Uso delle terapie di associazione per le infezioni gravi da gram positivi

Dr Carlo Tascini

U.O. Malattie Infettive

AOUP

Nuovo Ospedale S. Chiara Pisa

"6th INFECtivology TOday"

"L'infettivologia del 3° millennio: AIDS ed altro"

Conflitto di interessi

- Negli ultimi due anni grant educazionali da parte di Pfizer, Merck, Novartis, Astellas, Gilead, Astra e Zambon

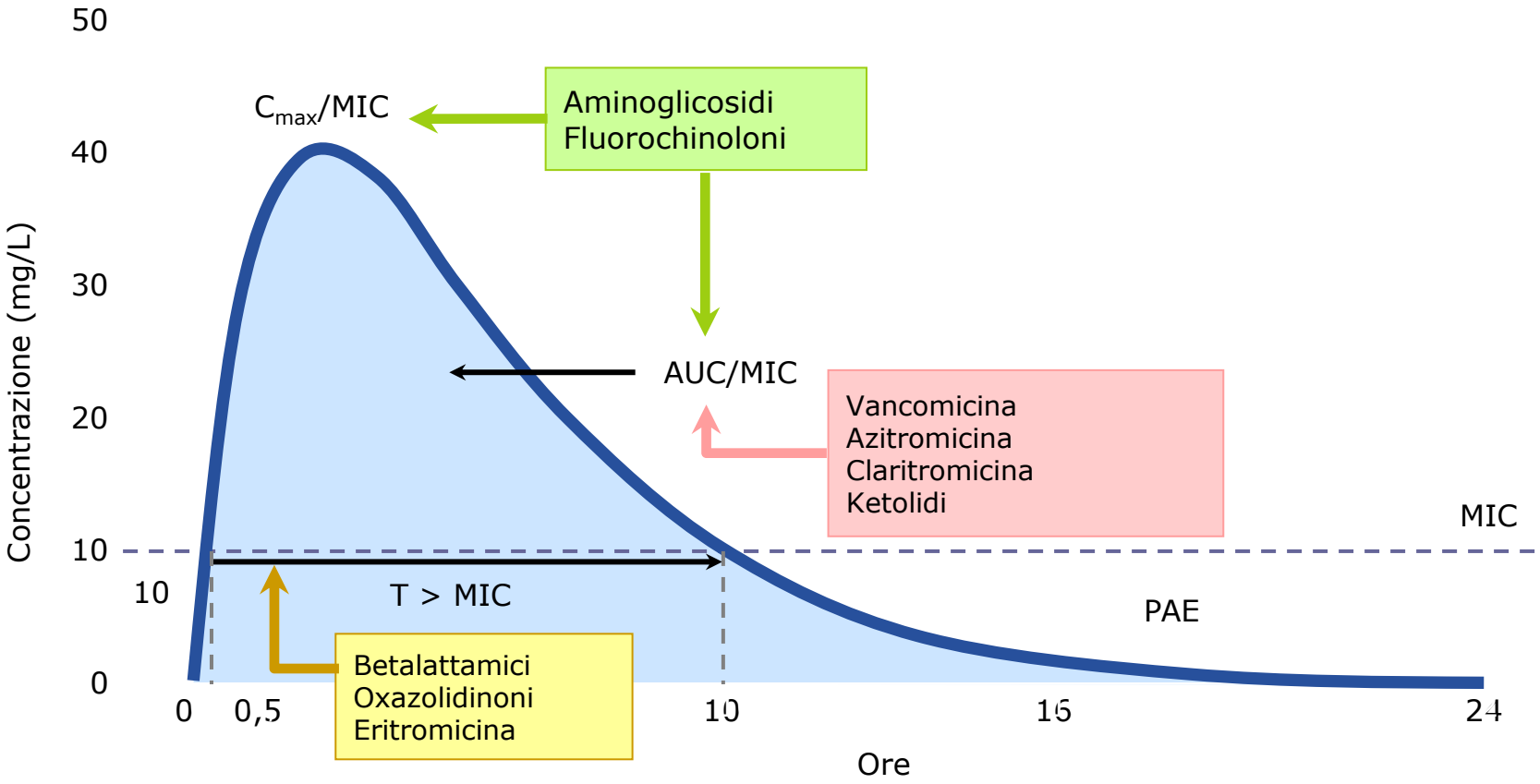
Argomenti

- Metodi per verificare il sinergismo
- Associazioni con linezolid
- Associazioni con daptomicina
- Associazioni per *E. faecalis*

Razionale della associazioni antibiotiche

- **Differente meccanismo d'azione**
- **Spettro d'attività antimicrobica più ampio**
- **Sinergismo (AB > A+B)**
- **Incremento dell'attività battericida**
- **Controllo dell'emergenza di ceppi resistenti (?)**
- **Riduzione delle dosi dei singoli farmaci (?)**

Correlazioni fra farmacocinetica e farmocodinamica



Hyatt JM et al., 1995

Sinergismo

- Diminuisce la MIC di un antibiotico da solo
- In caso di sinergismo: la MIC in combinazione è più bassa, pertanto i vari parametri farmacodinamici migliorano

Impiego clinico delle associazione di farmaci antinfettivi

- **Terapia anti-tubercolare (MT, MAC), serve per ridurre l'insorgenza di resistenza (insorgenza di resistenza per INI 10^{-5}, per Rifa 10^{-4} etc, la somma di quattro farmaci ha un'incidenza di insorgenza di resistenza di circa 10^{-13}, numero di batteri non presenti in nessuna lesione tubercolare)**
- **Terapia anti-HIV (serve per evitare mutanti resistenti)**
- **Terapia della meningite criptococcica**
- **Terapia dell'endocardite batterica (stafilococchi, enterococchi, streptococchi PCN-R)**
- **Terapia delle neutropenia febbrile (lavori anche a favore della monoterapia)**

Impiego clinico delle associazione di farmaci antinfettivi

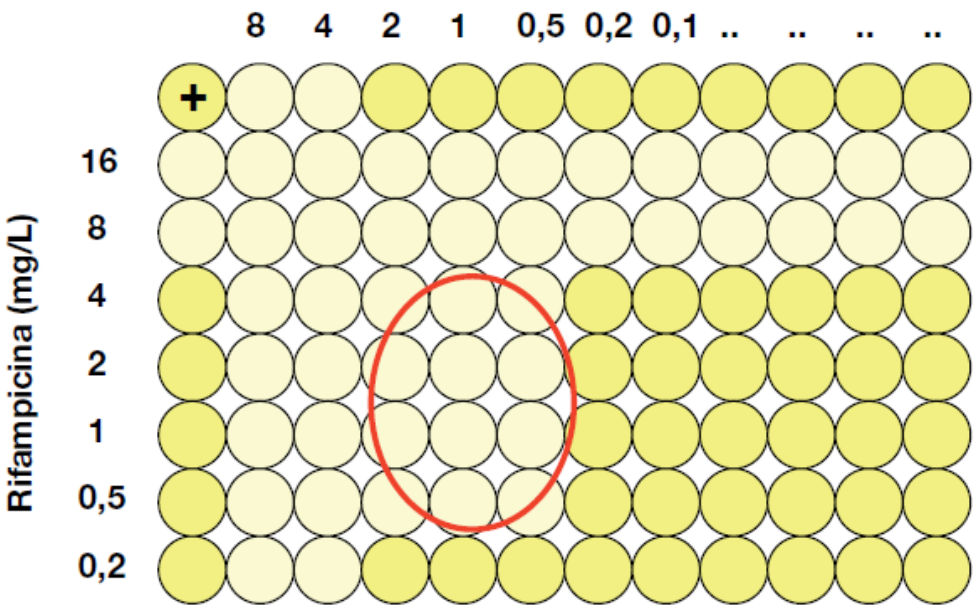
- **Terapia empirica delle infezioni nosocomiali**
- **Terapia di infezioni da germi "difficili" (ad es: *Ps. aeruginosa, A. baumannii, K. pneumoniae* KPC, MRSA*)***

Sinergismo

- Permette di ridurre la MIC di un farmaco A in presenza di un farmaco B
- L'associazione può rendere efficace un farmaco non attivo rispetto ad un dato microrganismo (aminoglicosidi vs *Enterococcus spp*, rifampicina vs gram-)
- Clinicamente rilevante solo se la MIC in associazione è nel range raggiungibile nella pratica clinica
- Migliora l'efficacia di una terapia, incrementa il rapporto AUC/MIC o T/MIC o Cmax/MIC
- Può rendere un farmaco battericida (cotrimossazolo)

Test di sinergismo con checkerboard

- **Che cos'è FIC?: Fractional Inibithory Concentration**
- **FIC farmaco A: MIC in associazione/MIC da solo**
- **$\sum$ FIC: MIC farmaco A in associazione/MIC farmaco A + MIC farmaco B in associazione/ MIC farmaco B**
- **Indica sinergismo completo se $\leq$ 0.5**
- **Indica sinergismo parziale se > 0.5 < 1.0**
- **Indica effetto additivo se = 1.0**
- **Indica indifferenza se > 1.0 < 4.0**
- **Indica antagonismo se > 4.0**
- **Checkerboard studia il sinergismo tra differenti combinazioni di concentrazioni dei due farmaci, lettura ad un tempo.**

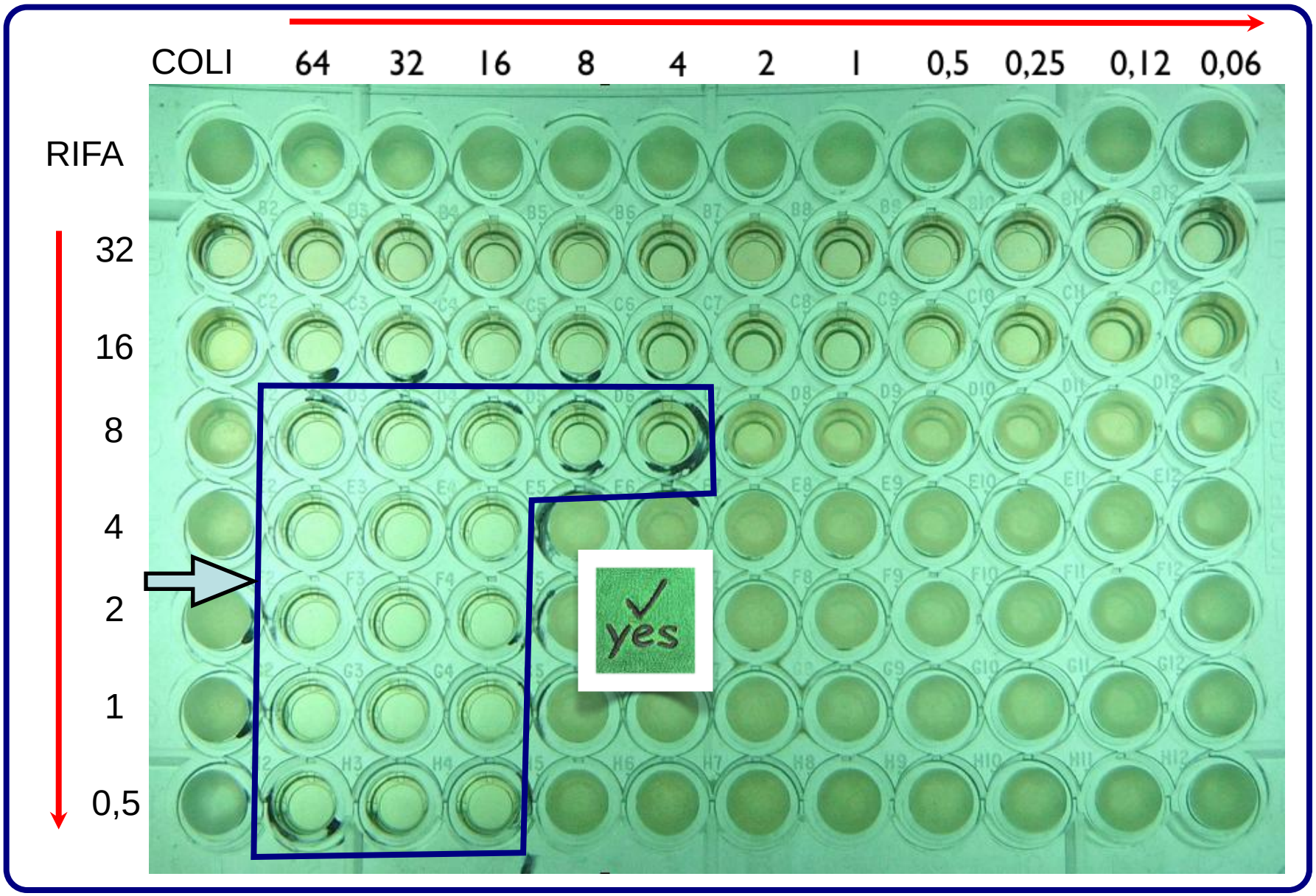


MIC (a) COLI = 4 µg/mL
MIC (c) COLI = 0,5 µg/mL
MIC (a) RIFA = 8 µg/mL
MIC (c) RIFA = 0,5 µg/mL

FIC (colistina) = 0,5/4 = 0,125
FIC (rifampicina) = 0,5/8 = 0,0625
ΣFIC = 0,125 + 0,0625 = 0,18
→ ASSOCIAZIONE SINERGICA

Sinergismo Rifampicina e Colistina

BSI da KPC-Kp



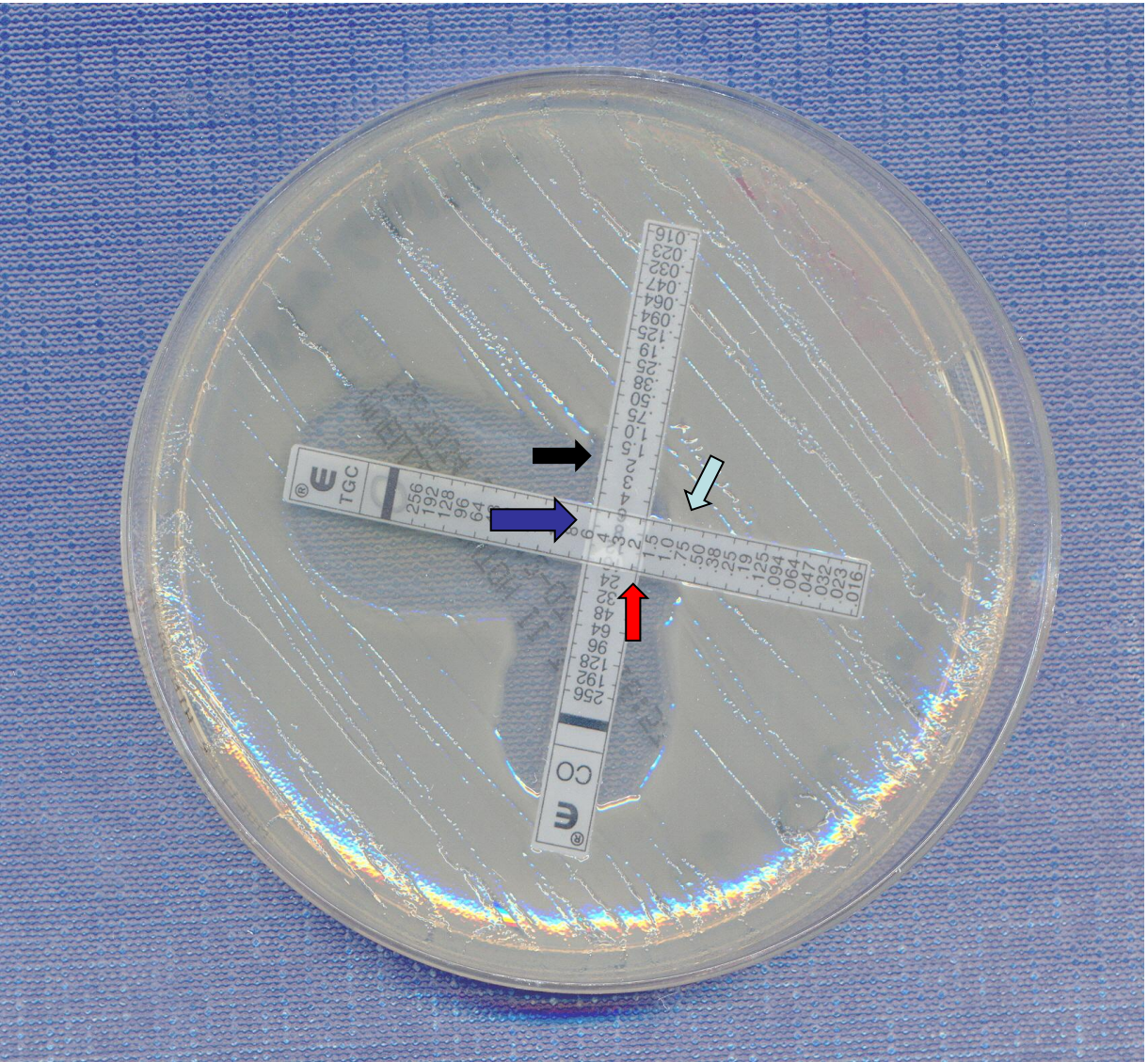
Time Kill curve

- Tre curve di killing (ATB 1, ATB 2 , ATB1+ATB2) in genere a tempo 0, 2h, 4h, 6h, 12 h, 24 h (subcolture su terreno senza antibotico)
- Abbattimento di > 2 $\log_{10}$ rispetto all'antibiotico più attivo
- Vede la velocità di batteriocidia
- Quale MIC?: ½ MIC, MIC al picco, MIC alla valle

E Test

- Il più semplice da eseguire
- Prima bisogna fare le MIC, il giorno dopo il sinergismo (incrocio alle MIC)
- Difficile da leggere
- Non vede sinergismo battericida

KPC: sinergismo tige + coli

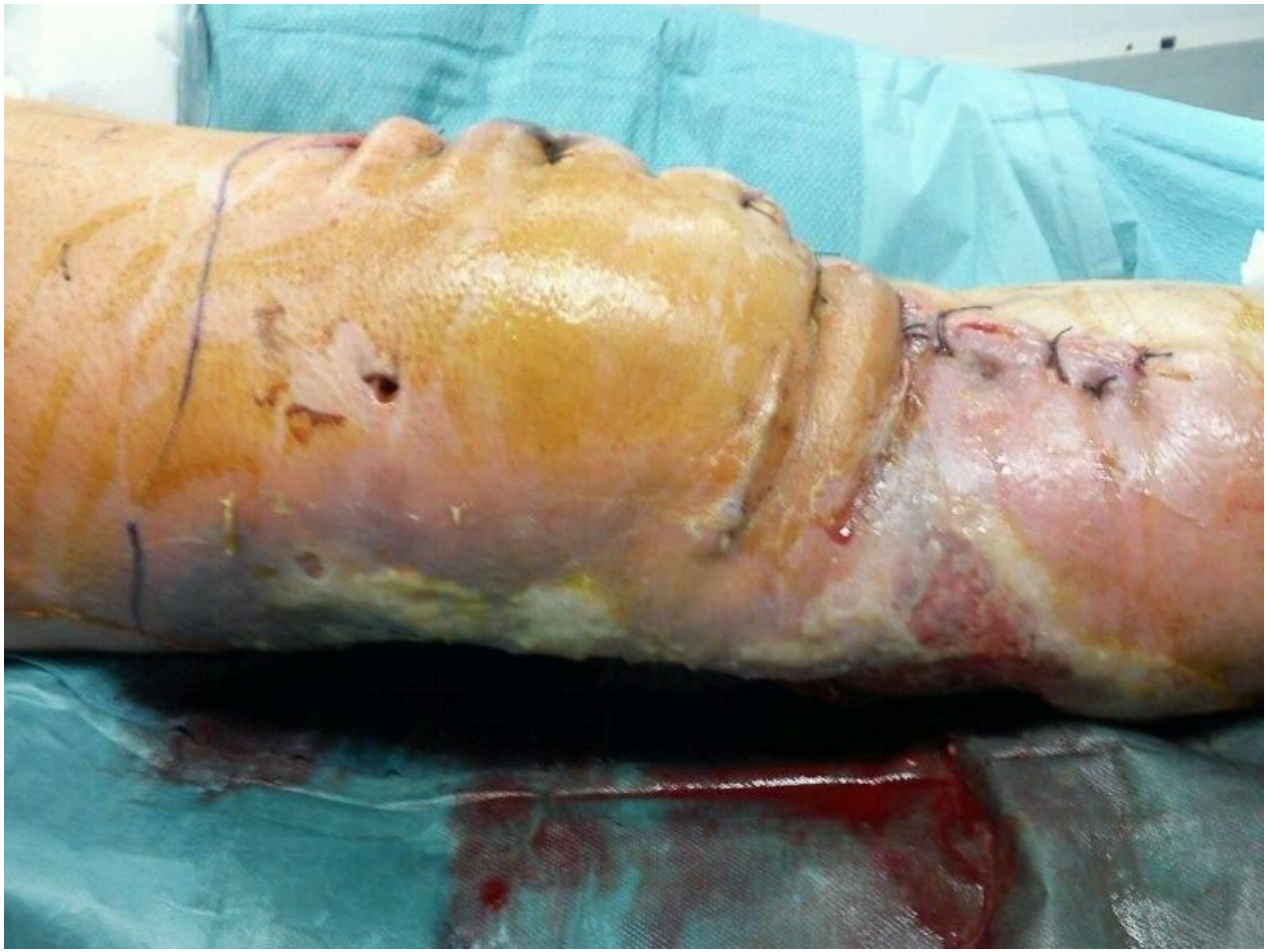


- MIC tige da sola 2 ⬆
- MIC tige + coli 1 ⇩
- MIC coli da sola 6 ➡
- MIC coli + tige 2 ➡
- SFIC:1/2+2/6: 0,5+0,33=0,88

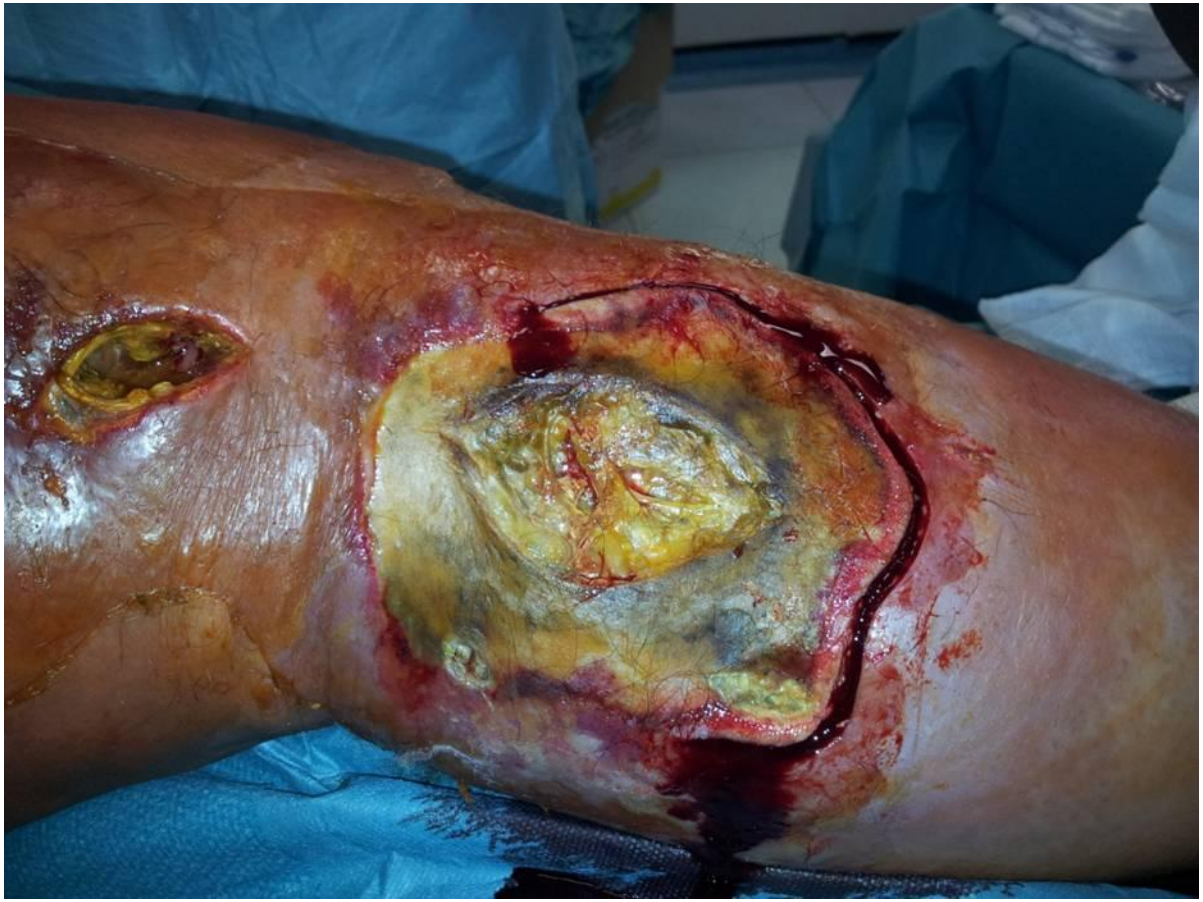
Problema del sinergismo

- Esigenze quotidiane
- Supporto della letteratura

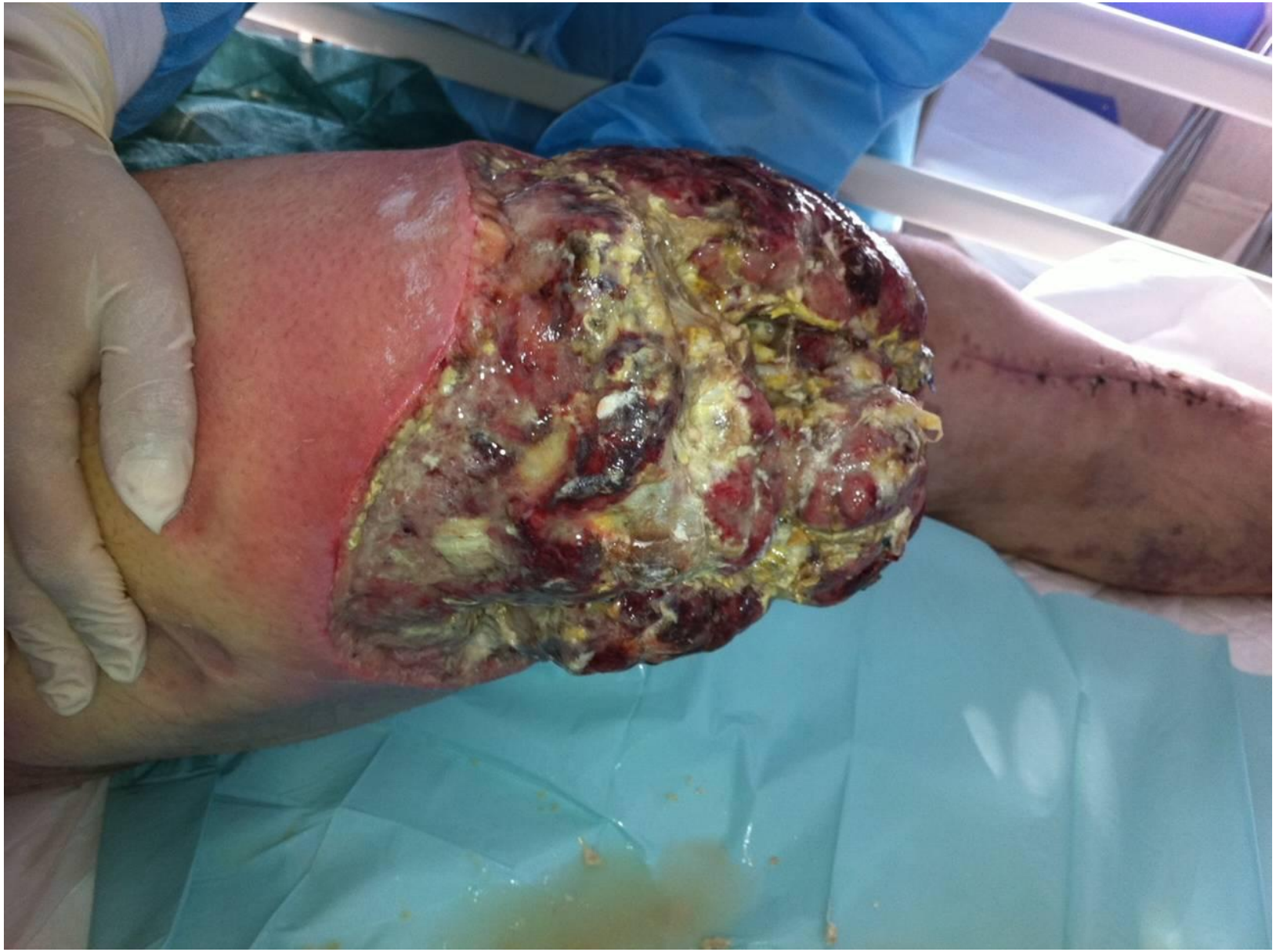
Fascite da *A. baumannii*



Cortesia del Dr G. Riccio

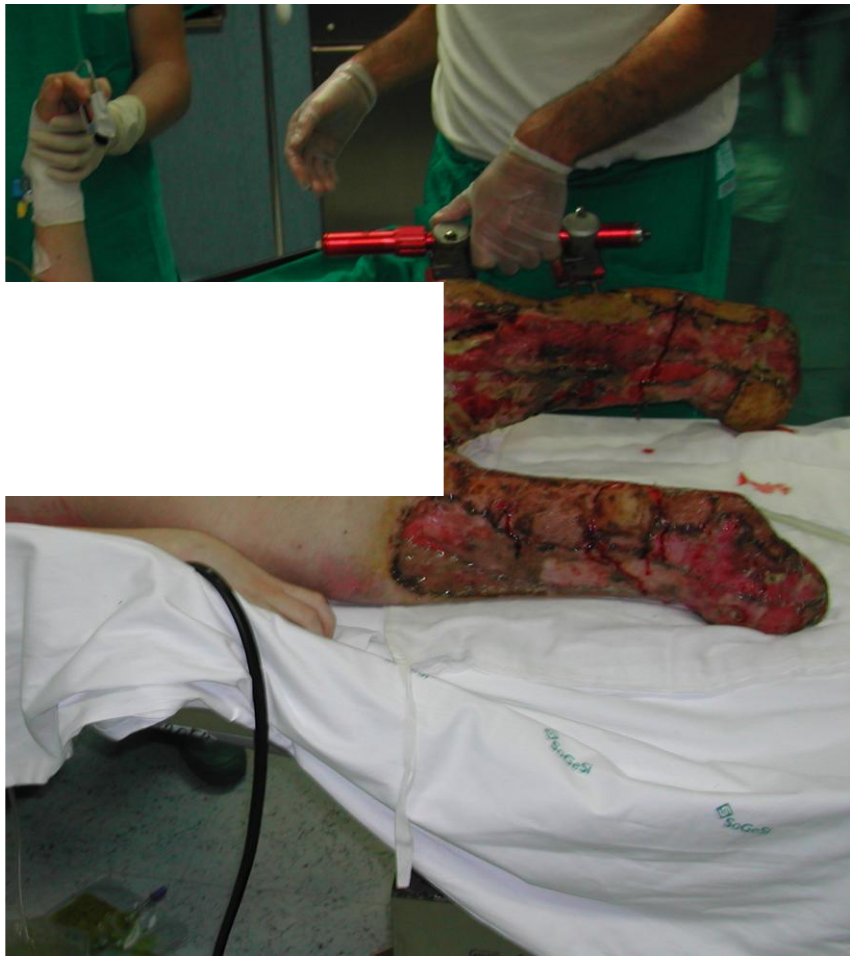


Cortesia del Dr G. Riccio



Cortesia del Dr G. Riccio: terapia con 4 antibiotici?

Fascite post-traumatica da *A. baumannii*



CASE REPORT

Colistin, meropenem and rifampin in a combination therapy for multi-drug-resistant *Acinetobacter baumannii* multifocal infection

A case report

G. BIANCOFIORE, C. TASCINI [1], M. BISÀ, G. GEMIGNANI [1], M. L. BINDI, A. LEONILDI [1]
G. GIANNOTTI [2], MENICHETTI F. [1]

[1]Unit of Infectious Diseases, Postsurgical and Transplant Intensive Care Unit Azienda Ospedaliero-Universitaria Pisana Cisanello Hospital, Pisa, Italy; [2]Unit of Plastic Surgery, Azienda Ospedaliero-Universitaria Pisana Cisanello Hospital, Pisa, Italy

MINERVA ANESTESIOL 2007;73:181-5

Sinergismo

- Letteratura prima degli anni ’90
- Le industrie hanno studiato il loro nuovo farmaco da solo, mai in associazione
- Non c’è letteratura a supporto ma contro

Sinergismo

- L’antibiogramma micro-diluizione non permette di confrontare molecole
- L’uso del Kirby-Bauer permette di osservare fenomeni naturali e svilupparli: ma nessuno lo usa più
- **Autoreferenzialità di chi vi espone**: concetti poi entrati nella pratica anche di altri colleghi
- Le terapie di associazione per KPC sono già immaginifiche se si guardano gli antibiogrammi

La nostra esperienza

- A Perugia laboratorio di batteriologia interno alla Clinica di Malattie Infettive
- A Pisa dal 2002 laboratorio di batteriologia interno alla Unità Operative di Malattie Infettive
- **Terapia antibiotica fenotipica**: basata sull'antibiogramma, ma anche sulla batteriocidia, sul potere battericida del siero, sui sinergismi
- Esperienza unica, non esportabile, autoreferenziale, non supportata da attività di pubblicazione adeguata ma osservata con interesse

La nostra esperienza

- *A. baumannii*, *P. aeruginosa* ma soprattutto *K. pneumoniae* KPC hanno riportato indietro la storia della medicina all'era pre-antibiotica ma hanno anche determinato la fine dell'antibiogramma (un germe - un antibiotico).
- La terapia fenotipica non deve essere buttata per quella genotipica: esperienza dell'HIV/AIDS dove la terapia è genotipica ma si sente la mancanza di quella fenotipica
- Devono essere trovate nuove strade, semplici ed alla portata di tutti i laboratori e gli ospedali: la standardizzazione può essere un idolo totemico

Batteriocidia

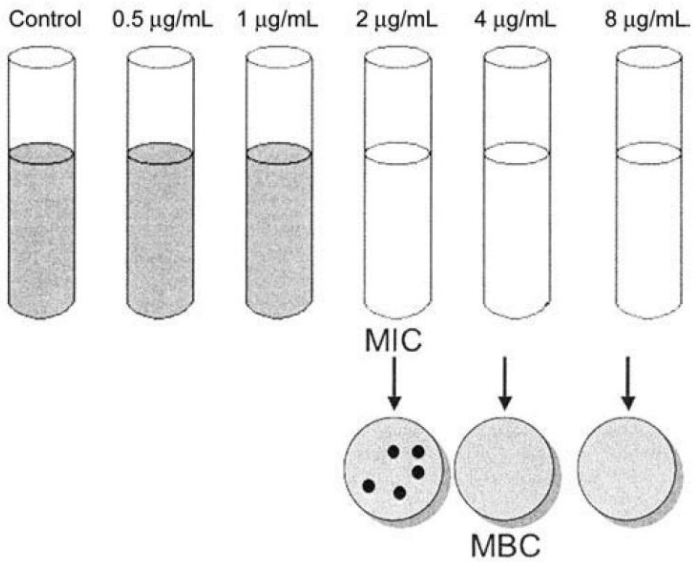


Figure 1. A fixed culture of bacteria is added to each of the 6 test tubes. The first tube serves as the growth control, and no antibiotic is added to this tube. Tubes 2–6 contain antibiotic in serially diluted proportions ranging from 0.5 to 8 μg/mL. After 18–24 h of incubation, the first tube that appears visibly clear represents the MIC. However, to determine the minimum bactericidal concentration (MBC), each tube is subsequently plated onto agar plates and incubated. The first serial plated agar dish demonstrating no growth (or a 99.9% decrease) represents the MBC. In the case above, the MIC is 2 μg/mL, and the MBC is 4 μg/mL.

MEDICAL INTELLIGENCE

DRUG THERAPY

SERUM BACTERICIDAL ACTIVITY AS A MONITOR OF ANTIBIOTIC THERAPY

JOHN S. WOLFSON AND MORTON N. SWARTZ

THE NEW ENGLAND JOURNAL OF MEDICINE April 11, 1985

measurement of serum antibiotic levels. Moreover, the test is easily performed in patients receiving more than one antibiotic.[4,25,26] In patients receiving two antibiotics, high serum bactericidal-activity titers may suggest in vitro synergism between the drugs.[27] In patients

I parametri farmacodinamici (AUC/MIC, C/MIC, T/MIC) studiano un solo farmaco. Il sinergismo necessita di simulazioni matematiche: Montecarlo Simulation

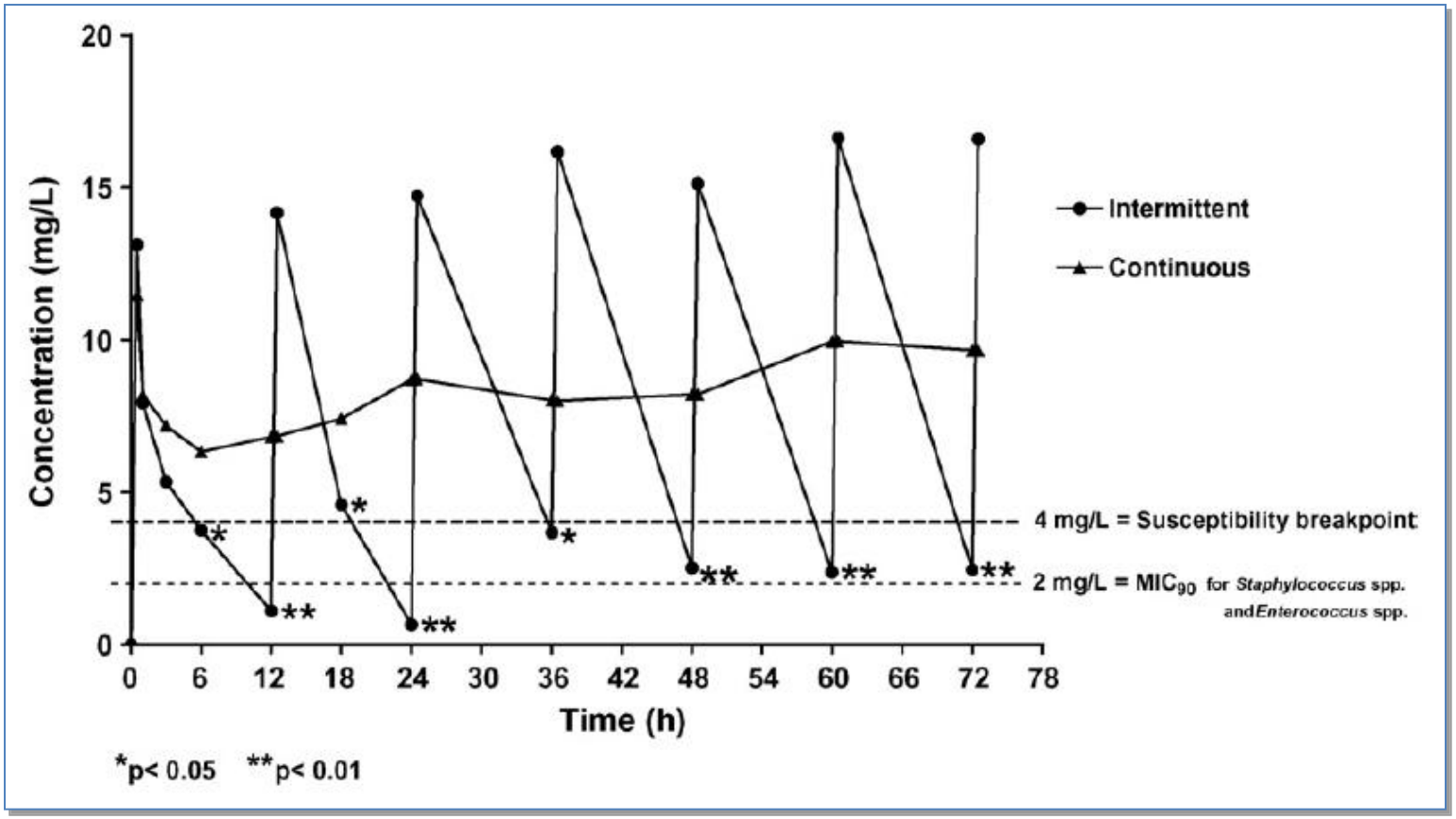
Table 1. Variables Known or Expected to Affect the Measurement of Serum Bactericidal Activity.

Known to Affect Serum Bactericidal Activity
Time of collection of sample (peak or trough)
Size of initial bacterial inoculum
Use of broth or human serum as the diluent
Definition of bactericidal end point
Known to Affect the Minimal Bactericidal Concentration and Therefore Expected to Affect Serum Bactericidal Activity
Type of broth
Supplementation of the diluent with magnesium and calcium ions
Method of mixing samples
Use of actively growing bacteria in the inoculum
"Tolerance" of the organism to the antibiotic under study
pH of the diluent
Serum complement
Antibiotic carryover onto antibiotic-free medium on subculture

Linezolid

Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion☆

Adembri et al. / International Journal of Antimicrobial Agents 31 (2008) 122–129



J Antimicrob Chemother
doi:10.1093/jac/dkq506

Linezolid for endocarditis: a case series of 14 patients

Carlo Tascini[1]*, Maria Grazia Bongiorni[2], Roberta Doria[1], Marina Polidori[1], Riccardo Iapoce[1], Serena Fondelli[1], Enrico Tagliaferri[1], Ezio Soldati[2], Antonello Di Paolo[3], Alessandro Leonildi[1] and Francesco Menichetti[1]

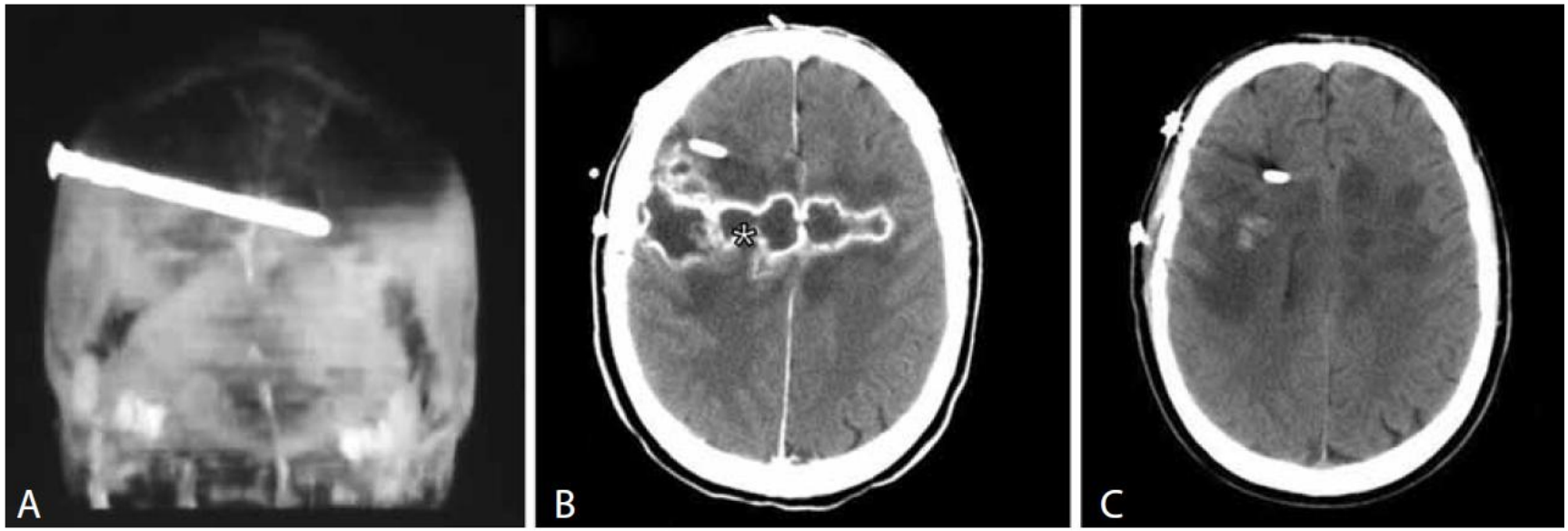
[1]U.O. Malattie Infettive, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; [2]U.O. Cardiologia II, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; [3]U.O. Farmacologia, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

The SBT titre of 1:16 in Patient 13 means that serum diluted 16 times was still bactericidal; the serum concentration of linezolid was 4 mg/L and the ratio between linezolid concentration and MBC (C/MBC) was only 2 and not 16. In Patient 14, the SBT titre was 1:8 with a linezolid concentration of 5 mg/L and the C/MBC was 2.5. Therefore, SBT titre might give a more accurate measure of bactericidal activity than the C/MBC. The high SBT titre in this case might be related to continuous infusion.

Linezolid

- In vitro sinergico con rifampicina

Caso Clinico



Caso clinico

- Ascesso da MRSE
- Terapia linezolid e rifampicina
- Livelli liquorali di linezolid negativi per 7 gg
- Terapia con vancomicina ev e intratecale

Daptomicina

Caso clinico

- Endocardite su ICD con vegetazione di 5 cm (3 elettro-cateteri)
- Emocolture positive durante terapia con daptomicina 8 mg/Kg (30° giornata)
- Ceppo a crescita lenta (SCV)
- MIC daptomicina 3 mg (eteroresistente)
- Aggiunta di ceftarolina 600 mg x 3 die
- Emocolture negative

Caso clinico

- Dopo altri 30 gg estrazione elettrocateteri, solo 2 CFU su uno dei 3 cateteri
- Dimesso con linezolid
- Guarito

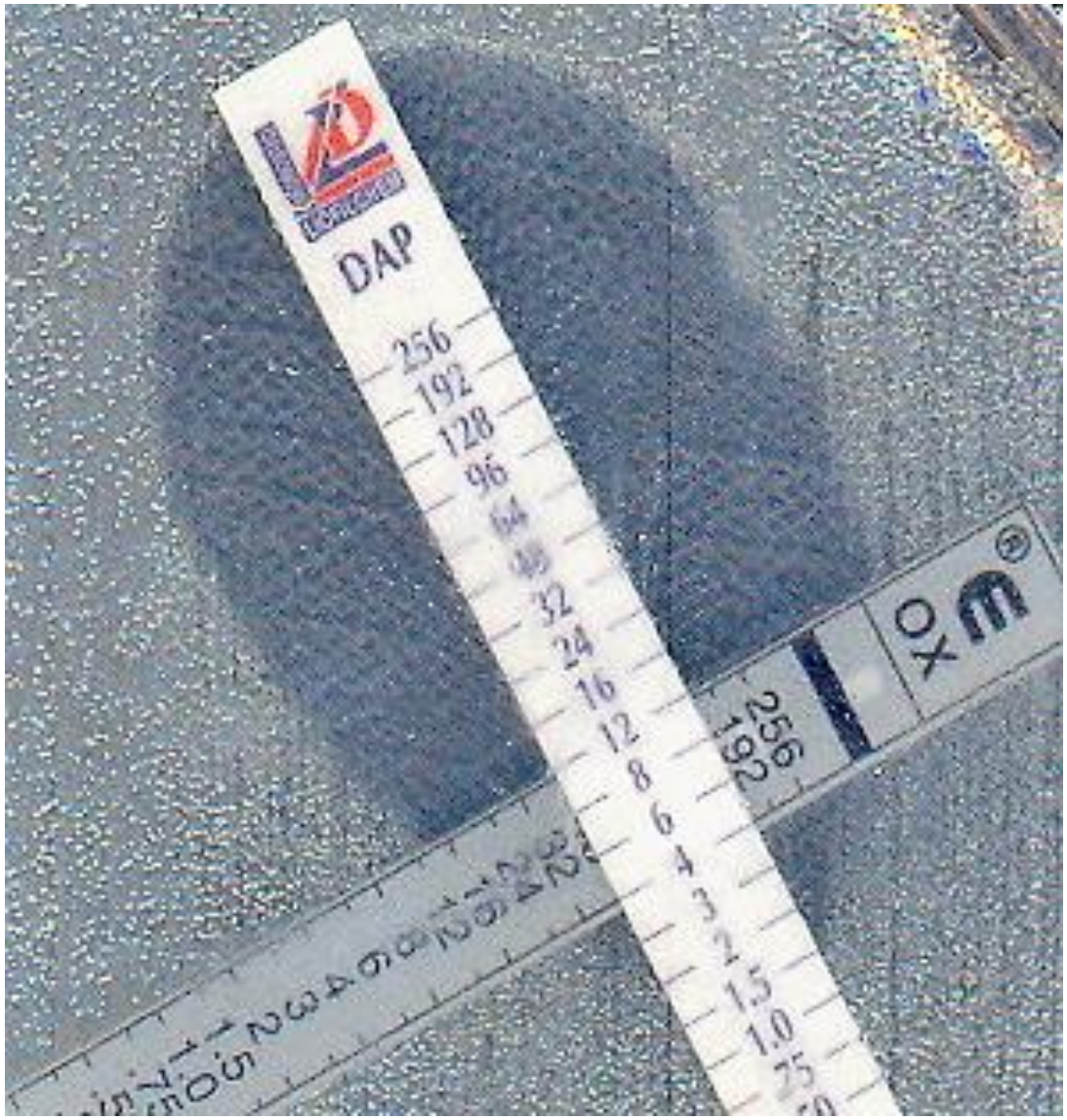
BRIEF REPORT

Use of Antistaphylococcal β-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus*: Role of Enhanced Daptomycin Binding

Abhay Dhand,[1] Arnold S. Bayer,[3,4] Joseph Pogliano,[5] Soo-Jin Yang,[3,4] Michael Bolaris,[3] Victor Nizet,[5] Guiquing Wang,[2] and George Sakoulas[1,5,6]

[1]Department of Medicine, Division of Infectious Diseases, and [2]Department of Pathology, New York Medical College, Valhalla, New York; [3]LA Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California; [4]David Geffen School of Medicine at UCLA, Los Angeles, California; [5]University of California San Diego School of Medicine, La Jolla, California; and [6]Department of Medicine, Sharp Memorial Hospital, San Diego, California

We used daptomycin plus antistaphylococcal β-lactams (ASBL) to clear refractory MRSA bacteremia. In vitro studies showed enhanced daptomycin bactericidal activity, increased membrane daptomycin binding, and decrease in positive surface charge induced by ASBLs against daptomycin non-susceptible MRSA. Addition of ASBLs to daptomycin may be of benefit in refractory MRSA bacteremia. (Although the official designation is "daptomycin nonsusceptiblity," we will use the term "daptomycin-resistance" in this paper for facility of presentation.)


DAP
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256
192
OXO

DAP
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Drug Resistance Updates 16 (2013) 73–79

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Reduced glycopeptide and lipopeptide susceptibility in *Staphylococcus aureus* and the "seesaw effect": Taking advantage of the back door left open?

Jessica K. Ortwine[a,**], Brian J. Werth[b,1], George Sakoulas[d,e], Michael J. Rybak[b,c,*]

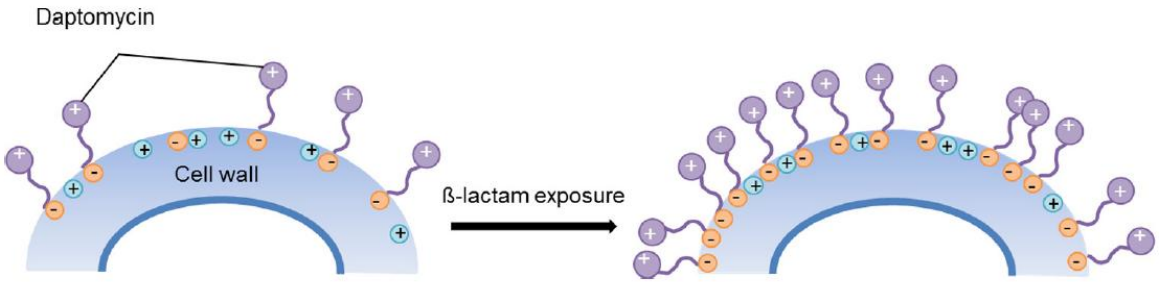

Figure 2. Proposed mechanisms for daptomycin and beta-lactam synergy. Daptomycin acts like a cationic peptide antibiotic and is attracted to the negative charge of the bacterial cell membrane. Once in contact with the cytoplasmic membrane (CM) daptomycin disrupts the CM causing a rapid release of electrolytes from the cytoplasm leading to depolarization and death of the cell. Exposure to beta-lactams increases the negative charge of the cell surface leading to an increase in daptomycin binding and improved bactericidal activity.

Drug Resistance Updates 16 (2013) 73–79

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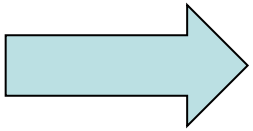
Reduced glycopeptide and lipopeptide susceptibility in *Staphylococcus aureus* and the "seesaw effect": Taking advantage of the back door left open?

Jessica K. Ortwine[a,**], Brian J. Werth[b,1], George Sakoulas[d,e], Michael J. Rybak[b,c,*]



(Werth et al., 2013b). A third study, utilizing a 96 h *in vitro* PK/PD model, employed two isogenic MRSA isolates, one a daptomycin-susceptible hVISA (D592) and the other a daptomycin-nonsusceptible VISA (D712) isolate (Werth et al., 2012). The activities of daptomycin, ceftaroline, and vancomycin alone, and daptomycin or vancomycin in combination with ceftaroline were evaluated. The results demonstrated that daptomycin plus ceftaroline had significantly greater *in vitro* activity than any monotherapy regimen against both isolates. When comparing the two combination regimens, daptomycin plus ceftaroline exhibited significantly greater activity against the daptomycin-nonsusceptible VISA strain as compared to vancomycin plus ceftaroline, but both regimens maintained bactericidal activity throughout the duration of the model. Ceftaroline does have high affinity for the mutated PBP2a produced by MRSA, which may appear to offer a simple explanation for its increased activity against these isolates. However, research has shown that with increasing glyco- and lipopeptide nonsusceptibility the concentration of PBP2a on the cell membrane decreases, and the concentrations of the other PBPs increase (Moreira et al., 1997; Sieradzki et al., 1999b). Thus, synergism, rather than a targeted anti-PBP2a effect, is likely the mechanism behind this observed antibacterial activity.

Daptomicina

- Cmax/MIC> 100: efficacia
- Cmax > 60 mg/L: efficacia
- Cmin< 24 mg/L: tollerabilità

Farmacocinetica di daptomicina

Cinetica lineare per livelli di dose da 6 a 12 mg/kg

	6 mg/kg
C_{max} (mg/L)	93.9 (6.0)
C_{min} (mg/L)	6.7 (1.6)
AUC_{0-24} (mg h/L)	632 (78)
$t_{1/2}$ (h)	7.9 (1.0)
CL_T (mL/h/kg)	9.1 (1.5)
V (L/kg)	0.101 (0.007)

Gould et al, Int J Antimicrob Agents 2013; 42; 202

PK PD di daptomicina

AUC/MIC

Effetto	Stafilococchi	Streptococchi
Batteriostatico	120-537	75-237
Battericida	800-4000	157-815

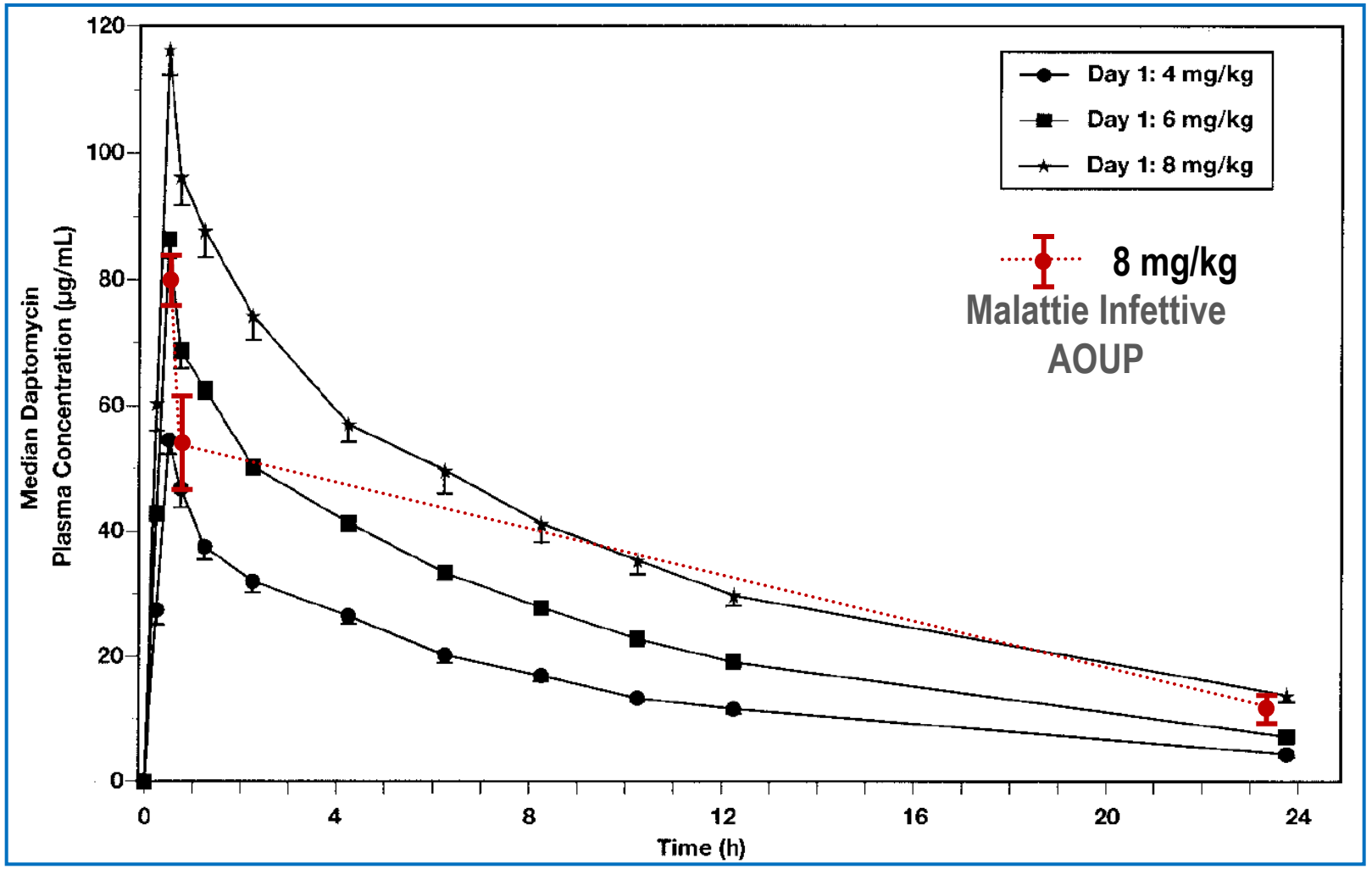
Dose di 4-6 mg/kg → **AUC di 500-750 hxmg/L**

Target attainment for 4mg/kg/day daptomycin

daptomycin MIC mg/L	% target attainment with an AUC/MIC target of		
	373 (- one standard deviation)	438 (mean)	503 (+ one standard deviation)
≥4	0	0	0
2	0	0	0
1	96.8	77.2	42.9
0.5	100.0	100.0	100.0
≤0.25	100.0	100.0	100.0

EUCAS

Dapto cinetica lineare



Ryback, Clin Microbiol Infect 2006;12(Suppl 1):24

Daptomycin

Mean pharmacokinetic parameters in healthy volunteers and severely ill patients

Parameter	6 mg/kg			8 mg/kg		
	Volunt.[a] (6)	Pts.[c] (13)	*P**	Volunt.[b] (6)	Pts.[c] (7)	*P**
C_{max} (mg/l)	86.4	55.7	< 0.01	106.2	85.1	= 0.05
t½ (h)	7.8	8.8	NS	7.3	8.6	NS
AUC (mg·h/l)	705	406.1	< 0.01	773.3	584.3	< 0.05
Cl (ml/h/kg)	8.6	18.0	< 0.05	10.1	20.4	< 0.05
Vd (l/kg)	0.096	0.22	< 0.01	0.102	0.25	< 0.01

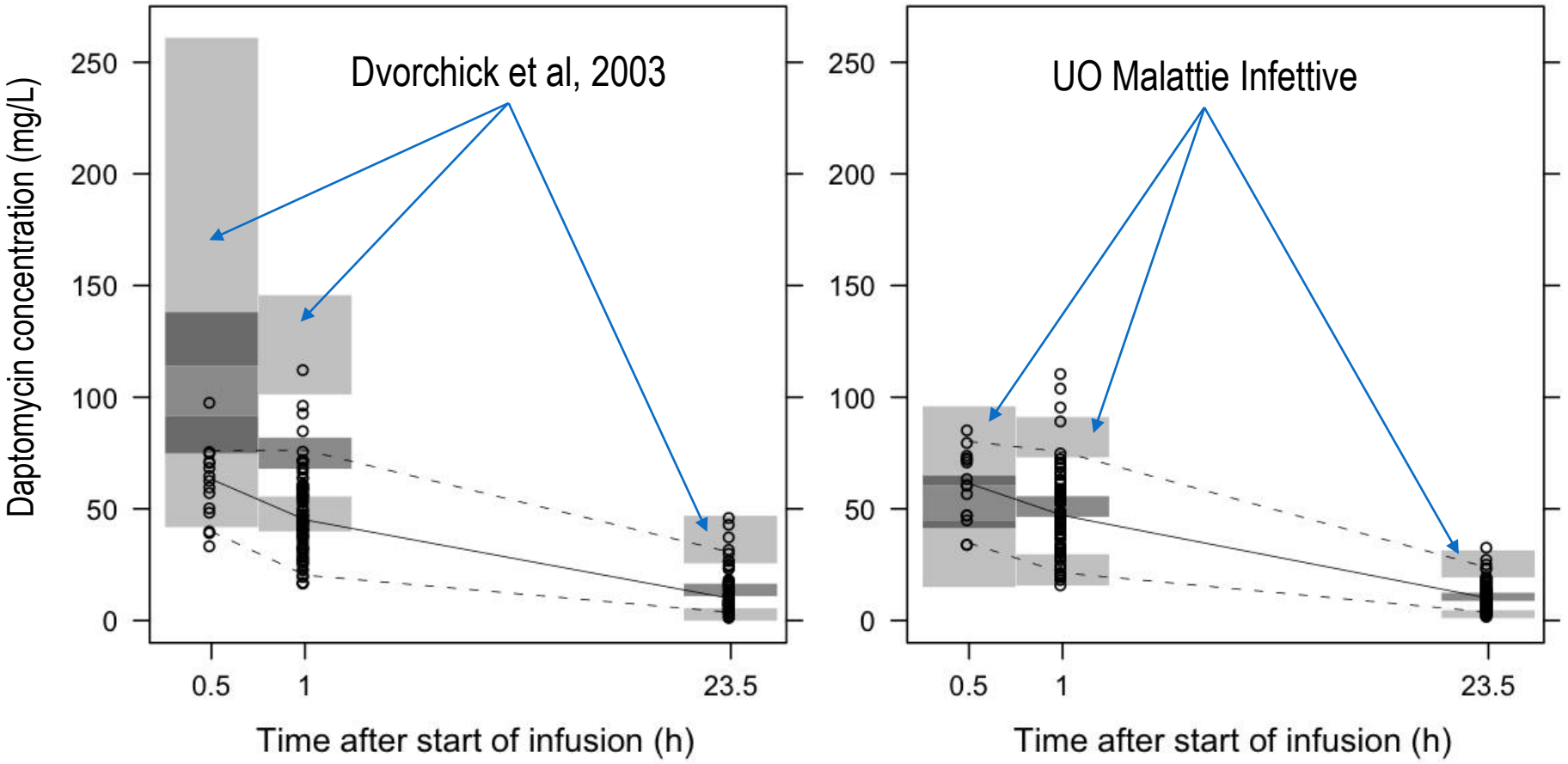
•( ) no. Cases * ANOVA test

•[a] Dvorchik BH et al., Antimicrob Agents Chemother, 2009
•[b] Benvenuto M et al., Antimicrob Agents Chemother, 2006
•[c] Falcone M, Venditti M, Novelli A, J Infect Chemother, 2013

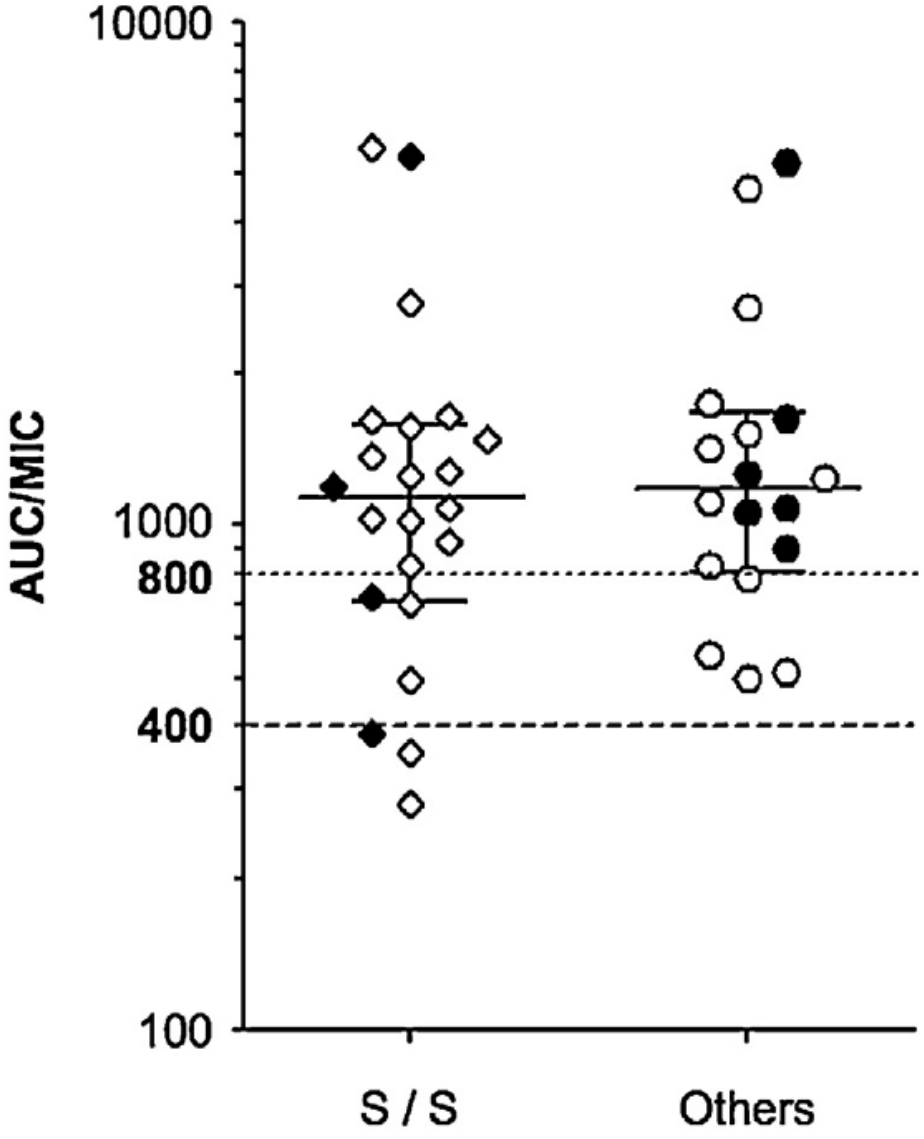
Cortesia Prof.ssa Mazzei

PK/POP di Dapto

Intervalli di confidenza al 95%

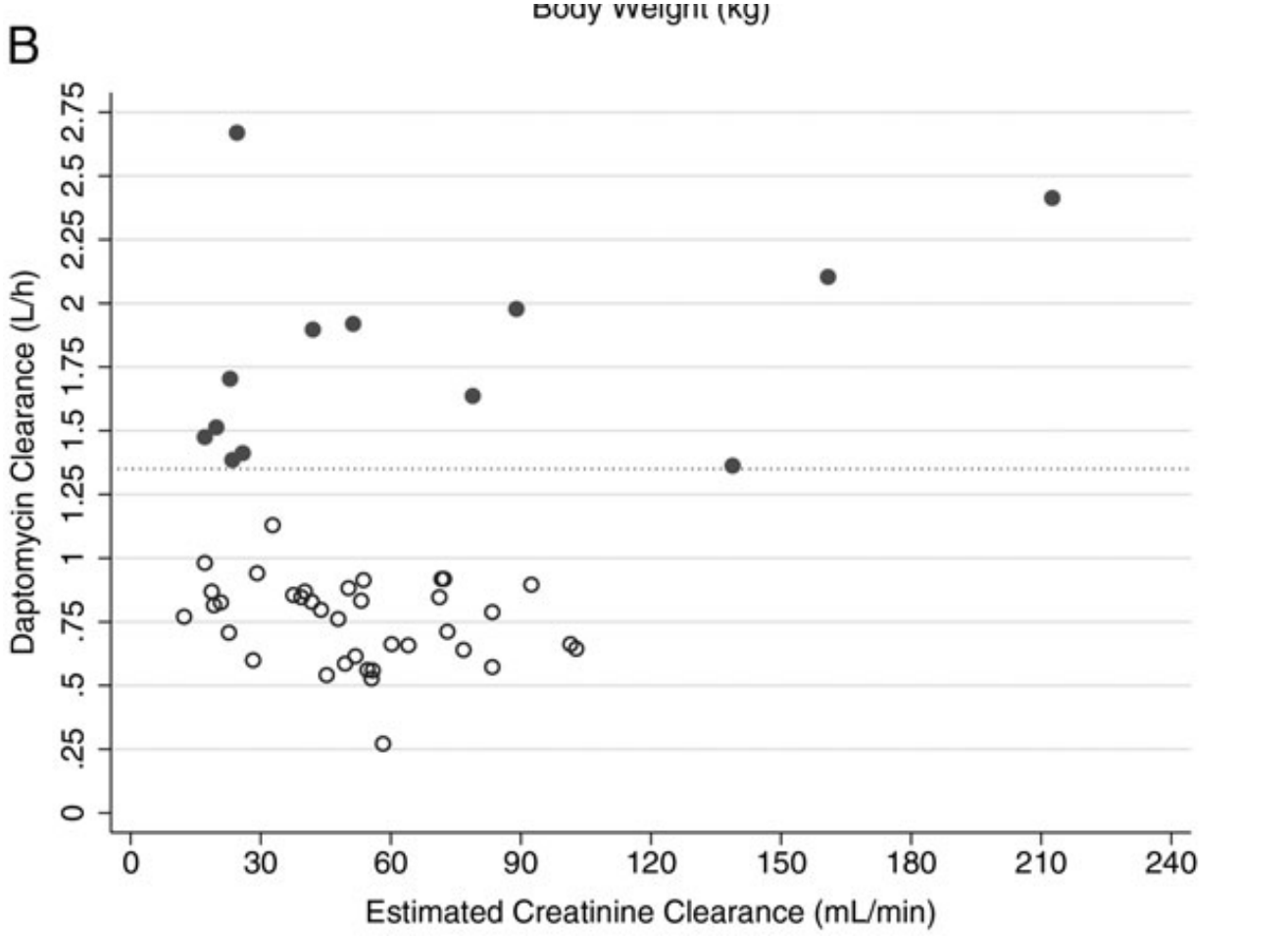


Di Paolo et al, Int J Antimicrob Agents 2013; 42: 250


10000
1000
800
400
100
AUC/MIC
S / S
Others

Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Marco Falcone,[1] Alessandro Russo,[1] Mario Venditti,[1] Andrea Novelli,[2] and Manjunath P. Pai[3]



Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Marco Falcone,[1] Alessandro Russo,[1] Mario Venditti,[1] Andrea Novelli,[2] and Manjunath P. Pai[3]

Table 3. Clinical Characteristics and Outcomes of Patients With or Without Severe Sepsis or Septic Shock

Variable	Sepsis (22 Patients)	No Sepsis (28 Patients)	*P* Value
Age, median, y	64.9	72.3	.03
Male sex	14 (63.6%)	14 (50%)	.39
Type of infection			
Bacteremia—endocarditis	20 (91%)	1 (3.6%)	<.001
Skin and soft tissue infections	2 (9.1%)	18 (64.3%)	<.001
Prosthetic joint infection	0	6 (21.4%)	<.001
Osteomyelitis	0	4 (14.3%)	<.001
Causative pathogens			
MRSA	12 (54.5%)	1 (5.2%)	<.001
MRSE	4 (18.2%)	4 (14.3%)	.03
MRSH	2 (9.1%)	5 (17.8%)	.02
Other	4 (18.2%)	12 (42.8%)	.003
Presence of at least 2 comorbidities	17 (77.3%)	14 (50%)	<.001
ICU acquisition of infection	15 (68.2%)	5 (17.9%)	<.001
Recent surgery, previous 30 d	11 (50%)	4 (14.3%)	<.001
SOFA score, median	3.95	1.65	<.001
Mean duration of antibiotic therapy, d	23.2	14.1	<.001
Mean length of hospital stay, d	45.1	17.2	<.001
In-hospital mortality	8 (36.3%)	0	<.001

Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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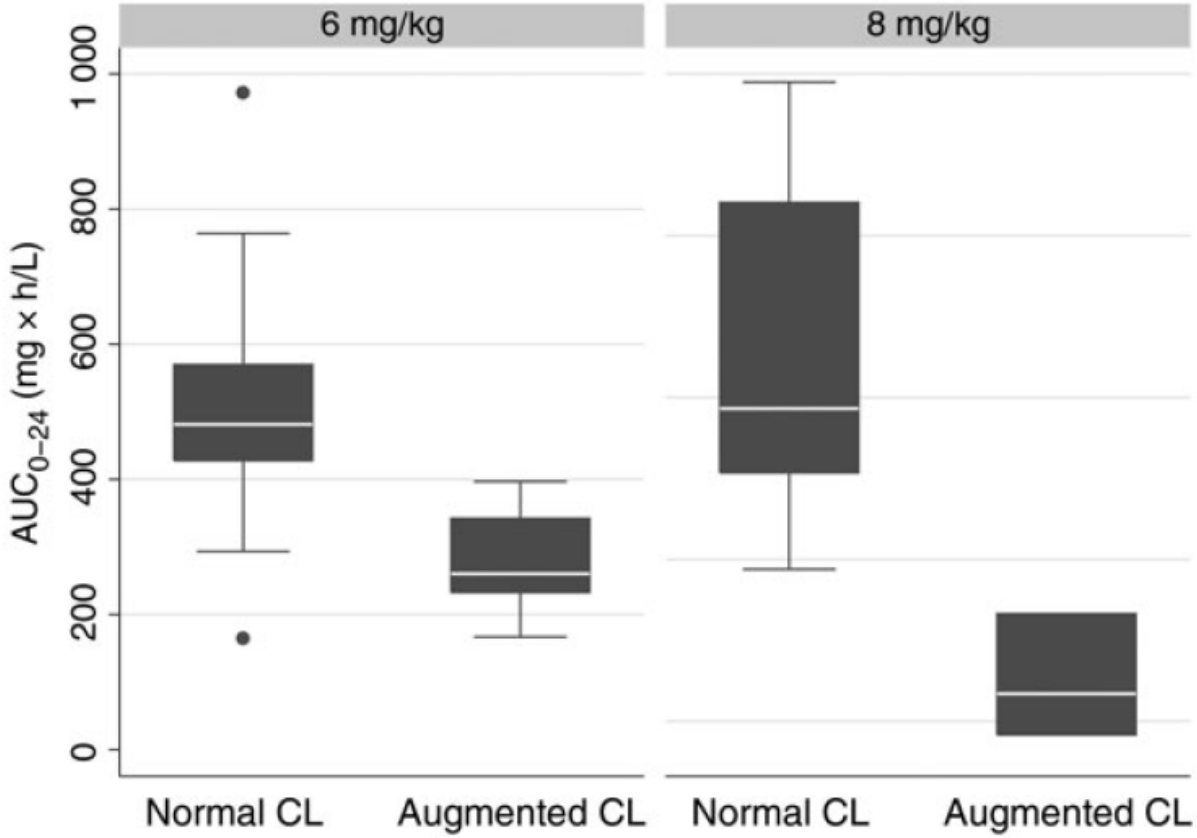

Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Marco Falcone,[1] Alessandro Russo,[1] Mario Venditti,[1] Andrea Novelli,[2] and Manjunath P. Pai[3]

Table 4. Cumulative Fraction of Response in Patients Without Sepsis

Daily Dose	% CFR Based on AUC_{0-24}/MIC ≥579	≥666	≥753	% Probability C_{min} ≥ 24.3 mg/L
Weight-based dosing				
6 mg/kg/d	94.8	92.3	89.5	1.52
8 mg/kg/d	97.9	96.7	95.1	4.88
10 mg/kg/d	99.1	98.6	97.6	11.0
Fixed dosing				
500 mg/d	96.8	95.1	92.9	1.38
750 mg/d	99.3	98.8	98.1	7.64
1000 mg/d	99.8	99.7	99.4	19.3

Table 5. Cumulative Fraction of Response in Patients With Sepsis

Daily Dose	% CFR Based on AUC_{0-24}/MIC ≥579	≥666	≥753	% Probability C_{min} ≥ 24.3 mg/L
Weight-based dosing				
6 mg/kg/d	87.3	82.1	77.2	0.08
8 mg/kg/d	94.1	91.3	88.0	0.78
10 mg/kg/d	97.1	95.4	93.4	2.64
Fixed dosing				
500 mg/d	93.1	89.2	84.8	0.02
750 mg/d	98.4	97.3	95.6	1.26
1000 mg/d	99.5	99.1	98.5	6.20

Antonello Di Paolo,[1] Marialuisa Polillo,[1]
Carlo Tascini,[2] Russell Lewis,[3]
Francesco Menichetti,[2] and Romano Danesi[1]
[1]Department of Clinical and Experimental Medicine, University of Pisa; [2]Infectious Disease Unit, Cisanello Hospital, Pisa; and [3]Infectious Disease Unit, Sant'Orsola- Malpighi Hospital, Department of Medical Sciences and Surgery, University of Bologna, Italy

Correspondence

Different Recommendations for Daptomycin Dosing Over Time in Patients With Severe Infections

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Table 1. Cumulative Fraction of Response and Probability of $C_{min,ss}$ Values >24.3 mg/L

	%CFR Based on AUC_{0-24}/MIC		Probability of	
Daily Dose	≥579	≥666	≥753	$C_{min,ss}$ >24.3 mg/L
Weight-based dosing				
6 mg/kg/d	98.9	97.9	96.6	2.50
8 mg/kg/d	99.4	99.0	98.2	6.17
10 mg/kg/d	99.7	99.4	99.0	8.35
Fixed dosing				
500 mg/d	99.3	98.9	98.4	2.54
750 mg/d	100	99.9	99.7	17.74
1000 mg/d	100	100	100	40.09

The cumulative fraction of response and the probability of $C_{min,ss}$ of daptomycin >24.3 mg/L for weight-based and fixed doses is shown. Results were obtained in 5000 simulated individuals with a median weight of 70.60 kg (95% confidence interval [CI], 46.84–98.71 kg) and creatinine clearance of 83.25 mL/minute (95% CI, 41.35–124.50 mL/minute).

Abbreviations: AUC_{0-24}, area under the time/concentration curve from time 0 up to 24 hours; $C_{min,ss}$, minimum plasma concentration at steady state; MIC, minimum inhibitory concentration.

Journal of Chemotherapy Vol. 23 - n. 4 (238-239) - 2011

LETTER

Daptomycin Blood Concentrations and Clinical Failure: Case Report

C. TASCINI [1] - E. TAGLIAFERRI [1] - A. LEONILDI [1]
A. DI LONARDO [2] - P. LAMBELET [3] - A. DI PAOLO [4]
F. MENICHETTI [1]

We report the case of an obese patient with central venous catheter (CVC) related sepsis. Suboptimal levels of daptomycin were not able to control the methicillin-resistant *Staphylococcus aureus* (MRSA) infection and probably induced emergence of daptomycin resistance in a *Corynebacterium striatum* strain isolated from the CVC.

Case history: A 59 year-old female was transferred to the Burn Unit of Cisanello Hospital, Pisa, on May 25, 2009. She came from a peripheral hospital where she had been admitted for erythrodermia, probably due to Steven-Johnson syndrome after treatment with azithromycin. She had a history of blood hypertension and food intolerance. She was also affected by severe obesity with an approximate body weight of 160 kilograms and body mass index of 45. She had received steroids and diflucan and CVC-associated thrombosis of the jugular vein was revealed by Doppler ultrasonography. The CVC was removed and *Acinetobacter baumannii* and daptomycin-resistant *Corynebacterium striatum* (MIC >32 mg/L) were isolated from the tip of the catheter. No other CVC was inserted. After removal of the catheter her body temperature normalized.

The patient finally recovered and she was transferred to a rehabilitation center for immobilization syndrome.

The results of TDM showed a peak level of 12.2 mg/L and a trough level of 2.5 mg/L, significantly below the recommended levels (Cmax 98.6 ± 12 mg/L and Cmin 9.4 ± 2.5 mg/L) [1]. In fact, the suggested dose of daptomycin is 6 mg/kg per body weight [2], and in this case the dose administered was not adequate to the weight of the patient, resulting in a dose of 3.28 mg/Kg body weight.

Discussion: We can hypothesize that inadequate blood concentrations of daptomycin failed to prevent and control CVC-related infection due to *S. aureus* and selected a resistant strain of *Corynebacterium striatum,* usually susceptible to this drug. A dose which was disproportionate for the patient's body weight was probably the main reason for low blood levels of daptomycin in our case. However, drug loss through the wide, exudative skin lesions cannot be excluded. No other fluid shifts, such as peripheral edema or serosal effusions were observed. Renal function and albumin levels were normal.

Corynebacterium striatum is considered part of the usual flora of the skin but our report, together with other recent pub-

Commento

- Nel paziente settico, se non si ha la possibilità di dosare la daptomicina, la dose è importante.
- 6 mg/kg appannaggio del paziente non settico

Daptomicina ad alte dosi

International Journal of Antimicrobial Agents 42 (2013) 202–210

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Daptomycin: The role of high-dose and combination therapy for Gram-positive infections

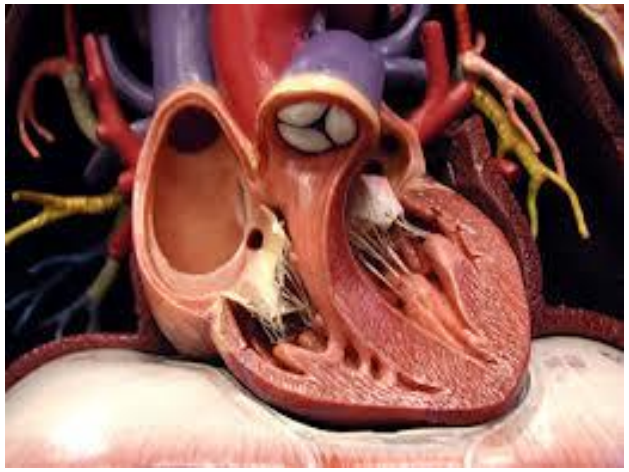
Ian M. Gould[a,*], José M. Miró[b], Michael J. Rybak[c]

Higher doses and combination therapy strategies have been investigated in some difficult-to-treat infections in order to: **enhance clinical success rates**; **treat pathogens that may be non-susceptible to standard doses**; and **minimise the risk of resistance development** in patients, particularly those who may need an extended treatment duration, who may have had suboptimal surgical management and/or who may have not responded to prior antibiotic therapy.

Daptomycin Concentrations in Valve Tissue and Vegetation in Patients with Bacterial Endocarditis

Carlo Tascini,[a] Antonello Di Paolo,[b] Roberta Poletti,[c] Sarah Flammini,[a] Michele Emdin,[c] Ilaria Ciullo,[a] Enrico Tagliaferri,[a] Annette Moter,[d] Francesco Menichetti[a]

Antimicrobial Agents and Chemotherapy, 2013; 57(1): 601



S. oralis **(MIC$_{daptomicina}$, 0,094 →0,25 mg/L)**

Daptomicina 10 mg/kg

C_{max}: 81,8 mg/L
C_{min}: 14,8 mg/L

Valvola aortica: 8,6 µg/g
Valvola mitralica: 30,8 µg/g
Vegetazione mitralica: 26,0 µg/g

Free drug 1/10

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Review

Daptomycin: The role of high-dose and combination therapy for Gram-positive infections

Ian M. Gould[a,*], José M. Miró[b], Michael J. Rybak[c]

in a C_{max} and C_{min} at Day 15 of 81.8 mg/L and 14.8 mg/L, respectively (corresponding to 8.2 mg/L and 1.5 mg/L of free drug). The patient underwent surgical replacement and the daptomycin concentrations in the aortic and mitral valves were 8.6 μg/g and 30.8 μg/g of tissue (equivalent to 0.9 μg/g and 3.1 μg/g of free drug), respectively, and 26.0 μg/g in the mitral vegetation (corresponding to 2.6 μg/g of free drug). The second patient had a porcine aortic valve *Staphylococcus epidermidis* IE. Daptomycin was given at 7 mg/kg/day and the concentrations in valve and perivalvular tissue were 53.1 μg/g and 18.1 μg/g of tissue (corresponding to 5.3 μg/g and 1.8 μg/g of free drug). These outcomes demonstrate that, despite the use of high-dose daptomycin, the free-drug antibiotic concentration that was reached in the vegetations and valve tissues is in the region of the MIC breakpoints for Gram-positive pathogens frequently associated with IE and, therefore, there is a risk of resistance developing. This is further evidence that supports the use of combination therapy in IE.

- Considerato che le MIC si eseguono con inoculi di 5 x 10^5 CFU/ml e che nelle vegetazioni ci sono 10^7-10^8 CFU/g di vegetazione

Daptomicina ed endocardite

Infezione da MRSA (MIC per daptomicina 2 mg/L) in un modello animale di endocardite su valvola aortica

		Caricabatterica, log_{10} CFU/g, media SD					
Gruppo	**n**	**Vegetazioni**		**Milza**		**Rene**	
Controllo	5	7,3	1,0	5,4	0,2	5,1	0,6
Daptomicina (12 mg/kg)	9	6,3	1,8	3,2	1,6*	2,1	1,9*
Daptomicina (18 mg/kg)	9	4,4	1,6*†	2,3	1,6*	2,5	1,2*

Daptomicina 12 e 18 mg/kg nel coniglio simula i dosaggi di 6 e 10 mg/kg nell'uomo, rispettivamente
*P <0,05 vs. controllo; †P<0,05 vs. daptomicina 12 mg/kg

Chambers et al, Antimicrob Agents and Chemother 2009; 53: 1463

High-Dose Daptomycin for Cardiac Implantable Electronic Device–Related Infective Endocarditis

Emanuele Durante-Mangoni, Roberta Casillo, Mariano Bernardo, Cristina Caianiello, Irene Mattucci, Daniela Pinto, Federica Agrusta, Roberta Caprioli, Rosina Albisinni, Enrico Ragone, and Riccardo Utili

Department of Internal Medicine, University of Naples S.U.N., and Unit of Infectious and Transplant Medicine, A.O.R.N. "V. Monaldi," Naples, Italy

Background. Cardiac implantable electronic device (CIED)–related endocarditis is a growing challenge because of increasing incidence and significant mortality. Current treatment is based on complete hardware removal coupled with long-term administration of effective and safe antimicrobials. Daptomycin at the dose of 6 mg/kg/day has been found to be effective in staphylococcal endocarditis, but limited data exist on CIED endocarditis. Moreover, whether higher doses could be more effective but equally safe in this setting is currently unknown.

Methods. We report here our experience with high-dose daptomycin in the treatment of 25 cases of CIED endocarditis due to staphylococci.

Results. Patients were mostly elderly and male, with large lead vegetations and severe comorbidities. Pathogens were *Staphylococcus epidermidis* (56%), *Staphylococcus aureus* (28%), and other coagulase-negative staphylococci (16%). Only 4 patients (16%) had a normal pretreatment renal function. The median daptomycin daily dose was 8.3 mg/kg (range, 6.4–10.7). Daptomycin was administered for a median of 20 days (range, 8–52). Percutaneous lead extraction was performed in 88% of patients. Two patients (8%) failed to clear bacteremia. The overall clinical success of treatment was 80%, whereas a complete microbiological success was observed in 92% of patients. Creatine phosphokinase values were monitored and increased above normal in 5 cases (20%). No serious adverse event related to high-dose daptomycin was observed and no patient required discontinuation because of muscle toxicity.

Conclusions. Our experience suggests that high-dose daptomycin may be a safe therapeutic option in staphylococcal CIED endocarditis and may be associated with high microbiological responses and clinical success.

Original Article

Cardiovascular implantable electronic device endocarditis treated with daptomycin with or without transvenous removal

Q24 C. Tascini [a], M.G. Bongiorni [b], Di Cori [b], A. Di Paolo [c], M. Polidori [a], E. Tagliaferri [a,*], S. Fondelli [a], E. Soldati [b], I. Ciullo [a], A. Leonildi [a], R. Danesi [c], G. Coluccia [b], Q1 F. Menichetti [a]

Dose of daptomycin (mg/kg)	Associated antibiotics	Duration (days)	CIED culture	Treatment after extraction or end of daptomycin treatment(months)	CIED implantation (days from explant)	Outcome (months of follow-up)
6	No	60	No extraction	AMC (1)	No	Cure (6)
6	No	110	No extraction	AMC (1)	No	Cure (12)
6	PIP/TZB (10)	30 (25 before)	Yes, MRSE, MSSE		Yes (4)	Death on day 5 from rupture of abdominal aneurysm
6	PIP/TZB (10)	20 (5 before)	Yes, negative		Yes (4)	Cure (18)
6	No	90 (90 before)	Yes, negative	DO + R (3)	Yes (165)	Cure (6)
6	No	30 (20 before)	Yes, negative	AMC + DO (1), DO + R (2)	Yes (2)	Cure (24)
6	No	20 (20 before)	Yes, negative	MOX + R (2)	Yes (2)	Cure (24)
6	No	26 (15 before)	Yes, MRSA	DO + R (15 days)	Yes (32)	Cure (24)
8	No	55 (30 before)	Yes, *Propionibacterium acnes*		No	Cure (24)

Original Article

Cardiovascular implantable electronic device endocarditis treated with daptomycin with or without transvenous removal

Q24 C. Tascini [a], M.G. Bongiorni [b], Di Cori [b], A. Di Paolo [c], M. Polidori [a], E. Tagliaferri [a,*], S. Fondelli [a], E. Soldati [b], I. Ciullo [a], A. Leonildi [a], R. Danesi [c], G. Coluccia [b], Q1 F. Menichetti [a]

Table 2 – Pharmacokinetic characteristics of patients with CIED endocarditis treated with daptomycin

Patient no.	Trough concentration (mg/L)	Peak concentration (mg/L)	MIC (mg/L)	MBC (mg/L)	Peak concentration/ MIC	Peak concentration/ MBC
1	14.2	32.8	1 MSSA		32.8	
2	5.5	19.2	1 MSSA	2	19.2	9.6
5	15.6	55.5	1 *Staphylococcus hominis*		55.5	
6	9.1	28.1	1 MSSA	2	28.1	14.05
8	11.8	51.3	2 MRSA	4	25.6	12.3
9	8.4	35.7	1 *S. epidermidis*	2	35.7	17.8
			0.5 *Propionibacterium acnes*		71.4	
Mean	10.7	37.1			38.32	13.2
SD	3.7	13.8			18.5	3.1

CIED, cardiovascular implantable electronic device; *MBC*, minimal bactericidal concentration; *MIC*, minimal inhibitory concentration; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *Staphylococcus aureus*.

HEART & LUNG

J Antimicrob Chemother 2013; **68**: 2921–2926
doi:10.1093/jac/dkt294 Advance Access publication 8 August 2013

Antimicrobial Chemotherapy

A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis

Ravina Kullar[1]†, Anthony M. Casapao[1], Susan L. Davis[1,2], Donald P. Levine[1,3], Jing J. Zhao[4], Christopher W. Crank[5], John Segreti[6], George Sakoulas[7], Sara E. Cosgrove[8] and Michael J. Rybak[1,3]*

Objectives: Despite significant medical advances, infective endocarditis (IE) remains an infection associated with high morbidity and mortality. The objective was to assess the safety and efficacy of high-dose daptomycin, defined as ≥8 mg/kg/day, in patients with confirmed or suspected staphylococcal and/or enterococcal IE.

Methods: This was a multicentre, retrospective observational study (2005–11). Adult patients, not undergoing haemodialysis, with blood cultures positive for staphylococci or enterococci and a definitive or possible diagnosis of IE, who received daptomycin ≥8 mg/kg/day (based on total body weight) for ≥72 h were included.

Results: Seventy patients met the inclusion criteria and comprised 33 (47.1%) with right-sided IE (RIE), 35 (50%) with left-sided IE (LIE) and 2 with both RIE and LIE. Several patients had concomitant sites of infection, with bone/joint infection being most prevalent (12.9%). Sixty-five patients received daptomycin as salvage therapy. Pathogens were isolated from 64 patients, with methicillin-resistant *Staphylococcus aureus* as the most common organism (84.4%), followed by vancomycin-resistant *Enterococcus faecium* (7.8%). The median (IQR) daptomycin dose was 9.8 mg/kg/day (8.2–10.0 mg/kg/day), and was similar in RIE and LIE patients (9.8 and 9.3 mg/kg/day, respectively). A total of 24 (34.3%) received combination therapy. For those patients with pathogens isolated ($n=64$), the organism was eradicated in 57 (89.1%) patients. Among 64 clinically evaluable patients, 55 (85.9%) achieved clinical success. No patients required discontinuation of high-dose daptomycin due to creatine phosphokinase elevations.

Conclusions: Patients with both RIE and LIE had successful outcomes with high-dose daptomycin therapy. Additional clinical trials evaluating high daptomycin dosages in patients with IE are warranted.

J Antimicrob Chemother
doi:10.1093/jac/dkt396

Emergence of resistance to daptomycin in a cohort of patients with methicillin-resistant *Staphylococcus aureus* persistent bacteraemia treated with daptomycin

O. Gasch[1]*, M. Camoez[1], M. A. Domínguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], C. Martín[5], F. López-Medrano[6], E. Ruiz de Gopegui[7], J. R. Blanco[8], G. García-Pardo[9], E. Calbo[10], M. Montero[11], A. Granados[12], A. Jover[13], C. Dueñas[14] and M. Pujol[1] on behalf of the REIPI/GEIH Study Groups†

Table 1. MRSA persistent bacteraemia episodes treated with daptomycin

	Patient			MRSA isolates		Therapy			Outcome	
ID	age (years)/ gender	previous VAN	source/acquisition	initial/ final DAP MIC (mg/L)	initial/ final VAN MIC (mg/L)	initial therapy	DAP[a], regimen dose (days from first dose to last blood culture yielding MRSA)	intervention on source (days from DAP first dose)	sterile blood culture	30 day mortality
1	84/M	no	catheter/HCR	**≤0.5/2**	0.5/1	DAP	10 mg/kg (18)	catheter withdrawal (−7)	no	yes
2	83/M	no	IE/HCR	**≤0.5/2**	**0.7/1.5**	DAP	10 mg/kg (13)	no	no	yes
3	76/F	no	catheter/ICU	**≤0.5/1.5**	0.5/1	VAN	10 mg/kg (13)	catheter withdrawal (−2)	no	yes
4	84/M	no	catheter/non-ICU	≤0.5/1	0.5/0.5	VAN	8 mg/kg (7)	catheter withdrawal (−1)	no	yes
5	58/M	no	SSTs/non-ICU	≤0.5/NA	1/NA	VAN	10 mg/kg (7)	no	no	yes
6	82/F	no	IE/HCR	≤0.5/≤0.5	0.5/0.5	LZD	8 mg/kg (9)+RIF	surgery (−3)	no	yes
7	41/M	no	catheter/non-ICU	≤0.5/≤0.5	1/1	VAN	8 mg/kg (9)	catheter withdrawal (−6)	yes, with DAP 8	yes
8	74/F	yes	bone and joint infection/HCR	**≤0.5/1.5**	0.5/0.5	DAP	10 mg/kg (28)	no	yes, with FOS+IPM	no
9	65/M	no	catheter/ICU	**≤0.5/2**	0.5/1	VAN	10 mg/kg (21)	catheter withdrawal (−2)	yes, with FOS+IPM	no
10	78/F	no	unknown/non-ICU	**<0.5/2**	0.5/1	no antibiotic	8 mg/kg (21)	no	yes, with LZD	no
11	81/M	no	SSTs/non-ICU	≤0.5/NA	1/NA	DAP	6 mg/kg (6)	no	yes, with DAP 8	no
12	69/F	no	SSTs/HCR	≤0.5/≤0.5	1/1	VAN	10 mg/kg (5)	no	yes, with DAP 10	no
13	69/M	yes	SSTs/non-ICU	**0.75/3**	1.5/2	DAP	10 mg/kg (8)	drainage (0)	yes, with DAP 10	no
14	80/M	no	urinary/HCR	0.5/0.5	1/1	no antibiotic	6 mg/kg (4)	no	yes, with DAP 6	no
15	58/M	no	catheter/non-ICU	≤0.5/NA	1/NA	VAN	10 mg/kg (16)	catheter withdrawal (−1)	yes, with DAP 10	no
16	73/M	no	catheter/HCR	≤0.5/NA	1/NA	DAP	8 mg/kg (9)	catheter withdrawal (0)	yes, with DAP 8	no
17	52/M	yes	catheter/HCR	≤0.5/≤0.5	1/≤0.5	VAN	8 mg/kg (3)+RIF	catheter withdrawal (−1)	yes, with DAP 8+RIF	no
18	82/M	no	catheter/non-ICU	≤0.5/≤0.5	1/1	DAP	8 mg/kg (6)	catheter withdrawal (−3); surgery on metastatic infection (+14)	yes, with DAP 8	no
19	77/M	no	IE/HCR	≤0.5/1	**0.5/2**	VAN	6 mg/kg (21)+GEN+RIF	no	yes, with DAP 6+GEN	no
20	70/M	no	catheter/HCR	≤0.5/≤0.5	2/0.5	DAP	6 mg/kg (5)	catheter withdrawal (+8)	yes, with DAP 6	no
21	66/M	no	unknown/non-ICU	≤0.5/≤0.5	0.5/0.5	DAP	6 mg/kg (11)	no	yes, with DAP 6	no
22	60/M	no	unknown/HCR	≤0.5/≤0.5	0.5/0.5	VAN	8 mg/kg (27)	surgery (+3)	yes, with DAP 8	no

Daptomicina

- L’associazione potrebbe essere più efficace delle alte dosi

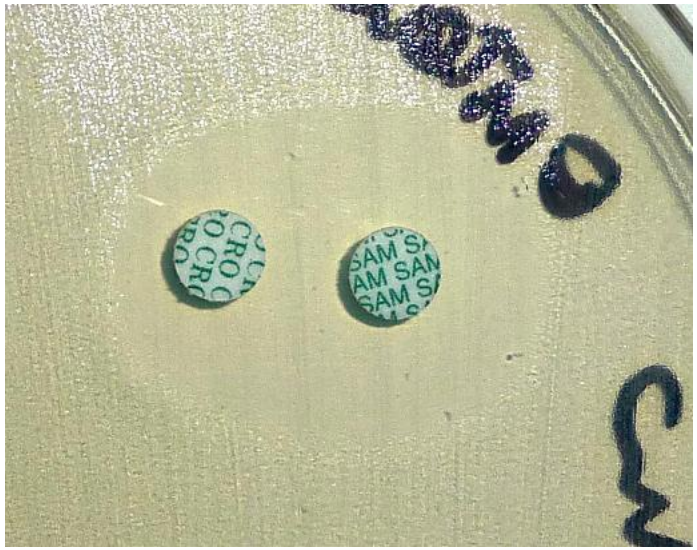
Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Arístides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[18] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

Clinical Infectious Diseases 2013;56(9):1261–8

Figure 1

PANEL A



PANEL B

Sinergismo ampicillina caftriaxone

- Non sempre presente
- Dalla letteratura meno del 5% dei ceppi non è sinergico

Journal of Chemotherapy Vol. 16 - n. 4 (400-403) - 2004

CASE REPORT

Efficacy of the Combination Ampicillin Plus Ceftriaxone in the Treatment of a Case of Enterococcal Endocarditis Due to *Enterococcus faecalis* Highly Resistant to Gentamicin: Efficacy of the *"Ex Vivo"* Synergism Method

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TABLE 1 - *Peak serum inhibitory activity (SIA) and serum bactericidal activity (SBA) of different antibiotic regimens.*

	SIA, peak	**SBA, peak**
Serum taken during ampicillin	1:32	>1:2
Serum taken during ampicillin + ceftriaxone	1:512	1:64

Daptomycin for the Treatment of Gram-Positive Bacteremia and Infective Endocarditis: A Retrospective Case Series of 31 Patients

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Study Objective. To evaluate the outcomes in patients with bacteremia and/or infective endocarditis who were treated with daptomycin.

Design. Retrospective chart review.

Setting. A university-affiliated medical center in Chicago, Illinois, and a regional hospital in Fountain Valley, California.

Patients. Thirty-one inpatients treated with daptomycin for bacteremia and/or infective endocarditis.

Measurements and Main Results. Patients were given daptomycin 4–6 mg/kg intravenously every 24–48 hours based on the practitioner's discretion and depending on the patient's clinical condition and presence of comorbidities. Primary end points were resolution of signs and symptoms of infection and discharge from the hospital. Methicillin-resistant *Staphylococcus aureus* ([MRSA] 11 patients) and vancomycin-resistant entercocci ([VRE] 11 patients) were the most common pathogens, whereas 7 patients had methicillin-sensitive *S. aureus* infection and 1 patient had coagulase-negative *Staphylococcus* infection. One patient with endocarditis had a negative culture result. Overall, 24 (77%) of the 31 patients achieved clinical resolution and were discharged, including all patients infected with MRSA; 7 patients died, 6 of whom had VRE infection. Duration of treatment for infective endocarditis lasted longer (typically 22–43 days) than that for bacteremia only (≤ 14 days), and no patients discontinued daptomycin because of adverse events.

Conclusion. In these patients, daptomycin was safe and well tolerated even for extended durations of treatment. Daptomycin may provide an effective option for treating drug-resistant gram-positive bloodstream infections and endocarditis.

Key Words: bacteremia, infective endocarditis, bloodstream infections, daptomycin, drug resistance.

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Combination Therapy with Ampicillin and Daptomycin for Treatment of Enterococcus faecalis Endocarditis

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Conclusioni

- Linezolid farmaco poco sinergico
- Daptomicina: combinazione probabilmente meglio delle alte dosi
- *Enterococcus faecalis*: associazione è d'obbligo, ampi/cro, ampi/genta, dapto/ampi
- Fare i test di sinergismo prima e poi verificare l'efficacia dell'associazione