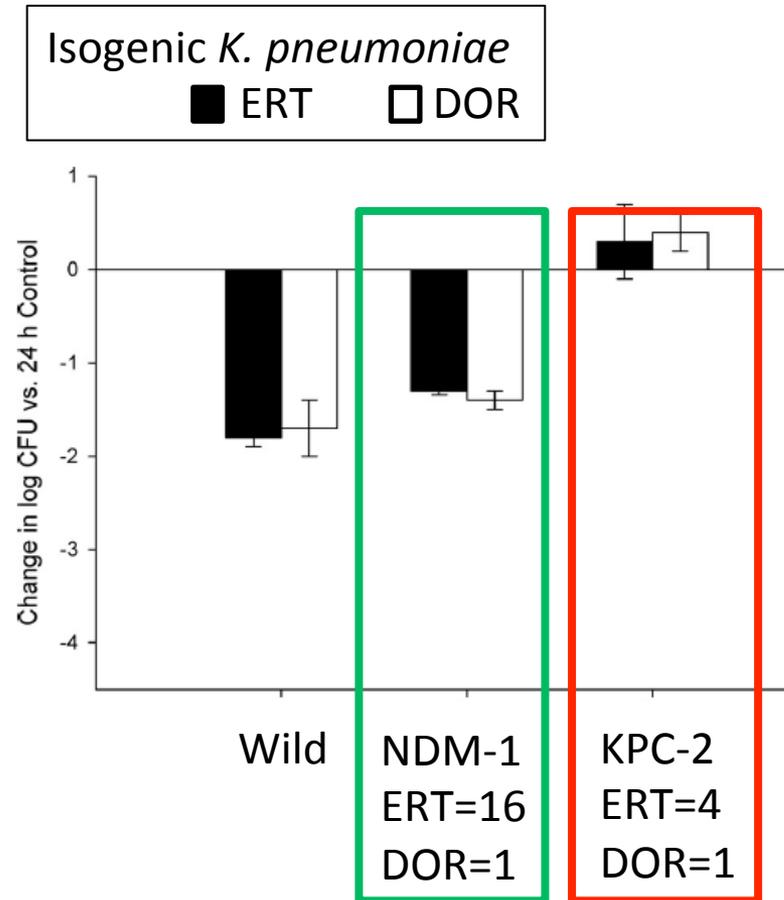
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KP431	>32	>32	KPC-2 producing

# Efficacy of Humanized Carbapenem Exposures against New Delhi Metallo- $\beta$ -Lactamase (NDM-1)-Producing *Enterobacteriaceae* in a Murine Infection Model

Antimicrob Agents Chemother 2013

Dora E. Wiskirchen,<sup>a</sup> Patrice Nordmann,<sup>b</sup> Jared L. Crandon,<sup>c</sup> David P. Nicolau<sup>c,d</sup>

Immunocompetent and neutropenic mouse thigh infection model  
Humanised dose: ERT 1 gr/d, DOR g/8h in 4h



# Clinical studies analysing combination therapy for CPE

Ref	Design	Patients	N	Lower mortality (adjusted )	Limitations
Zarcotou CMI 2011	Retrospective cohort	Bacteraemia KPC Kp	53	No <sup>1</sup> (adequate therapy) (infection-related)	+++
Tumbarello CID 2013	Retrospective cohort	Bacteraemia KPC Kp	124	Yes <sup>1</sup> (MER + COL + TIG)	++
Qureshi AAC 2013	Retrospective cohort	Bacteraemia KPC Kp	41	Yes <sup>2</sup>	+++
Daikos AAC 2014	Retrospective cohort	Bacteraemia KPC or VIM Kp	205	Yes <sup>1</sup>	++

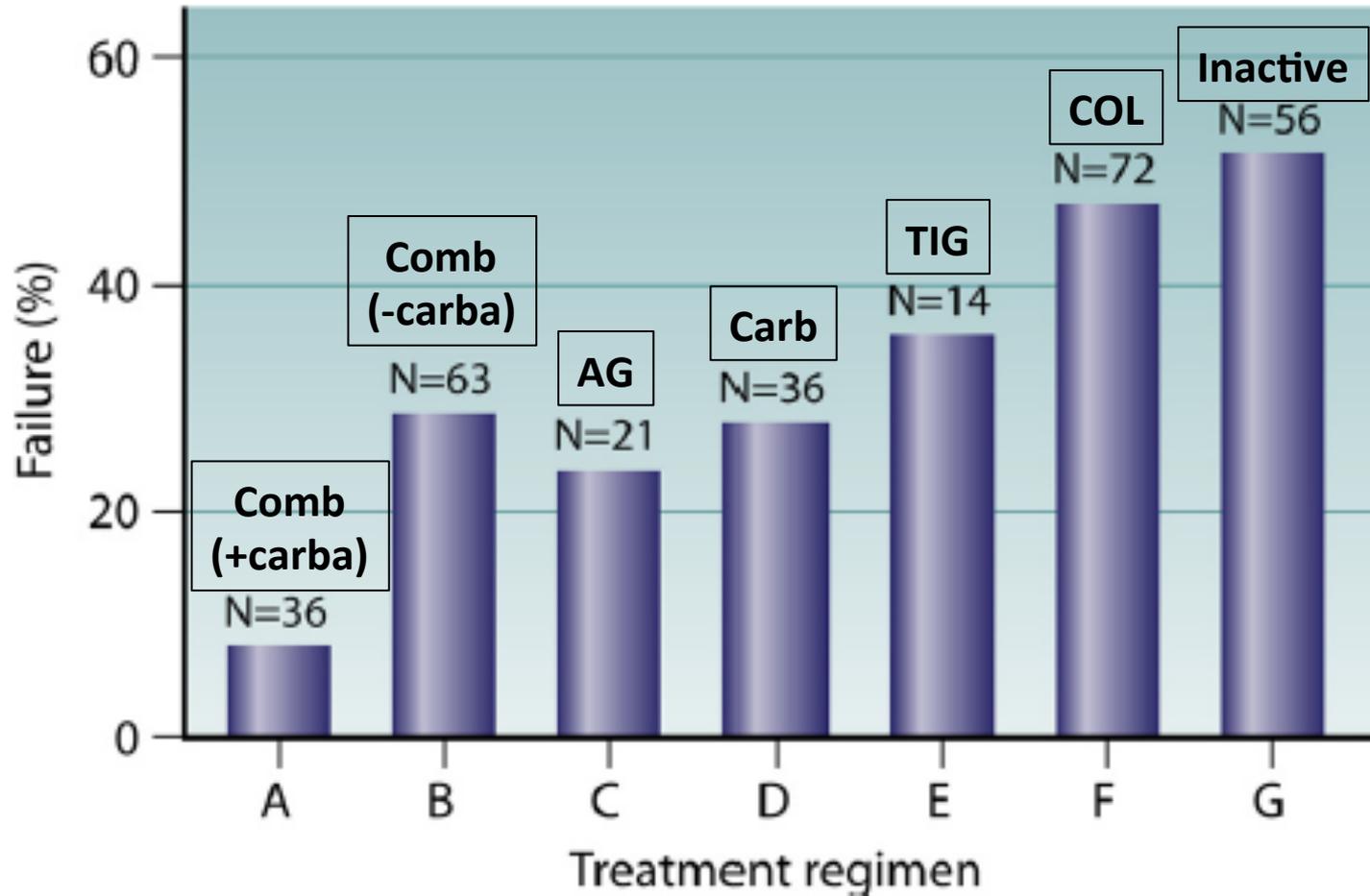
1. In vitro active (EUCAST)

2. With activity against gram negatives

# Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis,<sup>a</sup> A. Markogiannakis,<sup>b</sup> M. Psychogiou,<sup>c</sup> P. T. Tassios,<sup>a</sup> and G. L. Daikos<sup>c</sup>

Clin Microbiol Rev 2012



# Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

L. S. Tzouveleki<sup>a</sup>, A. Markogiannaki<sup>b</sup>, M. Psychogiou<sup>c</sup>, P. T. Tassios<sup>a</sup> and G. L. Daikos<sup>c</sup>

Clin Microbiol Rev 2012

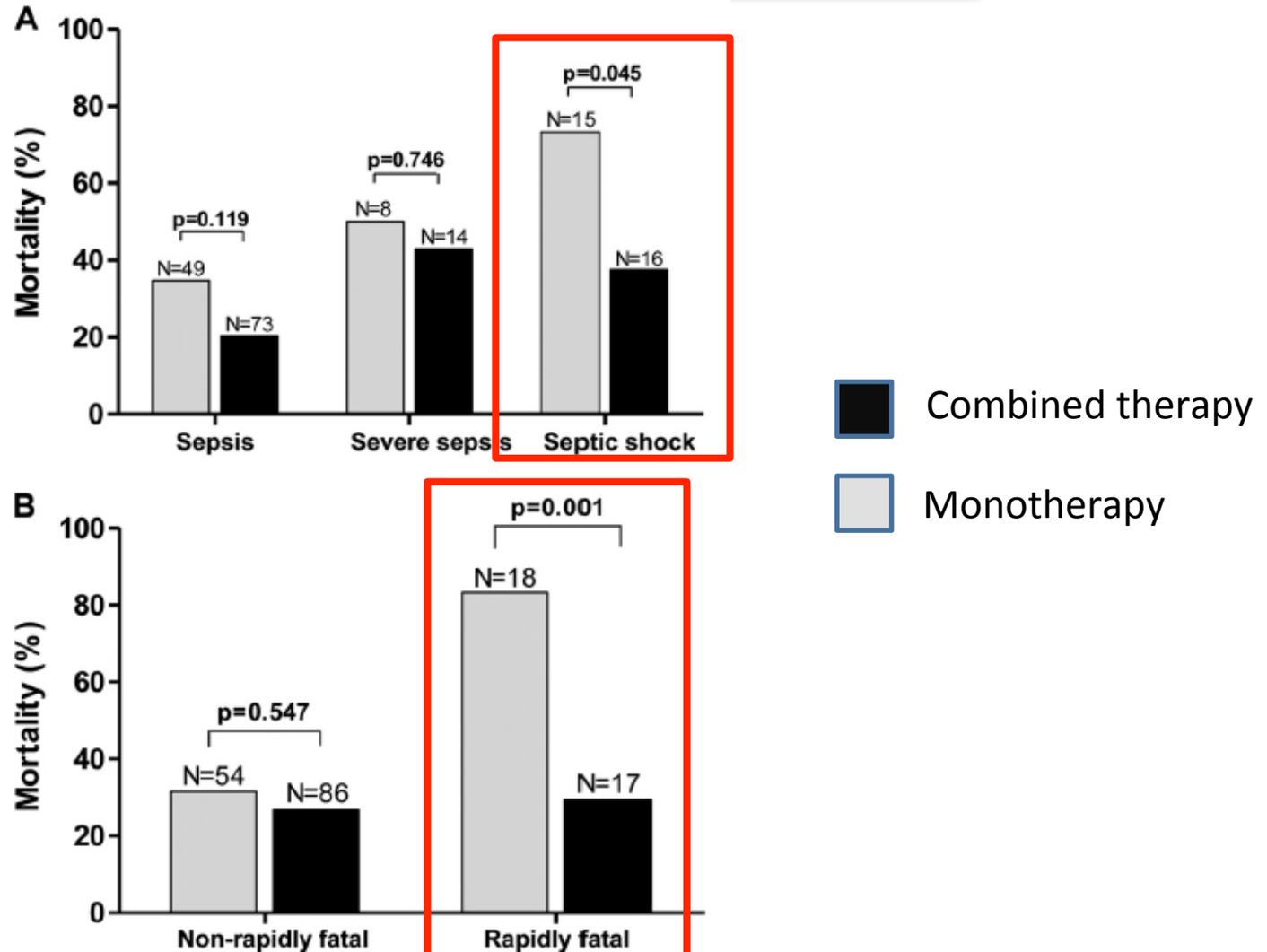
TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies<sup>a</sup>

MIC of carbapenem ( $\mu\text{g/ml}$ )	No. of patients	No. of successes	No. of failures	% Failure
$\leq 1$	17	12	5	29.4
2	12	9	3	25.0
4	7	5	2	28.6
8	6	4	2	33.3
Subtotal	42	30	12	28.6 <sup>b</sup>
$> 8$	8	2	6	75.0 <sup>b</sup>
Total	50	32	18	36

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

Antimicrob Agents Chemother 2014

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



# Carbapenem-Sparing Antibiotic Regimens for Infections Caused by *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* in Intensive Care Unit

Francesco Sbrana,<sup>1</sup> Paolo Malacarne,<sup>2</sup> Bruno Viaggi,<sup>2</sup> Sergio Costanzo,<sup>3</sup> Piero Leonetti,<sup>3</sup> Alessandro Leonildi,<sup>4</sup> Beatrice Casini,<sup>5</sup> Carlo Tascini,<sup>4</sup> and Francesco Menichetti<sup>4</sup>

Clin Infect Dis 2013

26 infections in 22 patients  
18 polytrauma

TIG + GEN: 16 (+ FOS 8)

TIG + COL 11 (+ FOS 5, GEN 5)

COS + GEN 1

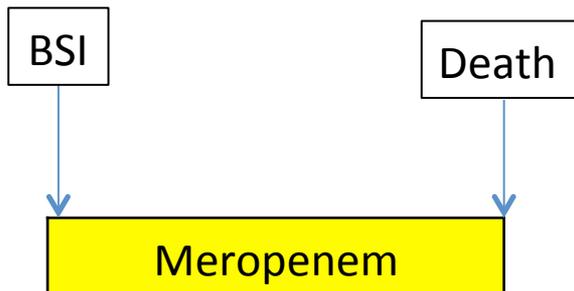
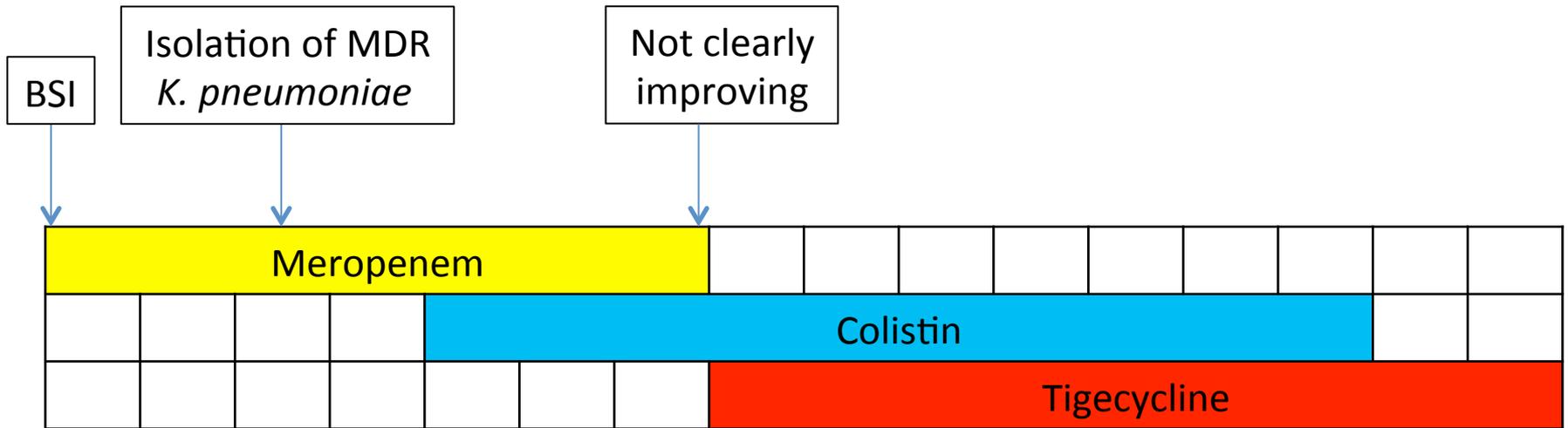
TIG 1

Site of Infection	No. of Infections			Survival at 30 Days After Discharge
	Appropriate Therapy by Vitek 2 System <sup>a</sup>	Appropriate Therapy by E-test <sup>a</sup>	Response to Therapy	
VAP	1/11	11/11	11/11	11/11
VAP with bacteremia	0/5	5/5	4/5	3/5 <sup>c</sup>
Bloodstream infection	1/7	7/7	7/7	7/7
Others <sup>b</sup>	1/3	3/3	2/3	2/3 <sup>d</sup>

23/26

# Survivor bias

Higher probability of receiving combination therapy in survivors?



# Back to our (not-real) case...

- KPC producer
- My choice would be meropenem 2 g/8h (extended infusion) + colistin 4.5 million IU/12h (loading dose, 6 M)
- May consider adding fosfomycin 4 gr/6h if no early response (48 h)

# Bacteraemia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge

C. Navarro-San Francisco<sup>1</sup>, M. Mora-Rillo<sup>1</sup>, M. P. Romero-Gómez<sup>2</sup>, F. Moreno-Ramos<sup>3</sup>, A. Rico-Nieto<sup>1</sup>, G. Ruiz-Carrascoso<sup>2</sup>, R. Gómez-Gil<sup>2</sup>, J. R. Arribas-López<sup>1</sup>, J. Mingorance<sup>2</sup> and J. R. Paño-Pardo<sup>1</sup>

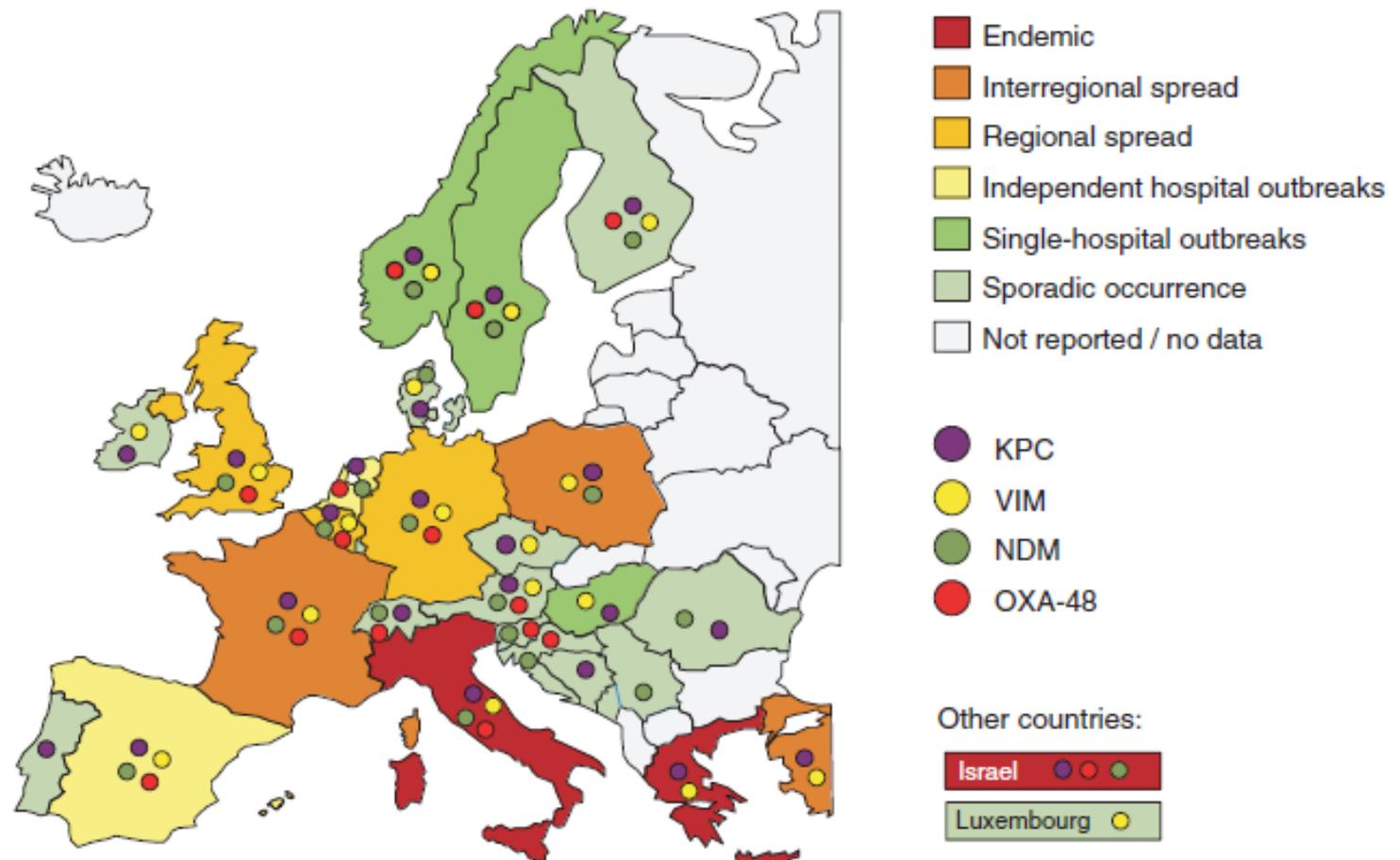
*Clin Microbiol Infect* 2012; **19**: E72–E79

Treatment	All patients (n = 34)	Patients alive at day 30 after onset of BSI (n = 19) (%)	Patients dead at day 30 after onset of BSI (n = 15) (%)	
<b>Monotherapy</b>				
Colistin	1	1 (5.2)	0 (0)	
Tigecycline	2	2 (10.5)	0 (0)	
Amikacin	3	2 (10.5)	1 (6.6)	
Carbapenem	1	0 (0)	1 (6.6)	
<b>Total monotherapy</b>	<b>7</b>	<b>5 (26.3)</b>	<b>2 (13.3)</b>	<b>2/5 (40%)</b>
<b>Combined therapy</b>				
Two or more active drugs (carbapenem not included)	21	10 (52.6)	11 (73.3)	
Two or more active drugs (carbapenem included)	6	4 (21.1)	2 (13.3)	
<b>Total combined therapy</b>	<b>27</b>	<b>14 (73.7)</b>	<b>13 (86.6)</b>	<b>13/27 (48%)</b>

# Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe

Clin Microbiol Infect 2012

R. Cantón<sup>1,2</sup>, M. Akóva<sup>3</sup>, Y. Carmeli<sup>4</sup>, C. G. Giske<sup>5</sup>, Y. Glupczynski<sup>6</sup>, M. Gniadkowski<sup>7</sup>, D. M. Livermore<sup>8,9</sup>, V. Miriagou<sup>10</sup>, T. Naas<sup>11</sup>, G. M. Rossolini<sup>12</sup>, Ø. Samuelsen<sup>13</sup>, H. Seifert<sup>14</sup>, N. Woodford<sup>9</sup> and P. Nordmann<sup>11</sup>; the European Network on Carbapenemases\*



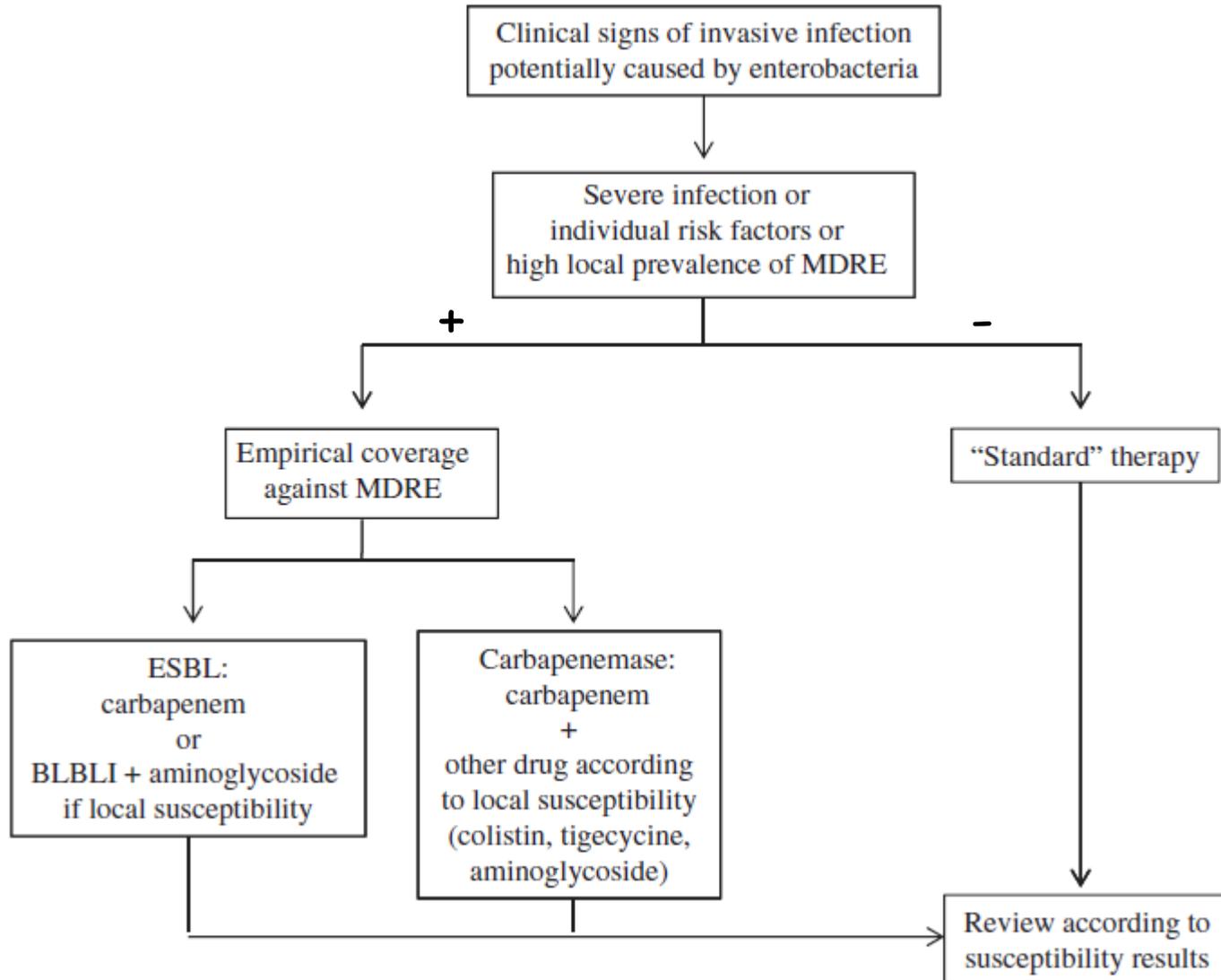
# Back to our (real) case...

- OXA-48 + ESBL producer
- Urologic work-up
- Gentamicin 5 mg/kg/day 5 days
- Follow-up cultures negative day 3
- Switched to oral fosfomicin tromethamine, 3 g / 48h to complete 14 days

# Clinical management of infections caused by multidrug-resistant *Enterobacteriaceae*

Mercedes Delgado-Valverde, Jesús Sojo-Dorado, Álvaro Pascual and Jesús Rodríguez-Baño

2013





✘ Det går inte att visa bilden. Det finns inte tillräckligt med ledigt minne för att kunna öppna bilden eller så är bilden skadad. Starta om datorn och öppna sedan filen igen. Om det röda X:et fortfarande visas måste du kanske ta bort bilden och sedan infoga den igen.



SPANISH NETWORK  
FOR RESEARCH IN  
INFECTIOUS DISEASES

**INCREMENT project: A multinational effort aimed at providing observational data on antibiotic therapy of bloodstream infections caused by multidrug-resistant *Enterobacteriaceae* (ESBL, carbapenemases)**

38 hospitals, 16 countries

Registered in [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01764490)

- Predefined hypothesis
- Statistical analysis plan

[www.incrementproject.org](http://www.incrementproject.org)



**13<sup>th</sup> ESCMID Summer School  
Sigtuna, Sweden  
July 5<sup>th</sup> - July 12<sup>th</sup> 2014**

**Organizers:  
Emmi Andersson, Tibor Paul**





Seville

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