# Perspectiva nacional y europea en el manejo de la infección por neumonías complicadas por SARM

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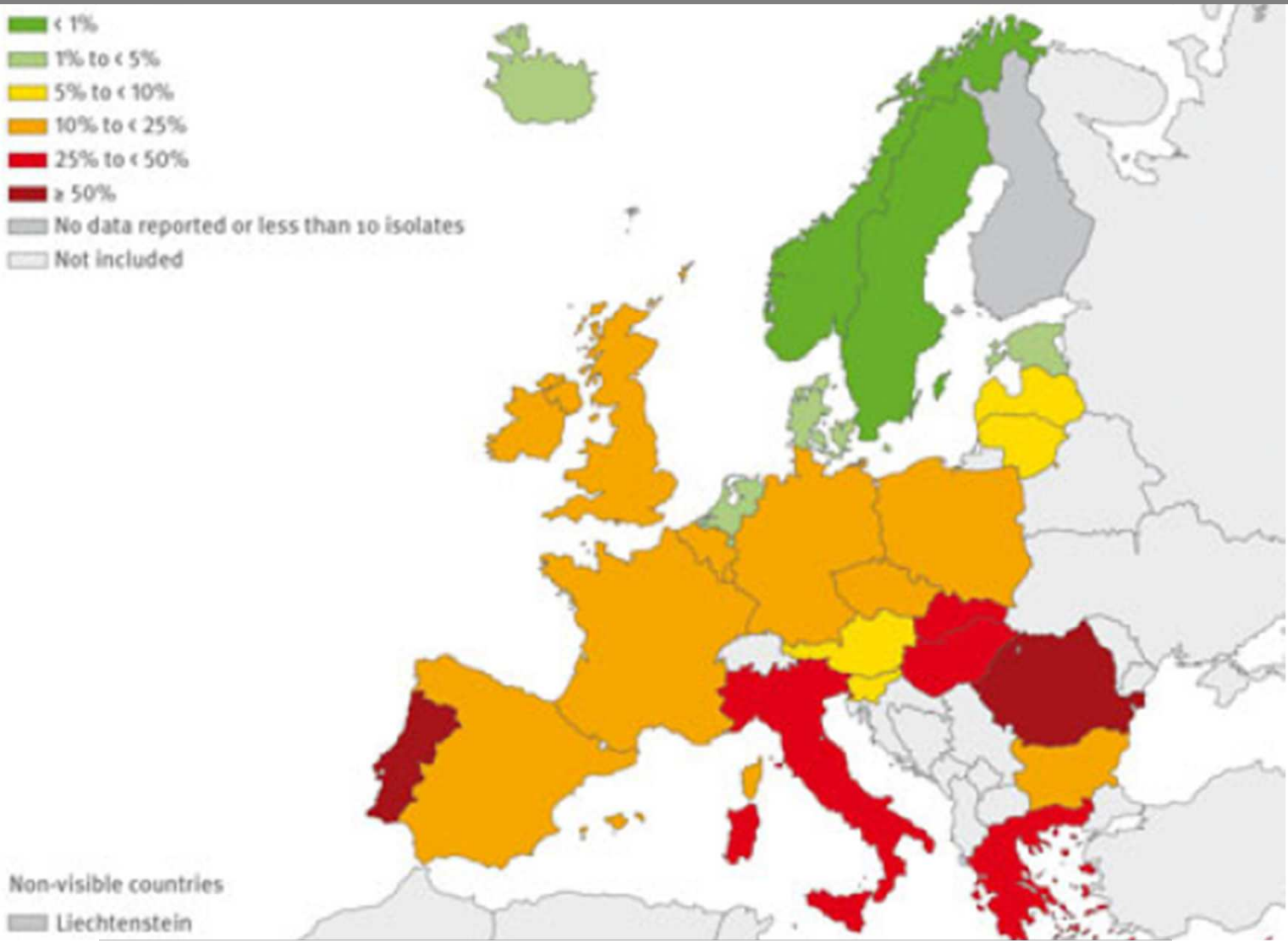
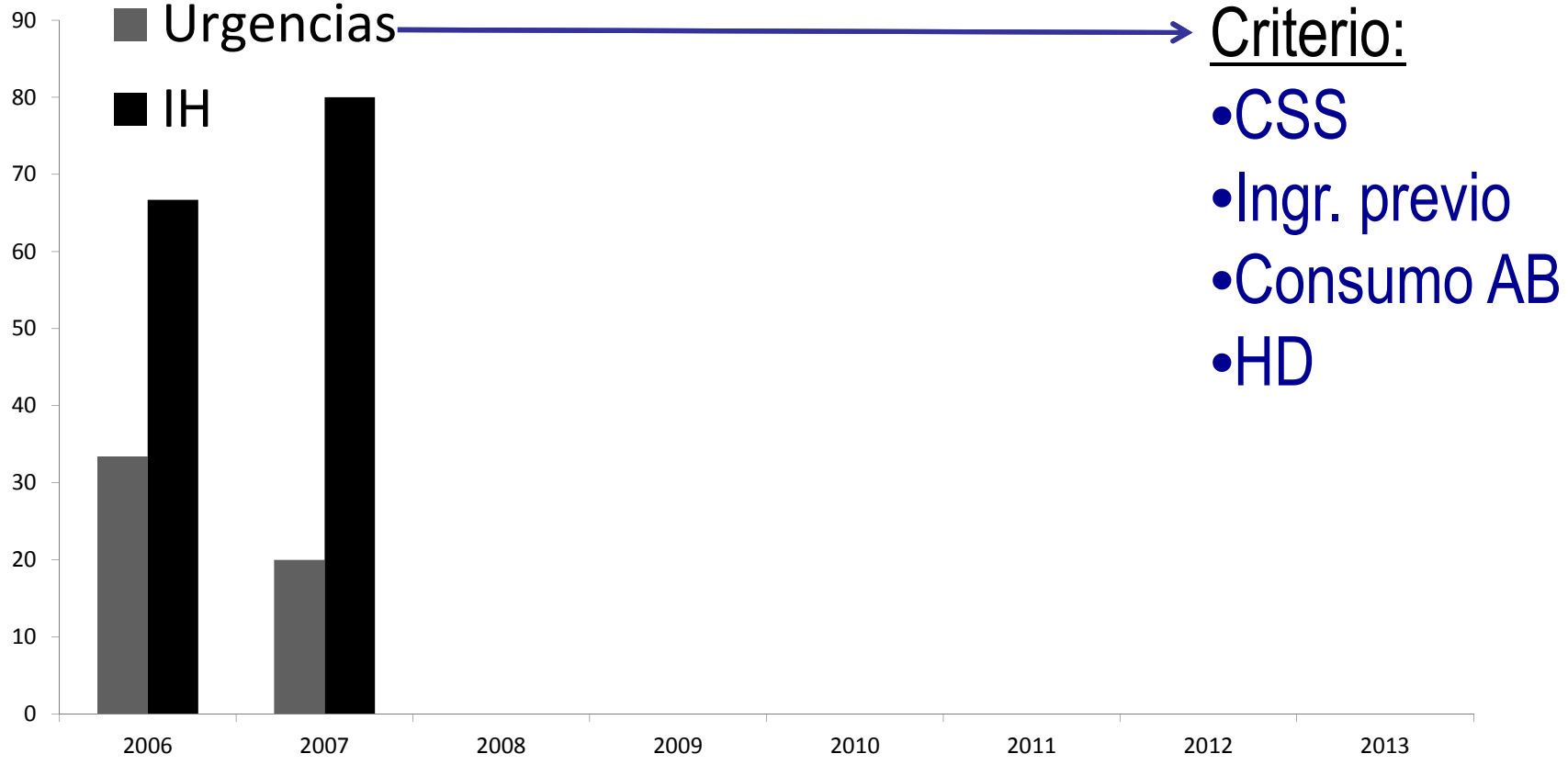
**_Chastre J, et al._ European perspective and update on the management of nosocomial pneumonia due to methicillin-resistant Staphylococcus aureus after more than 10 years of experience with linezolid.**
***Clin Microbiol Infect 2014; 20 (Supl 4): 19-36***



*Freixas N, et al.* **Surveillance of methicillin-resistant Staphylococcus aureus (MRSA) in acute care hospitals. Results of the VINCat Program (2008-2010).**
***Enferm Infecc Microbiol Clin 2012; 30 (Supl 3): 39-42***

| | % SARM (SAt/SARM) | | |
|---|---|---|---|
| Nº camas | 2008 | 2009 | 2010 |
| • >500 | 24 | 23 | 23 |
| • 200-500 | 24 | 22 | 19 |
| • <200 | 21 | 28 | 26 |

# Evolución de la bacteriemia por *S. aureus* RM en el Hospital Clínic de Barcelona entre 2006-2013



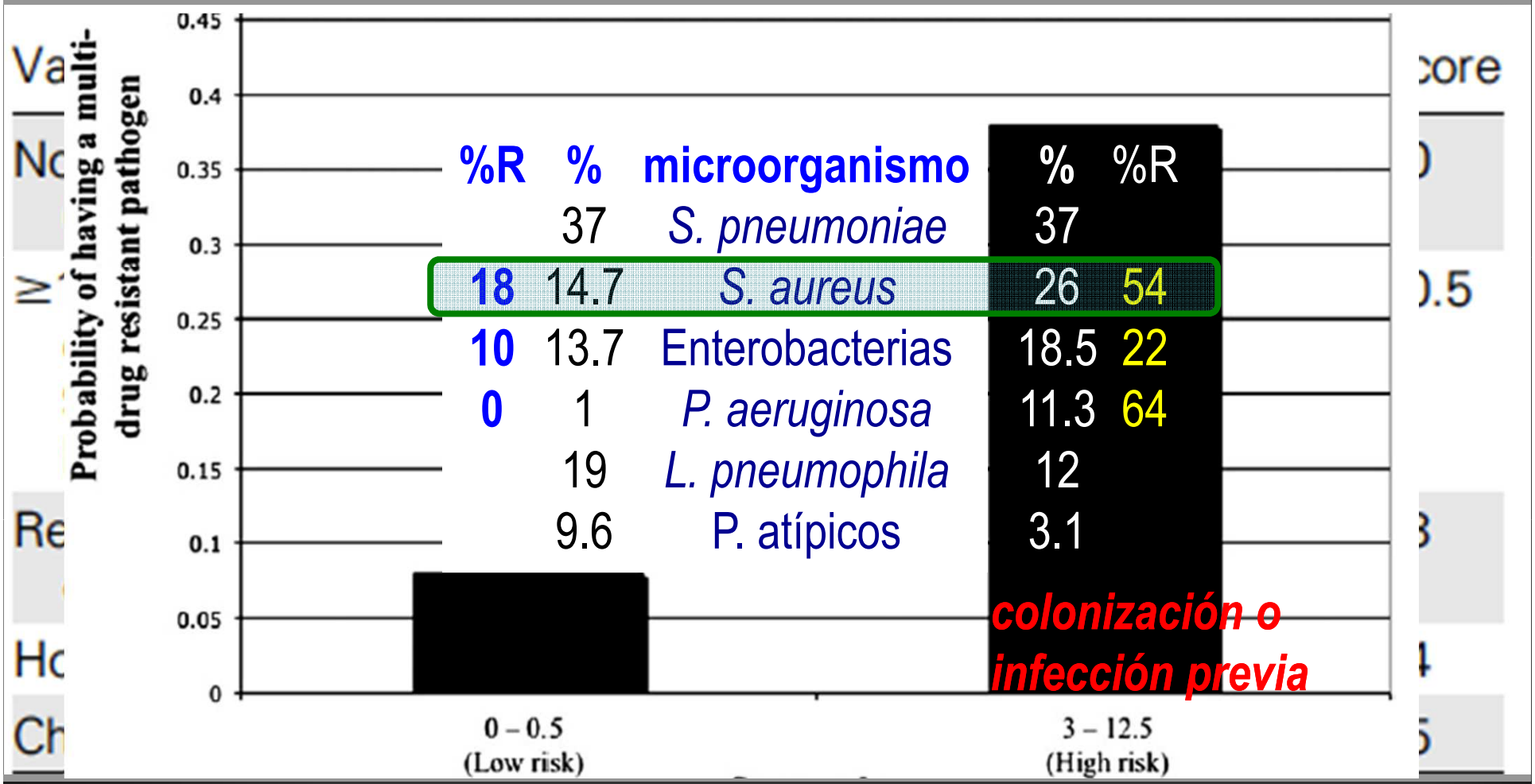
**Shorr AF et al. Validation of a Clinical Score for Assessing the Risk of Resistant Pathogens in Patients With Pneumonia Presenting to the Emergency Department. *Clin Infect Dis 2012; 54: 193-8***

**977 pacientes consecutivos que ingresaban por urgencias**

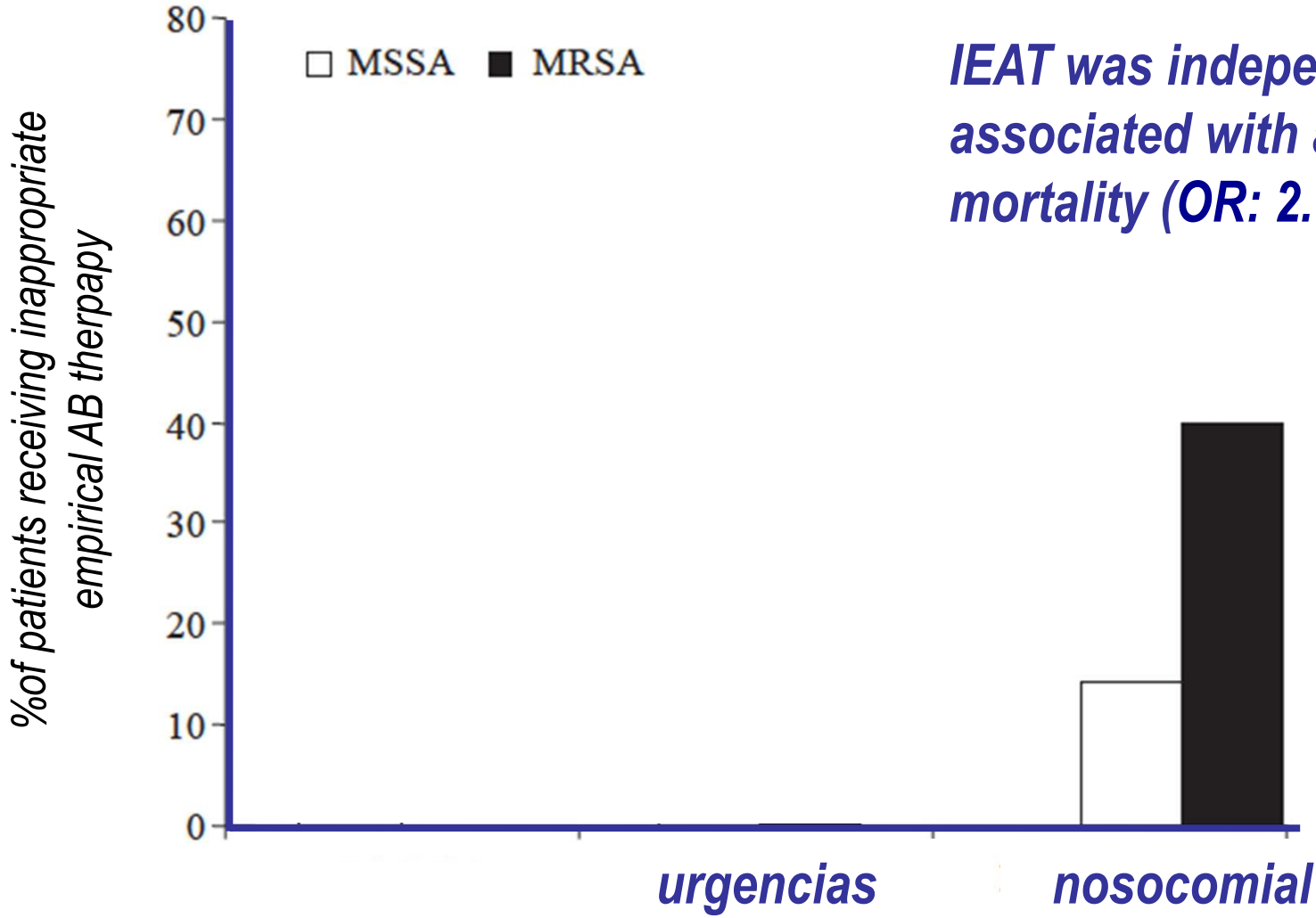
1. Procedencia de un centro socio-sanitario o residencia.
2. Hospitalización reciente >48h en los 3 meses previos.
3. Uso previo de antibióticos de amplio espectro durante el mes previo.
4. Inmunosupresión (SIDA, QT, corticoterapia).
5. Hemodiálisis o tratamiento domiciliario.

**415 (42%)**

**Aliberti S, et al. Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia. *Clin Infect Dis 2012; 54: 470-8***



**Bassetti M al. Risk factors and mortality of healthcare-associated and community- acquired Staphylococcus aureus bacteraemia.**
***Clin Microbiol Infect 2012; 18: 862-9***




***IEAT was independently associated with a higher mortality (OR: 2.79)***

## Etiología de la neumonía bacteriémica de acuerdo con el origen.

*Hospital Clínic de Barcelona 2000-2013 (n=1364)*

| Microorganismo | EH (%) | IH (%) | RCS (%) |
|---|---|---|---|
| *S. aureus* | 56 (6.5) | 46 (14) | 16 (10) |
| •formas graves (shock)<br>•lesiones cavitadas | •jóvenes<br>•post-gripal<br>•UDVP (EI) | •VM<br>•post-trauma<br>•ingreso prolongado (RM) | •residencia<br>•ingreso previo<br>•IRC, HD |
| mort (%): | 20 | 45 | 68 |

# Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. ATS/IDSA.

## *Am J Respir Crit Care Med 2005; 171: 388–416.*

**TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY**

| Potential Pathogens | Combination Antibiotic Therapy* |
|---|---|
| Pathogens listed in Table 3 and MDR pathogens<br>*Pseudomonas aeruginosa*<br>*Klebsiella pneumoniae* (ESBL$^+$)†<br>*Acinetobacter* species† | Antipseudomonal cephalosporin (cefepime, ceftazidime)<br>*or*<br>Antipseudomonal carbepenem (imipenem or meropenem)<br>*or*<br>β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam)<br>*plus*<br>Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin)<br>*or*<br>Aminoglycoside (amikacin, gentamicin, or tobramycin)<br>*plus* |
| Methicillin-resistant *Staphylococcus aureus* (MRSA) | Linezolid or vancomycin‡ |
| *Legionella pneumophila*† | |

* *See* Table 5 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.

**TABLE 5. INITIAL INTRAVENOUS, ADULT DOSES OF ANTIBIOTICS FOR EMPIRIC THERAPY OF HOSPITAL-ACQUIRED PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS**

| Antibiotic | Dosage* |
|---|---|
| Antipseudomonal cephalosporin | |
| Cefepime | 1–2 g every 8–12 h |
| Ceftazidime | 2 g every 8 h |
| Carbepenems | |
| Imipenem | 500 mg every 6 h or 1 g every 8 h |
| Meropenem | 1 g every 8 h |
| β-Lactam/β-lactamase inhibitor | |
| Piperacillin–tazobactam | 4.5 g every 6 h |
| Aminoglycosides | |
| Gentamicin | 7 mg/kg per d† |
| Tobramycin | 7 mg/kg per d† |
| Amikacin | 20 mg/kg per d† |
| Antipseudomonal quinolones | |
| Levofloxacin | 750 mg every d |
| Ciprofloxacin | 400 mg every 8 h |
| Vancomycin | 15 mg/kg every 12 h‡ |
| Linezolid | 600 mg every 12 h |

* Dosages are based on normal renal and hepatic function.

† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.

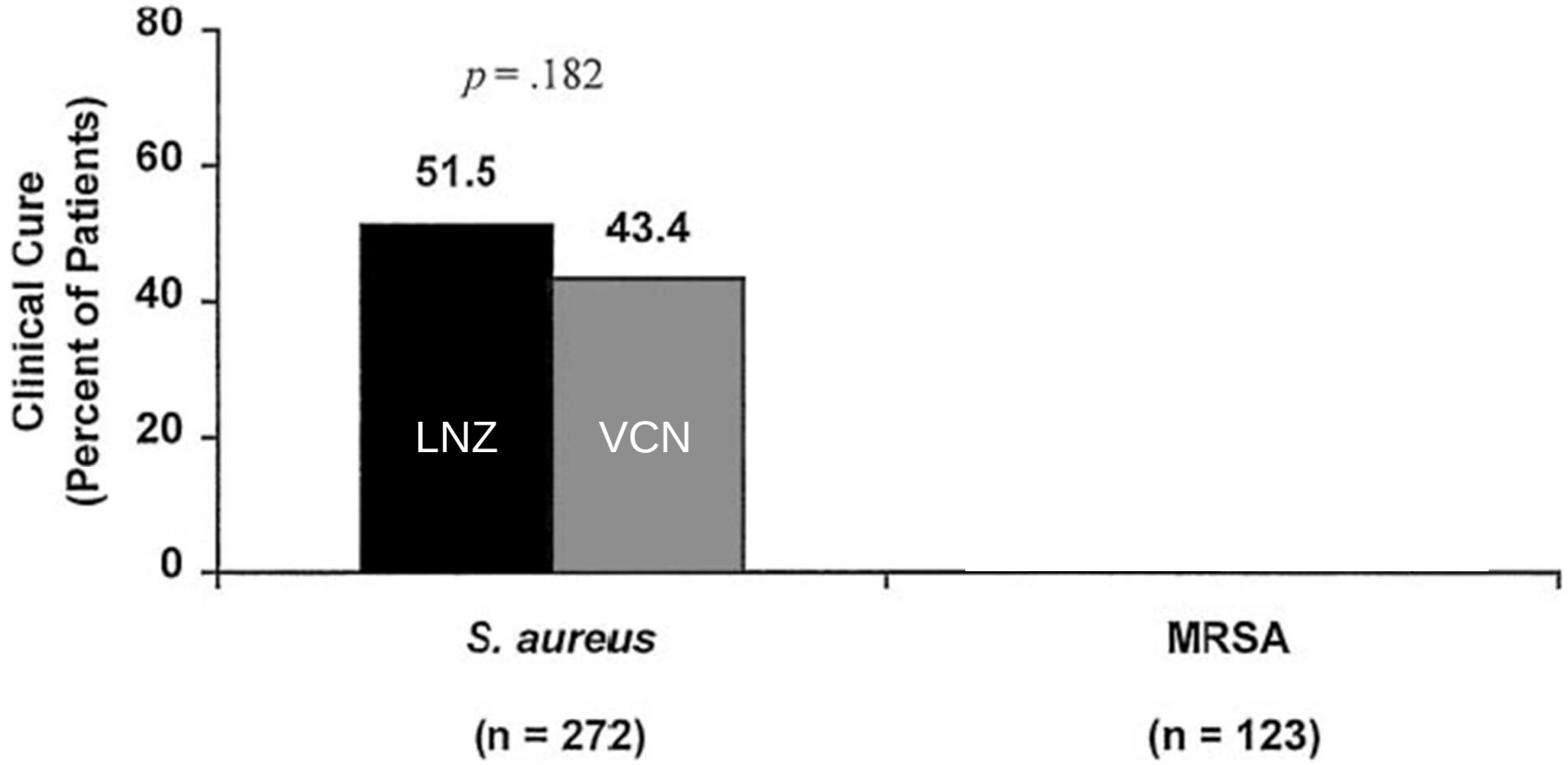
‡ Trough levels for vancomycin should be 15–20 μg/ml.

# Evidencia publicada en forma de meta-análisis sobre la eficacia de linezolid vs glicopéptidos

| Autor/año | Entidad/ Nº estudios | CC | EM |
|---|---|---|---|
| Falagas 08 | G/12 | 1.41 | 1.34 |
| BeiBei 10 | G/9 | 1.22 | 1.33 |
| Thamlikitkul 12 | N/6 | 1.23 | NA |
| Kalil 13 | N/9 | - | - |
| Jiang 13 | N/12 | - | 1.16 |
| Mao 13 | G/9 | 1.77 | 1.78 |
| Nemeth 14 | G/7 | 1.1 | NA |
| Wang 14 | N/9 | - | - |

favorece a linezolid / favorece a vancomicina

***Wunderick . et al.* Analysis of 2 doble-blind studies of patients with MRSA nosocomial pneumonia.**
***Chest 2003;124:1789-1797.***




**CMI ≤ 2 mg/L (80%, 1 mg/L)**
**Cmin: 5-10 mg/L**

## *Young Ju Jung, et al.* Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant S. aureus pneumonia.

*Crit Care Med 2010; 38: 175-80*

| Outcome Measures | Vancomycin+RFP * | Vancomycin-Only | *p* |
|---|---|---|---|
| Clinical Cure (%) | | | |
| Modified ITT | 22/41 (53.7) | 13/42 (31.0) | .047 |
| Per protocol | 19/30 (63.3) | 13/34 (38.2) | .079 |
| Microbiological eradication (%) | | | .472 |
| Modified ITT | 28/39 (71.8) | 24/39 (61.5) | .789 |
| Per protocol | 20/29 (69.0) | 21/33 (63.6) | |
| 28-Day mortality (%) | 9/41 (22.0) | 16/42 (38.1) | .151 |
| MRSA pneumonia-related | 6/41 (14.7) | 12/42 (28.6) | .183 |
| MRSA pneumonia-unrelated | 3/41 (7.3) | 4/42 (9.5) | >.999 |

*** Rifa-R en 14 casos (34%)**

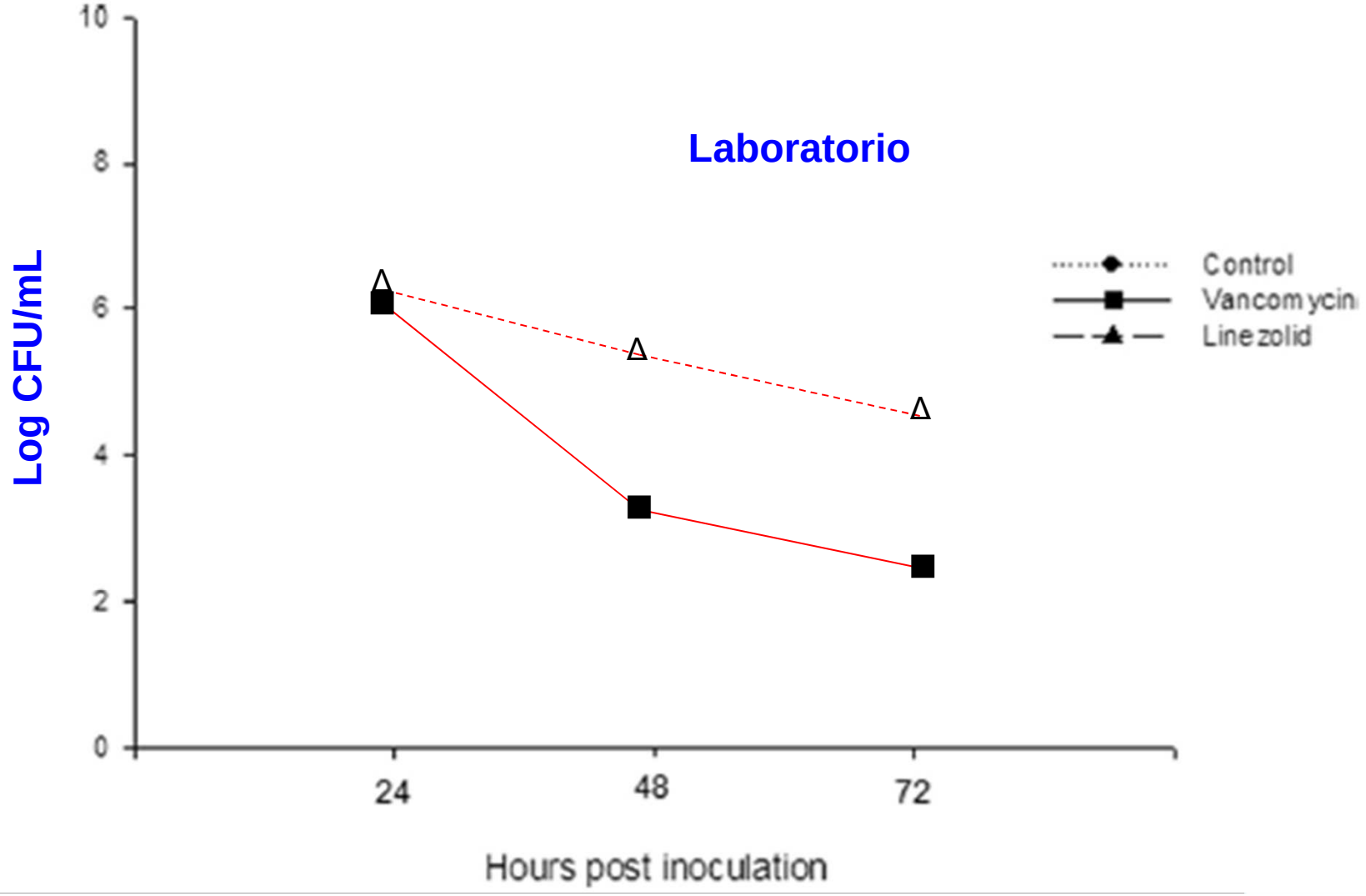
## Resultados según la dosis de vancomicina utilizada en pacientes con neumonía nosocomial por SARM

| referencia | Dosis vanco | Cmin diana (mg/L) | Cmin* (mg/L) | % vanco** | % line** |
|---|---|---|---|---|---|
| Wunderink 03 | 1 g/12h | 5-10 | - | 35.5 | 59 |
| Kollef 04 | 1 g/12h | 5-10 | - | 21 | 62 |
| Zephyr | 15 mg/kg/12h | >10 | 14 | 46.6 | 57.6 |

* niveles medios el tercer día
** % curación

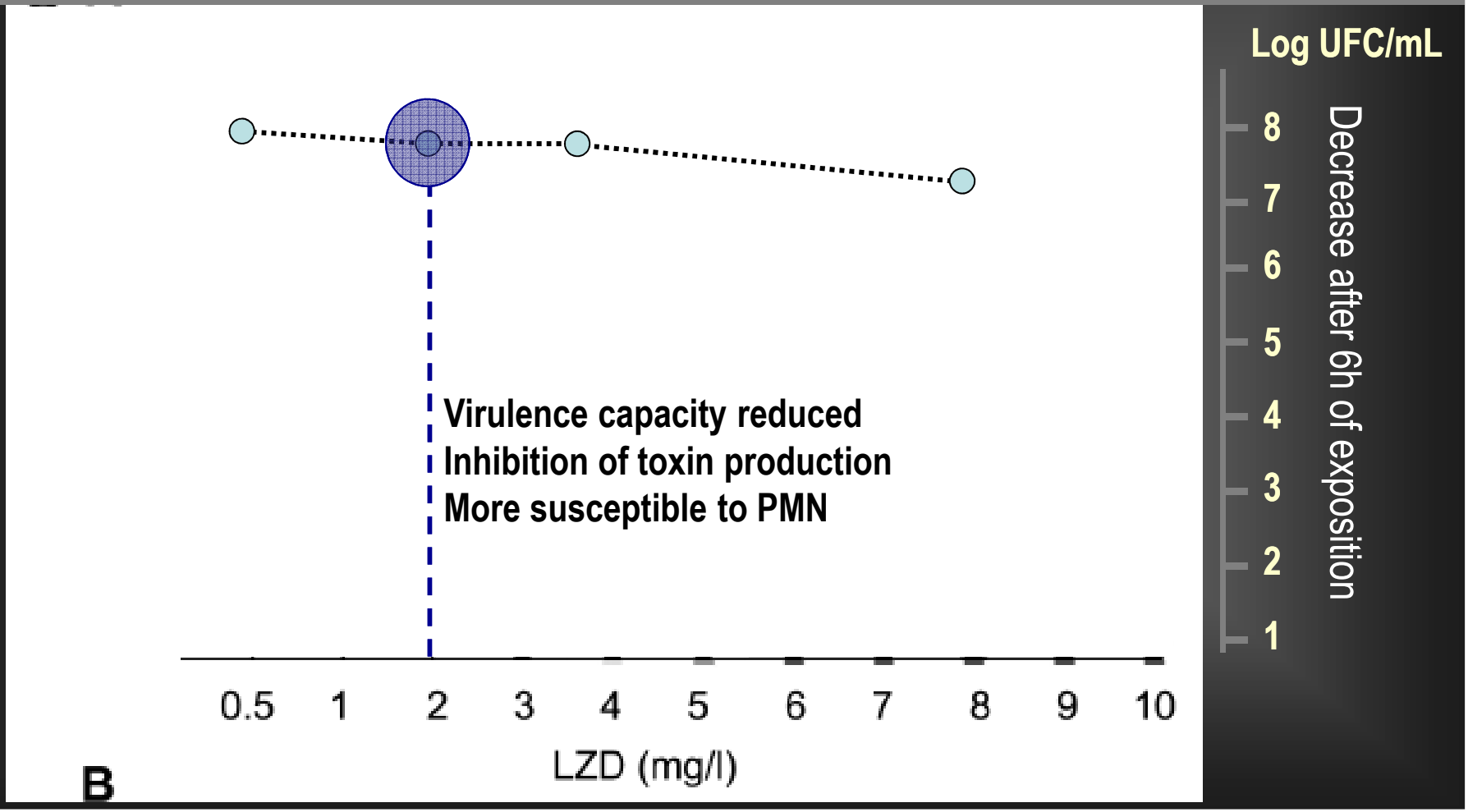
# Akinnusi ME, et al. Does linezolid modulate lung innate immunity in a murine model of methicillin-resistant *S. aureus* pneumonia?

*Crit Care Med 2011; 39: 1944-52*

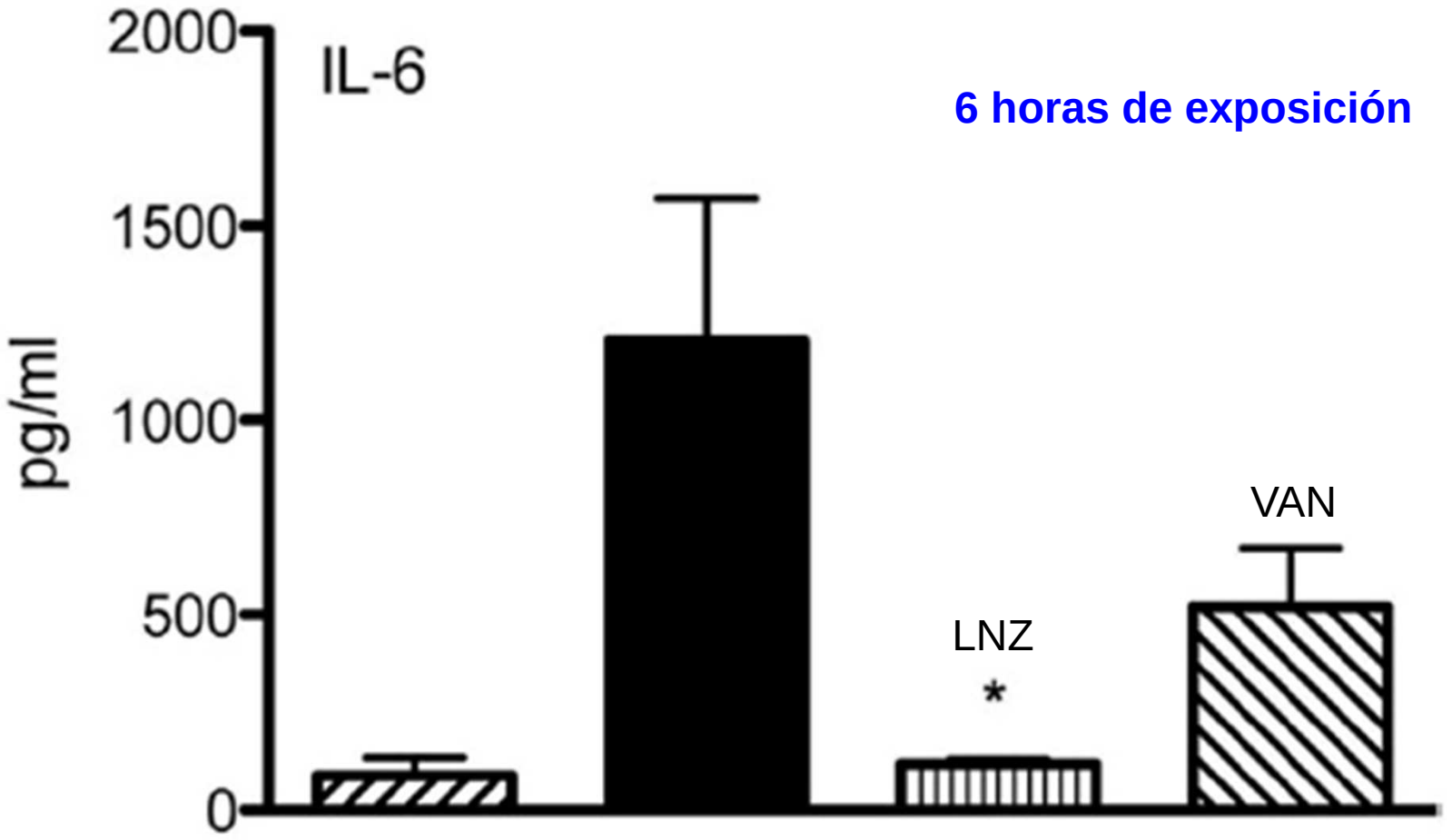


*Mitsutaka K, et al.* **Use of a Sensitive Chemiluminescence-Based Assay to Evaluate the Metabolic Suppression Activity of Linezolid on MRSA Showing Reduced Susceptibility to Vancomycin.**

*J. Microbiol. Biotechnol. 2009; 19: 734–741*

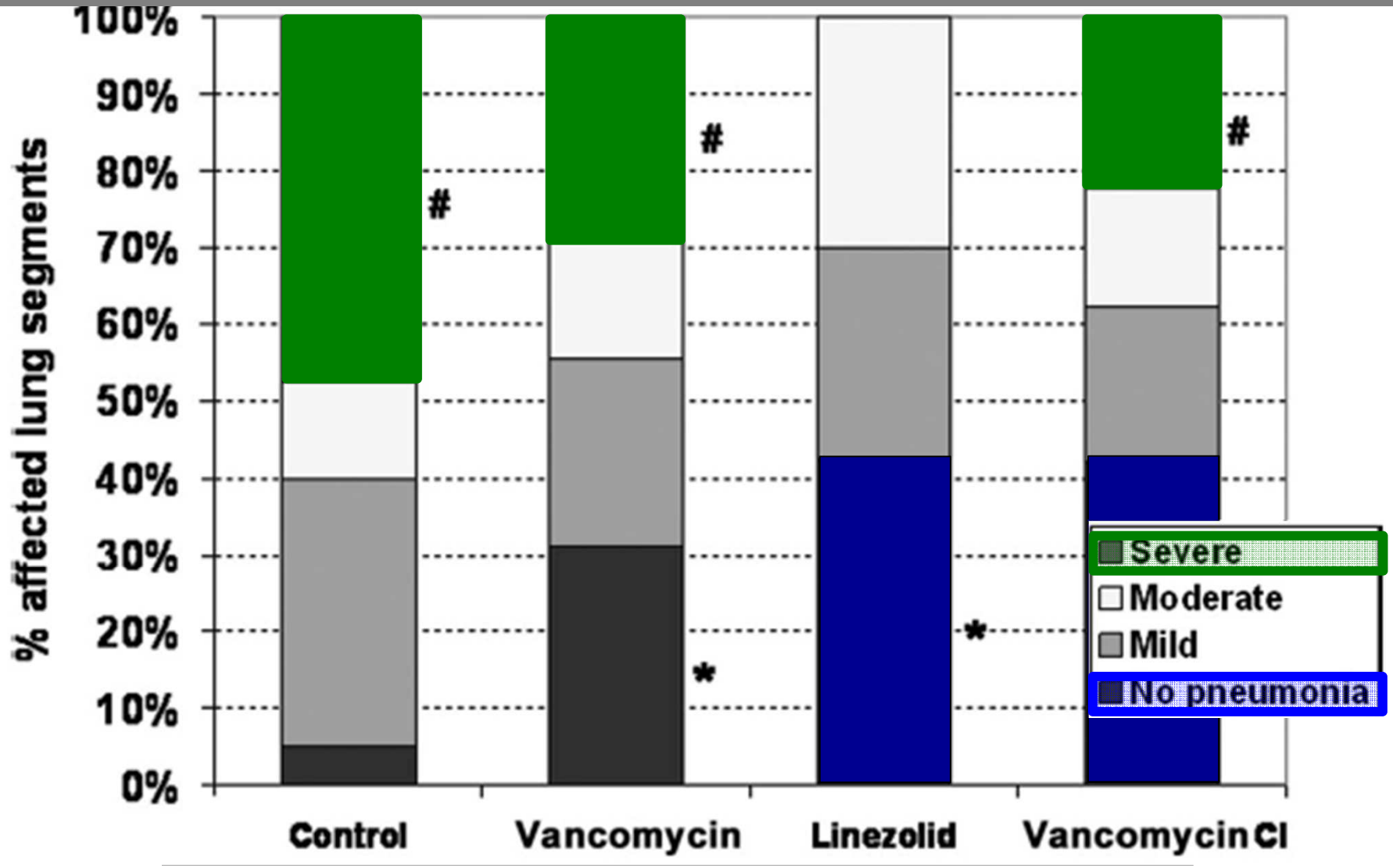


**Karau M, et al. Linezolid Is Superior to Vancomycin in Experimental Pneumonia Caused by Superantigen-Producing Staphylococcus aureus in HLA Class II Transgenic Mice.**
***Antimicrobial Agents Chemother 2012; 56: 5401-5***

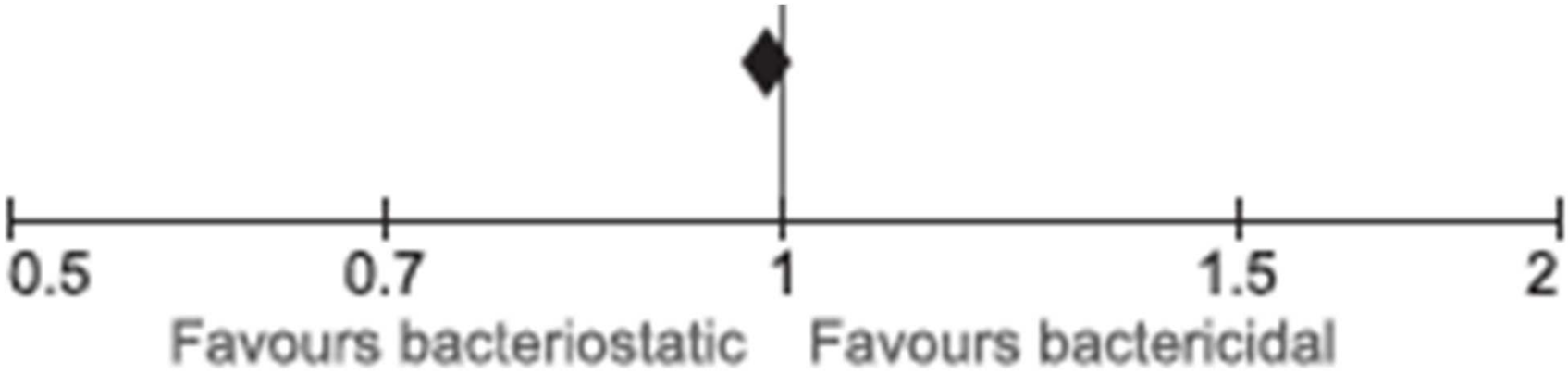



**DR3: modelo transgénico (HLA-DR3). Cepa de SARM SEB+**

*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*



Nemeth J, et al. **Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis.** *J Antimicrob Chemother 2014 in press*




| | | | | |
|---|---|---|---|---|
| Total (95% CI) | 0.99 [0.97, 1.01] | 4880 | 4717 | 100.0% |
| Total events | 3862 | 3753 | | |

Heterogeneity: Tau² = 0.00; Chi² = 41.83, df = 32 (P = 0.11); I² = 24%

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Chi² = 7.34, df = 3 (P = 0.06), I² = 59.1%

# Evidencia publicada en forma de meta-análisis sobre la eficacia de linezolid vs glicopéptidos

| Autor/año | Entidad/ Nº estudios | CC | EM | Mort |
|---|---|---|---|---|
| Falagas 08 | G/12 | 1.41 | 1.34 | - |
| BeiBei 10 | G/9 | 1.22 | 1.33 | - |
| Thamlikitkul 12 | N/6 | 1.23 | NA | - |
| Kalil 13 | N/9 | - | - | - |
| Jiang 13 | N/12 | - | 1.16 | - |
| Mao 13 | G/9 | 1.77 | 1.78 | - |
| Nemeth 14 | G/7 | 1.1 | NA | - |
| Wang 14 | N/9 | - | - | - |

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# Garin N, et al. β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia (open-randomized). *JAMA Intern Med 2014 (Oct)*

| End Point | Monotherapy (n = 291) | Combination Therapy (n = 289) | *P* Value |
|---|---|---|---|
| Primary end point | | | |
| Patients not reaching clinical stability at day 7[b] | | | |
| Secondary end points | | | |
| Intensive care unit admission | | | |
| Complicated pleural effusion[c] | | | |
| Length of stay, median (IQR), d | | | |
| Any change in the initial antibiotic treatment | | | |
| In-hospital death | | | |
| 30-Day death | | | |
| 90-Day death | | | |
| 30-Day readmission | | | |
| 90-Day readmission | | | |
| New pneumonia within 30 days[d] | | | |

proportion of patients who did not reach clinical stability at day 7, defined as a HR<

100/min, SBP> 90 mmHg, tympanic

**We were unable to demonstrate non-inferiority of initial empirical treatment with a β-lactam agent alone in hospitalized patients with moderately severe community-acquired pneumonia**

and maintained for a minimum of 24 hours

# Evidencia publicada en forma de meta-análisis sobre la eficacia de linezolid vs glicopéptidos

| Autor/año | Entidad/ Nº estudios | CC | EM | Mort | Plq | IR |
|---|---|---|---|---|---|---|
| Falagas 08 | G/12 | 1.41 | 1.34 | - | 11.7 | - |
| BeiBei 10 | G/9 | 1.22 | 1.33 | - | 3.26 | 0.31 |
| Thamlikitkul 12 | N/6 | 1.23 | NA | - | - | NA |
| Kalil 13 | N/9 | - | - | - | - | - |
| Jiang 13 | N/12 | - | 1.16 | - | - | 0.41 |
| Mao 13 | G/9 | 1.77 | 1.78 | - | - | 0.39 |
| Nemeth 14 | G/7 | 1.1 | NA | - | - | NA |
| Wang 14 | N/9 | - | - | - | - | 0.50 |

favorece a linezolid / favorece a vancomicina

## *Bosso JA, et al.* Relationship between Vancomycin Trough Concentrations and Nephrotoxicity: a Prospective Multicenter Trial.

*Antimicrob Agents Chemother 2011; 55: 5475-9*

| variable* | OR for nephrotoxicity | |
|---|---|---|
| Trough >15 mg/L | 3.64 | Trough ≤ 15, 8.9% NPT<br>Trough > 15, 29% NPT |
| Duration | 1.002 | mean: 9<br>Median: 7.5 |
| Black race | 2.58 | |
| Heart failure | 3.66 | |
| Neoplasia with M1 | 5.87 | |

*prospective study including 288 patients that received vancomycin and levels were measured after 72h of therapy

# Mensa J, et al. Guía de tratamiento antimicrobiano de la infección por *Staphylococcus aureus.* *Rev Esp Quimiot 2013; 26: 1-84*

Tabla 1 | Antimicrobianos recomendados para el tratamiento de la infección estafilocócica según localización del foco y sensibilidad de la cepa a meticilina

| entidad | SASM | SARM |
|---|---|---|
| Neumonía | Cloxacilina | Linezolid<br>Vancomicina ± rifampicina |