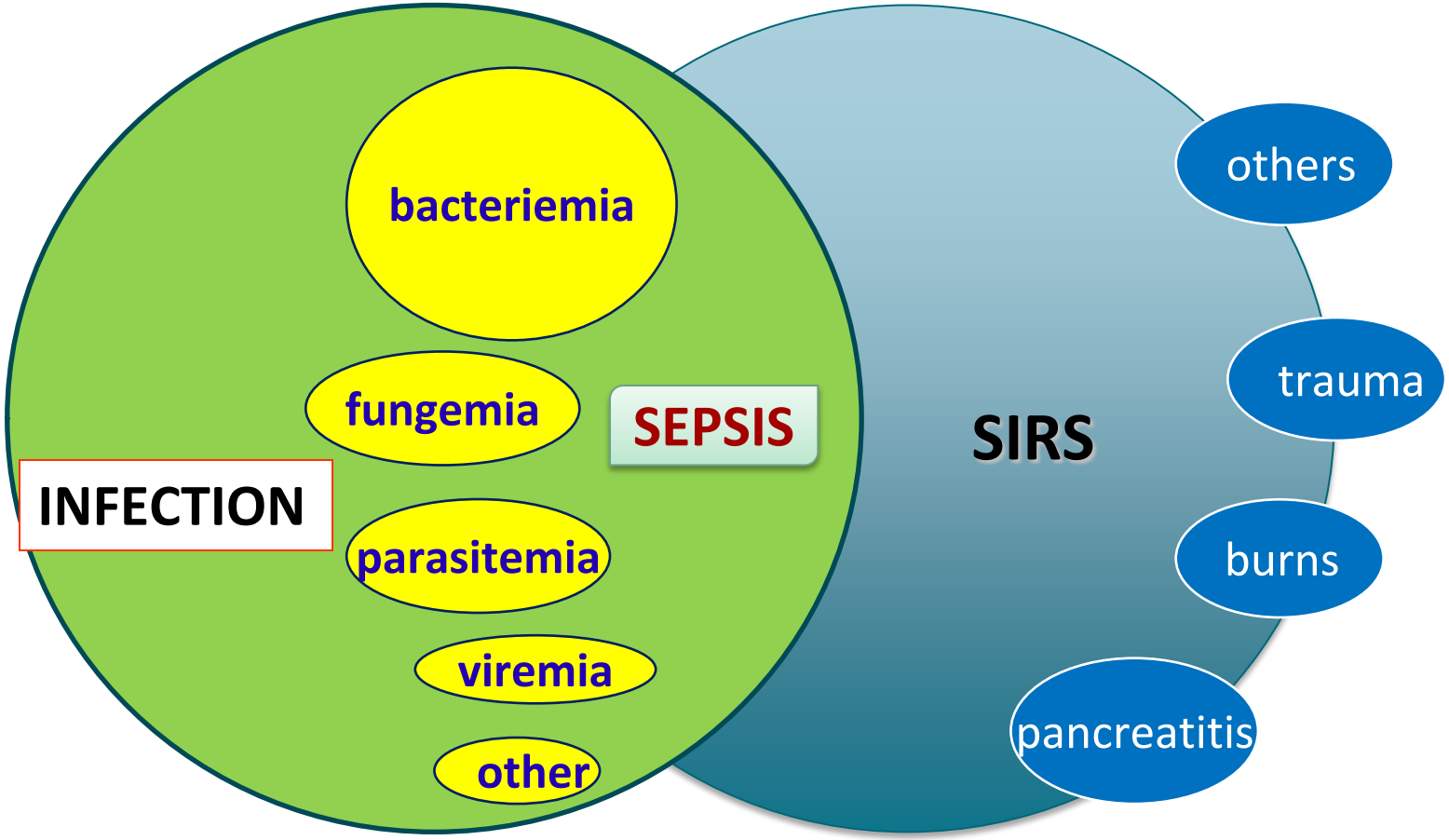
Salva il tuo paziente settico! Importanza di una terapia empirica precoce ed appropriata

Mario Venditti

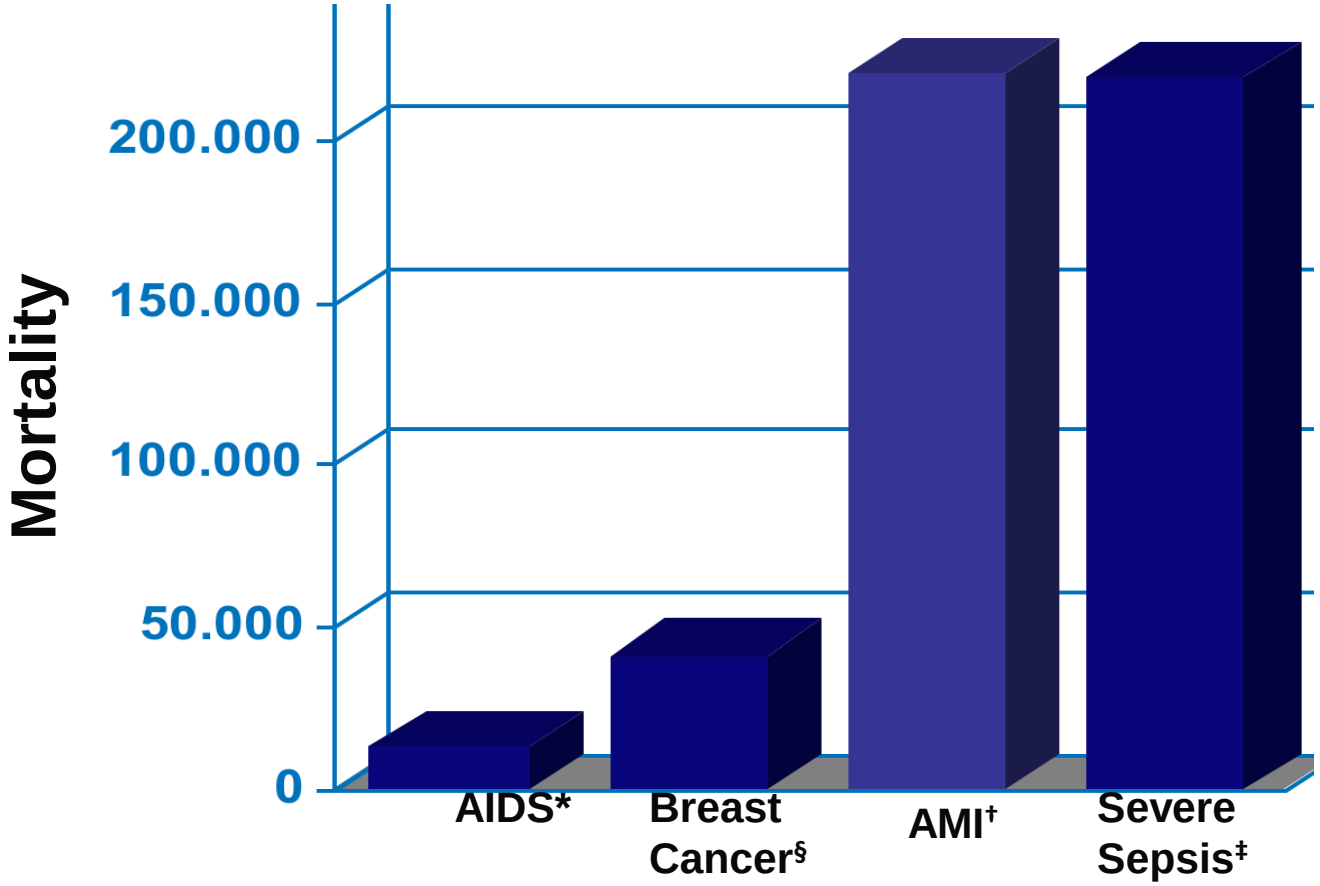
Department of Public Health and Infectious Diseases

Policlinico Umberto I, “Sapienza” University of Rome

Definitions



Comparison with other major diseases



†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001;29(7):1303-1310.

Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset BSIs

Hang Cheng C et al *J Antmicrob Chemother* 2013

	30 day mortality	HR (95%CI)
Uncomplicated bacteremia (n=60)	0	-
Sepsis (n=480)	3.8%	2.81(1.03-7.65)
Severe sepsis (n=269)	32.0%	1.65(1.07-2.56)
Septic shock (n=128)	43.0%	1.07(0.61-1.87)

Adequate antibiotic was considered when active antibiotic was administered within 24 hours

Sepsis incidence and outcome: Contrasting the ICU with the hospital ward

Esteban A et al, Crit Care Med 2007

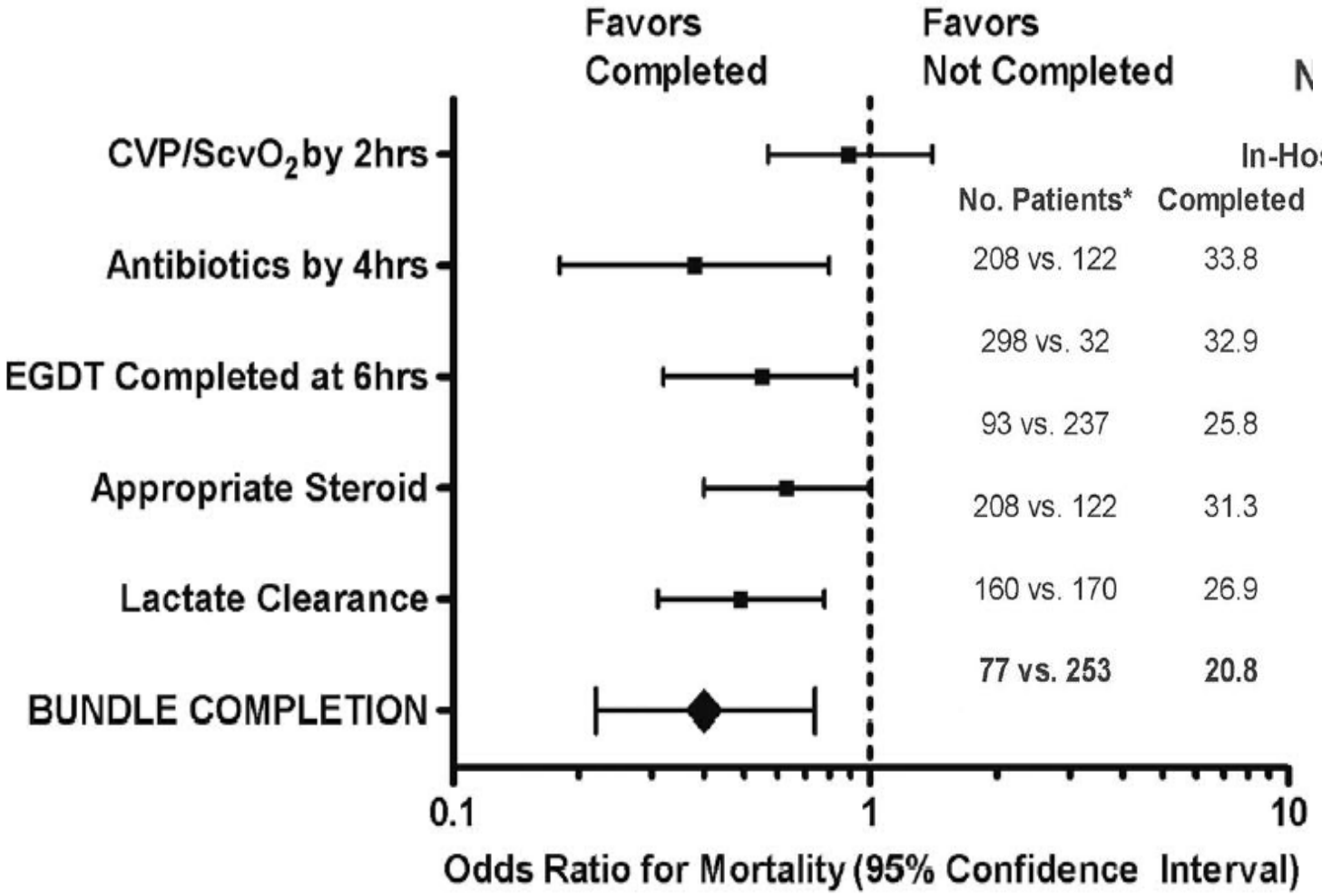
ICU utilization and mortality

	Sepsis	Severe Sepsis	Septic Shock
Number	702	199	59
Incidence (x 100,000)	367	104	31
ICU admission %	12%	32%	75%
Out ICU mortality		36%	53.3%
In ICU mortality		11%	33%

Courtesy of Viale PL

Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality

Nguyen BH et al, +



	In-Hospital Mortality (%)		
No. Patients*	Completed	Not Completed	P-value
208 vs. 122	33.8	36.4	0.65
298 vs. 32	32.9	56.0	0.03
93 vs. 237	25.8	38.8	0.03
208 vs. 122	31.3	41.8	0.06
160 vs. 170	26.9	42.9	<0.01
77 vs. 253	**20.8**	**39.5**	**<0.01**

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock The EUPHAS Randomized Controlled Trial

Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, Rottoli F, Giunta F, Ronco C

JAMA. 2009 Jun 17;301(23):2445-52

Relationship between the timing of administration of IgM and IgA enriched immunoglobulins in patients with severe sepsis and septic shock and the outcome: A retrospective analysis

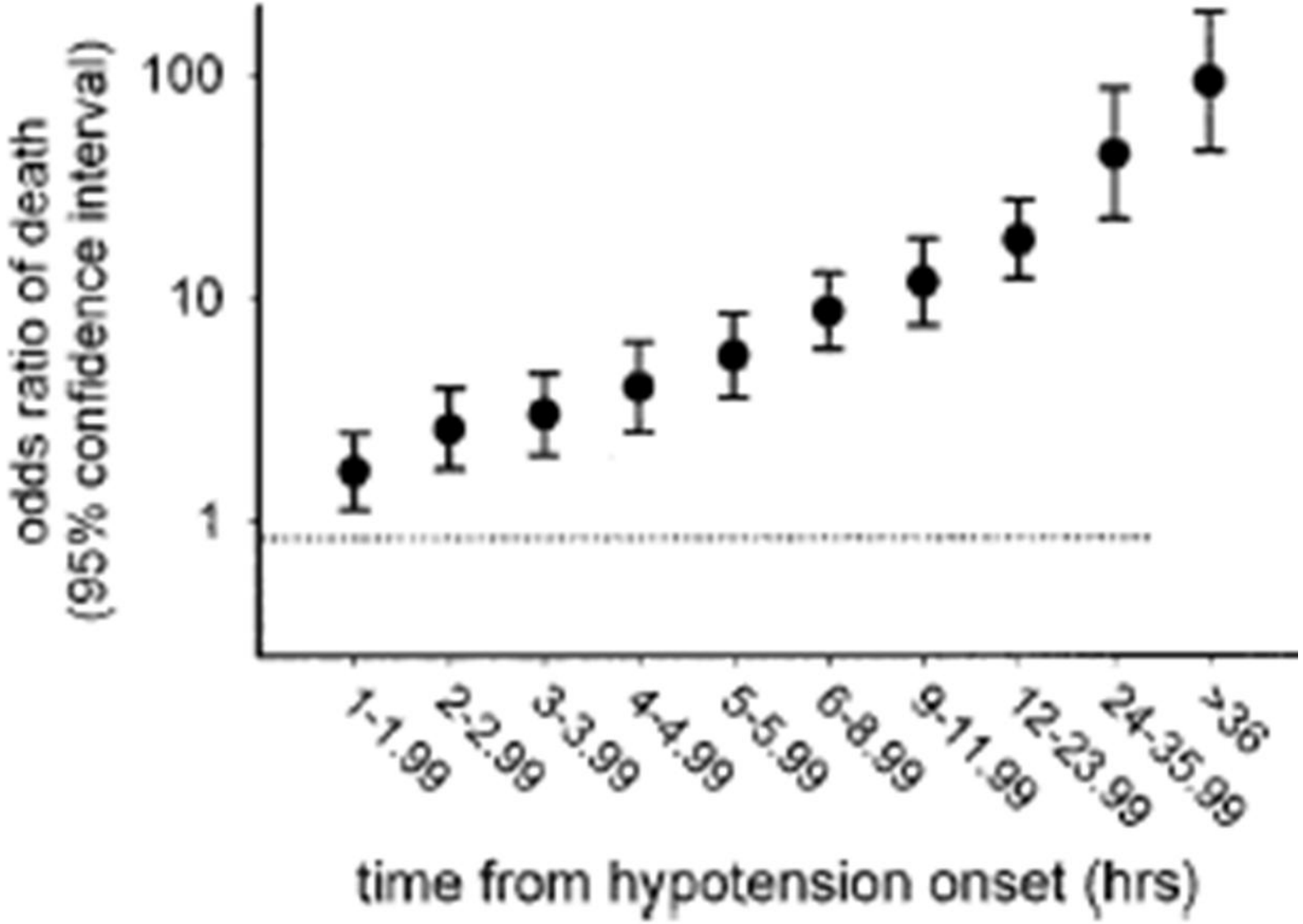
Berlot G, Vassallo MC, Busetto N, Bianchi M, Zornada F, Rosato I, Tartamella F, Prisco L, Bigotto F, Bigolin T, Ferluga M, Batticci I, Michelone E, Borelli M, Viviani M, Tomasini A.J

Crit Care. 2012 Apr;27(2):167-71.

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic ShockA Randomized Clinical Trial

Morelli M, Ertmer C, Westphal M, Rehberg S, , Kampmeier T, Ligges S,
Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone, R, Venditti M, GuarracinoF,
Girardis M, Tritapepe L, PietropaoliP, Mebazaa A, Singer M

JAMA. 2013 Oct 23;310(16):1683-91

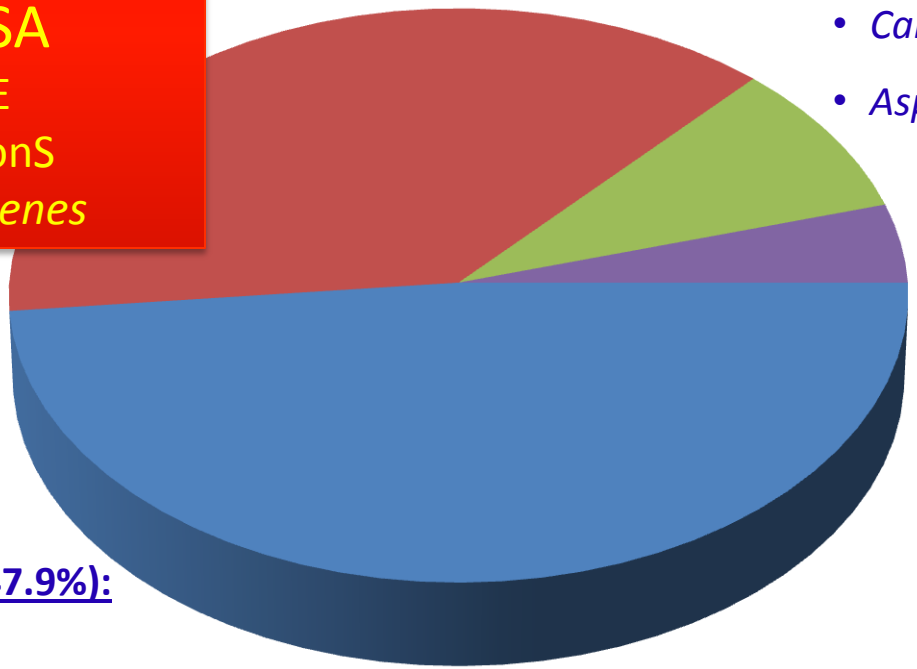


Crit Care Med 2006;34:1589-96

Etiology of sepsis

GRAM + (38%)

MRSA
VRE
MRConS
S. pyogenes



FUNGI (8.6%)

- *Candida spp*
- *Aspergillus spp*

Others (4.4%)

- *Anaerobes*
- *Mycobacterium tubercolosis*

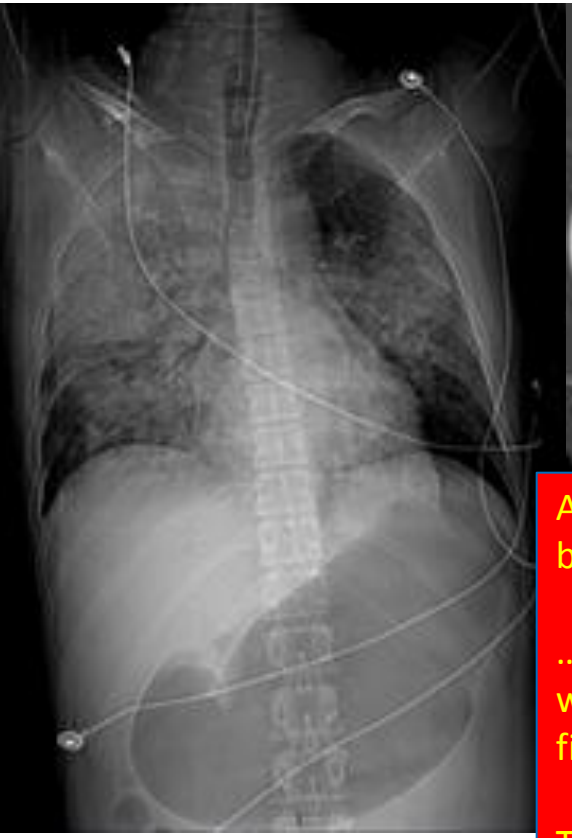
GRAM – (47.9%):

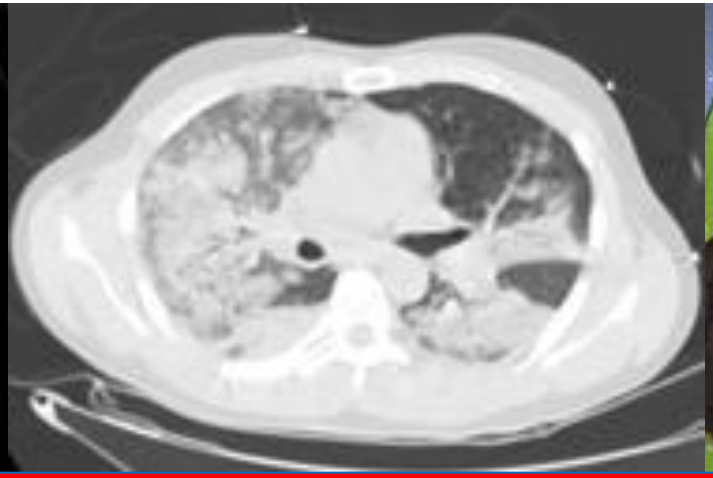
- *E. Coli*
- *Klebsiella spp*
- *Pseudomonas spp*

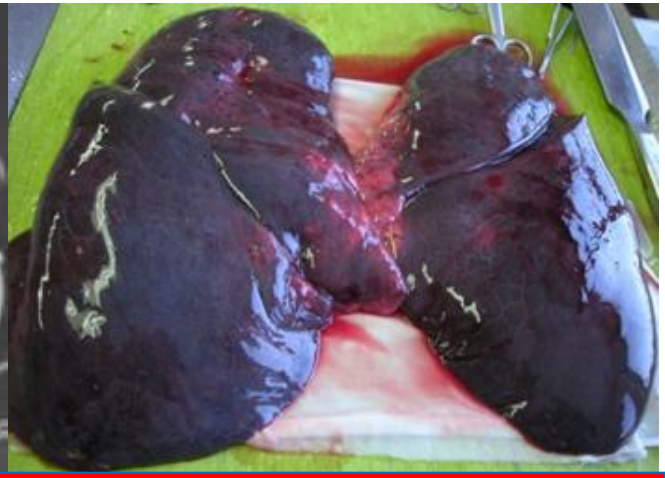
Crit Care Med. 2006.

FOUR FATAL CASES OF HEMORRHAGIC PNEUMONIAE DUE TO INVASIVE *S.PYOGENES* IN HEALTHY IMMUNOCOMPETENT INDIVIDUALS

Santagati M, Spanu T, Scillato M, Santangelo R, Cavallaro F, Arena V, Venditti M, Stefani S *Emerg Infect Dis* 2014







All strains were susceptible to the antibiotics tested and RM1, RMG1 and CT1 belonged to emm-type 1.0 while RMG2 was emm-type 3

…..sequence type (ST) analysis showed that RMG1 and CT1 belong to ST28 (CC28), while for RM1, we found a new single locus variant (slv) of ST28 designated ST648, finally RMG2 was ST15 (CC15)

Taken together these data with the presence of the Sag profile does not explain the ability of one strain to determine this type of severe infection, it has been demonstrated that the expression of virulence genes changes based on environmental conditions such as during human infection

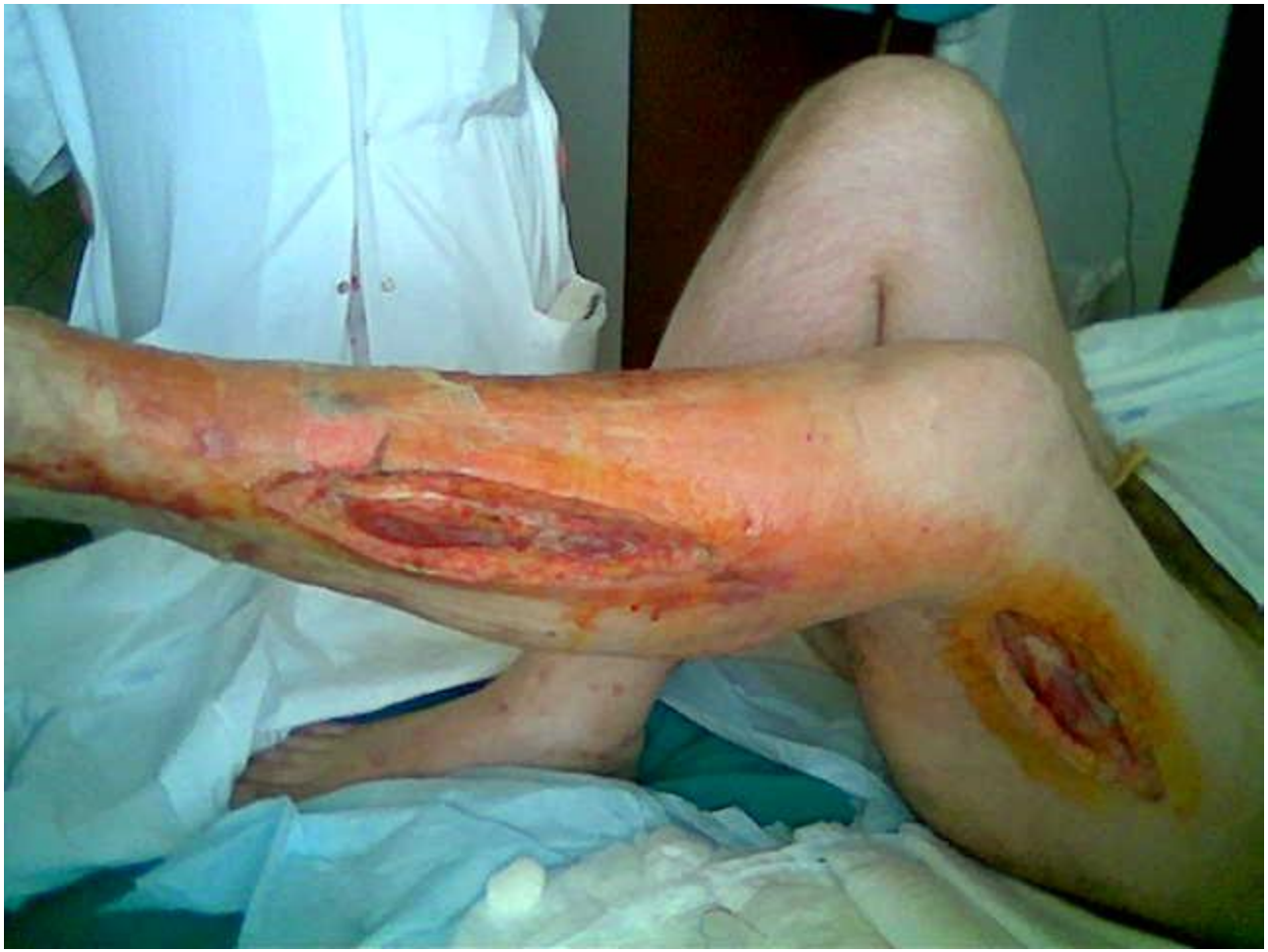
This study highlights the unusual dissemination of invasive GAS and indicates the need to understand what host factors and/or strain virulence characteristics could be involve in severe invasive GAS infections so as to be helpful in therapeutic strategy.

CASO CLINICO

Uomo di 36 aa, affetto da LES in trattamento steroideo; si presenta con febbre elevata, dolore, eritema e tumefazione della gamba sinistra che procede rapidamente verso il ginocchio in 48 ore, e comparsa di grosse lesioni bollose blu. GB 7500, ptl 70.000 poi 15000. diagnosi presuntiva di fascite necrotizzante tipo I. Richiesta coltura di biopsia cutanea, emocolture TAS, ….

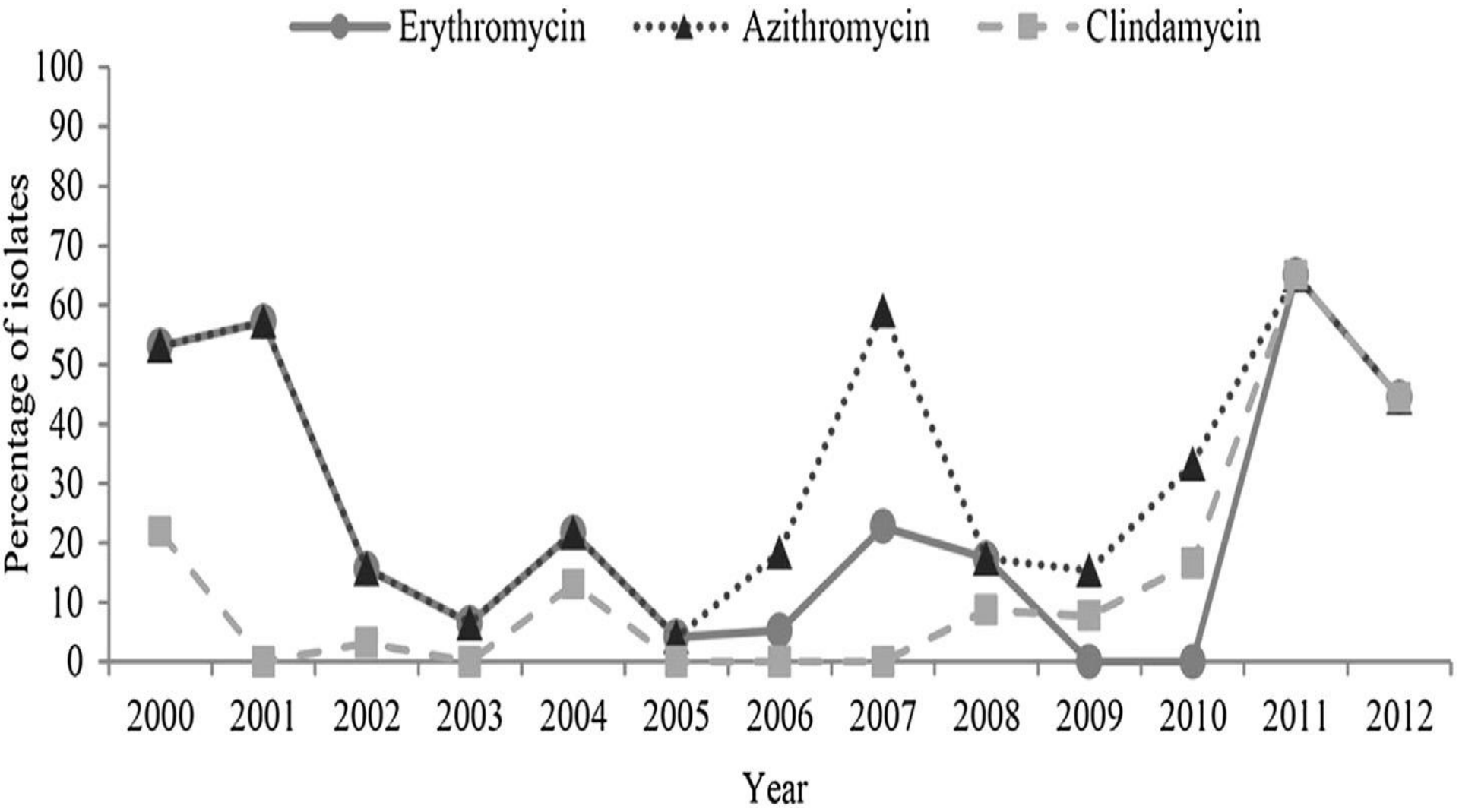
TERAPIA:
antibiotici
+
fasciotomia

CASO CLINICO:
fascite necrotizzante tipo II:
etiologia CA- MRSA



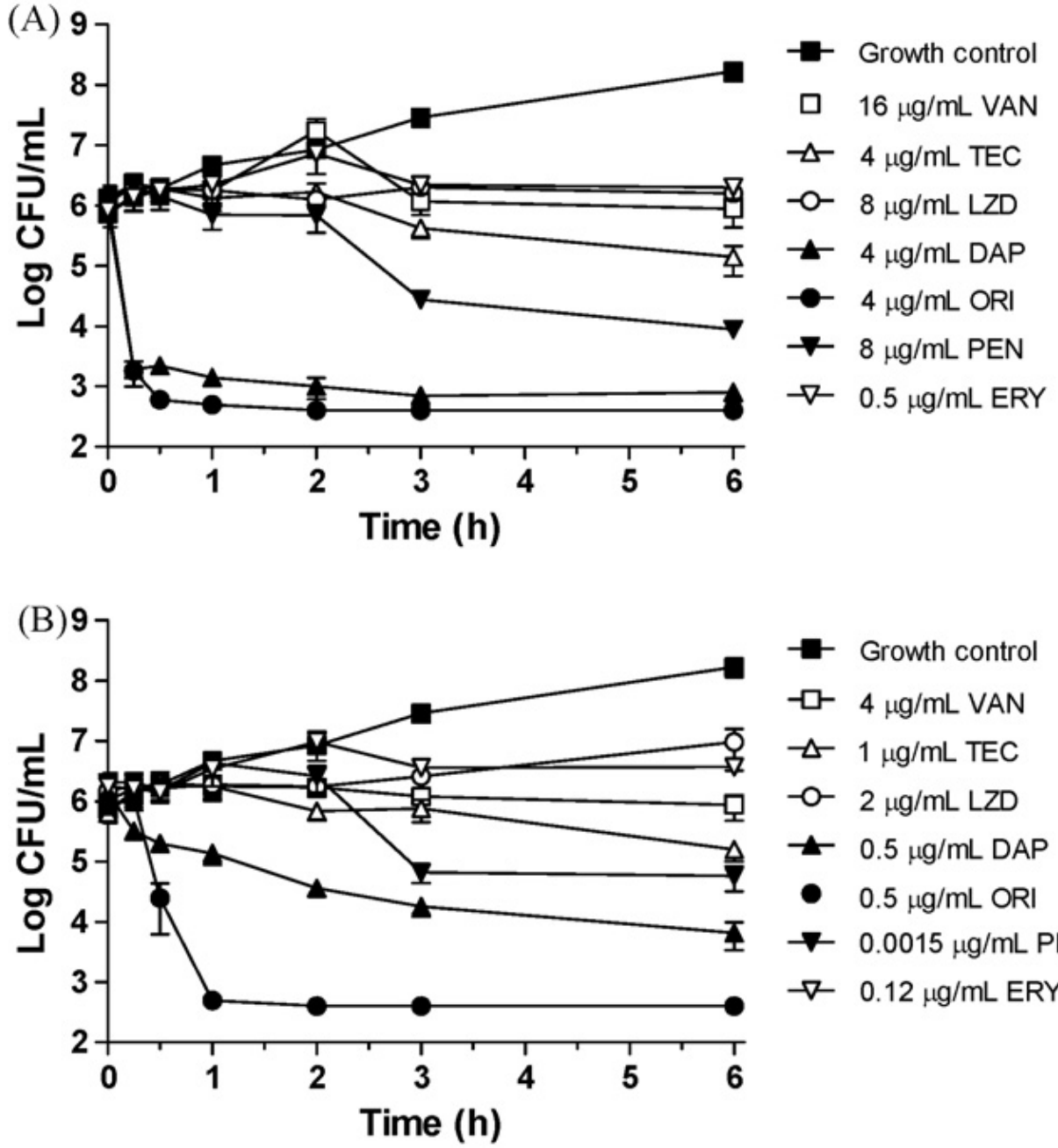
Antibiotics resistance rates of group A streptococci to erythro, azithro, and clinda between 2000 and 2012 at National Cheng Kung University Hospital in Tainan City, Taiwan.

Chuang et *al Journal of Microbiology, Immunology and Infection* (2013) early on line



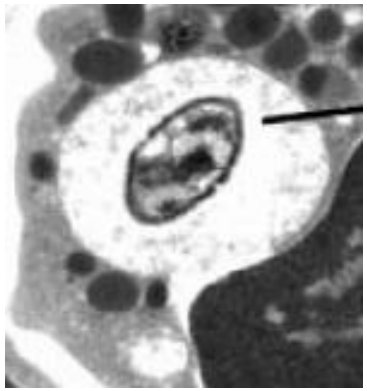
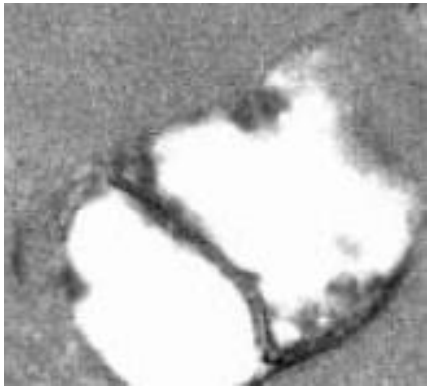
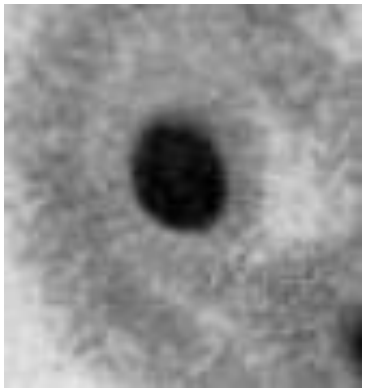
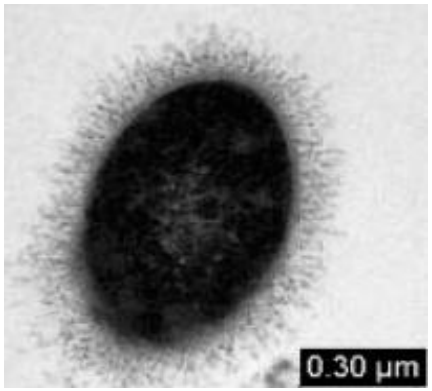
Time–kill kinetics of oritavancin and comparator agents against *S pyogenes*

Arhin et al *International Journal of Antimicrobial Agents 34 (2009) 550–554*

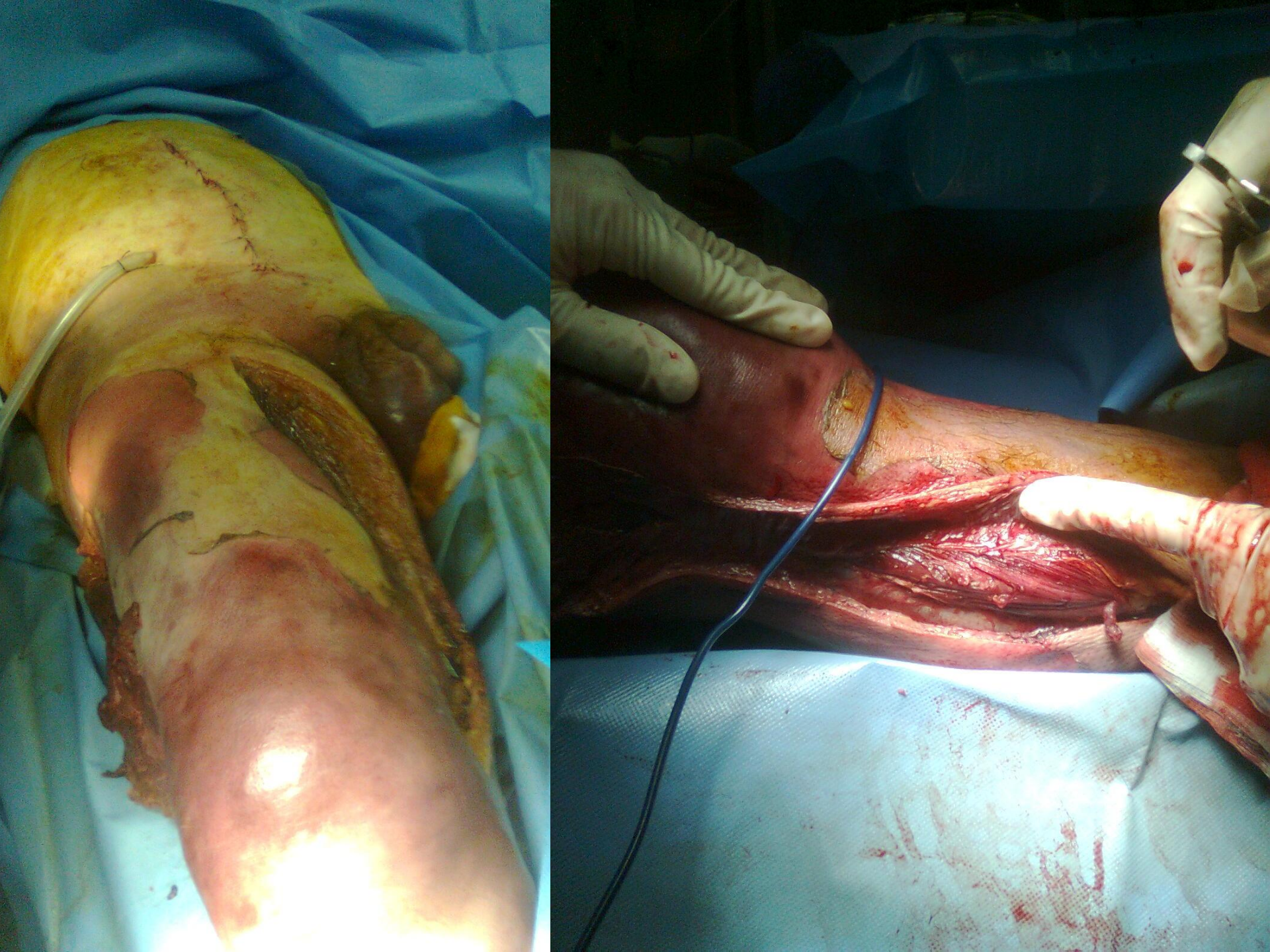


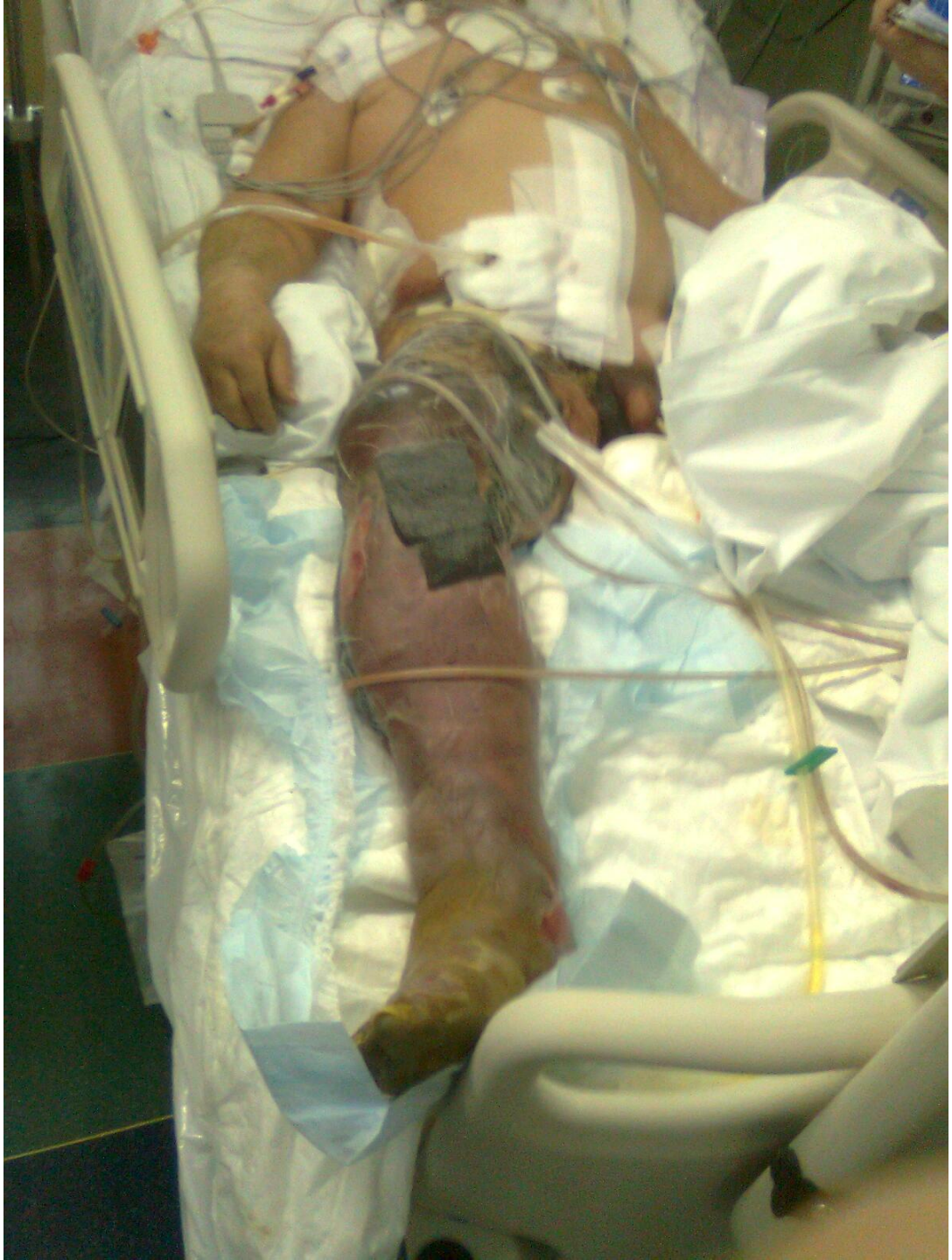
Minimo rilascio di mediatori di flogosi dopo esposizione di *S. pneumoniae* a daptomicina

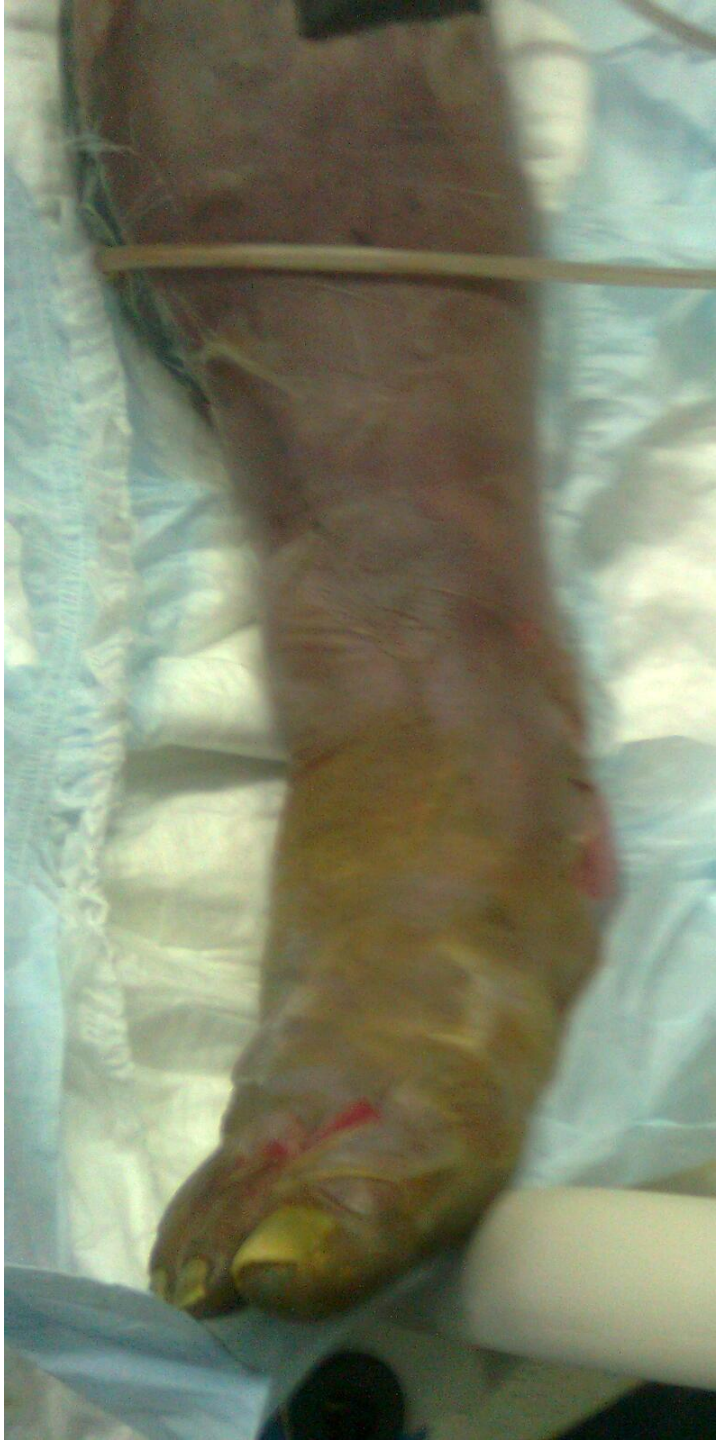
pneumococchi nel LCR dopo esposizione antibiotica

	2 ore dpo esposizione	6 ore dopo esposizione
Ceftriaxone		
Daptomicina		

Stucki A *et al*. *Antimicrob Agents Chemother* 2007;51:2249–2252







S. aureus?

1. Malattia di base

Diabete mellito
insufficienza renale acuta & dialisi
lesioni cutanee
tossicodipendenza EV

2. Porta di accesso

catetere vascolare
infezioni di cute e tessuti molli
corpi estranei
infezioni ossa e articolazioni

3. Presentazione clinica

metastasi settiche
ascessi
evoluzione necrotizzante
sepsi grave & shock settico

4. Microbiologia

Cocchi Gram-positivi a grappolo

Vi era il sospetto di una grave infezione da *S. aureus*?

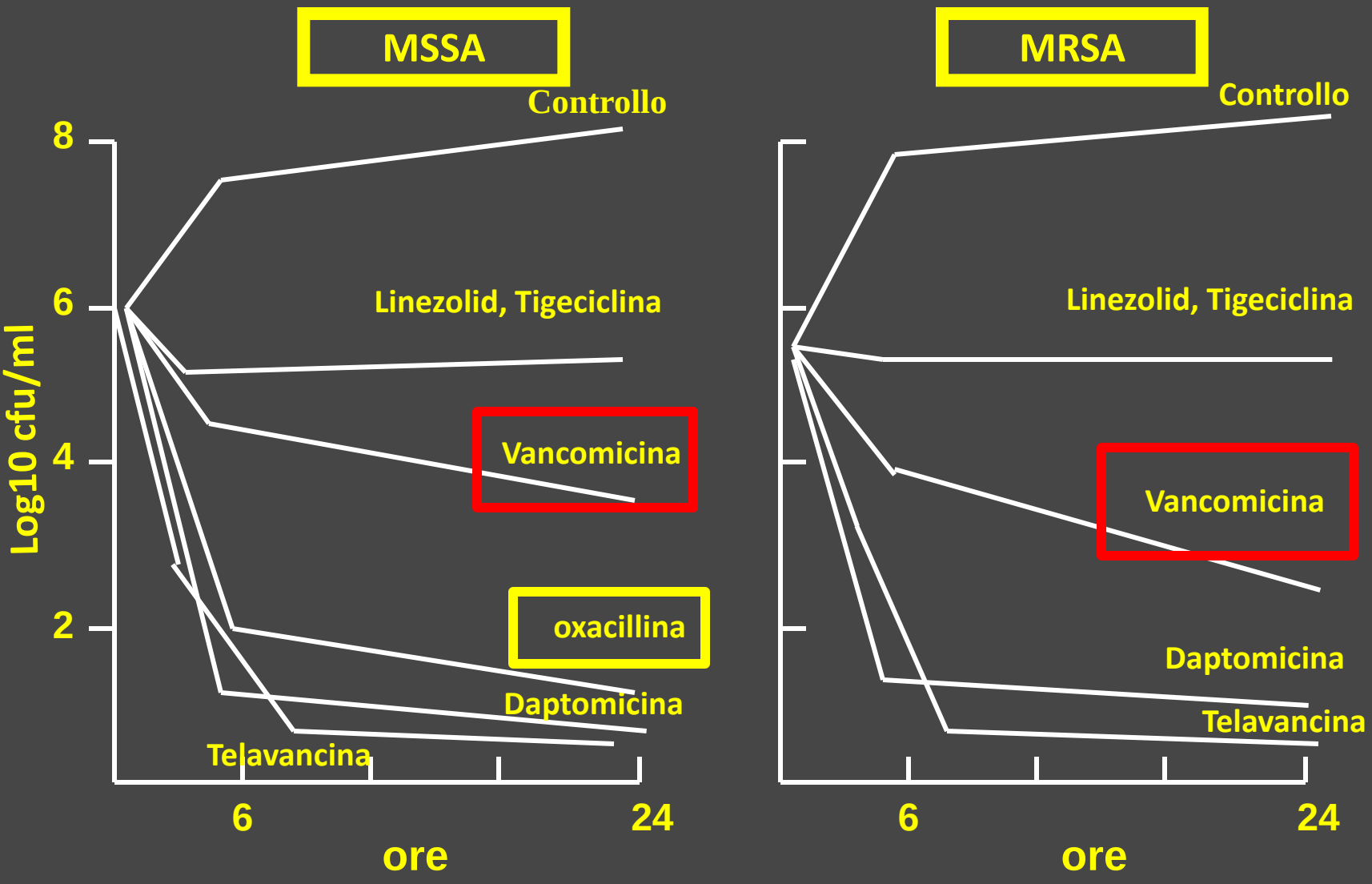
Sì!!

E' possibile/probabile che si tratti di MRSA?

- MRSA colonizzazione/ precedente infezione
- Prevalenza di MRSA >10%
- uno o più delle seguenti:
- Ospedale o cronicario negli ultimi 6- 12 mesi
- Chinoloni o antibiotici ev negli ultimi 30 gg
- >65 anni
- Emodialisi cronica

Mensa J *et al. Rev Esp Quimioter* 2008;21:234–258
Gemmell CG *et al. J Antimicrob Chemother* 2006;57:589–608
Falcone M, Serra P, Venditti M *Eur J Intern Med*,, 2009

Attività in vitro di diversi antibiotici vs MSSA and MRSA

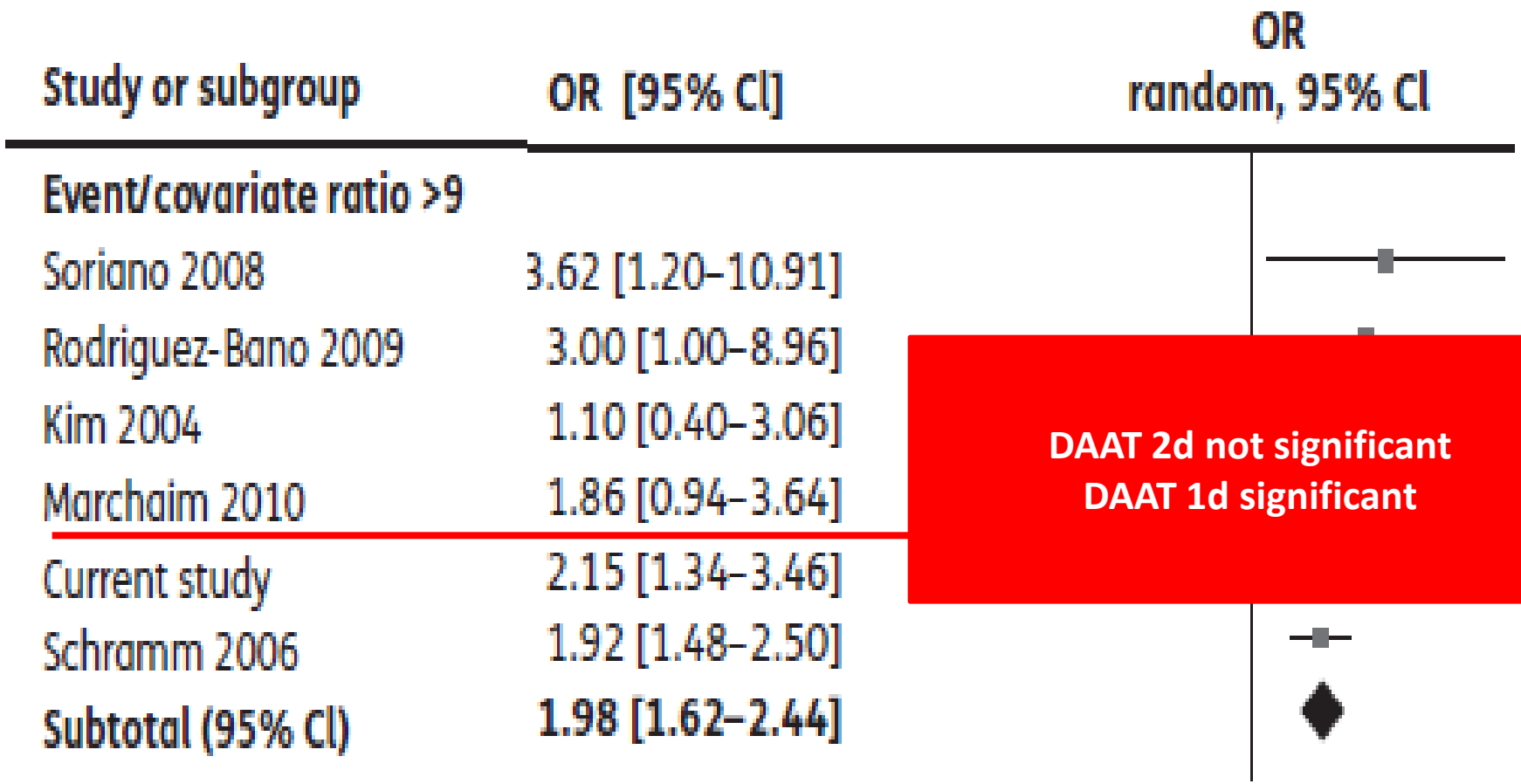


Small, Chambers AAC 1990; 34:1227 La Plante, AAC 2004; 48:4665; Pace AAC 2003;47:3602

Review: compilation of studies assessing the effects of inappropriate empirical antibiotic treatment for invasive MRSA infections (mainly bacteremia)

Paul M et al *J Antimicrob Chemother* 2010; 65: 2658–2665

ORs .1 indicate higher mortality with inappropriate empirical antibiotic treatment. Studies are subgrouped by performance of multivariable analysis and the event/covariate ratio in this analysis.



ISAC. International *S aureus* collaborative group.
Retrospective analysis (2006-10) of 3394 episodes of MRSA BSI from Europe and USA (ECCMID 2013)

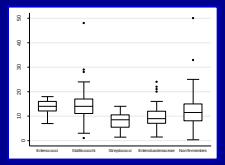
survival at	day 14	day 90
median (range)	84(91 –78)	72(78-63)
Difference	12%	15%

→ **S1 vs S8**
P=0.0001

Differences in mortality among 10 hospitals were significant after adjusting for age, MRSA, foci or nosocomial acquisition

Diagnostic strategies for rapid identification of MRSA BSIs at the Gemelli hospital

Blood cultures



Automated instrument

Record TTP

Detection of positivity

Time

Gram staining

Direct methods

Culture-based methods

Bruker BioTyper ID

ID/ AST

Genomera

AST

TTP, time to positivity; BSI, bloodstream infection ; ID, identification; AST, antimicrobial susceptibility testing

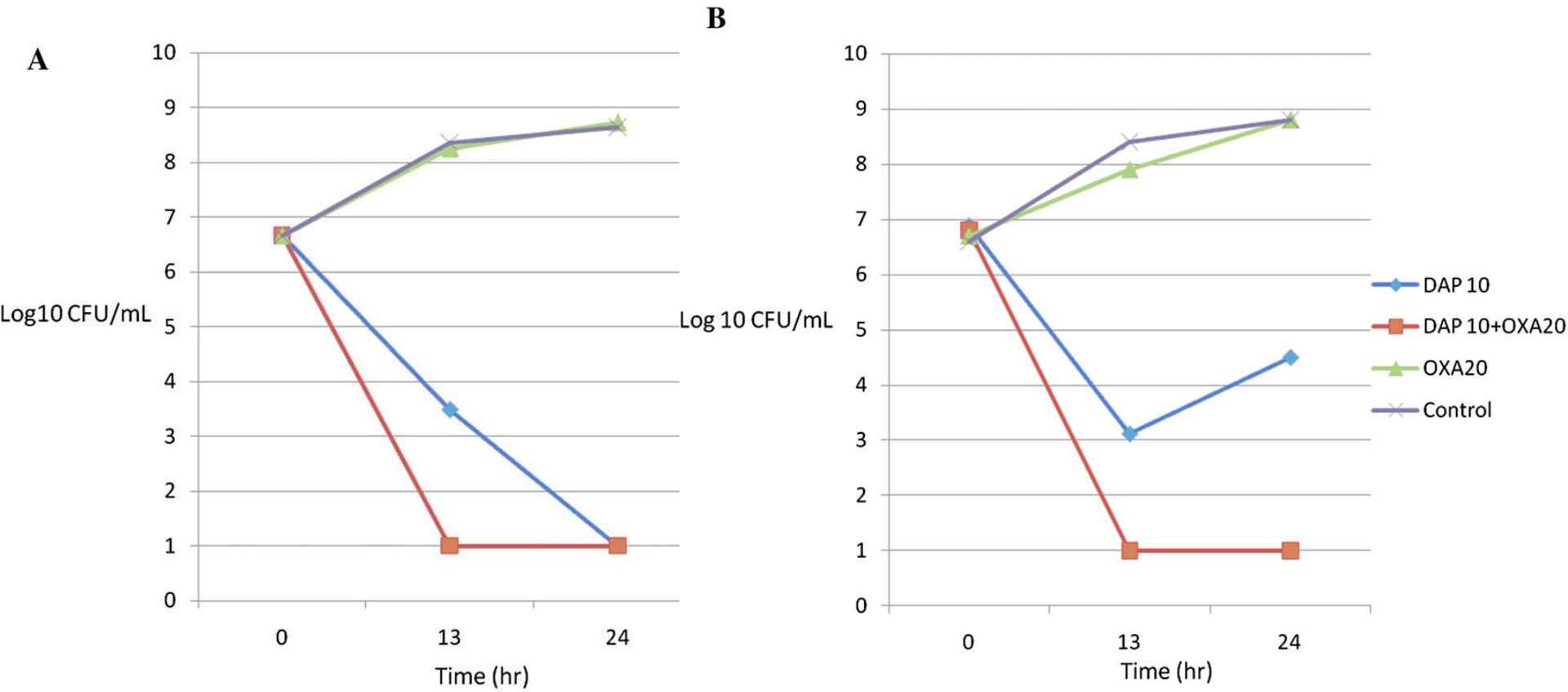
Time to positivity of microrganisms isolated in BSIs

hours	GNB(n=4683)	GP (3328)
7		
8	*Aeromonas*	Beta *strept*
9	*Klebsiella, E coli*	
10	*Enterobacter, Citrobacter*	*S pneumoniae*
11	*Proteus, Acinetobacter*	*S aureus*
12	*Salmonella*	*alfa strept, Enterococcus*
13		
14		
15	*P aeruginosa*	
16		
17		CoNs
>20	*H influenzae* and NF-GNB	

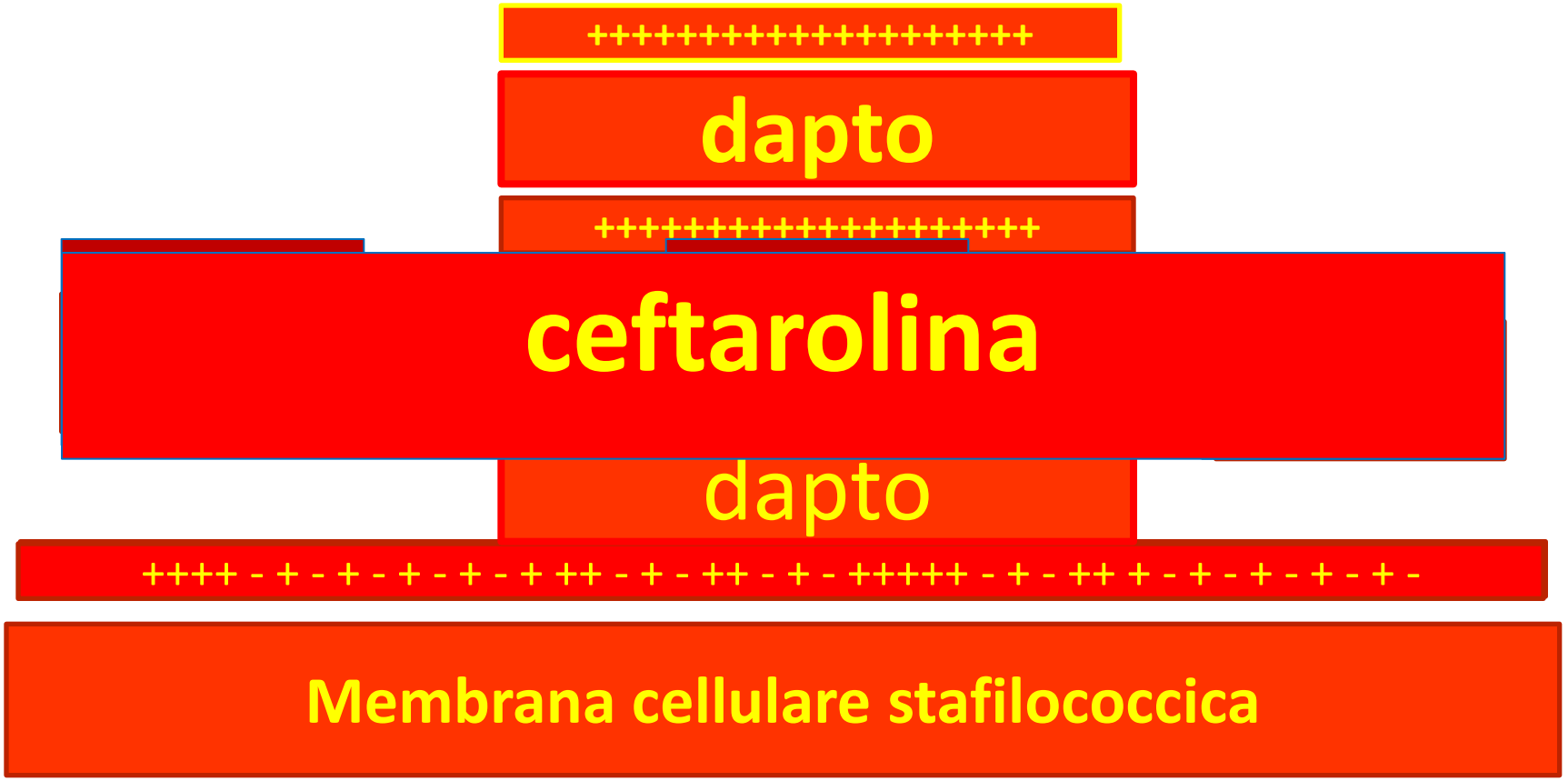
Soriano A. personal comunication 2013

Use of Antistaphylococcal b-Lactams to Increase DaptoActivity in Eradicating Persistent BSI aDue to MRSA: Role of Enhanced Dapto Binding

Dhand A et al CID 2011:53



Sinergismo dapto+oxacillina



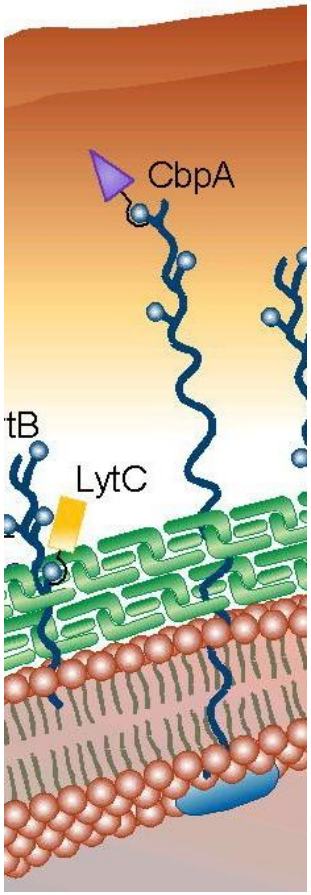
Confronto delle caratteristiche clinico-microbiologiche in 56 pazienti con sepsi da S. aureus con complicanze(53%)* o senza complicanze(47%).II.

	complicanze		P
	si	no	
gg a rx adeguato	2.5	1.1	< .03
febbre > 72 h	56%	33%	
gg batteriemia	3.6	1.5	< .01
shock settico	58%	3.7	< .002
polmonite batteriemica	17	0	< .03

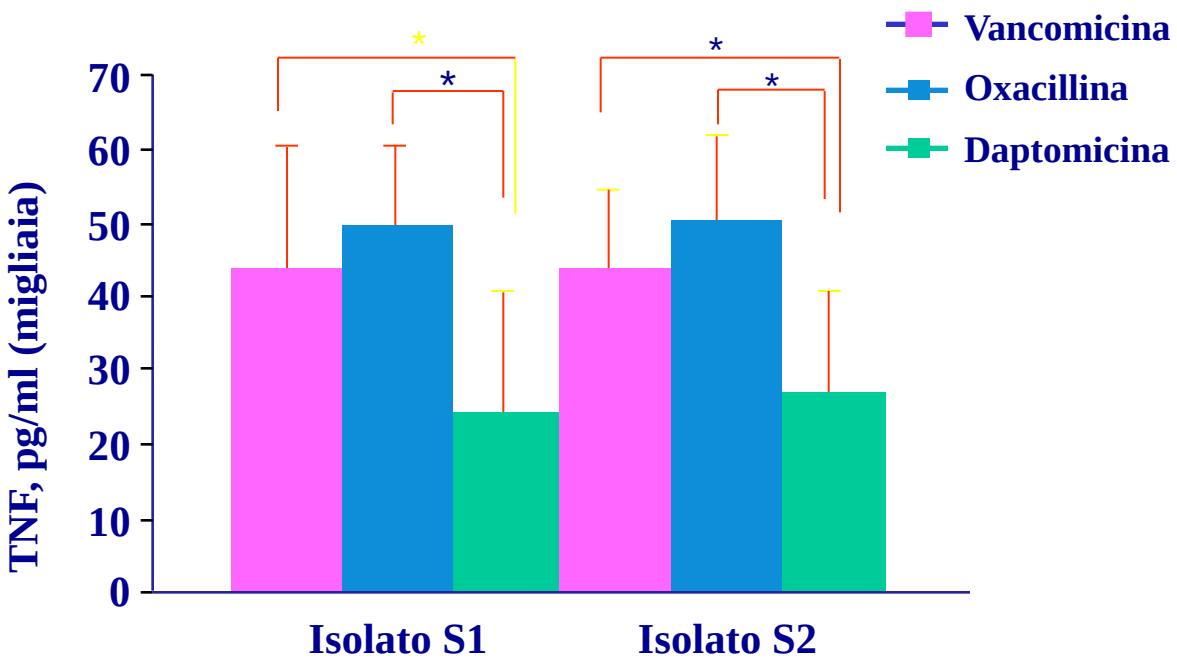
* complicanze: 16 morti x infezione, 5 recidive, 12 metastasi settiche(6 endocarditi)

Falcone & Venditti, AIMI 2002

Minimo rilascio di mediatori di flogosi dopo esposizione di *S. aureus* a daptomicina



Secrezione di TNF da cellule RAW 264.7 incubate con ceppi di MSSA in presenza di antibiotici



*** p<0.05**

English BK *et al. Antimicrob Agents Chemother* 2006; Gerber P et al *J Antimicrob Chemother*, 2006

Determinants of mortality in patients with severe infection

Vital organ invasion by growing bacteria

Duplication time

30’

Host inflammatory response

- **Exoproteins**
- **CW components**

(LPS, LT, etc..)

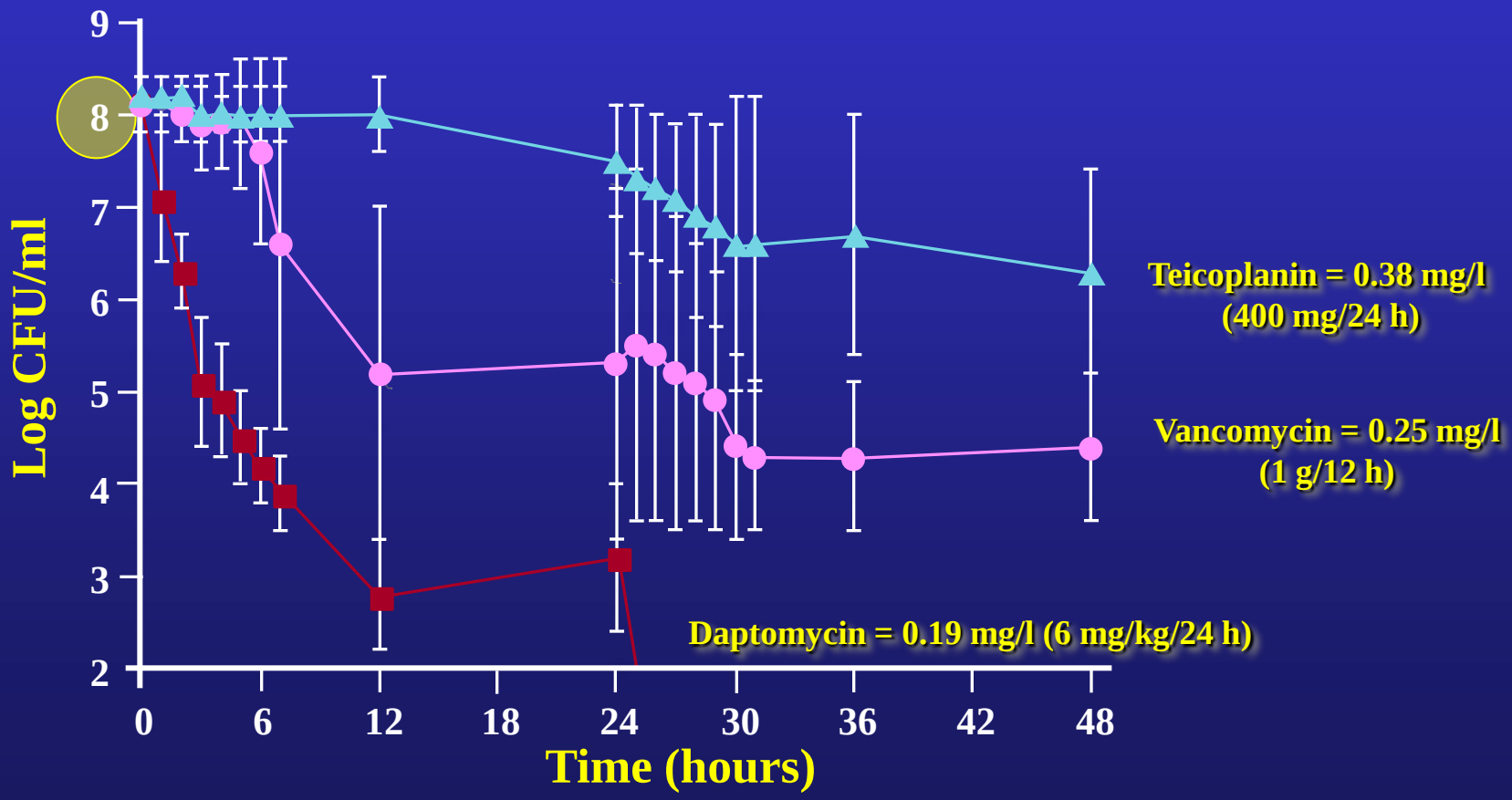
Early active antibiotic (PK/PD)

To avoid inflammatory response

Daptomycin retains potent bactericidal activity against high-inoculum MRSA *in vitro*

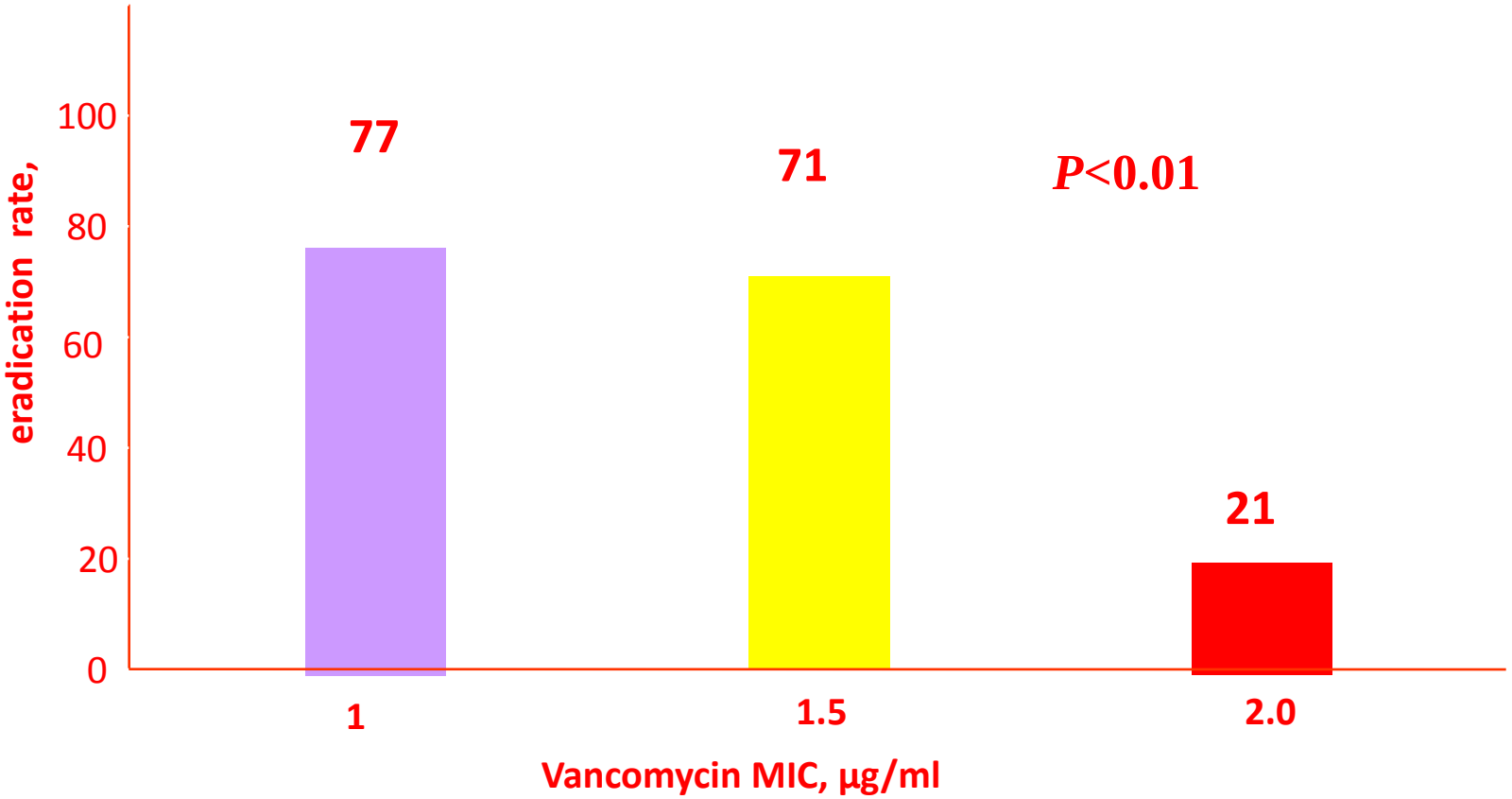
Bowker KE *et al. J Antimicrob Chemother* 2009;64:1044–1051

Bactericidal activity: daptomycin > vancomycin > teicoplanin



MIC predicts eradication rates in MRSA infections treated with vancomycin

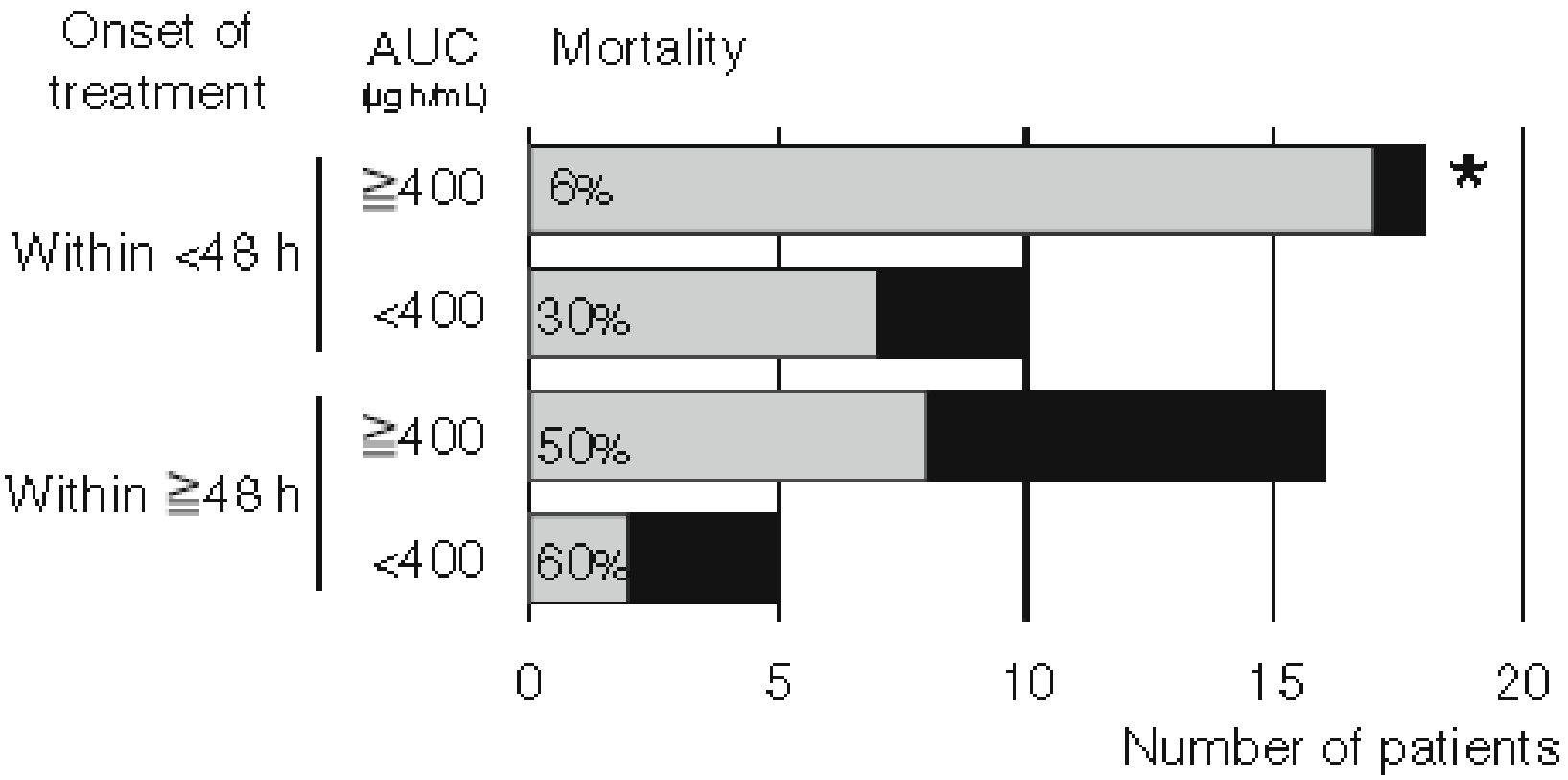
Moise *et al*. *Antimicrob Agents Chemother* 2007; 51: 2582



The importance of a judicious and early empiric choice of antimicrobial for MRSA bacteraemia

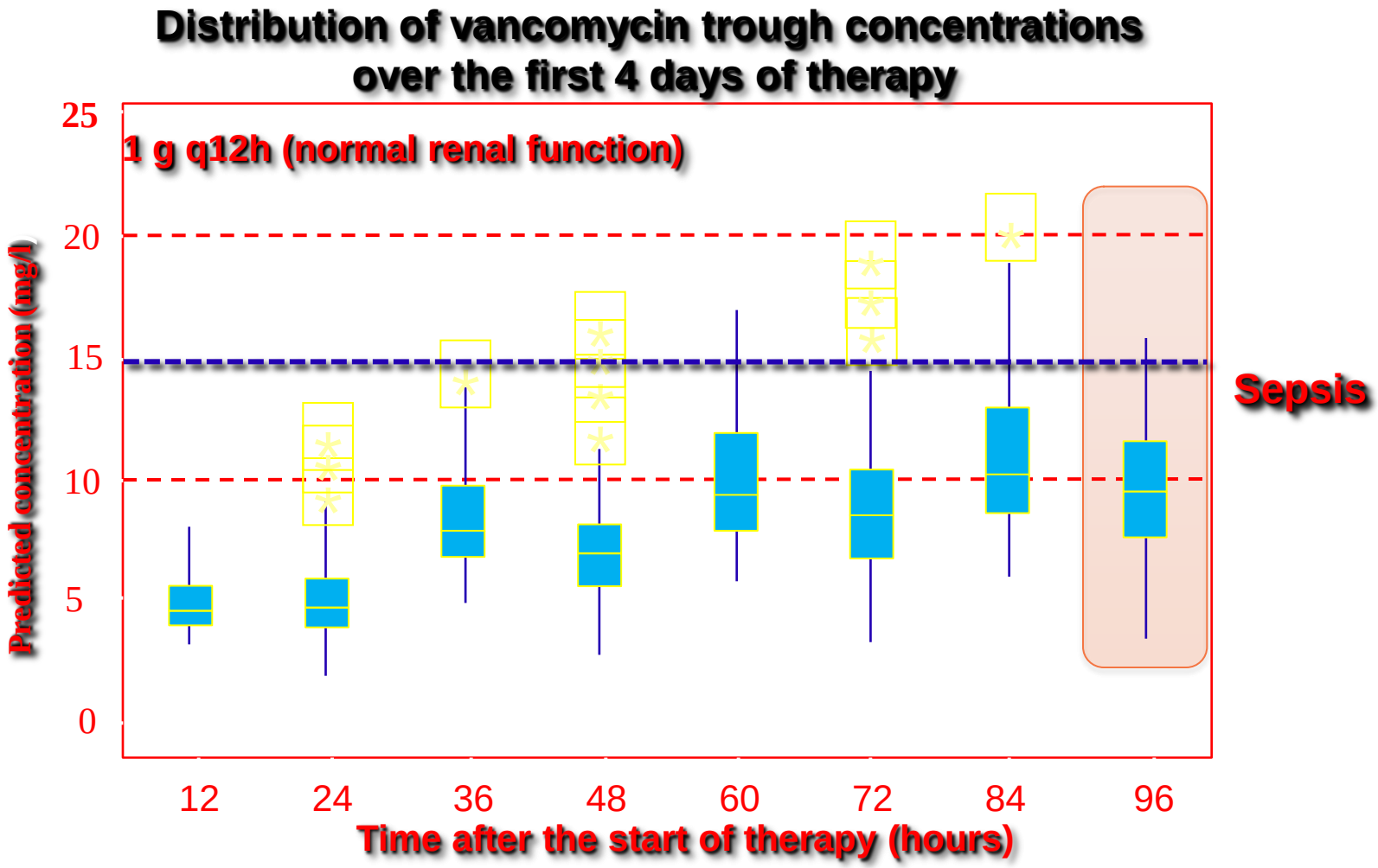
Shime N et al *Eur J Clin Microbiol Infect Dis* (2010) 29:1475–1479

Relationship between the onset of treatment, 24-h vancomycin concentration and mortality

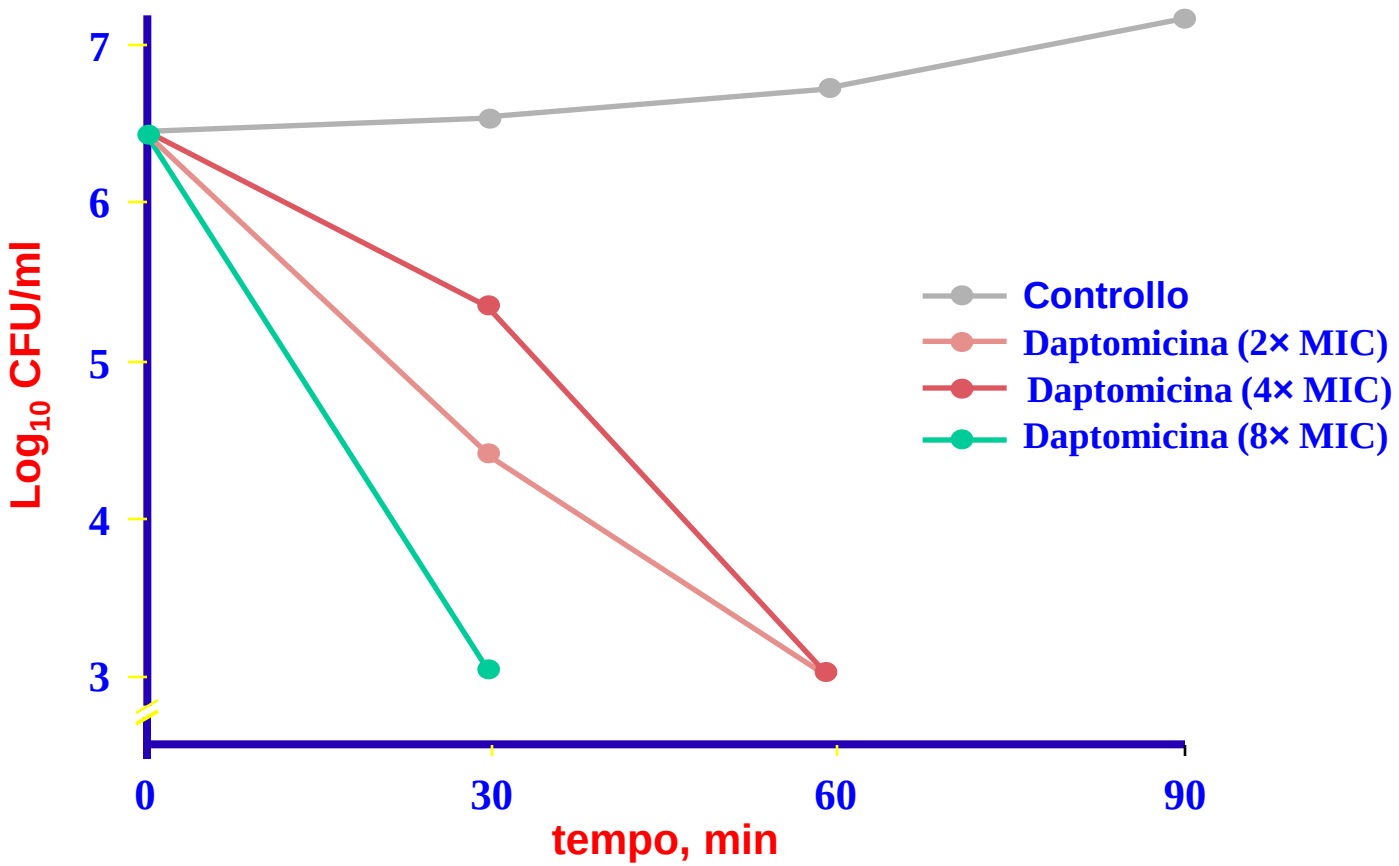


Typical vancomycin dosing fails to achieve target concentrations for sepsis even after 4 days

Thompson AH *et al. J Antimicrob Agents* 2009;63:1050–1057

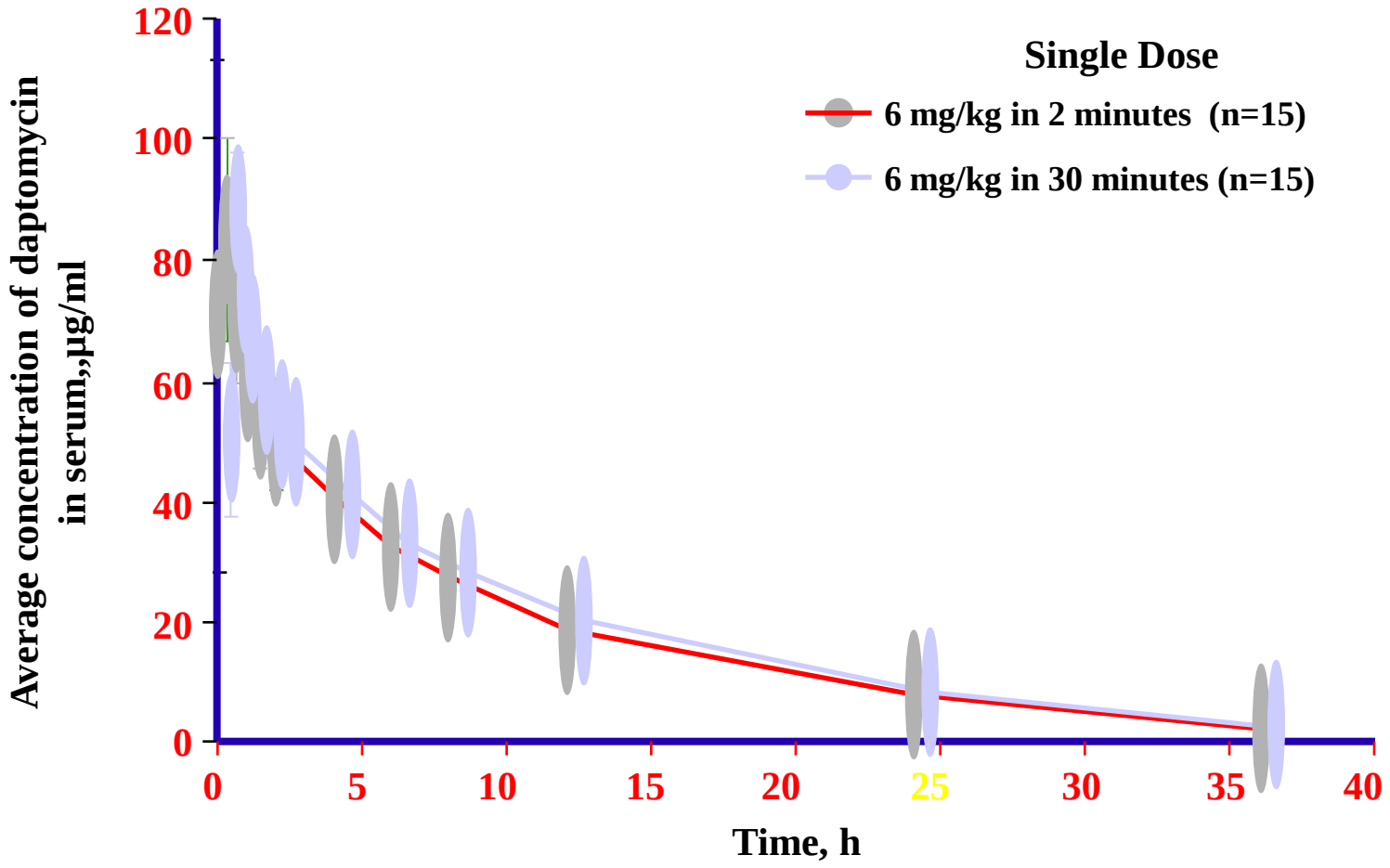


azione battericida rapida e concentrazione dipendente di daptomicina vs *S. aureus*



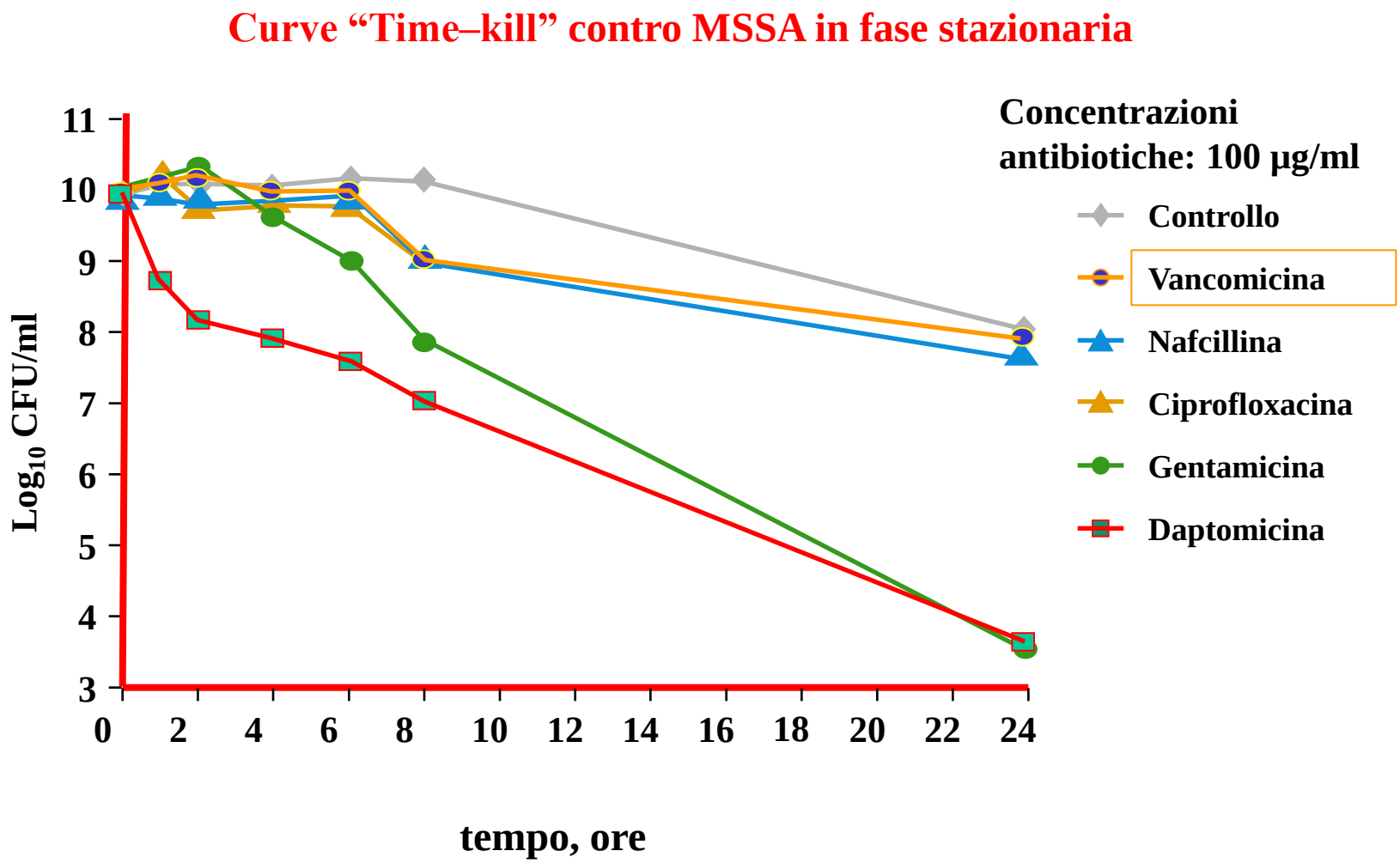
Hawkey PM. *J Antimicrob Chemother* 2008:62 (Suppl 3):iii7–iii14

Similar PK profile of daptomycin with intravenous infusion in 2 minutes Vs. 30 minutes



Chakraborty A *et al*. *J Antimicrob Chemother*. 2009 Jul;64(1):151-8.

Azione battericida *in vitro* di daptomicina contro un alto inoculum di cellule in fase stazionaria di MSSA



Mascio CTM *et al. Antimicrob Agents Chemother* 2007;51:4255–4260

Clinical Practice Guidelines by the InfectiousDiseases Society of America for the Treatment of MRSA Infections in Adults and Children

Liu C et al *Clin Infect Dis* 2011;52(3):e18–e55

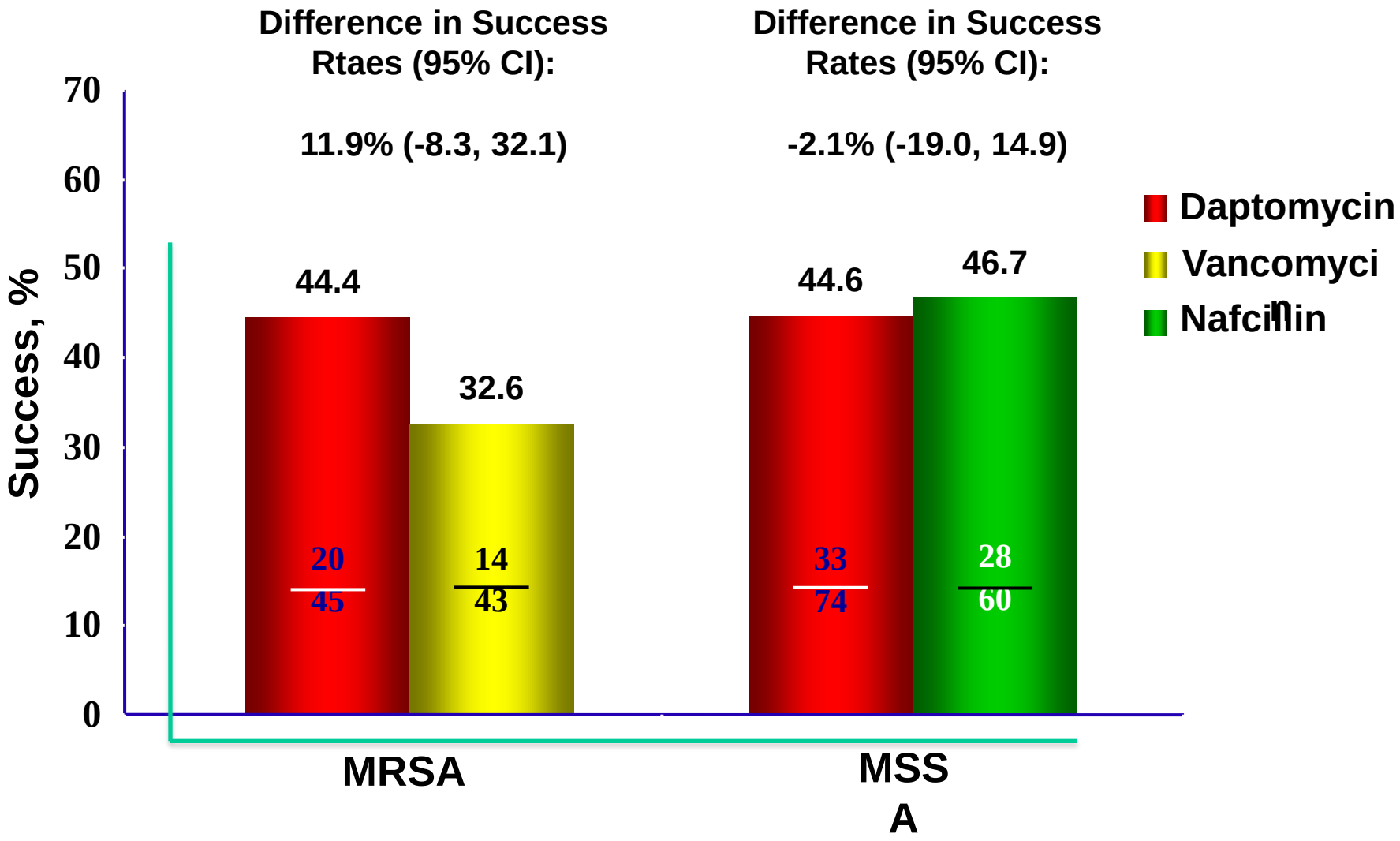
Batteriemia e endocardite su valvola nativa

infezione	antibiotico	dose adulti	dose bambini
Batteriemia			
	vancomicina	15-20 mg/kg/8-12h	15mg/kg/6h
	daptomicina	6(8-10)mg//kg/24h	8-10mg/kg/24h

	Durata
- non complicata	2 settimane
- complicata	4-6 settimane
- endocardite su valvola nativa	6 settimane

MRSA and MSSA Success at TOC: ITT Population

Fowler et al. *N Engl J Med*. 2006;355:653-665.



Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams

Joao Gonçalves-Pereira[1,2*] and Pedro Póvoa[1,2]

CRITICAL CARE

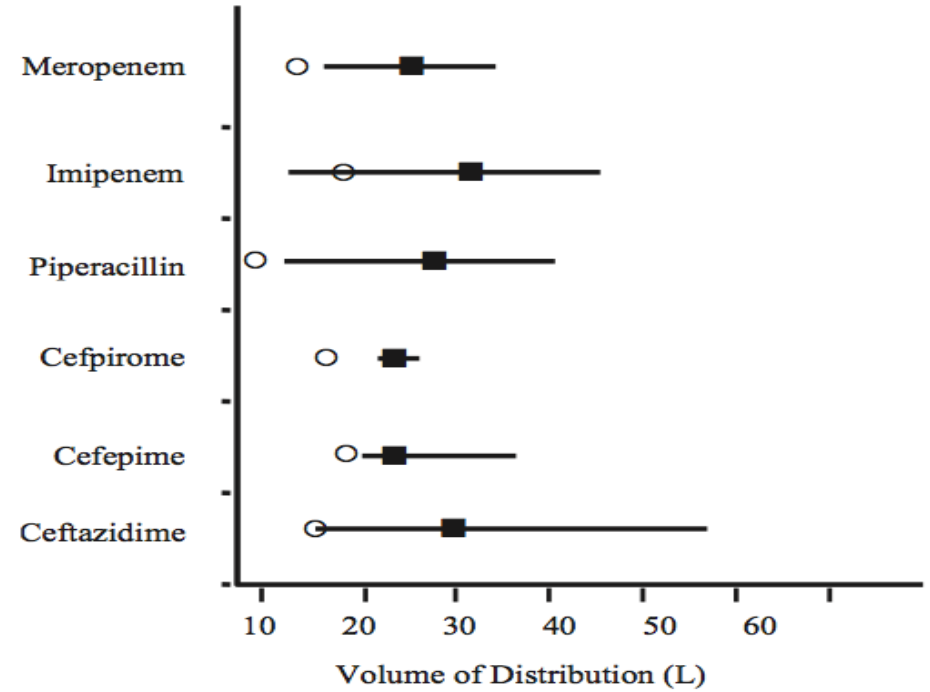
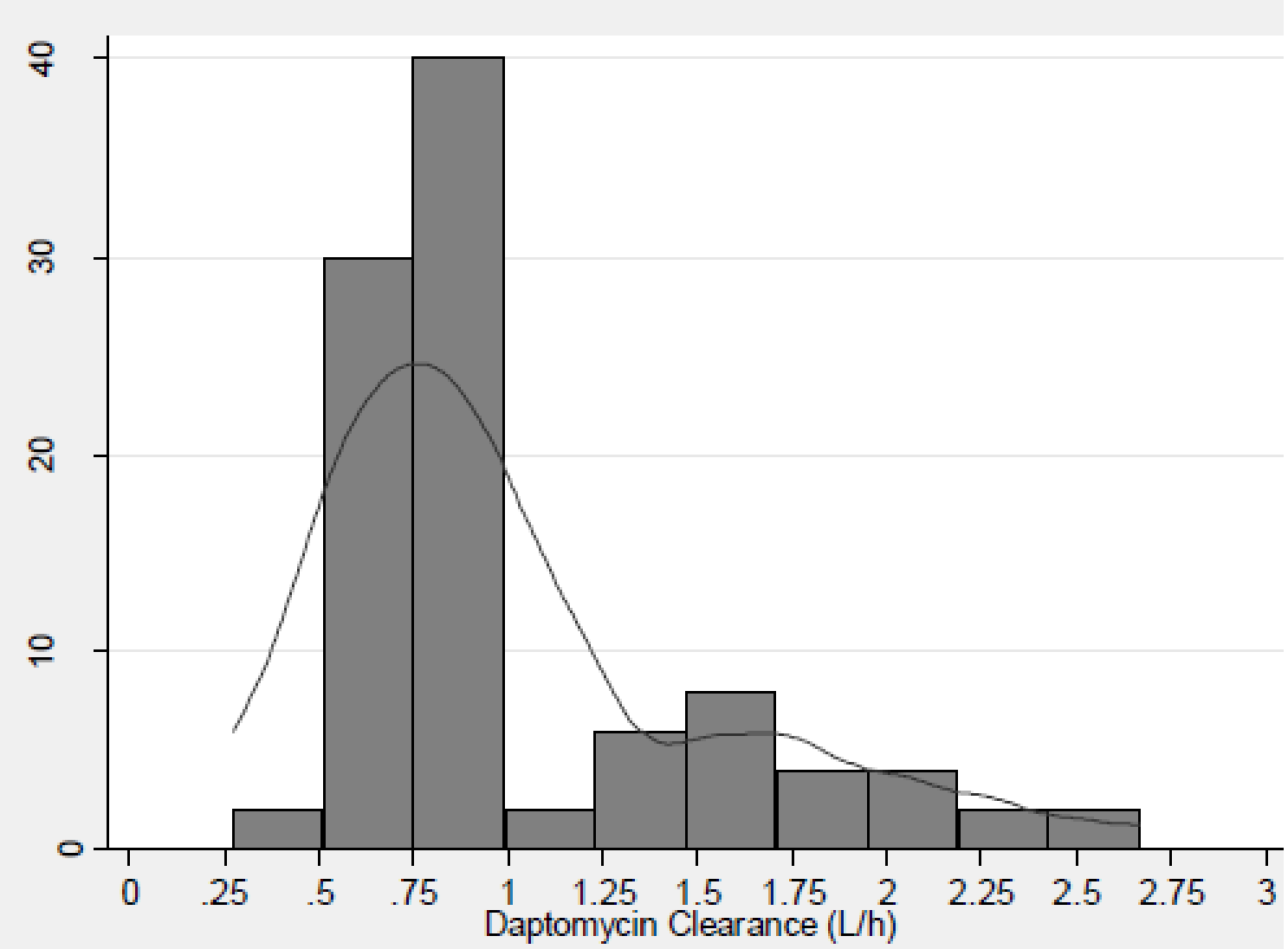


Figure 3 Heterogeneity of volume of distribution in litres of β-lactam antibiotics in ICU patients. Open circles: volume of distribution in healthy volunteers [44,51,89-92]; filled squares: weighted means of volume of distribution in the studies; straight lines: ranges of the means of volume of distribution in the studies.

Considerations for Higher Doses of Dapto in Critically ill Elderly Patients with MRSA-BSI

Falcone M, Russo A, Venditti M, Novelli A, Pai MP, *Clin Infetc Dis, early on line,* 2013

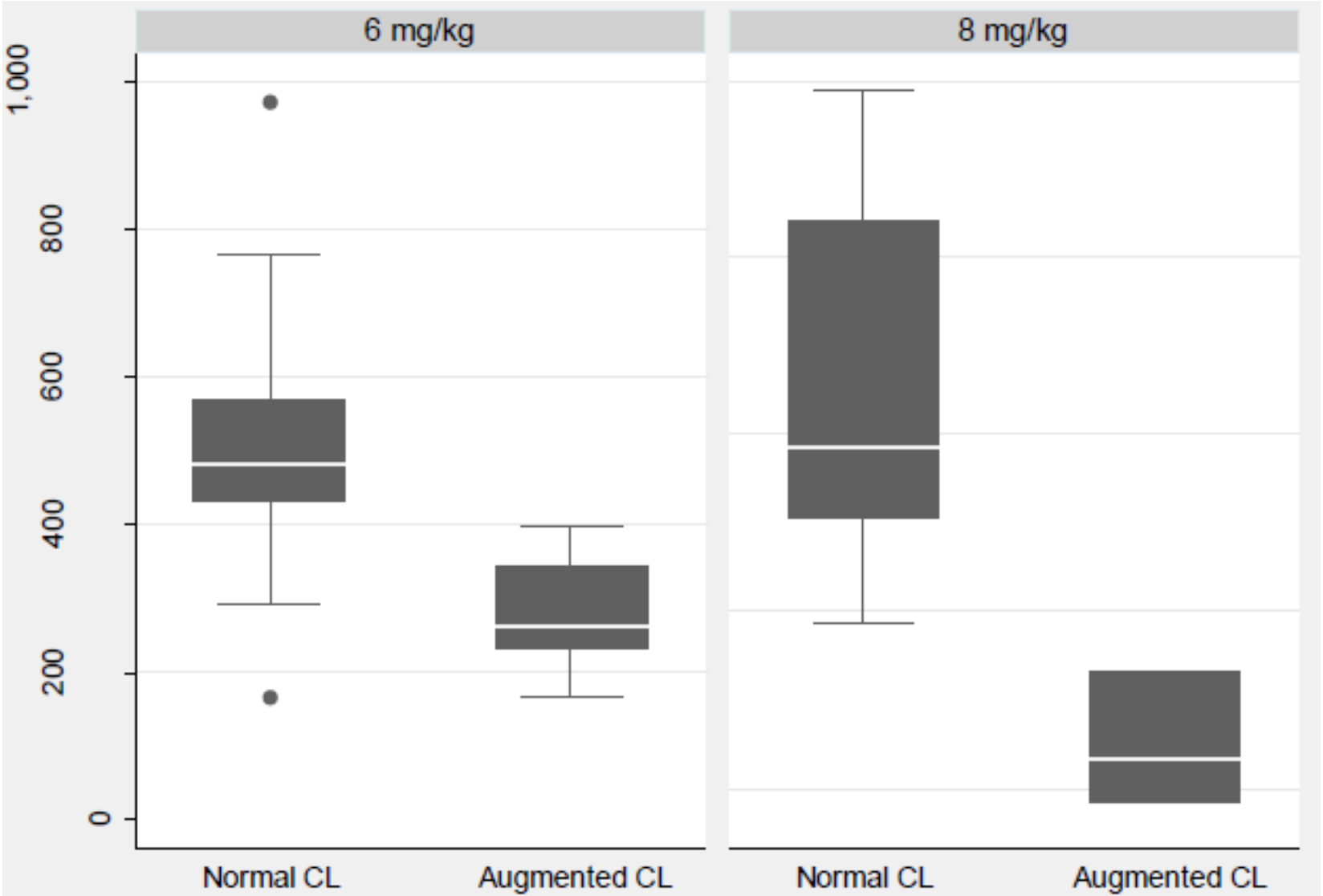
Histogram with kernel density overlay line plot of individual patient (n=50) dapto clearance



Considerations for Higher Doses of Dapto in Critically ill Elderly Patients with MRSA-BSI

Falcone M, Russo A, Venditti M, Novelli A, Pai MP, *Clin Infetc Dis*, early on line, 2013

Box and whisker plot of dapto AUC0-24 by the weight-based dose used in the population (n=50)



Comparison of clinical characteristics and outcomes of patients with augmented dapto CL compared to those with normal CL

Falcone M, Russo A, Venditti M, Novelli A, Pai MP, *Clin Infect Dis, early on line*, 2013

Variable	Augmented CL (n=13)	Normal CL (n=37)[A1]	P-value
Type of infection			
Bacteremia-Endocarditis	13 (100%)	8 (21.6%)	<0.001
Skin and soft tissue infections	0	20 (54.1%)	<0.001
Prosthetic joint infection	0	6 (16.2%)	<0.001
Osteomyelitis	0	4 (10.8%)	<0.001
Causative Pathogen			
MRSA	11 (84.6%)	2 (5.2%)	<0.001
MRSE	0	8 (21%)	<0.001
MRSH	0	7 (18.4%)	<0.001
ICU acquisition of infection	8 (61.5%)	12 (31.5%)	0.04
Severe sepsis or septic shock	13 (100%)	9 (24.3%)	0.01
SOFA score (mean (SD))	3.31 (1.03)	2.11 (0.84)	<0.001
Mean length of hospital stay (days)	36.8	22.5	<0.001
In-hospital mortality	4 (30.7%)	4 (10.8%)	<0.001

Cumulative fraction of response for three potential dapto AUC0-24 to MIC ratio targets and probability of minimum concentrations (Cmin) above a threshold associated with skeletal muscle toxicity for weight based and fixed dosing regimens in patients without sepsis

Falcone M, Russo A, Venditti M, Novelli A, Pai MP, *Clin Infect Dis, early on line*, 2013

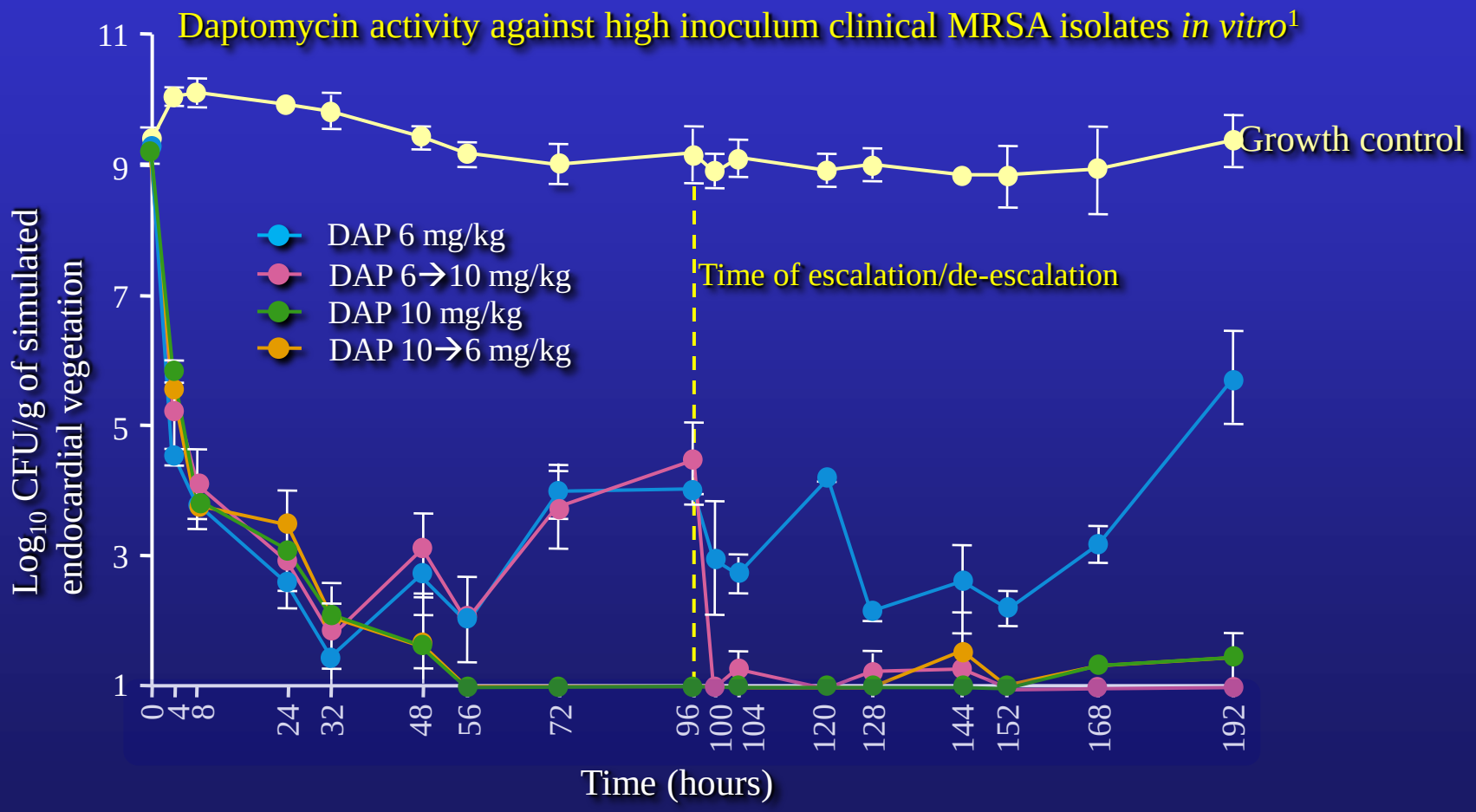
Daily Dose	% Cummulative Fraction of Response based on AUC_{0-24}/MIC			% Probability $C_{min} \geq 24.3$ mg/L
	≥579	≥666	≥753	
Weight Based Dosing				
6 mg/kg/day	94.8	92.3	89.5	1.52
8 mg/kg/day	97.9	96.7	95.1	4.88
10 mg/kg/day	99.1	98.6	97.6	11.0
Fixed Dosing				
500 mg/day	96.8	95.1	92.9	1.38
750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

Cumulative fraction of response for three potential dapto AUC0-24 to MIC ratio targets and probability of minimum concentrations (Cmin) above a threshold associated with skeletal muscle toxicity for weight based and fixed dosing regimens in patients with sepsis

Falcone M, Russo A, Venditti M, Novelli A, Pai MP, *Clin Infect Dis, early on line*, 2013

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

Support for initial high dose daptomycin followed by dose de-escalation



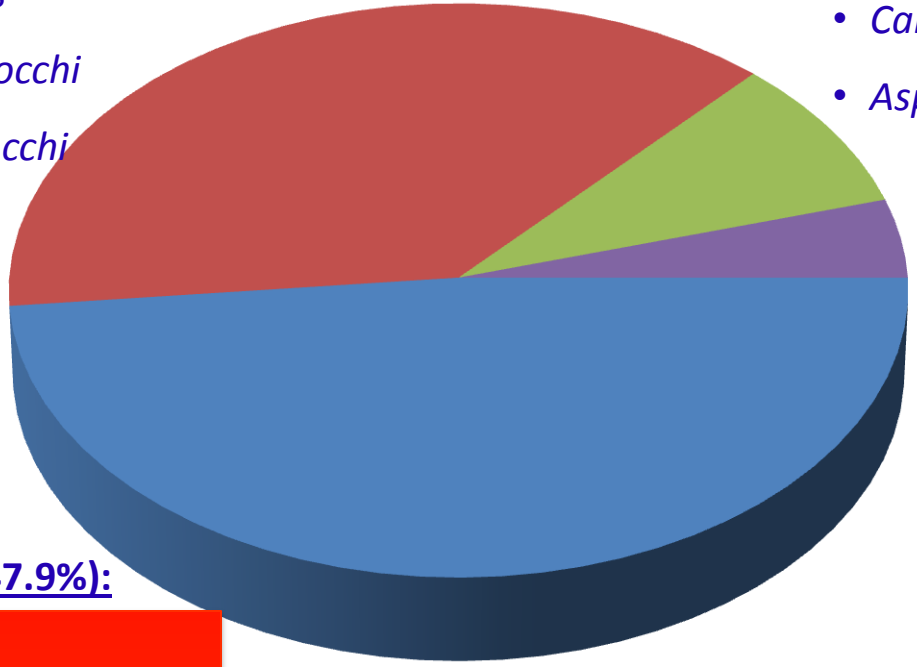
Refer to the daptomycin Summary of Product Characteristics for dosing recommendations[2]

1. Vidaillac C *et al. Antimicrob Agents Chemother* 2011;55:2160–2165
2. Novartis Europharm Ltd. Cubicin (daptomycin) Summary of Product Characteristics. 2011

Etiology of sepsis

GRAM + (38%)

- *S. aureus*
- *Streptococchi*
- *Enterococchi*
- *CONS*



FUNGI (8.6%)

- *Candida spp*
- *Aspergillus spp*

Others (4.4%)

- *Anaerobes*
- *Mycobacterium tubercolosis*

GRAM – (47.9%):

MDR

Crit Care Med. 2006.

Fattori di rischio

BGN MDR

K. Pneumoniae KPC

- Colonizzazione
- Charlson Index ≥3
- CVC
- Chirurgia recente
- Neutropenia
- ≥ 2 recenti ospedalizzazioni
- Tp antibiotica:
  - fluorochinoloni
  - carbapenemi

A. baumannii

- Precedente infezione/colonizzazione
- Durata degenza
- Chirurgia recente
- CVC
- NPT
- Ventilazione meccanica
- Tp antibiotica:
  - carbapenemi
  - pip/tazo
  - cefalosporine IV

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

Capone A, Giannella M, Venditti M, Tarasi A, …Carattoli A, Petrosillo & SEERBIO-GRAB network, *Clin Microbiol Infection*, 2012

Inter-hospital spread (7 roman hospitals) of two major clones, ST512 and ST258.
• 36.1% and 20.4% of strains were also resistant to colistin and tigecycline, respectively
•infection was diagnosed in 91 patients who received appropriate antibiotic treatment and combination therapy, in 73.6% and 59.3%, respectively
•Inhospital mortality was 25%

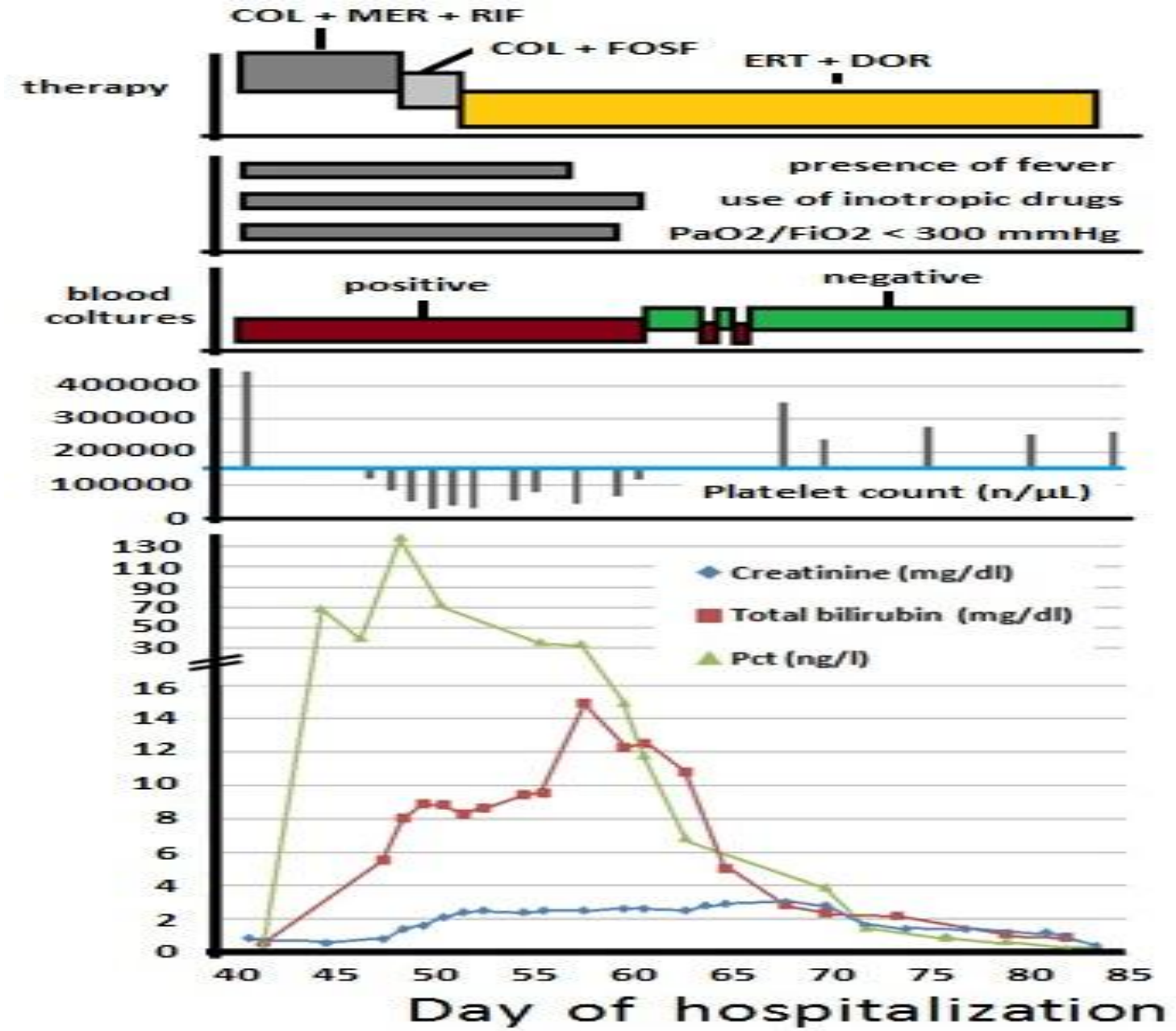
Multivariate analysis of risk factors for inhospital mortality in patients with infection due to CR-KP*

	OR(95% CI)	P
COPD	8.98(2.09-38.59)	0.003
Hosp. in ICU	15.76(33.35-74.10)	<0.001
BSI	11.42(2.68-48.63)	0.001
Colistin-R KP	5.54(1.40-21.91)	0.01

* Adjusted for appropriate antibiotic therapy, combination therapy and removal of the infectious source

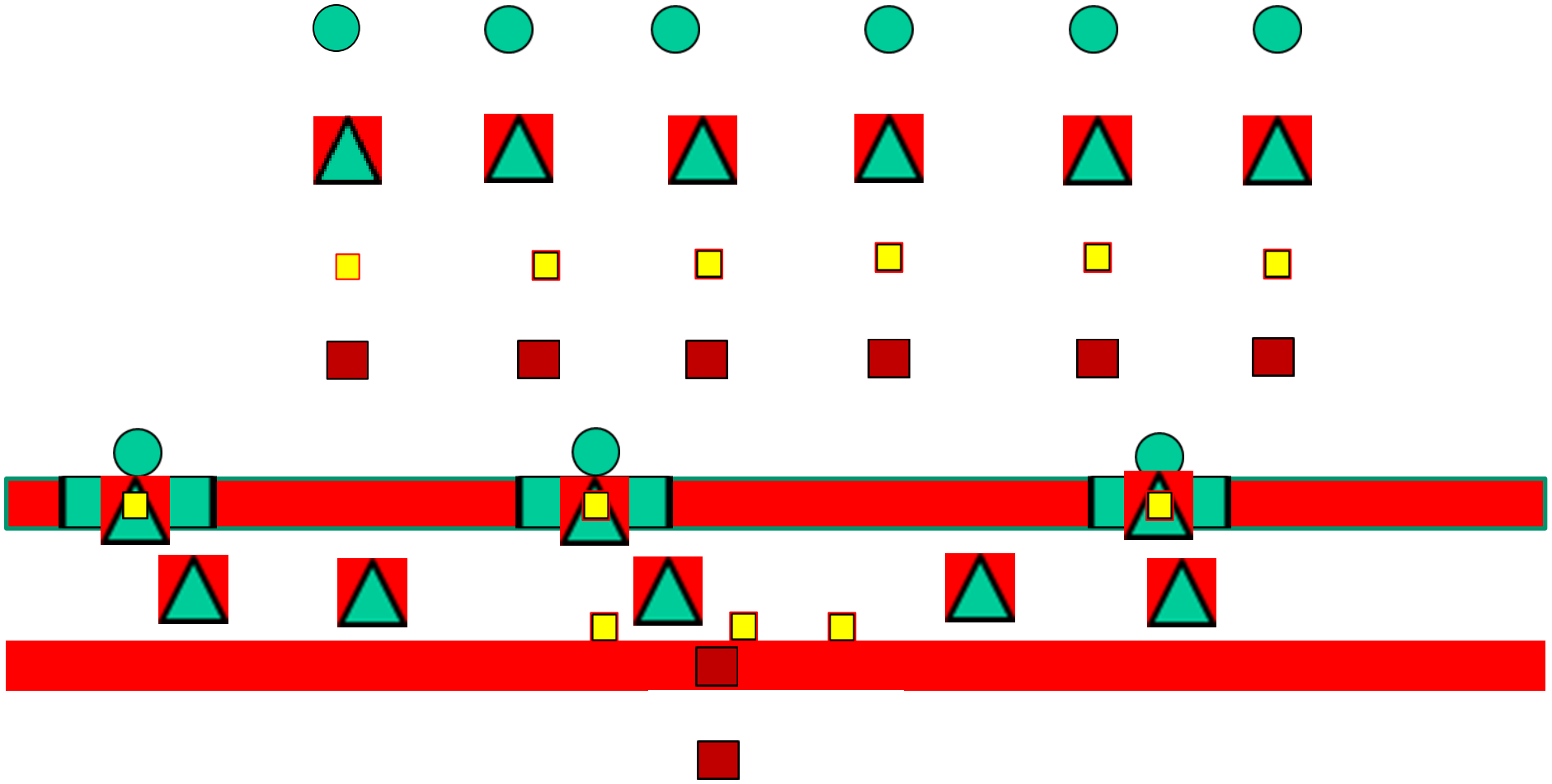
Successful Ertapenem-Doripenem Combination Treatment of Bacteremic VAP due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Ceccarelli G, Falcone M, Giordano A, Mezzatesta ML, Caio C, Stefani S & Venditti M *Antimicrob Agents Chemother* 2013



Sinergismo

colistina + ertapenem + meropenem + gentamicina



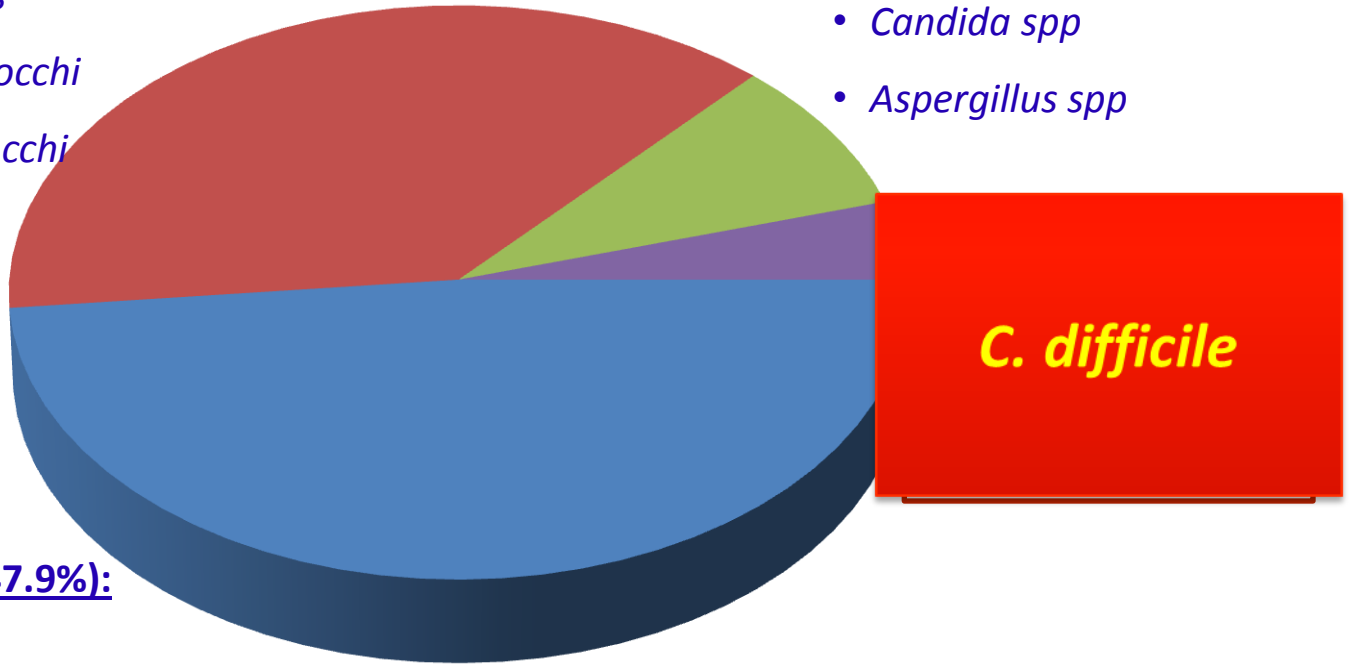
Etiology of sepsis

GRAM + (38%)

- *S. aureus*
- *Streptococchi*
- *Enterococchi*
- *CONS*

FUNGI (8.6%)

- *Candida spp*
- *Aspergillus spp*



GRAM – (47.9%):

- *E. Coli*
- *Klebsiella spp*
- *Pseudomonas spp*

Crit Care Med. 2006.

Fattori di rischio

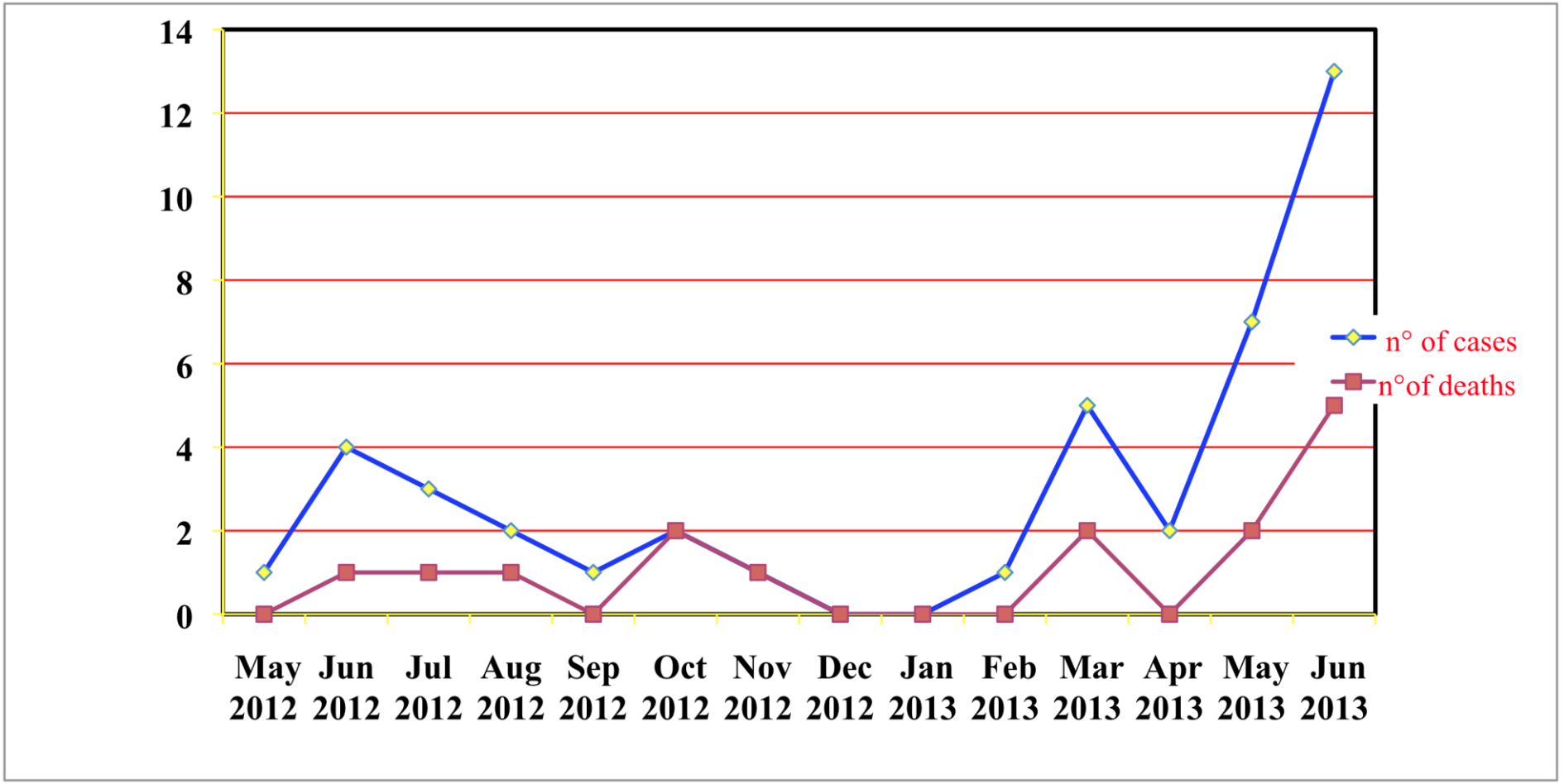
C. difficile

- Pregressa Tp antibiotica
  - fluorochinoloni; cefalosporine III
- Precedente episodio di CDI
- Età
- Durata degenza

Ribotipo 027 associato a rischio maggiore di complicanze
(Shock settico/megacolon tossico)

Casi di infezione da *C. difficile* in un ospedale di Roma

Guastalegname M,Grieco S,Giuliano S,Falcone M,Caccese R…,Venditti M. *Infection* 2014 (*IN PRESS)*



A cluster of fulminant *C. difficile* colitis in an Intensive Care Unit in Italy

Guastalegname M,Grieco S,Giuliano S,Falcone M,Caccese R…,Venditti M. *Infection* 2014

Patient number, sex, age	Previous hospitalization	Comorbidities	Previous antimicrobial chemotherapy	Lactate (mmol/L)	White blood cells (n/mmc)	Creatinine (mg/dl)	Albumin (mg/dl)	Symptoms	Time to treatment [a] (days)	CDI Relapse	CD Ribotype	Surgical treatment	Clinical outcome
1, female, 73	LTCF	HBP DM Type 2	Unknown	8,2	95.000	4.4	1.7	Diarrhea Fever	4	NO	027	NO	Death within 2 days of antimicrobial therapy
2, male, 85	Internal Medicine Ward	HBP CPOD CRF	Ciprofloxacin Ceftazidime	3,3	32.000	3.3	3-0	Diarrhea Fever	3	NO	027	NO	Death within 1 day of antimicrobial therapy
3, female, 64	Internal Medicine Ward	DM Type 2	Ciprofloxacin Meropenem Levofloxacin	3,0	37.000	2.9	2.9	Diarrhea Fever	3	NO	027	Cecostomy Subtotal colectomy	Death within 20 days of colectomy
4, female, 63	LTCF	HBP DM Type 2	Ceftriaxone	2,7	30.000	2.1	1.1	Diarrhea Fever	4	NO	027	Subtotal colectomy	Death within 1 day of colectomy
5, female, 91	LTCF	HBP CPOD	Unknown	1,4	140.000	3.0	1.4	Diarrhea Fever	4	YES	Test not performed	NO	Death within 1 day of antimicrobial therapy
6, male, 71	Internal Medicine Ward	HBP DM Type 2 Tetraparesis	Ciprofloxacin Cefotaxime	2,8	67.000	2.1	1.8	Diarrhea Fever	3	NO	Test not performed	NO	Death within 4 days of antimicrobial therapy
7, female, 69	Internal Medicine Ward	HBP	Cefotaxime	2,5	37.000	1.2	1.7	Diarrhea	3	NO	Test not performed	Cecostomy	Death within 4 days of antimicrobial therapy

FOOTNOTES: LCTF, Long Term Care Facility; HBP, high blood pressure; DM diabetes mellitus; COPD chronic obstructive pulmonary disease; CRF, chronic renal failure.

[a] time between the onset of symptoms and the beginning of antibiotic therapy.

C difficile & surgery
Indications, timing and …..

***Lamontagne F. et al. *Ann Surg* 2007; 245: 267-72**

- **Megacolon**
- **Colonic perforation**
- **Acute abdomen**
- **Septic shock (selected cases)**
- **Emergency colectomy for fulminant CDI caused by ribotype 027: mostly beneficial in pts with age > 65 years, immunocompetent, WBC> 20.000 cmm, lactate 2,2-4,9 mmol/l ***

Courtesy of F Menichetti

Impact of Emergency Colectomy on Survival of Pts With Fulminant CDAD During an Epidemic Caused by a Hypervirulent Strain

Lamontagne, Ann Surg 2007

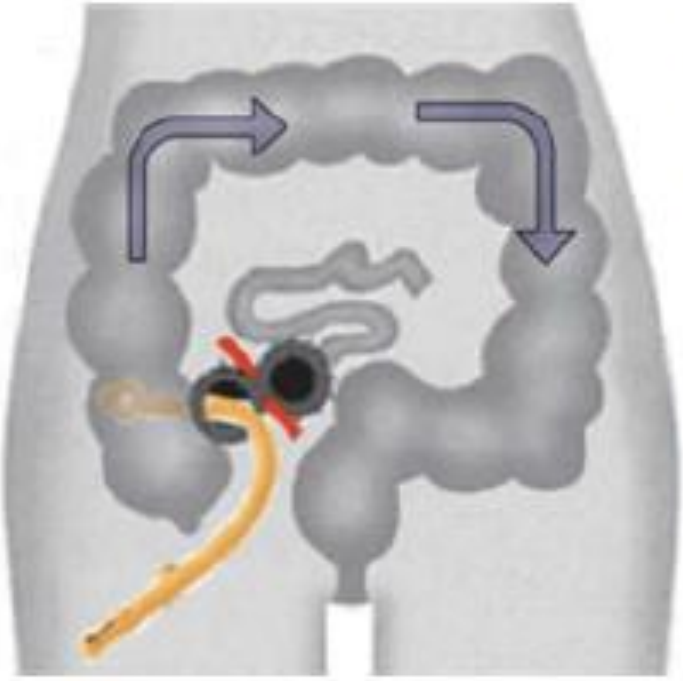
Risk factors for 30 day mortality among patients with fulminant CDAD

Colectomy	Died/total	unadjusted OR) (95%CI)	addjusted OR (95%CI)
No	74/127 (58%)	1.0	1.0
Yes	13/38 (34%)	0.4(0.2-0.8)*	0.2(0.1-0.7)*

* $p<0.05$

Diverting Loop Ileostomy and Colonic Lavage
An Alternative to Total Abdominal Colectomy for the Treatment of Severe, Complicated Clostridium difficile Associated Disease

Neal M et al . *Annals of Surgery* r 254: 423, 2011



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

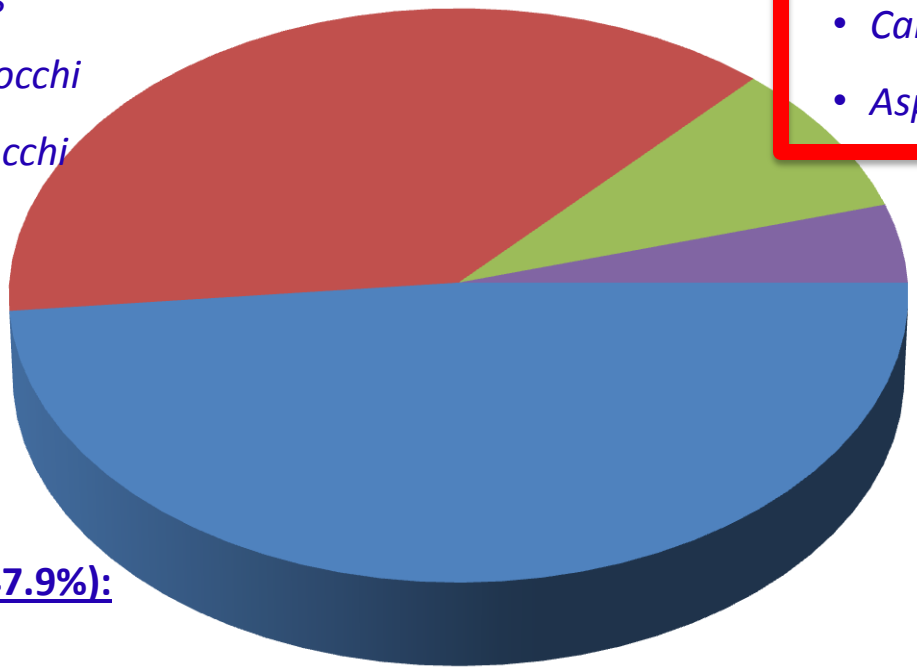
Ribotype 027 *C. difficile* colitis and candidemia: is there the link!!

Variables	*Candida-/Clostridium +*	*Candida-/Clostridium +*	p
	n= 19	n= 60	
Age years	76	75.8 years	n.s.
Sex male	10 (52.6%)	34 (56.6%)	n.s
Time at risk for clostridium infection (days)	12.2	13.1	n.s.
Severe CDI infection	19 (100%)	26 (43.3%)	<0.001
CDI relapse	15 (78.9%)	14 (23.3%)	<0.001
CDI Relapse (days)	21.7	34.1	<0.001
Ribotype 027	15 (78.9%)	8 (13.3%)	<0.001
Time at risk for candidemia (days)	20.1	-	<0.001
Candidemia risk factors	9 (47.3%)	19 (31.6%)	0.03
Candida score	1.7	1.4	n.s.
Previous antibiotic therapy	19 (100%)	32 (53.3%)	<0.001
Previous antifungal therapy	4 (21%)	4 (6.6%)	<0.001
Presence of at least 2 comorbidities	19 (100%)	43 (71.6%)	0.02
Transfer to ICU	4 (21%)	10 (16.6%)	0.02
Days of ICU stay	12.1	13.4	n.s.
Days of hospital stay	48.2	31.2	<0.001
SOFA score median	3.8	1.9	<0.001
Severe sepsis or Septic shock	14 (73.6%)	15 (25%)	<0.001
Dead	11 (57.8%)	15 (25%)	<0.001

Etiology of sepsis

GRAM + (38%)

- *S. aureus*
- *Streptococchi*
- *Enterococchi*
- *CONS*



FUNGI (8.6%)

- *Candida spp*
- *Aspergillus spp*

Others (4.4%)

- *Anaerobes*
- *Mycobacterium tubercolosis*

GRAM – (47.9%):

- *E. Coli*
- *Klebsiella spp*
- *Pseudomonas spp*

Crit Care Med. 2006.

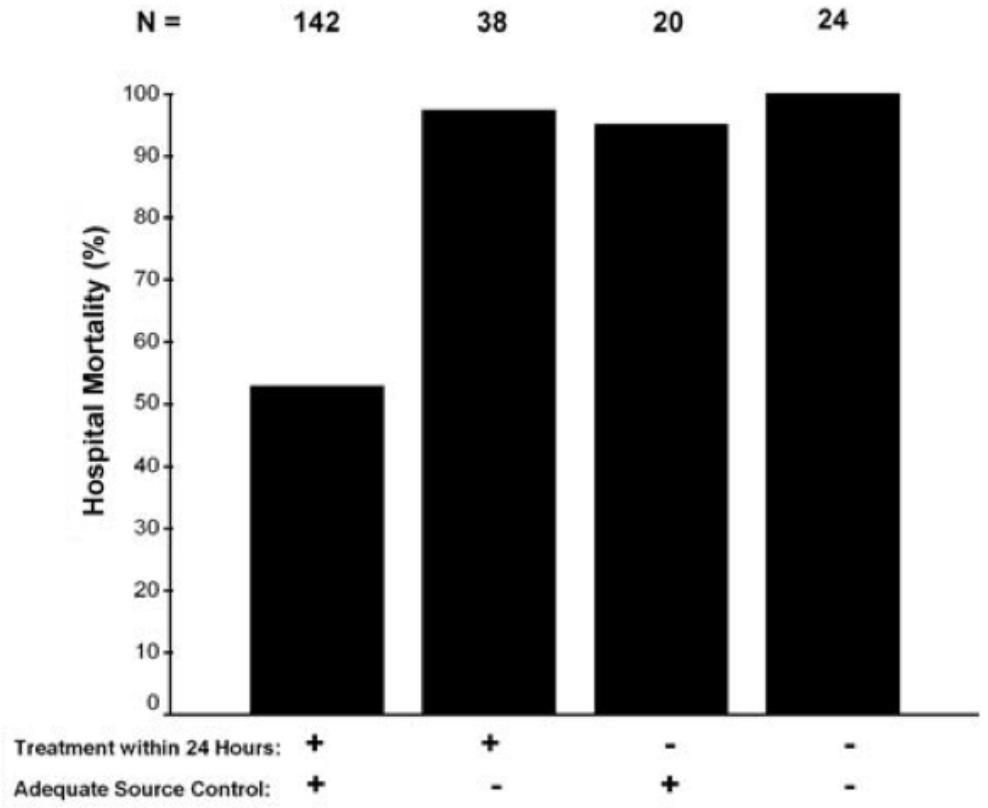
Fattori di rischio

Candida spp.

- **Terapia antibiotica**
- **Colonizzazione da *Candida* spp.**
- **CVC**
- **NPT**
- **Terapia steroidea**
- **Neoplasia**
- **DM**
- **Età**
- **Pazienti chirurgici:**
- **- Trapianto**
- **- Cardiochirurgia**
- **- Chirurgia addominale**

Septic Shock Attributed to *Candida* Infection: Importance of Empiric Therapy and Source Control

Marin Kollef,[1] Scott Micek,[2] Nicholas Hampton,[3] Joshua A. Doherty,[3] and Anand Kumar[4]



Clin Infect Dis 2012; 54:1739-46

Septic Shock Attributed to *Candida* Infection: Importance of Empiric Therapy and Source Control

Marin Kollef,[1] Scott Micek,[2] Nicholas Hampton,[3] Joshua A. Doherty,[3] and Anand Kumar[4]

Some reflections……

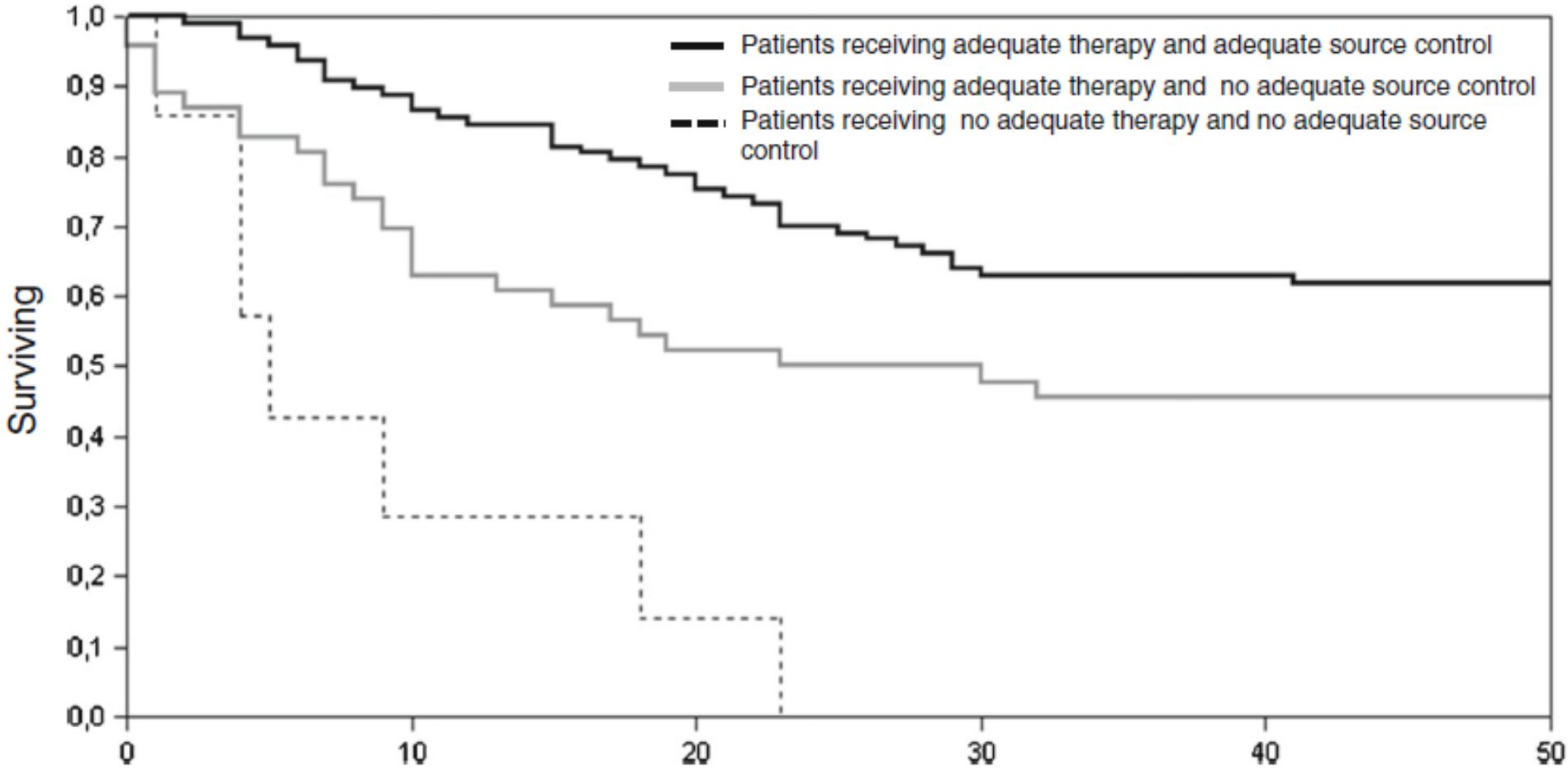
- Survivors 69 - Deaths 155
- Delayed therapy (after 24 h from blood culture positivity): 44 patients
- Out of these 44 patients, 41 did not receive any antifungal therapy because blood cultures became positive post mortem…….
- Importance of early diagnosis!

Clin Infect Dis 2012; 54:1739-46

A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality

Bassetti M et al *Intensive Care Med* 2014

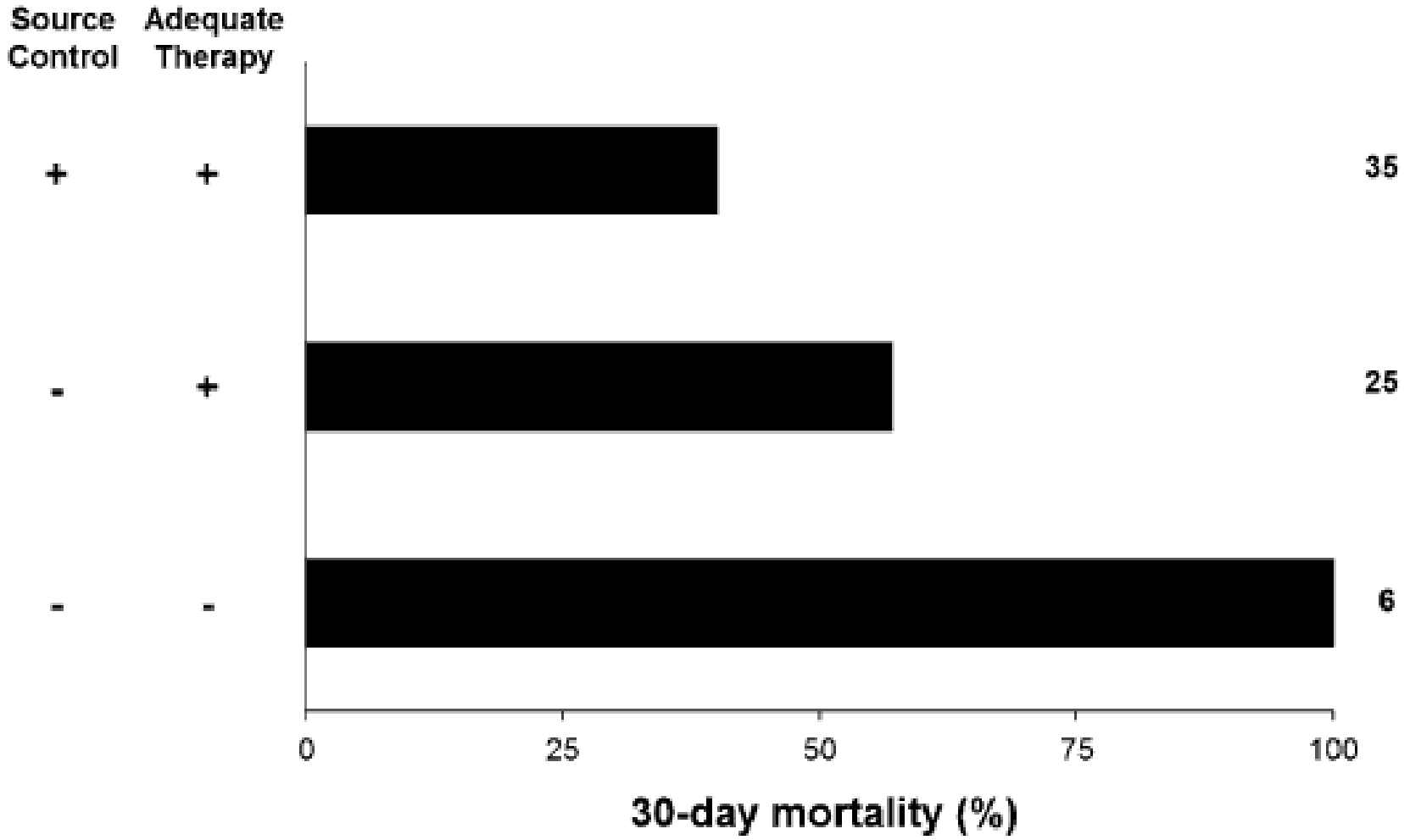
retrospective study in which patients with septic shock attributable to Candida who were treated during the 3-year study period at one or more of the five participating teaching hospitals in Italy and Spain (N=216)



A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality

Bassetti M et al *Intensive Care Med* 2014

retrospective study in which patients with septic shock attributable to Candida who were treated during the 3-year study period at one or more of the five participating teaching hospitals in Italy and Spain (N=216)



A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality

Bassetti M et al *Intensive Care Med* 2014

Multivariate analysis of risk factors for 30 day hospital mortality

Risk factor	Chi-square	Odds ratio	*P* value
APACHE II score (1-point increments)	12.79	0.93	<0.001*
Adequate antifungal therapy	3.9	5.99	0.048*
Source control	10.38	2.99	0.001*

Nuovi fattori di rischio

BPCO

Epatopatia grave (Child-Pugh C)

Trattamento corticosteroideo prolungato

….. A parte la granulocitopenia grave persitente da citostatici!

PREDICTORS OF MORTALITY IN NONNEUTROPENIC PATIENTS WITH INVASIVE PULMONARY ASPERGILLOSIS (IPA): DOES GALACTOMANNAN HAVE A ROLE?

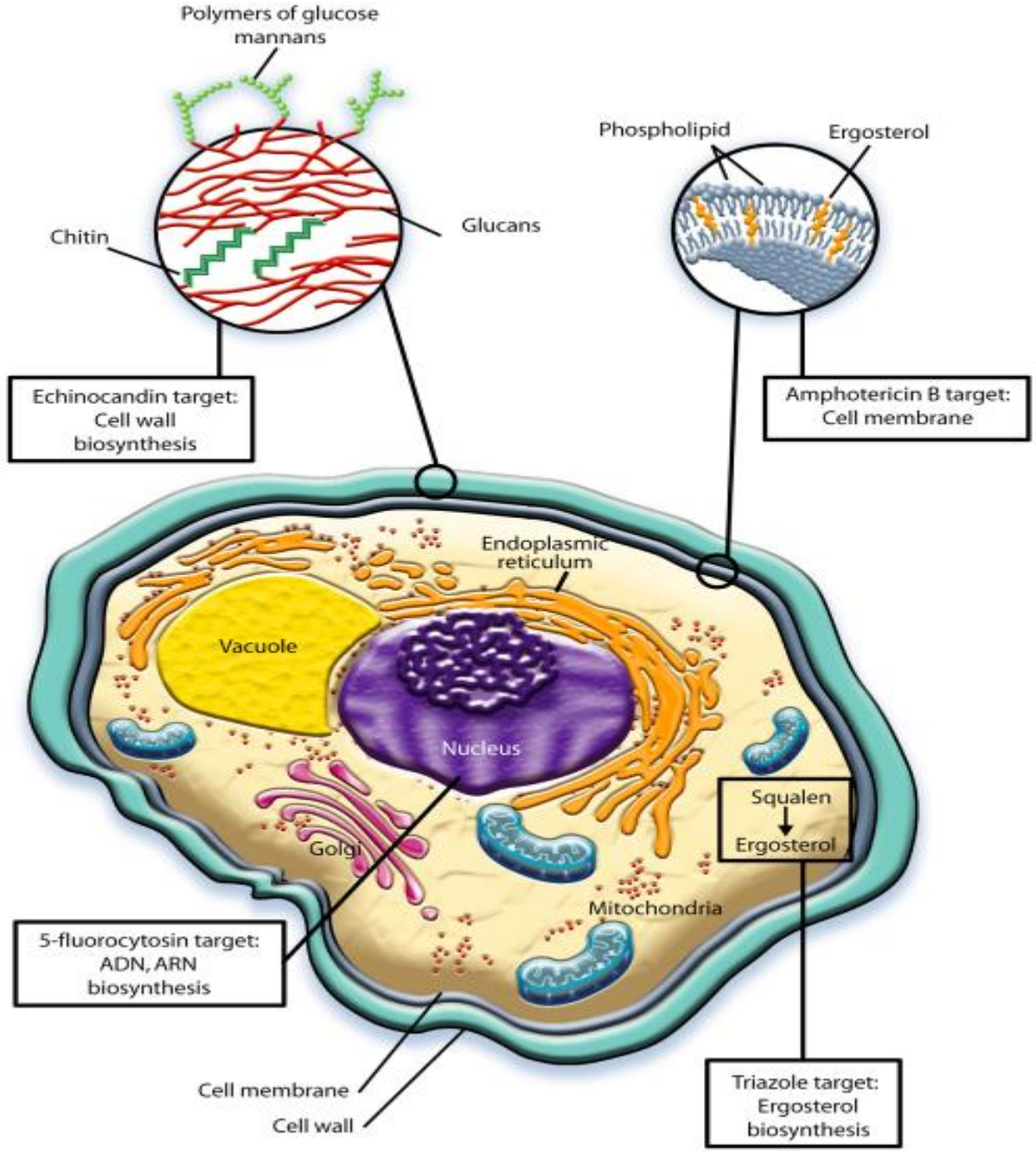
Russo A, Giuliano S, Vena A, Falcone M, Lucidi C, Merli M & Venditti M Diagn Microbiol Infect Dis, in press 2014

Univariate analysis of factors associated with death among patients with IPA.

Variable	Number (%) of patients		P	RR (95% CI)
	Survivors (n=17)	Nonsurvivors (n=7)		
Cirrhosis	1 (5.9)	6 (85.7)	>.01	1.45 (2.12-100)
Voriconazole	15 (88.2)	2 (28.6)	>.01	.17 (.04-.66)
GM index (mean ± SD)	1.9 ± .6	3.6 ± 2.8	.02	…

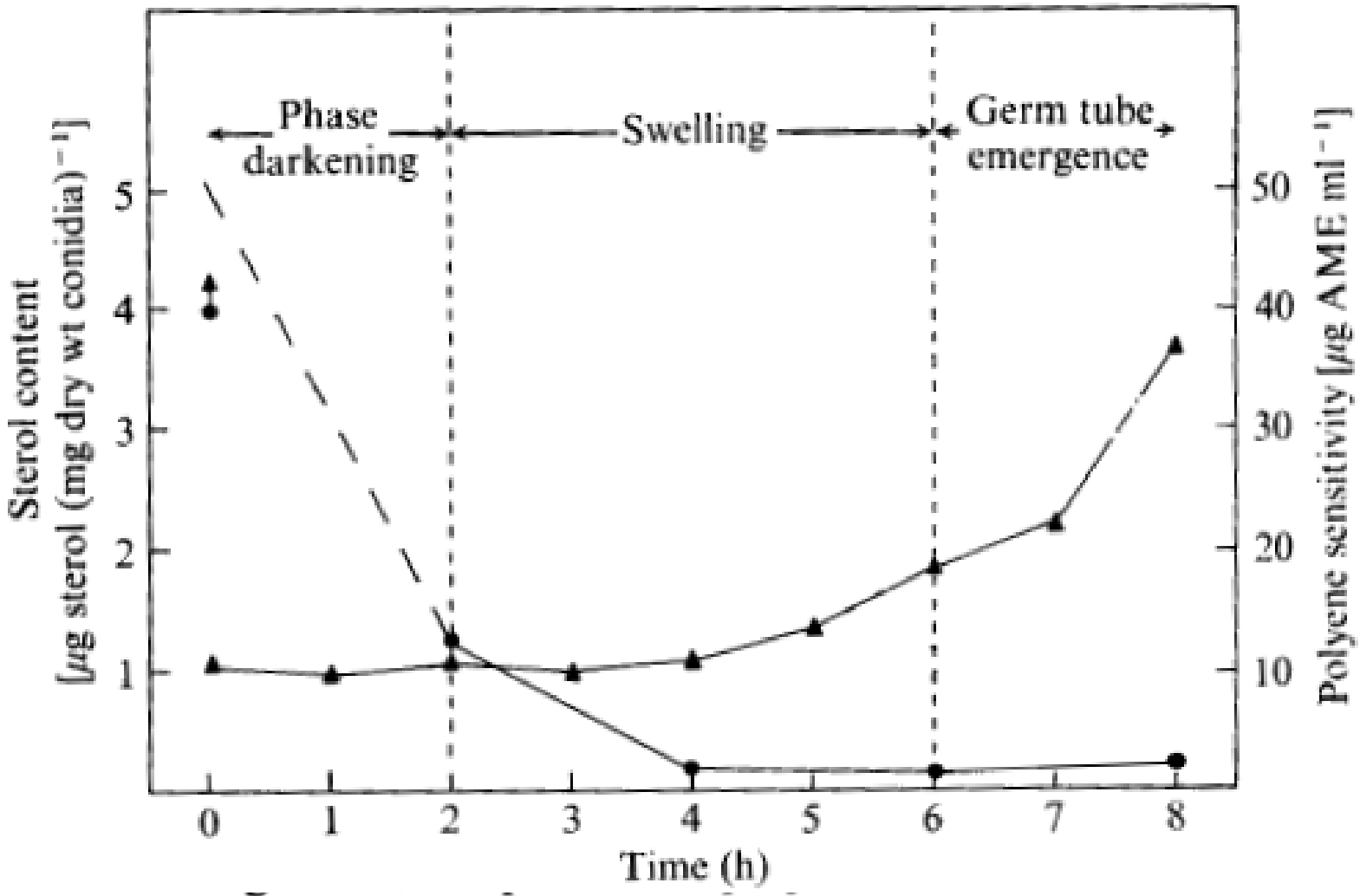
deaths
→cirrhosis vs non cirrhosis:
6% vs 87%

Mechanisms of action



Ungerminated conidia of *Aspergillus funigatus* were insensitive to amphotericin B methyl ester (AME) at concentrations > 50 ,ug/ml, but rapidly became sensitive to I to 2,ugAME/ml during the initial stages of germination. Relationship with sterol metabolism during germination of conidia…..

Russell B et al *Journal of'General Microbiology* (1977), 101, 197-206



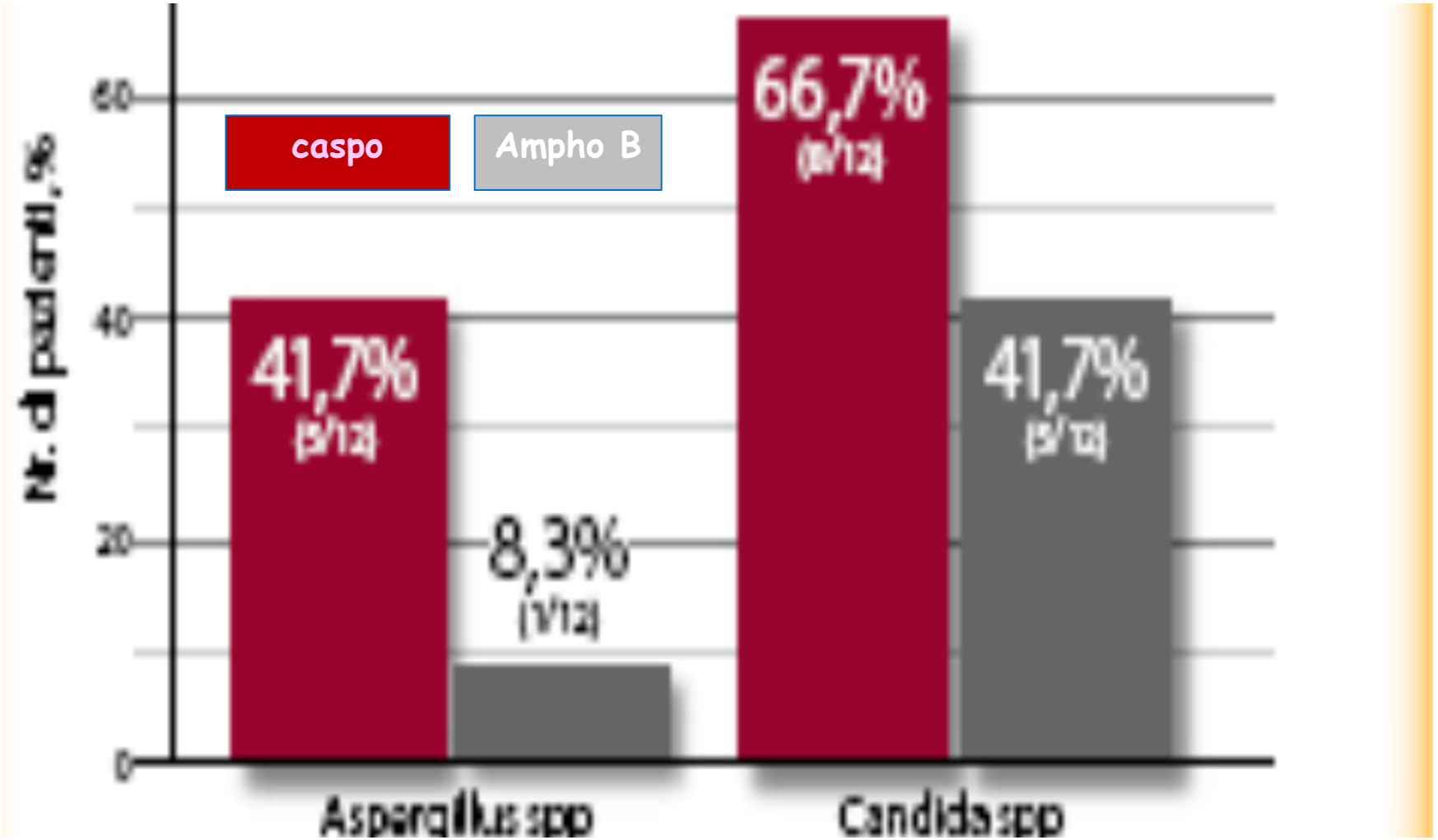
▲, Sterol content; ●, polyene sensitivity

Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

Walsh T et al *N Engl J Med* 2004;351:1391-402

Tassi di risposta nelle infezioni fungine documentate al «basale»

(cioè entro 48 h dall'inizio dell'antifungino)



conclusioni

Salvare il paziente settico richiede (a parte le terapie non strettamente antimicrobiche)….

1. **Conoscenza dei fattori di rischio ed epidemiologie locali per anticipare la possibile etiologia….**
2. **Per mettere in atto un trattamento adeguato precoce che è fondamentale per la «salvezza»…**
3. **…. Rivalutare e studiare varie forme di terapia combinata antimicrobica….**
4. **…. Molte sepsi sono superfinfezioni in corso di trattamento antimicrobico che forse oggi dobbiamo imparare a prevedere ed evitare… o riconoscere più tempestivamente (esempio candidemia in corso di *C difficile*, ……. O lo stesso *C difficile* …..)**