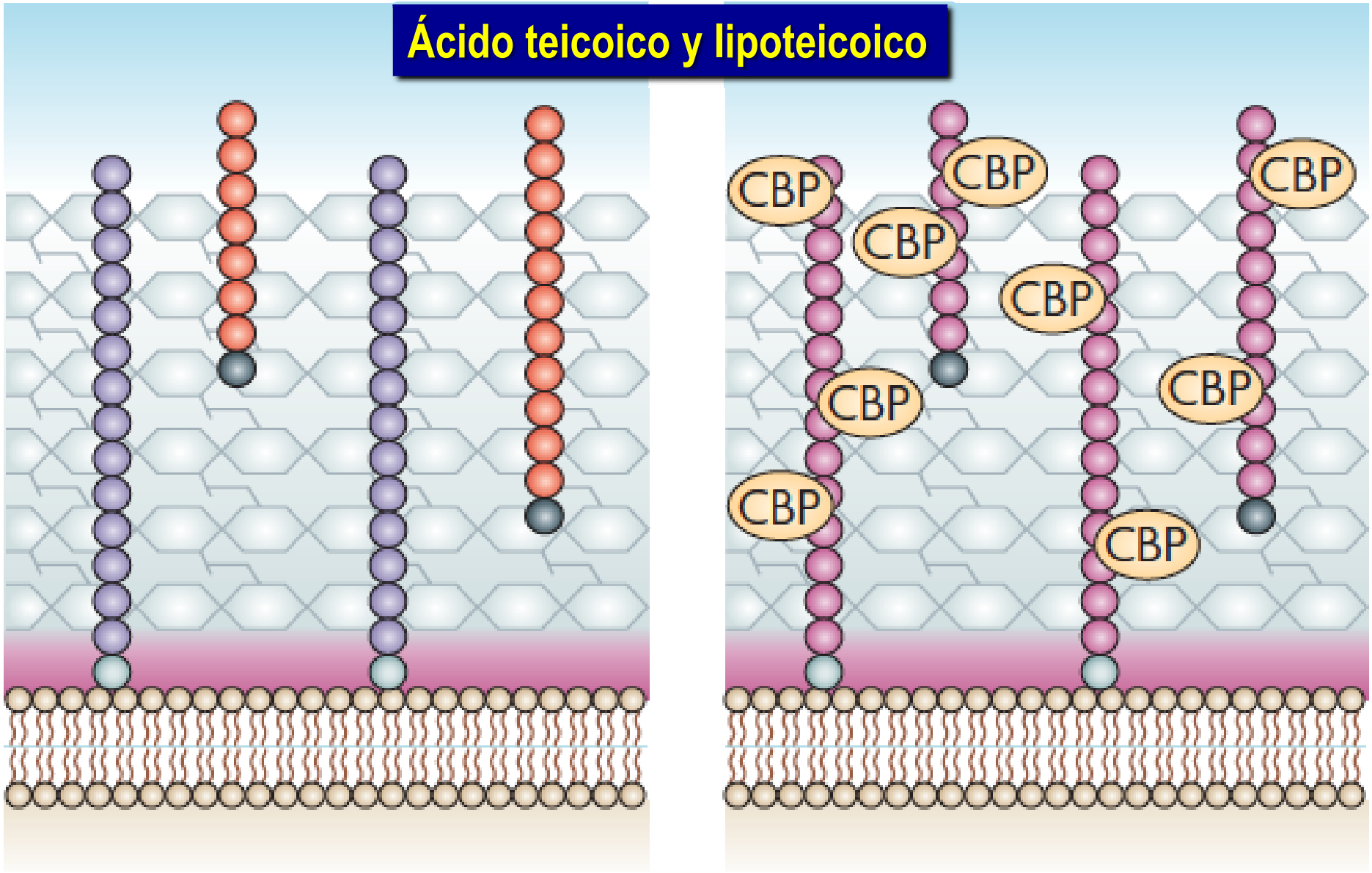
Papel de la respuesta inflamatoria desencadenada durante el tratamiento de la neumonía (infección)

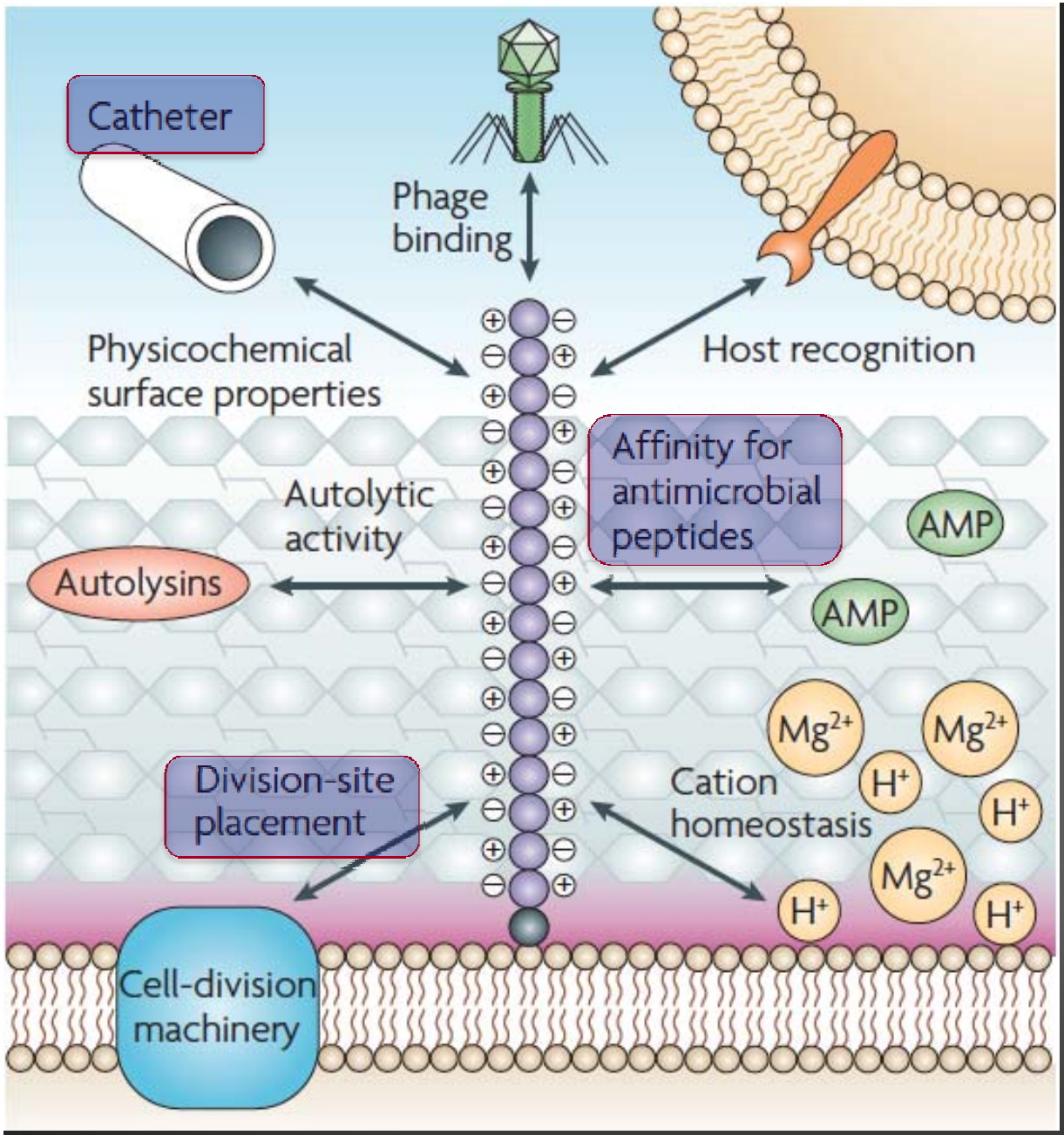
Alex Soriano
Hospital Clínic de Barcelona

Staphylococcus aureus

Streptococcus pneumoniae



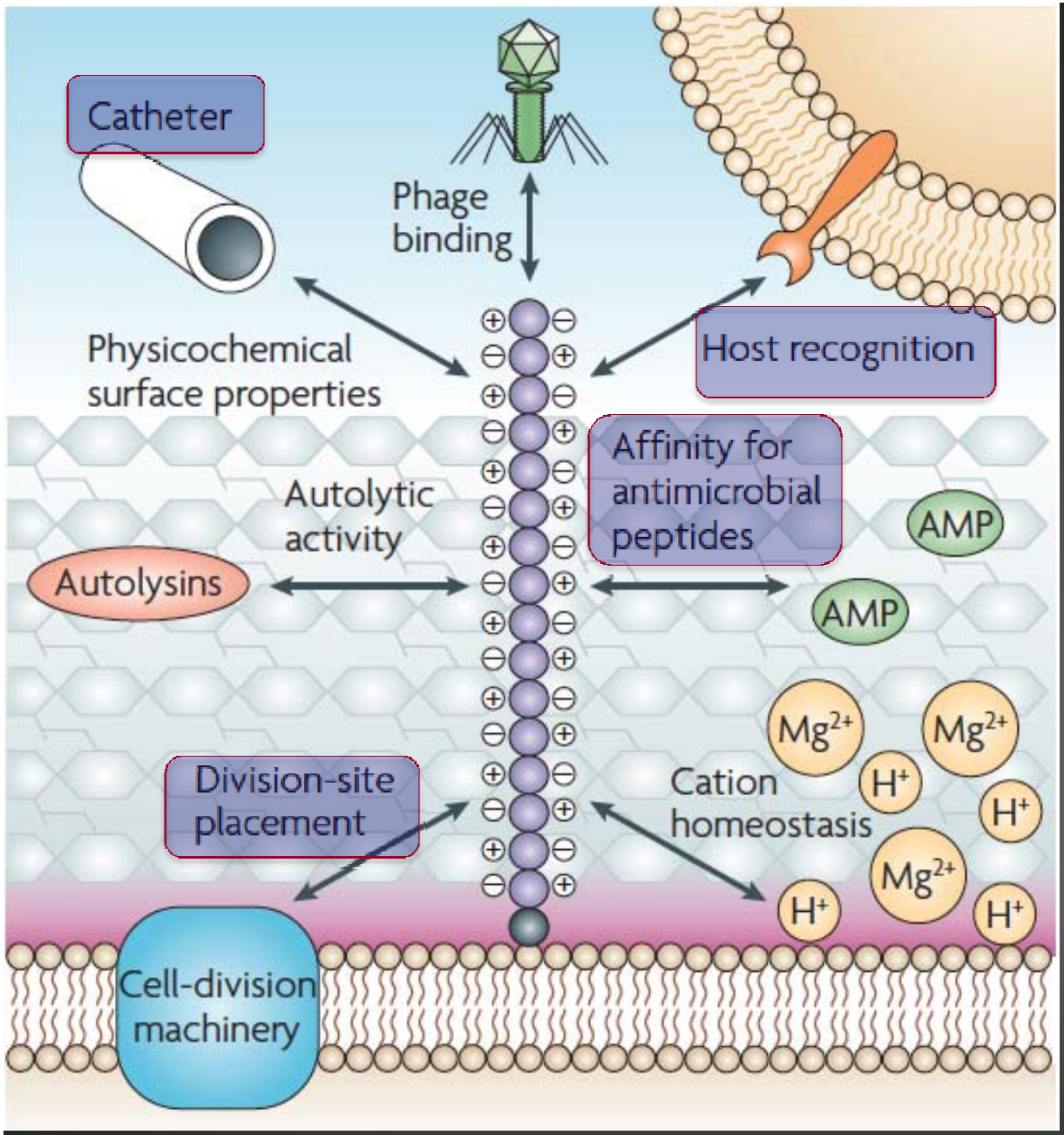
Weidenmaier Ch & Peschel A. **Nat Rev Microbiol 2008**



Funciones de GPB:

- Adherencia a biomateriales
- Fija la autolisinas en el septo de división.
- Determinan la afinidad por péptidos catiónicos.

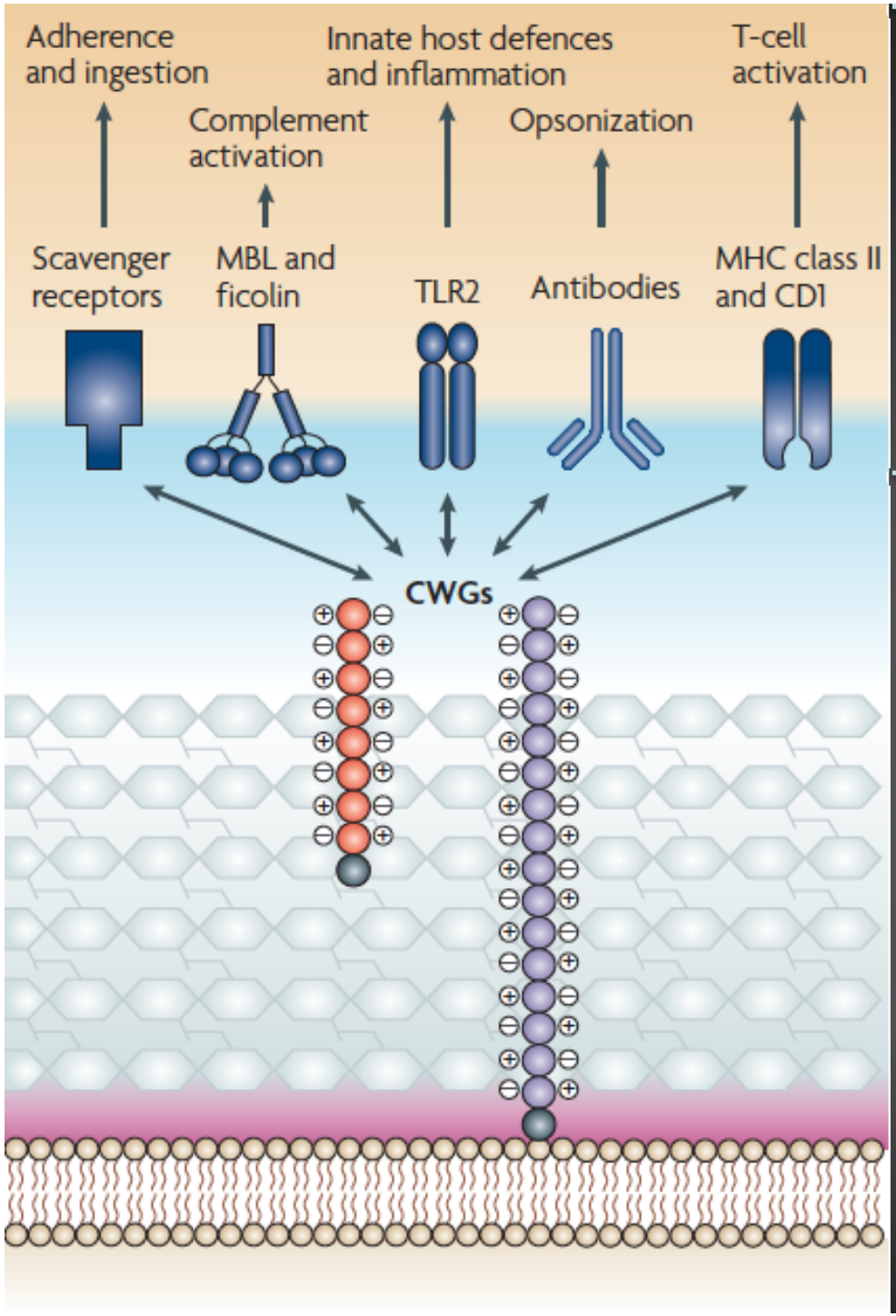
Weidenmaier Ch & Peschel A. **Nat Rev Microbiol 2008**



Funciones de GPB:

- Adherencia a biomateriales
- Fija la autolisinas en el septo de división.
- Determinan la afinidad por péptidos catiónicos.
- Activación de la respuesta inmune.

Weidenmaier Ch & Peschel A. **Nat Rev Microbiol 2008**



Activación del sistema inmunitario

- Glucopolímeros de la PB
- Peptidoglucano
- ADN bacteriano
- Proteínas bacterianas:
  - -Exotoxinas (TSST, enterotoxina, LPV)
  - -Hemolisinas: pneumolisina

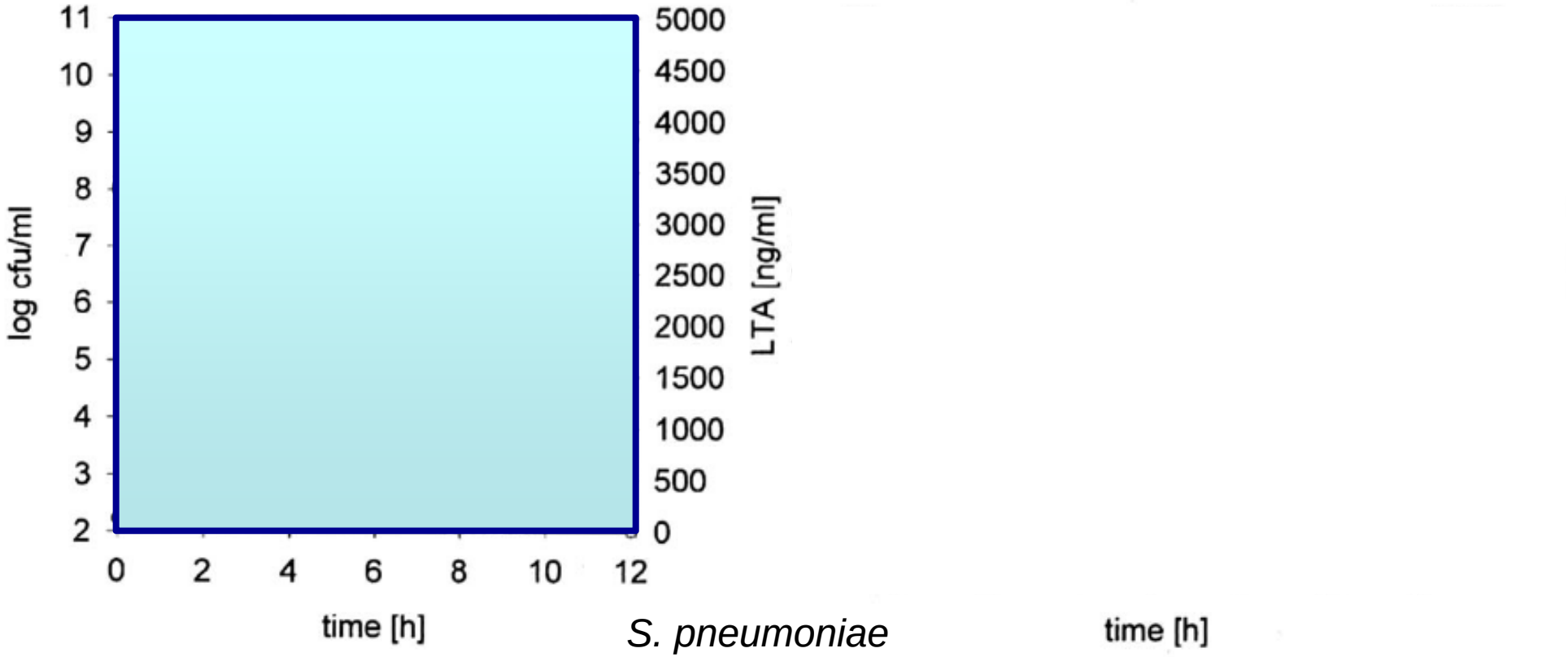
Rose W, et al. Elevated Serum Interleukin-10 at Time of Hospital Admission Is Predictive of Mortality in Patients With Staphylococcus aureus Bacteremia.
J Infect Dis 2012: 206: 1604-11

Análisis multivariado

Variable	OR	95% CI	*P* value
Bacteremia duration, per day	1.16	1.01–1.32	.031
Age, per year	1.16	1.02–1.31	.022

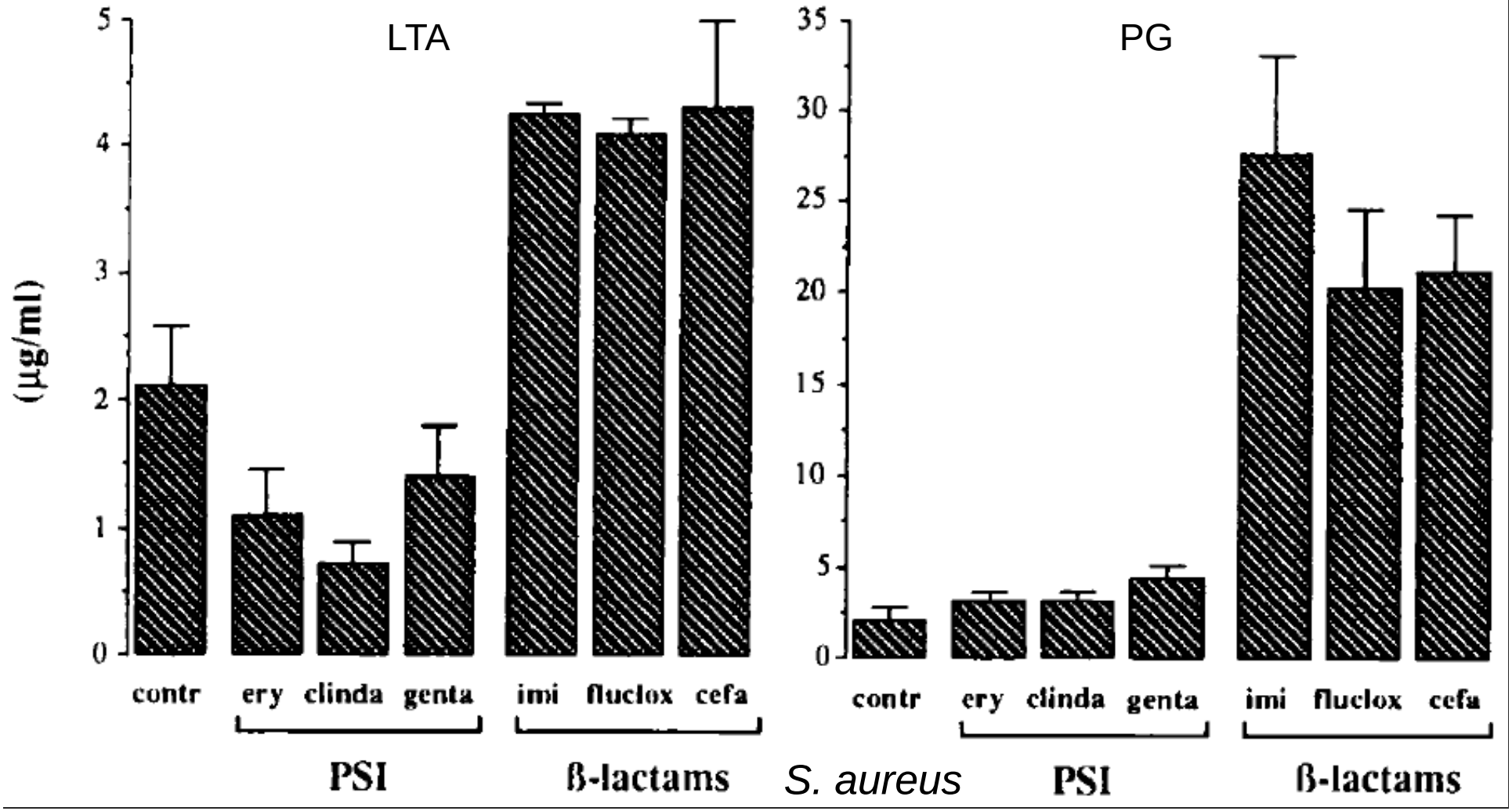
Determinación el primer día de bacteriemia. (IL estimulada por PG)

Nau R, et al. Modulation of Release of Proinflammatory Bacterial Compounds by Antibacterials: Potential Impact on Course of Inflammation and Outcome in Sepsis and Meningitis.
Clin Microbiol Rev 2002; 15: 95-110



Ceftriaxona **Rifampicina**

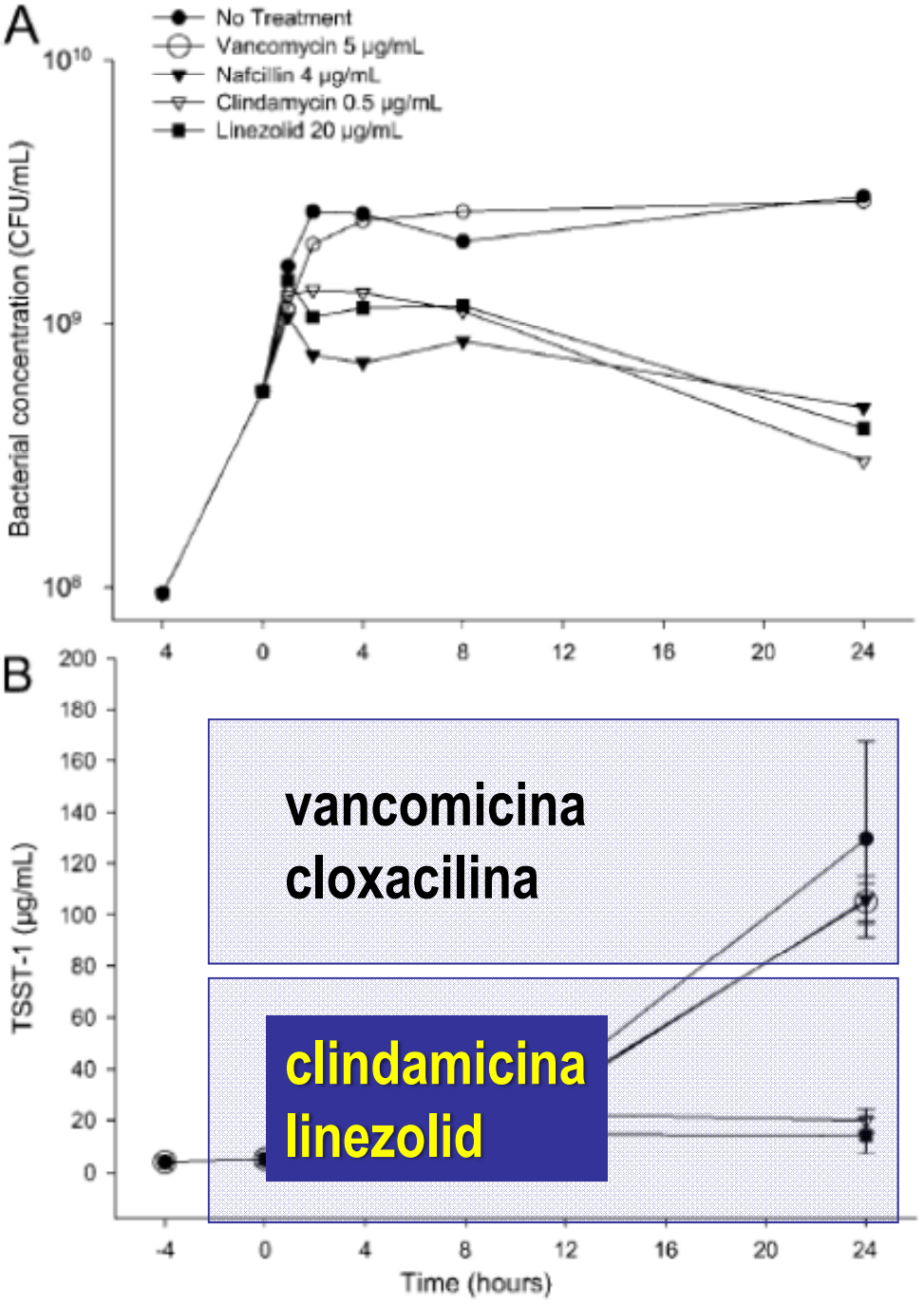
Nau R, et al. Modulation of Release of Proinflammatory Bacterial Compounds by Antibacterials: Potential Impact on Course of Inflammation and Outcome in Sepsis and Meningitis.
Clin Microbiol Rev 2002; 15: 95-110



Stevens DL, et al
Clin Infect Dis 2006

Acción antibacteriana

Producción de toxinas



Efficacy of penicillin, clindamycin or linezolid in streptococci myositis

	% dead animals	Days from incubation
• without treatment	100	5
• penicillin	100	9
• clindamycin / linezolid	20	12

*** Injection of 10^8 CFU/mL of** ßHSA

R. Kaul , et al. **Intravenous Immunoglobulin Therapy for Streptococcal Toxic Shock Syndrome. A Comparative Observational Study**

Clin Infect Dis 1999; 28: 800-804

variable	Supervivencia con el factor/ total (%)	Supervivencia sin el factor/ total (%)	P (OR, IC95%)
IGIV	14/21 (67)	11/32 (34)	0.02 (7.8, 1.5-41)
Clindamicina	22/37 (59)	3/15 (20)	0.11 (4.8, 1-25)
Cirugía	12/26 (65)	8/27 (30)	0.09 (4, 1-14)

Ortega M, et al.
In vitro antagonism between -lactam and macrolide in S. pneumoniae: how important is the antibiotic order?
Int Journal of Antimicrobial Agents 2004 :24 ;178-80

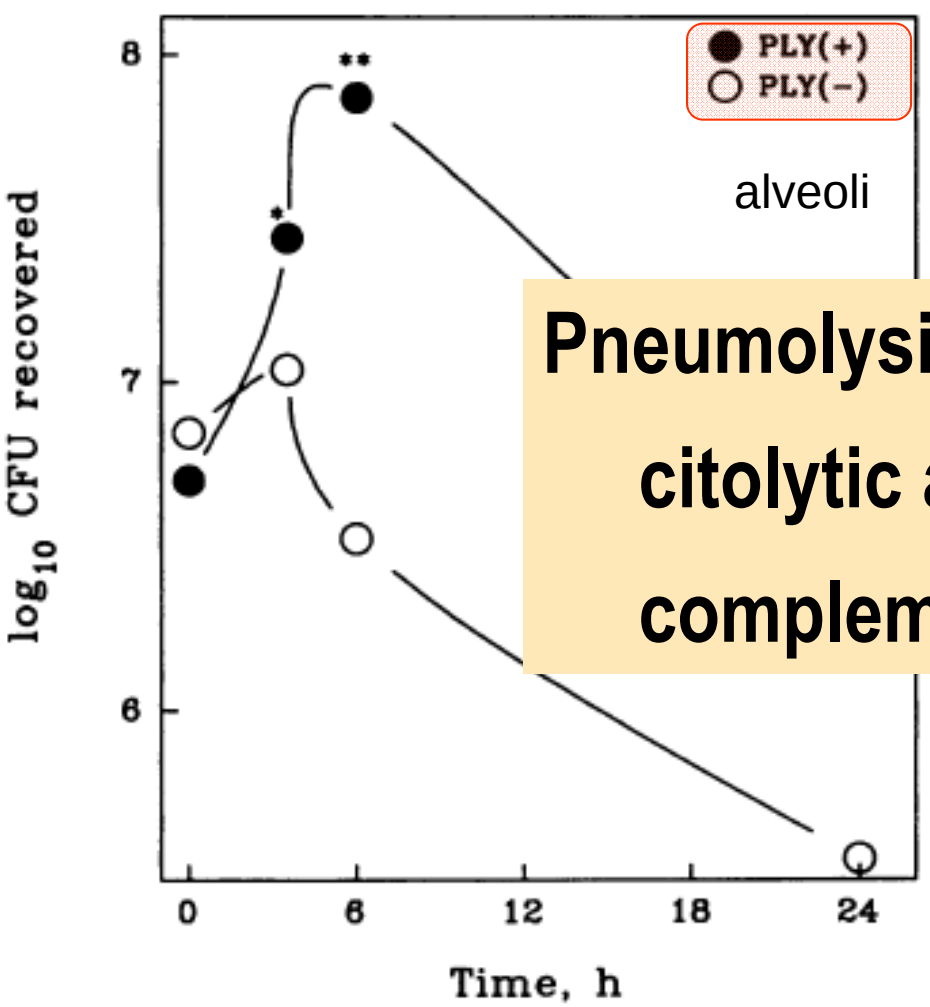
	Penicillin S, erythromycin S ($n = 10$)
Control	−1.4 (0.4)
Penicillin	3.5 (0.2)
Cefotaxime	2.4 (0.2)
Erythromycin	1.5 (0.1)
Penicillin + erythromycin	1.8 (0.3)
Cefotaxime + erythromycin	1.8 (0.1)

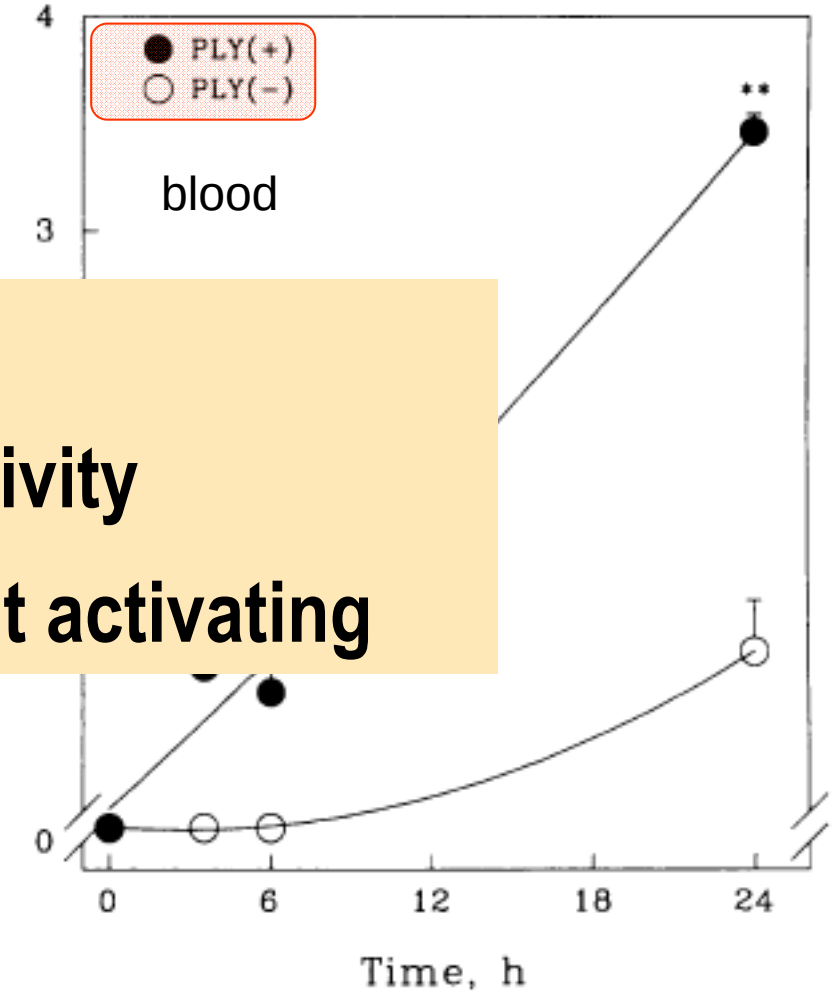
Martínez JA, et al.
Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with *bacteremic* pneumococcal pneumonia.
Clin Inf Dis 2003; 36: 389-395

Prognostic factor	OR (CI 95%)	p
Age ≥ 65 y	2.52 (1.12-5.67)	0.025
Shock	18.3 (7.48-45)	<0.0001
Empiric therapy with a macrolide	0.4 (0.17-0.92)	0.03

Tessmer A, et al.
J Antimicrob Agents 2009; 63: 1025-33

Rubins J, et al.
Dual Function of Pneumolysin in the Early Pathogenesis of Murine Pneumococcal Pneumonia
J Clin Invest 1995; 95: 142-50



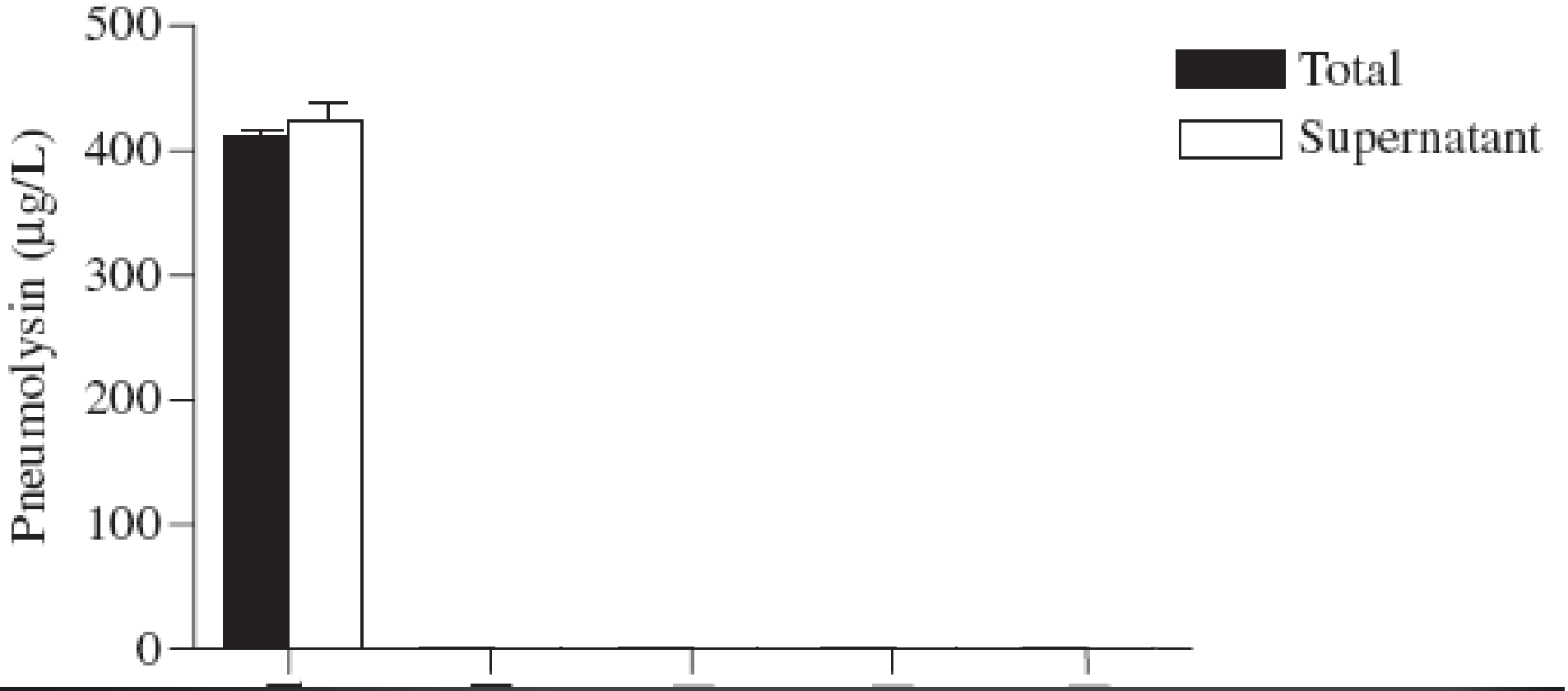


Pneumolysin:

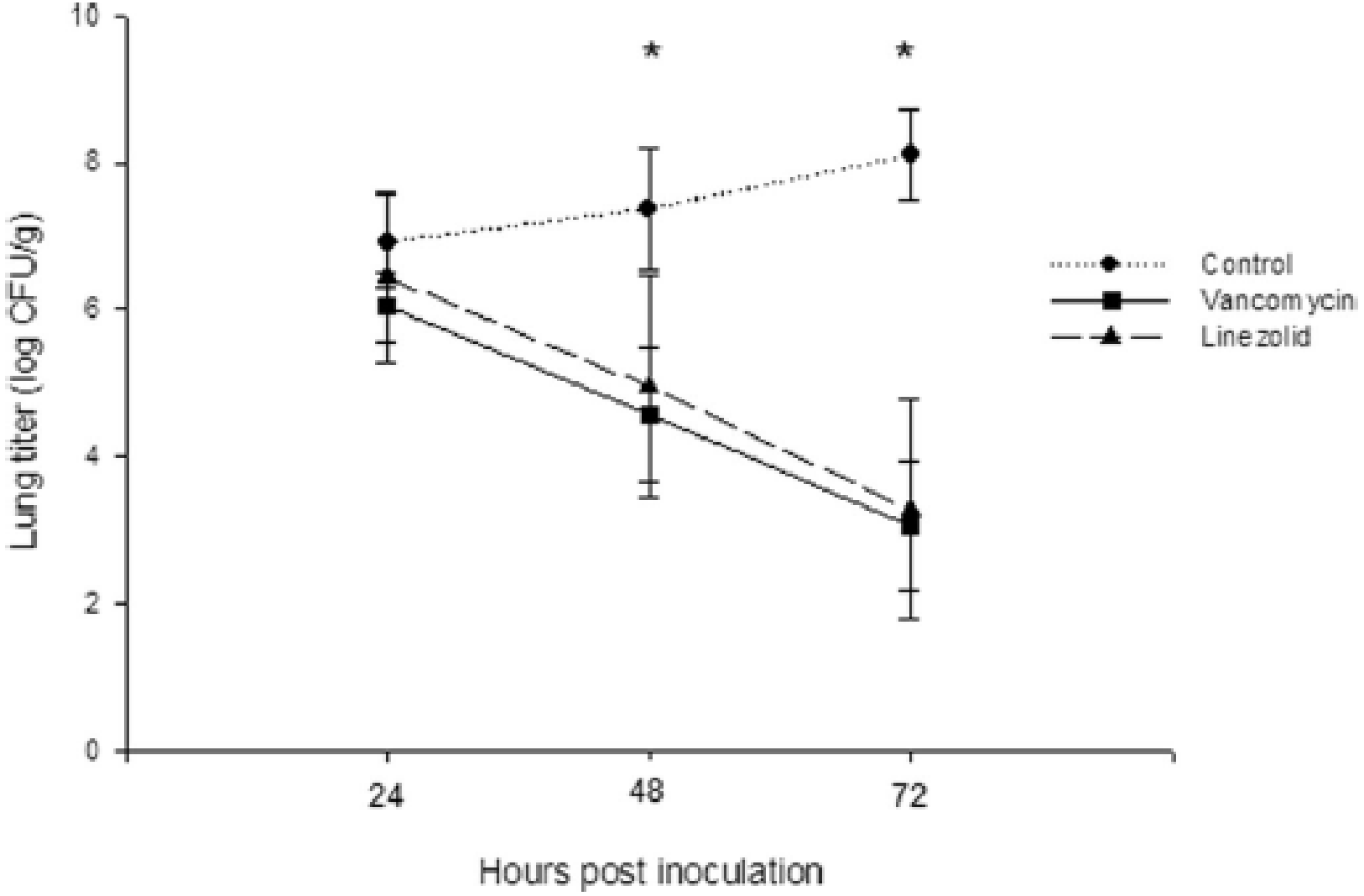
citolytic activity

complement activating

Anderson R, et al.
Clarithromycin alone and in combination with ceftriaxone inhibits the production of pneumolysin by both macrolide-susceptible and macrolide-resistant strains of S. peumoniae
Journal of Antimicrobial Chemotherapy 2007 :59 ;224–229



Akinnusi ME, et al. Does linezolid modulate lung innate immunity in a murine model of methicillin-resistant *Staphylococcus aureus* pneumonia?
Crit Care Med 2011; 39: 1944-52



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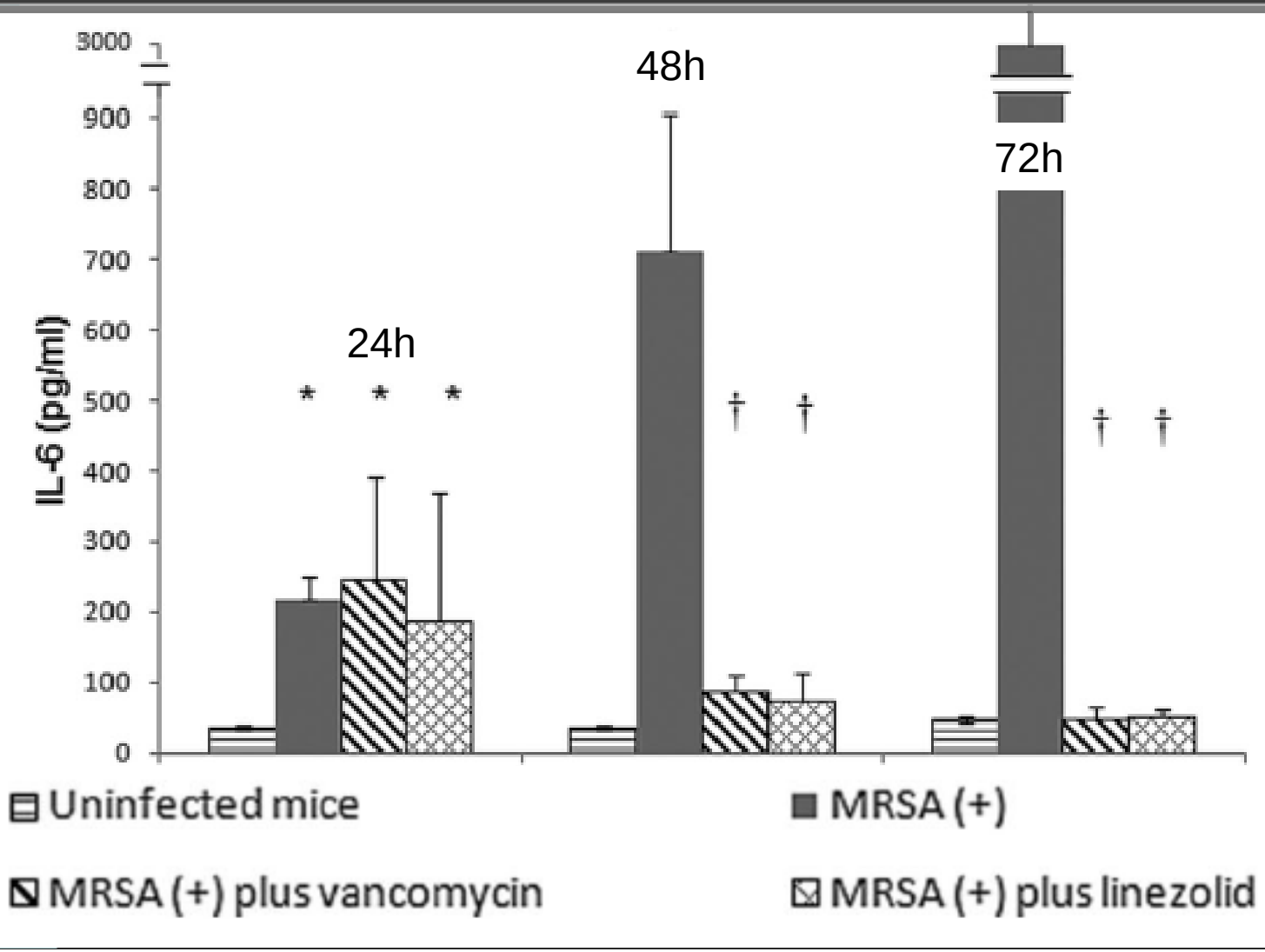


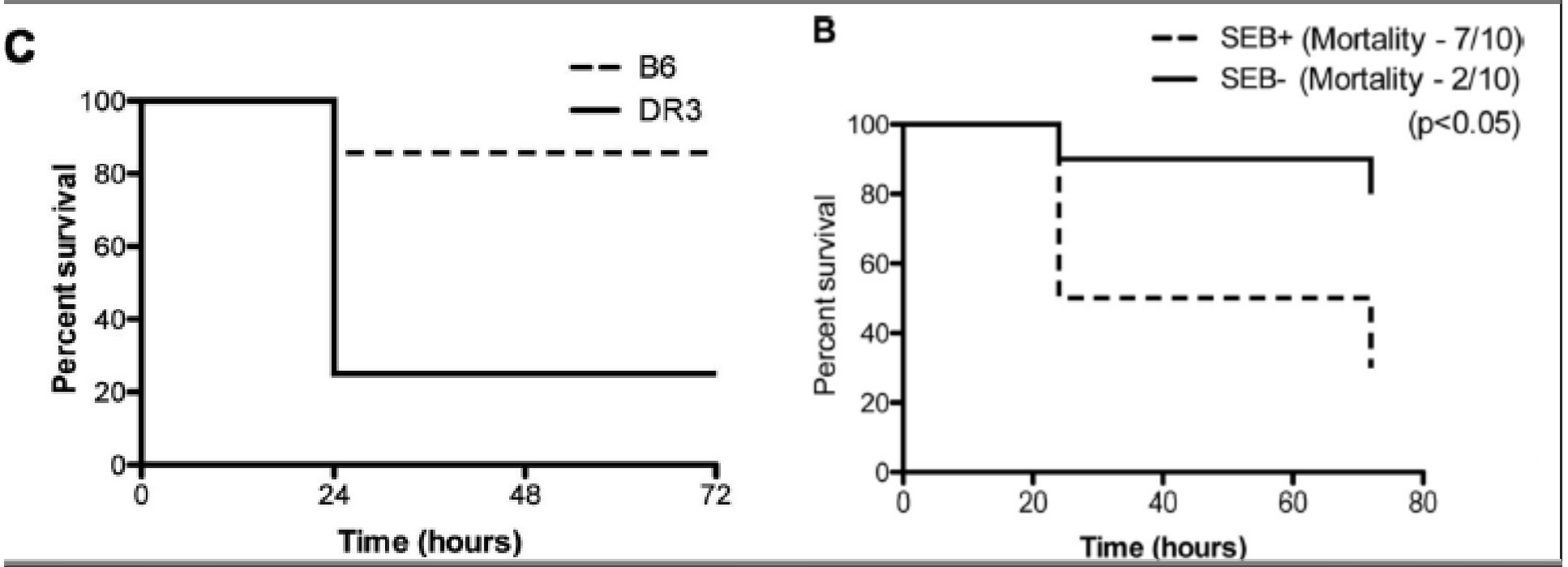
Kalil AC, et al. Linezolid does not show advantages over vancomycin in modulating the pulmonary immune response: How should we conciliate these new findings with the Zephyr trial results?
Crit Care Med 2011; 39: 2009-10

"both linezolid and vancomycin demonstrated a dose-dependent reduction in lung bacterial titers. Both drugs were associated with a statistically significant reduction in bacterial load at 48 hrs and 72 hrs compared to controls, and the degree of reduction was similar between linezolid and vancomycin… *linezolid did not display an advantage over vancomycin in modulating the pulmonary innate immune response in a murine model* of methicillin-resistant *S. aureus* pneumonia".

Karau M, et al. Linezolid Is Superior to Vancomycin in Experimental Pneumonia Caused by Superantigen-Producing Staphylococcus aureus in HLA Class II Transgenic Mice. *Antimicrobial Agents Chemother 2012; 56: 5401-5*

"Considering the enormous differences in the sensitivities of humans and conventional laboratory mice to SAg (conventional mice are believed to be *10^{11} times more resistant to SAg than humans*), we hypothesized that the benefits of linezolid or similar antibacterial agents do not become apparent in conventional mice. On the other hand, these agents might in fact be useful in humans. Since *transgenic mice expressing HLA class II molecules respond robustly to SAg similarly to humans*, they are more susceptible to *S. aureus* and *Streptococcus pyogenes* (which also produces SAg) infections than conventional mice".

Karau M, et al. Linezolid Is Superior to Vancomycin in Experimental Pneumonia Caused by Superantigen-Producing Staphylococcus aureus in HLA Class II Transgenic Mice. *Antimicrobial Agents Chemother 2012; 56: 5401-5*



B6: modelo clásico
DR3: modelo transgénico (HLA-DR3)
Cepa de SARM productora de SEB

Clinical experience in *S. aureus* pneumonia. *Bacteremia registry of Hospital Clínic 1991-2009*

Pattern of susceptibility (n)	Related mortality	30 days mortality	Global mortality
MSSA (n= 95)	26 (27.4)	8 (8.4)	34 (35.8)
MRSA (n= 68)	30 (44.1)	3 (7.7)	33 (46.1)

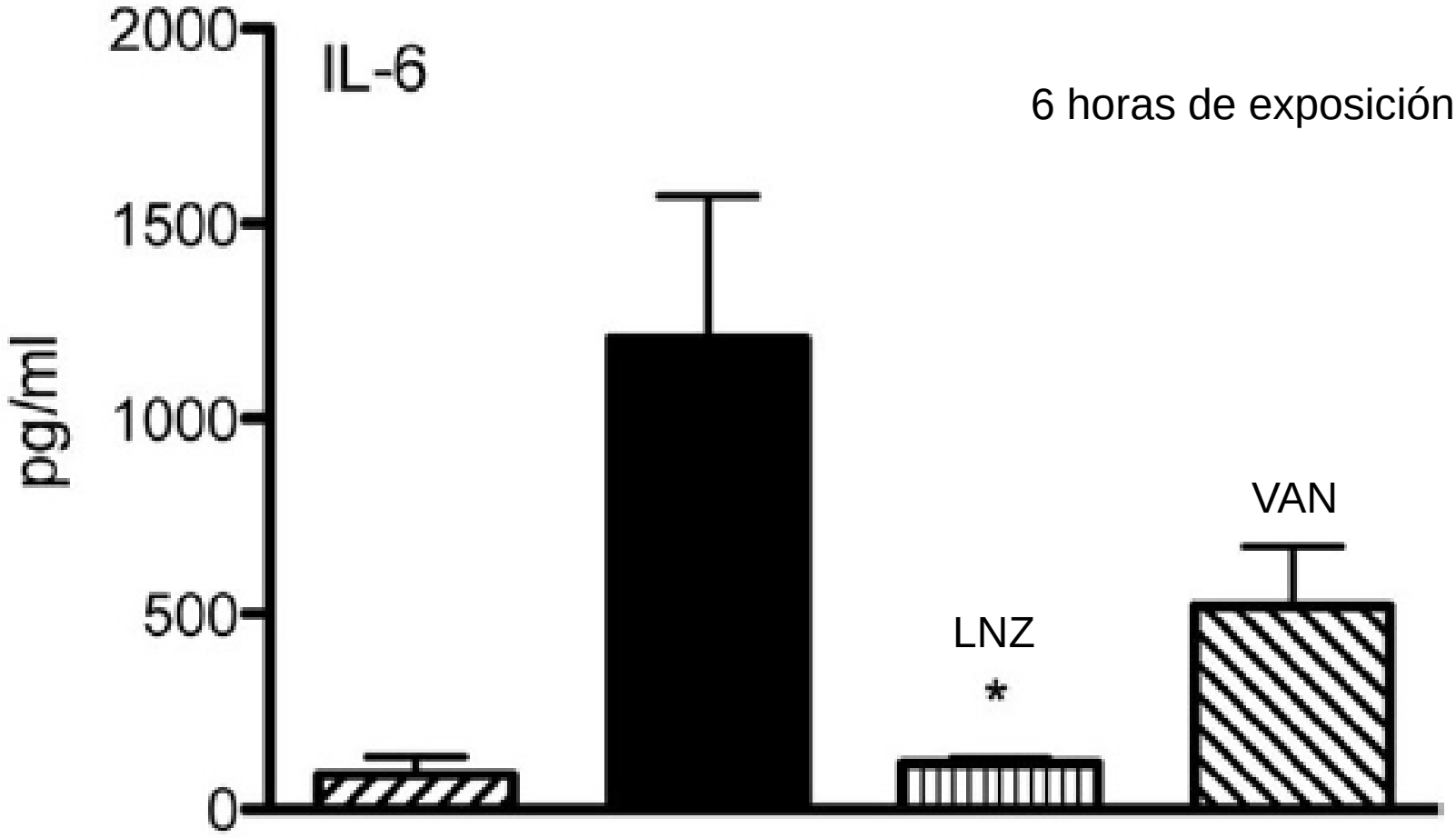
Clinical experience in *S. aureus* pneumonia. *Bacteremia registry of Hospital Clínic 1991-2009*

Pattern of susceptibility (n)	Related mortality	30 days mortality	Global mortality
MSSA(95)			
ß-lactam (79)	21 (26.5)	7 (8.8)	28 (29.5)
Glycopeptide (13)	5 (38.5)	1 (7.7)	6 (46.1)
inappropriate (3)	-	-	-

Clinical experience in *S. aureus* pneumonia. *Bacteremia registry of Hospital Clínic 1991-2009*

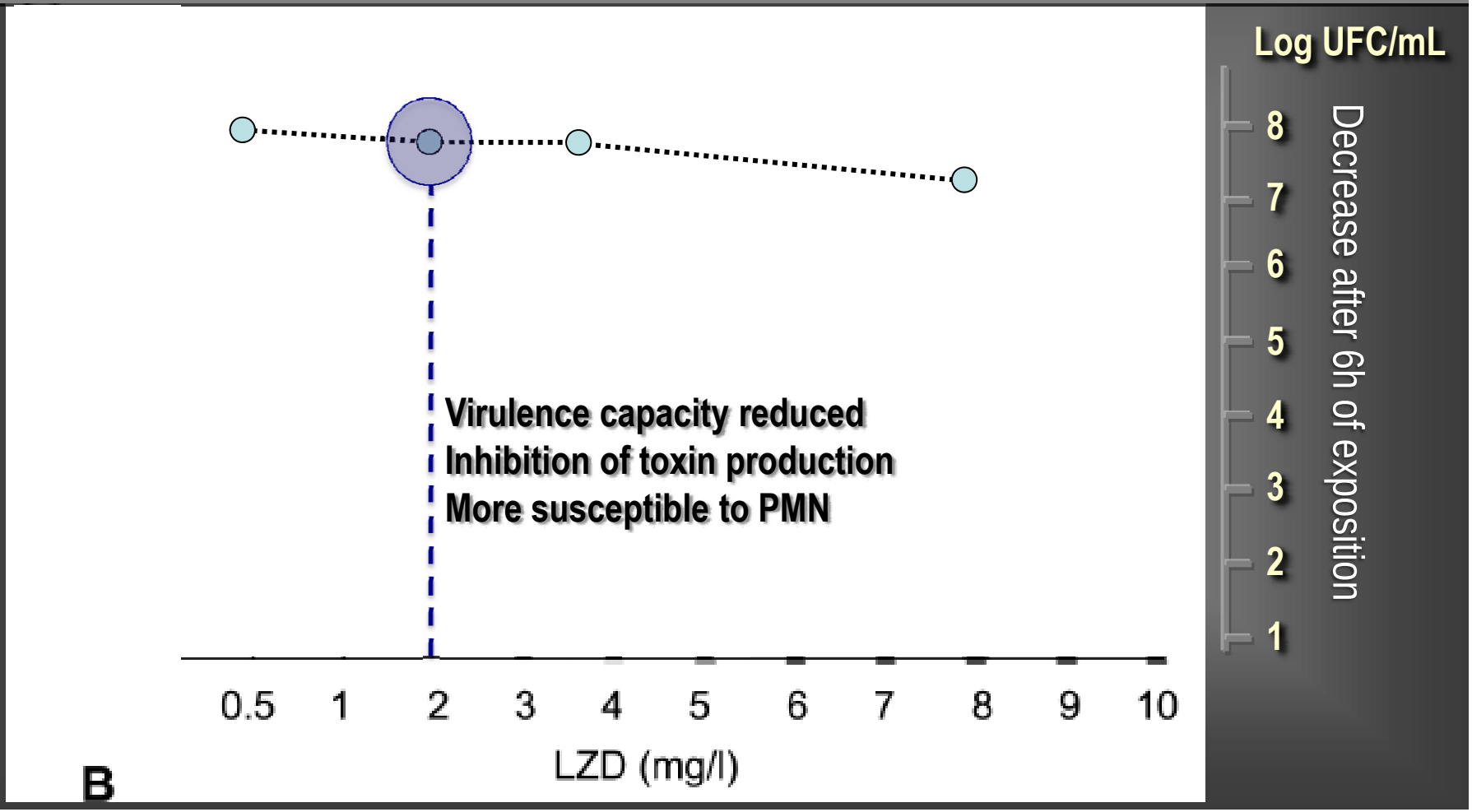
Pattern of susceptibility (n)	Related mortality	30 days mortality	Global mortality
MSSA(95)			
ß-lactam (79)	21 (26.5)	7 (8.8)	28 (29.5)
Glycopeptide (13)	5 (38.5)	1 (7.7)	6 (46.1)
inappropriate (3)	-	-	-
MRSA(68)			
Glycopeptide (25)	11 (44)	1 (4)	12 (48)
inappropriate (43)	19 (44.1)	2 (4.3)	21 (48.4)

Karau M, et al. Linezolid Is Superior to Vancomycin in Experimental Pneumonia Caused by Superantigen-Producing Staphylococcus aureus in HLA Class II Transgenic Mice. *Antimicrobial Agents Chemother 2012; 56: 5401-5*

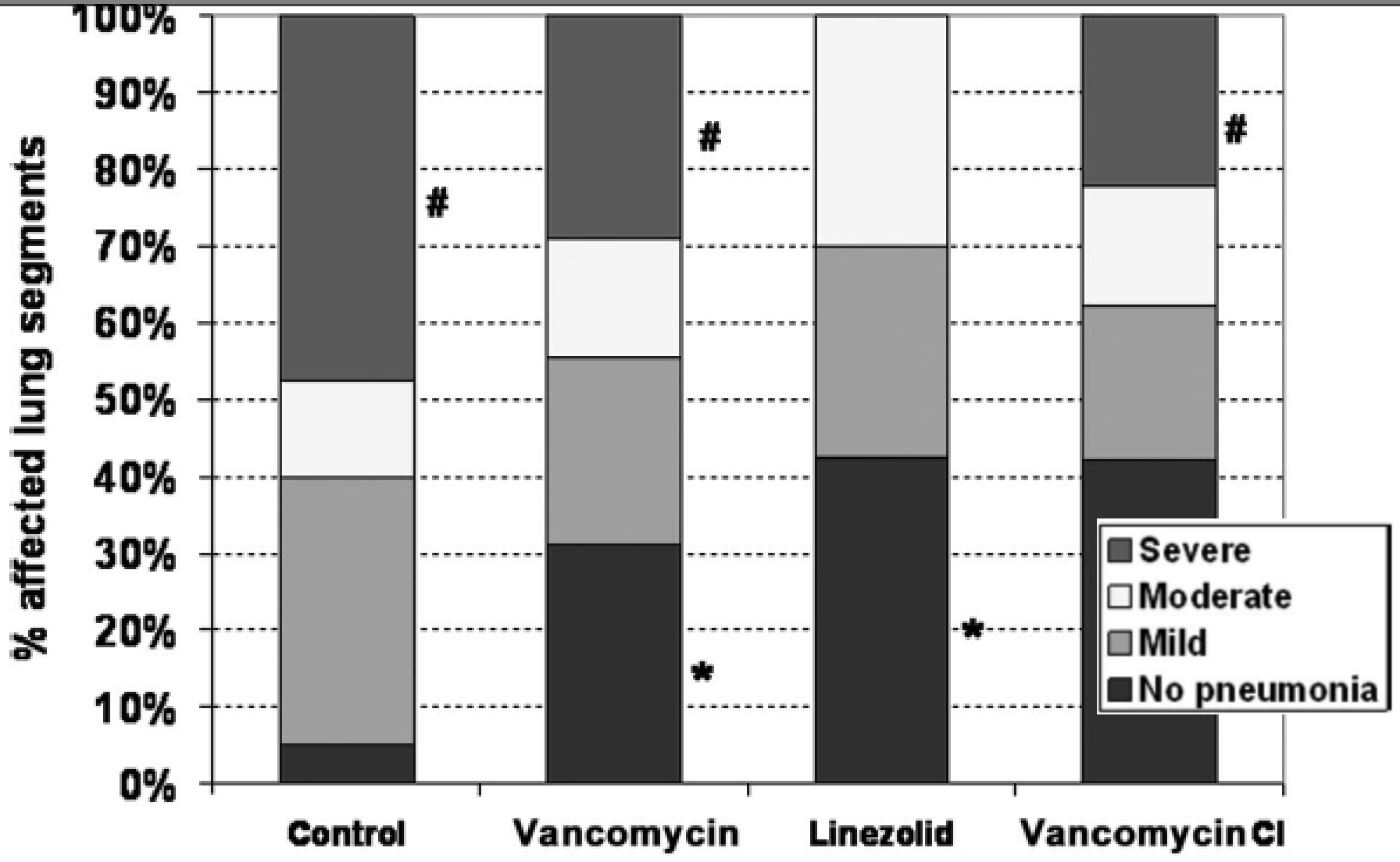


DR3: modelo transgénico (HLA-DR3). Cepa de SARM SEB+

Mitsutaka K, et al. **Use of a Sensitive Chemiluminescence-Based Assay to Evaluate the Metabolic Suppression Activity of Linezolid on MRSA Showing Reduced Susceptibility to Vancomycin.** *J. Microbiol. Biotechnol. 2009; 19: 734–741*



Martínez-Olondris P, et al. **Efficacy of linezolid compared to vancomycin in an experimental model of pneumonia induced by MRSA in ventilated pigs.** *Crit Care Med 2011; 40: 1-7*



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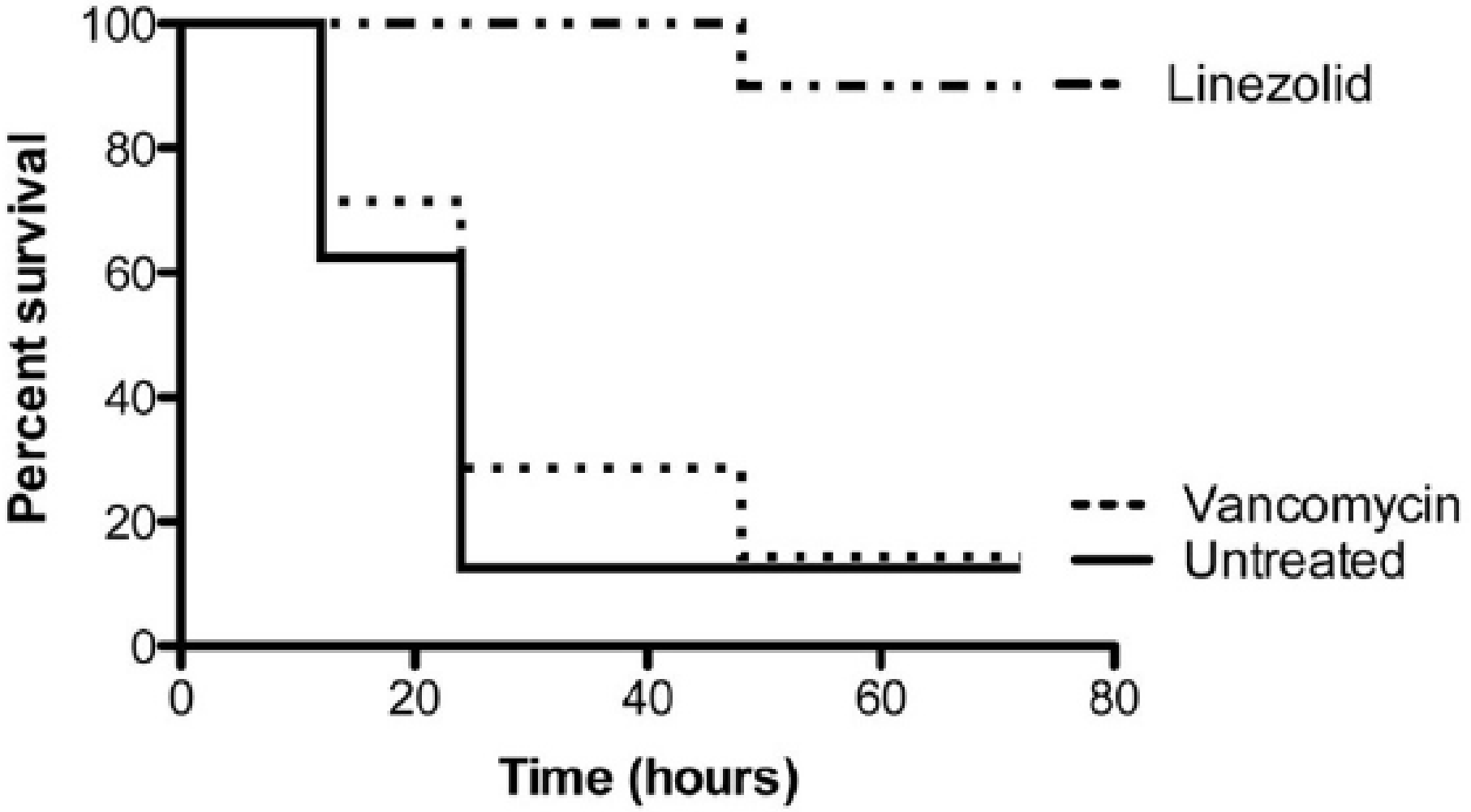
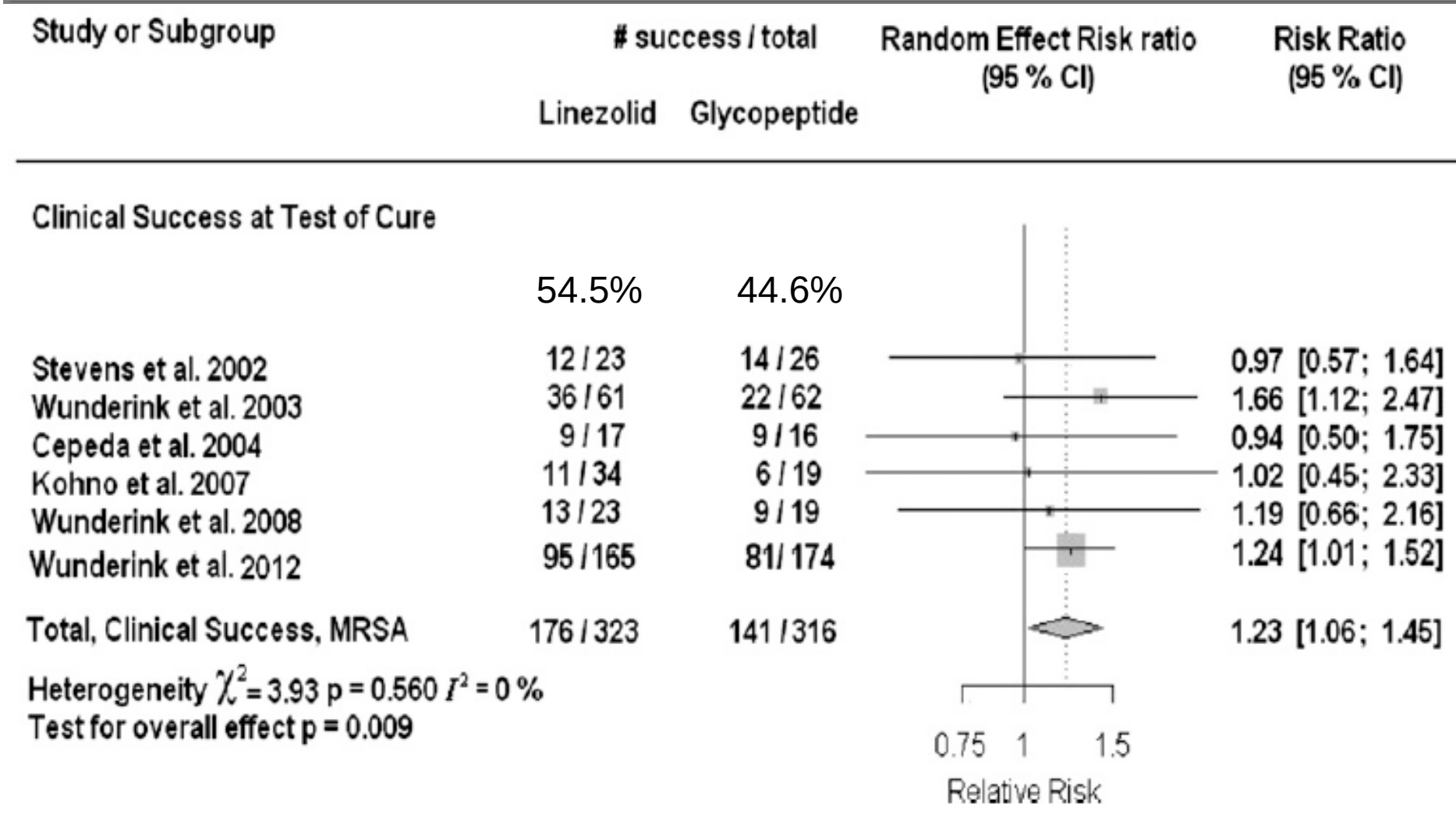
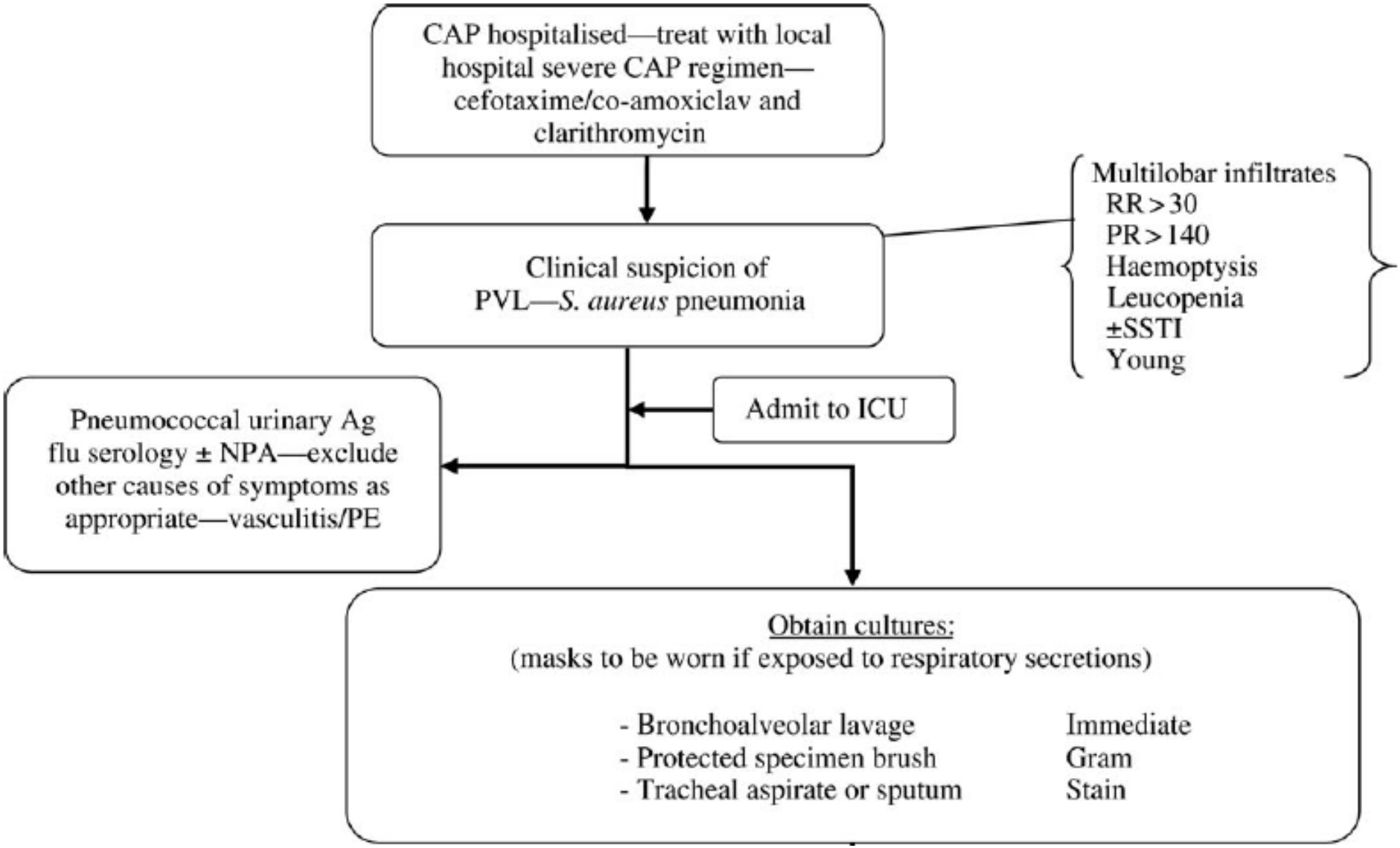


Thamlikitul, et al. Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia. *Chest 2012; 142: 269*



Nathwani D, et al. Guidelines for UK practice for the diagnosis and management of MRSA infections presenting in the community. *J Antimicrob Chemother 2008; 61: 976-94*



Nathwani. Guidelines for UK practice for diagnosis, management of MRSA infections presenting in the community. *JAC 2008; 61: 976-94*