Infections à Staphylocoques: quelle place donner aux molécules récentes?

G Potel, J Caillon, C Jacqueline,

E Batard

EA3826 Nantes

Déclaration d’intérêts

Sanofi-Aventis: participation à

Un symposium national en 2011 (orateur)

Une réunion régionale en 2012 (orateur)

BayerPharma: participation à une FMC régionale (modérateur)

Astellas: invitation à l’ICAAC 2012

Ou…..la Vancomycine est-elle encore un anti-staphylococcique de première intention??

-Linézolide

-Daptomycine

-Ceftaroline

Pourquoi les données cliniques sont-elles les moins informatives?

- **Etudes de non-infériorité aboutissant à des AMM indigentes…**
- **Trop de paramètres non contrôlés**
  - **Ancienneté de l'infection (en heures)**
  - **Qualité de la prise en charge en dehors du traitement antibiotique**
  - **Virulence (génétique) de la souche responsable de l'infection**
  - **Statut immunitaire (génétique) de l'hôte**
  - **Environnement biochimique du site infecté**
  - **Comorbidités, âge**
  - **Gravité**
  - **etc…..**

In Vivo Efficacy of Continuous Infusion versus Intermittent Dosing of Linezolid Compared to Vancomycin in a Methicillin-Resistant *Staphylococcus aureus* Rabbit Endocarditis Model

Cédric Jacqueline, Eric Batard, Lucia Perez, David Boutoille, Antoine Hamel, Jocelyne Caillon, Marie-France Kergueris, Gilles Potel,* and Denis Bugnon

TABLE 1. Concentrations of linezolid or vancomycin (in serum) after continuous infusion

Day	Concn (mg/liter) after administration of the following continuous infusion regimen[a]:		
	Linezolid		Vancomycin
	20 mg/kg[b]	40 mg/kg[c]	
1	10.4 (1.6)	27.1 (13.6)	ND
2	19.4 (6.8)	47.1 (18.8)	22.3 (4.2)
3	22.8 (4.2)	49.7 (18.3)	ND
5	32.5 (8.8)	64.6 (6.3)	25.1 (3.7)

[a] The values are means (standard deviations). ND, not done.
[b] Simulated (daily) dose for humans.
[c] Twice the recommended dose for humans.

AAC, 2002

TABLE 2. Bacterial titers in vegetations

Regimen[a]	Mean ± SD $\log_{10}$ CFU/g of vegetation (no. of animals)		
	Strain SA-1	Strain SA-2	Strain SA-3
Control	8.8 ± 0.8 (14)	9.0 ± 0.3 (8)	9.1 ± 0.7 (9)
Linezolid ID, 5 days	6.7 ± 1.3 (9)[b]	7.3 ± 0.7 (9)[b]	6.4 ± 1.0 (8)[b]
Vancomycin ID, 5 days	8.8 ± 0.6 (5)	2.9 ± 0.8 (5)[c,d]	3.6 ± 1.2 (5)[c]
Linezolid CIV, 20 mg/kg, 5 days	2.5 ± 0.2 (5)[c,d]	4.8 ± 1.8 (6)[c,d]	4.5 ± 1.7 (6)[c]
Linezolid CIV, 40 mg/kg, 3 days	4.6 ± 2.1 (5)[c]	4.4 ± 1.5 (6)[c,d]	5.8 ± 2.4 (6)[b]
Linezolid CIV, 40 mg/kg, 5 days	3.7 ± 1.1 (5)[c,d]	2.5 ± 0.3 (5)[c,d]	2.7 ± 0.5 (5)[c,d]
Vancomycin CIV, 30 mg/kg, 5 days	8.5 ± 0.6 (5)	2.8 ± 0.9 (5)[c,d]	4.0 ± 0.9 (5)[c]

[a] ID, intermittent dosing simulating a human 10-mg/kg b.i.d. dose of linezolid or an intramuscular 50-mg/kg b.i.d. dose of vancomycin in humans; CIV, continuous (constant-rate) infusion simulating a 20- or 40-mg/kg daily dose of linezolid or a 30-mg/kg daily dose of vancomycin in humans.

[b] $P < 0.05$ versus controls.

[c] $P < 0.001$ versus controls.

[d] $P < 0.005$ versus linezolid intermittent dosing at 5 days.

AAC, 2002

In Vitro and In Vivo Assessment of Linezolid Combined with Ertapenem: a Highly Synergistic Combination against Methicillin-Resistant *Staphylococcus aureus*

Cedric Jacqueline, Jocelyne Caillon,* Olivier Grossi, Virginie Le Mabecque, Anne-Françoise Miegeville, Denis Bugnon, Eric Batard, and Gilles Potel

TABLE 2. Bacterial titers in vegetations after 4 days of treatment

Regimen	Mean $\log_{10}$ CFU/g of vegetation ± SD (no. of sterile vegetations/total no. of vegetations)		
	BCB8	P9	COL
Control	8.7 ± 0.9 (0/7)	9.1 ± 0.4 (0/6)	9.6 ± 0.5 (0/6)
Linezolid (10 mg/kg every 12 h)[c]	6.9 ± 0.7 (0/6)[a]	7.3 ± 0.8 (0/6)[a]	6.9 ± 0.9 (0/6)[a]
Ertapenem (1 g/day)[c]	8.0 ± 0.2 (0/4)	9.9 ± 0.4 (0/4)	10.1 ± 0.1 (0/4)
Linezolid plus ertapenem	2.6 ± 0.3 (6/6)[a,b]	2.7 ± 0.6 (5/6)[a,b]	3.6 ± 0.8 (2/6)[a,b]

[a] $P < 0.0001$ versus controls.
[b] $P < 0.0001$ versus linezolid and ertapenem treatment by Scheffe's test after analysis of variance.
[c] Simulated dose for humans.

AAC, 2006

Daptomycin Is Effective in Treatment of Experimental Endocarditis Due to Methicillin-Resistant and Glycopeptide-Intermediate *Staphylococcus aureus*▽

Francesc Marco,[1] Cristina García de la Mària,[1] Yolanda Armero,[1] Eurídice Amat,[1] Dolors Soy,[2] Asunción Moreno,[3] Ana del Río,[3] Manel Almela,[1] Carlos A. Mestres,[4] José M. Gatell,[3] María Teresa Jiménez de Anta,[1] and José M. Miró[3]* for the Hospital Clinic Experimental Endocarditis Study Group†

TABLE 2. Treatment of experimental endocarditis caused by MRSA 277 and GISA ATCC 700788

Treatment group	No. of sterile vegetations/ total no. (%)	Median (IQR[g]) $\log_{10}$ CFU/g of vegetation
MRSA 277		
Control[a]	0/20 (0)	9 (8.6–9.3)
Daptomycin[b]	13/18 (72)[c,g]	0 (0–1.5)[d,j]
Vancomycin RD[e]	7/20 (35)[c,h]	2 (0–5.6)[d,j]
Vancomycin HD[f]	9/18 (50)[g,h]	1 (0–2)[i,j]
GISA ATCC 700788		
Control[a]	0/17 (0)	9.5 (8.3–9.8)
Daptomycin[b]	12/19 (63)[k,m]	2 (0–2)[l,p]
Vancomycin RD[e]	4/20 (20)[k,n]	6.6 (2–6.9)[l,p]
Vancomycin HD[f]	4/20 (20)[m,n]	2.4 (2–4)[o,p]

AAC, 2008

Comparison of ceftaroline fosamil, daptomycin and tigecycline in an experimental rabbit endocarditis model caused by methicillin-susceptible, methicillin-resistant and glycopeptide-intermediate *Staphylococcus aureus*

Cédric Jacqueline[1]*, Gilles Amador[1], Eric Batard[1], Virginie Le Mabecque[1], Anne-Françoise Miègeville[1], Donald Biek[2], Jocelyne Caillon[1] and Gilles Potel[1]

Table 1. MICs of ceftaroline, daptomycin and tigecycline for MSSA, MRSA and GISA isolates

	MICs (mg/L)		
Strain	ceftaroline	daptomycin	tigecycline
MSSA	0.5	0.5	0.25
MRSA	1	0.5	0.5
GISA	1	0.5	0.5

JAC, 2011

Table 2. Bacterial titres in vegetations after 4 days of treatment

Treatment	Mean ± SD $\log_{10}$ cfu/g of vegetation (*n*)[d]		
	MSSA	MRSA	GISA
Controls	9.63 ± 0.80 (0/8)	8.80 ± 0.33 (0/10)	8.51 ± 0.39 (0/8)
Ceftaroline (HE 10 mg/kg/12 h)	≤2.44 ± 0.27 (8/8)[a,b]	≤2.59 ± 0.12 (8/8)[a,b]	≤2.48 ± 0.12 (8/8)[a,b]
Daptomycin (HE 6 mg/kg/24 h)	3.85 ± 2.43 (5/8)[a,b]	3.52 ± 1.98 (4/7)[a,b]	≤2.57 ± 0.31 (8/8)[a,b]
Tigecycline (HE 50 mg/12 h)	6.89 ± 1.83 (0/6)[c]	7.11 ± 1.18 (0/5)[c]	7.20 ± 1.27 (0/6)[c]

HE, human equivalent.

[a]$P < 0.001$ versus controls; Bonferroni's test after analysis of variance.

[b]$P < 0.01$ versus tigecycline; Bonferroni's test after analysis of variance.

[c]$P < 0.05$ versus controls; Bonferroni's test after analysis of variance.

[d]*n* = no. of sterile vegetations (below the limit of detection)/total no. of vegetations.

JAC, 2011

Efficacy of linezolid compared to vancomycin in an experimental model of pneumonia induced by methicillin-resistant *Staphylococcus aureus* in ventilated pigs*

Pilar Martinez-Olondris, MD; Montserrat Rigol, MVD, PhD; Dolors Soy, PharmD, PhD; Laura Guerrero, PhD; Carlos Agusti, MD; Maria Angels Quera, MD; Gianluigi Li Bassi, MD; Mariano Esperatti, MD; Nestor Luque, MD; Manto Liapikou, MD; Xavier Filella, MD; Francesc Marco, MD; Jordi Puig de la Bellacasa, MD; Antoni Torres, MD

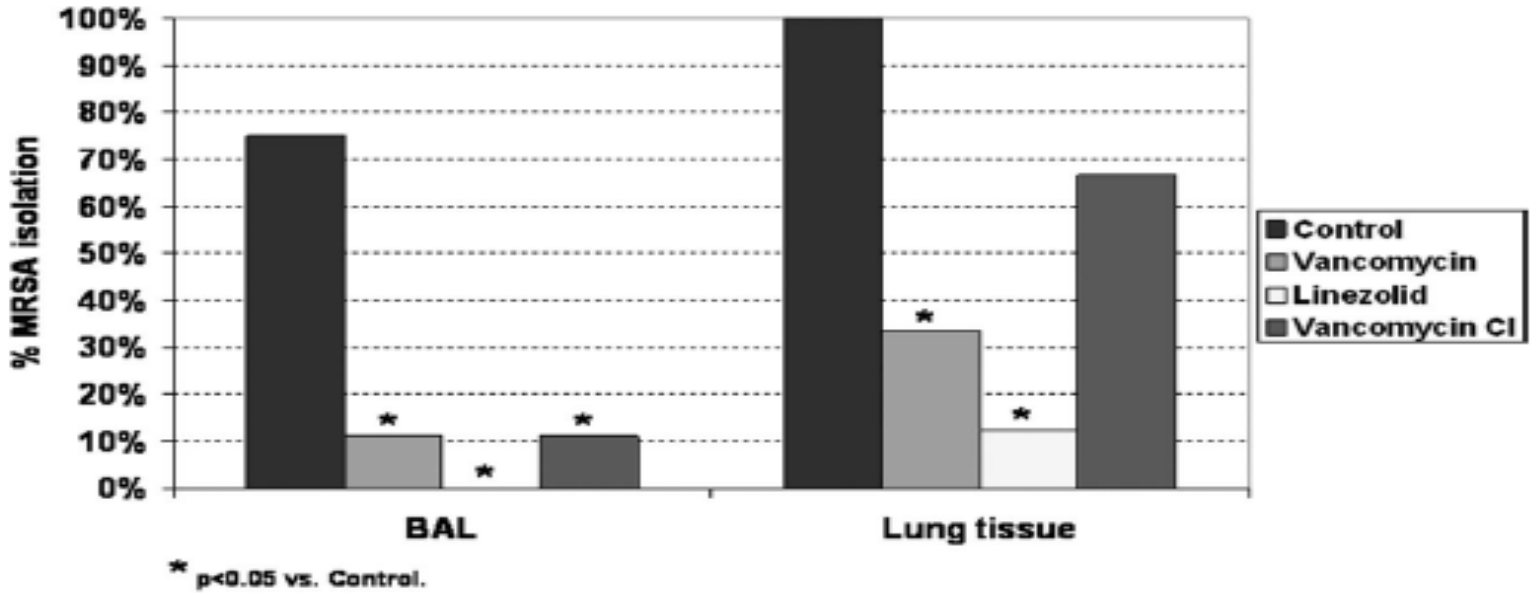


Figure 1. Microbiological findings in bronchoalveolar lavage and in lung tissue. *CI*, continuous infusion; *MRSA*, methicillin-resistant Staphylococcus aureus.

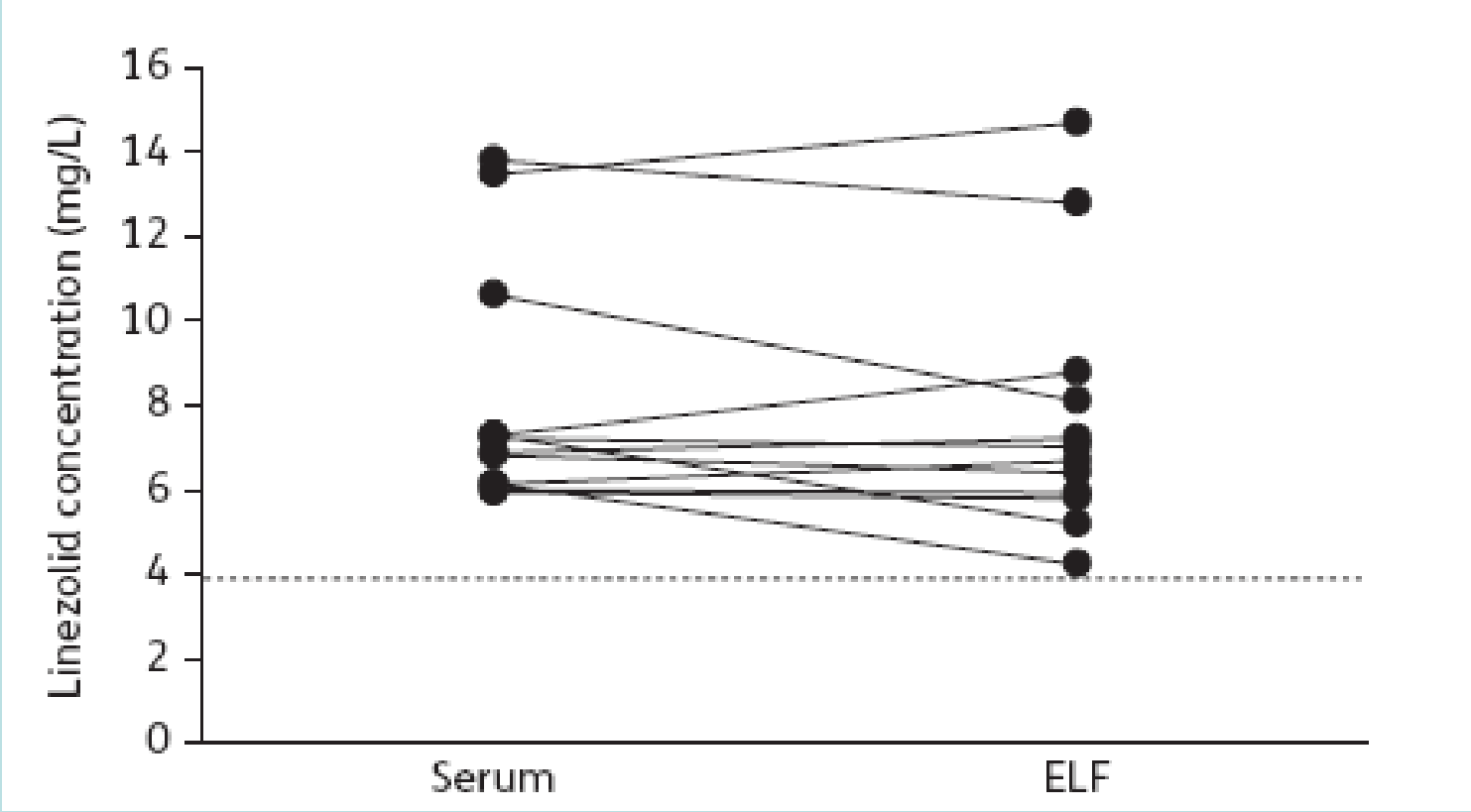
Traitement:4j

JNI Tours 13/06/2012

Crit Care Med, 2012

Alveolar diffusion and pharmacokinetics of linezolid administered in continuous infusion to critically ill patients with ventilator-associated pneumonia

Emmanuel Boselli[1,2]*, Dominique Breilh[2], Aurore Caillault-Sergent[1], Sarah Djabarouti[2], Christian Guillaume[1], Fabien Xuereb[2], Lionel Bouvet[1], Thomas Rimmelé[1], Marie-Claude Saux[2] and Bernard Allaouchiche[1]



JAC, juin 2012

Efficacy of daptomycin combined with rifampicin for the treatment of experimental meticillin-resistant *Staphylococcus aureus* (MRSA) acute osteomyelitis

M. Lefebvre, C. Jacqueline, G. Amador, V. Le Mabecque, A. Miegeville, G. Potel, J. Caillon, N. Asseray*

Université de Nantes, Faculté de Médecine, EA3826, 1 rue Gaston Veil, F-44035 Nantes, France

Table 1

Bacterial counts in bone, bone marrow and joint fluid (difference between Day 7 and Day 3).

Treatment	Mean ± S.D. $\Delta \log_{10}$ CFU/g of tissue (no. of sterile samples/total no.)		
	Bone	Bone marrow	Joint fluid
Control (n = 8)	0,11 ± 0,80 (0/8)	0,20 ± 0,59 (0/8)	0,10 ± 0,60 (0/8)
Daptomycin (n = 8)	−0,85 ± 1,08 (0/8)	−0,69 ± 0,67 (0/8)	−1,06 ± 0,99 (0/8)
Vancomycin (n = 14)	−0,75 ± 0,81 (0/14)	−0,61 ± 1,50 (0/14)	−0,72 ± 1,39 (0/14)
Daptomycin + rifampicin (n = 9)	−4,51 ± 0,81*,** (9/9)	−5,00 ± 1,16*,** (8/9)	−4,568 ± 1,32*,**,‡ (4/9)
Vancomycin + rifampicin (n = 8)	−3,85 ± 1,83*,** (1/8)	−4,24 ± 1,98*,** (1/8)	−2,46 ± 1,34*,† (1/8)

S.D., standard deviation; CFU, colony-forming units.

* P < 0,01 versus untreated controls.

** P < 0,001 versus corresponding monotherapy.

† P < 0,05 versus corresponding monotherapy.

‡ P < 0,01 versus vancomycin + rifampicin.

JNI Tours 13/06/2012

IJAA, 2010

Efficacy of the new cephalosporin ceftaroline in the treatment of experimental methicillin-resistant *Staphylococcus aureus* acute osteomyelitis

Cédric Jacqueline[1]*, Gilles Amador[1], Jocelyne Caillon[1], Virginie Le Mabecque[1], Eric Batard[1], Anne-Françoise Miègeville[1], Donald Biek[2], Yigong Ge[2], Gilles Potel[1] and Antoine Hamel[1]

Table 1. Bacterial titres in MRSA-infected tissues after 4 days of treatment

Treatment (no. of animals)	Mean ± SD $\Delta\log_{10}$ cfu/g of tissue (day 7 − day 3)[a]		
	joint fluid	bone marrow	bone
Controls (8)	0.09 ± 0.59	0.20 ± 0.59	0.11 ± 0.81
Ceftaroline (10)	−1.98 ± 1.00[b,c,d]	−2.95 ± 0.44[e,f]	−2.83 ± 1.50[e,f]
Linezolid (8)	−0.77 ± 1.39	−2.69 ± 1.92[b,c]	−2.25 ± 1.55[b,c]
Vancomycin (10)	−0.19 ± 1.19	−0.39 ± 1.60	−0.52 ± 0.69

[a]The efficacy measurement was made by comparing the bacterial load before (day 3 after infection) and after (day 7 after infection) antibacterial therapy.
[b]$P < 0.05$ versus controls.
[c]$P < 0.05$ versus vancomycin.
[d]$P < 0.05$ versus linezolid.
[e]$P < 0.001$ versus controls.
[f]$P < 0.01$ versus vancomycin.

JAC, 2010

Table 2. Bacterial titres in GISA-infected tissues after 4 days of treatment

Treatment (no. of animals)	Mean ± SD $\Delta\log_{10}$ cfu/g of tissue (day 7 − day 3)[a]		
	joint fluid	bone marrow	bone
Controls (8)	0.86 ± 0.30	0.63 ± 0.57	0.23 ± 0.41
Ceftaroline (8)	−1.55 ± 0.52[b]	−2.02 ± 0.93[b,c]	−2.01 ± 0.90[b,c]
Linezolid (8)	−1.10 ± 1.15[d]	−2.38 ± 1.02[b,c]	−2.23 ± 1.08[b,c]
Vancomycin (8)	−0.68 ± 0.34[d]	−0.41 ± 0.43	−0.57 ± 0.44

[a]The efficacy measurement was made by comparing the bacterial load before (day 3 after infection) and after (day 7 after infection) antibacterial therapy.
[b]$P < 0.001$ versus controls.
[c]$P < 0.01$ versus vancomycin.
[d]$P < 0.05$ versus controls.

JAC, 2010

Antibiotic Combinations with Daptomycin for Treatment of *Staphylococcus aureus* Infections

Kristina Nadrah and Franc Strle

Chemotherapy Research and Practice

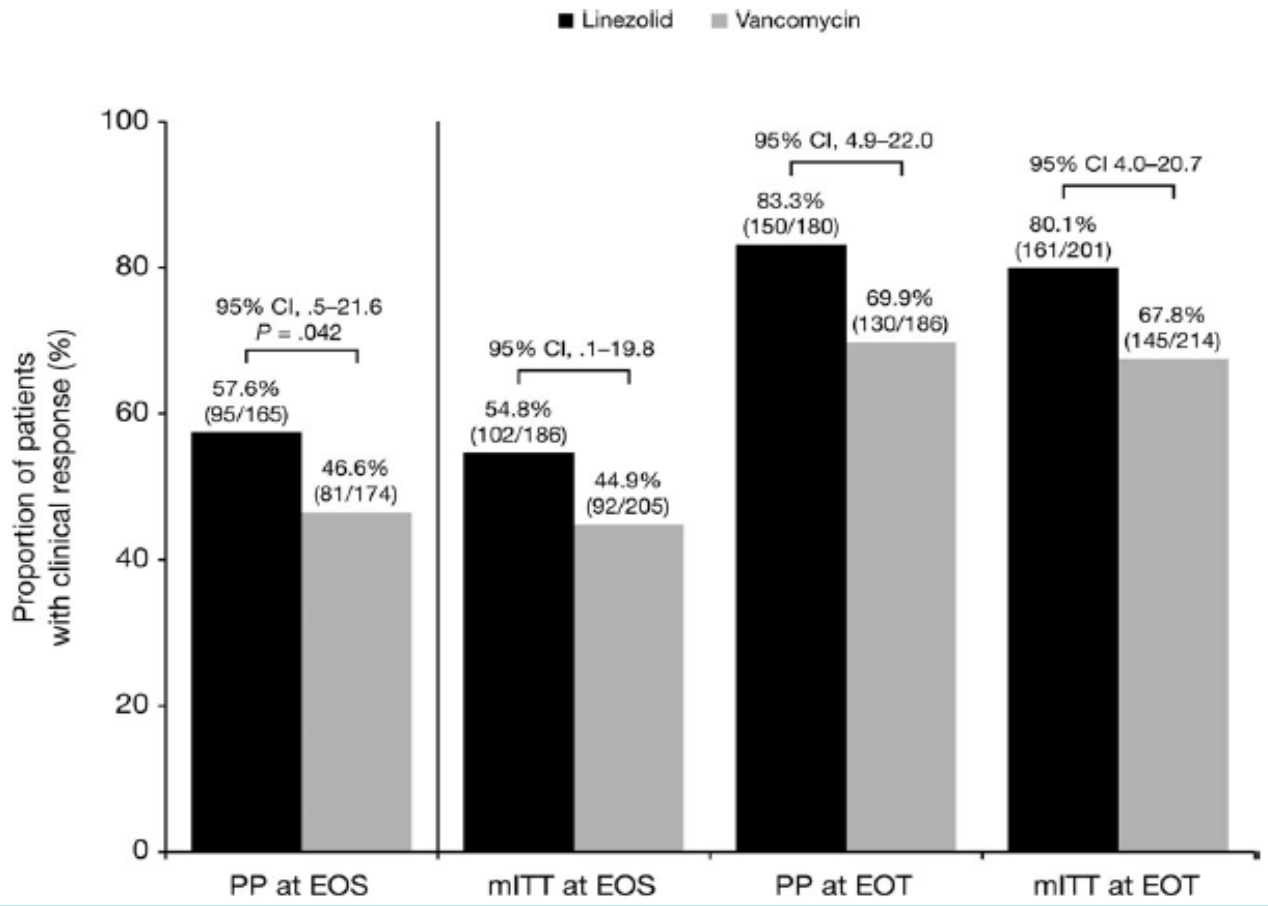
Table 2: Information on *in vivo* synergy of antibiotic combinations.

Model	Strain	Combination	Observation	Ref.
Experimental model of IE	MRSA	Daptomycin 6 mg/kg q24 h + rifampin 300 mg q8 h	Rifampin and gentamicin antagonized/delayed the bactericidal activity of daptomycin	[39]
		Daptomycin 6 mg/kg q24 h + gentamicin 1.3 mg/kg q12 h		
Rabbit model of IE	MRSA	Daptomycin 6 mg/kg q24 h + gentamicin 1 mg/kg q8 h	60% vegetations sterilized	[41]
		Daptomycin 6 mg/kg q24 h + rifampin 300 mg q8 h	20% vegetations sterilized	
Rabbit model of IE	DNS MRSA	Daptomycin 12 mg/kg q24 h + oxacillin 200 mg/kg q8 h	Enhanced bacterial clearance from tissues	[56]
Case report on IE	MRSA with progressive loss of susceptibility during treatment	Treated with vancomycin, then daptomycin 6 mg/kg q24 h, then daptomycin 12 mg/kg q24 h + rifampin 300 mg q8 h	Clinical success	[42]
Rabbit acute osteomyelitis model	MRSA	Daptomycin 6 mg/kg q24 h	Failure to eradicate bacteria	[50]
		Daptomycin 6 mg/kg q24 h + rifampin 20[a] mg/kg q12 h	Eradication of bacteria: bone 100%, bone marrow 89%, and joint fluid 44%	

- **….les conclusions des études études cliniques**

Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Richard G. Wunderink,[1] Michael S. Niederman,[2] Marin H. Kollef,[3] Andrew F. Shorr,[4] Mark J. Kunkel,[5] Alice Baruch,[5,a] William T. McGee,[6] Arlene Reisman,[5] and Jean Chastre[7]



JNI Tours 13/06/2012

CID, 2012

Antibiotic Treatment Against Methicillin-Resistant *Staphylococcus aureus* Hospital- and Ventilator-acquired Pneumonia: A Step Forward but the Battle Continues

Antoni Torres

Pneumology Department, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer -University of Barcelona, Ciber de Enfermedades Respiratorias, Spain

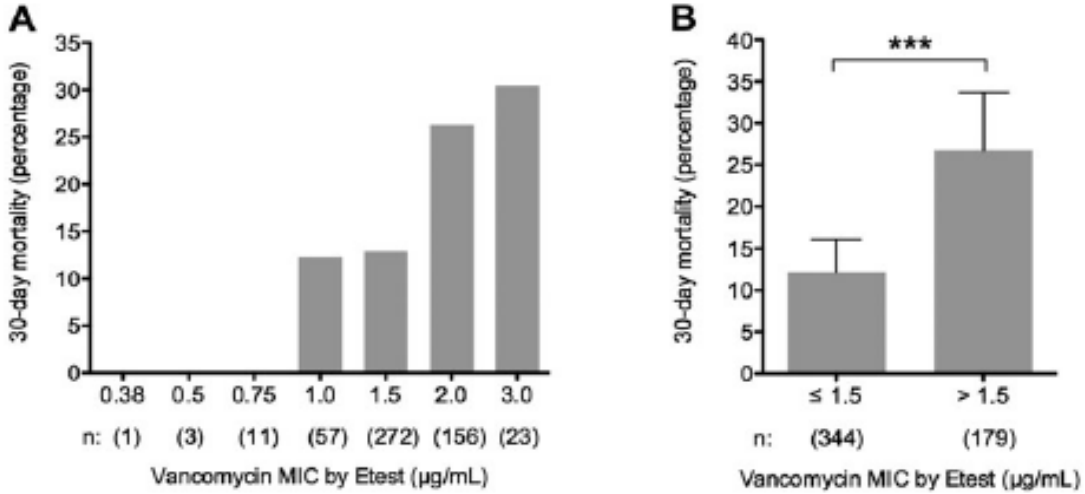
---

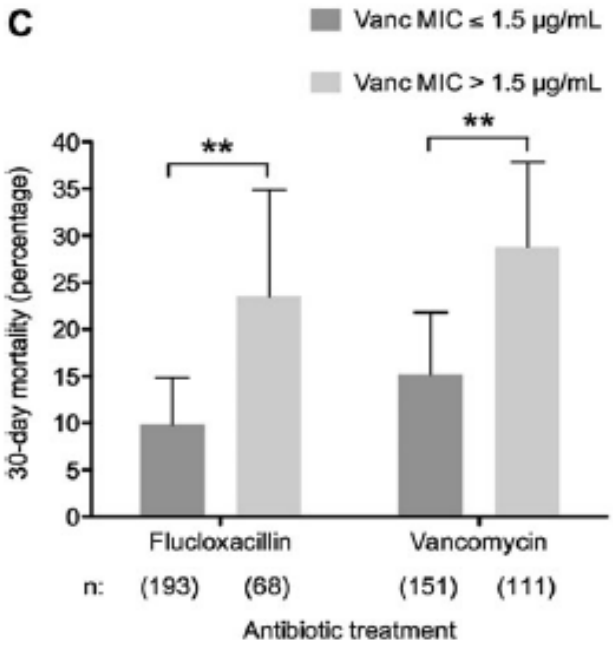
(See the Major Article by Wunderink et al, on pages 621–9.)

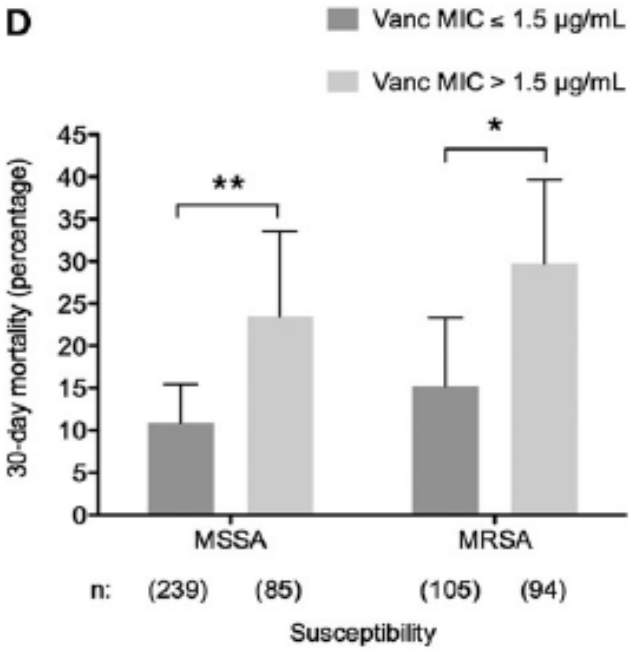
Antibiotic Choice May Not Explain Poorer Outcomes in Patients With *Staphylococcus aureus* Bacteremia and High Vancomycin Minimum Inhibitory Concentrations

Natasha E. Holmes,[1] John D. Turnidge,[2,3] Wendy J. Munckhof,[4,5] James O. Robinson,[6] Tony M. Korman,[7,8] Matthew V. N. O'Sullivan,[9] Tara L. Anderson,[10,11] Sally A. Roberts,[2] Wei Gao,[12] Keryn J. Christiansen,[13,14] Geoffrey W. Coombs,[13] Paul D. R. Johnson,[1,15,16,a] and Benjamin P. Howden[1,12,15,17,a]

JID, 2011







JNI Tours 13/06/2012

JID, 2011

Vancomycin Minimum Inhibitory Concentration and Outcome in Patients With *Staphylococcus aureus* Bacteremia: Pearl or Pellet?

Thomas L. Holland and Vance G. Fowler Jr

the practice of systematically switching patients infected with MRSA exhibiting vancomycin MIC ≤2 μg/mL from vancomycin to an alternative antibiotic is probably often unnecessary. Vancomycin's long reign as first-line therapy for serious MRSA infections may be in its twilight, but there is still no proven heir to the throne.

JID, 2011

New Gram-positive antibiotics: better than vancomycin?

Sebastiaan J. van Hal[a,b] and David L. Paterson[c]

Based on current evidence, greater microbiological and clinical cure rates are achieved with alternative agents. However, these differences do not translate into mortality benefits compared with vancomycin for the treatment of *S. aureus* infections.

Current Opinion in Infectious Diseases 2011

Et Alors?

1- Le Linezolide, la Daptomycine et la Ceftaroline sont des alternatives crédibles pour le traitement des infections staphylococciques sévères….en cas d'échec ou de contre-indication à la vancomycine

2-Situations cliniques: poumon (sauf la daptomycine), os, bactériémies/endocardites

3-…sous couvert d'un contrôle de la prescription par les médecins référents

High-Dose Daptomycin Plus Fosfomycin Was Safe and Effective in Treating Methicillin-Susceptible (MSSA) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) Endocarditis: From Bench to Bedside.

José M. Miró, José M. Entenza, Ana del Río, Maria Velasco, Ximena Castañeda, Cristina Garcia de la Mària, Marlyse Giddey, Yolanda Armero, Juan M. Pericàs, Carlos Cervera, Carlos A. Mestres, Manuel Almela, Carlos Falces, Francesc Marco, Philippe Moreillon, Asuncion Moreno, and the Hospital Clinic Experimental Endocarditis Study Group*

A paraître AAC 2012