

Stato dell'arte della terapia delle infezioni da MRSA?

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Disclosures

- Research grants
 - Astellas, Pfizer, MSD, Gilead
- Advisor/consultant
 - Astellas, Bayer, Basilea, Cubist, Pfizer, MSD, Gilead, Angelini, Vifor, Shionogi, Novartis
- Speaker/chairman
 - Astellas, Pfizer, MSD, Gilead, Angelini, Vifor, Shionogi, Novartis, Bayer

Il «farmaco appropriato» per le infezioni da Gram-positivi

- Attività microbiologica su ceppi MS, MR, VH, streptococchi
- Dosaggio e modalità di somministrazione semplici
- Buon profilo di tollerabilità
- Battericida
- Attività su biofilm
- Ottima penetrazione tissutale (polmone, osso, cute, endocardio)
- Dati di efficacia in batteriemie, endocarditi, polmoniti, infezioni ossee, cute e tessuti molli
- Disponibile in formulazione endovenosa/orale
- Supportato dalla linee guida
- Poco costoso

Vancomicina e teicoplanina
sono i farmaci più
appropriati?

Attività microbiologica

Vancomicina e teicoplanina
funzionano su ceppi MS?

Efficacy of vancomycin in bacteraemia due to MSSA compared with β -lactams

Gonzalez C. et al.

Clin Infect Dis 1999; 29: 1171-7

Fortun J. et al.

Clin Infect Dis 2001; 33: 120-5

Chang F et al.

Medicine (Baltimore) 2003;82:333–339

Lodise TP, et al.

ArchIntern Med 2006;166:2138–214

Stryjewski ME et al.

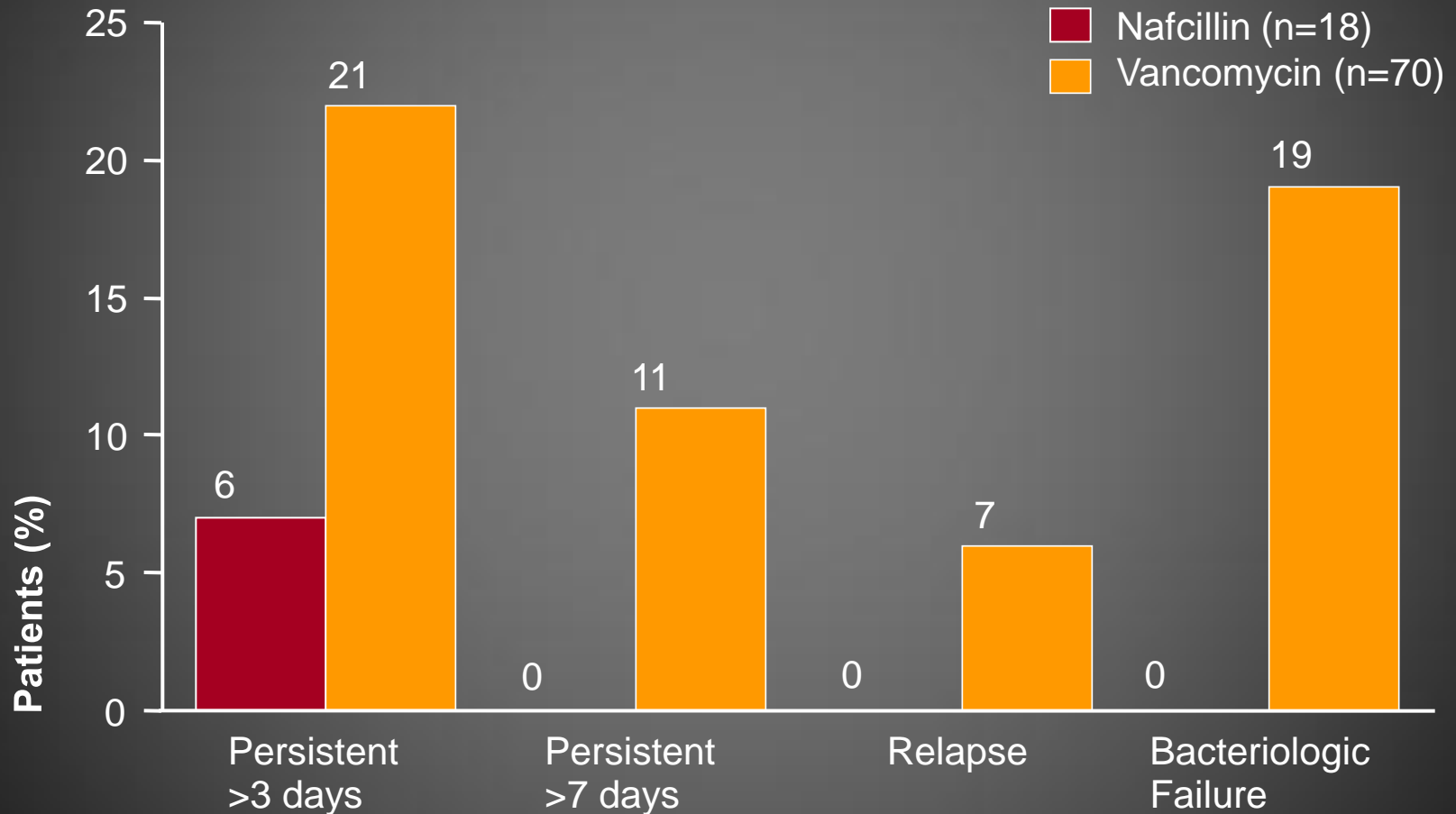
Clin Infect Dis 2007; 44: 190.

Sung-Han K, et al.

Antimicrob Agents Chemother 2008; 52: 192-7

Empiric antimicrobial therapy with vancomycin in bacteraemia due to **MSSA** was associated with poor prognosis (failure or death)

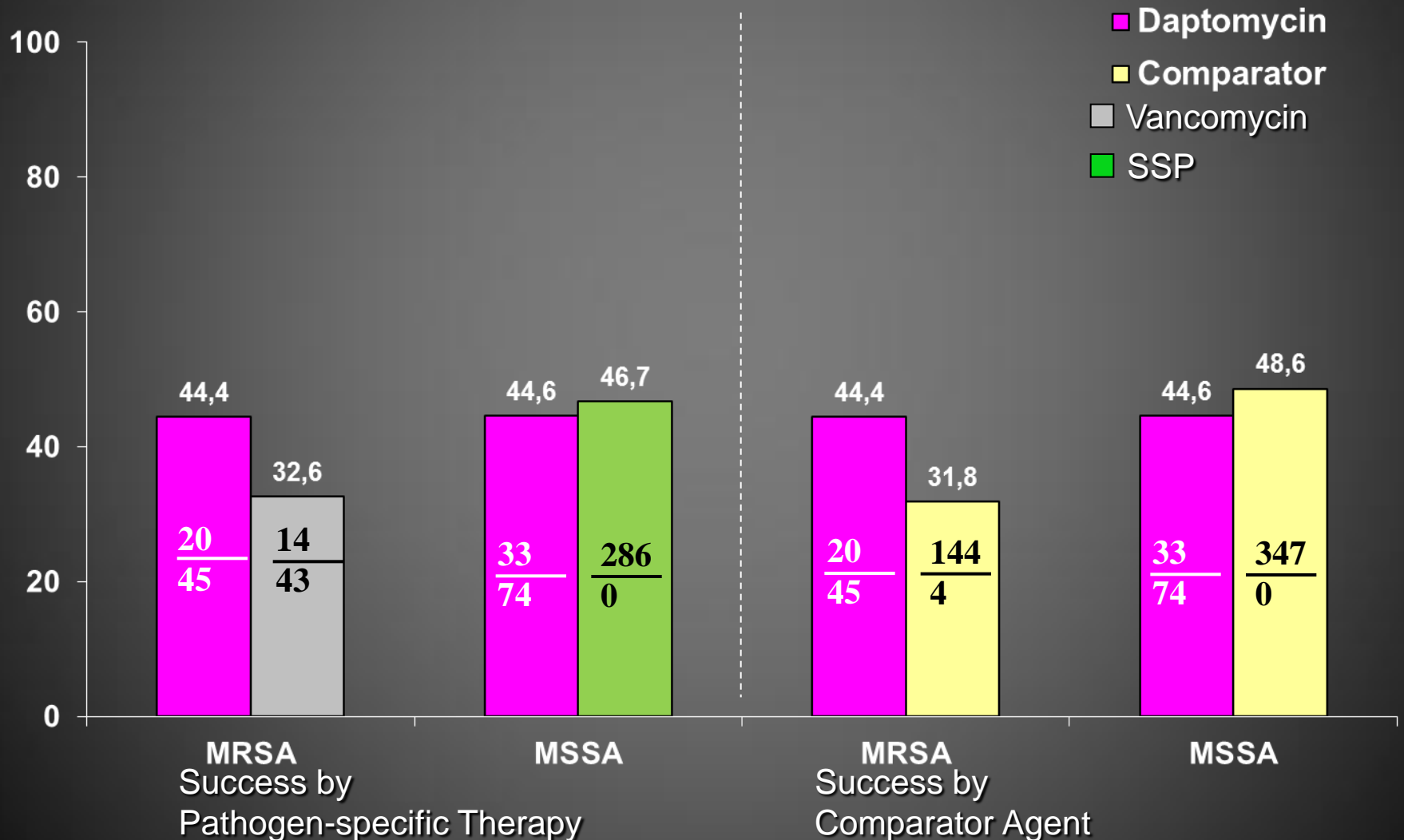
Efficacy of nafcillin versus vancomycin in preventing persistent bacteraemia and relapse in MSSA bacteraemia



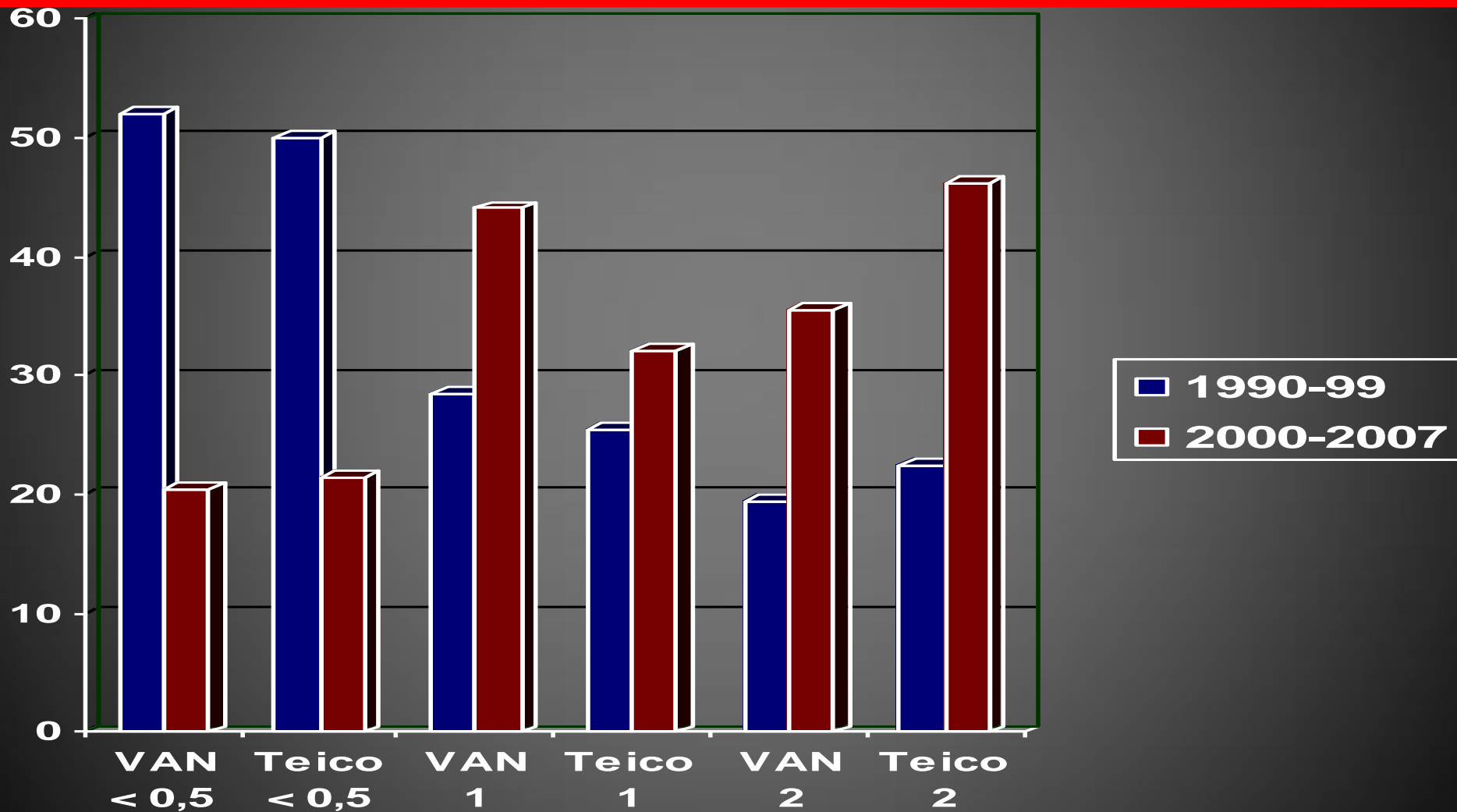
What to do?

- *“The empirical combination of vancomycin and a beta-lactam (either nafcillin, oxacillin or cefazolin) for Staphylococcal bacteremia may improve infection-related clinical outcomes”*

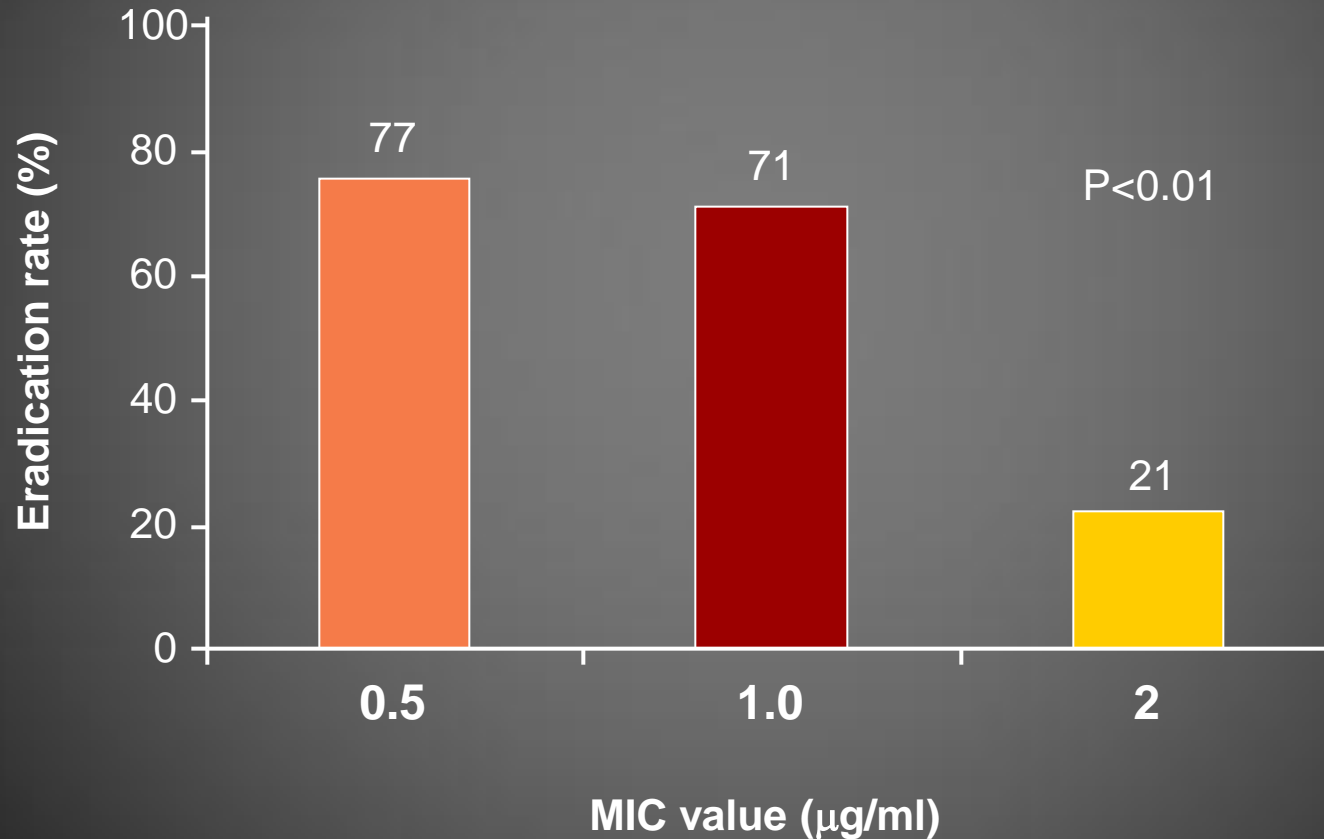
Success by Pathogen-specific Therapy vs Comparator Agent in Staph. aureus endocarditis



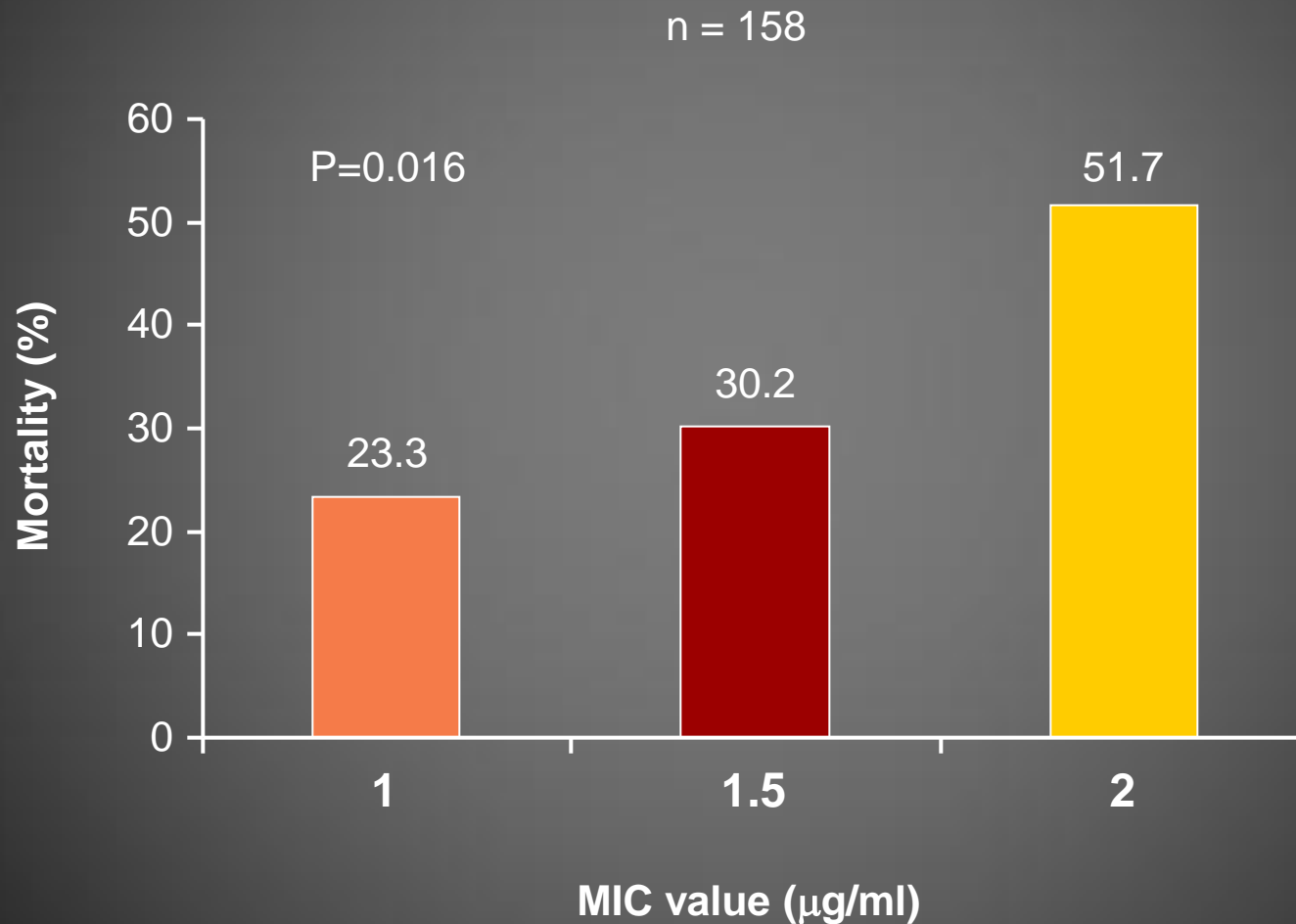
Number of MRSA strains with glycopeptide MICs of ≤ 0.5 , 1, and ≥ 2 mg/L in Italy



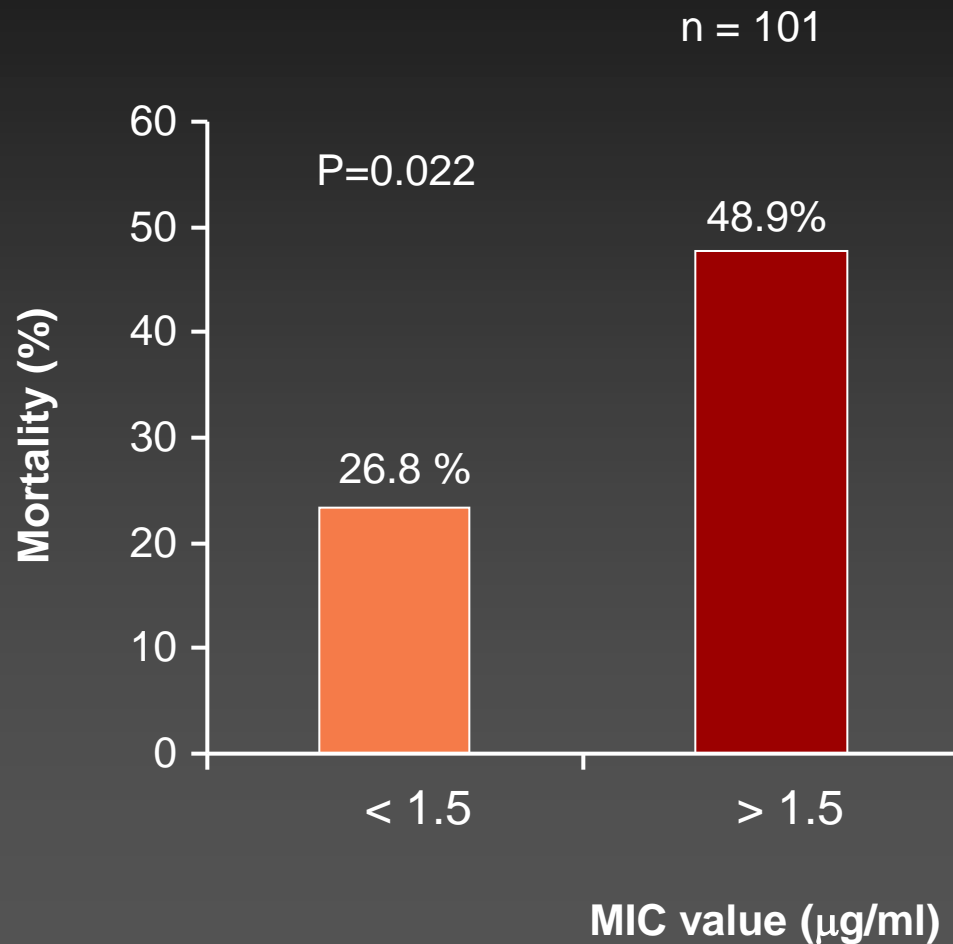
Eradication rates of MRSA related to vancomycin MIC



Vancomycin MICs and outcome in MRSA pneumonia



Teicoplanin MICs and outcome in MRSA bacteremia



Dosaggio e tollerabilità

Recommended trough serum concentrations and dosage adjustments

- To improve penetration
- To increase the probability of optimal PD target
- To improve clinical outcomes of complicated infections*

15–20 $\mu\text{g/ml}$
(>400 AUC/MIC)

2g/day in 70kg pts

MRSA MIC ≤ 1 $\mu\text{g/ml}$

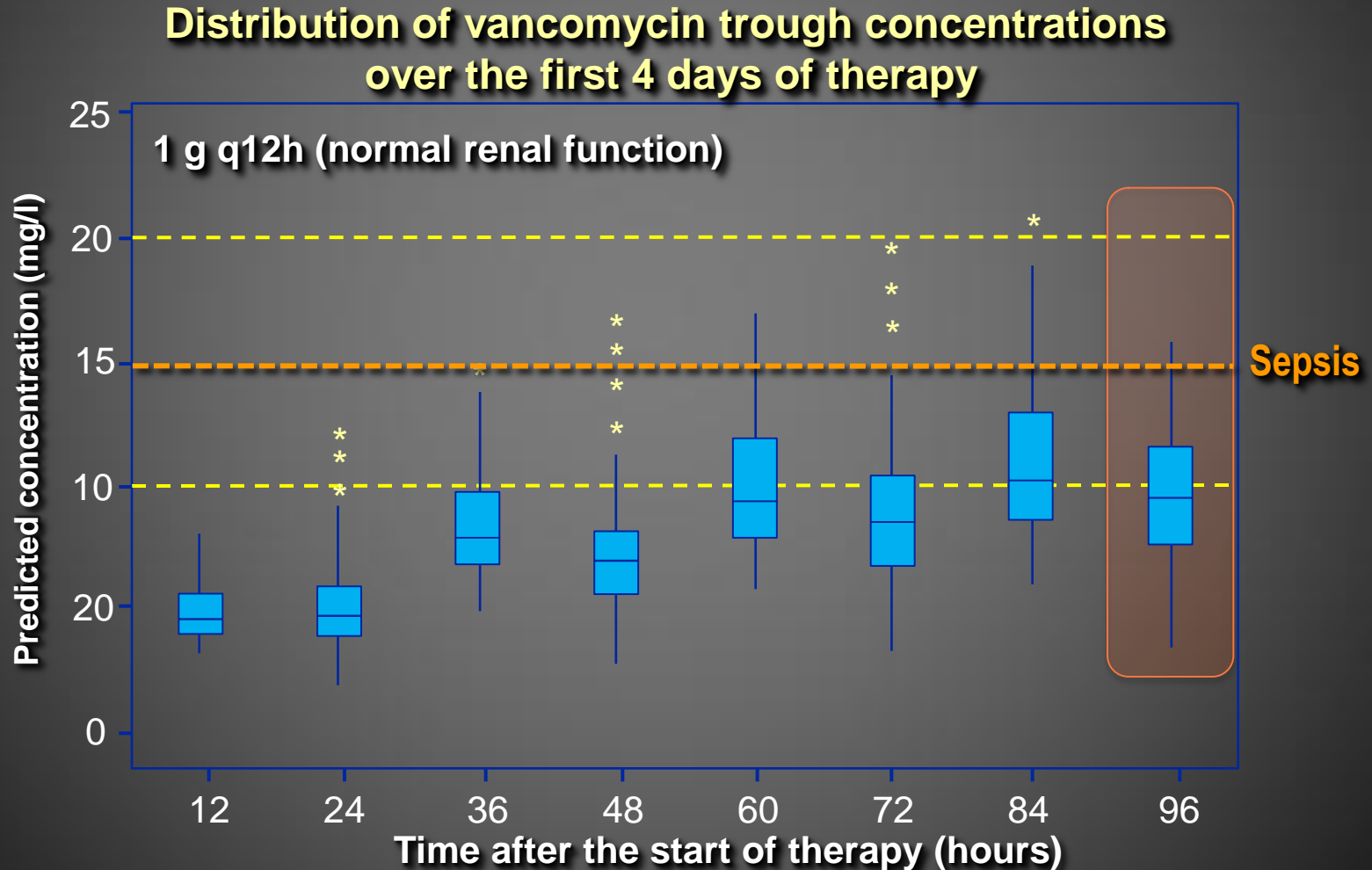
>400 AUC/MIC

MRSA MIC ≥ 2 $\mu\text{g/ml}$

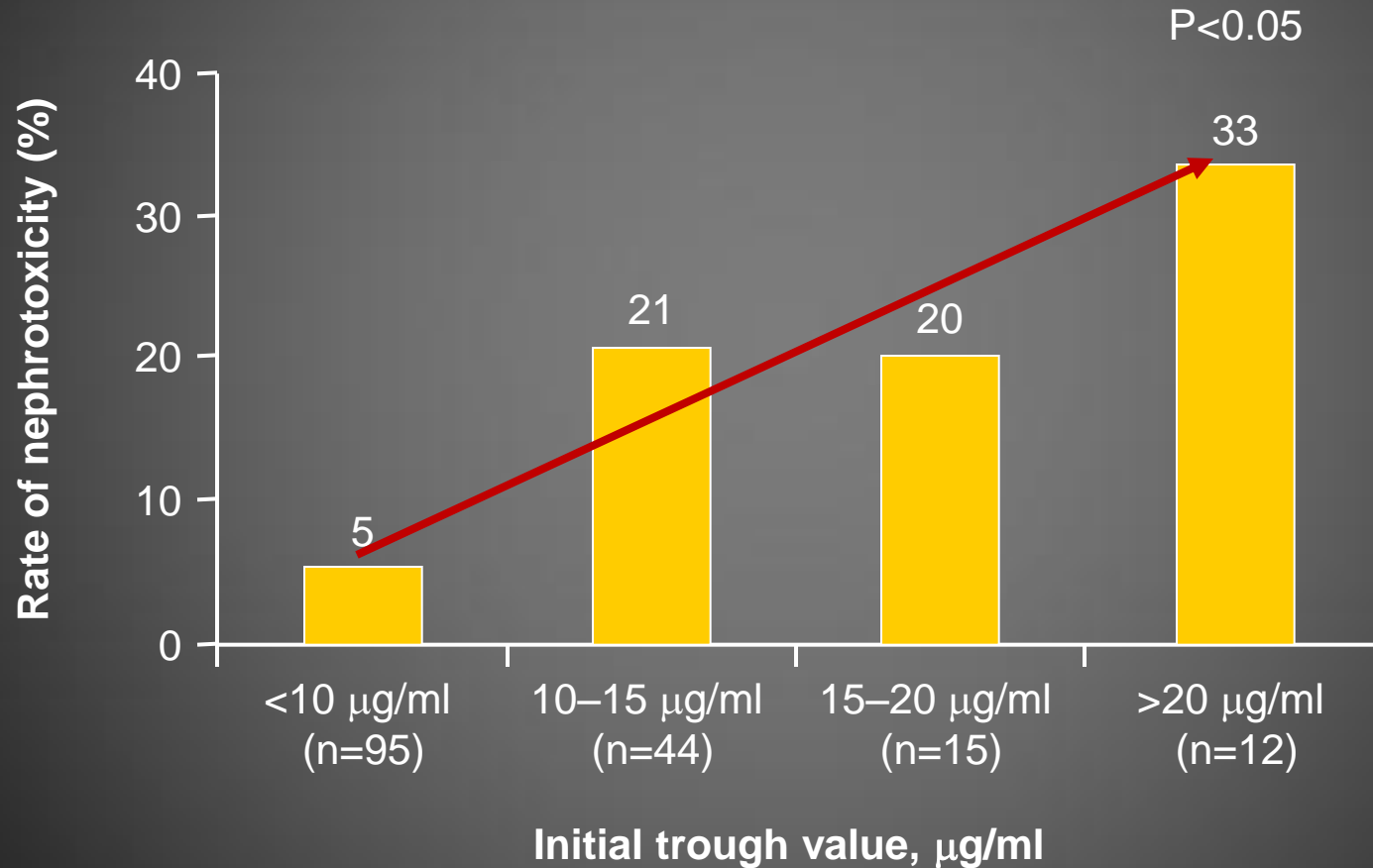
<400 AUC/MIC

*bacteraemia, endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia

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

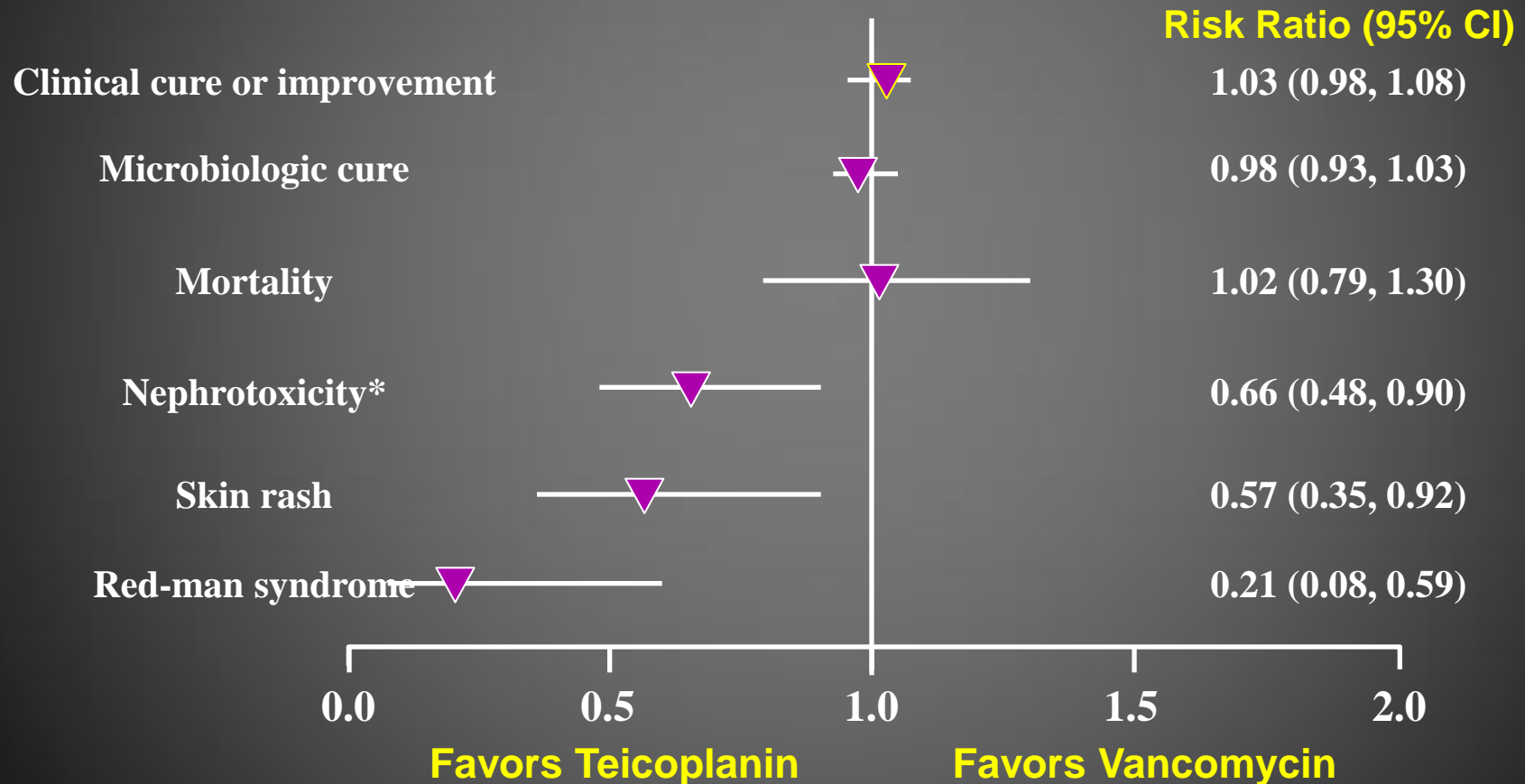


The significance of a vancomycin AUC > 400



Teicoplanin vs Vancomycin for Proven or Suspected Gram-positive Infection

Cochrane Review of 24 studies (N=2610)



* Nephrotoxicity difference was a consistent finding: Present when vancomycin monitoring was used to guide dosing; present with or without aminoglycosides

Cavalcanti AB et al. *Cochrane Database Syst Rev.* 2010;(6):CD007022.

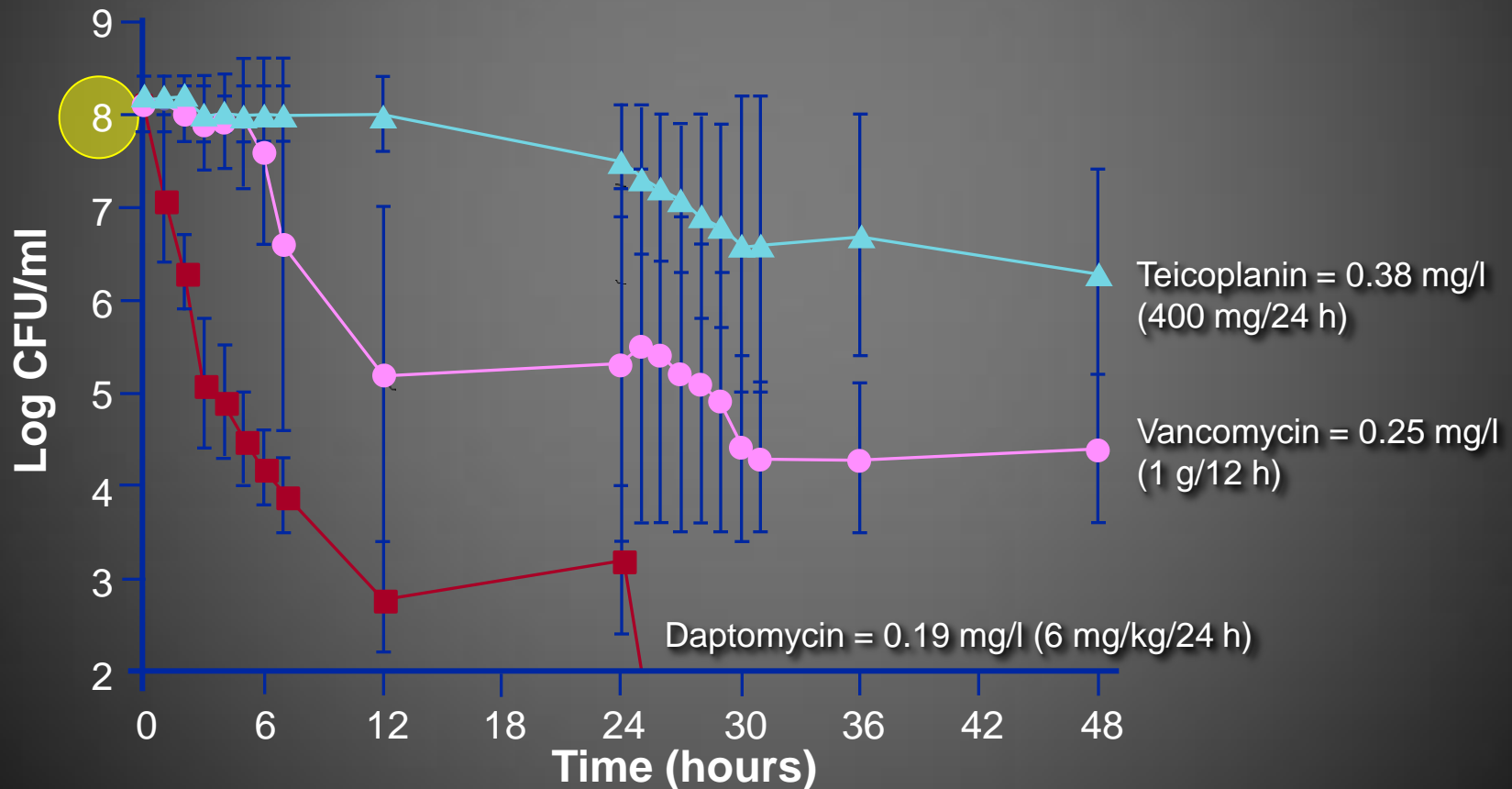
Vancomycin vs teicoplanin with equal trough concentrations

	Teicoplanin 15-20 mg/L	Vancomycin > 20 mg/L	P
Treatment success	24/28 (85.7%)	31/34 (91.2%)	NS
Nephrotoxicity	2/28 (7.1%)	4/34 (11.8%)	NS

Bacteriocidia

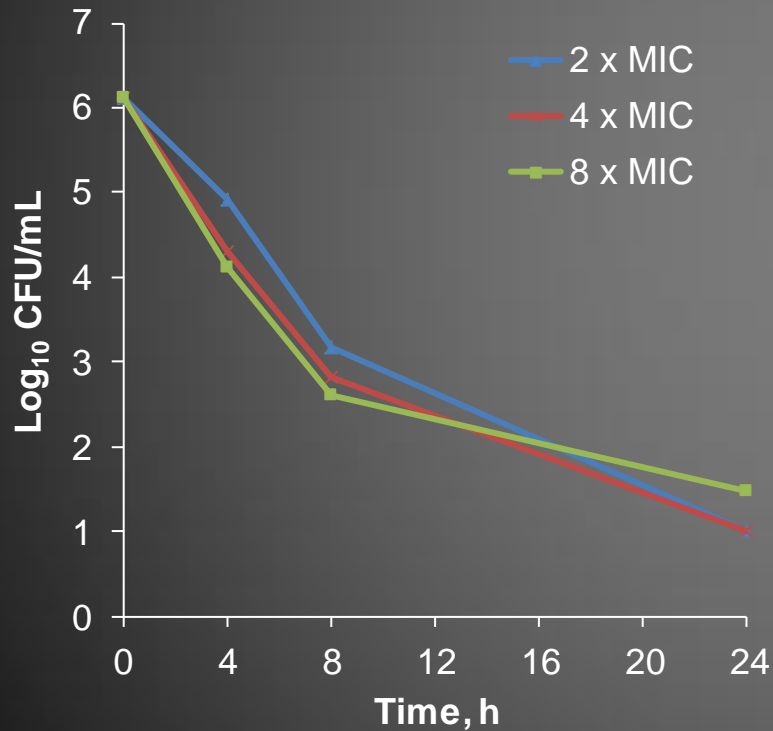
Daptomycin retains potent bactericidal activity against high-inoculum MRSA *in vitro*

Bactericidal activity: daptomycin > vancomycin > teicoplanin

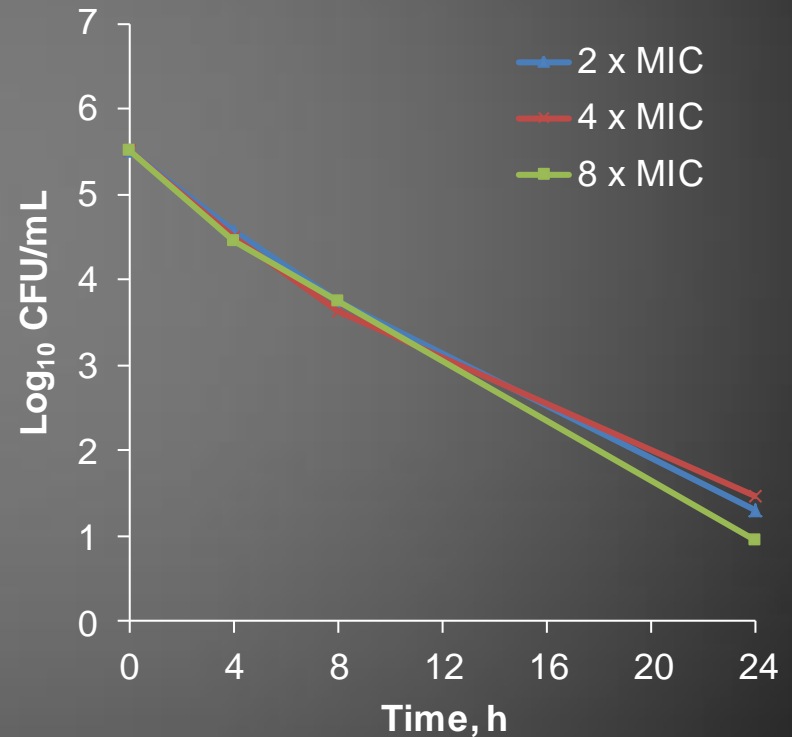


Ceftaroline fosamil is bactericidal against Gram-positive organisms *in vitro*

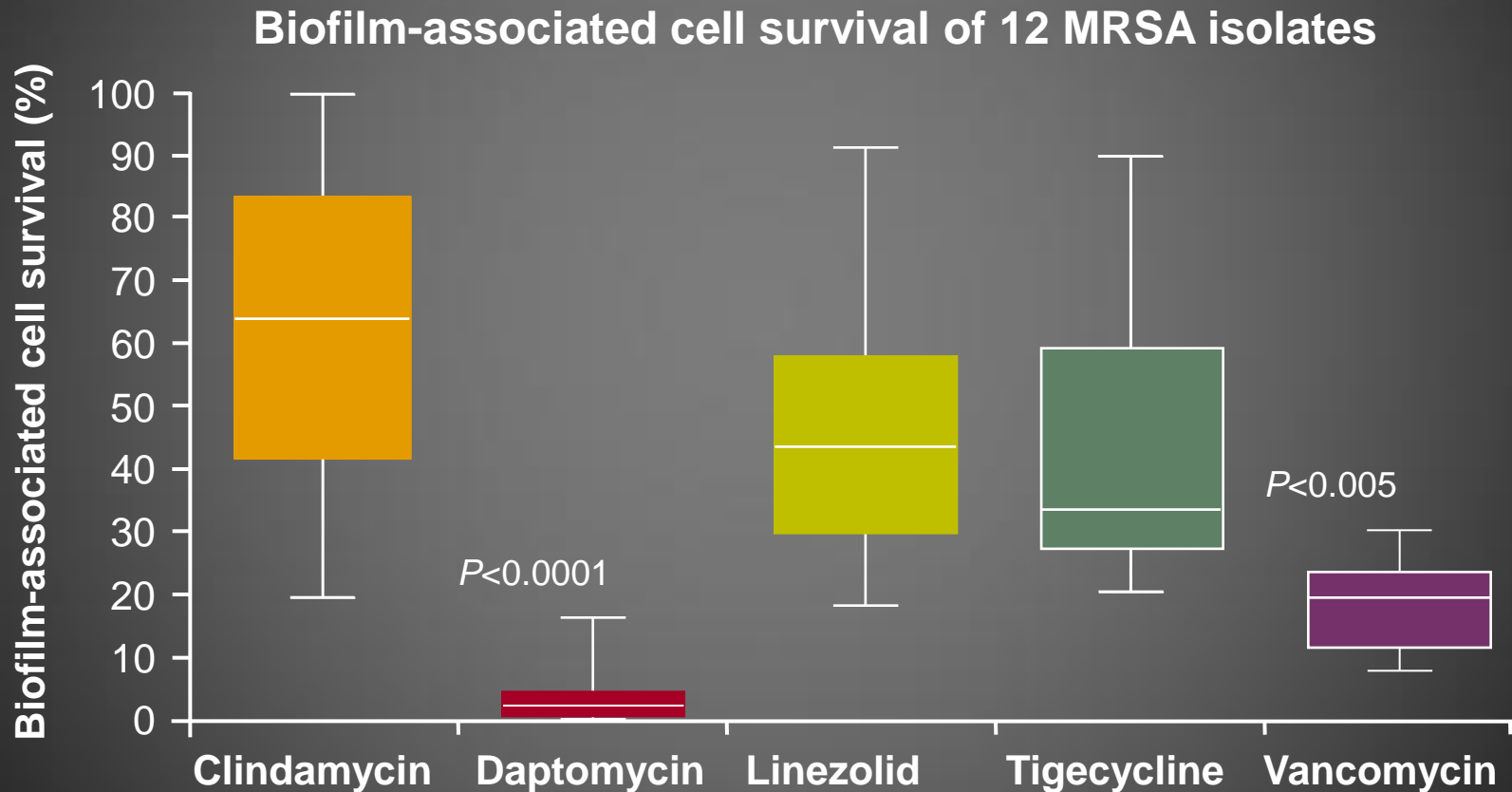
Staphylococcus aureus (MRSA)
Strain 1-170A (ceftaroline MIC 0.5 mg/L)



Streptococcus pneumoniae
Strain 90-71B (ceftaroline MIC 0.12 mg/L)



In vitro survival of methicillin-resistant *S. aureus* biofilms to antibiotics



MRSA exposed to antibiotics at concentrations of 64 $\mu\text{g}/\text{mL}$. Each box plot represents the spread of cell survival across the different clinical isolates; error bars are the standard deviation

Penetrazione tissutale

Tissue penetration (% tissue/serum)

Tissue	Vancomycin	Teicoplanin	Linezolid
Bone	7–13%	50–60%	60%
CNS	0–18%	10%	70%
ELF	11–17%	30%	450%
Muscle	30%	40%	94%
Perit. dial fluid	20%	40%	61%

Antibiotics for MRSA cSSTIs have different tissue penetration

	Molecular weight	Ratio of skin and soft tissue: plasma penetration
Linezolid	337.35 ¹	104% ^{9,a}
Vancomycin	1485.74 ²	10-30% ^{10,b}
Teicoplanin	1879.7 ³	24-77% ^{11,12,a}
Daptomycin	1620.67 ⁴	68% ^{13,a}
Clindamycin	424.98 ⁵	24-82% ¹⁴
Tigecycline	585.65 ⁶	380% ^{15,c}
Ceftaroline	762.75 ⁷	Not available
Fusidic acid	516.71 ⁸	49% ^{16,d}

^aHealthy volunteers/patients; ^bDiabetic vs non-diabetic post-cardiac surgery patients;

^ccSSTI patients requiring surgical intervention, 1 hr post infusion (peak);

^dHealthy volunteers, after 5.5 days repeated oral administration (1g/d)

1. ZYVOX® [package insert]. New York, NY: Pfizer Inc., 2012;

2. Vancomycin Hydrochloride [package insert]. Lake Forest, IL: Hospira, Inc., 2010;

3. Teicoplanin Complex [product data sheet]. Bioaustralis.com;

4. Cubicin [package insert]. Lexington, MA:

Cubist Pharmaceuticals, Inc., 2010;

5. <http://www.drugbank.ca/drugs/DB01190>;

6. <http://www.drugbank.ca/drugs/DB00580>;

7. Saravolatz et al. Clin Infect Dis

2011;52:1156-63;

8. <http://www.chemnet.com/cas/en/6990-06-3/fusidic-acid.html>;

9. Gee et al. Antimicrob Agents Chemother 2001;45:1843-6;

10. Skhirtladze et al. Antimicrob Agents Chemother 2006;50:1372-5;

11. Wise et al. J Hosp Infect 1986;7 Suppl A:47-55;

12. de Lalla et al. Antimicrob Agents Chemother 1993;37:2693-8;

13. Wise et al. Antimicrob Agents Chemother 2002;46:31-3;

14. Stoehr et al. Clin Pharm 1988;7:820-4;

15. Stein et al. Surg Infect (Larchmt) 2011;12:465-7;

16. Vaillant et al. Ann Dermatol Venereol 2000;127:33-9

Ceftaroline penetration

- CSF penetration: 14% +/- 5%
- Lung penetration: 42.0 +/- 11.2%

TABLE 1. Bacterial titers in vegetations after 4 days of treatment

Regimen	Mean \pm SD log ₁₀ CFU/g of vegetation (no. of sterile vegetations ^a /total no. of vegetations) (%)	
	MRSA	hGISA
Control	8.9 \pm 0.5 (0/6) (0)	9.4 \pm 0.3 (0/6) (0)
Ceftaroline (10 mg/kg q12h) ^e	2.5 \pm 0.3 (9/10) (90) ^{b,c}	3.0 \pm 0.9 (6/10) (60) ^{b,d}
Linezolid (10 mg/kg q12h) ^e	7.1 \pm 0.6 (0/7) (0) ^b	6.9 \pm 0.4 (0/8) (0) ^b
Vancomycin	2.7 \pm 0.8 (4/6) (67) ^{b,c}	6.7 \pm 0.4 (0/5) (0) ^b

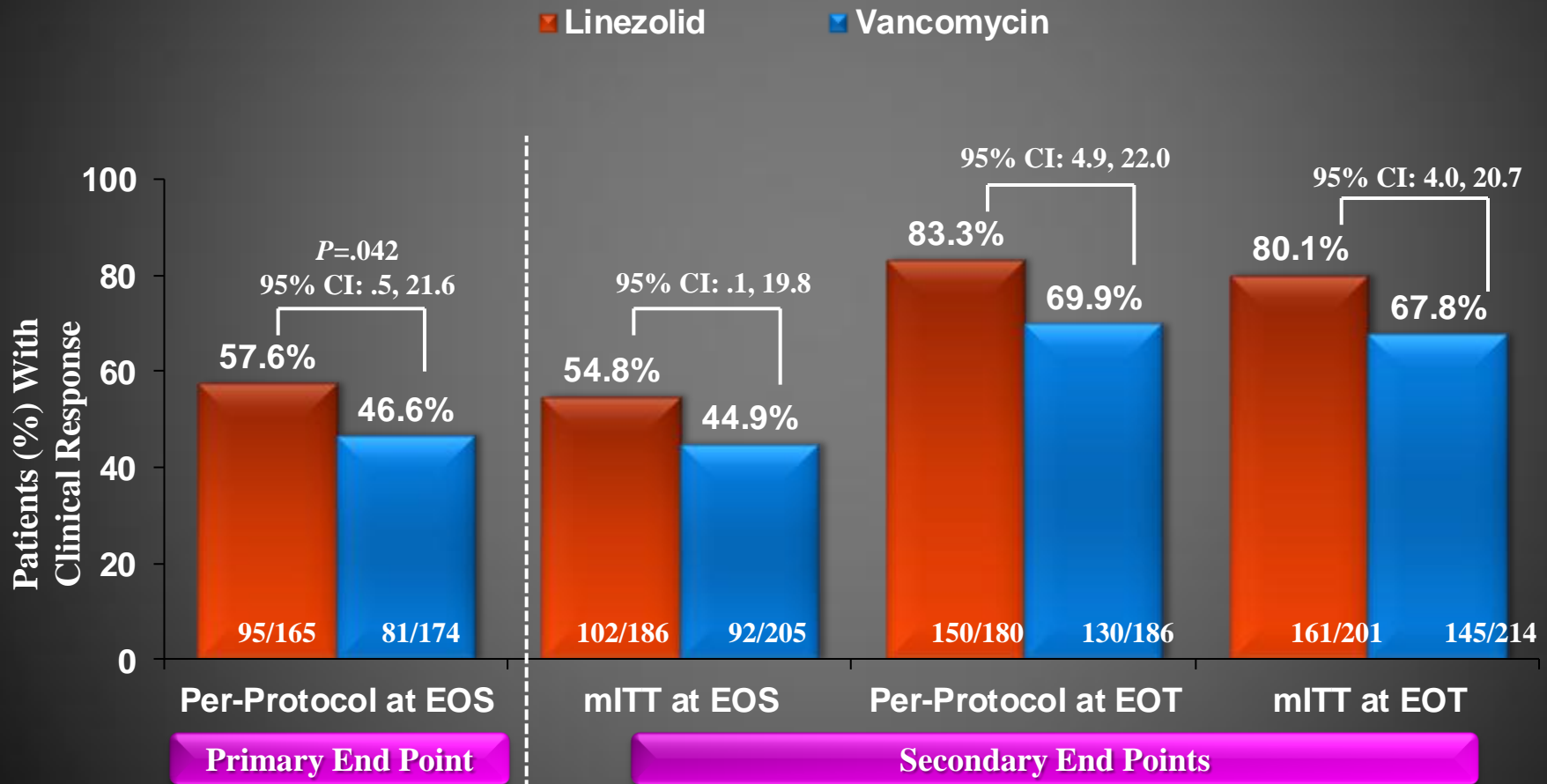
Cottanoud et al. 50th ICAAC Boston 2010- Abstract B702

Jacqueline C et al. 46th ICAAC San Francisco 2006 Abstract A-1938

Garrison et al. Expt Rev Anti Infect Ther 2012

Dati di efficacia

ZEPHyR Clinical Response at EOS and EOT (Per-Protocol and mITT Populations)



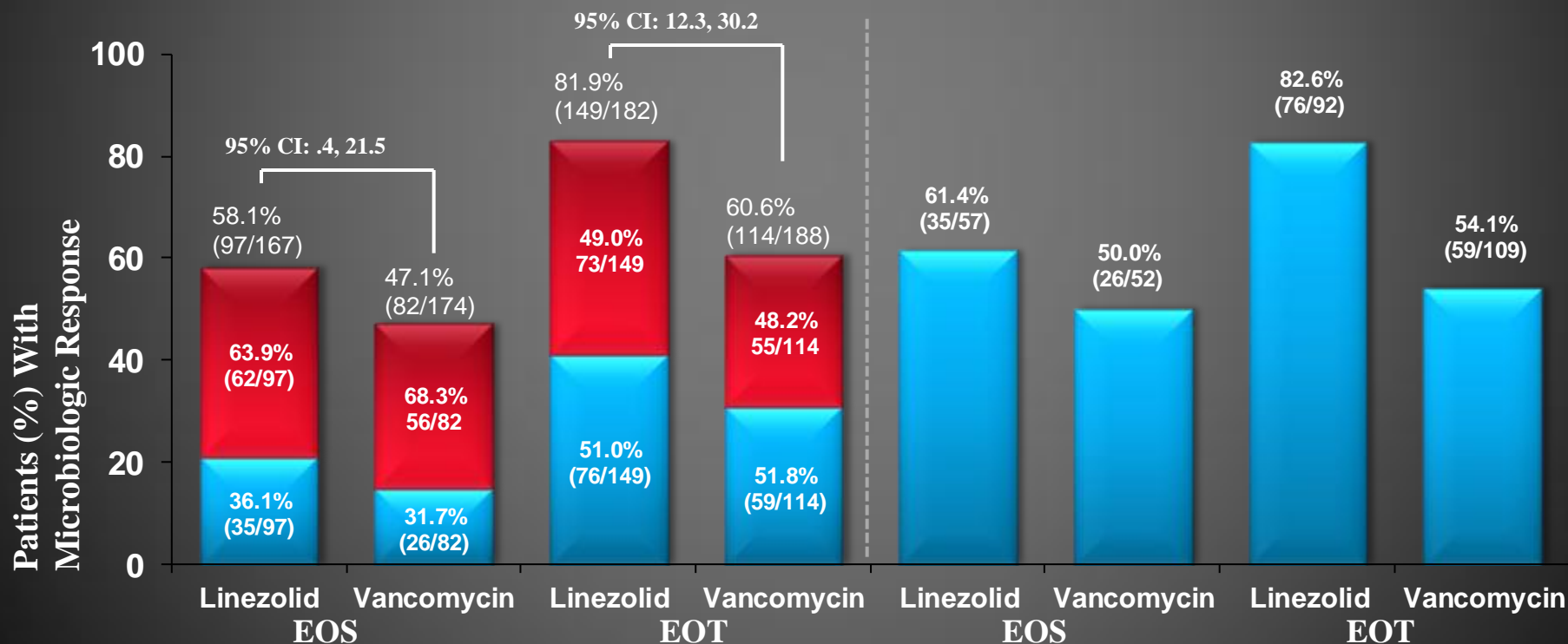
ZEPHyR Secondary End Point: Microbiologic Response Rates at EOS and EOT

Per-Protocol Population

Patients With Respiratory Secretions for Culture

■ Documented eradication*

■ Presumed eradication†

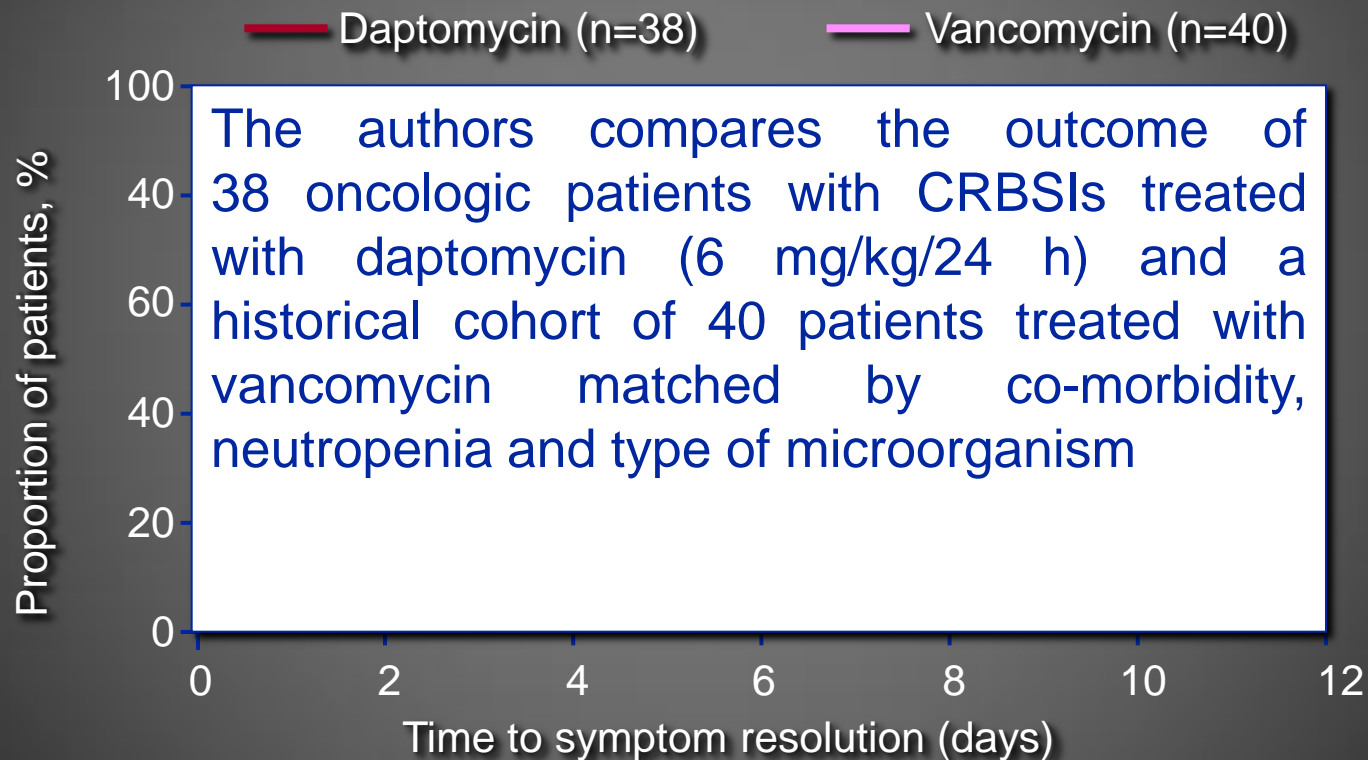


* No microbiologic data, but confirmed clinical cure.

† Microbiologic data available, confirmed microbiologic eradication.

Reduced time to symptom resolution with daptomycin versus vancomycin in CRBSIs in cancer patients

Time to symptom resolution in cancer patients with Gram-positive CRBSIs



CRBSI, catheter-related bloodstream infection

Chaftari A *et al. Int J Antimicrob Agents* 2010;36:182–186

Linee guida

IDSA Guidelines 2011: What is the management of MRSA bacteraemia and infective endocarditis?

- For adults with uncomplicated (at least 2 weeks) and complicated bacteraemia (4–6 weeks):
 - Vancomycin (A-II) or
 - Daptomycin 6 mg/kg/dose IV once daily (A-I)
Some experts recommend higher dosages of daptomycin at 8–10mg/kg/dose IV once daily (B-III)

IDSA Guidelines 2011:

What is the management of empirical MRSA treatment for hospitalised patients with cSSTI?

Options include the following:

- IV vancomycin (A-I)
- PO or IV linezolid 600 mg twice daily (A-I)
- Daptomycin 4 mg/kg/dose IV once daily (A-I)
- Telavancin 10 mg/kg/dose IV once daily (A-I)
- Clindamycin 600 mg IV or PO 3 times a day (A-III)

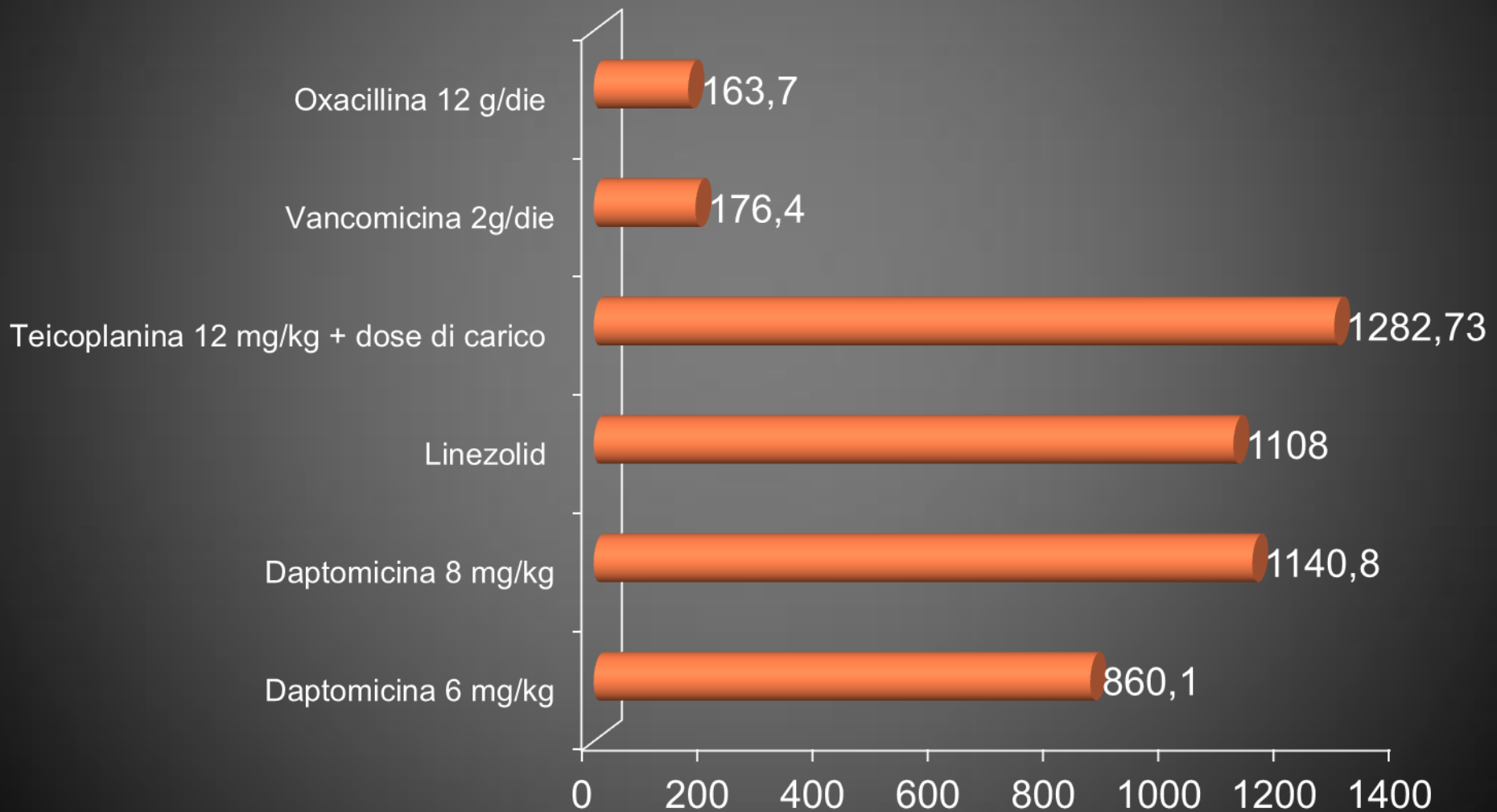
Quale dosaggio?

Dosaggi nelle Sepsis

	Anni '80 (mg)	Anni '90 (mg)	Oggi	Domani
Vancomicina	1000 x 2	500 x 4	Dose di carico poi 30 mg/Kg Infusione continua	?
Teicoplanina	200 – 400	600 – 800	10-12 mg/Kg + dose di carico	?
Daptomicina			8 mg/Kg	10 mg/kg

Costo

Costo di 10 giorni di terapia per un uomo di 70 kg



Costi ex factory marzo 2012

Empirical and targeted therapy for *MRSA* infections

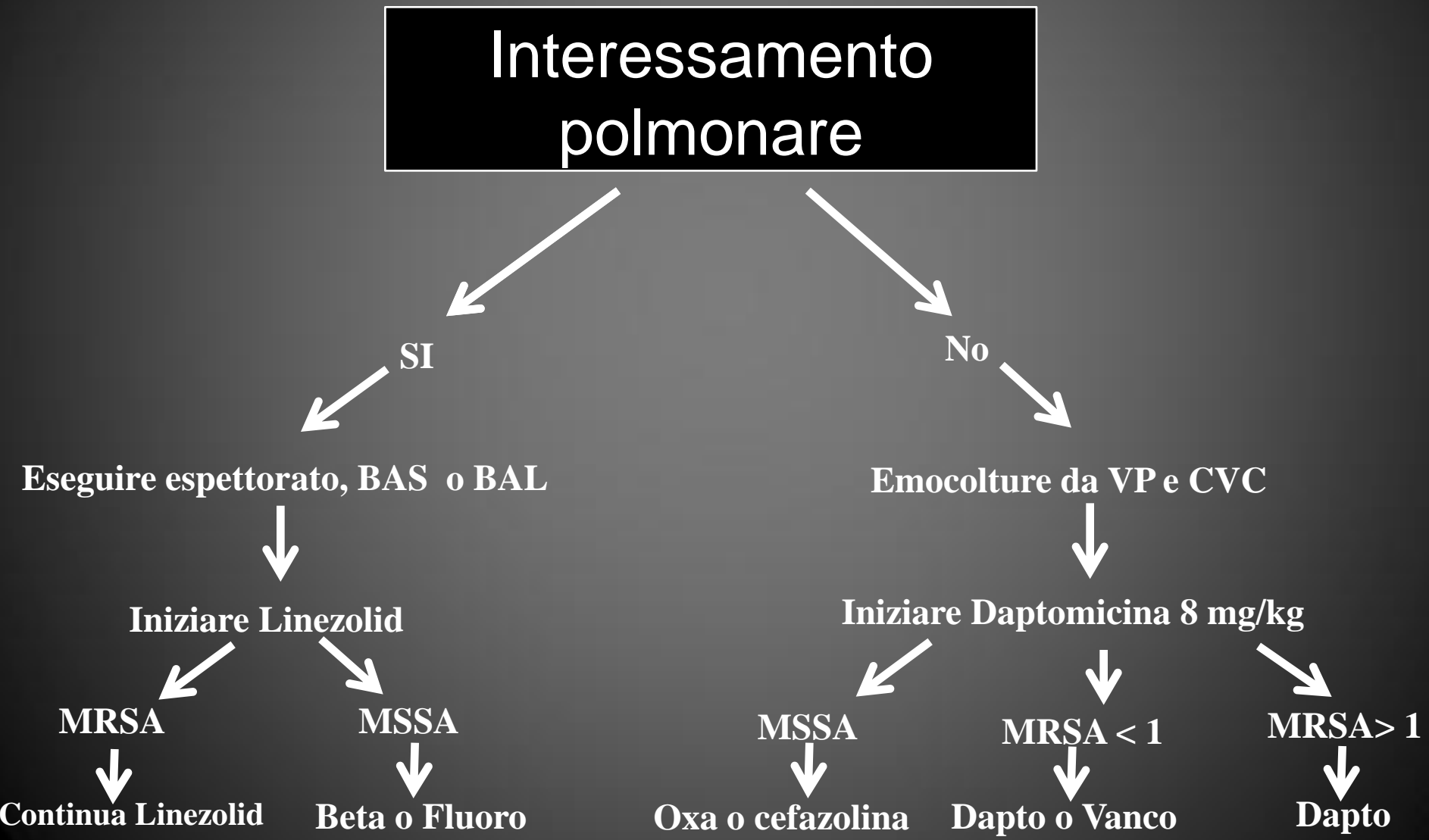
Antibiotic	cSSTI	Pneumonia	CR- BSI	Primary BSI
Vancomycin/ Teicoplanin	++	++	++	++
Daptomycin	+++	-	+++	+++
Linezolid	+++	+++	+	+
Tigecycline	+++	+	+	+
Ceftaroline	+++	++	++	++

CR- BSI: catheter-related bloodstream infections; BSI: bloodstream infections

-: Do not use; + use only as alternative; ++: good drug in this indication; +++: very good drug in this indication

Bassetti M et al. *Minerva Anestesiol* 2011; **77**:821-7 mod.

Terapia ragionata delle infezioni stafilococciche



Therapy of empiric MRSA infections

Suspect MRSA infection



Bacteremia
Sepsis
Endocarditis

Pneumonia
CNS infections

cSSSI



Vancomycin
DAPTOMYCIN
Ceftaroline

LINEZOLID
Ceftaroline

Vancomycin
DAPTOMYCIN
LINEZOLID
CEFTAROLINE

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