Ferrara, 20 giugno 2013

High-Risk MDR clones news in treatment

Pierluigi Viale **Clinica di Malattie Infettive** **Policlinico S. Orsola – Malpighi**

Characteristics and determinants of outcome of hospital-acquired BSI in ICUs. the EUROBACT International Cohort Study. *Tabah A et al, Intensive Care Med 2012 Sep 26.*

Prospective, multicentre non-representative cohort study was conducted in 162 intensive care units in 24 countries.

1,156 patients were included

Among monomicrobial infections,

58.3 % gram-negative,
32.8 % gram-positive,
7.8 % fungal
1.2 % strict anaerobes.

Overall, 629 (47.8 %) isolates were MDR,
including 270 (20.5 %) XDR, and 5 (0.4 %) PDR

Characteristics and determinants of outcome of hospital-acquired BSI in ICUs. the EUROBACT International Cohort Study. *Tabah A et al, Intensive Care Med 2012 Sep 26.*

logistic regression model of the effect of patient related variables on 28-day mortality

Variable	OR [95 %CI]
Centres	
ICU mortality in 2008 (per percentage point)	1.02 [1.00–1.04]
Turn-over >40 admissions/bed/year (median ICU turn-over)	1.64 [1.08–2.49]
Patients	
Female	1.34 [1.01–1.79]
Medical patient	1.40 [1.04–1.90]
Age (per year)	1.02 [1.01–1.03]
SAPS II (per point)[b]	1.01 [1.00–1.02]
Chronic respiratory disease	1.75 [1.09–2.80]
Chronic immunological disease	2.11 [1.40–3.19]
SOFA without cardiovascular points (per point)[c]	1.20 [1.14–1.26]
Septic shock	1.46 [1.09–1.96]
Intra-abdominal source	1.61 [1.07–2.44]
MDR	1.49 [1.07–2.06]
XDR/PDR	1.42 [0.95–2.11]

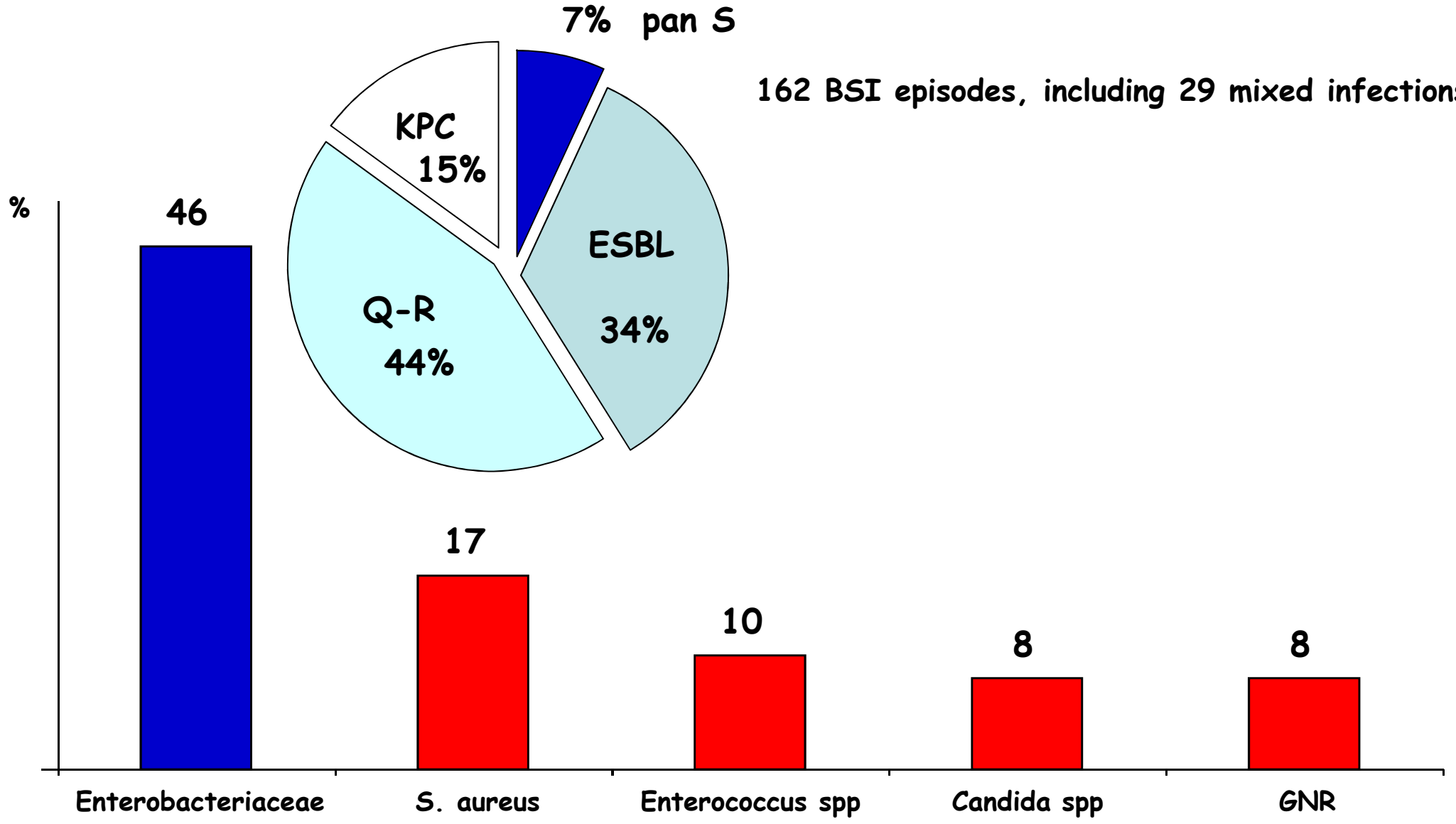
Recommended empirical antibiotic therapy

Type of infection	Type of empirical antibiotic therapy
SBP	Ceftriaxone
UTI	Ceftriaxone
Cellulitis	Ceftriaxone+cloxacillin or Amoxicillin-Clav Acid
Community-acquired pneumonia	Ceftriaxone + Macrolide or Levofloxacin
Nosocomial pneumonia	Ceftazidime + Ciprofloxacin

Acevedo et al. J Hepatol 2009

Epidemiology of bloodstream infections among patients with liver cirrhosis

Bartoletti M et al, EASL Monothematic Conference: Bacterial Infections in Cirrhosis May 24-25, 2013 Barcelona,



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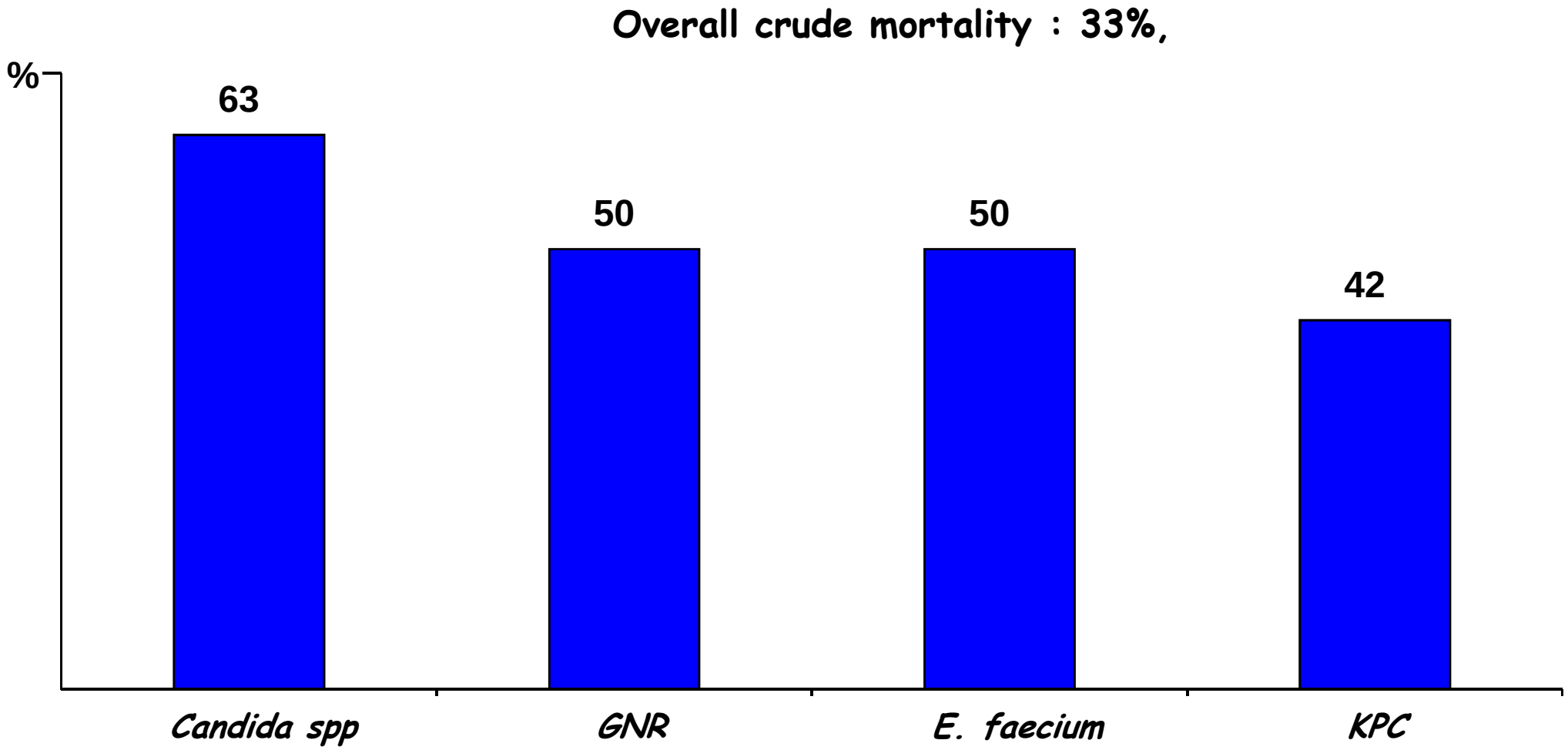

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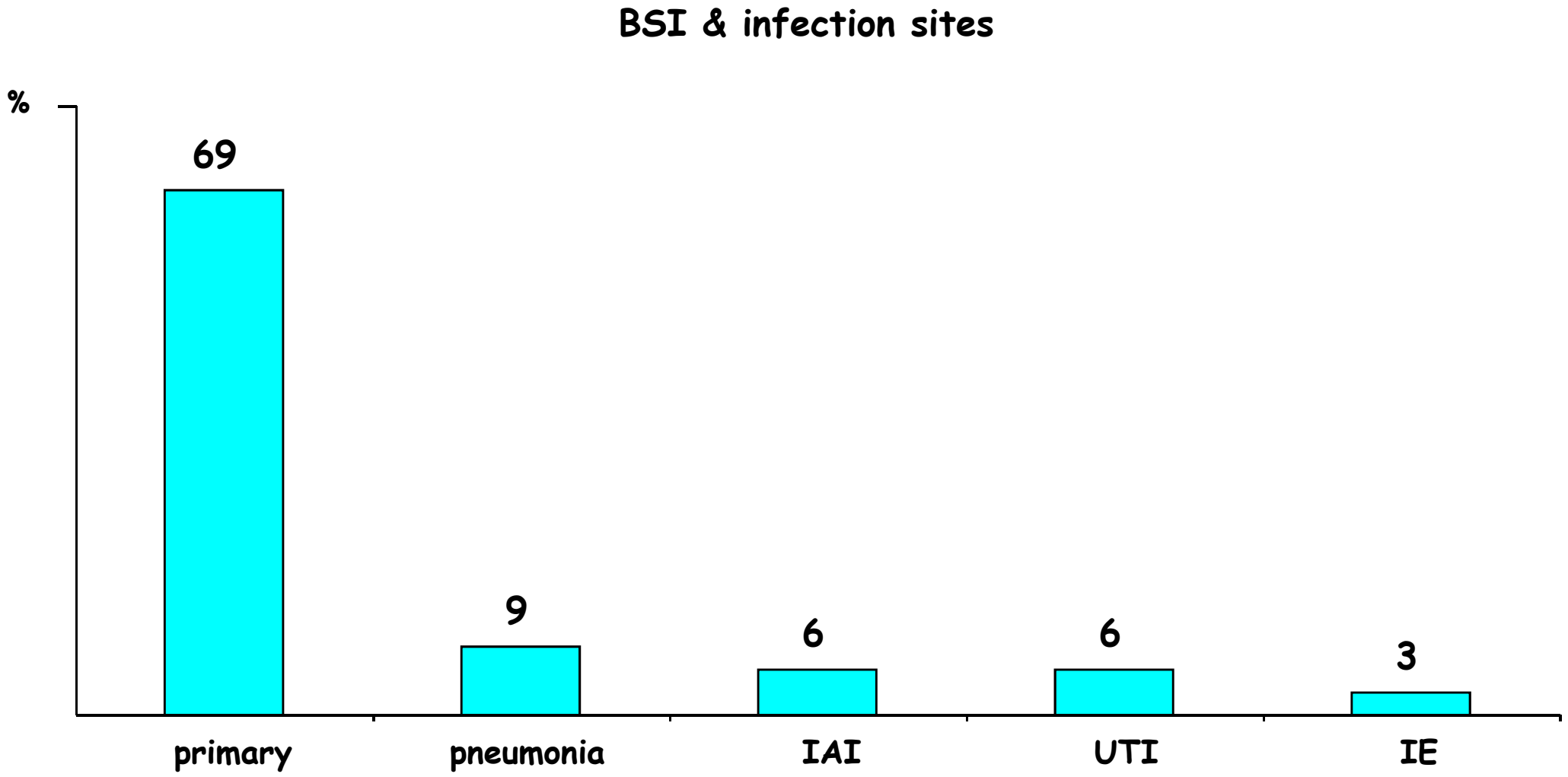


The new resistance era : MAIN CHALLENGES

THE VANCO MIC CREEP OF MRSA

THE PERSISTENT CHALLENGE OF *ENTEROCOCCUS SPP*

THE EXPLOSION OF ESBL *ENTEROBACTERIACEAE*

THE INCREASING INCIDENCE of CARBAPENEMASES PRODUCING STRAINS

THE OMINOUS SPREAD OF KPC *ENTEROBACTERIACEAE*

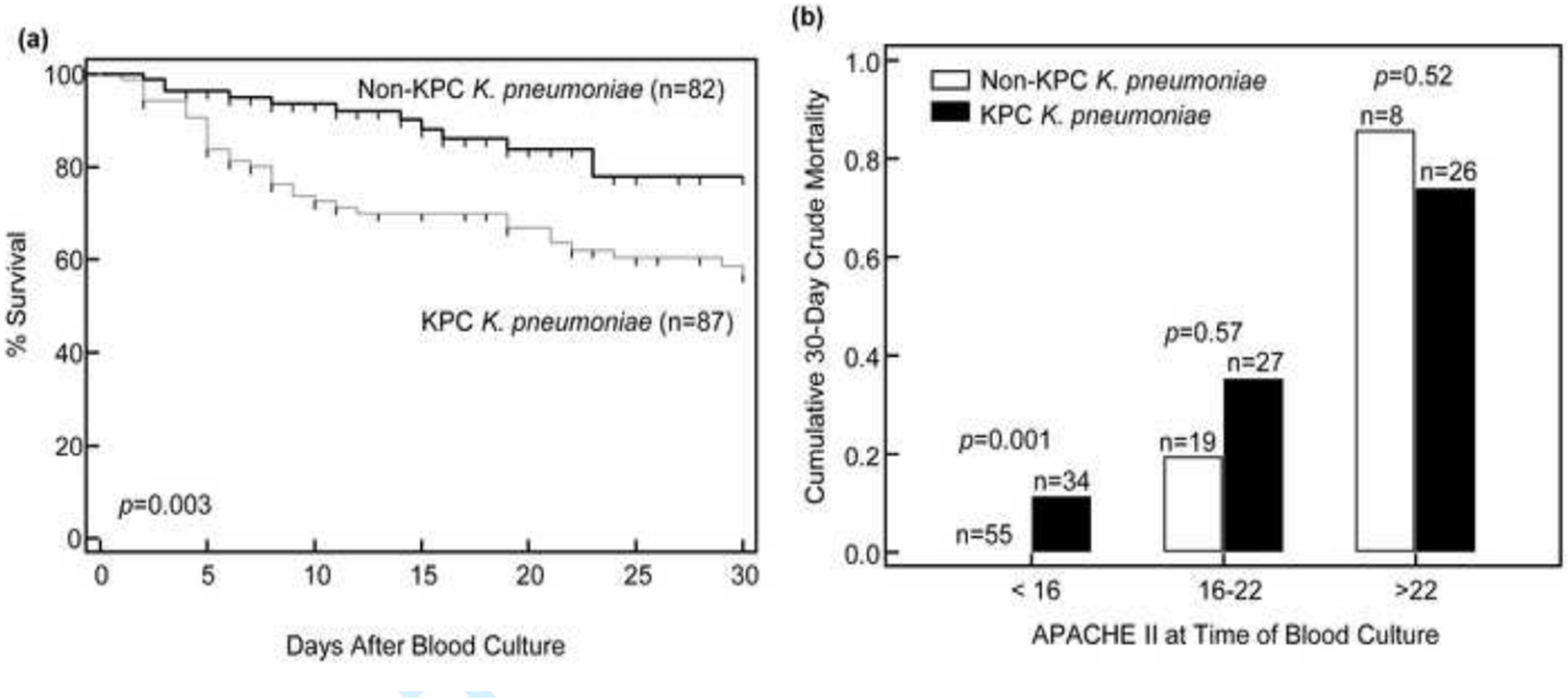
THE MDR ACINETOBACTER REBUS

THE CHALLENGING EPIDEMIOLOGY OF *CLOSTRIDIUM DIFFICILE*

Epidemiology and Outcomes of Carbapenemase-Producing Klebsiella pneumoniae Bloodstream Infections.

Girometti N et al, submitted

observational, retrospective case-control study finalized to analyze 30-day crude mortality, antibiotic treatment variables, and 30-day infection BSI recurrence rates in 87 consecutive patients with a KPC Klebsiella pneumoniae (KPC Kp) and 82 patients with carbapenem susceptible non-KPC Klebsiella pneumonia (non-KPC Kp).



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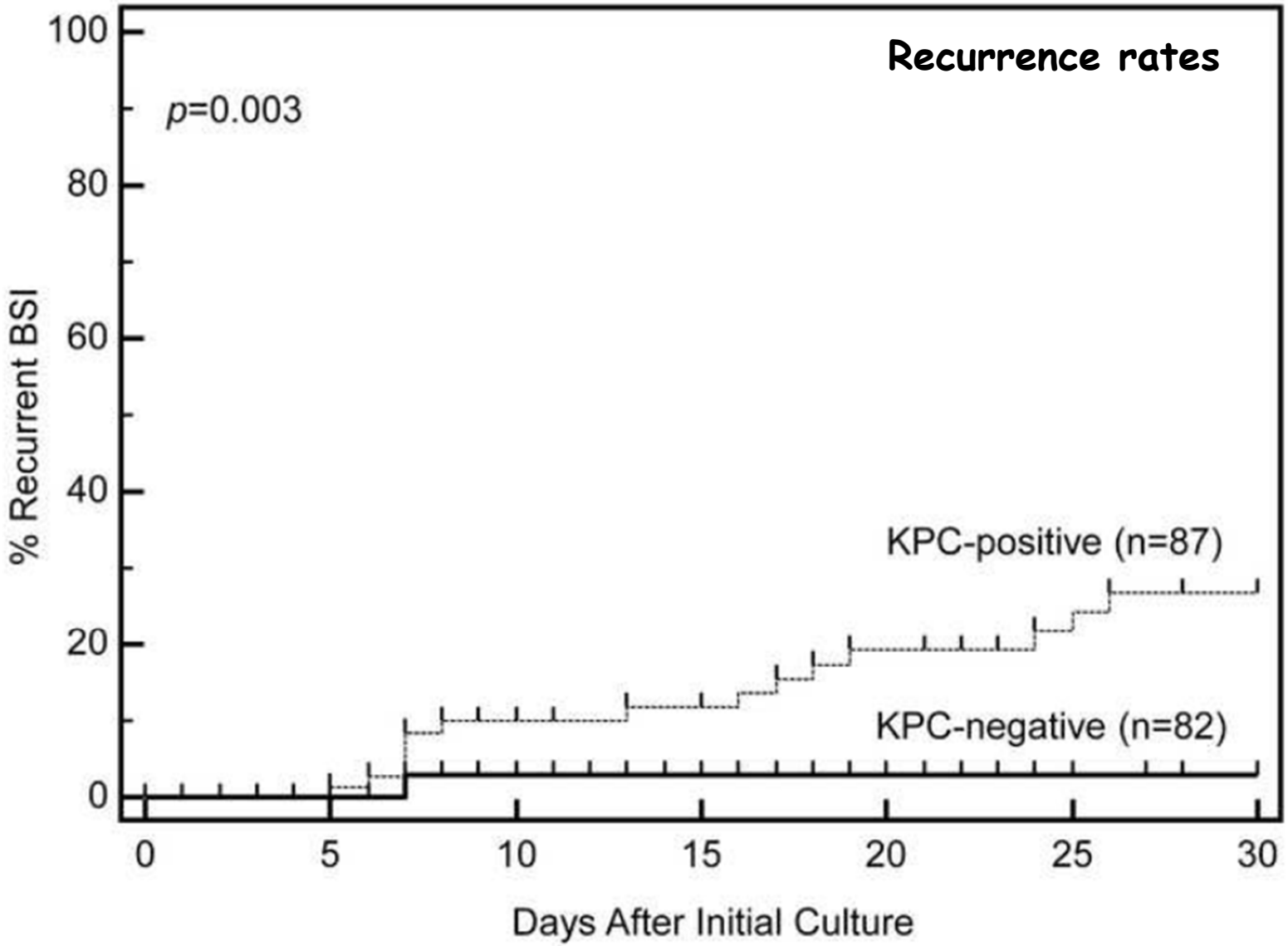


KPC-Kp (and other CRE)
Principles of therapeutic management

- RESIDUAL IN VITRO ACTIVE DRUGS
- HIGH DOSES of CARBAPENEMS
- COMBO REGIMENS

Confronting the threat of MDR Gram-negative bacteria in critically ill patients

Jonathan Cohen J Antimicrob Chemother 2012, November 14, 2012

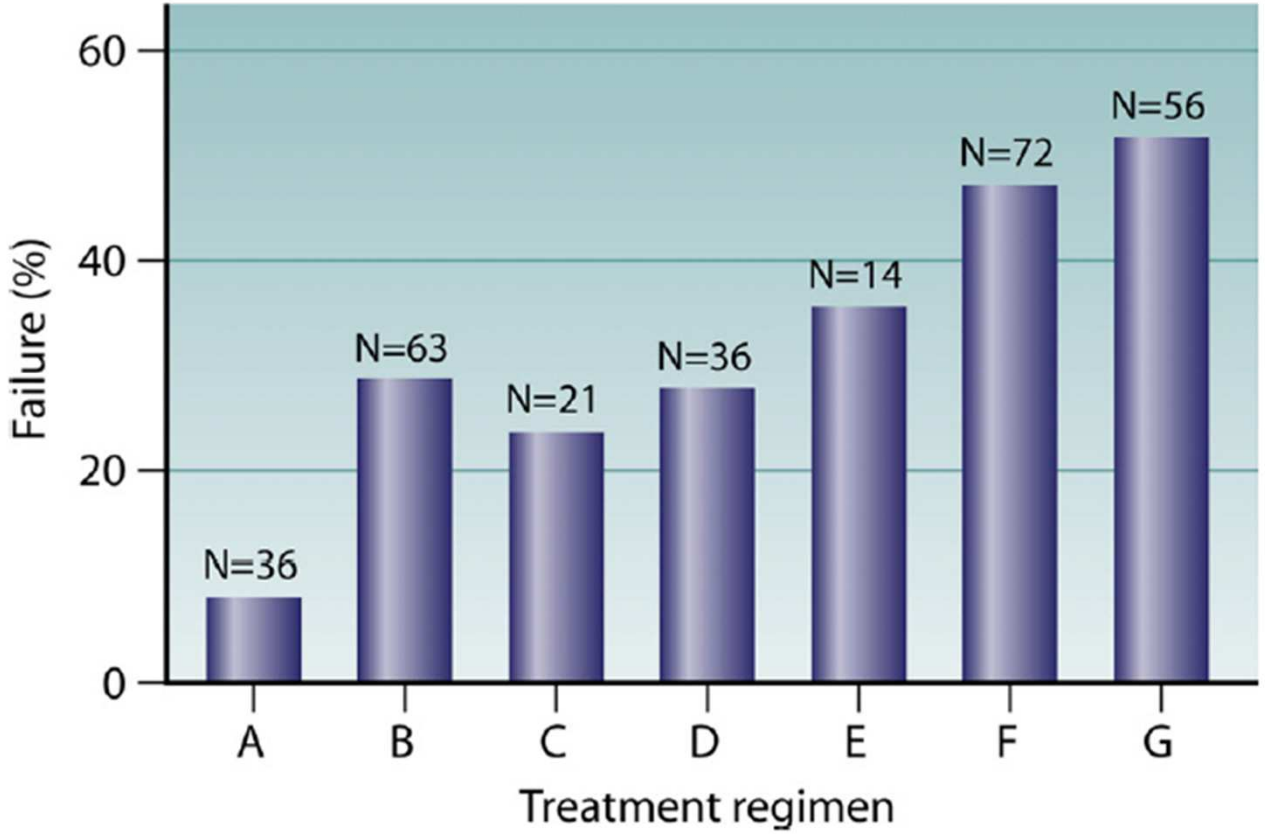
Empirical combination therapy using a carbapenem with other antibiotic classes should be used first-line in critically ill patients at risk for MDR Gram-negative bacteria

Pharmacokinec/pharmacodynamic optimization of antibiotics with Gram-negative activity can overcome resistance associated with MDR Gram-negave bacteria

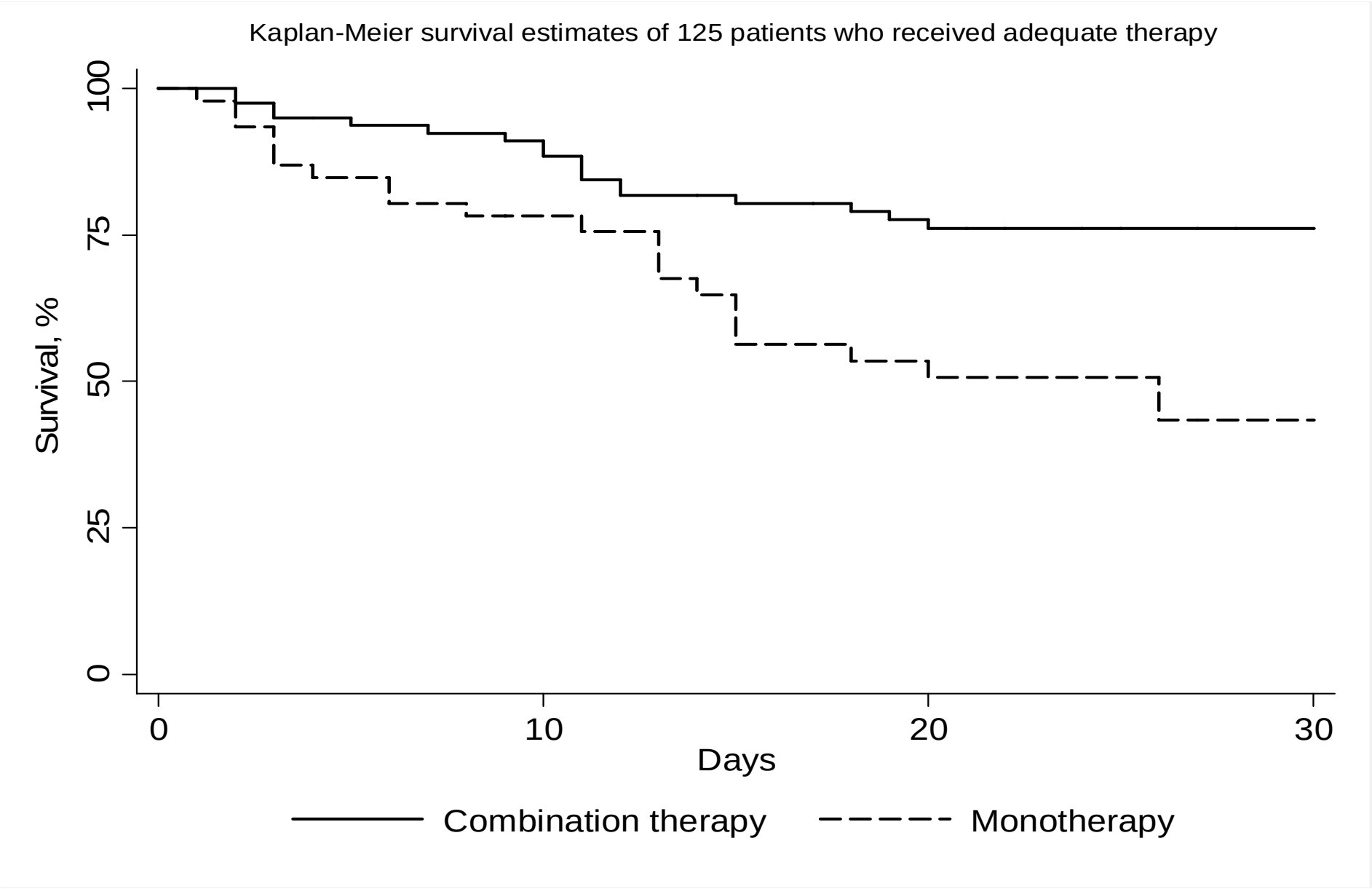
Strategies to limit antibiotic exposure, such as shorter courses of Treatment, attenuate the emergence of resistant Gram-negative Bacteria

Active surveillance of MDR Gram-negative bacteria with isolation should be an active component of infection control bundles to prevent the proliferation of MDR Gram-negative bacteria

Outcomes of infections caused by carbapenemase-producing *Klebsiella pneumoniae*, according to treatment regimen.



A, combination therapy with 2 active drugs, one of which was a carbapenem
B, combination therapy with 2 active drugs, not including a carbapenem
C, monotherapy with an aminoglycoside;
D, monotherapy with a carbapenem;
E, monotherapy with tigecycline;
F, monotherapy with colistin;
G, inappropriate therapy.



Tumbarello M et al Clin Infect Dis 2012 in press

Multivariate analysis of factors associated with death among patients with bloodstream infection due to KPC producing Klebsiella Pneumoniae.

Shock	-	-	0.008	7.17 (1.65-31.03)
Inadequate initial treatment	-	-	0.003	4.17 (1.61-10.76)
APACHE III score (mean ± SD)	-	-	<0.001	1.04 (1.02-1.07)
Tigecycline & Colistin & Meropenem	-	-	0.01	0.11 (0.02-0.69)

Tumbarello M et al Clin Infect Dis 2012 in press

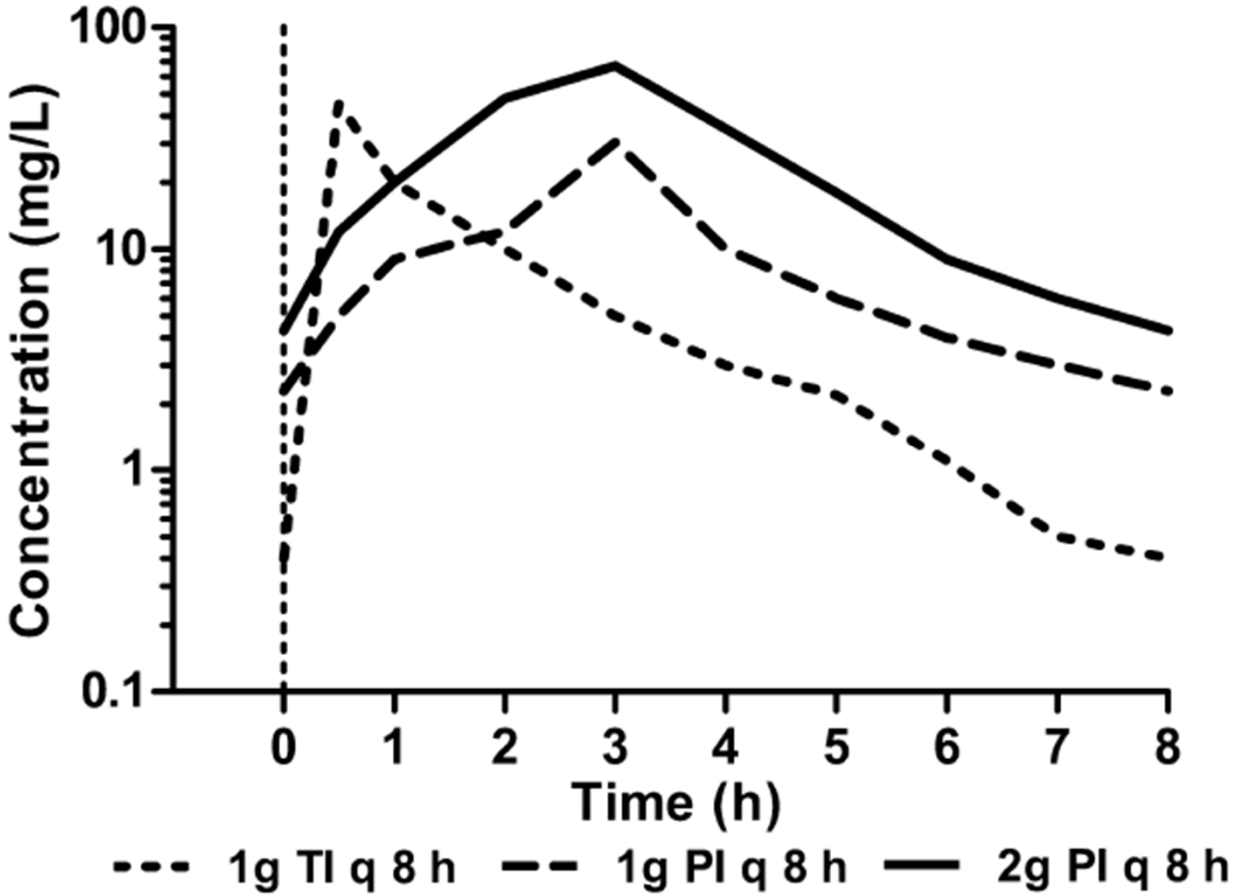
Outcome of the 36 patients with BSI due to KPC producing K. pneumoniae treated with a combination therapy including also meropenem, according to the MICs for meropenem.

		No. (%) of patients	
Meropenem MIC	Total	Non survivors	Survivors
MIC ≤2	5	0	5 (100)
MIC =4	10	2 (20)	8 (80)
MIC =8	4	1 (25)	3 (75)
MIC ≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Tumbarello M et al Clin Infect Dis 2012 in press

Carbapenemase-producing K. pneumoniae: (when) might we still consider treating with carbapenems? *Daikos GL & Markogiannakis A Clin Microbiol Infect 2011; 17: 1135–1141*

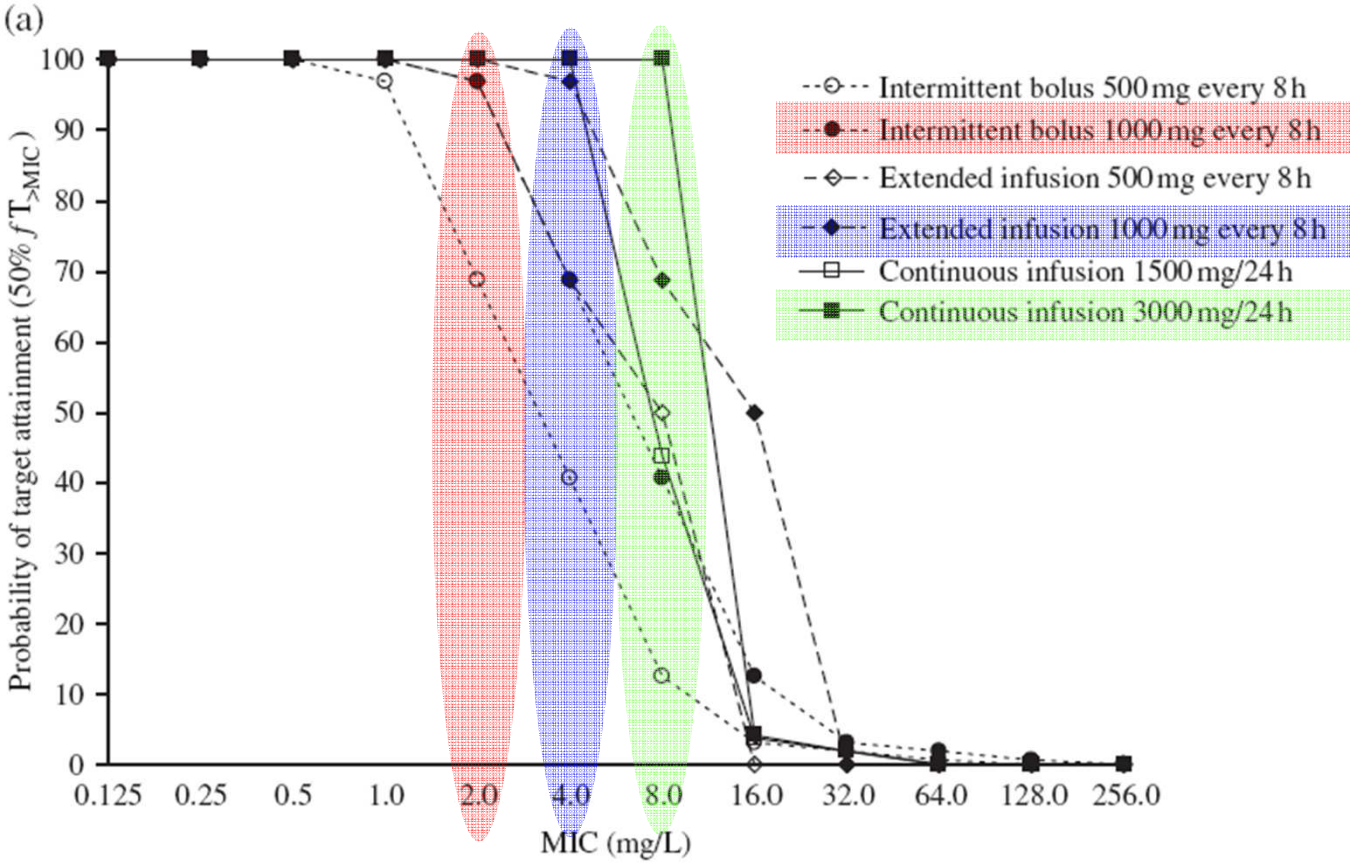
Simulated concentration–time profiles of three different dosing regimens of meropenem.



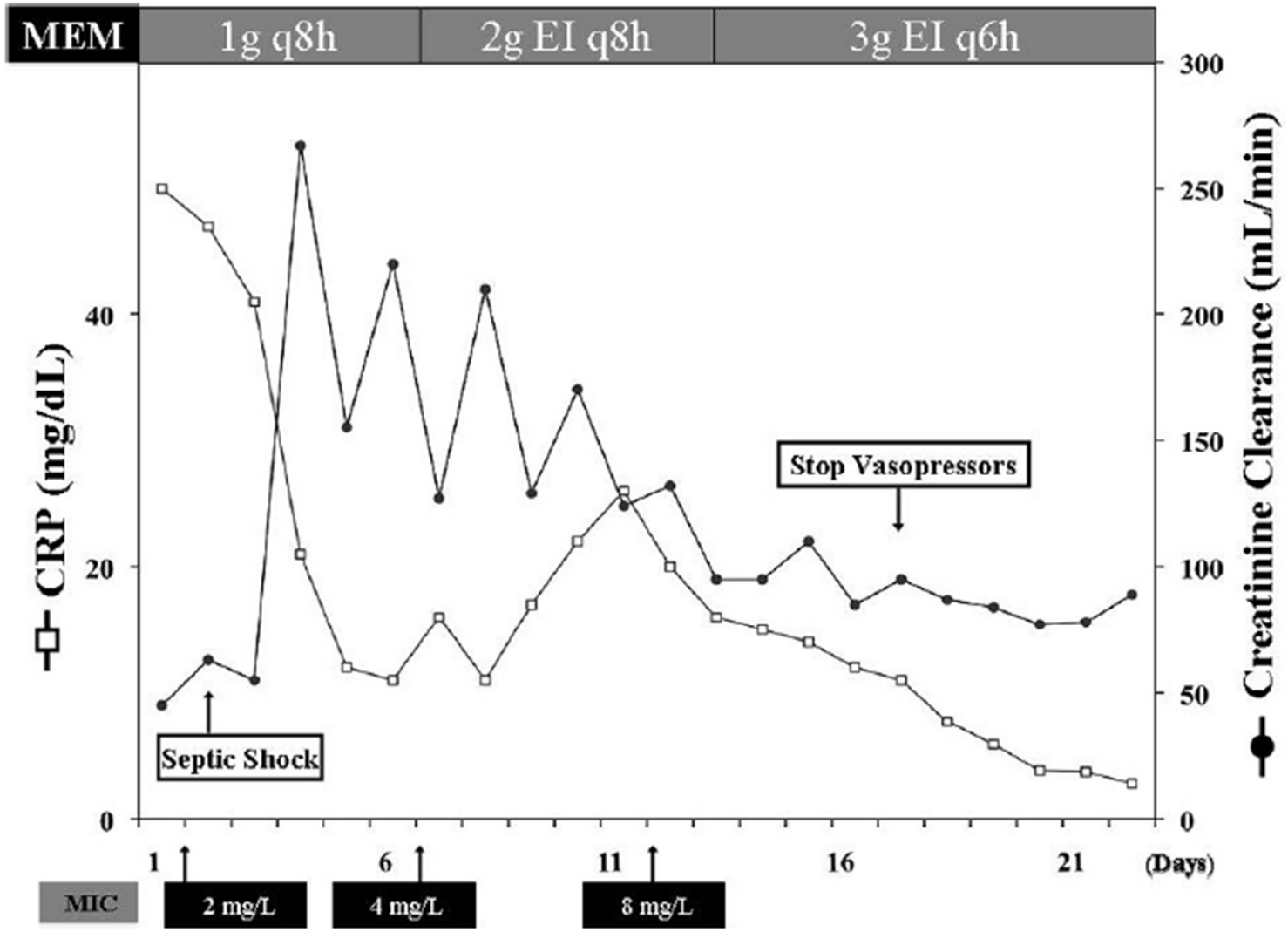
MEROPENEM DOSING IN CRITICALLY ILL PATIENTS WITH SEPSIS AND WITHOUT RENAL DYSFUNCTION: INTERMITTENT BOLUS vs CONTINUOUS ADMINISTRATION?

Roberts JA et al. *J Antimicrob Chemother* 2009 July; 64:142-150

PROBABILITY OF PD TARGET ATTAINMENT (50% free T>MIC)

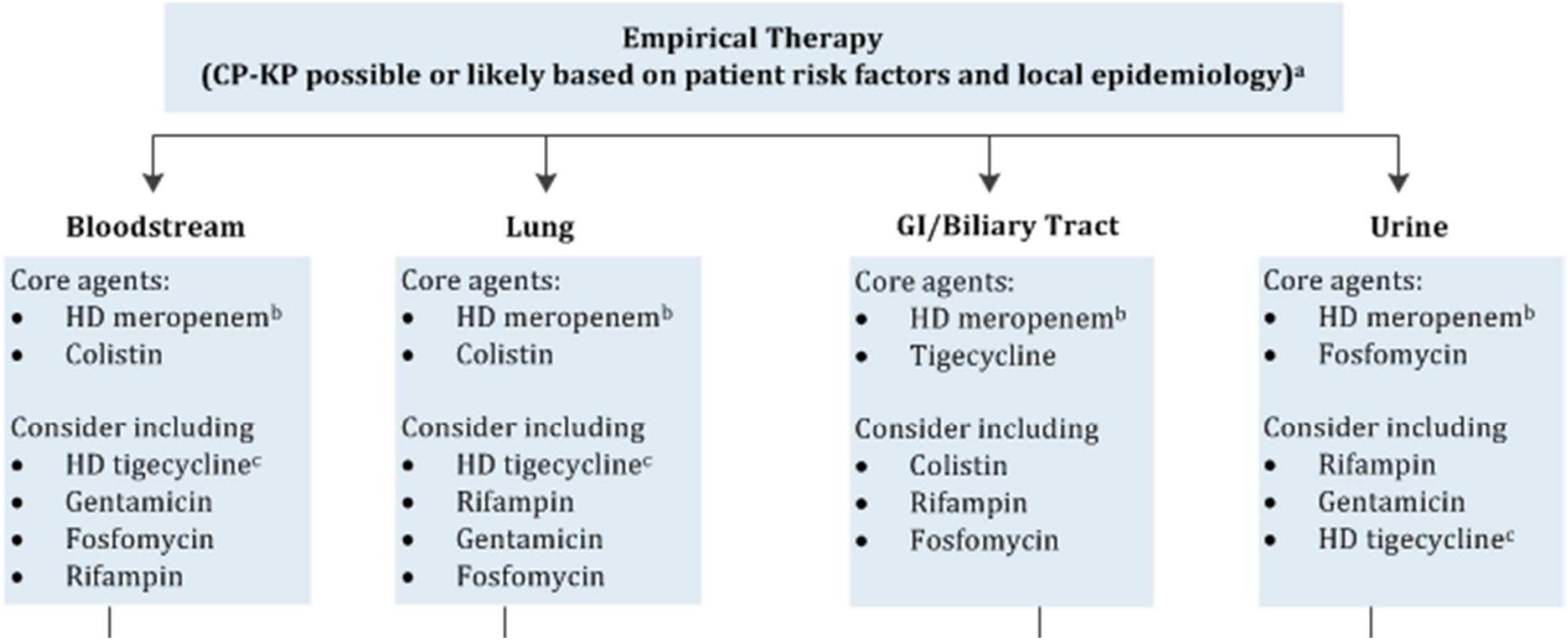


Optimal Meropenem Concentrations To Treat Multidrug-Resistant *Pseudomonas aeruginosa* Septic Shock *Taccone FS et al, Antimicrob. Agents Chemother. 2012; 56:2129*



Combination therapy for carbapenem-resistant *Klebsiella pneumoniae*: light and shadows

Petrosillo N, Giannella M, Lewis RE, Viale P Ext Rev Infect Dis 2013



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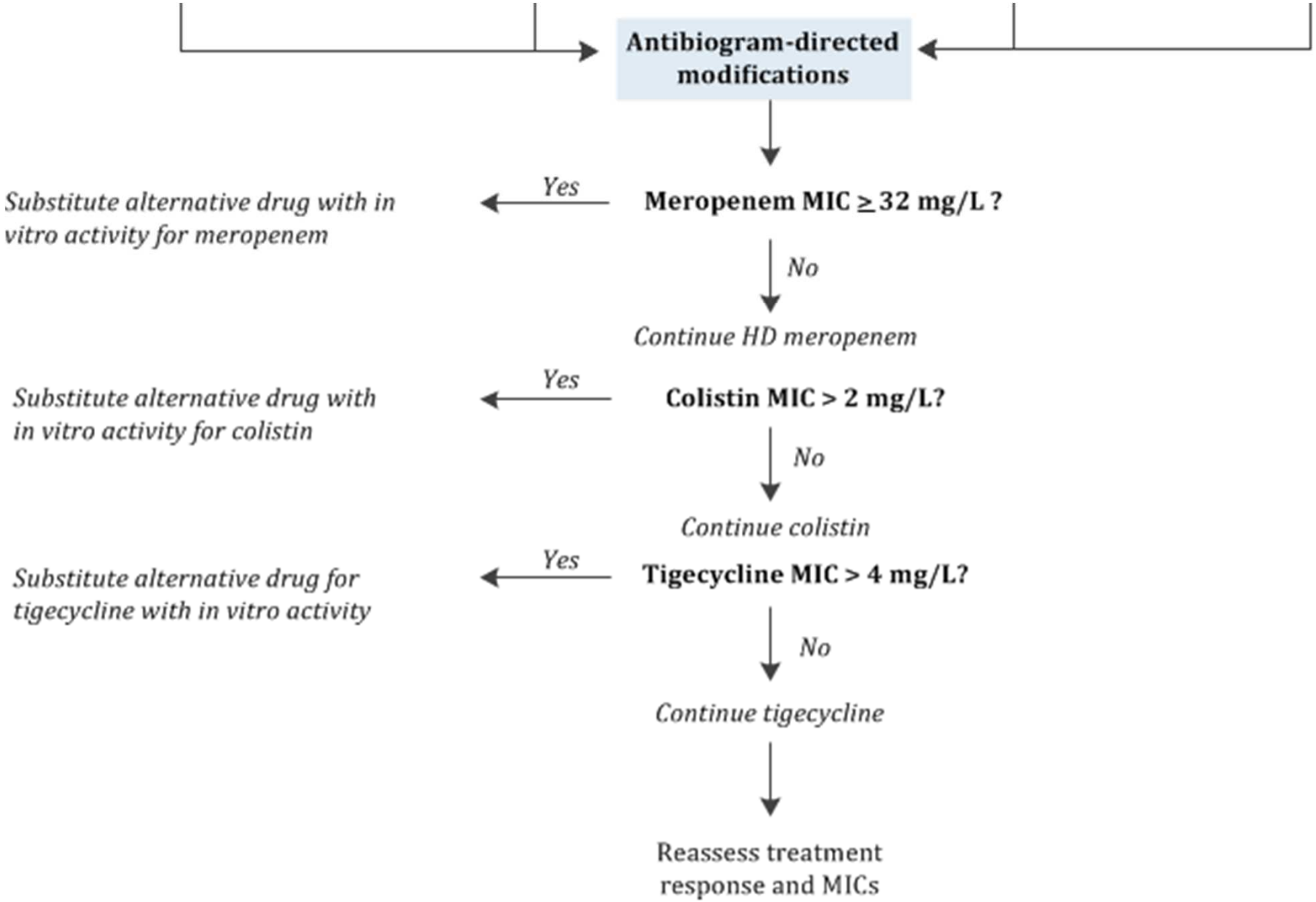
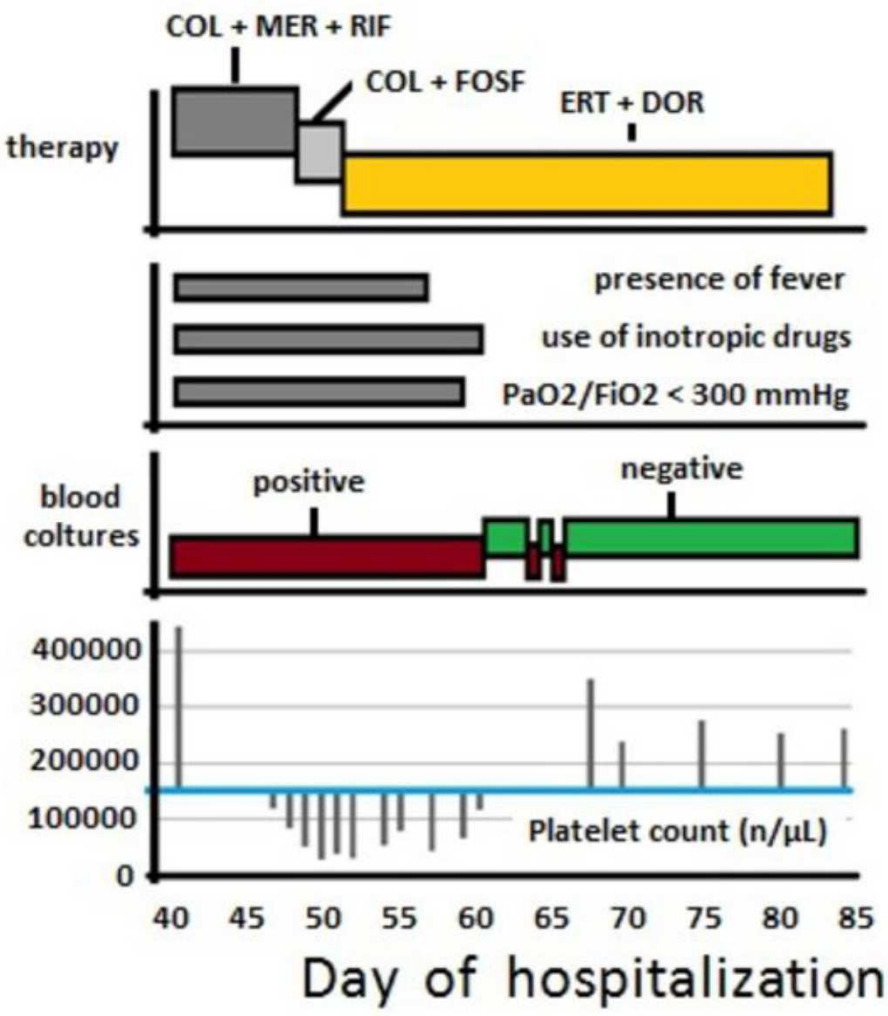
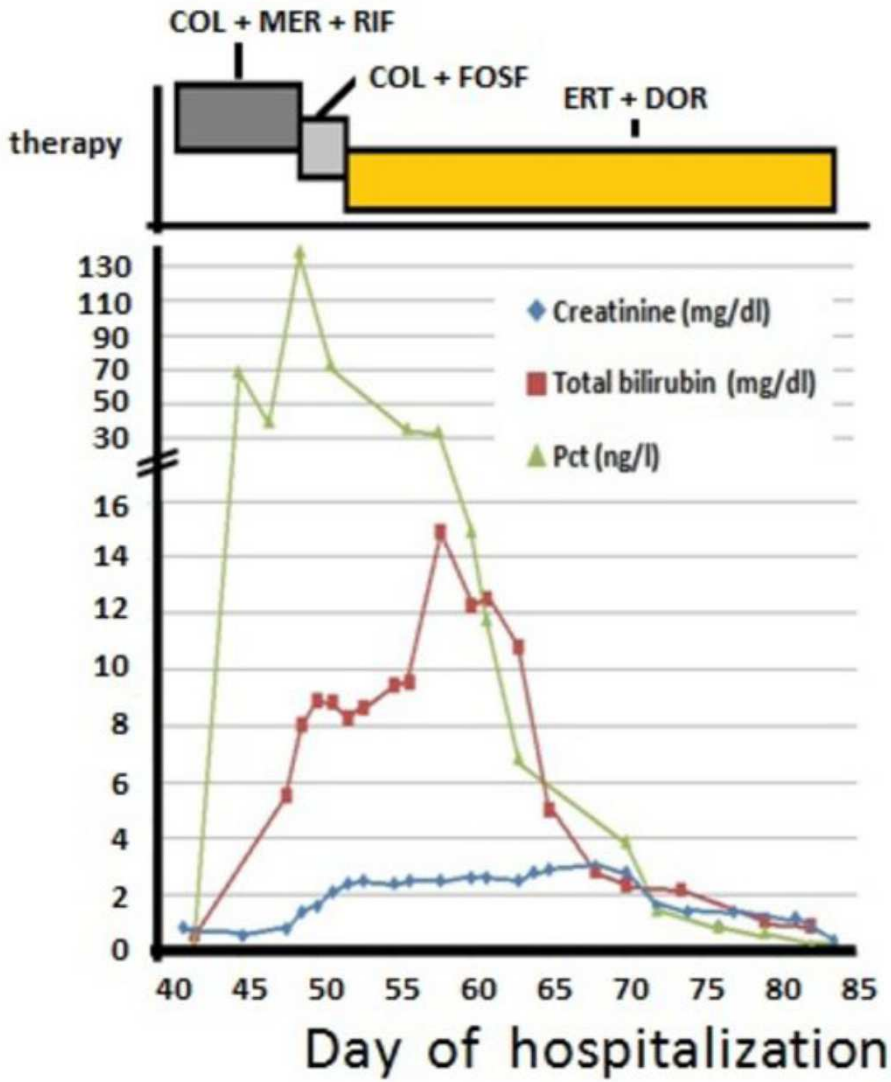


Double-carbapenem therapy with ertapenem plus doripenem for the treatment of severe KPC-producing *Klebsiella pneumoniae* bacteremic pneumonia

Ceccarelli GC et al, Antimicrob Ag Chemother submitted





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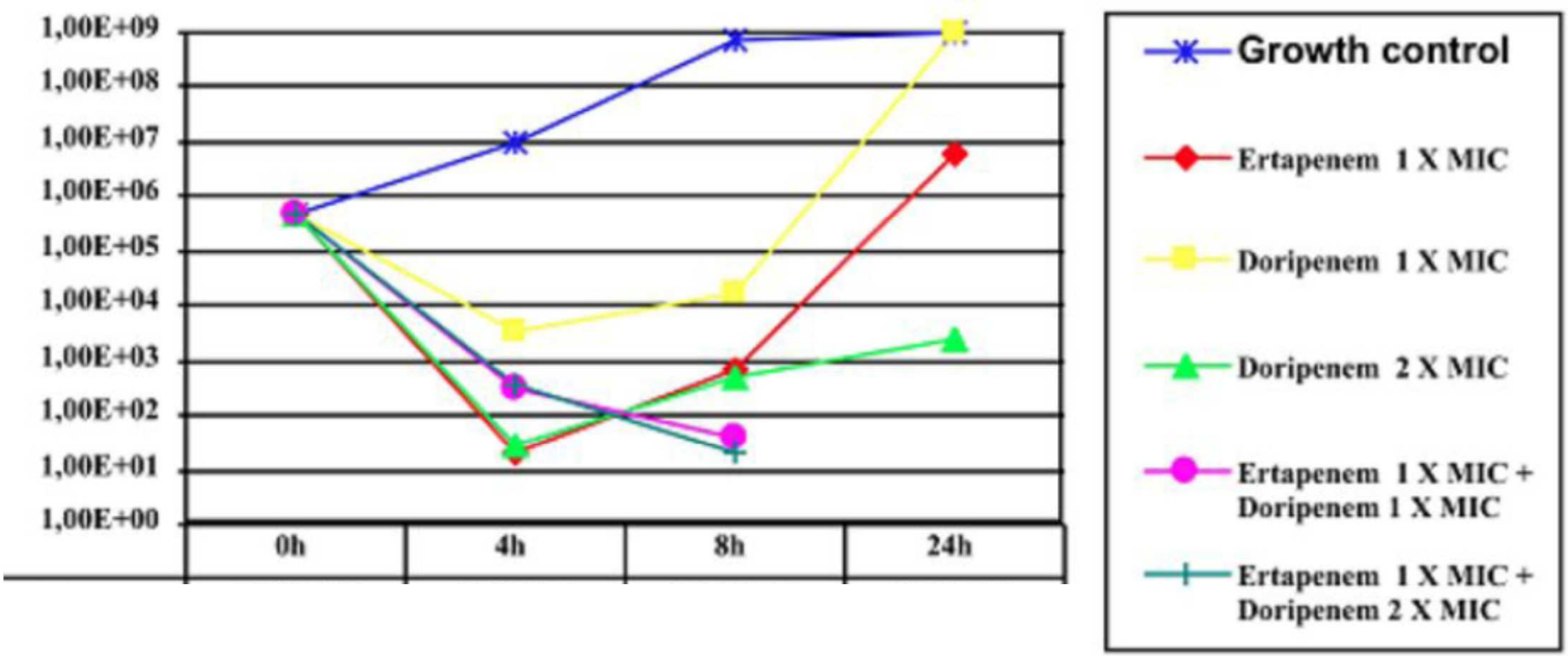
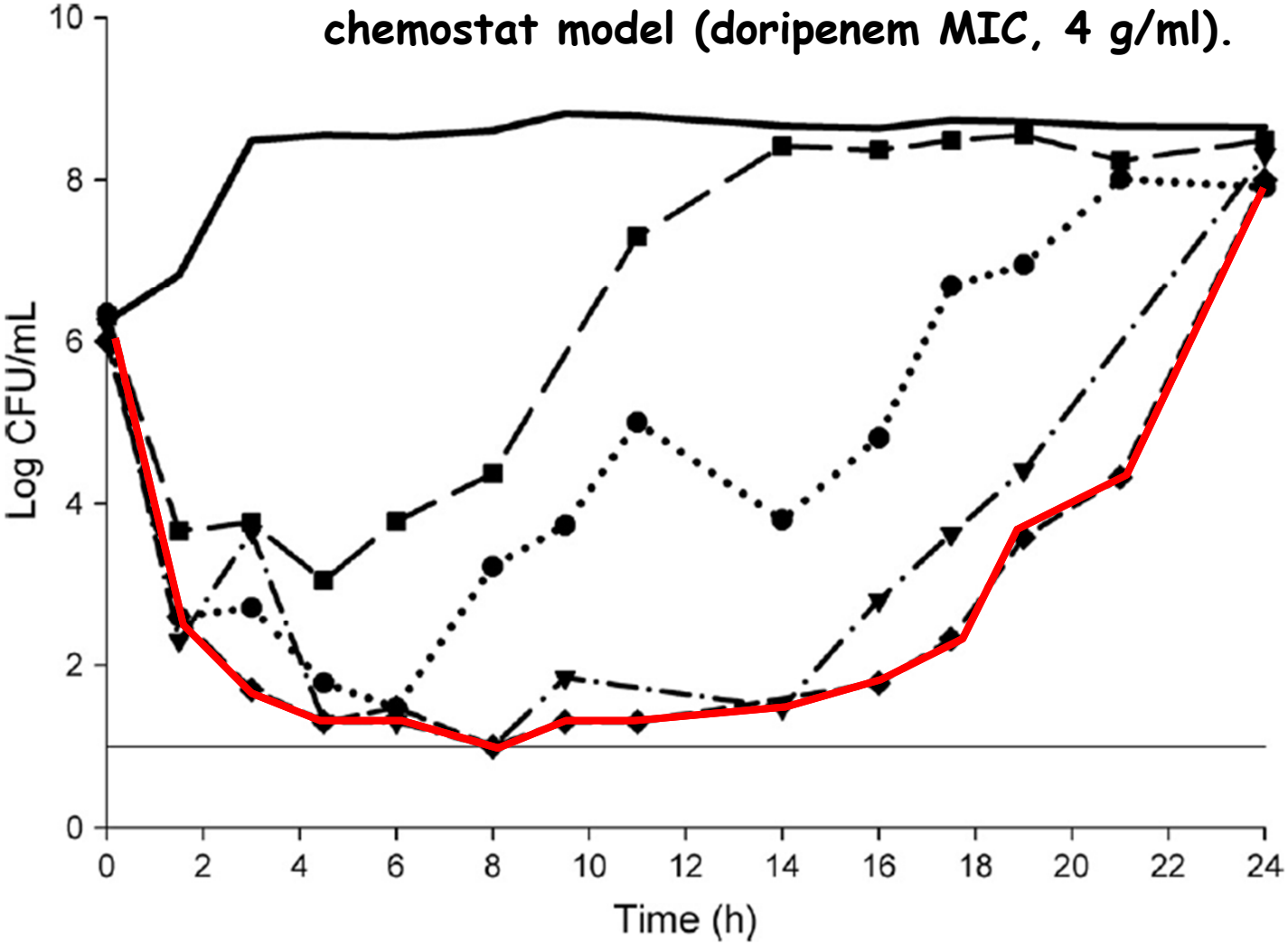


Double-Carbapenem Therapy for Carbapenemase-Producing *Klebsiella pneumoniae*

Bulik CC & Nicolau DP Antimicrob. Agents Chemother. 2011, 55:3002

Bacterial densities of KPC 354 over 24 h in the *in vitro* chemostat model (doripenem MIC, 4 g/ml).



Double-Carbapenem Therapy Not Proven To Be More Active than Carbapenem Monotherapy against KPC-Positive Klebsiella pneumoniae

Kenneth S. Thomson
Antimicrob. Agents Chemother. 2012, 56(7):4037. DOI:

Nosocomial bloodstream infections due to Acinetobacter baumannii, Acinetobacter pittii and Acinetobacter nosocomialis in the United States. ***Wisplinghoff H et al, J Infect. 2012;64:282-90***

295 Acinetobacter isolates collected prospectively from patients with bloodstream infections (BSI) in 52 US hospitals were identified to species level. Clinical and microbiological features were compared between species.

RESULTS:
Acinetobacter baumannii (63%) was the most prevalent species, followed by A. nosocomialis (21%), and A. pittii (8%). Intravascular catheters (15.3%) and the respiratory tract (12.9%) were the most frequent sources of BSI. A higher overall mortality was observed in patients with A. baumannii BSI than in patients with BSI caused by A. nosocomialis and A. pittii (36.9% vs. 16.4% and 13.0%, resp., p < 0.001).

The most active antimicrobial agents as determined by broth microdilution were tigecycline (99.6% of isolates susceptible), colistin (99.3%), amikacin (98.5%), and imipenem (95.2%). 27 isolates (10.0%) were multi-drug resistant, all but one of these were A. baumannii.

In vitro time-kill studies of antimicrobial agents against blood isolates of imipenem -resistant A. baumannii, including colistin- or tigecycline-resistant isolates

Peck KR, et al, J Med Microbiol. 2012;61:353-60

The bactericidal and synergistic effects of several combinations of antimicrobial agents against imipenem-, colistin- or tigecycline-resistant A. baumannii isolates were investigated by in vitro time-kill experiments.

Six imipenem-resistant A. baumannii blood isolates were examined in this study, including colistin- and tigecycline-susceptible, colistin-resistant but tigecycline-susceptible, and colistin-susceptible but tigecycline-resistant isolates.

Time-kill studies were performed using five antimicrobial agents singly or in combinations (imipenem plus colistin, imipenem plus ampicillin-sulbactam, colistin plus rifampicin, colistin plus tigecycline, and tigecycline plus rifampicin) at concentrations of 0.5× and 1× their MICs.

Although the effectiveness of combinations of 0.5× MIC antimicrobial agents was inconsistent, combination regimens using 1× MIC of the antimicrobial agents displayed excellent bactericidal activities against all six A. baumannii isolates. Among the combinations of 0.5× MIC antimicrobial agents, the combination of colistin and tigecycline showed synergistic or bactericidal effects against four of the isolates.

This in vitro time-kill analysis suggests that antimicrobial combinations are effective for killing imipenem-resistant A. baumannii isolates, even if they are simultaneously resistant to either colistin or tigecycline

The Combination of Colistin and Doripenem Is Synergistic against Klebsiella pneumoniae at Multiple Inocula and suppresses Colistin Resistance in an In Vitro PK/PD Model

Deris ZZ et al Antimicrobial Ag Chemother 2012; 56: 5103

The Combination of Doripenem and Colistin Is Bactericidal and Synergistic against Colistin-Resistant, Carbapenemase-Producing *K. pneumoniae*

Jernigan MG et al , Antimicrobial Ag Chemother 2012; 56: 3395

Macrolides decrease the minimal inhibitory concentrations of anti-pseudomonal agents against Pseudomonas aeruginosa from cystic fibrosis patients in biofilm

Lutz L et al, BMC Microbiology 2012, 12:196

Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant A, baumannii VAP.

Aydemir H et al, Epidemiol Infect 2012 Sep 7:1-9.

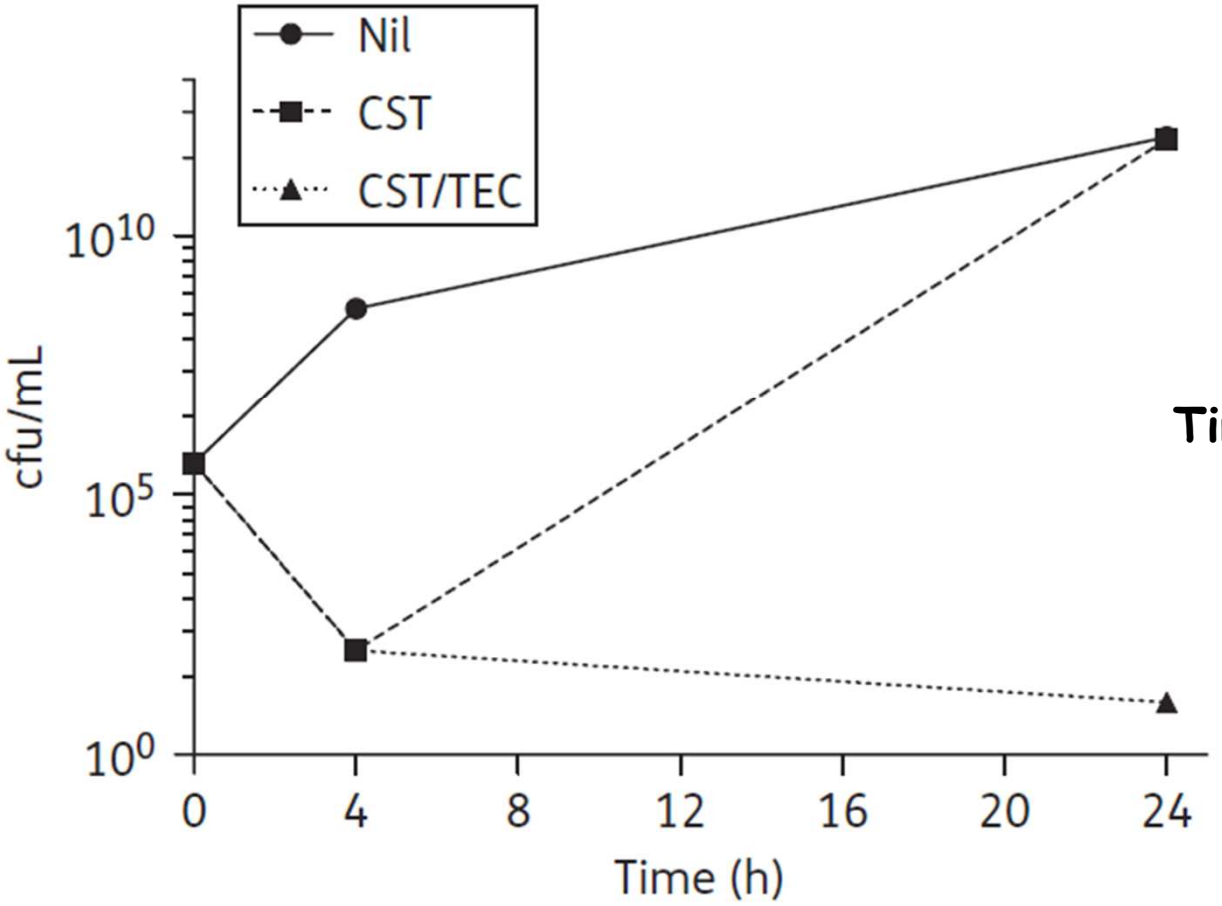
Forty-three patients were randomly assigned to one of two treatment groups.

Clinical (P = 0·654), laboratory (P = 0·645), radiological (P = 0·290) and microbiological (P = 0·597) response rates were better in the combination group, but these differences were not significant.

Time to microbiological clearance (3·1 ± 0·5 days, P = 0·029) was significantly shorter in the combination group.

The VAP-related mortality rates were 63·6% (14/22) and 38·1% (8/21) for the colistin and the combination groups (P = 0·171), respectively.

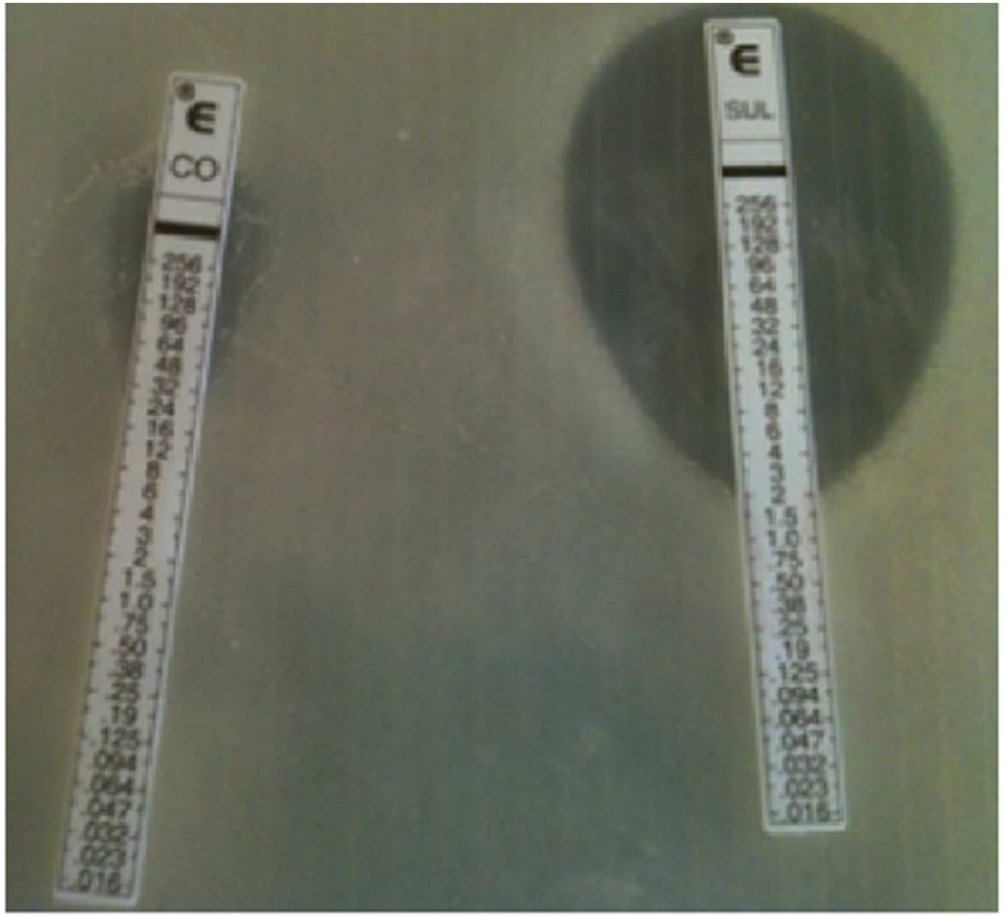
In vitro activity of teicoplanin combined with colistin versus multidrug-resistant strains of A. baumannii. ***Wareham DW et al, J Antimicrob Chemother. 2011 May;66(5):1047-51***

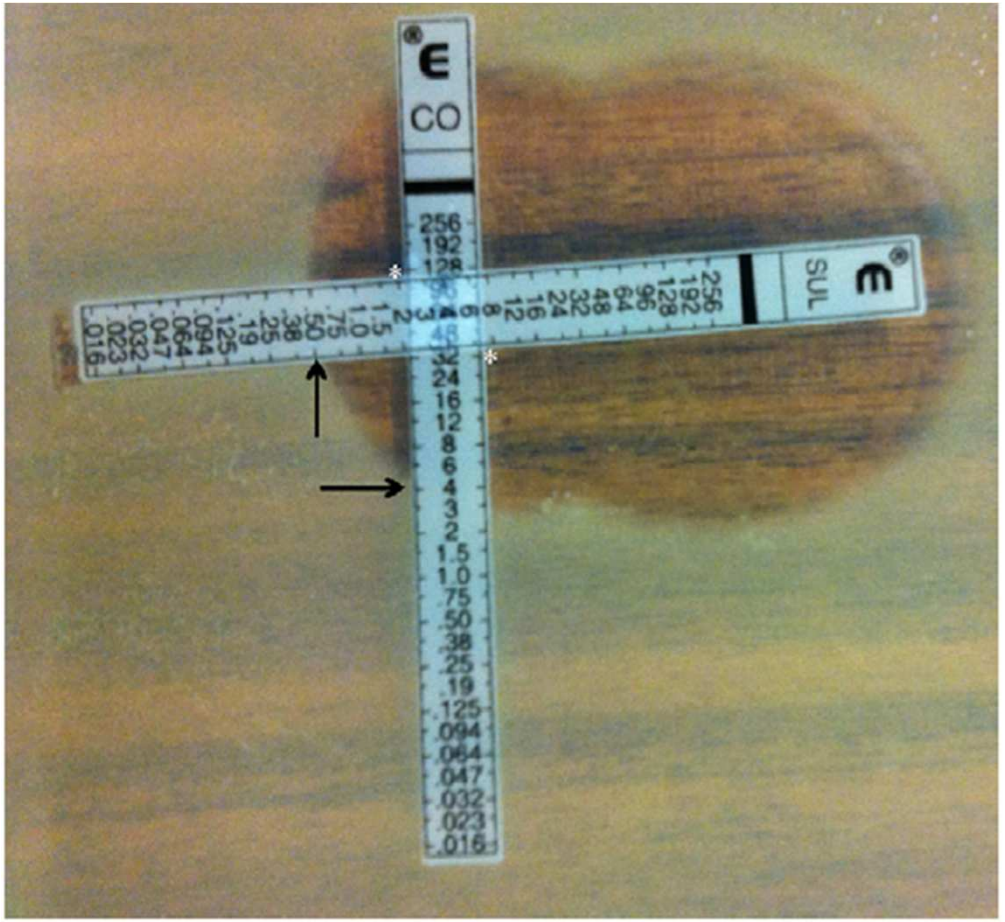


Time-killing assays

Synergistic activity of sulbactam combined with colistin against colistin-resistant Acinetobacter baumannii

Kempf M et al, Int J Antimicrob Chemother 2011





Successful Treatment of Extensively Drug-Resistant *A. baumannii* Peritoneal Dialysis Peritonitis with Intraperitoneal Polymyxin B and Ampicillin-Sulbactam.

Fitzpatrick MA et al, Ann Pharmacother 2012;46:e17

A 54-year-old woman with end-stage renal disease, receiving CAPD for the past 15 months was admitted with a diagnosi of peritonitis. The patient was initially treated with vancomycin + metronidazole and ceftazidime. On the third day of hospitalization, peritoneal fluid culture results showed few *A. baumannii*.

Intraperitoneal polymyxin B 300,000 IU (30 mg) per 2-L bag was initiated and dwelled for the entire 6 hours of every peritoneal dialysate exchange.
IV ampicillin-sulbactam 3 g every 12 hours was initiated.

Table 1. Peritoneal Fluid Analysis Results

Hospital Day	White Blood Cell Count (PMN %)	Culture Results
1	6150 cells/μL (95)	Few *Acinetobacter baumannii*
3[a]	9100 cells/μL (95)	Rare *A. baumannii*
6	320 cells/μL (73)	Negative
10	23 cells/μL (3)	Negative

Table 2. Susceptibility Results for *Acinetobacter baumannii* Isolate

Testing Method	Antibiotic	MIC (μg/mL)	Interpretation
Vitek 2	Ampicillin-sulbactam	16	Intermediate
Vitek 2	Cefepime	≥64	Resistant
Vitek 2	Ceftriaxone	≥64	Resistant
Vitek 2	Ciprofloxacin	≥4	Resistant
Vitek 2	Gentamicin	≥16	Resistant
Vitek 2	Imipenem	≥16	Resistant
Vitek 2	Tobramycin	≥16	Resistant
Vitek 2	TMP/SMX	≥16/304	Resistant
Kirby-Bauer	Amikacin		Resistant
Kirby-Bauer	Meropenem		Resistant
Kirby-Bauer	Doxycycline		Resistant
Kirby-Bauer	Minocycline		Resistant
Kirby-Bauer	Tetracycline		Resistant
Kirby-Bauer	Piperacillin/tazobactam		Resistant
Etest	Tigecycline	4	No CLSI guidelines
Etest	Colistin	0.5	Susceptible
Kirby-Bauer	Polymyxin B	(14-mm zone)	No CLSI guidelines

High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant A. baumannii. *Betrosian AP et al, Scand J Infect Dis. 2007;39:38-43.*

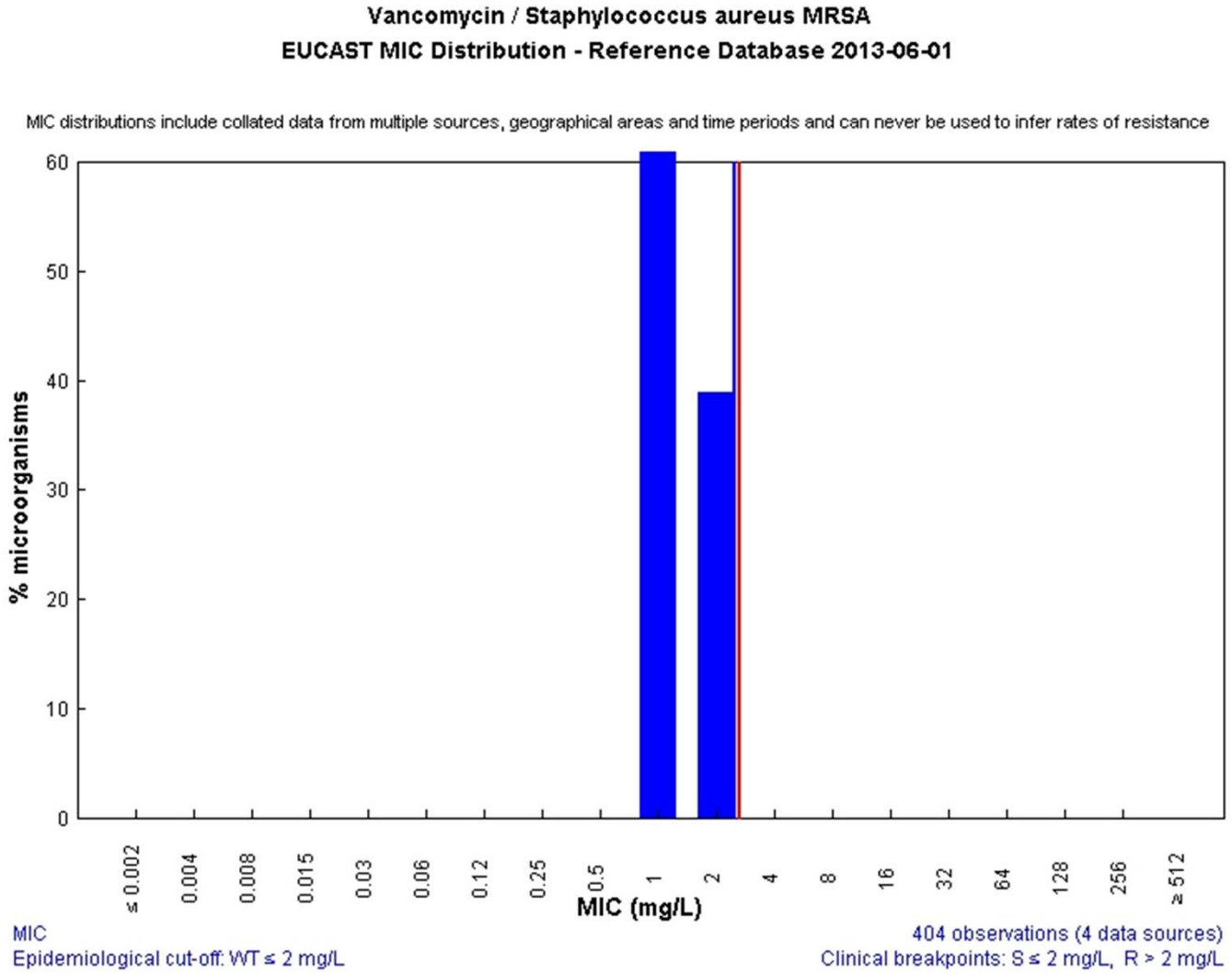
A randomized, prospective trial of critically ill patents with (MDR) Acinetobacter baumannii VAP. to evaluate the efficacy and safety of 2 high-dose treatment regimens of ampicillin-sulbactam for MDR Acinetobacter baumannii VAP. Patients were randomly assigned to 1 of 2 treatment regimens of A/S (at a rate 2:1 every 8 h): 1) group A, 18/9 g daily dose (n = 14); and 2) group B, 24/12 g daily dose (n = 13). The duration of therapy was 8+/-2 d for both groups. A total of 27 patients were enrolled in the study.

Clinical improvement was seen in 66.7% of the study population
Group A 9/14 (64.3%)
Group B 9/13 (69.2%)

Bacteriological success was achieved in 77.8% of the study population
Group A 12/14, 85.7%
Gropu B 9/13 (69.2%)

The 14-d mortality rate was 25.9% and the all cause 30-d mortality was 48.1%.
Both mortality rates did not differ significantly between the 2 groups.
No major adverse reactions were recorded.

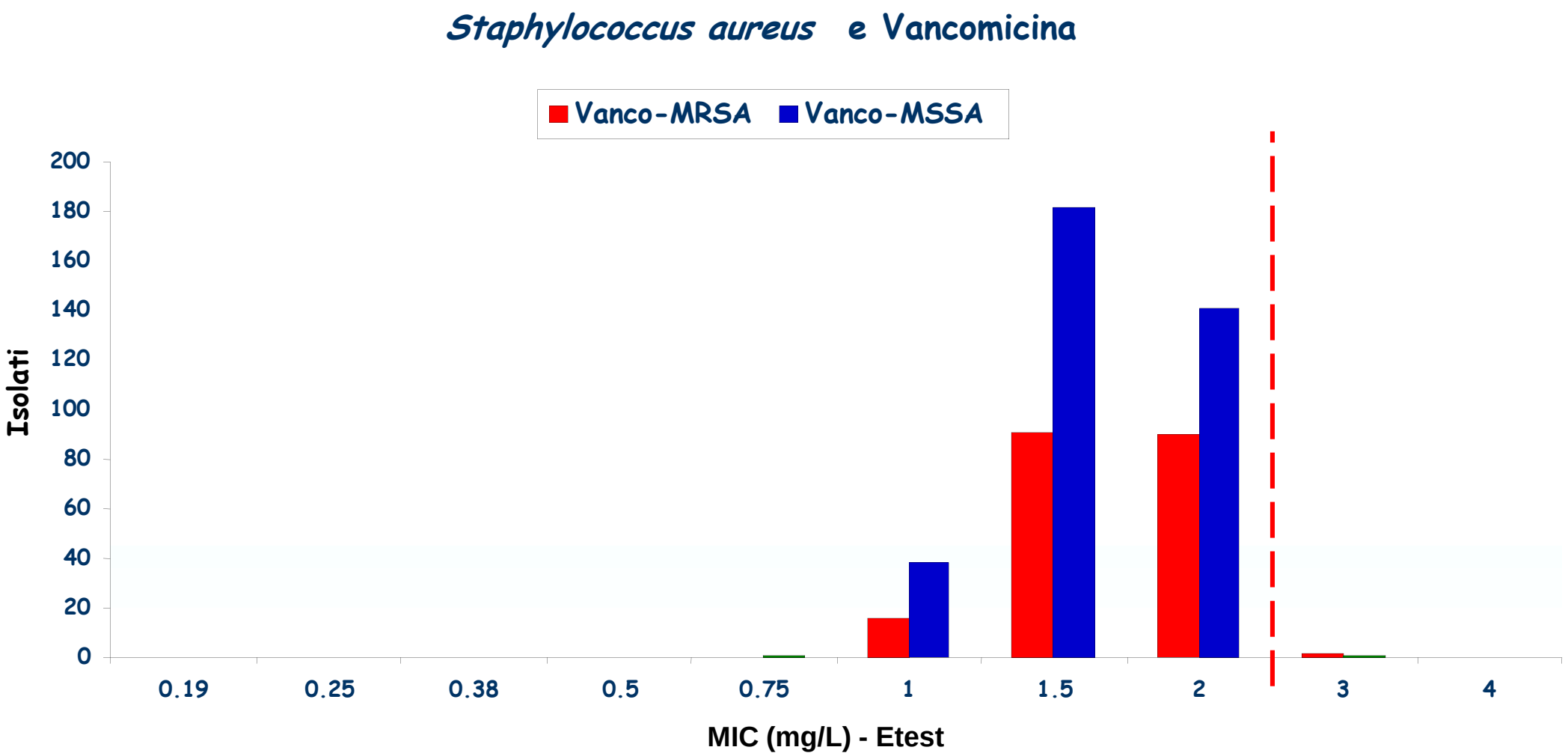
VANCO MIC CREEP OF MRSA



European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, last accessed 1st June 2013

Studio OASIS

Vancomicina e *S. aureus* (n=562)



Impact of vancomycin exposure on outcomes in patients with MRSA bacteremia: support for consensus guidelines suggested targets.

Kullar R et al, Clin Infect Dis. 2011;52:975-81

AIMS: The primary objective of the study was to determine the impact of vancomycin exposure and outcomes in patients with MRSA bacteremia initially treated with vancomycin.
METHODS: A single-center retrospective analysis of 320 patients with documented MRSA bacteremia initially treated with vancomycin from January 2005 through April 2010.

RESULTS:

Among a cohort of 320 patients, 52.5% experienced vancomycin failure.

Independent predictors of vancomycin failure in logistic regression included:

- infective endocarditis (AOR 4.55; 95% CI 2.26-9.15),
- nosocomial-acquired infection (AOR, 2.19; 95% CI, 1.21-3.97),
- initial vancomycin trough <15 mg/L (AOR, 2.00; 95% CI, 1.25-3.22),
- vancomycin MIC >1 mg/L by Etest (AOR, 1.52; 95% CI, 1.09-2.49).

patients with vancomycin AUC 24h to MIC ratios <421 were found to have significantly higher rates of failure, compared with patients with AUC 24h to MIC ratios >421 (61.2% vs 48.6%; P = .038).

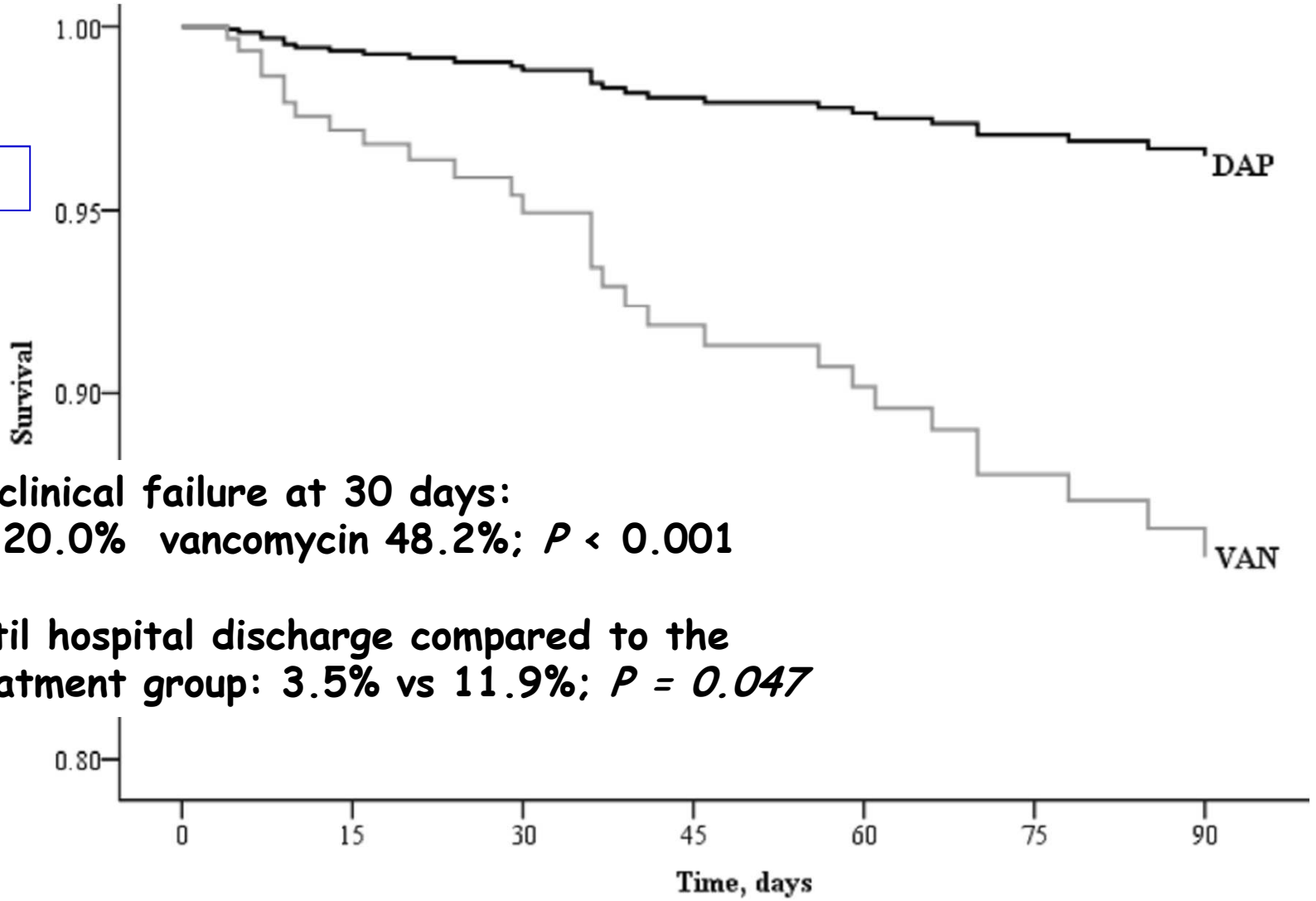
Early use of daptomycin versus vancomycin for MRSA bacteremia with vancomycin MIC > 1 mg/L: a matched cohort study *Murray KP et al, Clin Infect Dis 2013, Feb 28,2013*

A matched, retrospective cohort study compared the clinical effectiveness of daptomycin with that of vancomycin for the treatment of MRSAB with vancomycin MICs >1 µg/mL. The primary outcome was clinical failure, defined as a composite of 30 day mortality or bacteremia persisting for ≥7 days.
One-hundred seventy patients were matched 1:1 with respect to the antimicrobial. In the daptomycin group, all patients received <72 hours of vancomycin (median, 1.7 days [range, 1.1-2.3 days]) prior to switching to daptomycin.
Baseline patient characteristics were similar between groups.

The most common primary sources of MRSAB were cSSTI, bone or joint infection, and nfective endocarditis. Vancomycin susceptibility for the majority of isolates was determined via MicroScan versus Etest (85.3% vs 14.7%). Overall, 160 (94.1%) isolates had vancomycin MICs of 2 µg/mL, while 10 (5.9%) had MICs of 1.5 µg/mL. Seventy-nine (92.9%) patients in the daptomycin group were switched from vancomycin once a vancomycin MIC of > 1 µg/mL was identified; the remaining 6 patients had MRSA therapy initiated with daptomycin.

Early use of daptomycin versus vancomycin for MRSA bacteremia with vancomycin MIC > 1 mg/L: a matched cohort study *Murray KP et al, Clin Infect Dis 2013, Feb 28,2013*

Surival to 90 days

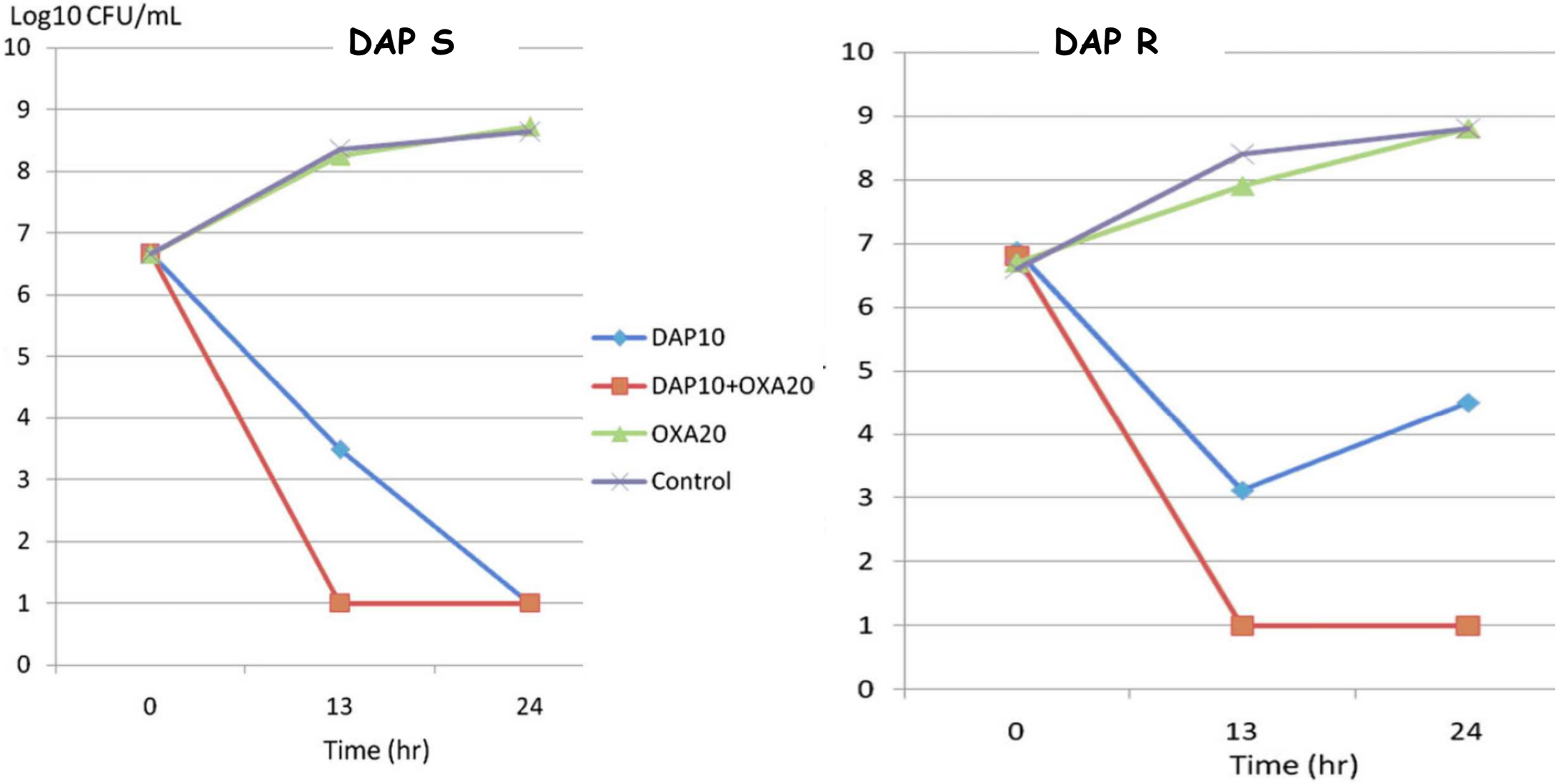


clinical failure at 30 days:
daptomycin 20.0% vancomycin 48.2%; *P* < 0.001

Survival until hospital discharge compared to the vancomycin treatment group: 3.5% vs 11.9%; *P = 0.047*

Use of Antistaphylococcal b-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to MRSA: Role of Enhanced Daptomycin Binding

Dhand A et al, Clin Infect Dis 2011;53:158–163



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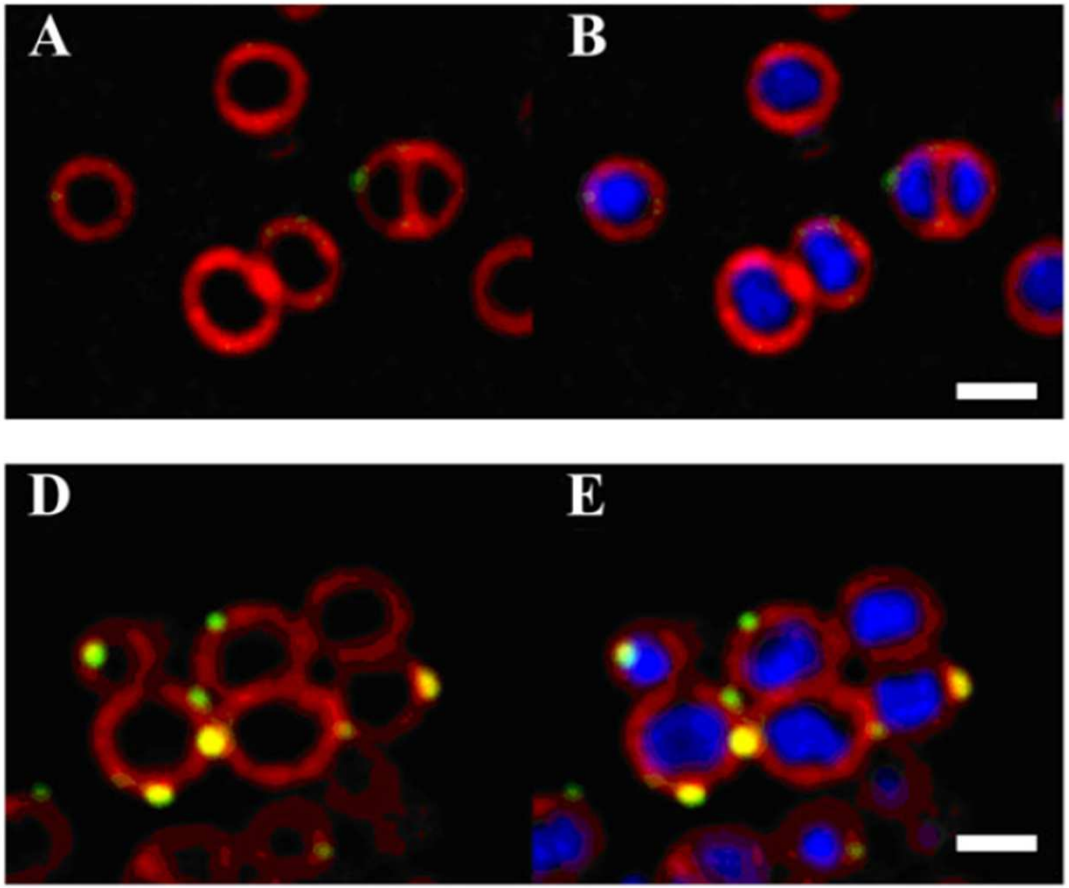
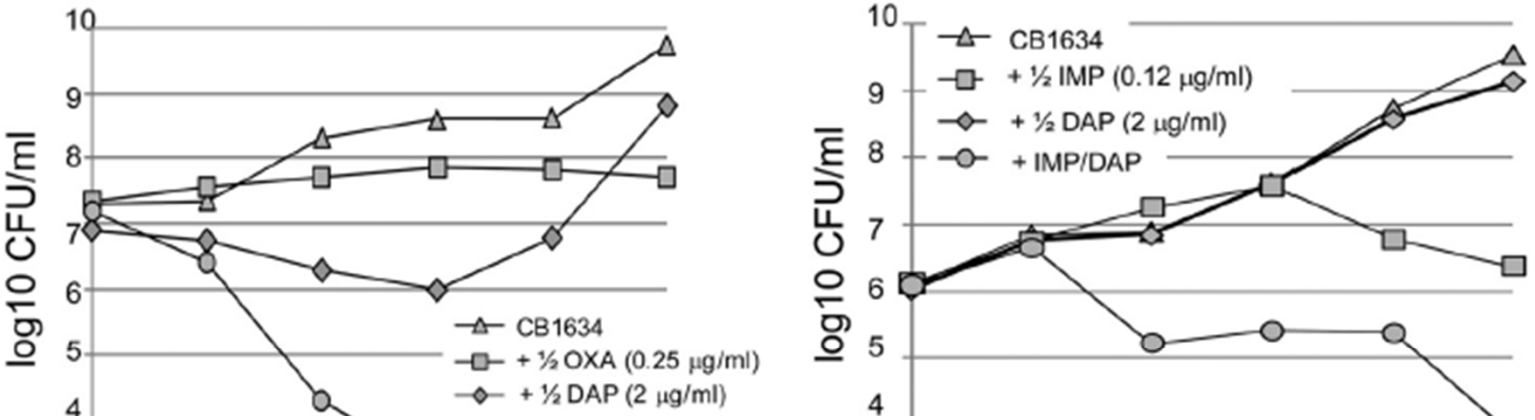


In vitro studies showed several important observations:

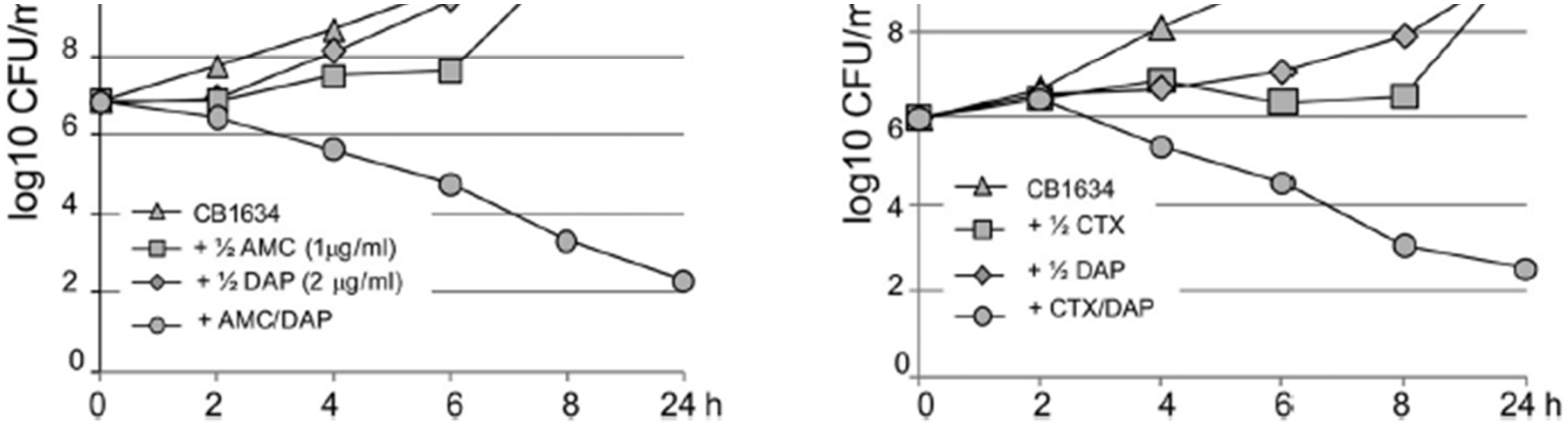
1. Restoration of in vitro DAP susceptibility of one DAP-R-VISA strain that emerged during therapy in ASBL containing media,
2. Enhanced killing of this isolate by DAP plus ASBLs
3. Notable increases in DAP membrane bindingafter organism growth in ASBLs,
4. Reduction in net positive membrane surface charge by ASBLs that was more pronounced in the DAP-R strain, compared with the DAP susceptible parent.

Beta-Lactams Increase the Antibacterial Activity of Daptomycin against Clinical MRSA Strains and Prevent Selection of Daptomycin-Resistant Derivatives

Mehta S et al, Antimicrob Ag Chemother, 2012; 56: 6192-6200

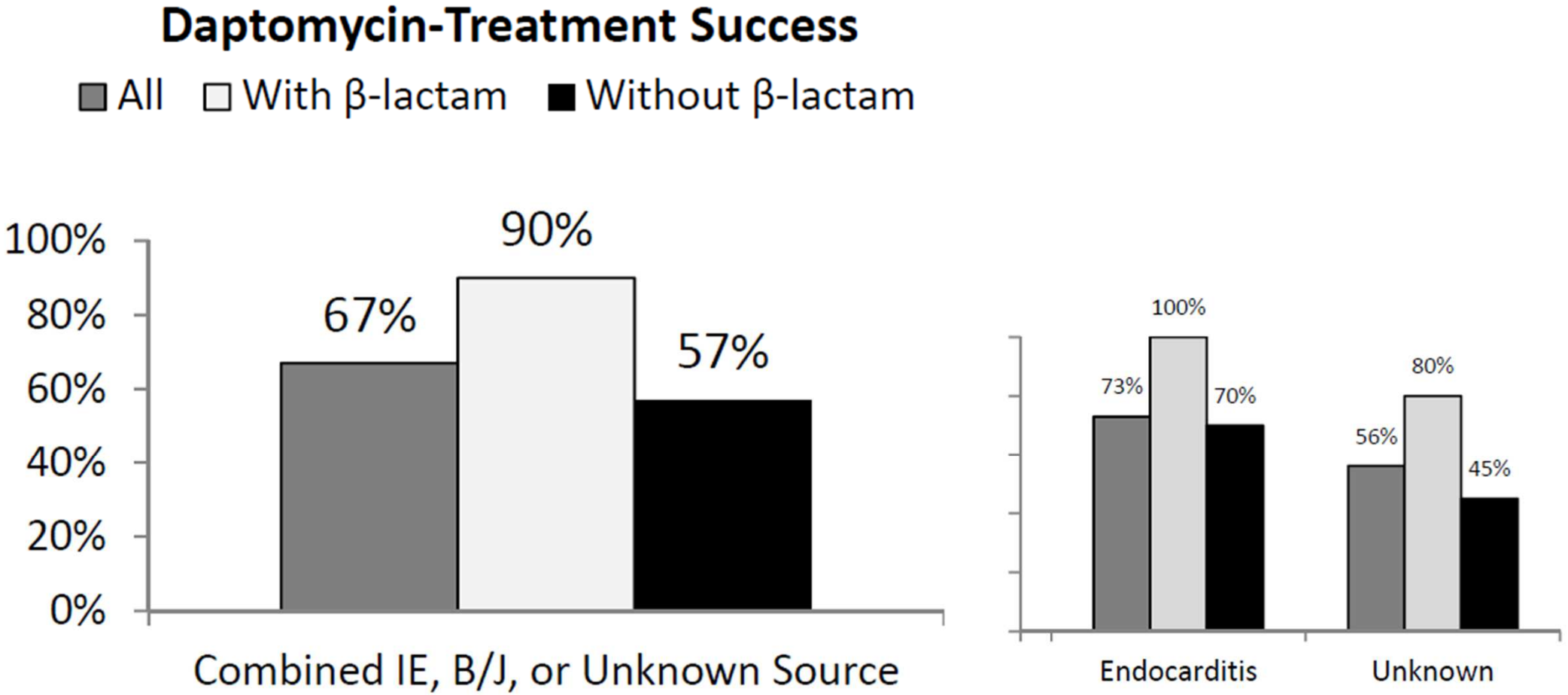


DAP–betalactam combination may significantly enhance both the *in vitro* and *in vivo* efficacy of anti-MRSA therapeutic options against DAP-R MRSA infections and represent an option in preventing DAP-R selection in persistent or refractory MRSA infections.



Clinical Outcomes of Daptomycin with and without Concomitant β-lactams in Patients with *S. aureus* Bacteremia and Mild to Moderate Renal Impairment: A Multicenter Evaluation

Moise PA et al, Antimicrob. Agents Chemother 17 Dec 2012



Efficacy of Daptomycin-Cloxacillin combination in experimental foreign-body infection due to MRSA *Garrigós C et al, Antimicrob Ag Chemother 2012;56: 3806-3811*

Decreases in bacterial counts from TCF at day 8 and day 11

	Decrease in bacterial count from TCF	
Treatment (n^b)	D8	D11
DAP 45 (21)	−2.76 (±1.3)	−2.80 (±1.4)
DAP 100 (20)	−2.82 (±0.7)	−3.24 (±0.7)
DAP 45 + CXA (22)	−3.24 (±1.2)	−3.19 (±1.1)
DAP 100 + CXA (24)	−3.19 (±1.1)	−3.22 (±1.1)
DAP 100 + RIF (16)	−4.94 (±0.8)**	−4.88 (±1.4)**
Control (17)	0.39 (±0.8)	0.85 (±0.8)