Vancomycine et Linezolid: quelle place dans les infections à Gram(+) ?

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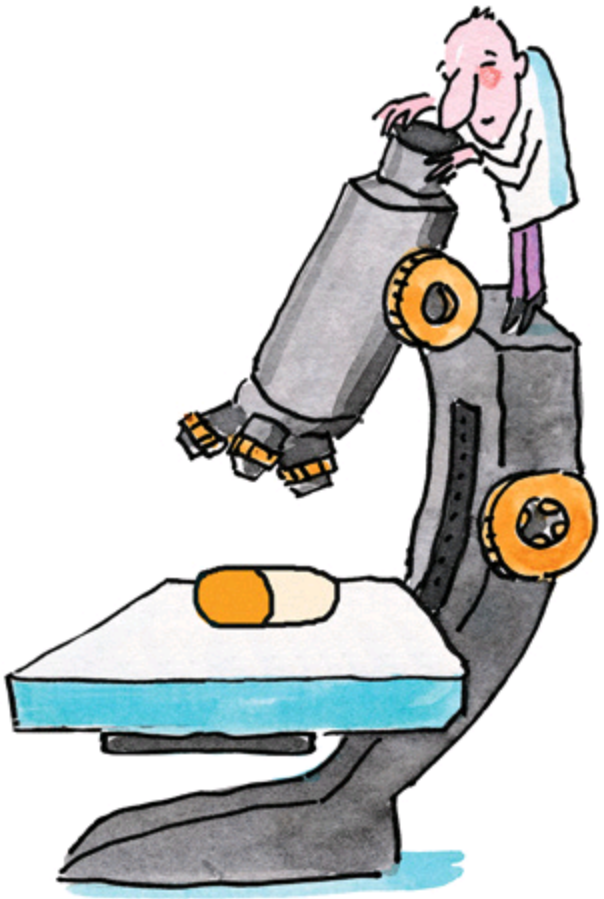
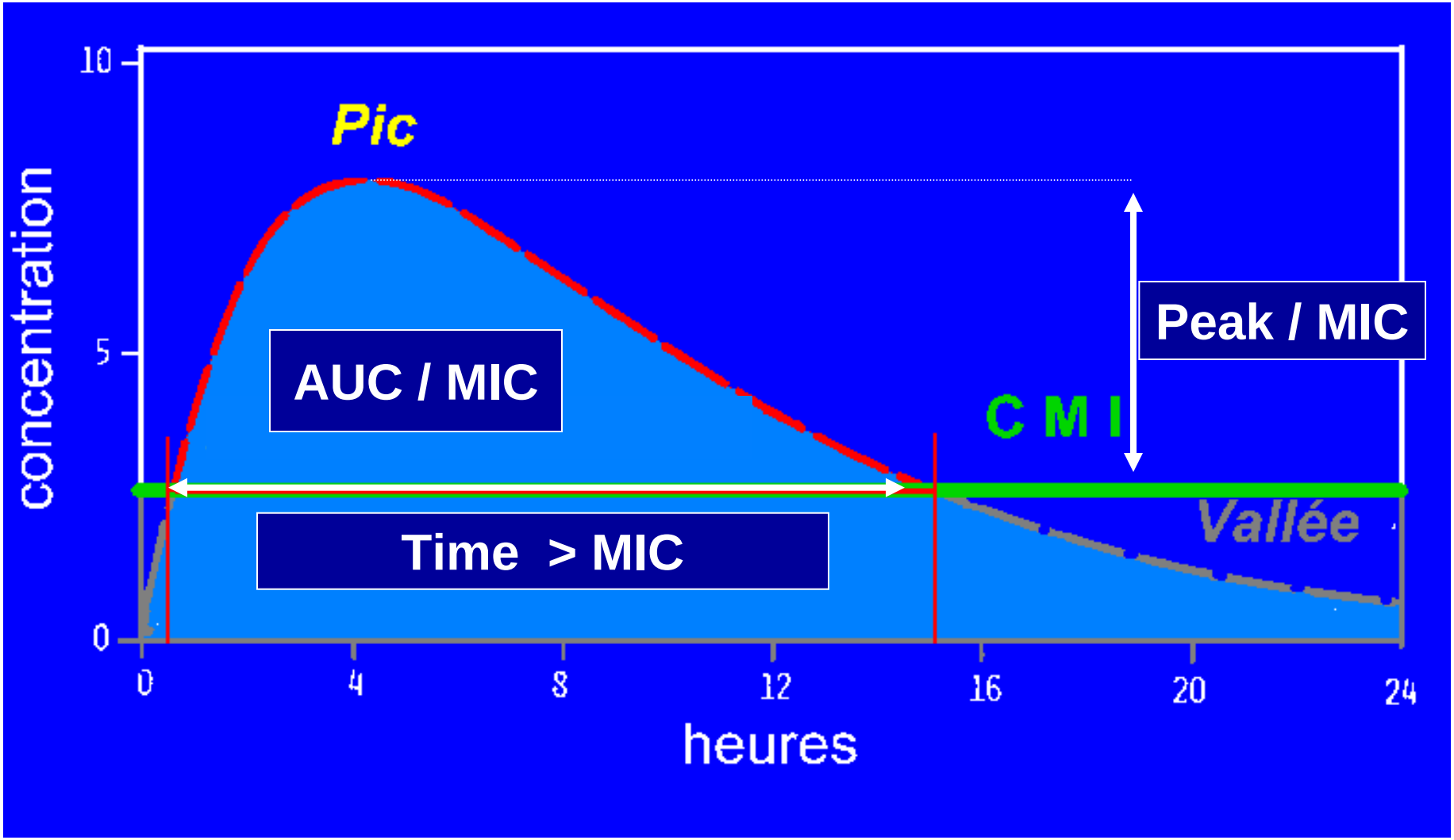
et centre de pharmacie clinique

Université catholique de Louvain

Optimisation du dosage



La pharmacodynamie: principe général

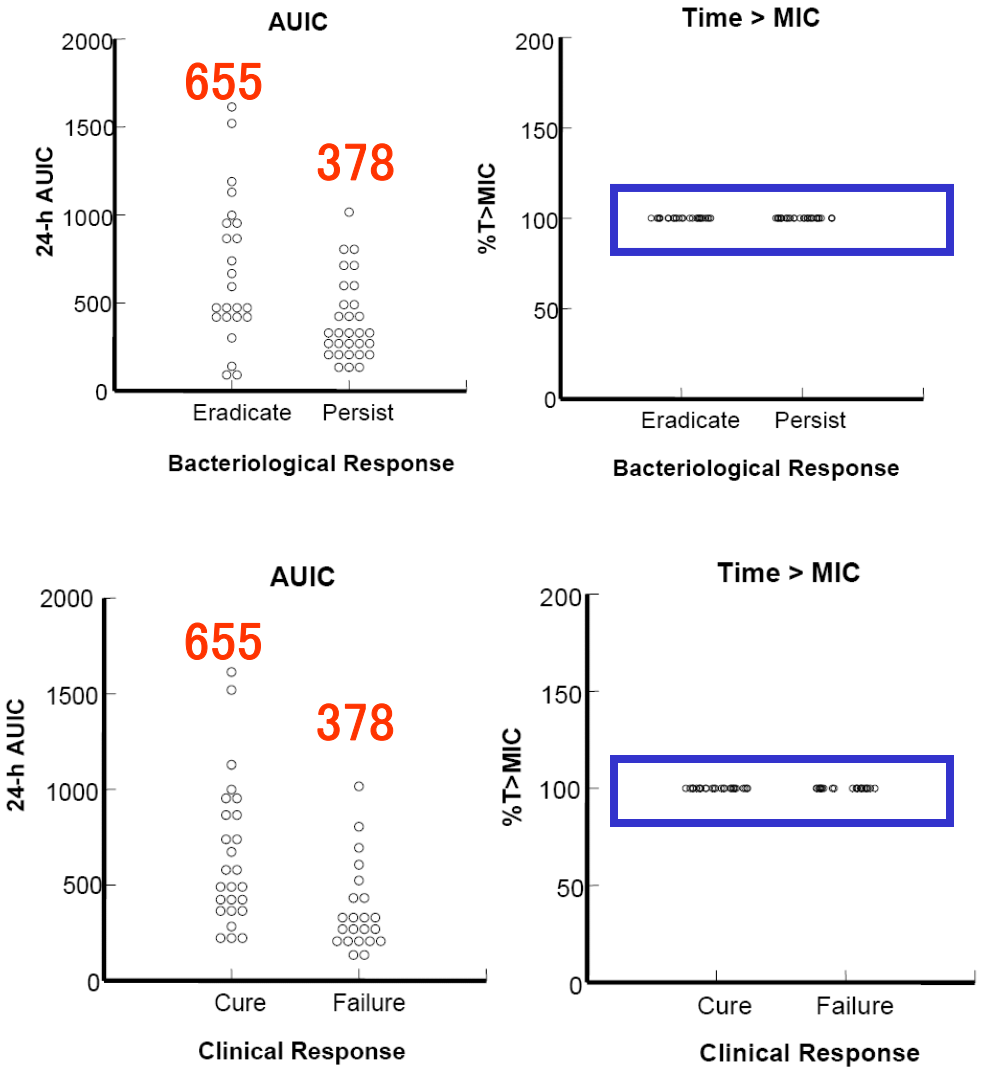


Pharmacodynamie de la vancomycine

Comment optimiser le dosage de vancomycine ?

108 patients; pneumonie à S. aureus

AUC / CMI plus élevée associée au succès!



% T > CMI = 100 !

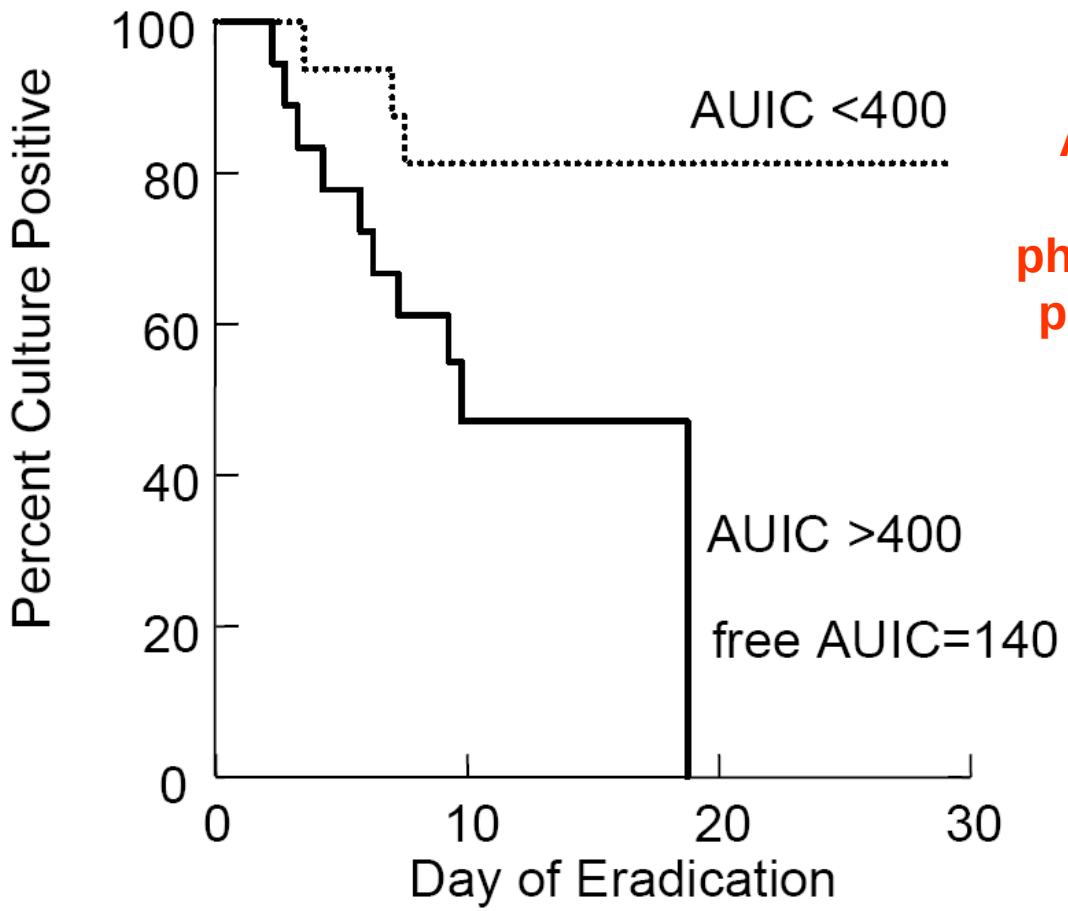
↓

non discriminant

Moise-Broder et al. (2004) Clin. Pharmacokinet. 43:925-42

Comment optimiser le dosage de vancomycine ?

108 patients; pneumonie à S. aureus



AUC / CMI > 400 : critère pharmacodynamique prédictif du succès (éradication)

Moise-Broder et al. Clin. Pharmacokinet. (2004) 43:925-42

Comment optimiser le dosage de vancomycine ?

un peu de mathématique...

Comment optimiser le dosage de vancomycine ?

administration discontinue

↓

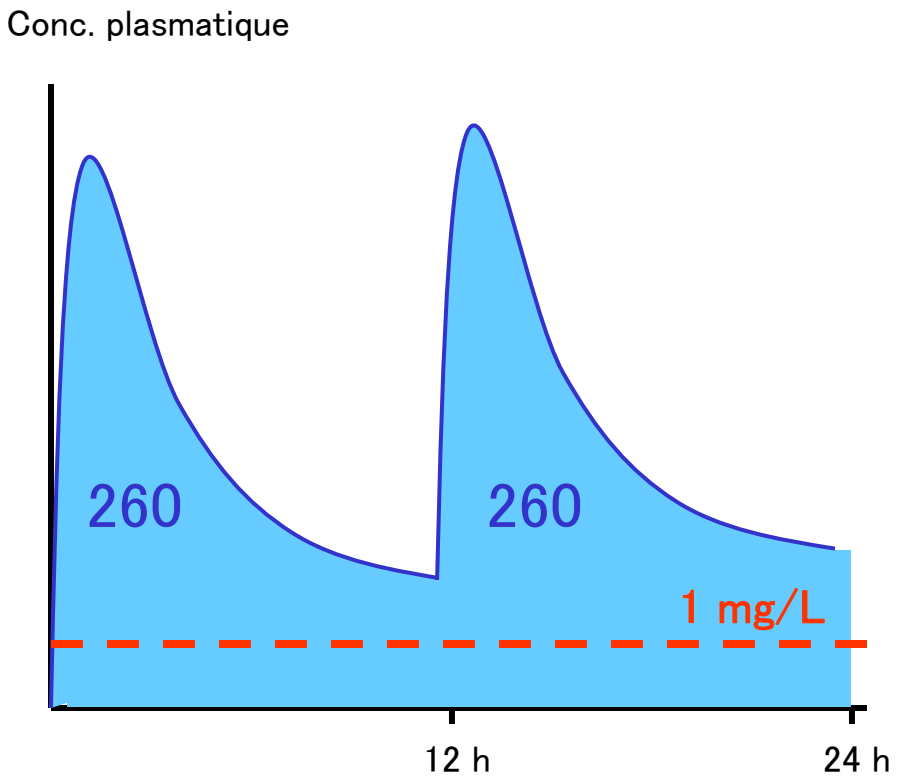
dose de 1 g (15 mg/kg)
AUC = 260 mg.h/L

↓

AUC / CMI = 400 h^{-1}

↓

CMI = AUC / 400
(260 x 2) / 400 ~ 1 mg/L



La dose conventionnelle (1g X 2) peut être efficace si CMI ≤ 1 mg/L

Comment optimiser le dosage de vancomycine ?

administration continue

↓

AUC / CMI = 400 h^{-1}

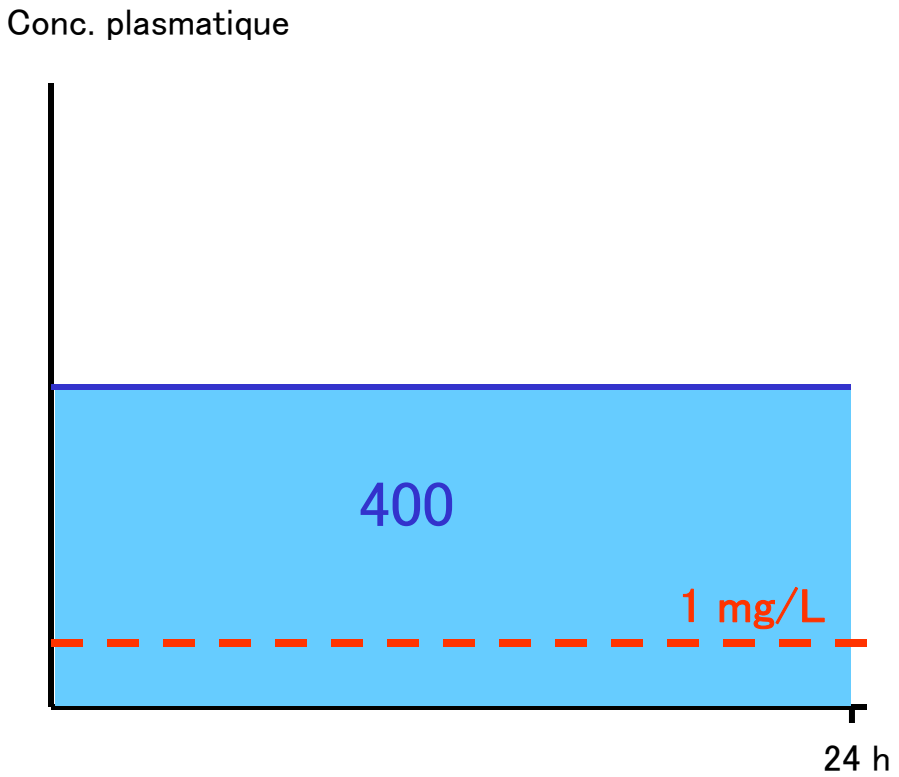
↓

AUC = 400 x CMI

↓

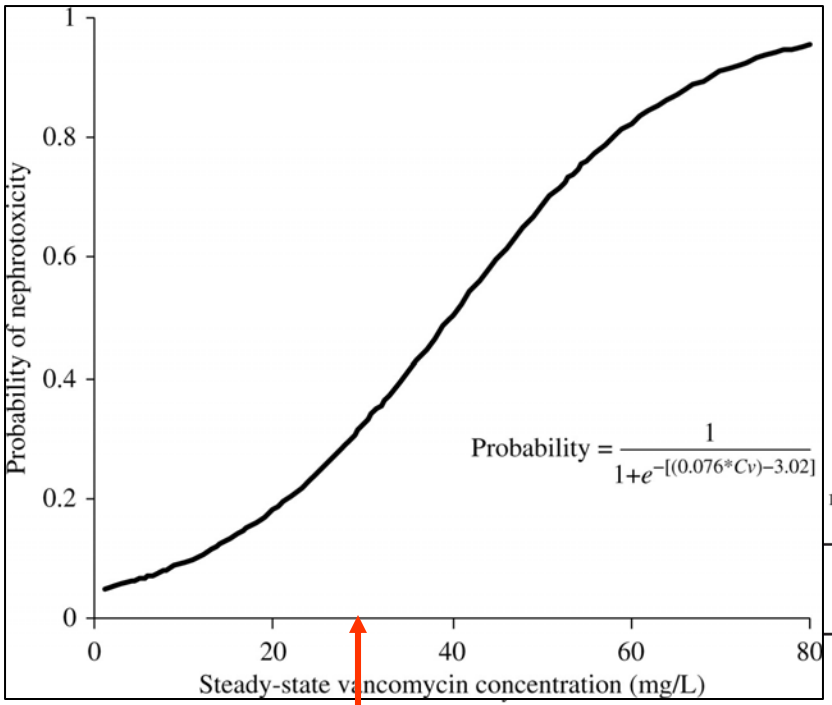
AUC = 24 h x conc. cible
→ conc. cible = AUC / 24 h
= 400 x CMI / 24

- Si CMI = 1 mg/L :
  Conc. = 400 x 1 / 24 = 17 mg/L
- Si CMI = 2 mg/L :
  Conc. = 400 x 2 / 24 = 34 mg/L



La dose en infusion continue peut être adaptée à la CMI…mais jusqu'où?

La toxicité limite la dose max !



nephrotoxicity associated with continuous vancomycin infusion

	Univariate analysis odds ratio (95% CI)	*P* value	Multivariate analysis odds ratio (95% CI)	*P* value
	3.157 (1.029–9.688)	0.049		
Indian	0.235 (0.029–1.896)	0.174		
male	0.390 (0.129–1.179)	0.095		
Baseline serum creatinine ≥133 μmol/L	14.000 (2.310–84.859)	0.004		
Bone and joint infections	0.433 (0.147–1.279)	0.130		
Co-morbidities				
hypertension	3.321 (1.112–9.922)	0.032	5.302 (1.159–24.246)	0.031
congestive cardiac failure	3.952 (0.605–25.816)	0.151		
renal diseases	6.833 (1.506–31.011)	0.013		
Concomitant exposure to				
aminoglycosides	3.455 (0.994–12.008)	0.051	6.594 (1.026–42.385)	0.047
loop diuretics	4.444 (1.093–18.079)	0.037	8.123 (1.449–45.528)	0.017
ACEI/ARB	3.700 (1.135–12.062)	0.030		
Vancomycin concentration[a]	1.079 (1.023–1.139)	0.006		
Vancomycin concentration ≥28 mg/L	19.091 (3.297–110.536)	0.001	21.236 (2.687–167.857)	0.004

Ingram et al. J. Antimicrob. Chemother. (2008) 62:168-171

Comment optimiser le dosage de vancomycine ?

administration continue

↓

AUC / CMI = 400 h^{-1}

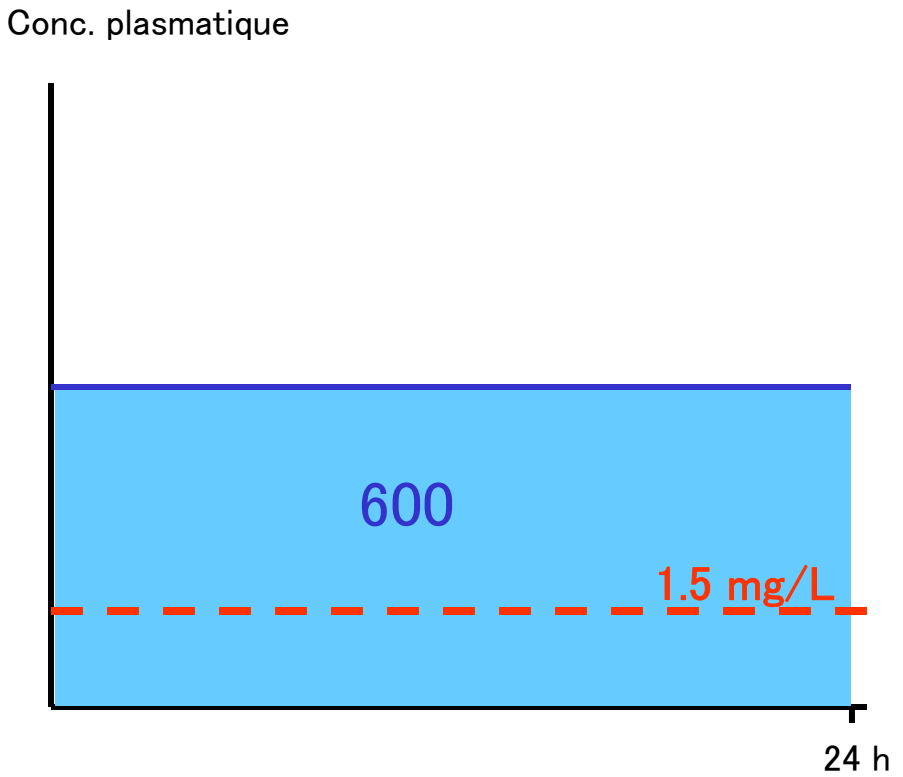
↓

AUC = 400 x CMI

↓

AUC = 24 h x conc. cible
→CMI = AUC / 400
= 24 x conc. / 400

· Conc. = 28 mg/L
→ CMI = 24 x 28 / 400
~ 1.5 mg/L



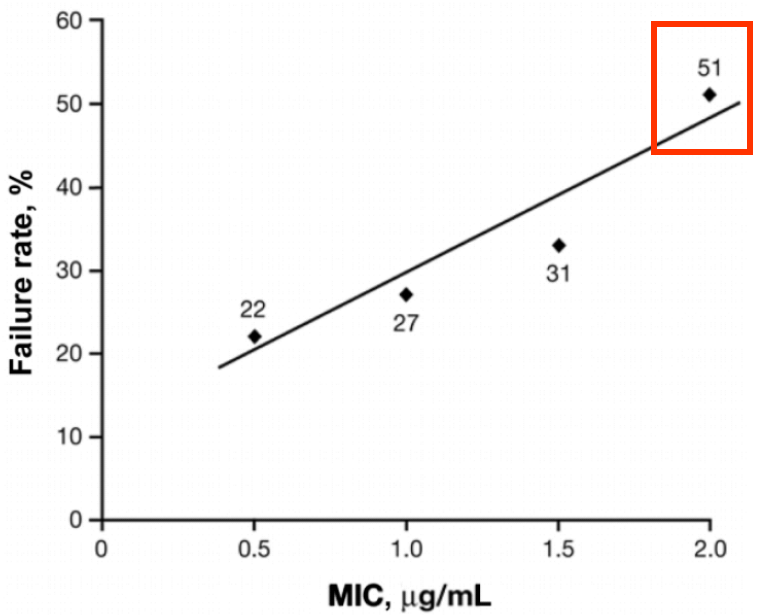
L'infusion continue peut être efficace et sûre pour un CMI ≤ 1.5 mg/L

Echecs thérapeutiques : lien avec les CMI

Types and sites of methicillin-resistant *Staphylococcus aureus* infection.

Infection type or site	Response to vancomycin therapy, no. of patients		
	Success (*n* = 18)	Failure (*n* = 45)	Indeterminate (*n* = 24)
Central catheter–related bacteremia	9	4	6
Bacteremia of unknown origin	1	5	0
Bone and joint	1	7	0
Device	0	1	0
Endocarditis	0	3	0
Intraabdominal	1	1	0
Respiratory	5	17	12
Skin and skin structure	1	6	6
Urinoma[a]	0	1	0

Renal allograft pyelonephritis with infected extrarenal urine collection.



Relationship of MIC to vancomycin treatment failure in patients with methicillin-resistant *Staphylococcus aureus* infections. Data points denote the percentage of patients for whom treatment failed.

Stevens, Clin. Infect. Dis. (2006) 42 : S51-57

Moise-Broder et al. Clin. Infect. Dis. (2004) 38:1700-1705

Echecs thérapeutiques : lien avec les CMI

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2008, p. 3315–3320 Vol. 52, No. 9
0066-4804/08/$08.00+0 doi:10.1128/AAC.00113-08

Relationship between Vancomycin MIC and Failure among Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia Treated with Vancomycin▽

T. P. Lodise,[1,2]* J. Graves,[1] A. Evans,[3] E. Graffunder,[4] M. Helmecke,[4] B. M. Lomaestro,[5] and K. Stellrecht[3]

Albany College of Pharmacy, Pharmacy Practice Department, Albany, New York[1]; Ordway Research Institute, Albany, New York[2]; Albany Medical Center Hospital, Department of Pathology and Laboratory Medicine, Albany, New York[3]; Albany Medical Center Hospital, Department of Epidemiology, Albany, New York[4]; and Albany Medical Center Hospital, Department of Pharmacy, Albany, New York[5]

TABLE 1. Comparison of outcomes between high (≥1.5 mg/liter) and low (<1.5 mg/liter) vancomycin MICs

Outcome	High MIC (n = 66)	Low MIC (n = 26)	P value
Overall failure[a]	24 (36.4)	4 (15.4)	0.049
30-day mortality[a]	12 (18.2)	3 (11.5)	0.5
Microbiologic failure[a]	6 (9.1)	0 (0)	0.18
Recurrence within 60 days[a]	11 (16.7)	1 (3.8)	0.17
Hospital length of stay after blood culture collection, median (IQR)	21 (9.0–43.0)	10.5 (9.0–16.5)	0.02
Switched to alternative antibiotic[a]	13 (19.7)	2 (7.7)	0.21

[a] All data presented are no. (percent) of patients.

Echecs thérapeutiques : lien avec les CMI

Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Clinical Infectious Diseases 2008; 46:193–200

Alex Soriano,[1] Francesc Marco,[2] José A. Martínez,[1] Elena Pisos,[1] Manel Almela,[2] Veselka P. Dimova,[2] Dolores Alamo,[2] Mar Ortega,[1] Josefina Lopez,[1] and Josep Mensa[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain

Table 3. Factors independently associated with shock in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
MIC		
1 μg/mL	1	
1.5 μg/mL	0.59 (0.33–1.05)	.07
2 μg/mL	0.33 (0.15–0.75)	.012
Female sex	1.81 (1.07–3.05)	.025
Liver cirrhosis	2.09 (1.06–4.11)	.03
Source of bacteremia		
Low risk	1	
Intermediate risk	1.25 (0.66–2.36)	.48
High risk	2.40 (1.28–4.49)	.008
Receipt of mechanical ventilation	3.19 (1.53–6.66)	.002

Vancomycine: où rencontre-t-on les échecs thérapeutiques ?

Journal of Infection (2008) 57, 110–115

Clinical failures of appropriately-treated methicillin-resistant *Staphylococcus aureus* infections

Julia C. Dombrowski [a,*], Lisa G. Winston [a,b]

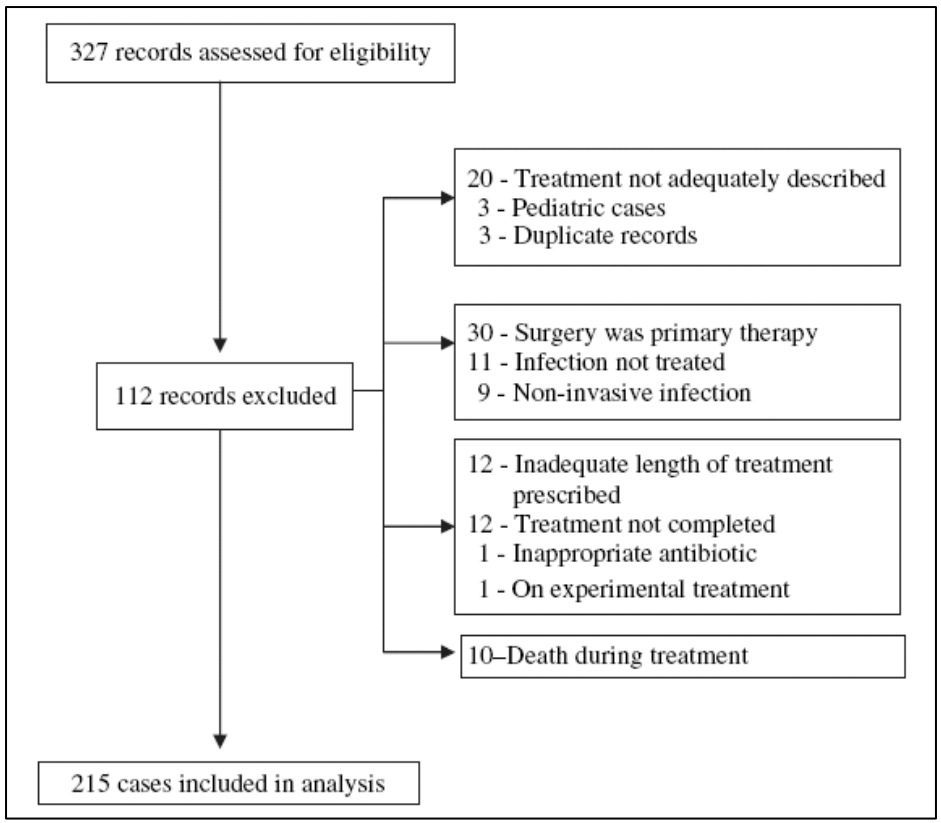


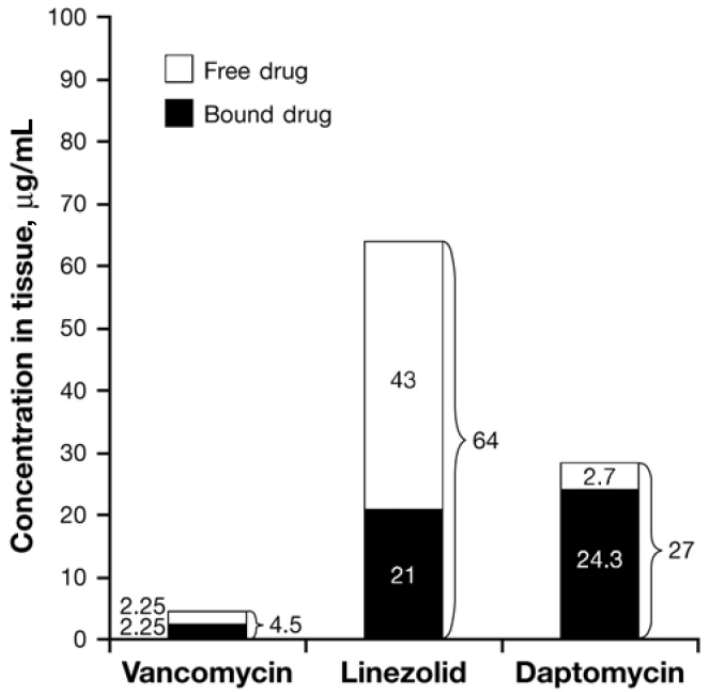
Table 2 Treatment and outcome by site of infection

Site	Total	Failure (%)	Treatment duration (days)	Monotherapy (%)
Osteomyelitis	81	37 (46)	42.9 (SD 5.1)	55 (68)
Bloodstream (without endocarditis)	42	5 (12)	25.8 (14.5)	32 (76)
Pneumonia	45	8 (18)	24.3 (14.8)	36 (80)
Endocarditis	32	5 (16)	37.4 (8.4)	19 (59)
Joint	23	1 (4)	39 (5.7)	19 (83)
Epidural abscess	18	5 (28)	40.1 (3.6)	12 (67)
Surgical site	15	4 (27)	34.6 (9.2)	13 (87)
Meningitis	1	0 (0)	42 (0)	1 (100)
Overall (by patient)[a]	215	53 (23)	see note	157 (73)

NOTE. Data not included since treatment duration was based primarily on site of infection.
[a] 25% of patients had infections at more than one site.

Vancomycine: où rencontre-t-on les échecs thérapeutiques ?

Est-ce une question de distribution ?



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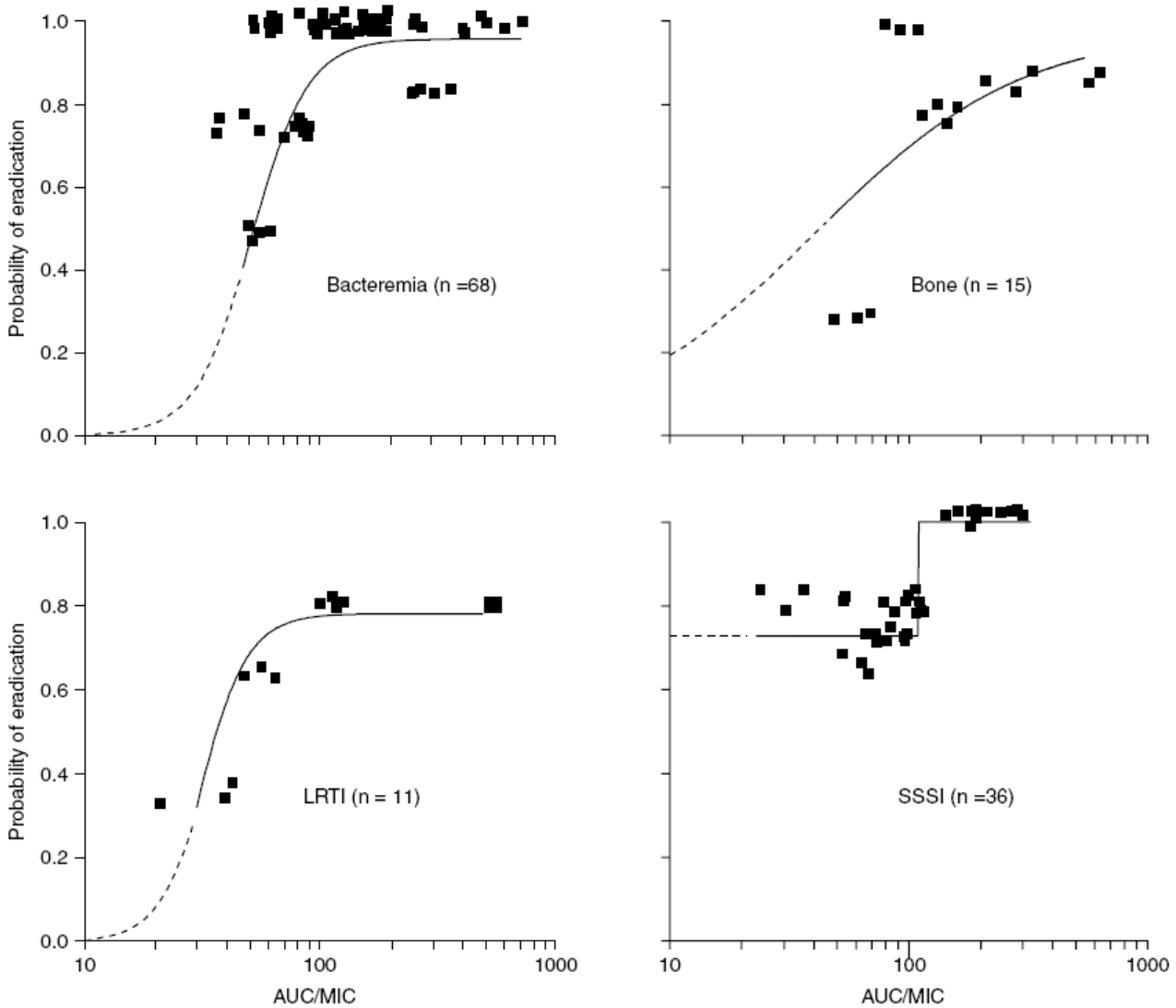
Stevens, Clin. Infect. Dis. (2006) 42 : S51-57

Pharmacodynamie du linezolid

Comment optimiser le dosage de linezolid ?

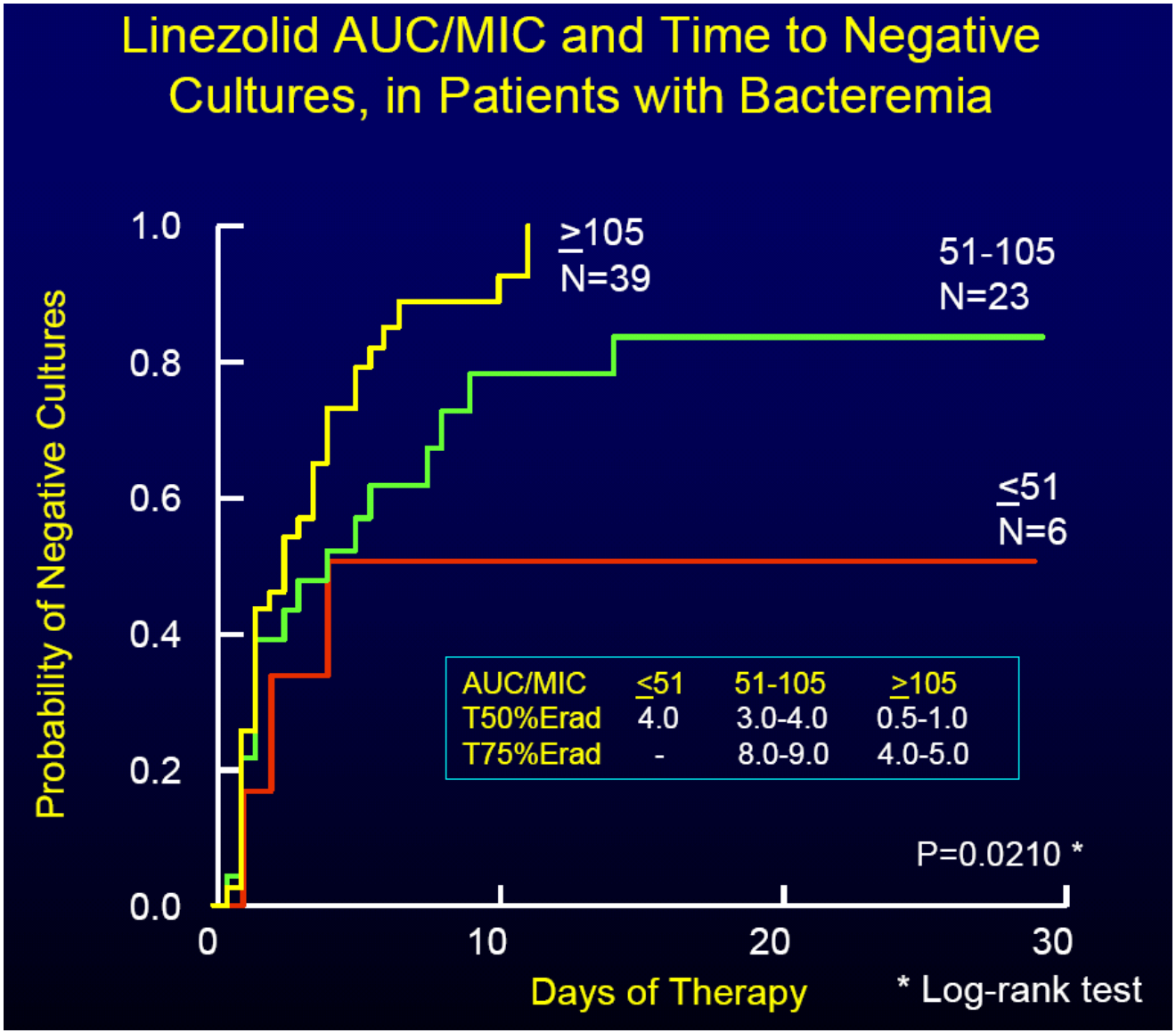
288 patients; linezolid 600 mg IV q12h



AUC /MIC > 100 pour différents types d'infections

Rayner et al. Clin. Pharmacokinet. (2003) 42:1411-23

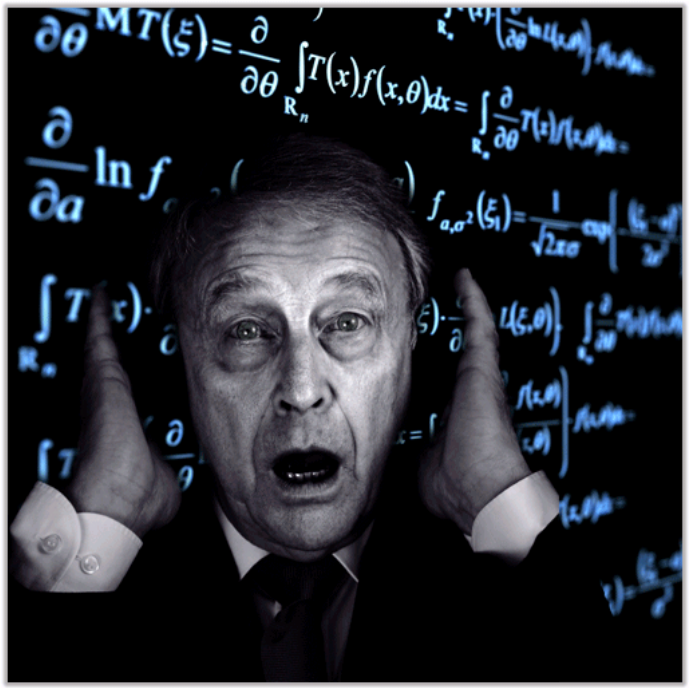
Comment optimiser le dosage de linezolid ?



Forrest et al. AAC & Clin. Pharmacother. (2003)

Comment optimiser le dosage de linezolid ?

back to maths...



Comment optimiser le dosage de linezolid ?

administration discontinue

↓

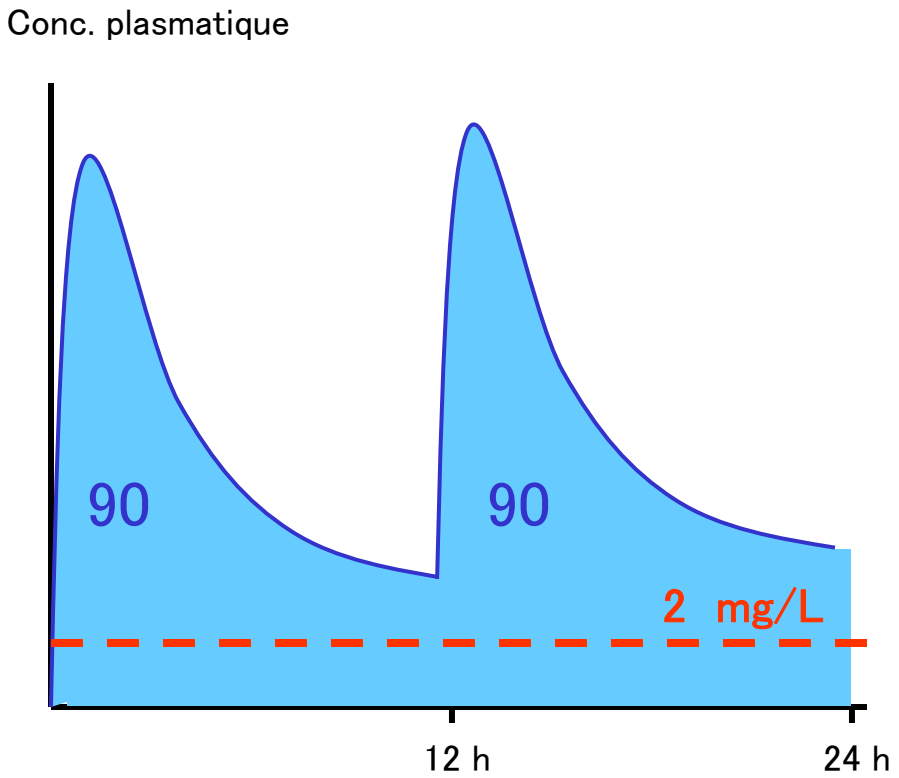
dose de 600 mg
AUC = 90 mg.h/L

↓

AUC / CMI = 100 h^{-1}

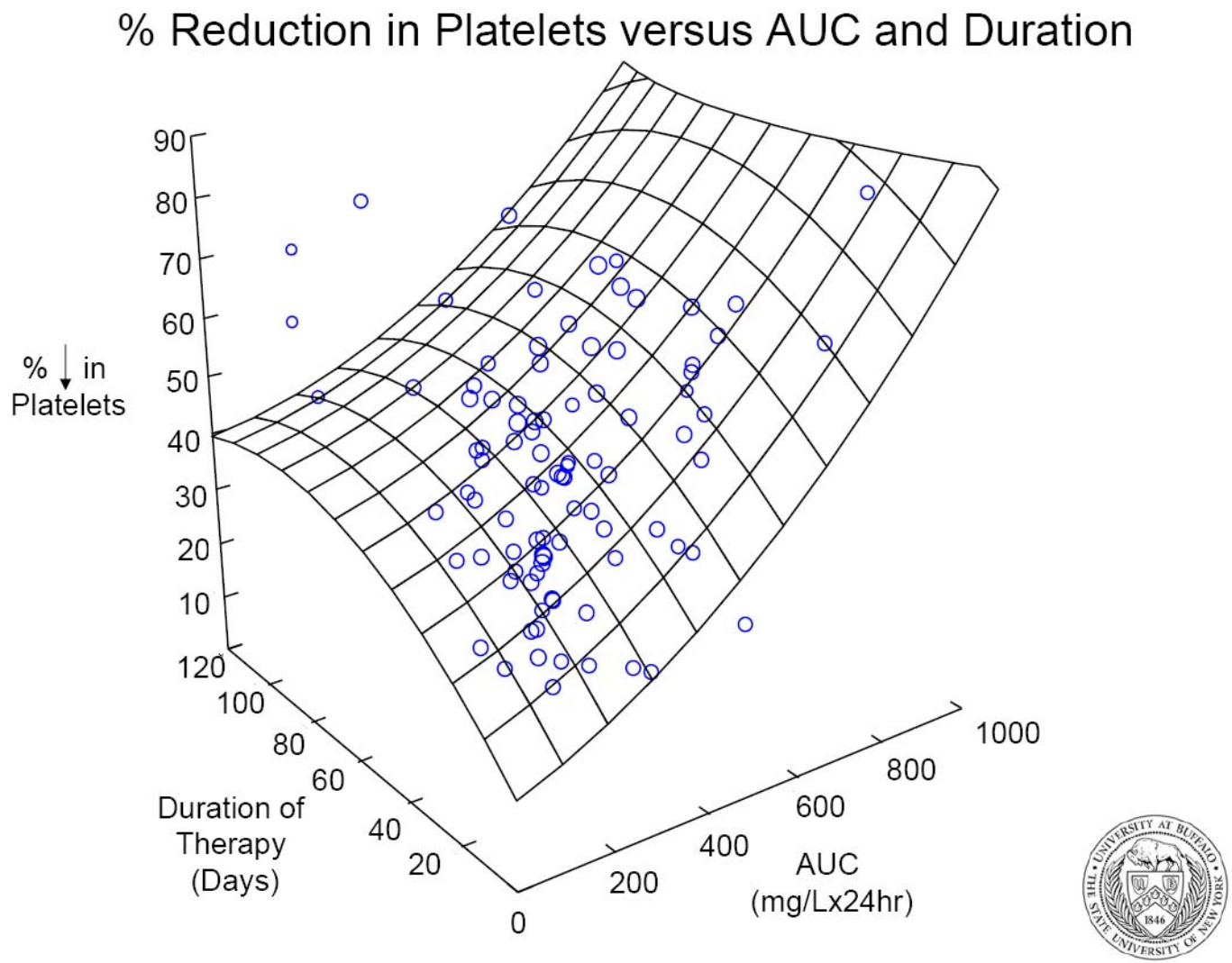
↓

CMI = AUC / 100
(90 x 2) / 100 ~ 2 mg/L



La dose conventionnelle (600 mg X 2) peut être efficace si CMI ≤ 2 mg/L

Quid de la toxicité ?



Forrest et al. ICAAC (2000) abstract 283

Linezolid: où rencontre-t-on les échecs thérapeutiques ?

Information for Healthcare Professionals

Linezolid
(marketed as Zyvox)

FDA ALERT [3/16/2007]: FDA is issuing this alert to advise you of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. In this study, patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to infection. Patients with Gram positive infections to their antibiotic treatment. In contrast, mortali linezolid who were infected with Gram negative o and Gram negative organisms, or who had no inf

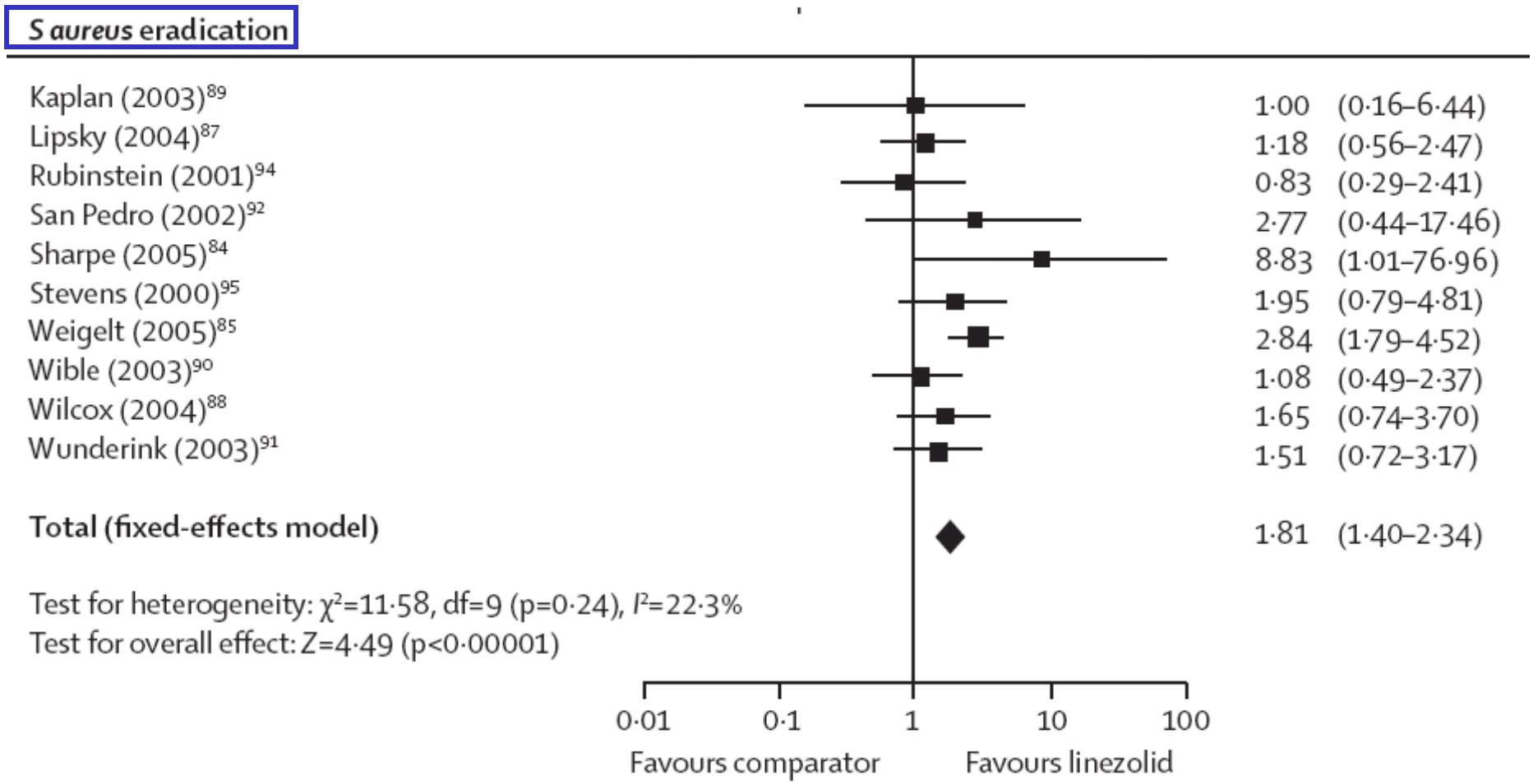
The following table summarizes deaths by baseline pathogen (all culture sources).

Type of organism	Linezolid N=363	Comparator N=363
	Number died N=78	Number died N=58
Gram positive only	37/222 (16.7%)	37/215 (17.2%)
Gram negative only	4/15 (26.7%)	1/11 (9.1%)
Gram positive and Gram negative	16/46 (34.8%)	7/39 (17.9%)
No organism	20/76 (26.3%)	12/92 (13%)
Other	1/4 (25%)	1/6 (16.7%)

Etudes cliniques

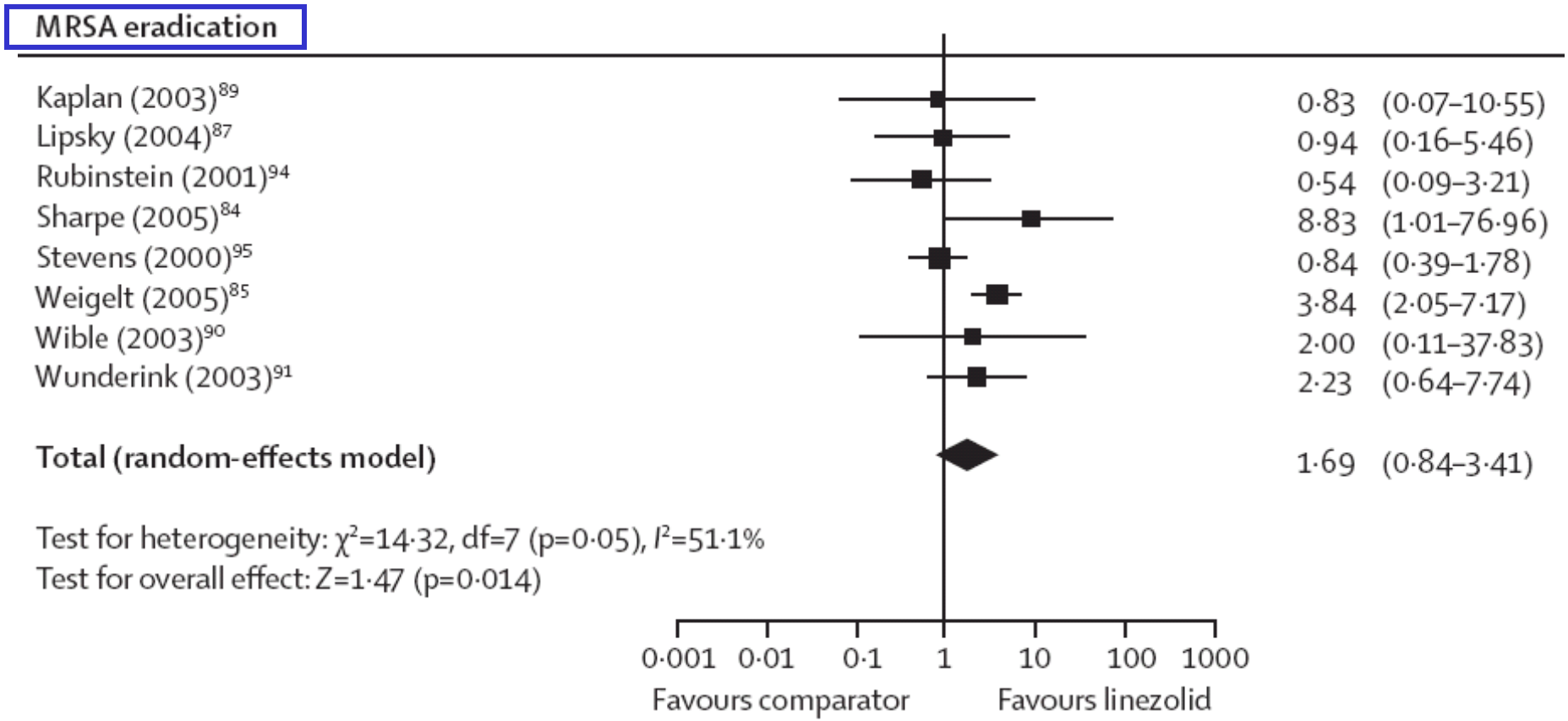
Succès bactériologique

Vancomycine vs linezolid: éradication bactérienne



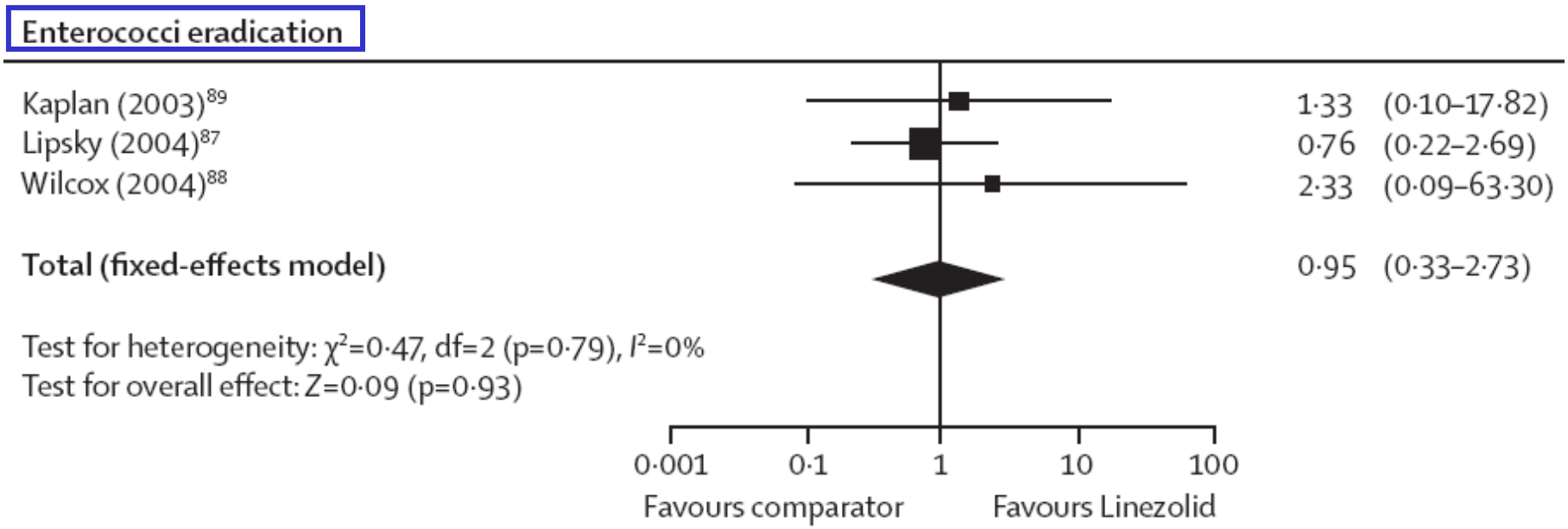
Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: éradication bactérienne



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: éradication bactérienne



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: MRSA

Journal of Antimicrobial Chemotherapy (2007) **60**, 1361–1369
doi:10.1093/jac/dkm369
Advance Access publication 3 October 2007

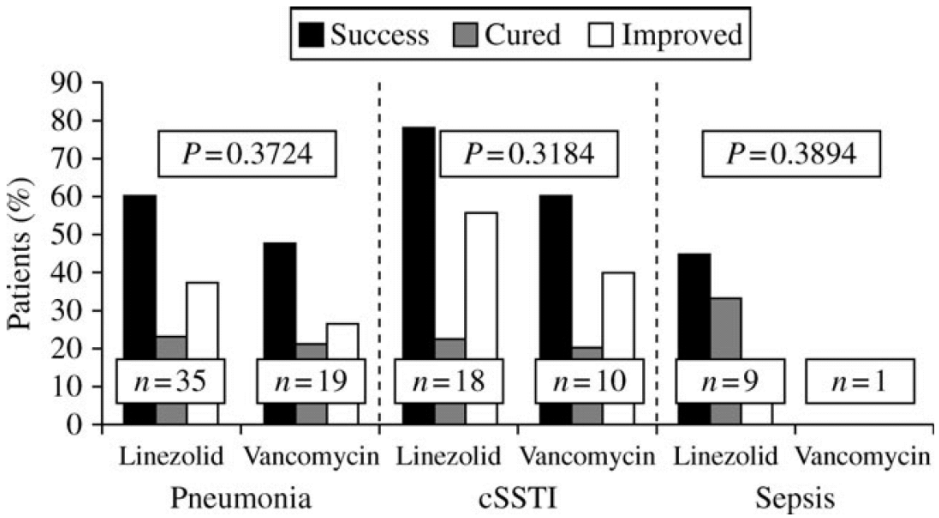
JAC

Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan

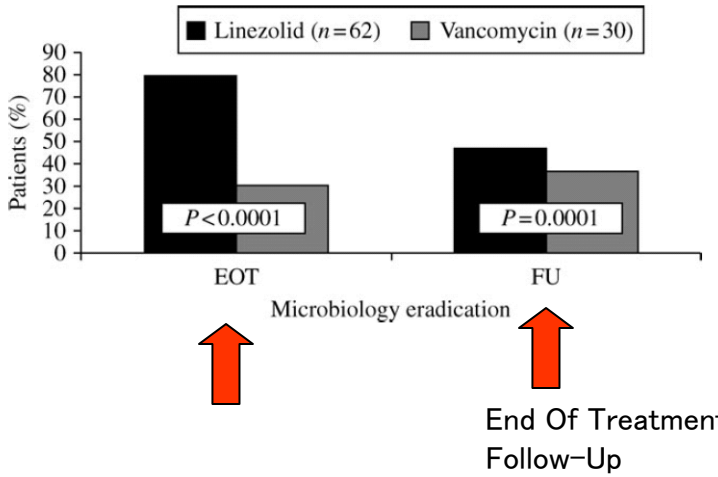
S. Kohno[1], K. Yamaguchi[2], N. Aikawa[3], Y. Sumiyama[4], S. Odagiri[5], N. Aoki[6], Y. Niki[7], S. Watanabe[8], M. Furue[9], T. Ito[10], R. Croos-Dabrera[11] and K. J. Tack[11]*†

100–51 patients

Efficacité clinique



Eradication bactérienne



End Of Treatment
Follow-Up

Indications actuelles

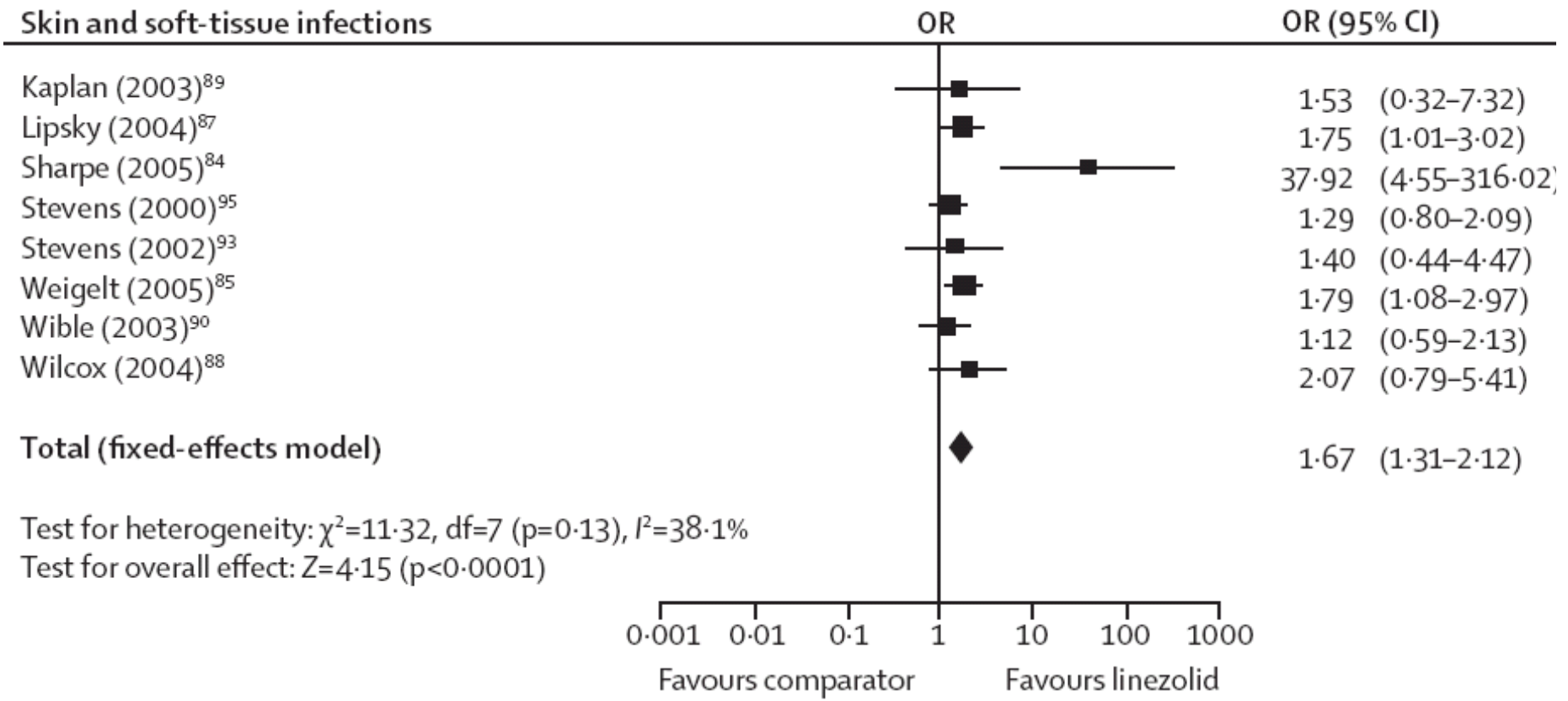
Vancomycine

- **infections graves staphylococciques résistantes à la méthicilline**.
- **infection staphylococcique sévère chez des patients allergiques** à la pénicilline ou chez des patients qui n'ont pas répondu à un traitement aux pénicillines ou aux céphalosporines.
- **endocardite** à streptocoque ou entérocoque (+ AG); prophylaxie de l'endocardite bactérienne chez les patients allergiques à la pénicilline
- **entérocolite** staphylococcique et colite pseudomembraneuse à *C. difficile*.

Linezolid

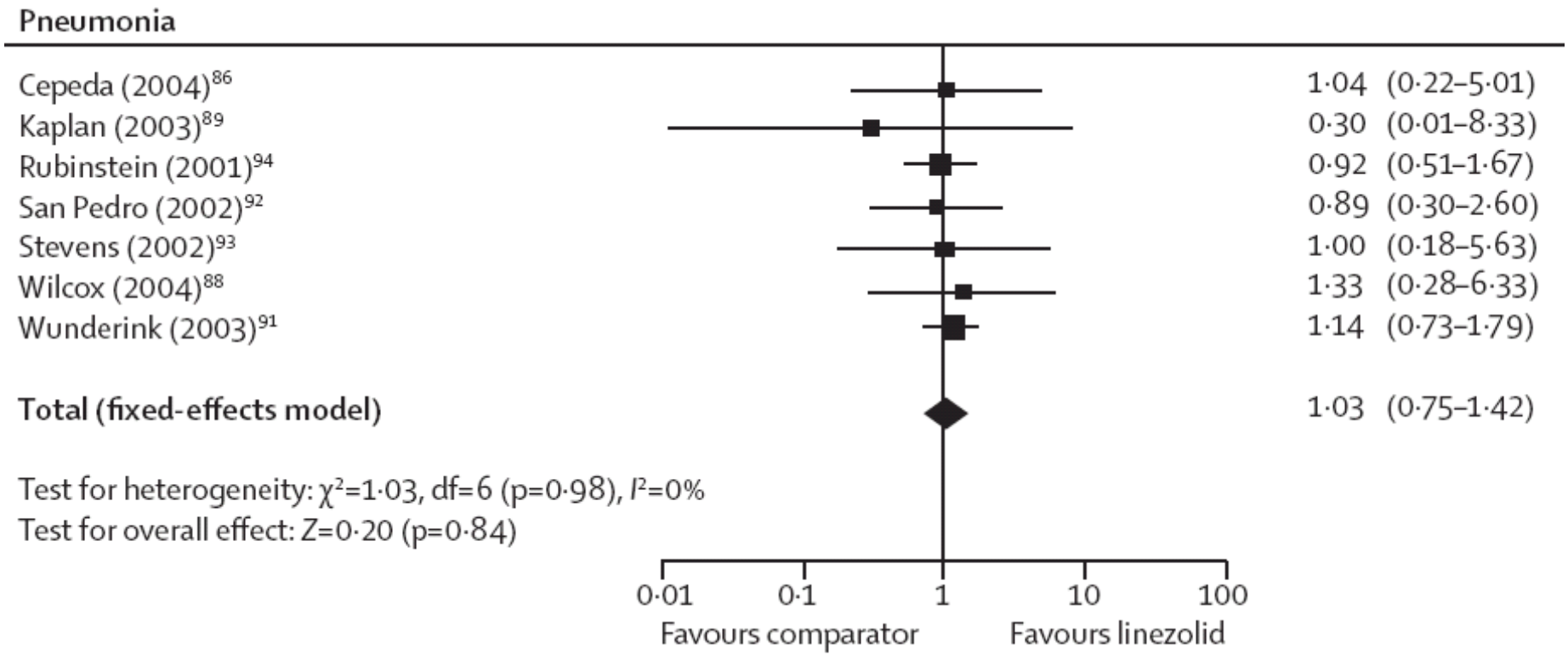
- **infections de la peau et des tissus mous, ne peut s'utiliser QUE**
  - si démonstration que l'infection est due à un Gram(+) sensible
  - en absence d'autres alternatives et en combinaison avec un anti Gram(-) si infection mixte suspectée
- **pneumonie nosocomiale / communautaire ne peut s'utiliser QUE**
  - si infection suspectée à un Gram(+) sensible
  - en combinaison avec un anti Gram(-) si infection mixte suspectée

Vancomycine vs linezolid: infections peau-tissus mous



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: pneumonie



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: pneumonie

30–20 patients

CHEST Original Research

CRITICAL CARE MEDICINE

Early Microbiological Response to Linezolid vs Vancomycin in Ventilator-Associated Pneumonia Due to Methicillin-Resistant *Staphylococcus aureus**

Chest 2008;134;1200-1207

Richard G. Wunderink, MD, FCCP; Meryl H. Mendelson, MD; Michael S. Somero, MD; Timothy C. Fabian, MD; Addison K. May, MD; Helen Bhattacharyya, PhD; Kenneth V. Leeper, Jr., MD, FCCP; and Joseph S. Solomkin, MD

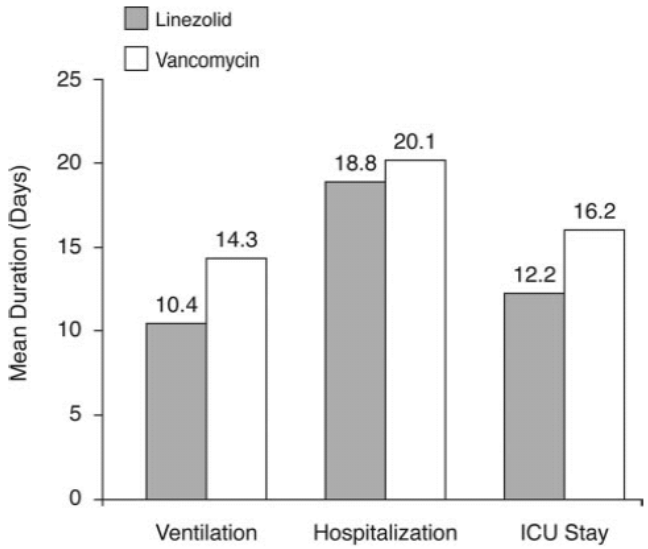


FIGURE 2. Health resource outcomes at end of the study after LZD and VAN therapy in mITT patients with MRSA VAP. Data are reported as the duration (days) of mechanical ventilation, hospitalization, and ICU stay.

Vancomycine vs linezolid: pneumonie

CHEST Original Research

CRITICAL CARE MEDICINE

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30–20 patients

Table 2—*Early MR in the mITT Population Based on BBAL Results at 72 to 96 h Following Start of Treatment

Variables	LZD-Treated Group	VAN-Treated Group	p Value	95% CI
mITT population	30	20		
Patients analyzed	23	19		
Microbiological cure, %	13 (56.5)	9 (47.4)	0.757	-21.1, 39.4
Treatment failure, %	10 (43.5)	10 (52.6)		
No repeat BBAL	7	1		

*Values are No. (%), unless otherwise indicated. Patients analyzed = patients who underwent BBAL 72 to 96 h following the start of treatment.

Vancomycine vs linezolid: pneumonie

Intensive Care Med (2004) 30:388–394
DOI 10.1007/s00134-003-2088-1

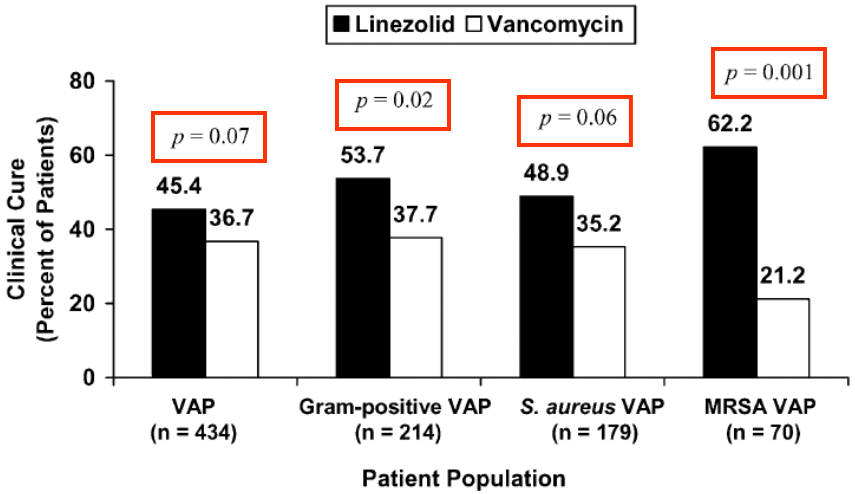
ORIGINAL

Marin H. Kollef
Jordi Rello
Sue K. Cammarata
Rodney V. Croos-Dabrera
Richard G. Wunderink

Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin

282–262 patients

Efficacité clinique



Eradication bactérienne

Table 3 Bacterial eradication rates (*ITT* intention to treat, *MRSA* methicillin-resistant *S. aureus*, *VAP* ventilator-associated pneumonia)

	Linezolid		Vancomycin		*p*
	n	%	*n*	%	
ITT Gram-positive VAP	63/128	49.2	44/112	37.6	0.067
ITT *S. aureus*	41/90	45.6	31/93	33.3	0.091
ITT MRSA VAP	23/38	60.5	8/35	22.9	0.001

Autres études cliniques
"OFF-label use" ~ linezolid

Vancomycine vs linezolid: bactériémie

Journal of Antimicrobial Chemotherapy (2005) **56**, 923–929
doi:10.1093/jac/dki355
Advance Access publication 29 September 2005

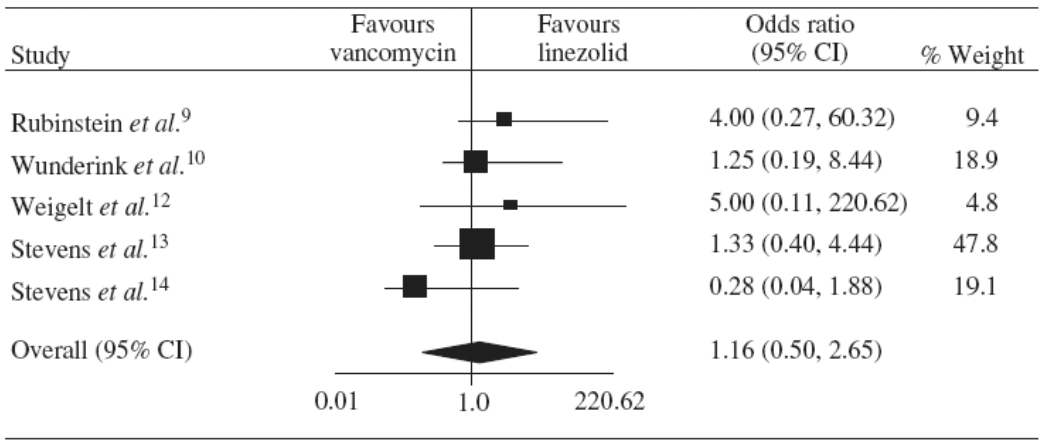
JAC

Linezolid versus vancomycin for *Staphylococcus aureus* bacteraemia: pooled analysis of randomized studies

Andrew F. Shorr[1]*, Mark J. Kunkel[2] and Marin Kollef[3]

74–70 patients

Efficacité clinique



*Random-effects model; test for heterogeneity, $P = 0.467$

Toxicité

Safety in randomized studies comparing linezolid and vancomycin

Type of adverse event	Number of patients (%) linezolid ($n = 74$)	vancomycin ($n = 70$)	P value
Any adverse event, including those not related to study drug	59/74 (79.7)	48/69 (69.6)	0.16
Serious adverse event, as assessed by investigators	35/74 (47.3)	26/70 (37.1)	0.22
Discontinuation from treatment	27/74 (36.5)	27/70 (38.6)	0.80
New-onset thrombocytopenia[a]	5/36 (13.9)	0 (0)	0.02

[a]New-onset thrombocytopenia = decrease from baseline of ≥150 × 10^9 platelets/L to <150 × 10^9 platelets/L.

Vancomycine vs linezolid: fièvre neutropénique

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Clinical Infectious Diseases 2006; 42:597–607

Branimir Jaksic,[1] Giovanni Martinelli,[2] Jaime Perez-Oteyza,[3] Charlotte S. Hartman,[4] Linda B. Leonard,[4] and Kenneth J. Tack[4]

304–301 patients

Efficacité clinique

Table 3. Clinical outcome at 7 days after the completion of therapy (i.e., at the test of cure assessment).

Population, presentation	No. of successes/no. of patients assessed (%)[a] Linezolid group	Vancomycin group	95% CI, %[b]	P[c]
ITT	219/251 (87.3)	202/237 (85.2)	−4.1 to 8.1	.52
Primary malignancy				
Leukemia	119/143 (83.2)	111/138 (80.4)	−6.2 to 11.8	.55
Lymphoma	63/71 (88.7)	56/62 (90.3)	−12.0 to 8.8	.77
Myeloma	24/24 (100)	23/24 (95.8)	−3.8 to 12.2	.31
Tumor	11/11 (100)	11/12 (91.7)	−7.3 to 24.0	.33
Other	2/2 (100)	1/1 (100.0)	Not calculable	
Type of infection				
Fever of uncertain origin	72/78 (92.3)	66/74 (89.2)	−6.1 to 12.3	.51
Bacteremia of unknown source	59/72 (81.9)	53/67 (79.1)	−10.3 to 16.0	.67
Vascular catheter–related infection	23/27 (85.2)	24/28 (85.7)	−19.2 to 18.1	.96
Skin and soft-tissue infection	19/21 (90.5)	14/17 (82.4)	−13.9 to 30.2	.46
Pneumonia	19/23 (82.6)	13/15 (86.7)	−27.2 to 19.1	.74
Urinary tract infection	2/2 (100)	2/3 (66.7)	−20.0 to 86.7	.36
Other	25/28 (89.3)	30/33 (90.9)	−16.7 to 13.5	.83
MITT	55/63 (87.3)	43/50 (86.0)	−11.4 to 14.0	.84
Clinically evaluable	171/185 (92.4)	158/177 (89.3)	−2.8 to 9.1	.30
Microbiologically evaluable	41/47 (87.2)	32/37 (86.5)	−13.8 to 15.3	.92

Vancomycine vs linezolid: fièvre neutropénique

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304–301 patients

Eradication bactérienne

Table 4. Microbiologic outcome at 7 days after the completion of therapy (i.e., the test of cure assessment).

Variable	No. of successes/no. of patients assessed (%)[a] Linezolid	Vancomycin	95% CI, %[b]	*P*[c]
Population				
MITT	41/71 (58)	29/58 (50)	−9.5 to 25.0	.38
Microbiologically evaluable	32/51 (63)	24/43 (56)	−13.0 to 26.8	.50
Gram-positive pathogen				
Staphylococcus aureus	5/9 (56)	1/3 (33)	−40.2 to 84.7	.51
Staphylococcus epidermidis	27/44 (61)	18/29 (62)	−23.5 to 22.1	.95
Staphylococcus hemolyticus	7/12 (58)	3/8 (38)	−22.8 to 64.5	.36
Viridans streptococci	3/6 (50)	4/8 (50)	−0.5 to 0.5	1.00[d]
Enterococcus faecium	4/4 (100)	2/7 (29)	38.0 to 100.0	.02
Enterococcus faecalis	5/6 (83)	1/4 (25)	6.5 to 100.0	.07

Vancomycine vs linezolid: fièvre neutropénique

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Branimir Jaksic,[1] Giovanni Martinelli,[2] Jaime Perez-Oteyza,[3] Charlotte S. Hartman,[4] Linda B. Leonard,[4] and Kenneth J. Tack[4]

304–301 patients

Toxicité

Table 5. Adverse events observed in linezolid and vancomycin recipients.

Type of adverse event	No. (%) of adverse events: Linezolid group[a] (*n* = 303)	Vancomycin group[a] (*n* = 300)	*P*[b]
Adverse event			
Any	229 (75.6)	232 (77.3)	.61
Serious event	37 (12.2)	48 (16.0)	.18
Drug-related adverse event[c]			
Any	52 (17.2)	72 (24.0)	.04
Serious event	3 (1.0)	12 (4.0)	
Drug-related adverse event leading to discontinuation	11 (3.6)	15 (5.0)	.41
Drug-related adverse events occurring in ⩾5 patients/group			
Nausea	10 (3.3)	8 (2.7)	NS
Rash	6 (2.0)	10 (3.3)	NS
Vomiting	9 (3.0)	6 (2.0)	NS
Diarrhea	3 (1.0)	8 (2.7)	NS
Erythema	4 (1.3)	6 (2.0)	NS
Increased serum creatinine level	1 (0.3)	5 (1.7)	NS
Renal failure[d]	1 (0.3)	7 (2.3)	.04[e]

Vancomycine vs linezolid: fièvre neutropénique

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Clinical Infectious Diseases 2006; 42:597–607

Branimir Jaksic,[1] Giovanni Martinelli,[2] Jaime Perez-Oteyza,[3] Charlotte S. Hartman,[4] Linda B. Leonard,[4] and Kenneth J. Tack[4]

304–301 patients

Toxicité

Table 6. Hematologic variables before and after treatment.

Hematologic variable, treatment group	Baseline Mean ± SD	Baseline P^a	End of treatment Mean ± SD	End of treatment P^a	7 Days after completion of therapy Mean ± SD	7 Days after completion of therapy P^a
Hemoglobin, g/dL						
Linezolid	8.8 ± 1.6		9.4 ± 1.5		10.0 ± 1.6	
Vancomycin	8.8 ± 1.6	.58	9.3 ± 1.5	.43	10.0 ± 1.7	.80
Platelet count, × 10^3 cells/mm^3						
Linezolid	28.2 ± 30.5		74.7 ± 115.8		141.0 ± 148.4	
Vancomycin	31.5 ± 53.6	.36	75.2 ± 98.6	.96	149.9 ± 165.3	.52
WBC count, × 10^3 cells/mm^3						
Linezolid	0.77 ± 2.43		3.85 ± 5.16		4.79 ± 5.16	
Vancomycin	1.18 ± 9.04	.44	4.39 ± 5.54	.22	5.12 ± 6.45	.51
ANC, cells/mm^3						
Linezolid	118 ± 341		2480 ± 4136		2991 ± 4412	
Vancomycin	107 ± 290	.71	2788 ± 4365	.41	2935 ± 3592	.88

NOTE. ANC, absolute neutrophil count.

[a] Determined by analysis of variance.

Vancomycine vs linezolid: endocardite

Scandinavian Journal of Infectious Diseases, 2008; 40: 67–73

informa
healthcare

Methicillin-resistant Staphylococcus epidermidis (MRSE) endocarditis treated with linezolid

PAOLA MANCINO, CLAUDIO UCCIFERRI, KATIA FALASCA, ELIGIO PIZZIGALLO & JACOPO VECCHIET

From the Clinic of Infectious Diseases, Centre of Excellence on Ageing, University 'G. d'Annunzio' School of Medicine, Chieti-Pescara, Italy

46 case reports

Male (%)	29/45 (64.4%)
Average age/y (range)	62 (1–82)
Underlying conditions, *n* (%)	45 (97.8%)
Previous heart disease	26 (56.5%)
Renal insufficiency	13 (28.2%)
Cancer	8 (17.3%)
Diabetes mellitus	7 (15.2%)
Transplantation	4 (8.6%)
Endocarditis characteristic, *n* (%)	
Left-sided	34 (73.9%)
Prosthetic valve	13 (28.2%)
Multiple valve involvement	9 (19.5%)
Septic metastases	7 (15.2%)
Aetiology, *n* (%)	
Staphylococcus	34 (73.9%)
Methicillin-resistant S. aureus (MRSA)	11
S. aureus with reduced susceptibility to vancomycin	11
Methicillin-susceptible S. aureus	4
Coagulase negative Staphylococcus	8
Enterococcus spp.	9 (19.5%)
Vancomycin-resistant E. faecalis	3
Vancomycin-resistant E. faecium	3
Vancomycin-susceptible E. faecalis	3
Others (Streptococcus spp., Corynebacterium striatum, Listeria monocytogenes)	4

Reasons for administering linezolid, *n* (%)	
Failure of previous treatment	19 (48.7%)
Intolerance	13 (33.3%)
Refusal or inability to receive i.v. antibiotics	3 (7.6%)
Outpatient therapy	3 (7.6%)
Isolation of MDR bacteria	1
Therapy of the endocarditis	
Average duration of previous therapy	30 (4–90) d
Average duration of linezolid administration	37 (7–148) d
Simultaneous drugs, *n*	13
(rifampicin *n* = 7; aminoglycosides *n* = 7; vancomycin *n* = 3; fusidic acid *n* = 3)	
Adverse effects of linezolid therapy, *n* (%)	12 (26%)
Thrombocytopenia	10
Anaemia	3
Others (vomiting, diarrhoea)	1
Outcome	
Average follow-up period	8.5 month
Cure (%)	33 (71.7%)

Vancomycine vs linezolid: infections du SNC

42 case reports

Linezolid for the Treatment of Patients with Central Nervous System Infection

Fotinie Ntziora and Matthew E Falagas

296 ▪ *The Annals of Pharmacotherapy* ▪ *2007 February, Volume 41*

OBJECTIVE: To review the available evidence regarding the use of linezolid for the treatment of patients with central nervous system (CNS) infections.

DATA SOURCES: Relevant studies were identified through searches of the PubMed, Current Contents, and Cochrane databases (publications archived until October 2006).

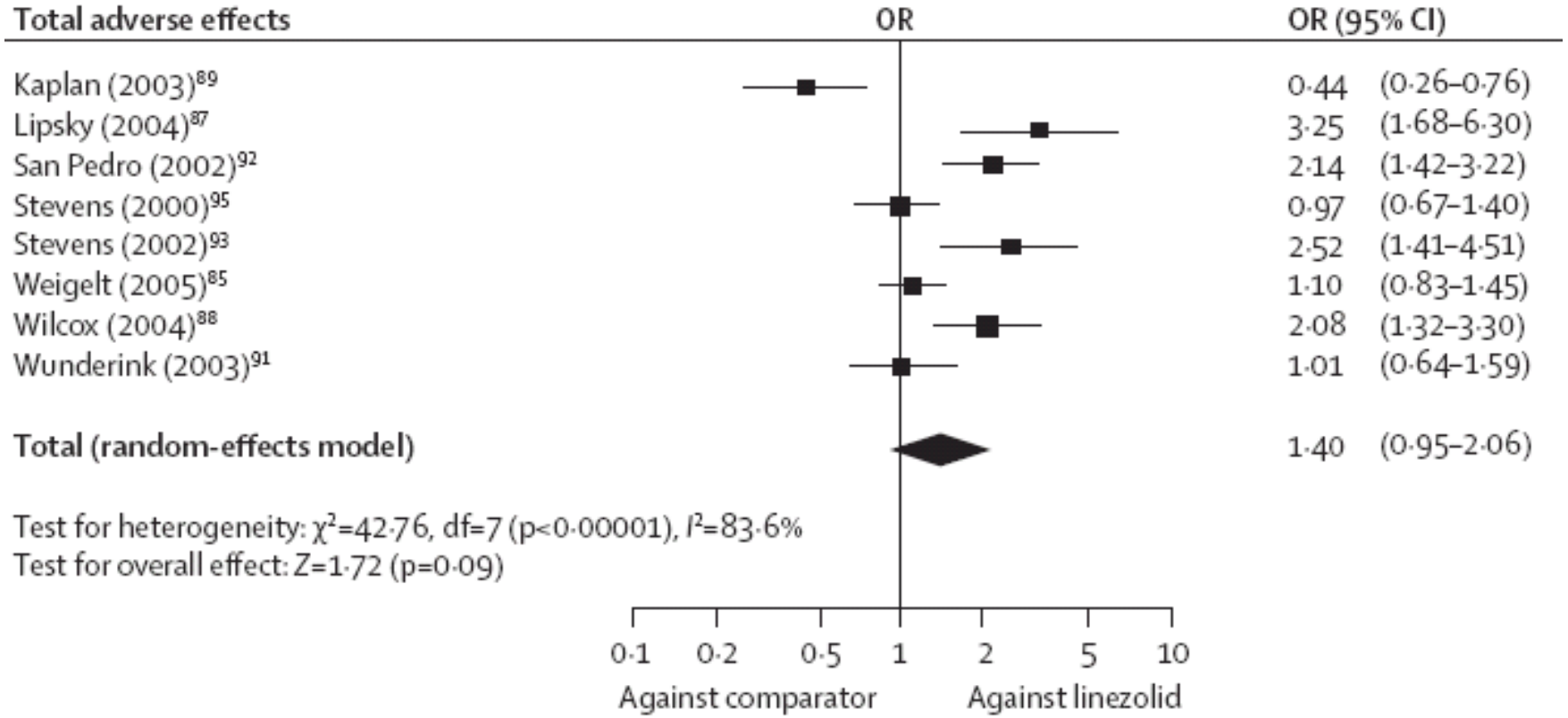
STUDY SELECTION AND DATA EXTRACTION: Case reports, case series, prospective and retrospective studies, and randomized controlled trials were eligible for inclusion in our review if they evaluated the effectiveness and safety of linezolid for the treatment of patients with CNS infections.

DATA SYNTHESIS: In 18 (42.9%) of the 42 relevant cases identified, patients had undergone neurosurgical operations and/or had prosthetic devices. Meningitis was the most common CNS infection, accounting for 20 (47.6%) cases. Other CNS infections included brain abscesses (14; 33.3%), ventriculitis (5; 11.9%), and ventriculo-peritoneal shunt infection (3; 7.1%). In the 39 patients in whom the responsible pathogen was isolated, those predominantly responsible for the CNS infections were: penicillin–nonsusceptible *Streptococcus pneumoniae* (7; 17.9%), vancomycin-resistant enterococci (6; 15.4%), *Nocardia* spp. (5; 12.8%), methicillin-resistant *Staphylococcus epidermidis* (4; 10.3%), and methicillin-resistant *Staphylococcus aureus* (3; 7.7%). Of the 42 patients who received linezolid for the treatment of CNS infections, 38 (90.5%) were either cured or showed clinical improvement of the infection. The mean duration of follow-up was 7.2 months; no recurrent CNS infection was reported.

CONCLUSIONS: The limited published data suggest that linezolid may be considered for the treatment of patients with CNS infections in cases of failure of previously administered treatment or limited available options.

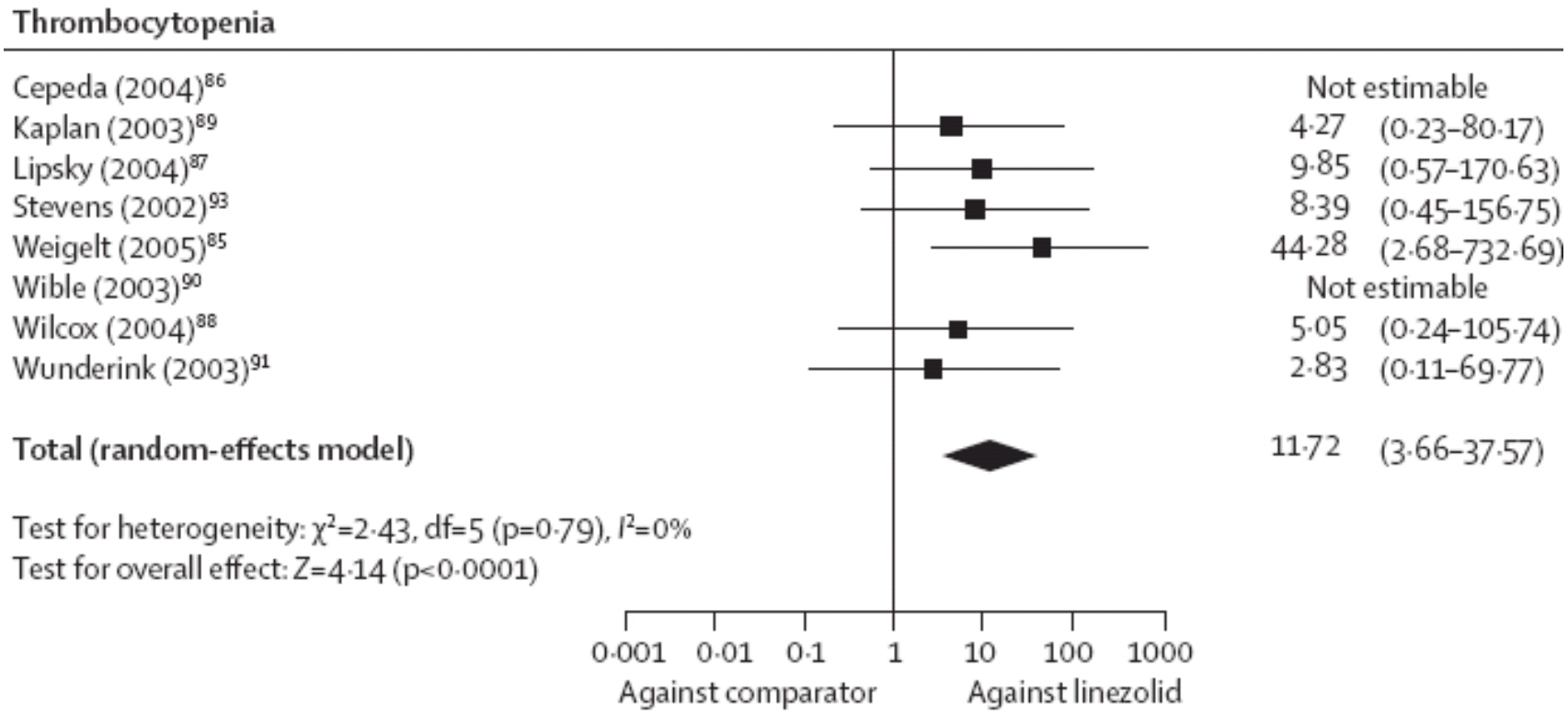
Toxicité dans les études cliniques

Vancomycine vs linezolid: toxicité



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Vancomycine vs linezolid: toxicité



Falagas et al. Lancet Infect Dis. (2008) 8:53–66

Crise oblige:
quid de la pharmacoéconomie ?

Qu'est-ce qui fait le coût du traitement ?

→ **Prix du médicament *:**

Vancomycine 2 x 1 g IV : ~ 60 €

Linezolid 2 x 600 mg IV: ~ 150 €

* Prix d'acquisition;
les deux médicaments entrent dans le forfait.

Qu'est-ce qui fait le coût du traitement ?

→ **mais aussi le coût de la prise en charge du patient :**

- mode et voie d'administration
- durée du traitement
- durée d'hospitalisation
- …

→ **mais aussi le résultat thérapeutique**

- succès ou échec thérapeutique
- survenue d'effets secondaires
- …

A l'heure des comptes ….

Calcul du "COST-EFFECTIVENESS"

- Compare deux traitements différant par leur efficacité / sécurité, pour lesquels
  - les coûts sont exprimés en unités monétaires
  - Les résultats sont exprimés en unités non monétaires (nb vies sauvées, durée de vie , …)
- Les résultats sont exprimées en
  - cost/effectiveness ratio (ACER)
  - incremental cost/effectiveness ratio (ICER)

  → information sur le coût nécessaire pour atteindre un objectif clinique
- Indicatif du traitement qui donne le meilleur résultat par unité de monnaie dépensée
- Limitation: ne prend pas en compte les préférences du patient et la qualité de vie

Vancomycine vs linezolid: impact pharmacoéconomique

Médecine et maladies infectieuses xxx (2009) xxx–xxx

Médecine et maladies infectieuses

Original article

Cost-effectiveness of linezolid versus vancomycin for hospitalized patients with complicated skin and soft-tissue infections in France☆

E. De Cock [a,*], S. Sorensen [b], F. Levrat [c], J.-M. Besnier [d], M. Dupon [e], B. Guery [f], S. Duttagupta [g]

Length of treatment and hospitalization.

	MSSA				MRSA			
	Length of tx		LOS		Length of tx		LOS	
	IV	Oral	Total	Isolation	IV	Oral linezolid	Total	Isolation
First-line treatment[a]								
Linezolid	5.0	12.3	9.9	8.9	5.0	12.3	9.9	8.9
Vancomycin	15.1	2.8	14.5	13.1	15.1	2.8	14.5	13.1
Oxacillin			10.3	2.4				
Second-line treatment[a]								
Linezolid					5.6	13.5	9.5	9.5
Vancomycin					16.3	2.8	15.8	15.8
Oxacillin or clindamycin	5.4	10.6	11.4	5.3				
Linezolid + piperacillin/tazobactam							19.1	19.1
Vancomycin + imipenem							19.1	19.1
Average LOS for patients who die								
Linezolid	3.0[b]	9.0[b]	24.2[a]	2.4[a]	3.0[b]	9.0[b]	24.2 [a]	24.2[a]
Vancomycin	7.0[b]	0.0[b]	24.2[a]	2.4[a]	7.0[b]	0.0[b]	24.2[a]	24.2[a]
Miscellaneous parameters[a]								
Length of tx before empiric switch	2.4							
Days on tx before failure due to lack of efficacy	3.4				3.4			
Days on tx before discontinue due to adverse events	5.1				5.1			

Vancomycine vs linezolid: impact pharmacoéconomique

Médecine et maladies infectieuses xxx (2009) xxx–xxx

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Original article

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Comparison of costs and cure rates by treatment arm.

	Linezolid	Vancomycin	Difference [a]
Cure rates (%)			
Overall cure rate	98.5	98.0	0.48
First-line cure rate	90.7	85.5	5.2
Second-line cure rate	7.8	12.5	−4.7
First-line MRSA cure	94.0	83.6	10.4
Survival	99.6	99.1	0.54
Expected life years (65-year-old)	18.6	18.5	0.1
Costs (€)			
Hospitalization	5,416	6,678	−1,262
Antibiotic drug	1,595	964	631
Tests (in-patient)	429	646	−217
Co-medications	62	95	−33
Treat AEs	72	89	−17
Post-discharge (visits and tests)	204	305	−101
Total costs	7,778	8,777	−999

[a] The difference was calculated by subtracting the value for vancomycin from the corresponding value for linezolid.

Conclusion

- La vancomycine reste un traitement efficace et sûr
  - pour des CMI < 2 mg/L
  - pour des infections dans des compartiments accessibles

  MAIS
  - monitoring nécessaire pour l'optimisation des doses

- Le linezolid est une alternative utile et pharmacoéconomiquement intéressante
  - pour les infections à germes moins sensibles à la vancomycine
  - dans des compartiments profonds peu accessibles à la vancomycine
  - où un relais oral est utile

  MAIS
  - attention aux infections polymicrobiennes
  - risque de thrombopénie