Carbapenemase-producing Enterobacteriaceae with low-level resistance to carbapenems. Do we have more treatment options?

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ESCMID Postgraduate Education Course, Athens
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Carbapenem Resistant Enterobacteriaceae
A major Public Health Threat

- Increased mortality (25%-70%)
- Limited treatment options
- High potential for spread

Estimated Mortality Rate Among Hospitalized Patients with CRKP Infections

- ✓ Israel 2007: 8/100,000 population

  Schwaber MJ *JAMA 2008; 300:2911*

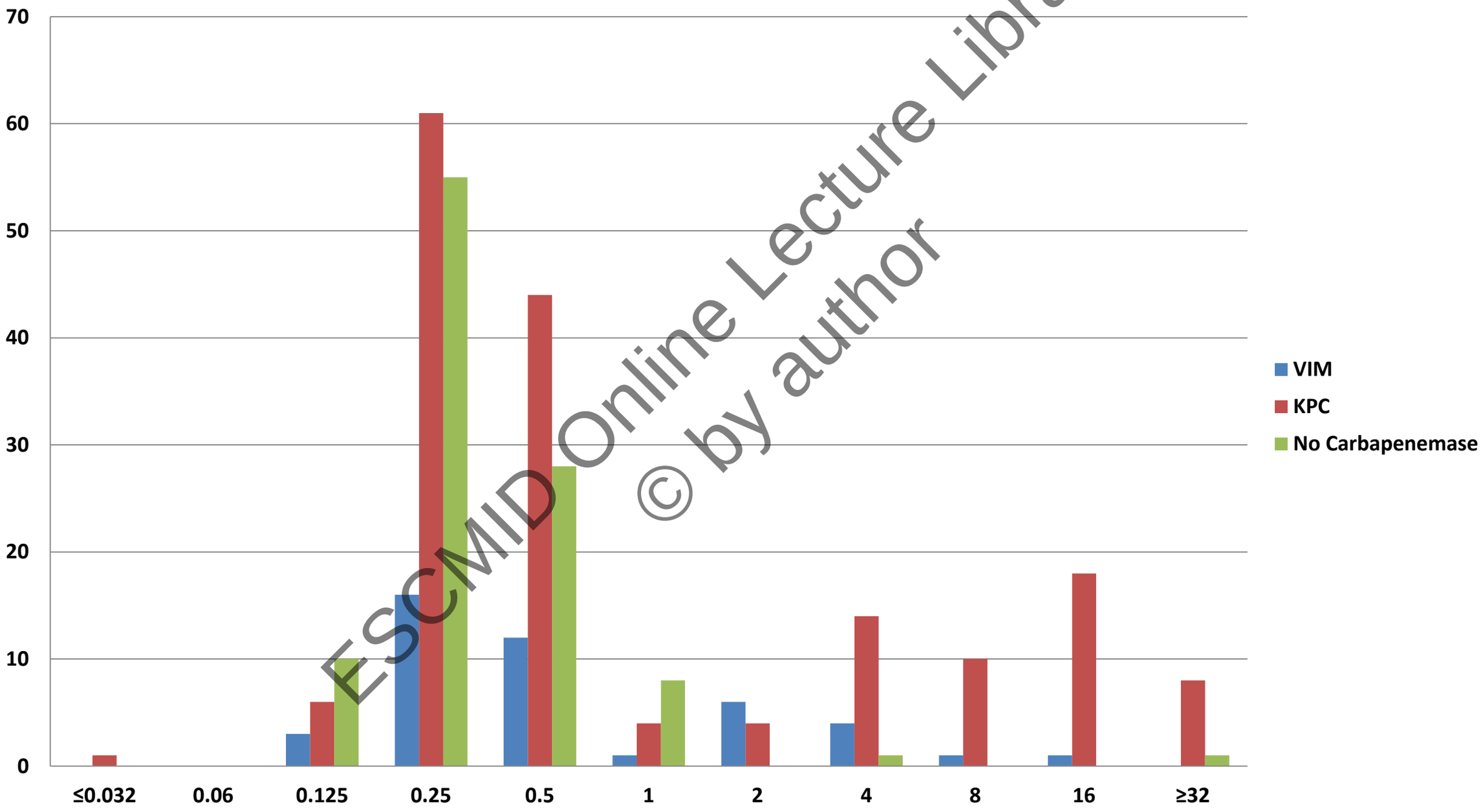
- ✓ Greece 2011: 10/100,000 population

  Hellenic Center for Disease Control and Prevention (National Action Plan)

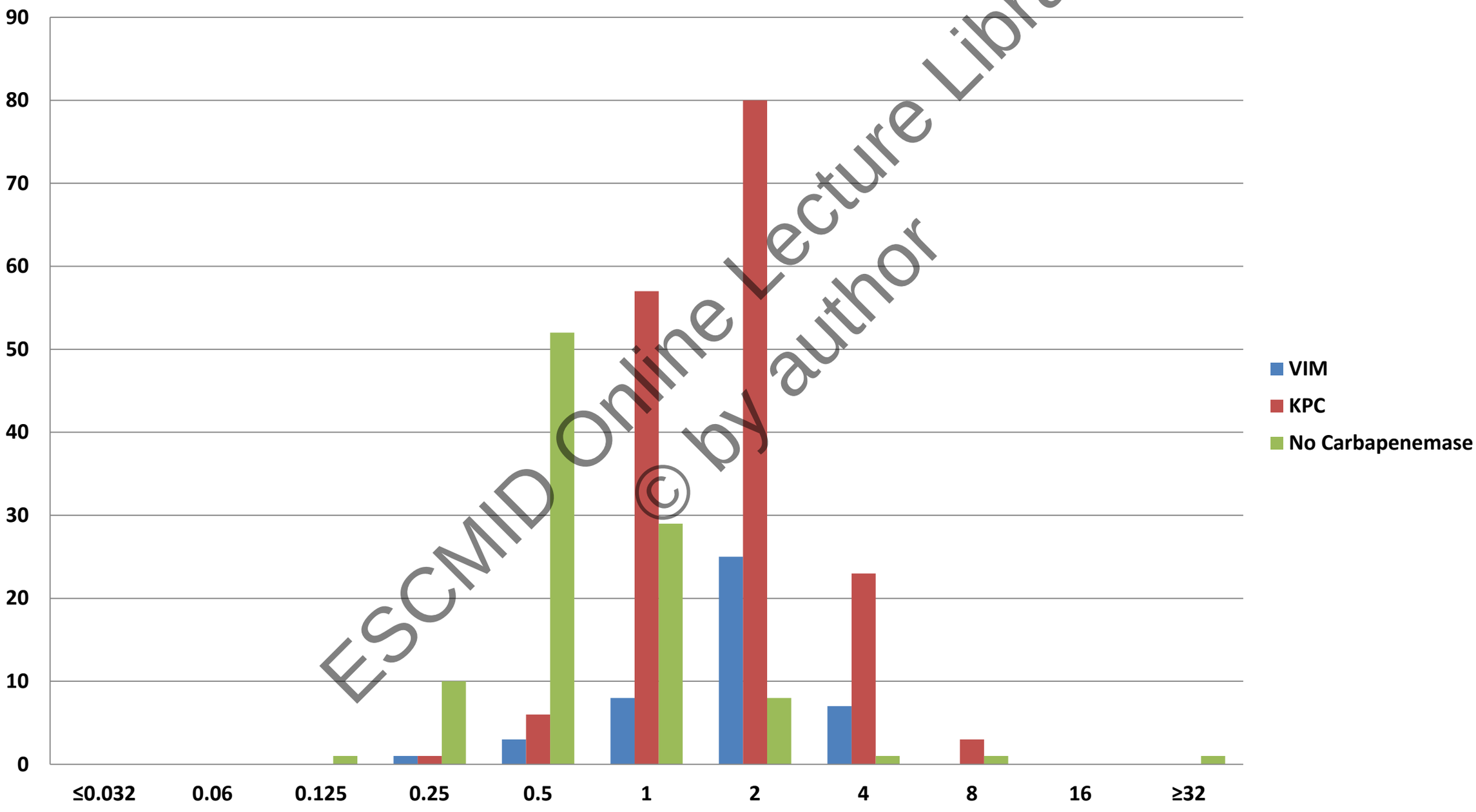
Antimicrobial Agents with *in Vitro* Activity against CPE

- ✓ Aztreonam (MBL in the absence of ESBL)
- ✓ Carbapenems
- ✓ Gentamicin
- ✓ Colistin
- ✓ Tigecycline
- ✓ Fosfomycin

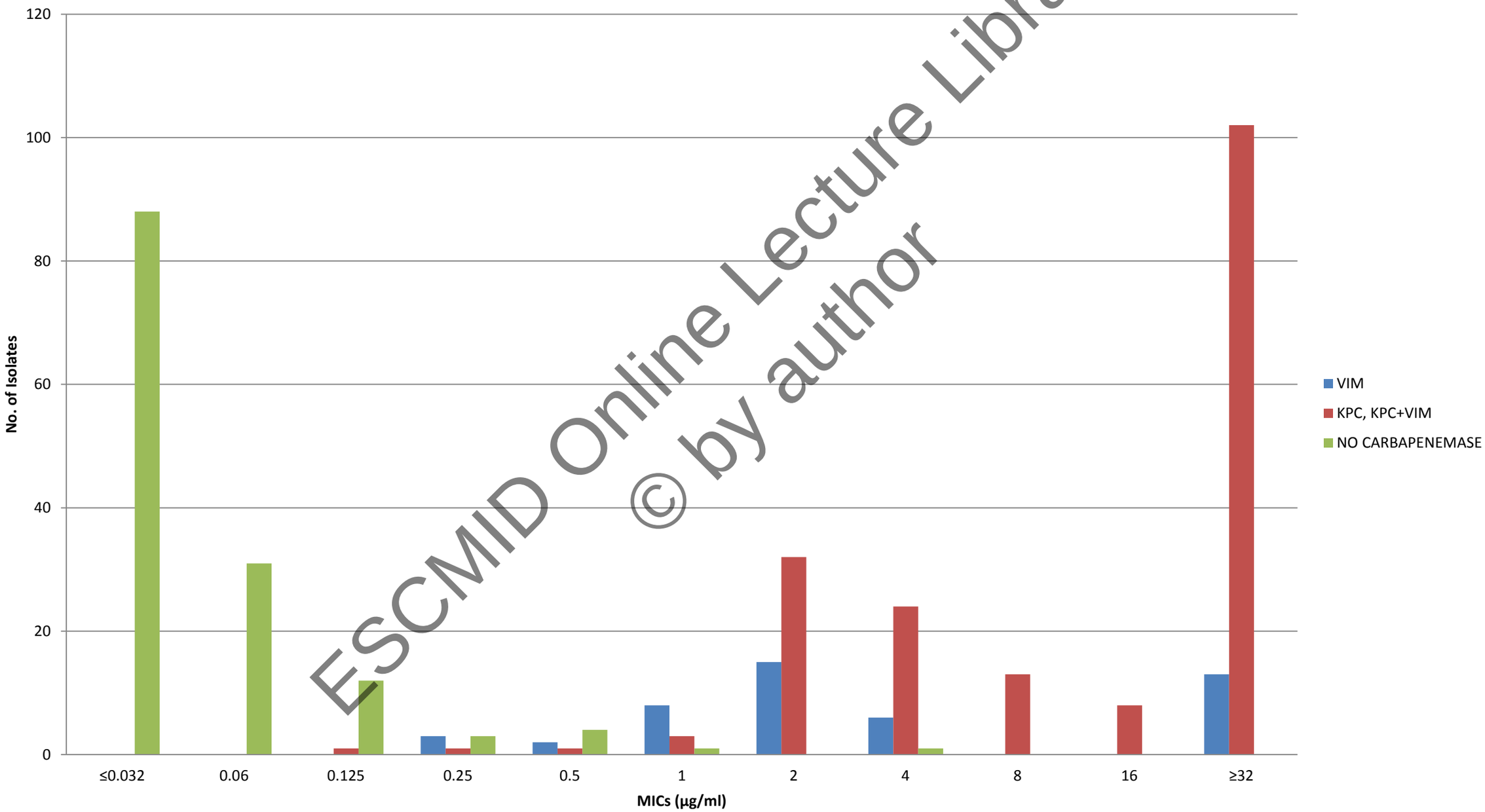
Distribution of Colistin MICs for 317 *K. pneumoniae* Blood Isolates



Distribution of Tigecyclin MICs for 317 *K. pneumoniae* Blood Isolates



Distribution of Meropenem MICs for 372 Consecutive Kp Bloodstream Isolates



Enterobacteriaceae - Carbapenems
Revised… Breakpoints (MIC µg/ml)*

Agent	CLSI 2010 (Old)			CLSI June 2010 (New)		
	Susc	Int	Res	Susc	Int	Res
Doripenem	-	-	-	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.25	0.5	≥1
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

*June 2010
Corresponding disk diffusion breakpoints also revised

New Paradigm

Isolation of Enterobacteriaceae

↓

Perform tests for susceptibility and apply the new "lower" breakpoints

↓

Report the susceptibility results for treatment purposes - no editing of "S" results

↓

Perform special tests for resistance mechanisms only for infection control and epidemiological purposes

Enterobacteriaceae

% Capture of Carbapenemases at MIC (μg/ml)

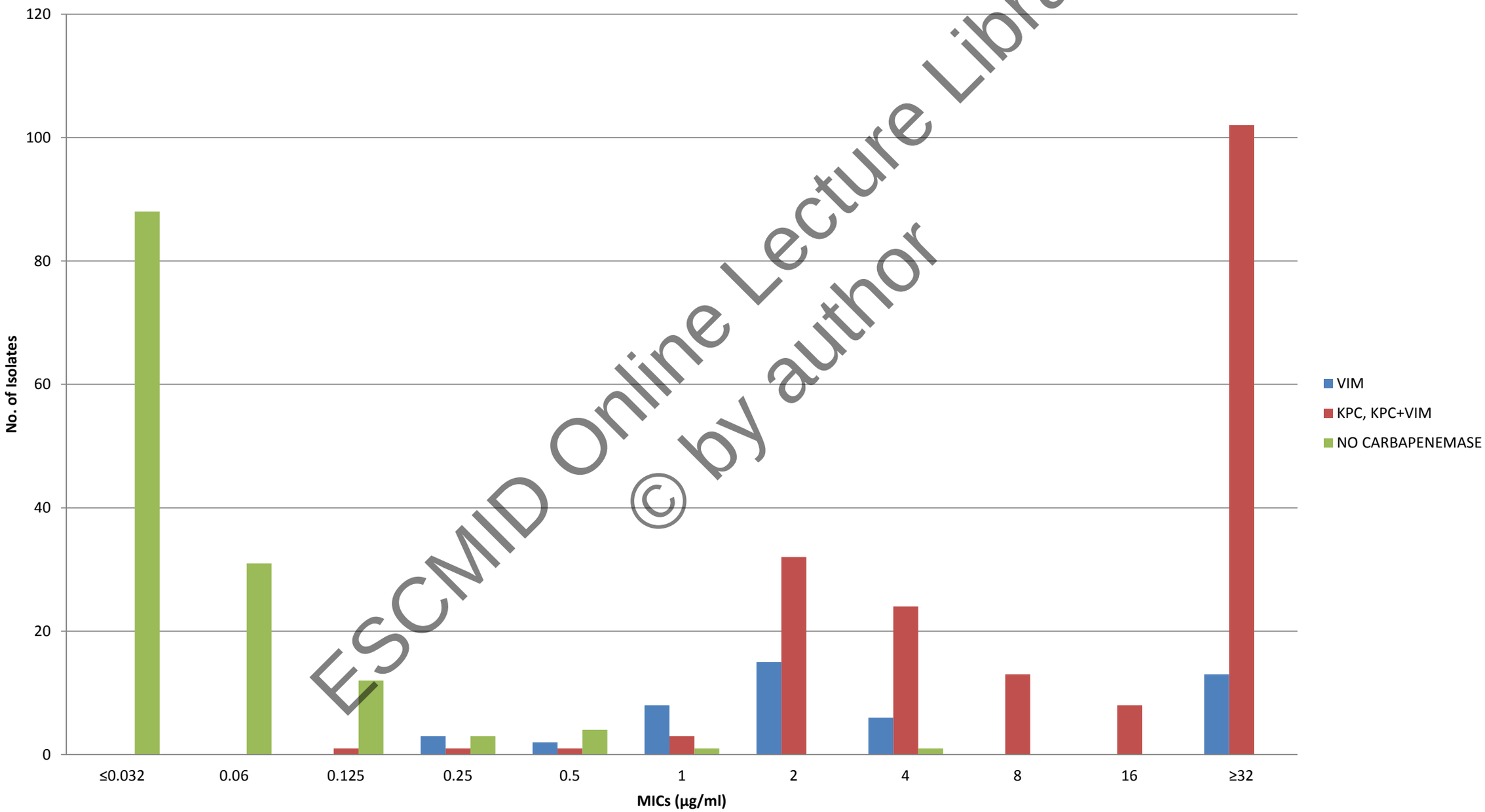
Antimicrobial Agent	New CLSI Breakpoints			Old CLSI Breakpoints
	S	I	R	
Imipenem	≤1 0%*	2 14%	≥4 86%	≤4 / 8 / ≥16
Meropenem	≤1 1.2%	2 15%	≥4 84%	≤4 / 8 / ≥16
Ertapenem	≤0.25 0%	0.5 0.3%	≥1 99.7%	≤2 / 4 / ≥8
Doripenem	≤1 0%	2 2.3%	≥4 97.7%	≤0.5 (FDA BP)

N = 474 Enterobacteriaceae; 328 KPC or MBL strains

* % of carbapenemase producers that have Imipenem MIC ≤1 μg/ml

CLSI Agenda Book, January 2010.

Distribution of Meropenem MICs for 372 Consecutive Kp Bloodstream Isolates

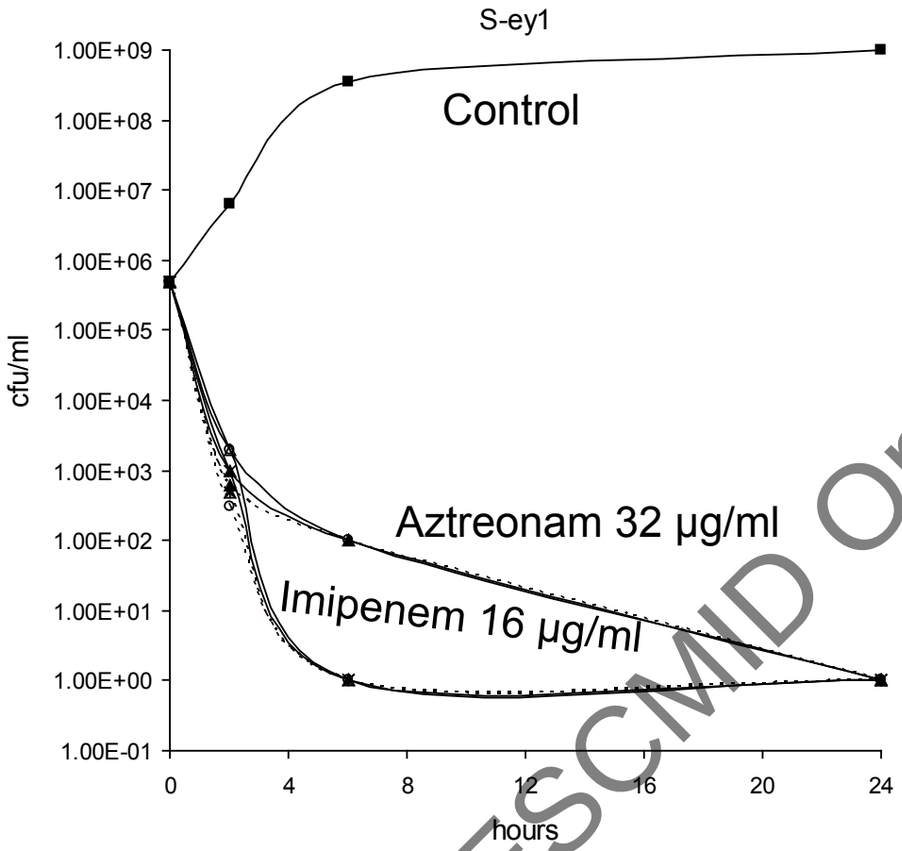


- Automated systems have inherent problems in reliably determining MICs
  - Broth microdilution
  - Etest

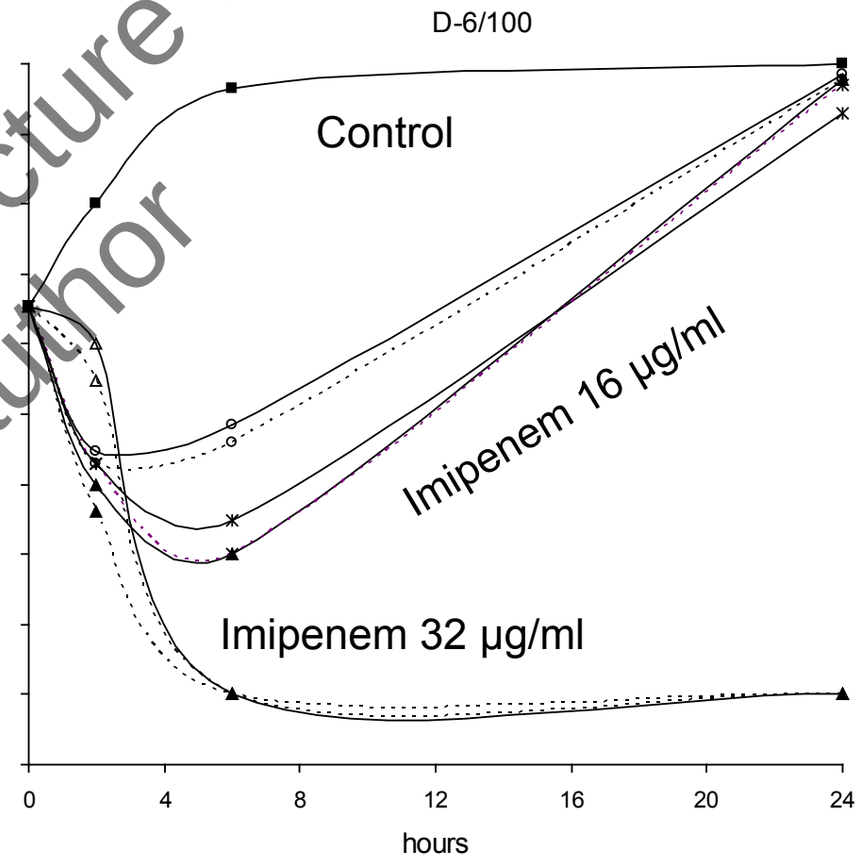
Can we use carbapenems against carbapenemase-producing organisms ?

In Vitro Killing Kinetics of Imipenem on VIM and non-VIM Producing *K. pneumoniae*

VIM-negative, MIC=0.125 µg/ml

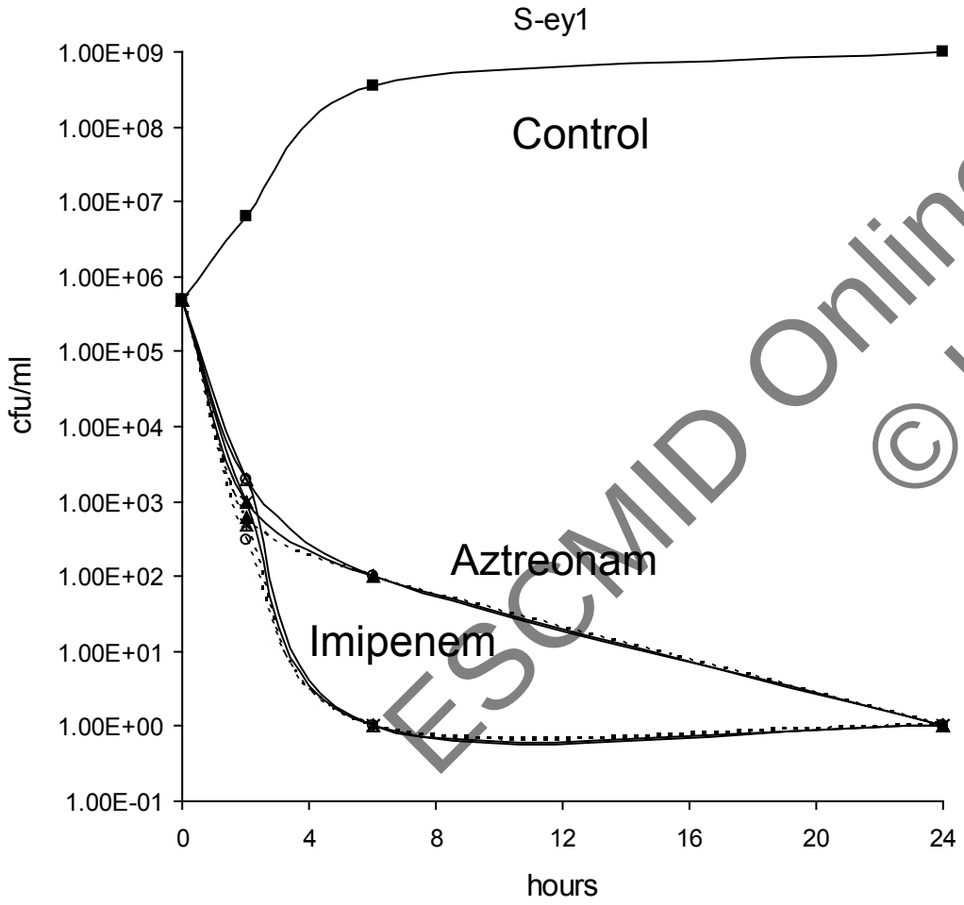


VIM-positive, MIC=2 µg/ml

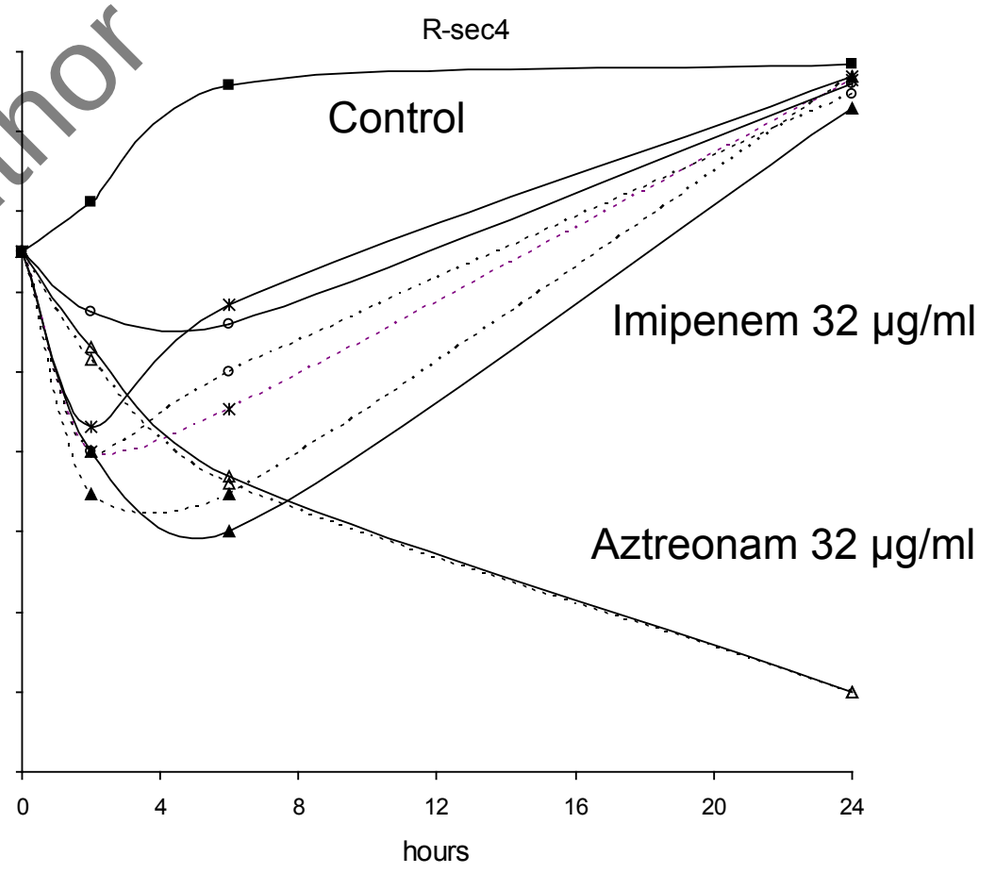


In Vitro Killing Kinetics of Imipenem on VIM and non-VIM Producing *K. pneumoniae*

VIM-negative, MIC=0.125 µg/ml

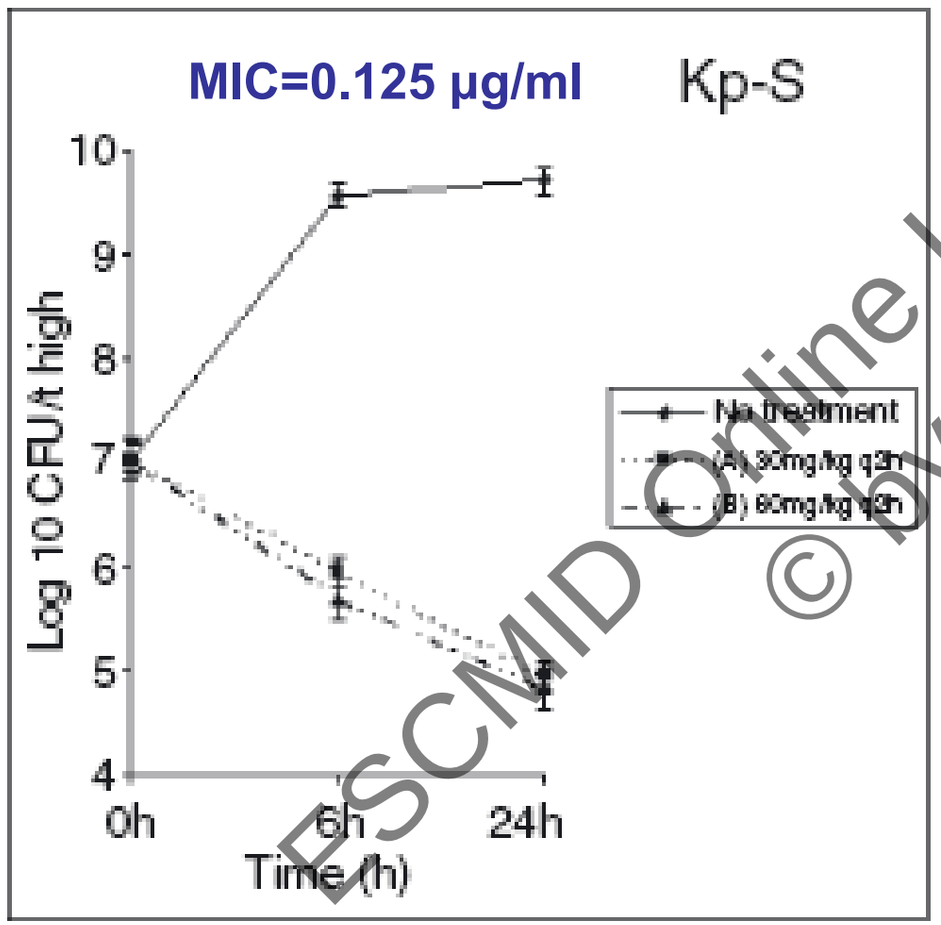


VIM-positive, MIC=32 µg/ml

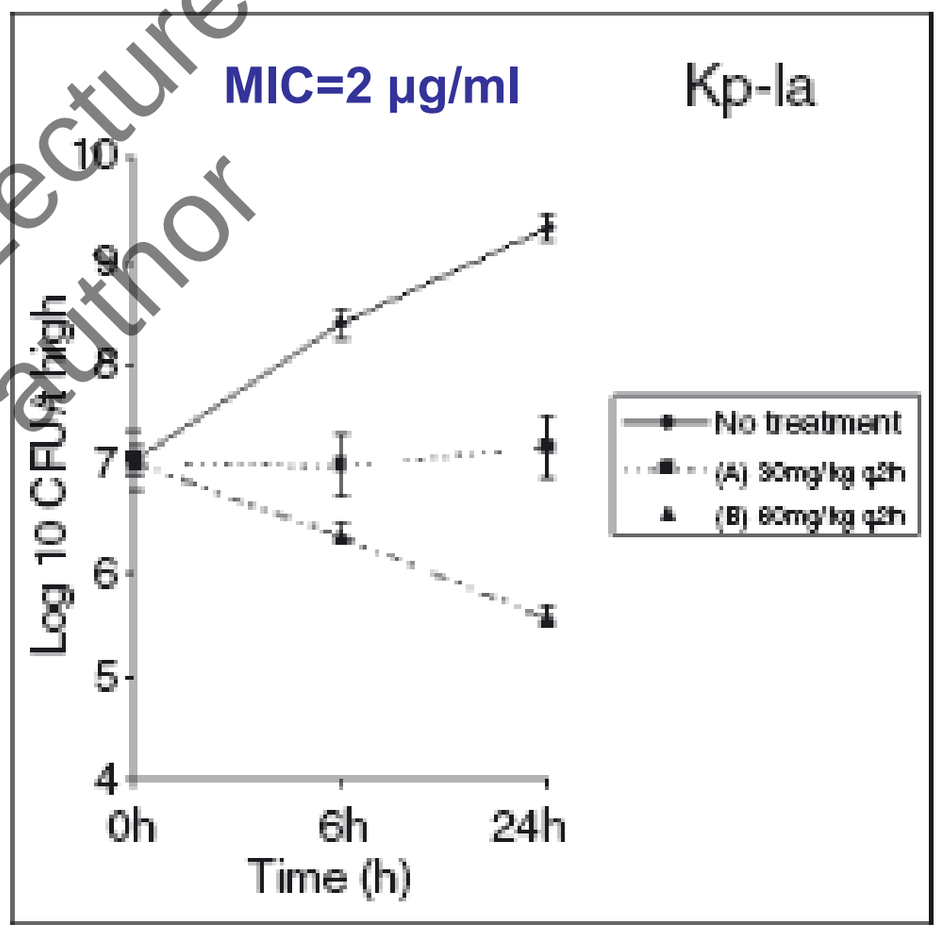


In Vivo Killing Kinetics of VIM and Non-VIM-Producing *K. pneumoniae* in the Thighs of Neutropenic Mice Treated with Imipenem

VIM-negative

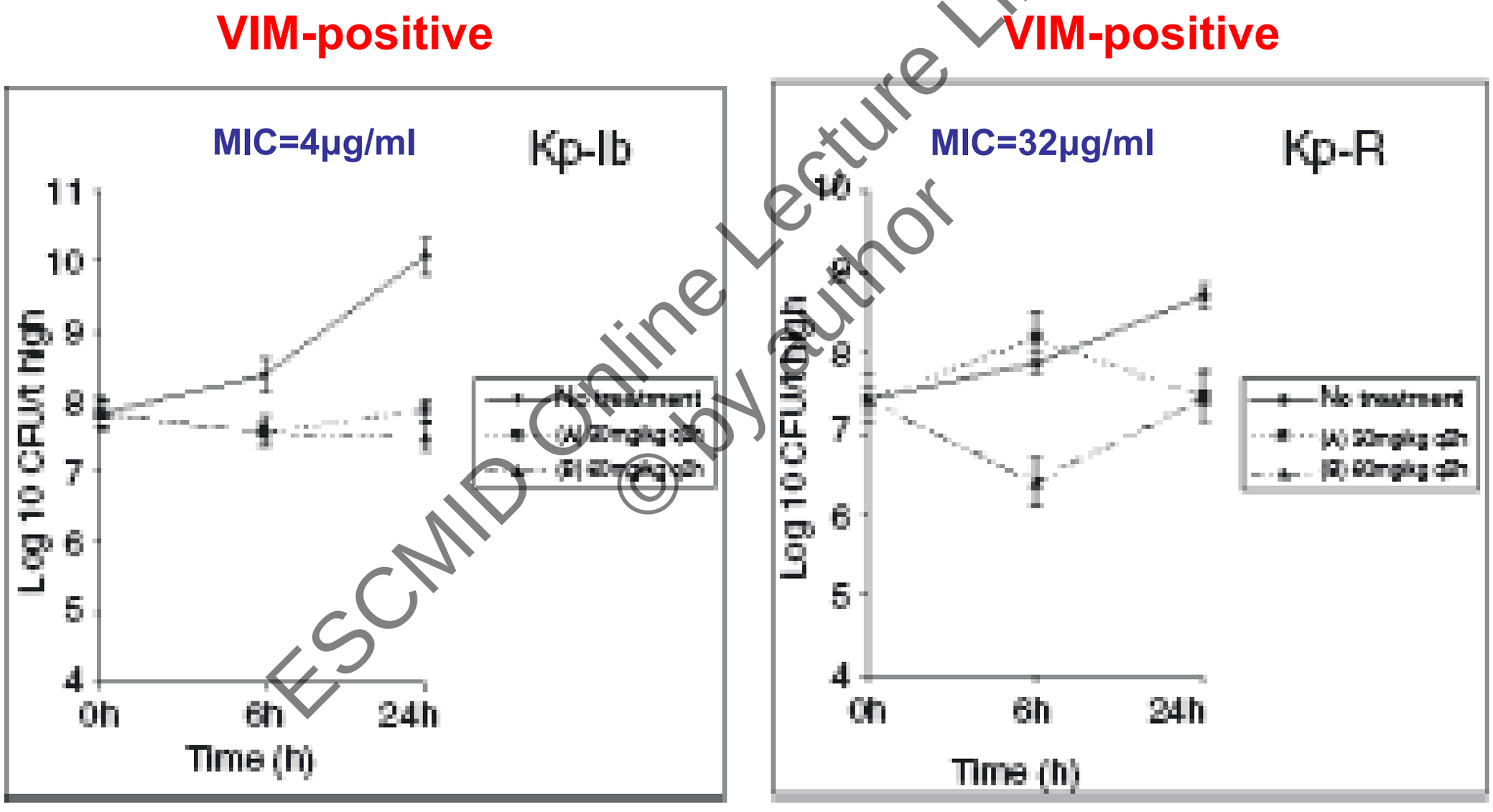


VIM-positive



Daikos GL et al Clin Microbiol Infect 2007; 13: 202-205

In Vivo Killing Kinetics of VIM-Producing *K. pneumoniae* in the Thighs of Neutropenic Mice Treated with Imipenem

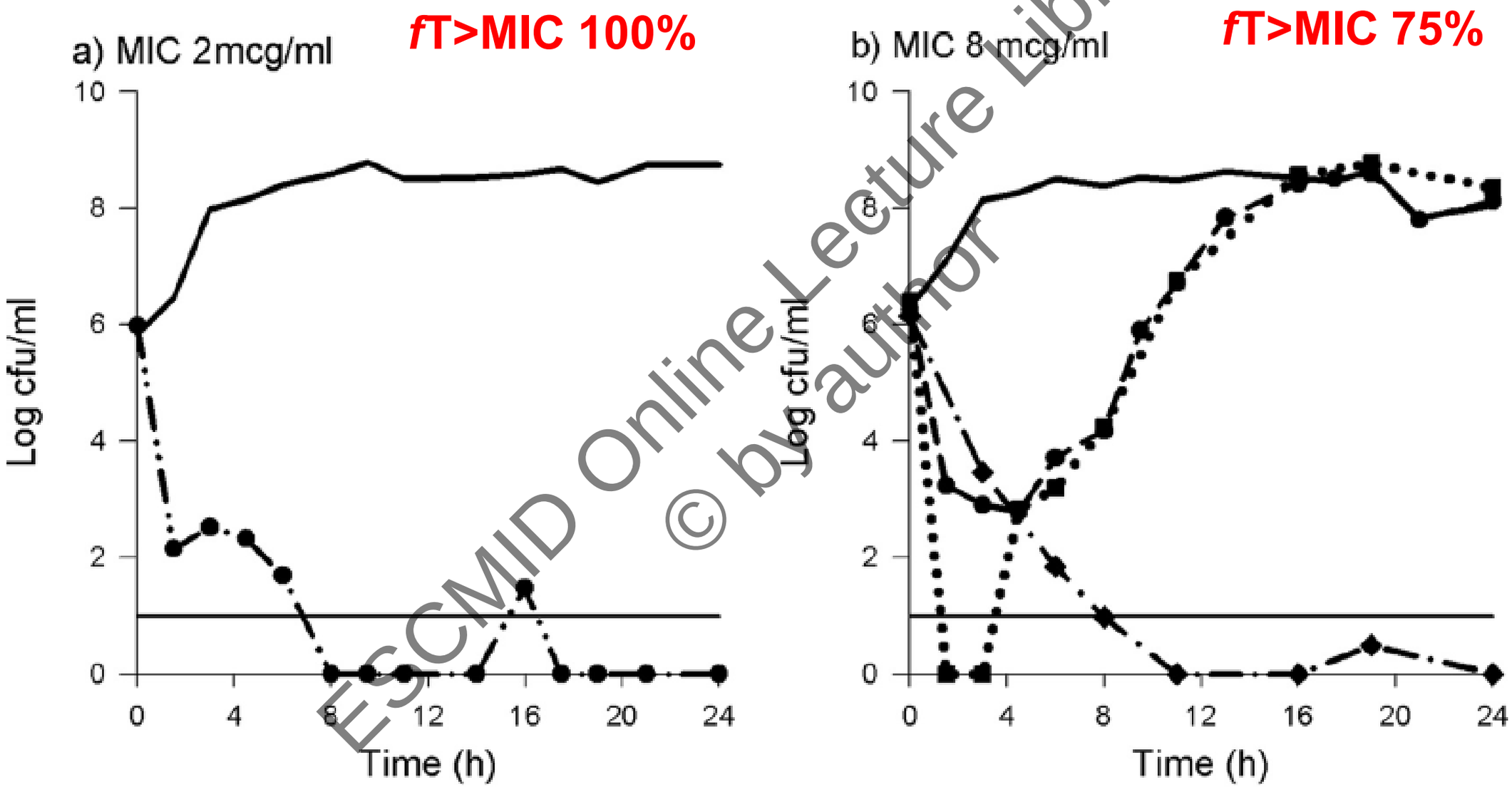


Daikos GL et al Clin Microbiol Infect 2007; 13: 202-205

Pharmacokinetics of Imipenem in Neutropenic Mice

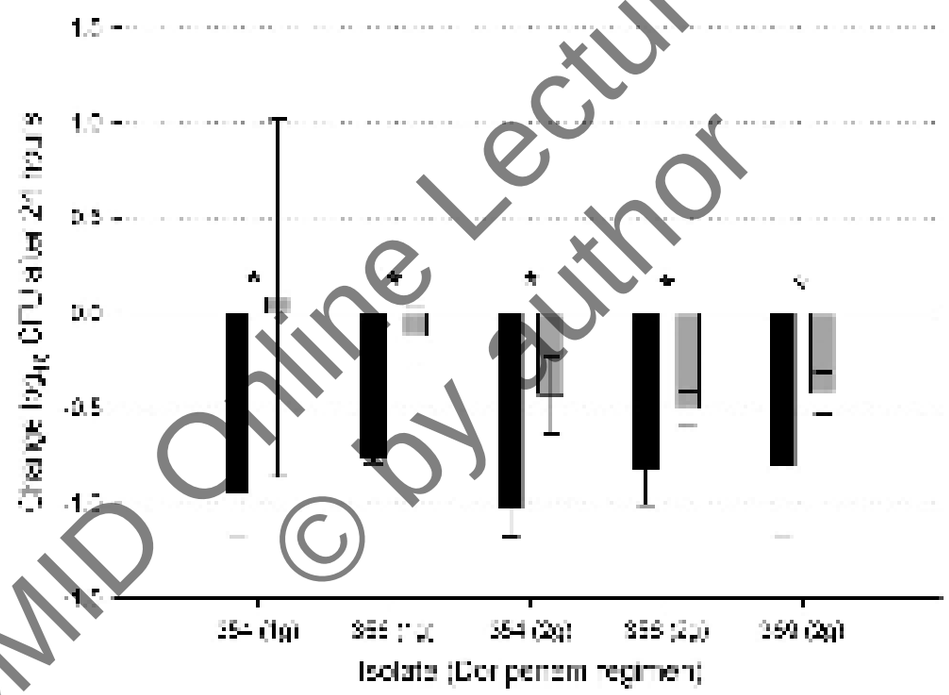
Microorganism	%T>MIC Imipenem, 30 mg/Kg	%T>MIC Imipenem, 60 mg/Kg
Kp-S VIM- MIC= 0.125	63	72
Kp-IA VIM+ MIC=2	37	46
Kp-IB VIM+ MIC=4	33	39
Kp-R VIM+ MIC=32		18

Comparison of the Activity of a Human Simulated, High-Dose, Prolonged Infusion of Meropenem against *Klebsiella pneumoniae* Producing the KPC Carbapenemase versus That against *Pseudomonas aeruginosa* in an *In Vitro* Pharmacodynamic Model[▽]



Bulic CC et al Antimicrob Agents Chemother 2010; 54: 804

In Vivo Efficacy of Simulated Human Dosing Regimens of Prolonged-Infusion Doripenem against Carbapenemase-Producing Klebsiella pneumonia



Bulik CC AAC 2010; 54: 4112-4115

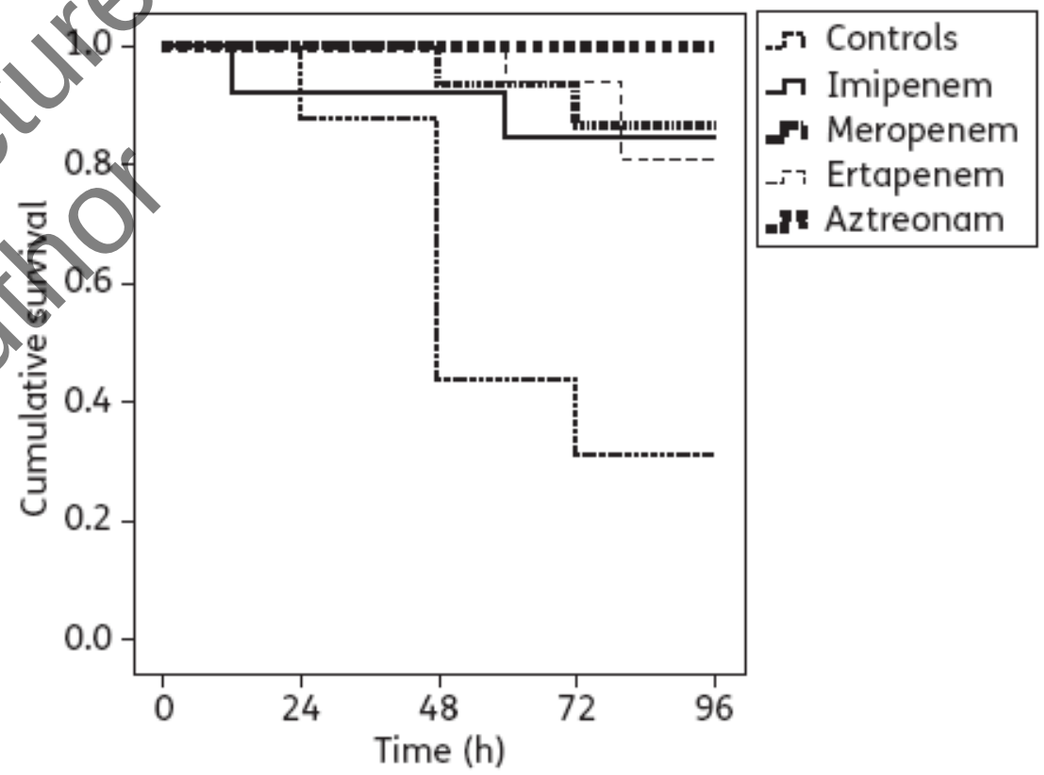
Efficacy of carbapenems against a metallo-β-lactamase-producing *Escherichia coli* clinical isolate in a rabbit intra-abdominal abscess model

M.Souli et al. JAC 2010

Viable counts in abscesses and serum concentrations of antibiotics

Regimen	No. of animals	Mean peak/trough concentration ±SD (mg/L)[a]	Mean abscess bacterial density ±SD (log_{10} cfu/g)	P[b]
Controls	16		8.71±1.34	
Imipenem	15	99.8±66/<0.2	4.89±2.42	<0.001
Meropenem	15	256.4±127.8/<0.2	4.24±2.44	<0.001
Ertapenem	16	207.4±102.8/ 1.7±2.1	3.17±1.85[c]	<0.001
Aztreonam	15	383.3±176.9/<0.2	3.62±3.05	<0.001

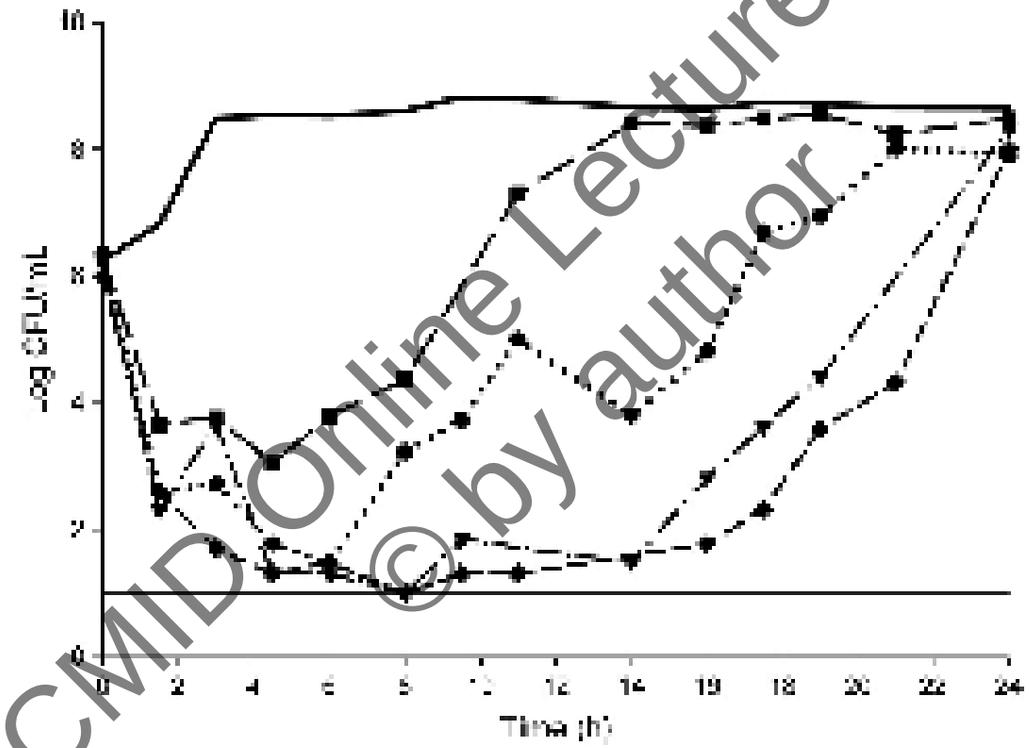
Cumulative survival



Carbapenems were effective in the treatment of intra-abdominal infection due to an ESBL-negative carbapenem-susceptible VIM-1-producing clinical *E. coli* strain, but treatment with aztreonam resulted in a more favourable outcome overall (26.7% of animals culture-negative and no mortality)

Double-Carbapenem Therapy for Carbapenemase-Producing *Klebsiella pneumoniae*[▽]

Catharine C. Bulik[1] and David P. Nicolau[1,2]*



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2011, p. 3002–3004

Synergism of Colistin and Imipenem

Colistin	Synergism	
	No. of Isolates	%
Susceptible	**12/24**	**50%**
Resistant	**2/18**	**11%**

Souli M Antimicrob. Agents Chemother 2009; 53: 2133-35.

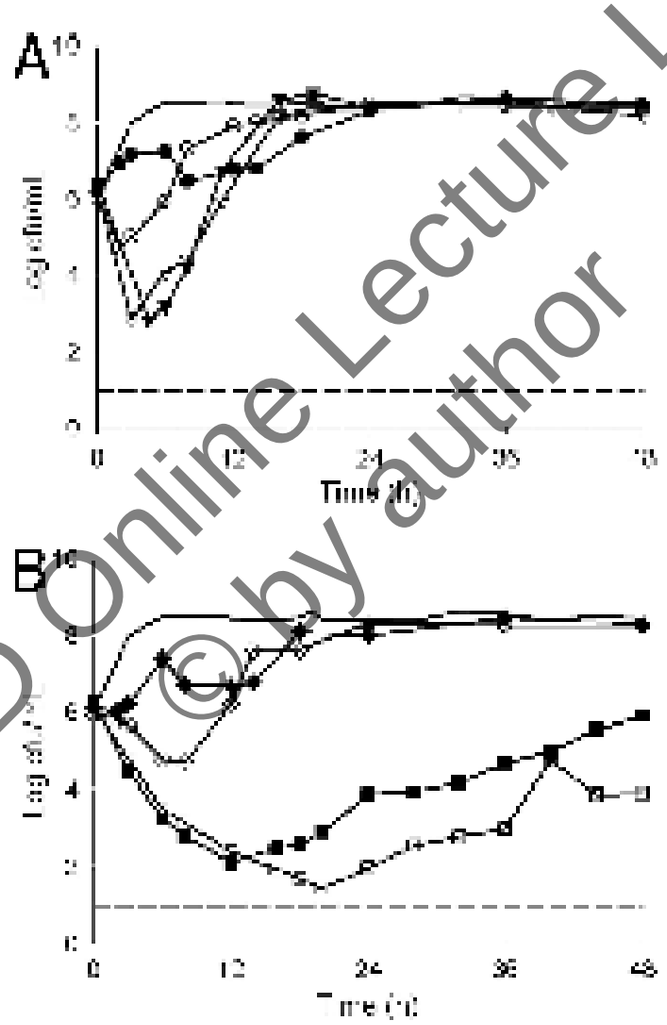
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 2395–2397 Vol. 55, No. 5
0066-4804/11/$12.00 doi:10.1128/AAC.01086-10

In Vitro Interactions of Antimicrobial Combinations with Fosfomycin against KPC-2-Producing *Klebsiella pneumoniae* and Protection of Resistance Development[▽]

Maria Souli,* Irene Galani, Stefanos Boukovalas, Michael George Gourgoulis, Zoi Chryssouli, Kyriaki Kanellakopoulou, Theofano Panagea, and Helen Giamarellou†

In Vitro Pharmacodynamics of Simulated Pulmonary Exposures of Tigecycline Alone and in Combination against *Klebsiella pneumoniae* Isolates Producing a KPC Carbapenemase[▽]

Dora E. Wiskirchen,[1] Pornpan Koomanachai,[1,2] Anthony M. Nicasio,[1] David P. Nicolau,[1,3] and Joseph L. Kuti[1]*



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2011, p. 1420–1427

A critical interpretation of the animal infection model data suggests that optimized regimens of carbapenems are able to achieve at least a static effect in severely compromised hosts and a modest bactericidal effect in immunocompetent animals infected with KPC-positive isolates with MICs up to 8 µg/ml.

PK-PD Target Attainment for β-lactams

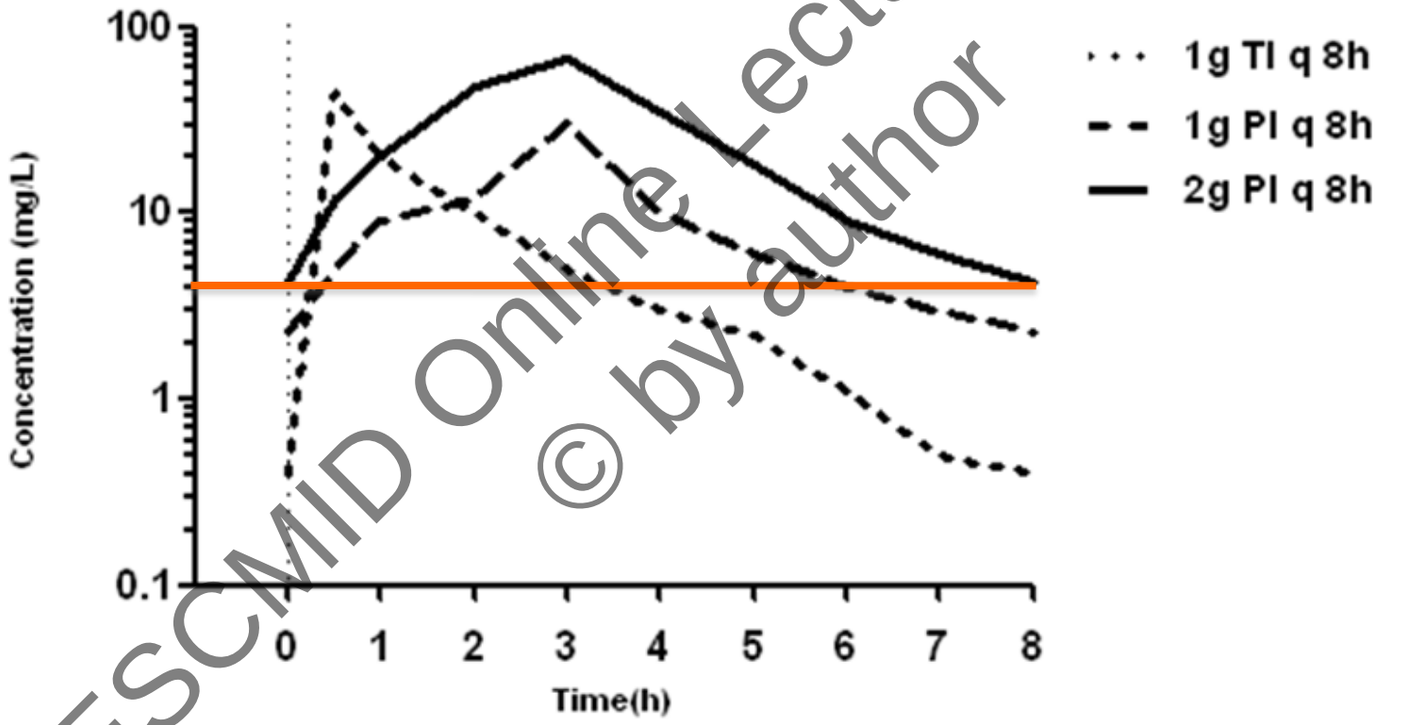
- **Bacteriostatic and bactericidal activity of β-lactams depends on duration of time that free (unbound) drug levels exceed MIC (% T > MIC)**

Antimicrobials	Free Drug % Time > MIC	
	Bacteriostatic (%)	Bactericidal* (%)
Cephalosporins	35-40	60-70
Penicillins	30	50
Carbapenems	20-30	30-40

*3 log reduction in colony-forming units

Drusano GL. 2004. Nat Rev Microbiol. 2:289.

Pharmacokinetics of three different dosing regimens of meropenem

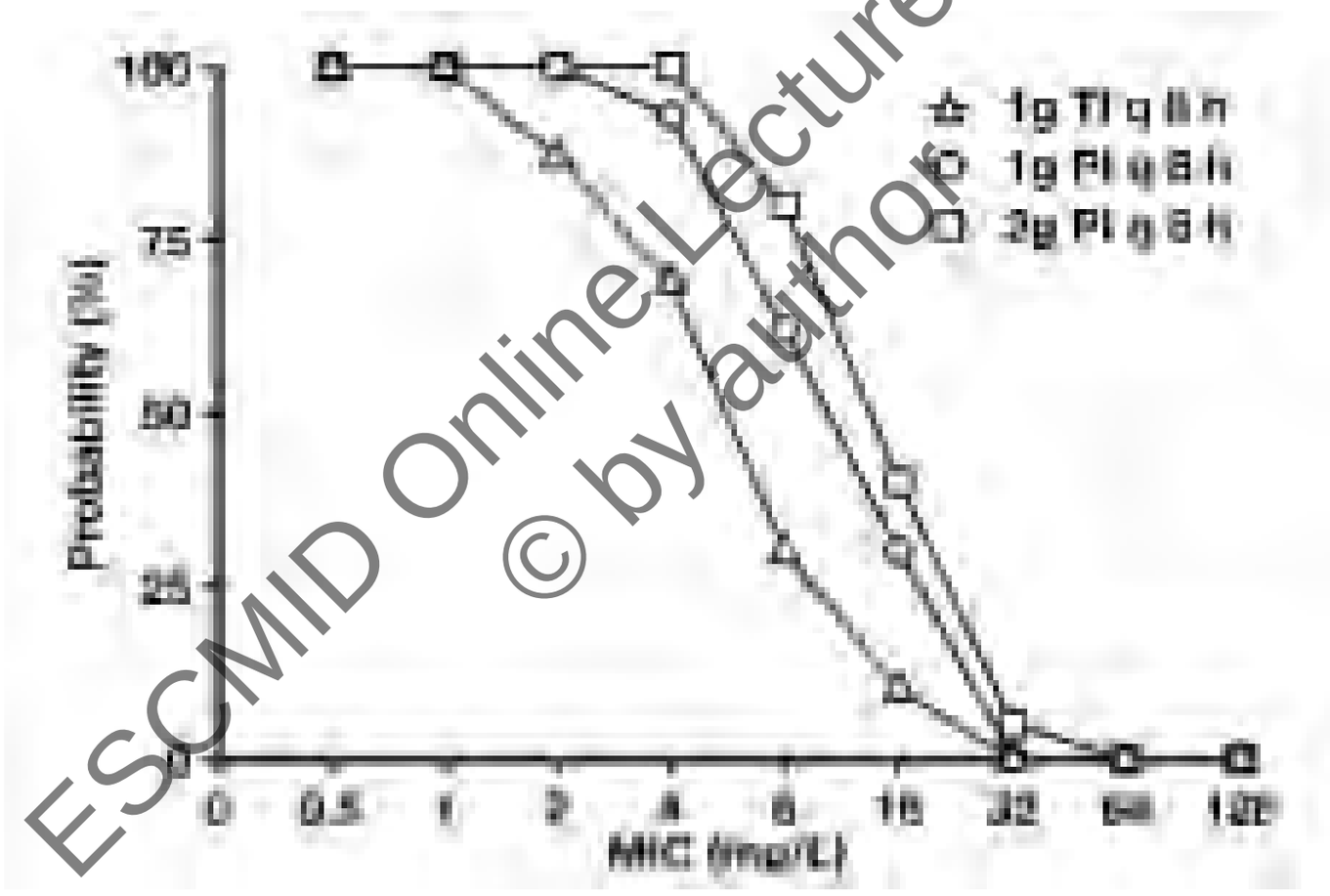


Monte Carlo Simulation

- Examine PK-PD data by simulating dosing regimens and drug levels among a large sample of patients and various MICs for pathogens that would be treated with the drug
  - Plug in various dosages and drug levels that might be encountered in many different patients (e.g., 1000)
- Used to answer question…What percentage of patients are likely to attain the "target"?

  For carbapenems = %T > MIC
    - 40% = bactericidal activity

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



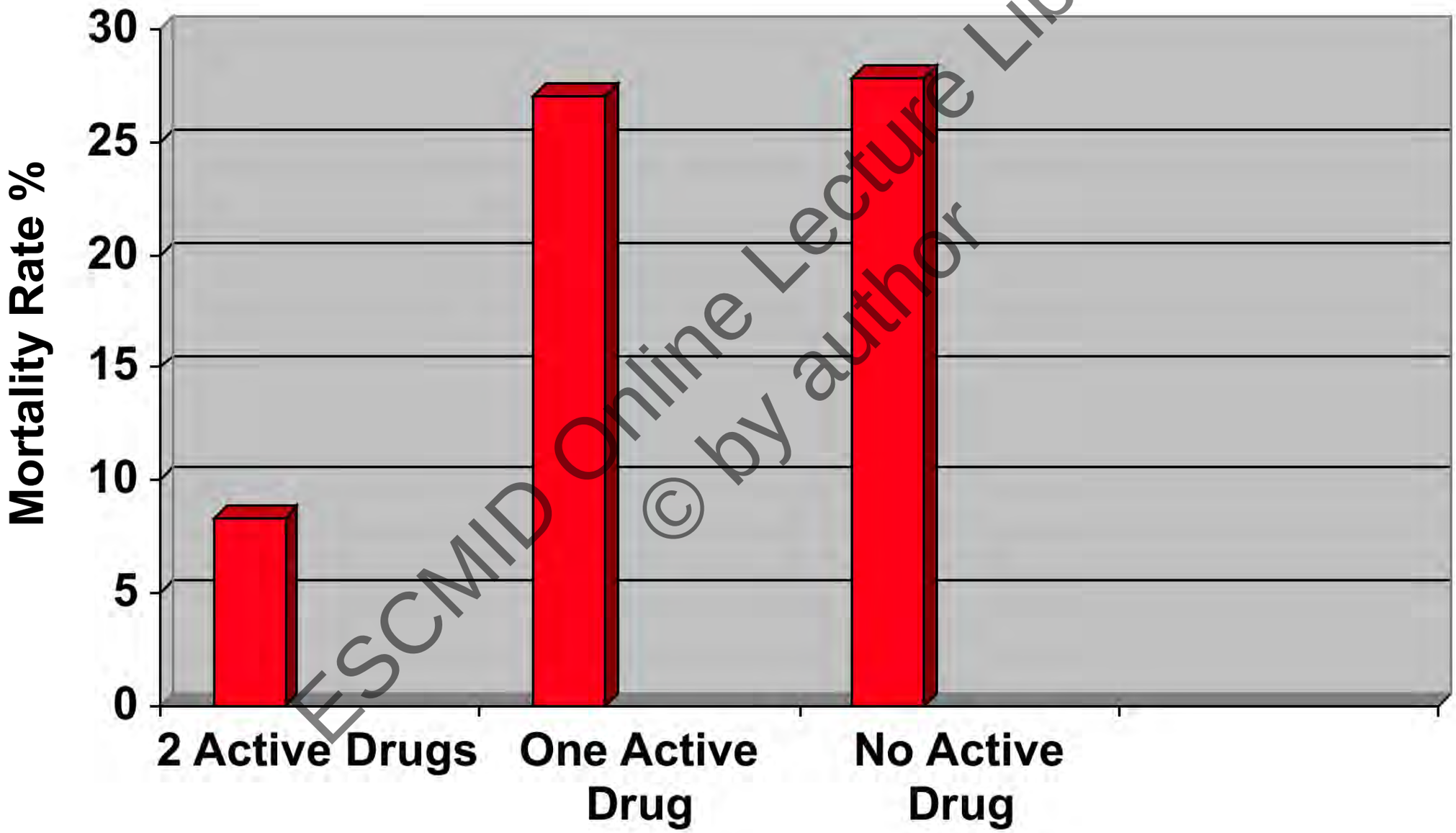
Prospective Observational Study of *K. pneumoniae* BSIs

- **Consecutive patients with *K. pneumoniae* BSIs**
- **A total of 162 patients were included in the analysis**
  - **95 VIM-negative**
  - **67 VIM-positive: 14 with MIC >4 µg/ml for both carbapenems and 53 with MICs ≤4 µg/ml**

Treatment Regimens of 67 Patients Infected with VPKP

- 12 received combination therapy with two active drugs (a carbapenem with colistin or an aminoglycoside)
- 37 received monotherapy with one active drug
  - 14 a carbapenem
  - 15 colistin
  - 8 an aminoglycoside
- 18 received inappropriate empiric therapy

Mortality Rates According to Treatment Regimens



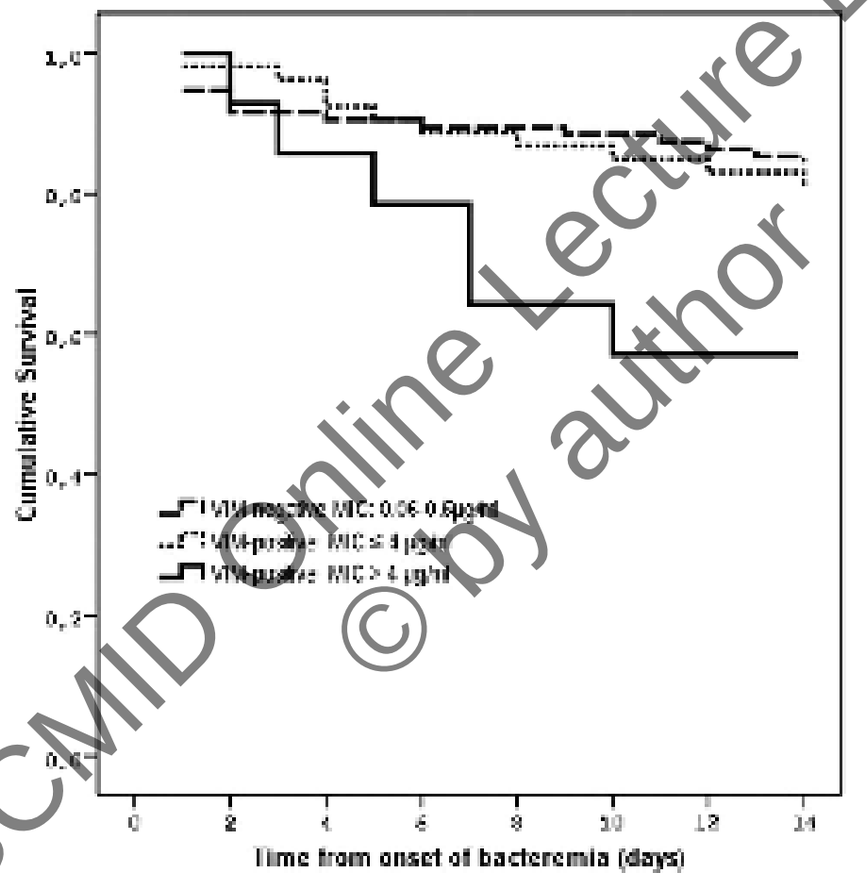
Daikos GL et al Antimicrob Agents Chemother 2009; 53: 1868-73

Cox Regression Analysis of Factors Associated with all-cause 14-day Mortality

Variable	*HR (95% CI)*
Age	1.03 (1.01-1.06)
MIC of carbapenems > 4 µg/ml	2.83 (1.08-7.41)
Rapidly fatal underlying disease	2.84 (1.26-6.39)

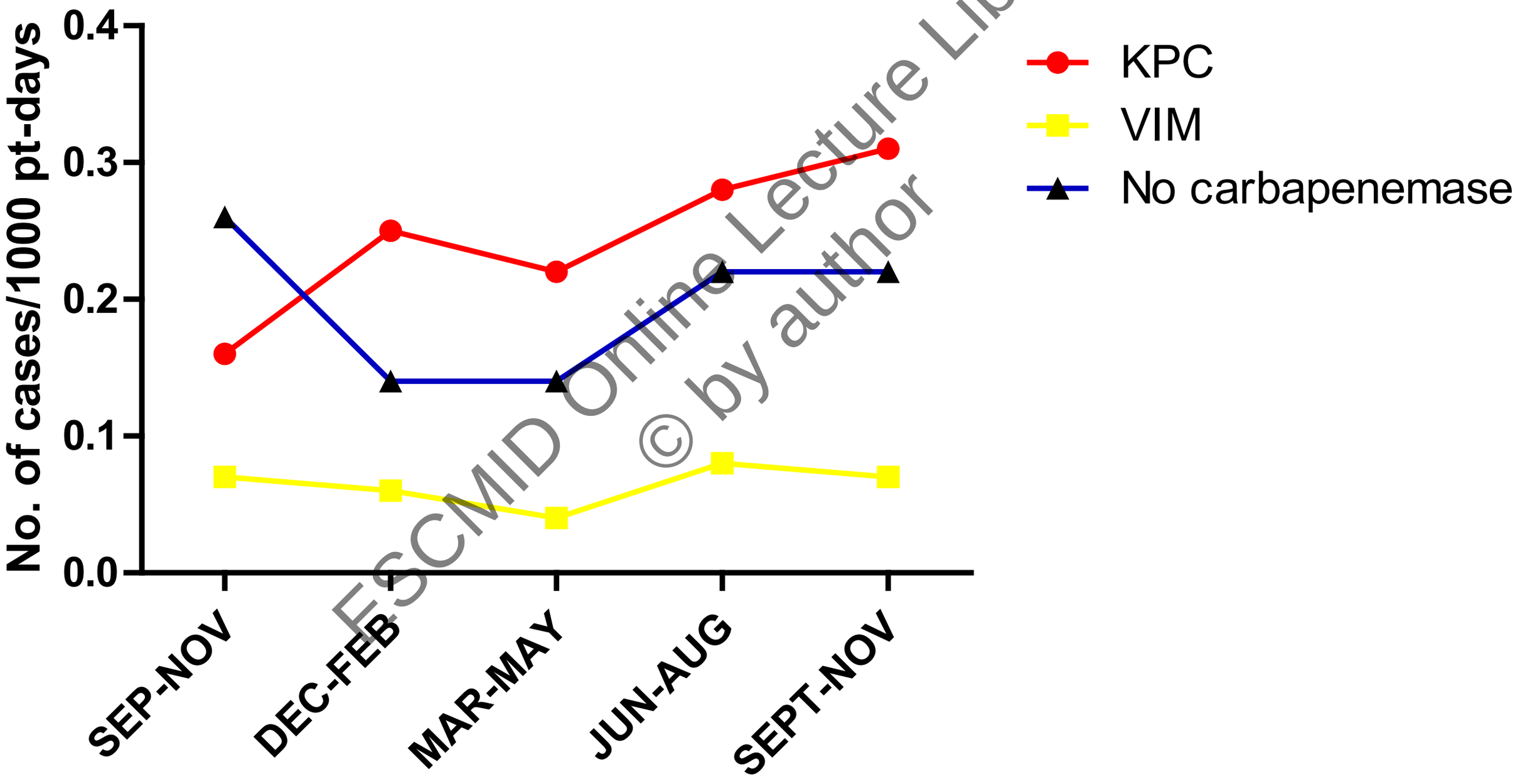
Daikos GL et al Antimicrob Agents Chemother 2009; 53: 1868-73

Prospective Observational Study of the Impact of VIM-1 Metallo-β-Lactamase on the Outcome of Patients with Klebsiella pneumoniae Bloodstream Infections



Daikos GL et al Antimicrob Agents Chemother 2009; 53: 1868-73

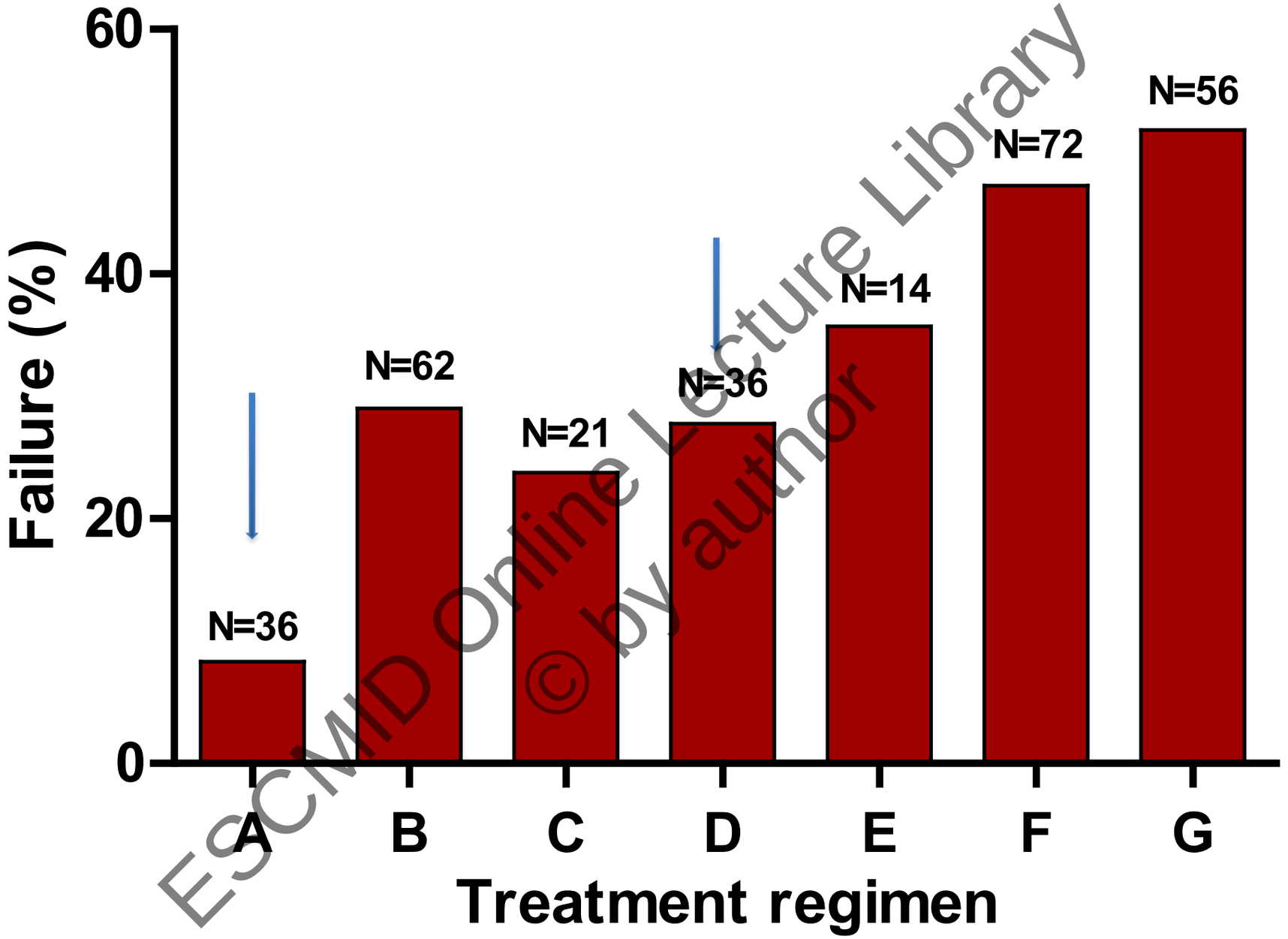
Incidence of *Klebsiella pneumoniae* BSIs in two Tertiary care Hospitals (2009-2010)



Multivariate Analysis of Factors Associated with all-cause 14 day Mortality

	Odds Ratio	P	Odds Ratio	P
Charlson's Comorbidity score	1.24	0.001	1.23	0.002
Severity of sepsis				
Sepsis				
Severe sepsis	2.7	0.006	2.75	0.006
Septic shock	3.97	<0.001	3.92	<0.001
Polymicrobial bacteremia	2.84	0.03	3.04	0.002
KPC production	1.99	0.003	1.68	0.125
Appropriate treatment			3.2	0.006

Outcome of Patients with Serious Infections Caused by CPKP



Ανάλυση δεδομένων από 34 μελέτες

Outcome of Patients with CPKP Infections Treated with a Carbapenem According to MICs

MIC (µg/ml)	No. of failures/ No. of patients	Failure rate (%)
≤ 1	5/17	29.4
2	3/12	33.3
4	2/7	28.6
8	2/6	33.3
>8☐	6/8	75

☐P=0.02; Data compiled from 15 studies published in English literature

Conclusions

When we faced with the daily challenge of managing critically ill patients and the dearth of alternative therapeutic options, some of which have not been satisfactorily investigated and/or whose efficacy remains questionable, use of a carbapenem against an organism with MICs ≤4 or even ≤8 µg/ml in a high-dose/prolonged-infusion regimen and in combination with another active agent, preferentially gentamicin or colistin seems reasonable.