Nuevas alternativas para el tratamiento de las infecciones por Grampositivos

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Hospital Clínic
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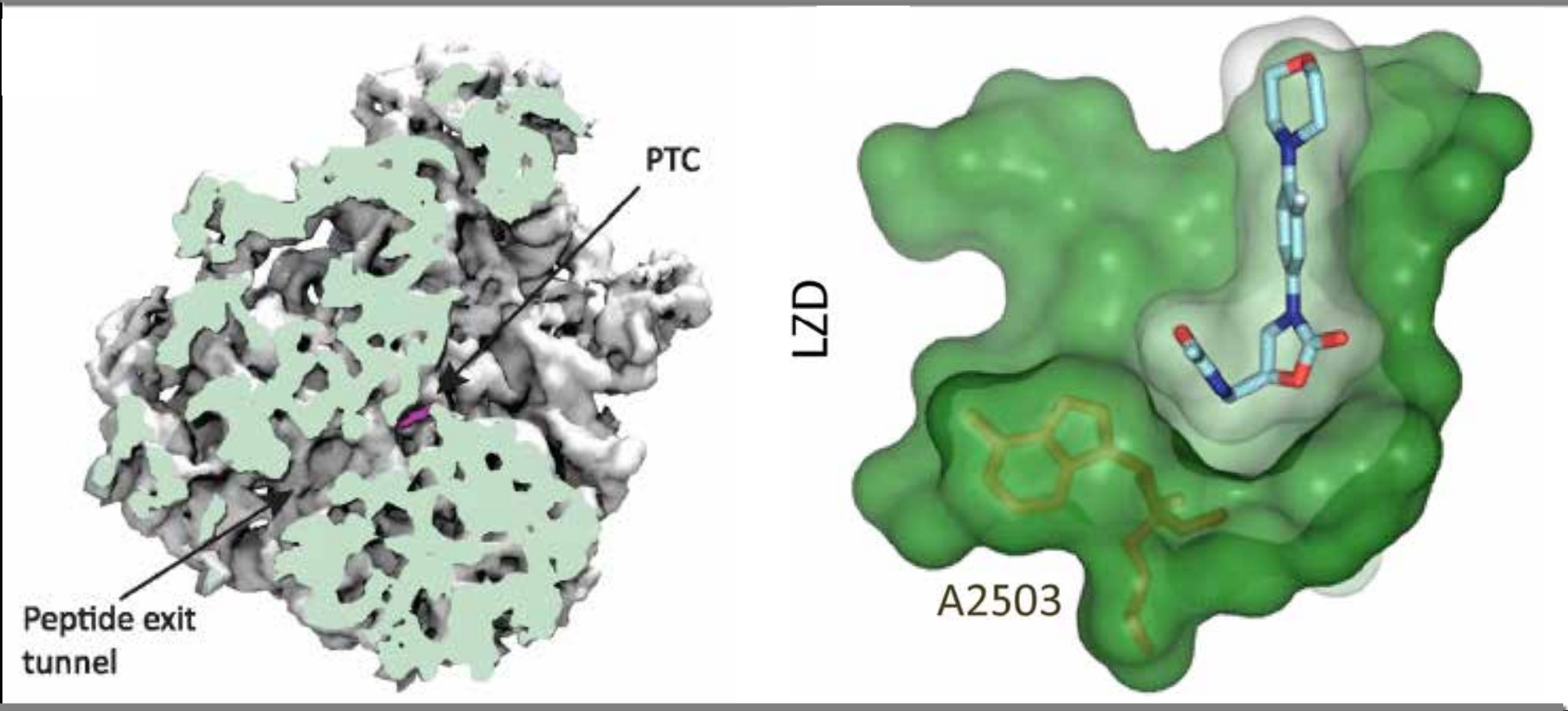
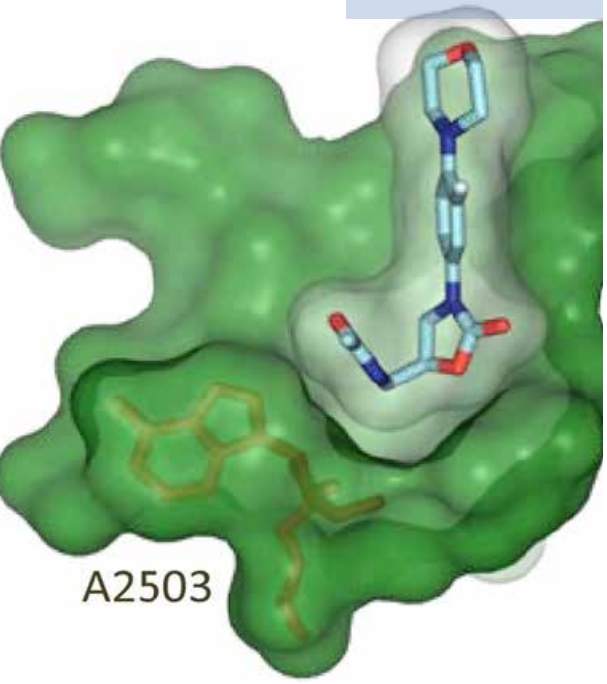
Long KS. et al. Mutations in 23S rRNA at the Peptidyl Transferase Center and TheirRelationship to Linezolid Binding and Cross-Resistance. *Antimicrob Agents Chemother 2010; 54: 4705–4713*

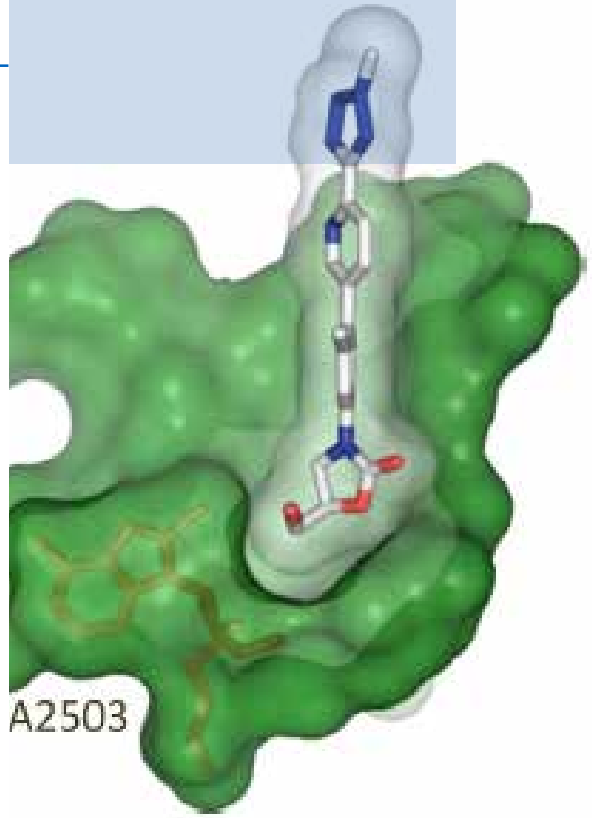


la diana de linezolid es original y por este motivo no tiene resistencia cruzada con otros antibióticos

Locke J. et al. Structure-Activity Relationships of Diverse Oxazolidinones for Linezolid-Resistant Staphylococcus aureus Strains Possessing the *cfr* Methyltransferase Gene or Ribosomal Mutations. *Antimicrob Agents Chemother 2010; 54: 5337-43*



MIC_{90}	microorganismo	MIC_{90}
2	*S. aureus* (S-RM)	0.5
2	ECN (S-RM)	0,5
2	*E. faecalis* (S-RV)	0,5
4	*E. faecium* (S-RV)	0,5
1	*S. pyogenes*	0,25
2	*S. agalactiae*	0,25
2	*S. pneumoniae*	0,25
2	*L. monocytogenes*	0,25

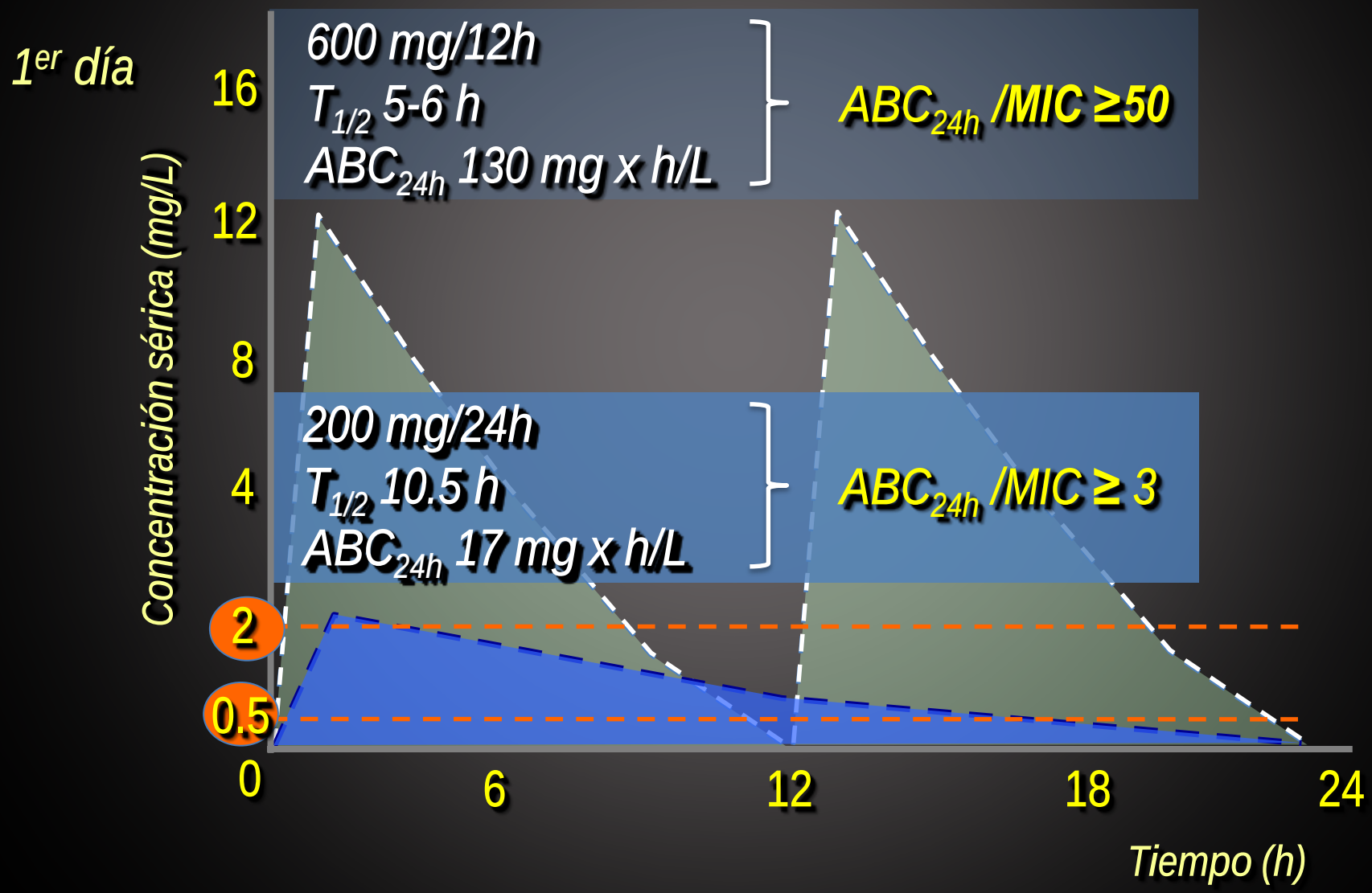


linezolid

tedizolid

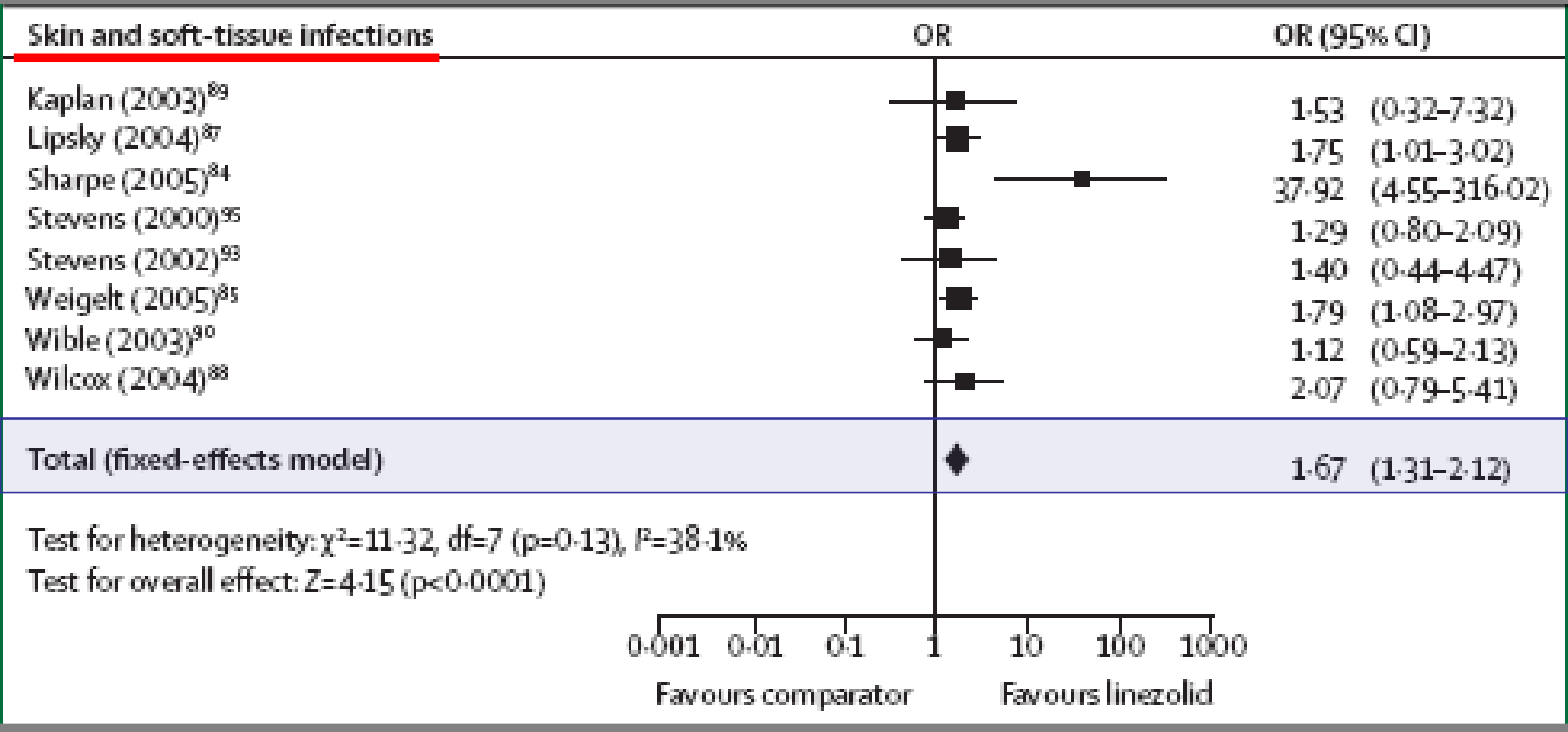
Zhanel G, et al. Drugs 2015;75: 253

Flanagan Sh. et al. Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug. *Pharmacotherapy 2014; 34: 240–250*

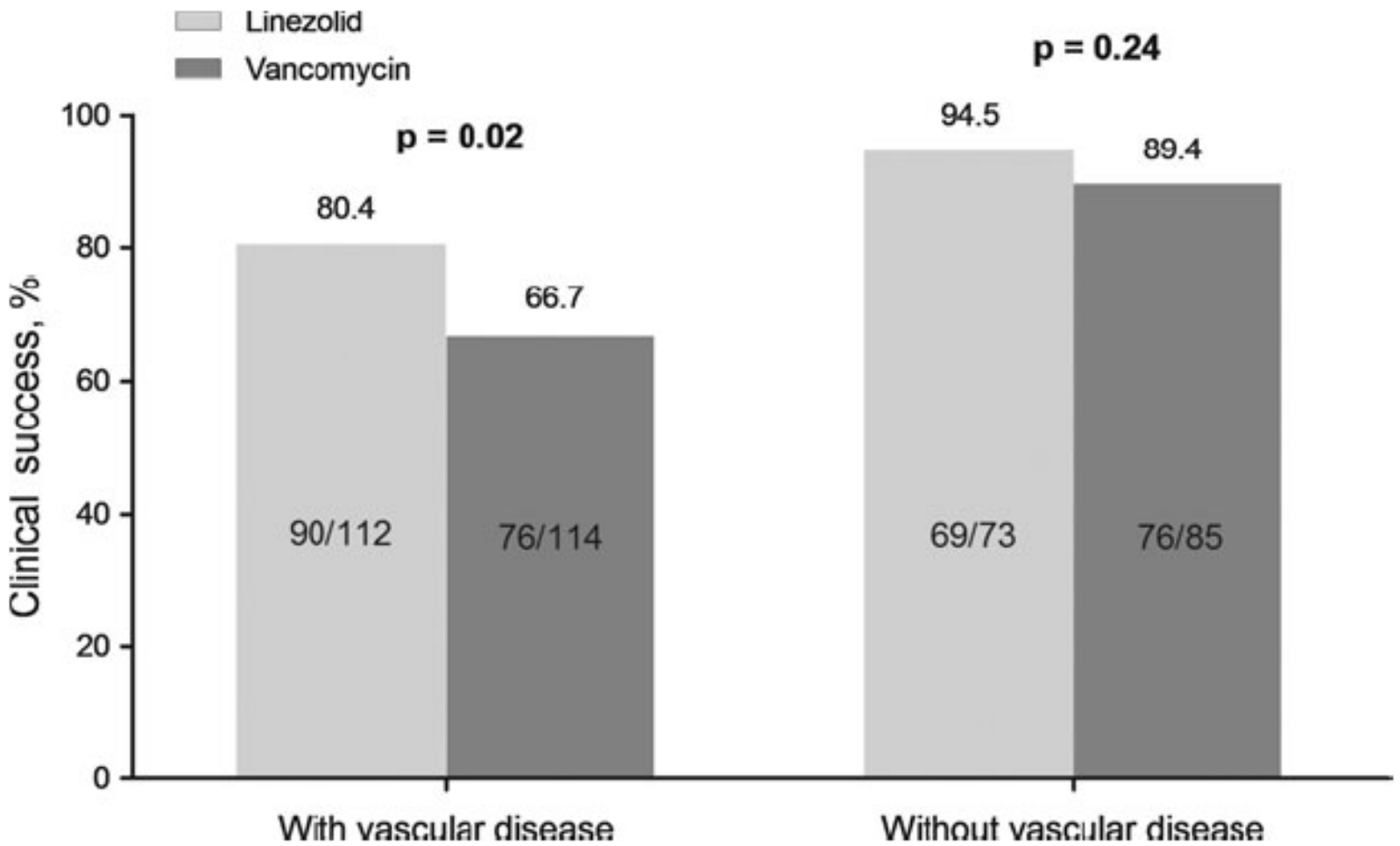


Falagas M, et al. Linezolid versus glycopeptide or b-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials.

Lancet Infect Dis 2008; 29:377–82

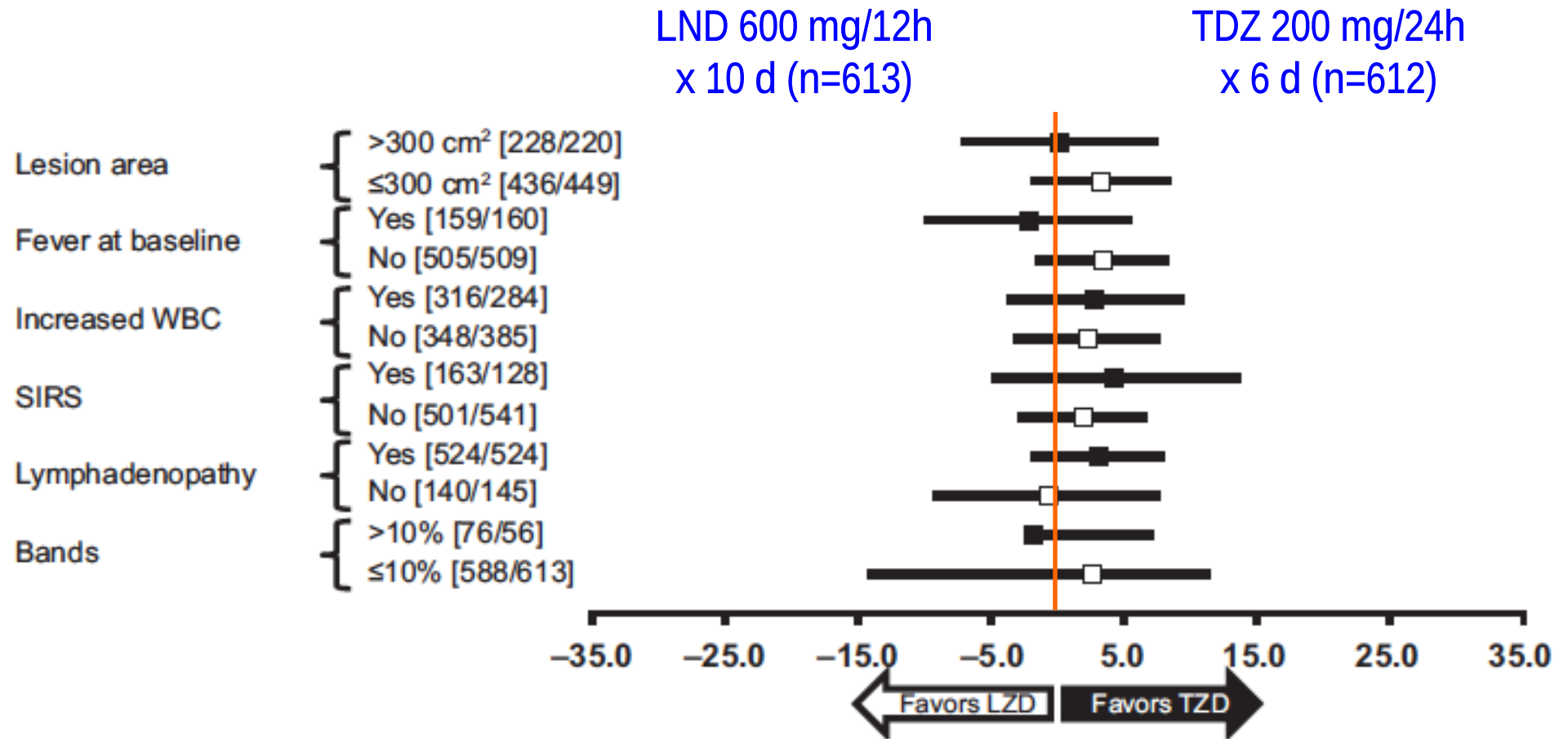


Duane TH, et al. Linezolid and Vancomycin in Treatment of Lower-Extremity Complicated Skin and Skin Structure Infections Caused by Methicillin-Resistant *Staphylococcus aureus* in Patients with and without Vascular Disease. *Surgical Infections 2012; 13: 1-7*



Shorr AF, et al. Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in Acute Bacterial Skin and Skin Structure Infections.

Antimicrob Agents Chemother 2015; 59: 864-871



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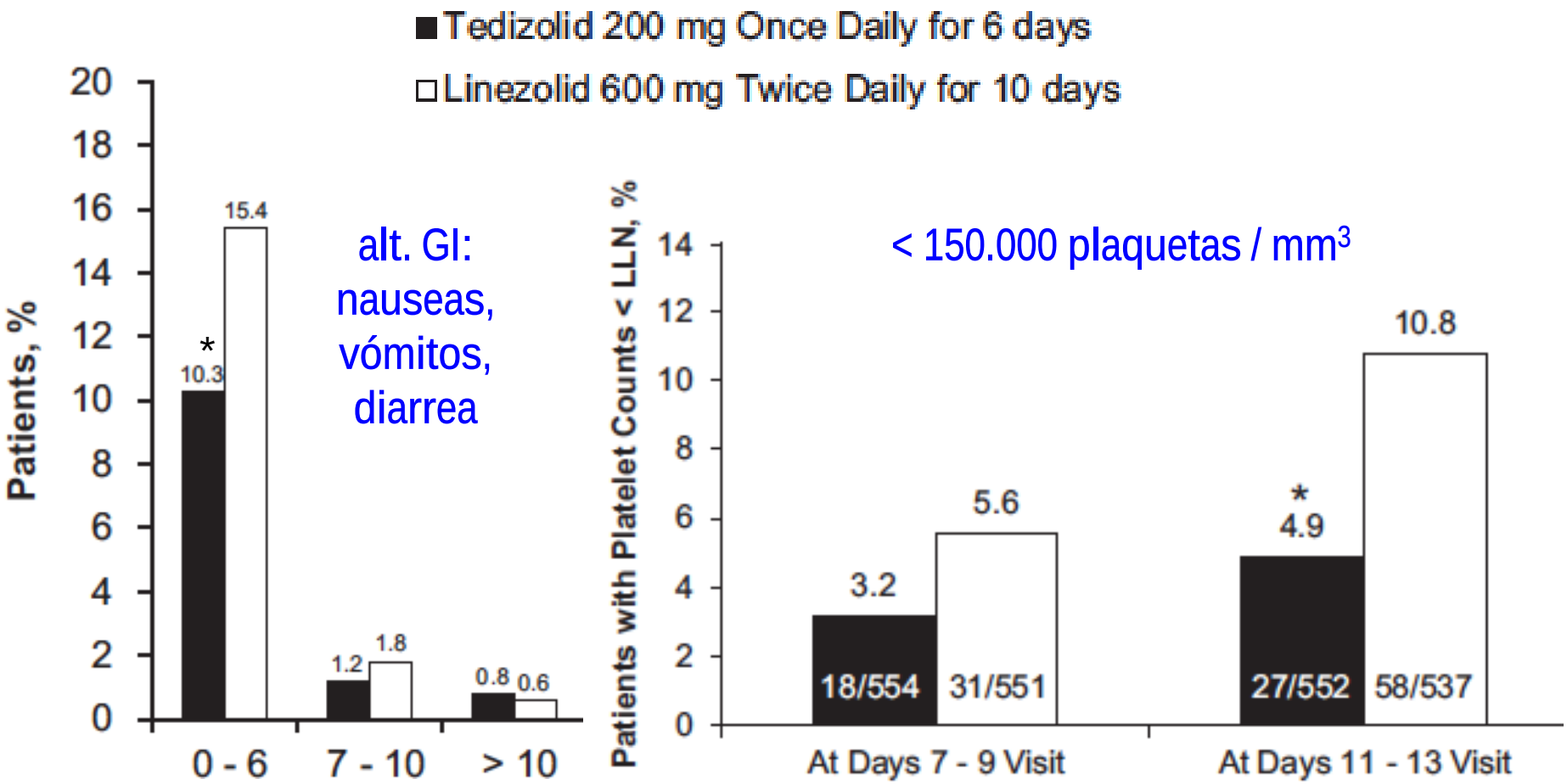
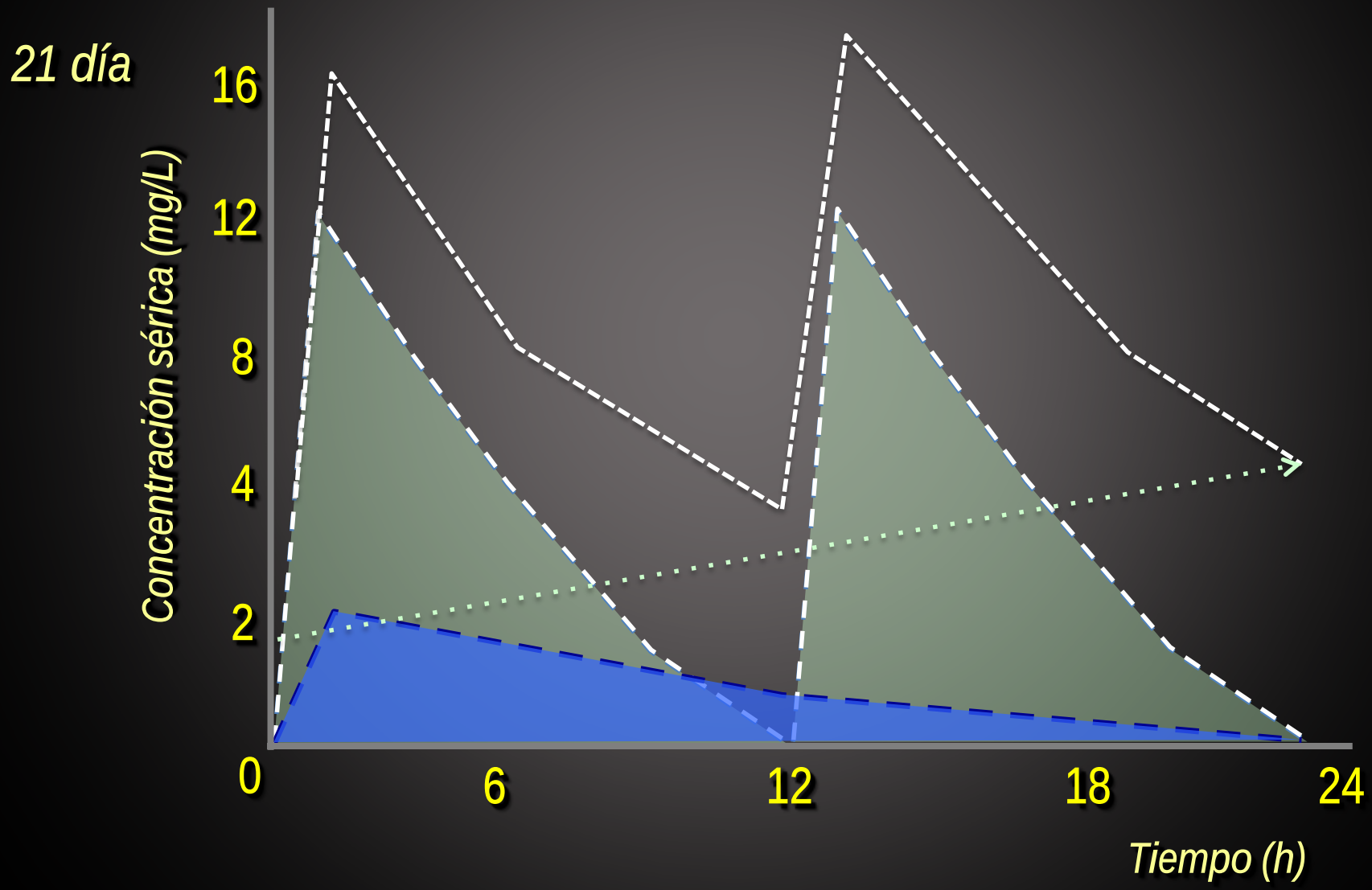


* P<0.05

Flanagan Sh. et al. Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug. *Pharmacotherapy 2013; 34: 240–250*



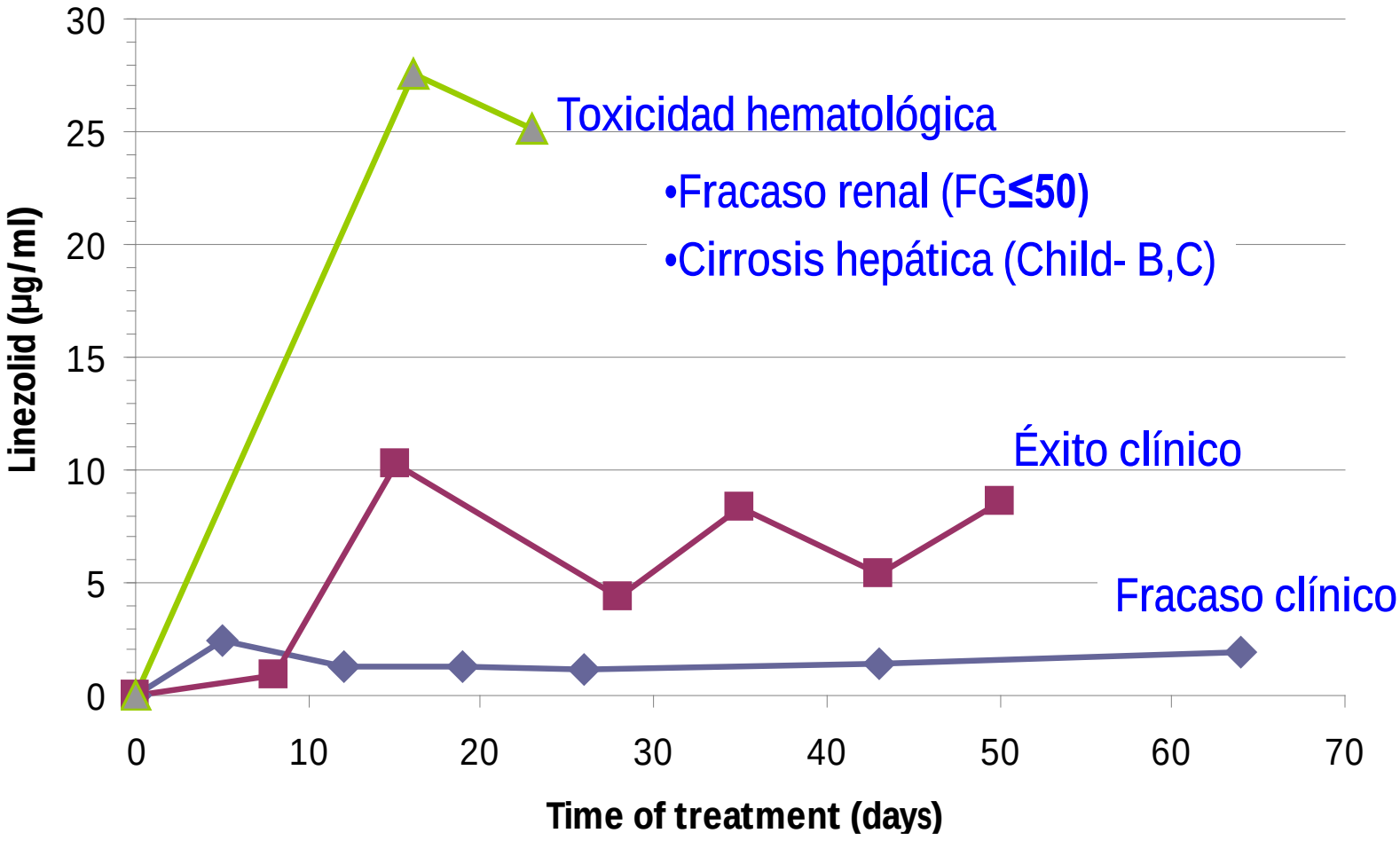
Flanagan Sh. et al. Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug. *Pharmacotherapy 2013; 34: 240–250*

antibiótico	*1 día*	*21 días* ⟶
Linezolid (mg/L)		
C_{max}	12	16
C_{min}	-	5
ABC_{24}	130	230
Tedizolid (mg/L)		
C_{max}	1.8	1.8
C_{min}	-	0.4
ABC_{24}	17	22

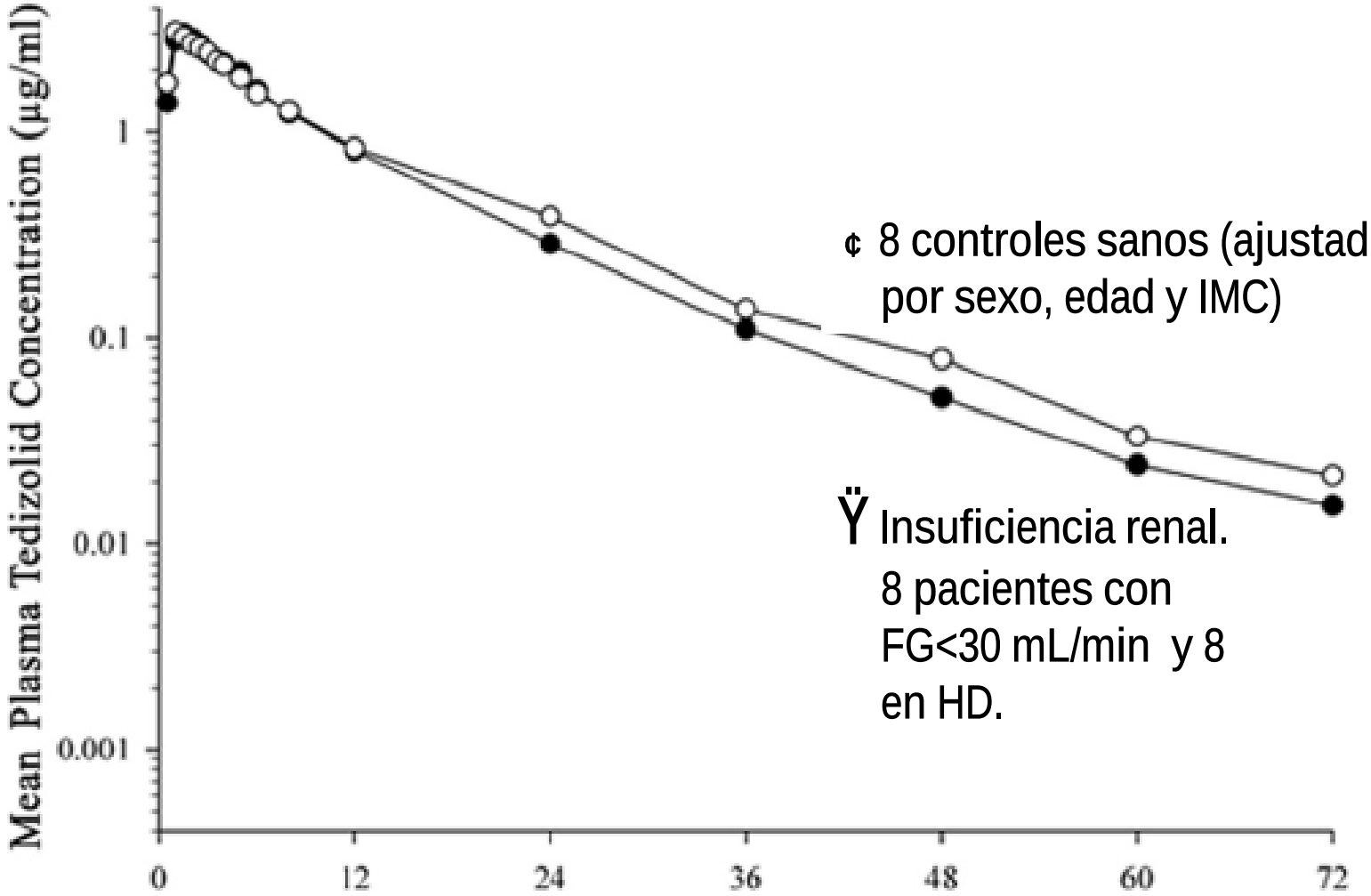
- Infección sobre implantes
- osteomielitis
- Infecciones por *Mycobacterias* spp, *Nocardia* spp

Sousa R, et al. Usefulness of Monitoring Linezolid Trough Serum Concentration in Prolonged Treatments.

Rev Esp Quimioter 2011; 24: 151-153



Flanagan S, et al. Pharmacokinetics of Tedizolid in Subjects with Renal or Hepatic Impairment. *Antimicrob Agents Chemother 2014; 58: 6471-76*

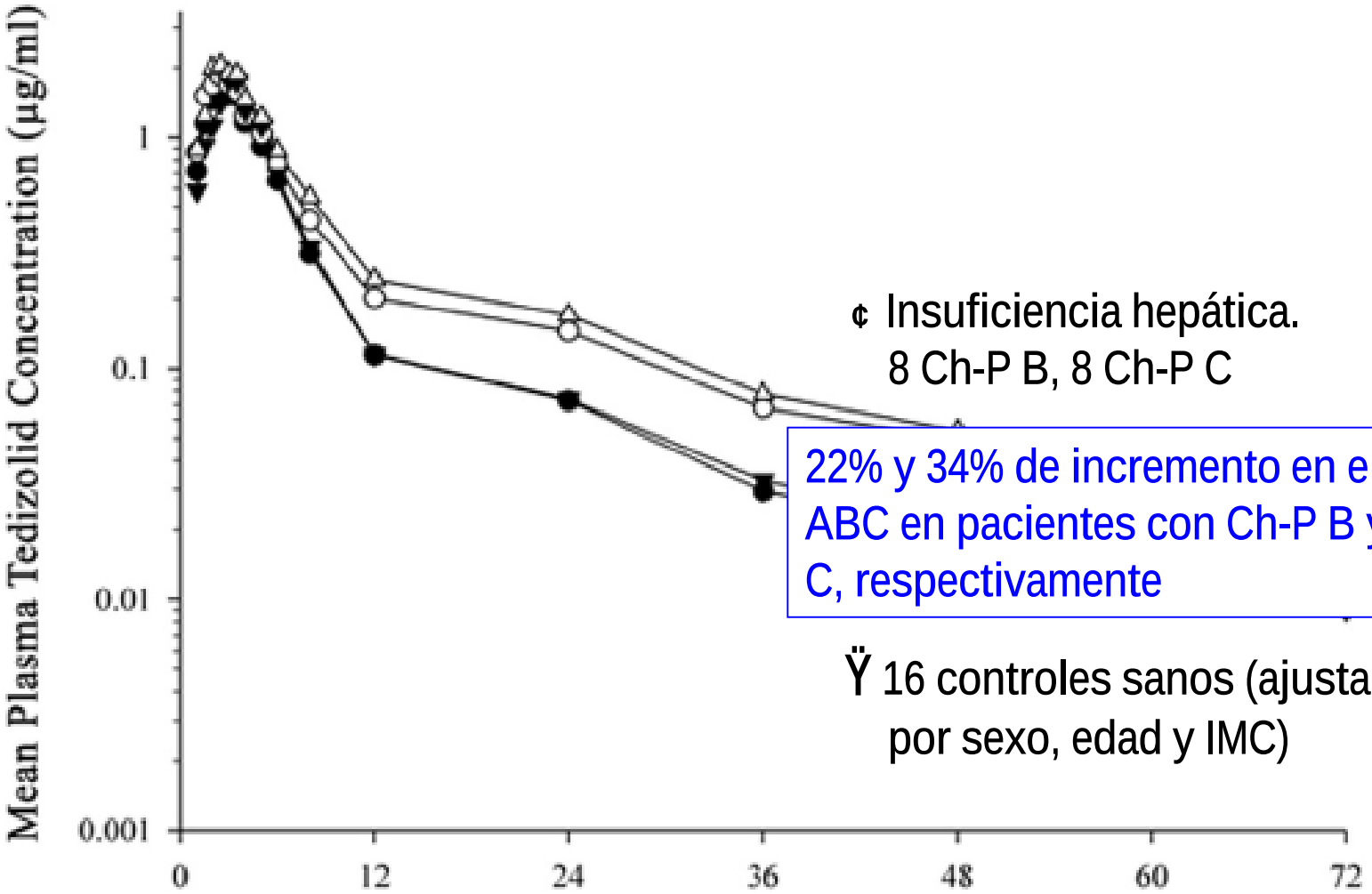


¢ 8 controles sanos (ajustados por sexo, edad y IMC)

Ÿ Insuficiencia renal. 8 pacientes con FG<30 mL/min y 8 en HD.

200 mg dosis única

Flanagan S, et al. Pharmacokinetics of Tedizolid in Subjects with Renal or Hepatic Impairment. *Antimicrob Agents Chemother 2014; 58: 6471-76*



¢ Insuficiencia hepática.
8 Ch-P B, 8 Ch-P C

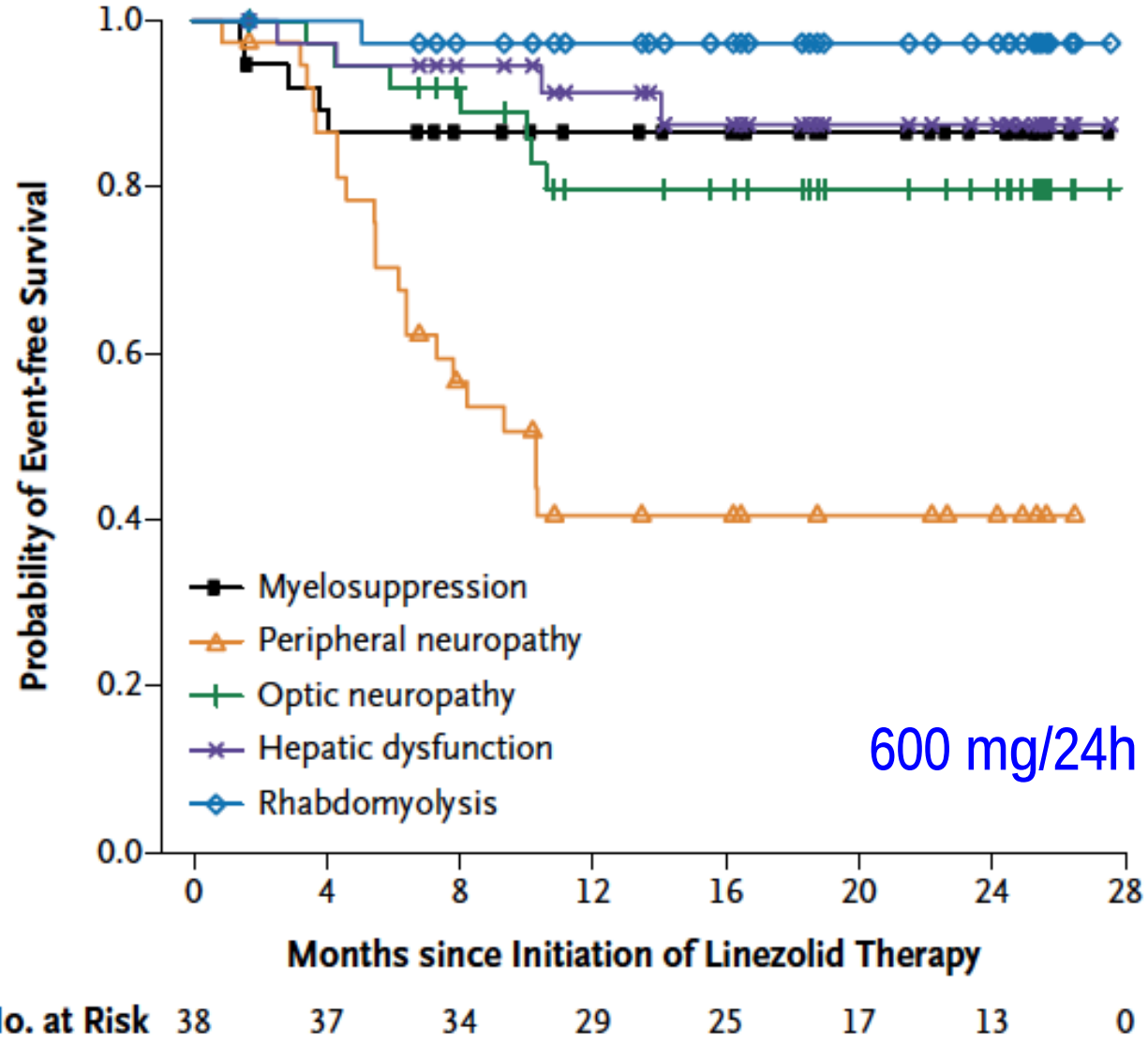
22% y 34% de incremento en el ABC en pacientes con Ch-P B y C, respectivamente

Ÿ 16 controles sanos (ajustados por sexo, edad y IMC)

200 mg dosis única

Lee M, et al. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis.

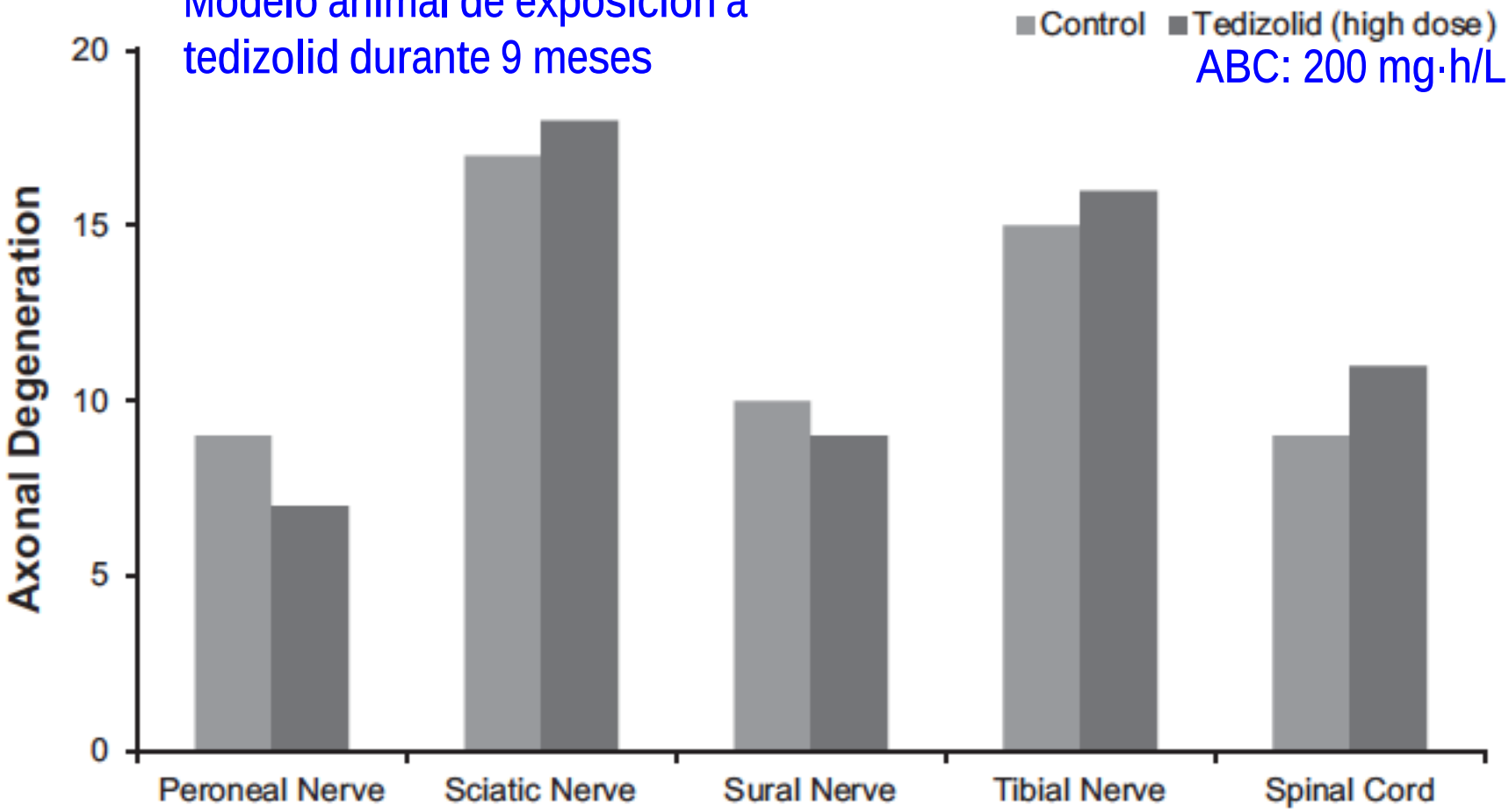
N Engl J Med 2012; 367: 1508-1518



Flanagan S, et al. Nonclinical and Pharmacokinetic Assessments To Evaluate the Potential of Tedizolid and Linezolid To Affect Mitochondrial Function.

Antimicrob Agents Chemother 2015; 59: 178-85

Modelo animal de exposición a tedizolid durante 9 meses



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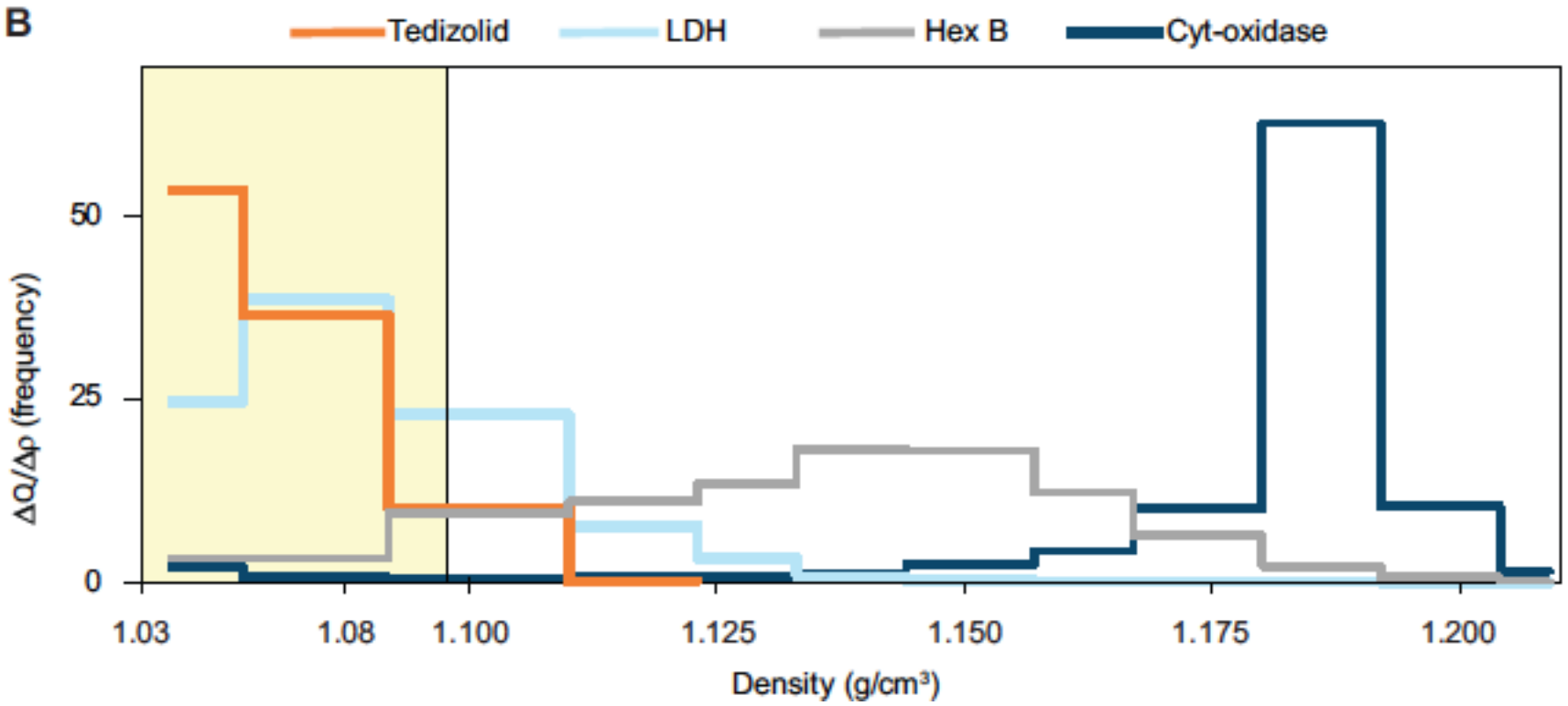
citosol

mitocondria



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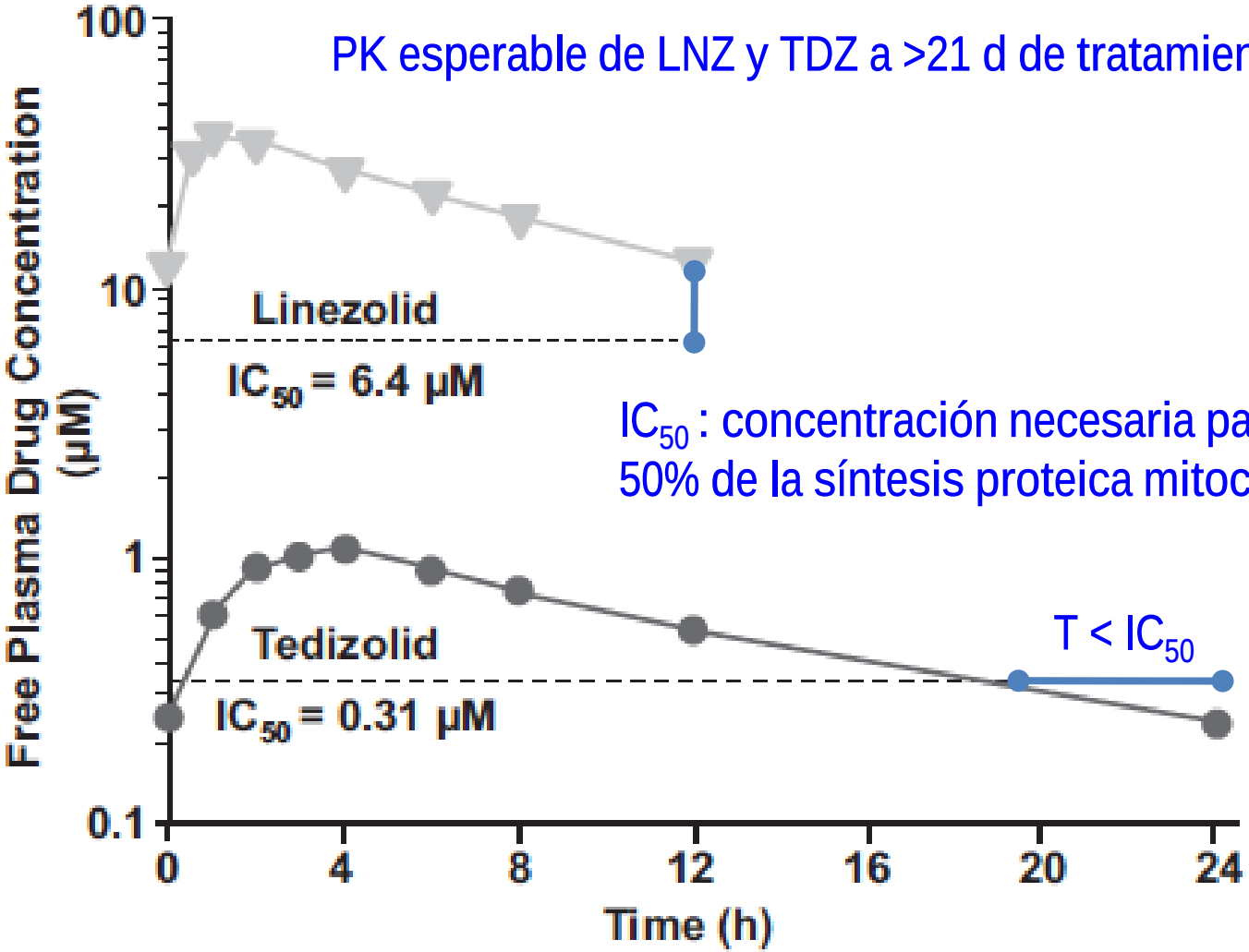
PK esperable de LNZ y TDZ a >21 d de tratamiento.



IC_{50} : concentración necesaria para inhibir el 50% de la síntesis proteica mitocondrial (MPS)

$T < IC_{50}$

Flanagan S, et al. Nonclinical and Pharmacokinetic Assessments To Evaluate the Potential of Tedizolid and Linezolid To Affect Mitochondrial Function.

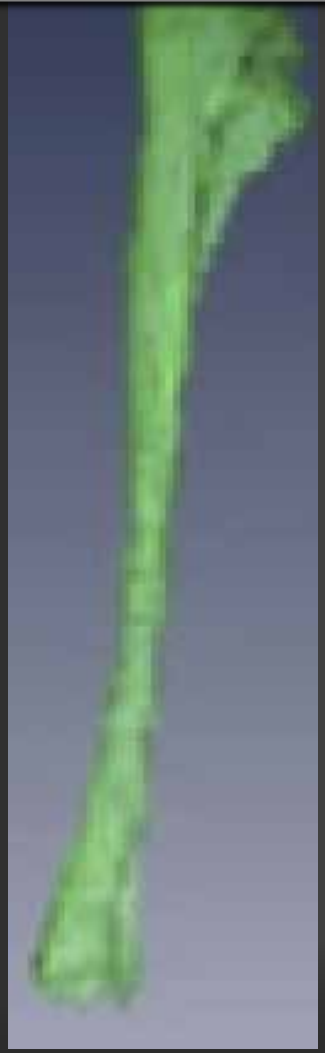
Antimicrob Agents Chemother 2015; 59: 178-85

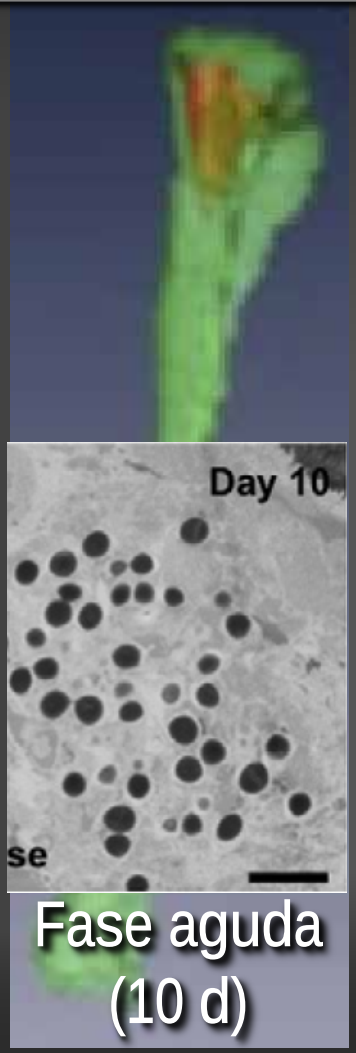
Parameter[a]	Value	
	Tedizolid[b]	Linezolid[c]
Mean (SE) MPS IC_{50} (μM)	0.31 (0.02)	6.4 (1.2)
Time below MPS IC_{50} (h)		
Mean (SD)	7.62 (5.49)	3.17 (5.29)
Median	7.94	0
25th–75th percentiles	2.48–11.92	0–4.93
% of patients with all free drug concentrations above the IC_{50}	16	62

IC_{50} : concentración necesaria para inhibir el 50% de la síntesis proteica mitocondrial (MPS)

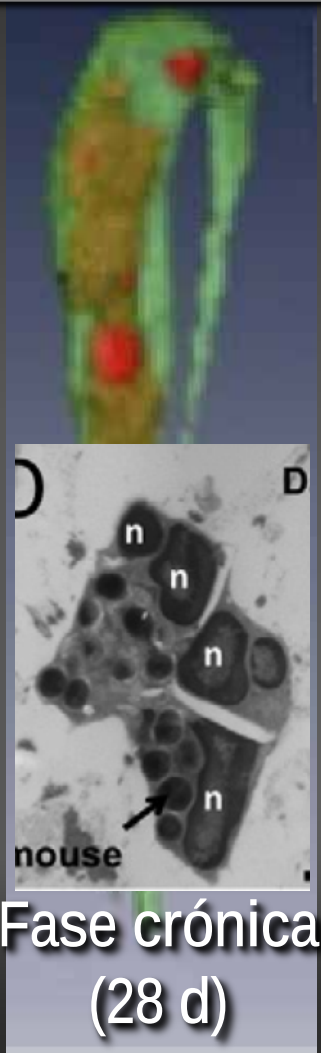
Horst S, et al. A Novel Mouse Model of Staphylococcus aureus Chronic Osteomyelitis That Closely Mimics the Human Infection. *Am J Pathol 2012; 181: 1206-14*

Modelo animal de osteomielitis hematógena

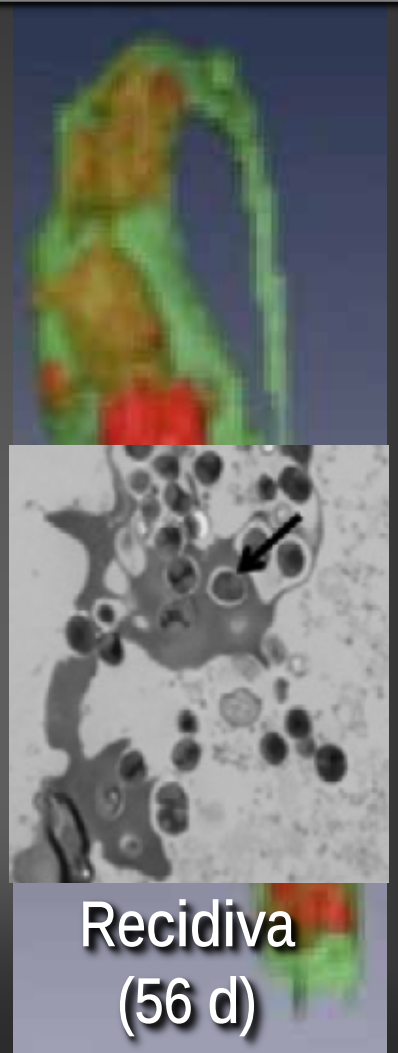




Fase aguda (10 d)



Fase crónica (28 d)

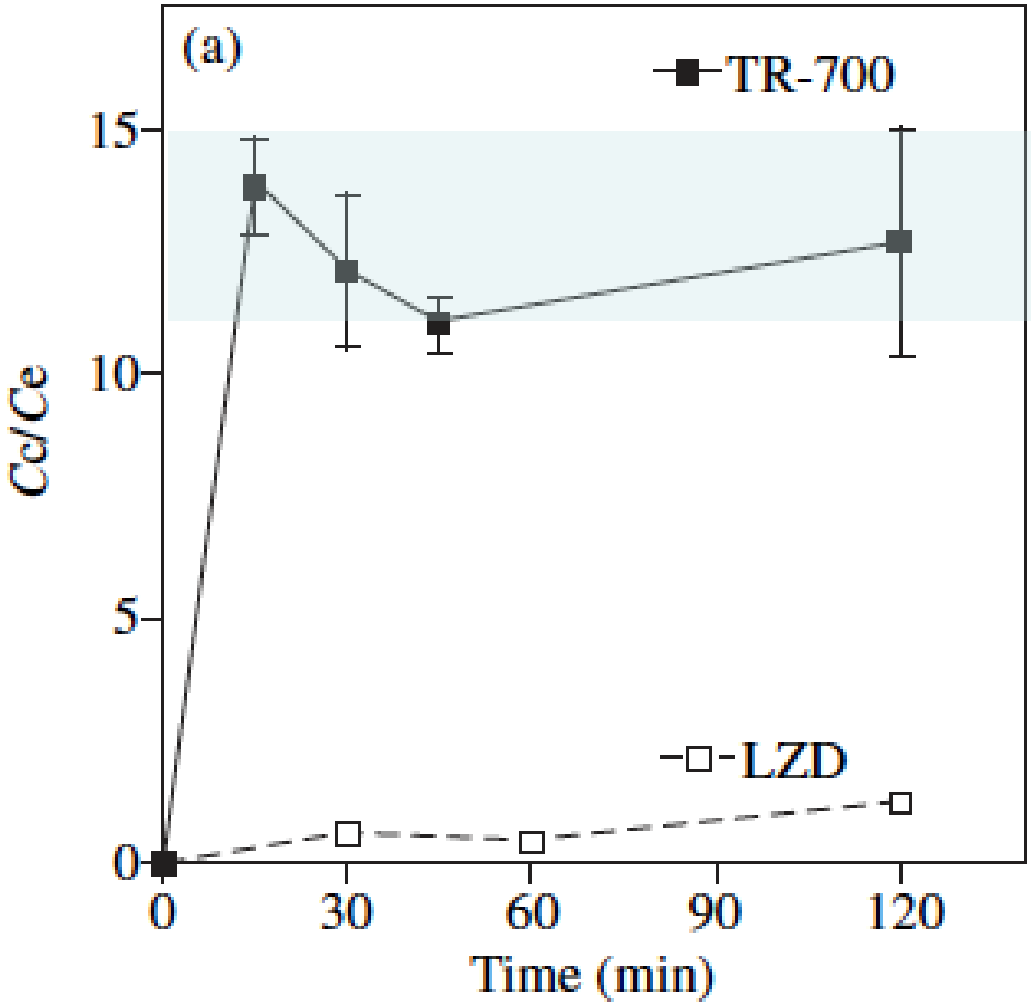


Recidiva (56 d)

Lemaire S, et al. Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines.

J Antimicrob Chemother 2009; 64: 1035–1043

Relación entre la concentración celular y extracelular

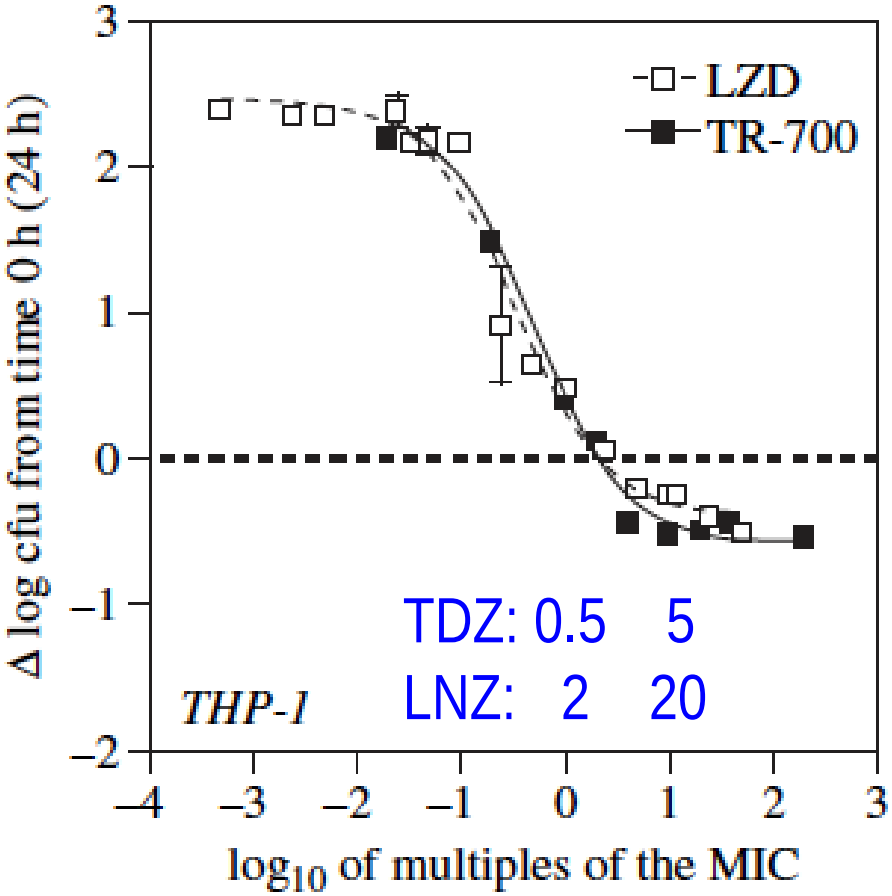


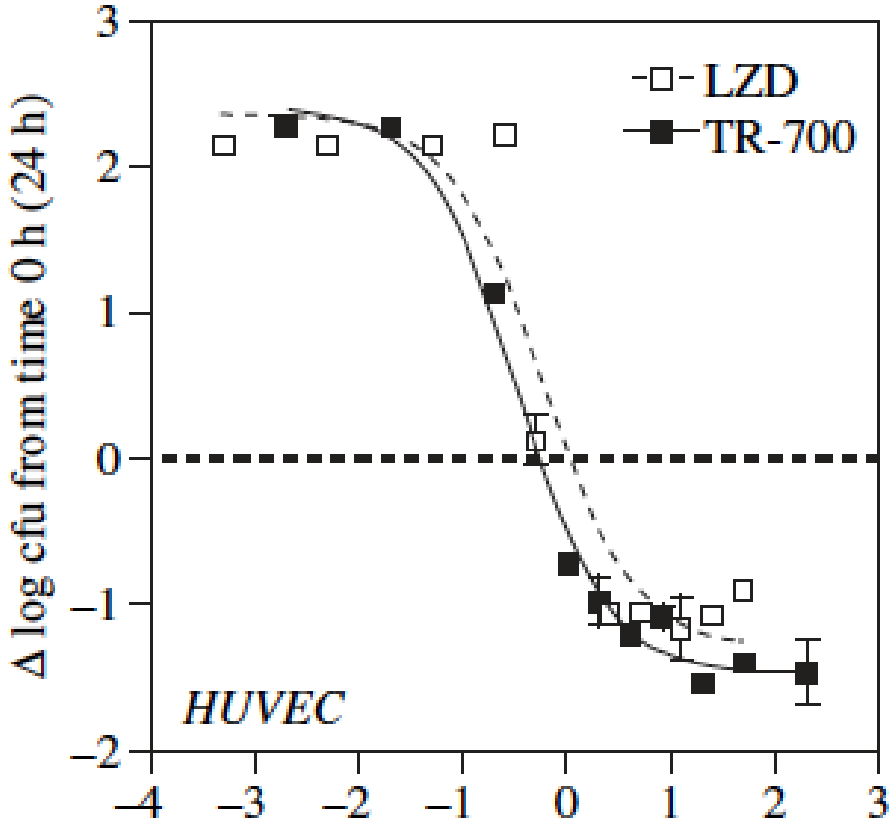
1 mg/L = 10 mg/L

8 mg/L = 8 mg/L

Lemaire S, et al. Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines.

J Antimicrob Chemother 2009; 64: 1035–1043





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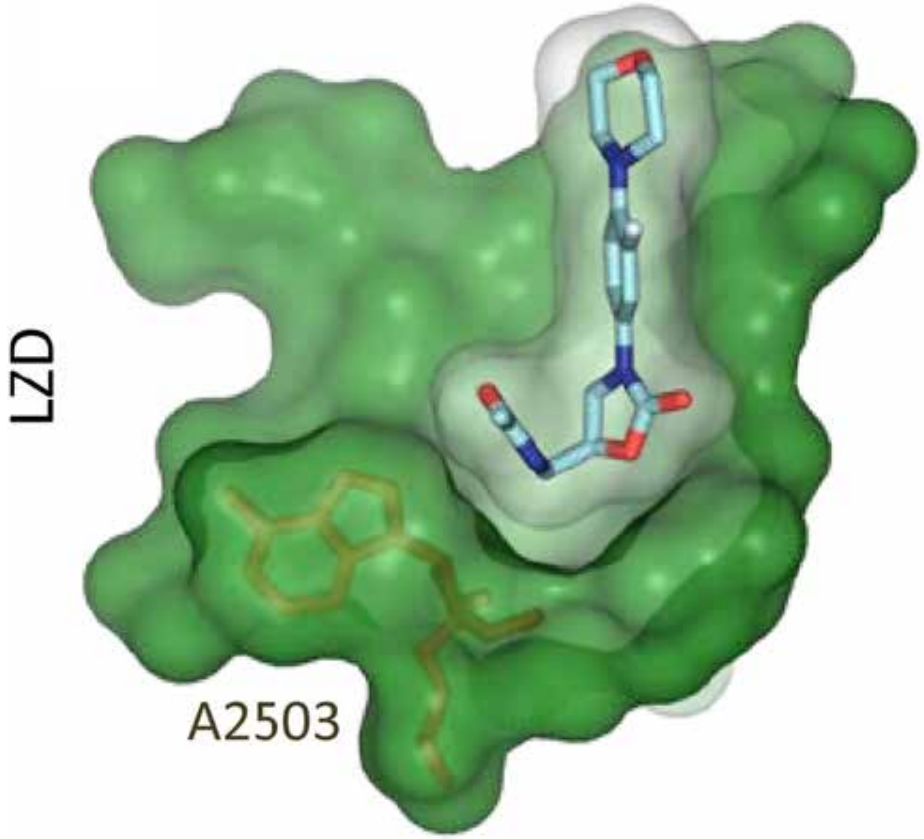
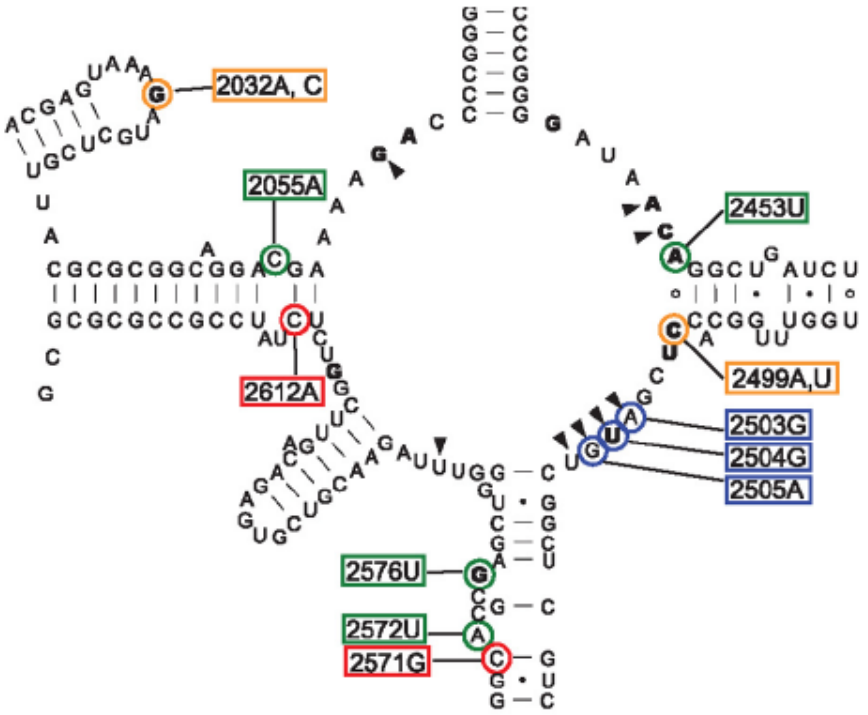
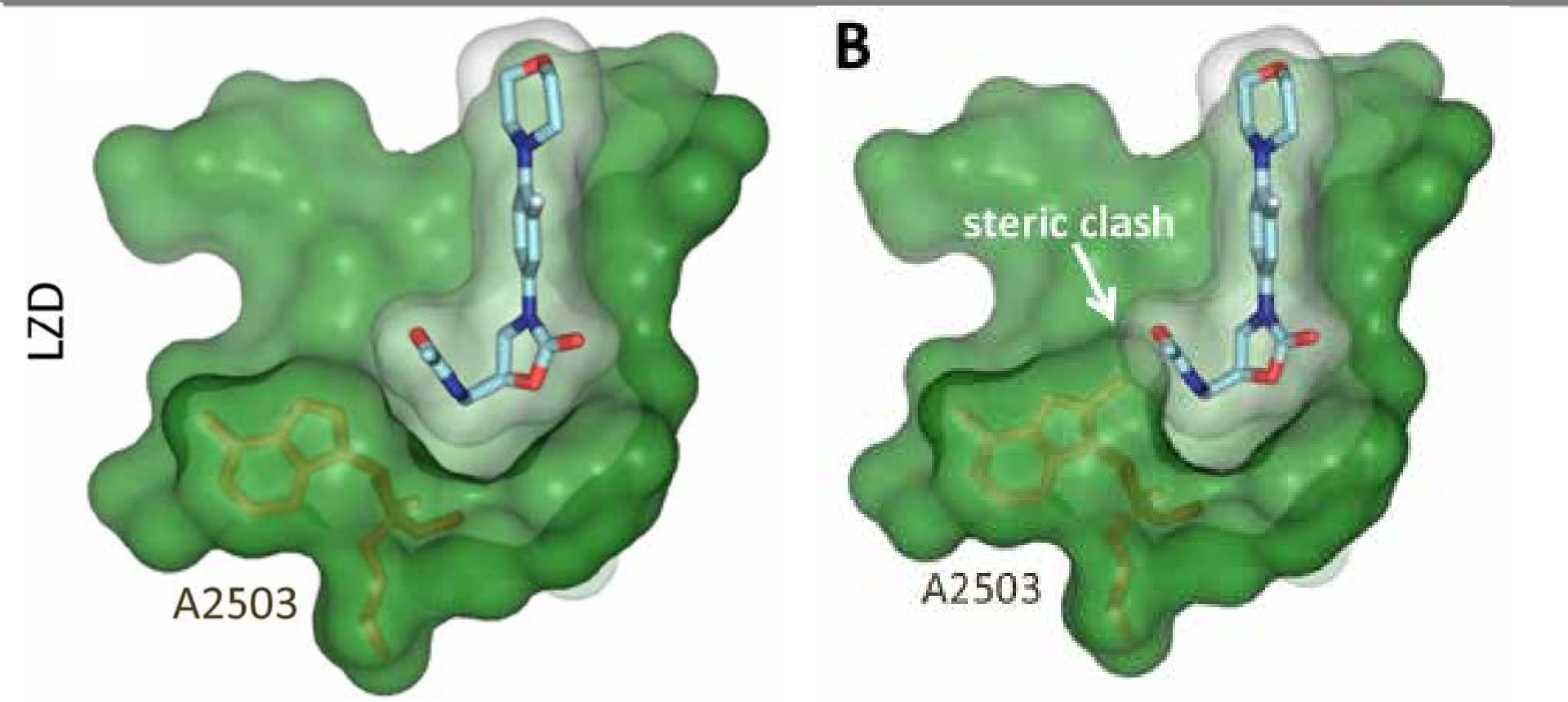




mutaciones puntuales del rRNA confieren resistencia a linezolid (y a tedizolid)

Long KS. et al. Mutations in 23S rRNA at the Peptidyl Transferase Center and TheirRelationship to Linezolid Binding and Cross-Resistance. *Antimicrob Agents Chemother 2010; 54: 4705–4713*



metilación mediada por *cfr-gen* (plásmido) confiere resistencia a linezolid

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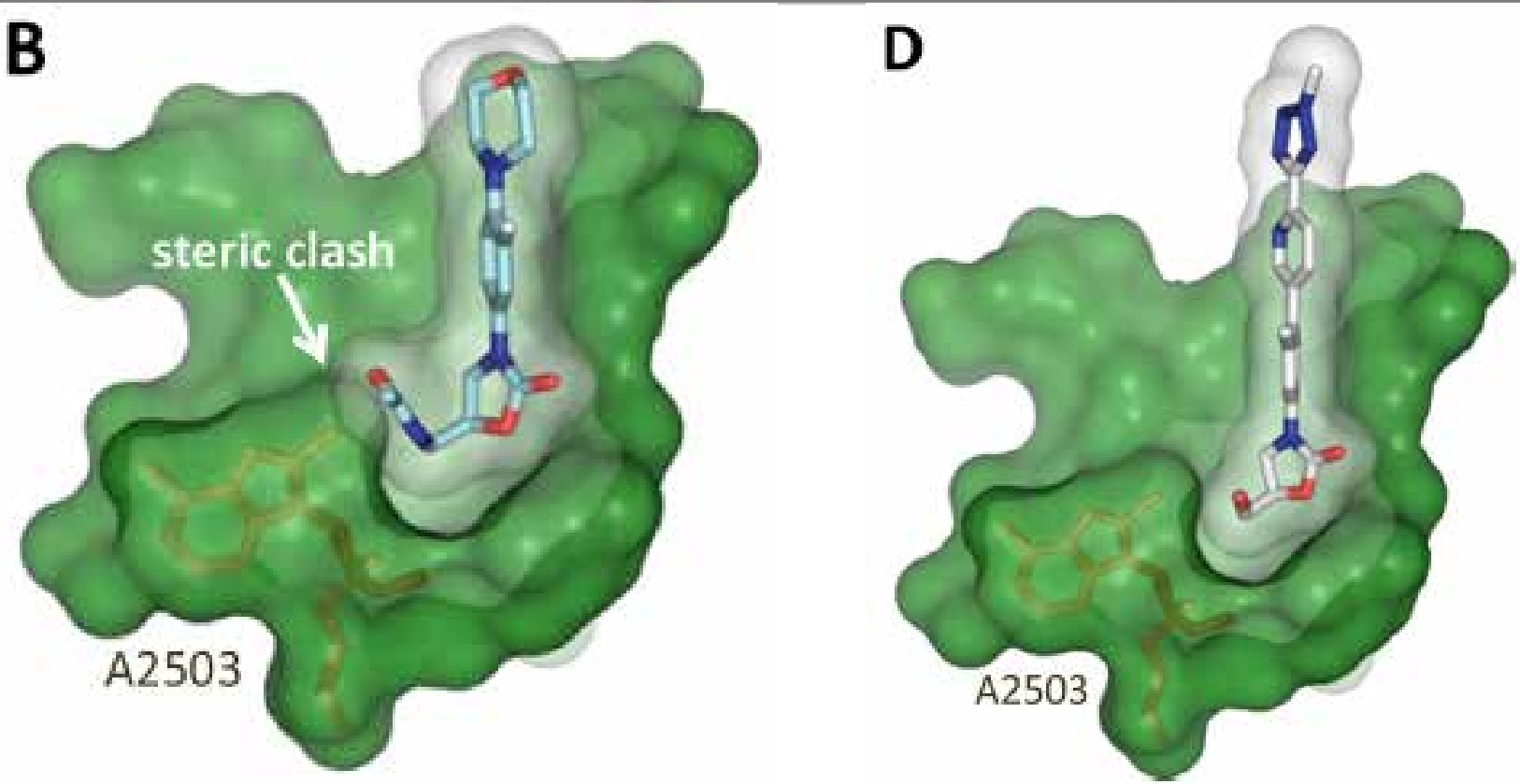


metilación mediada por *cfr-gen* (plásmido) confiere resistencia a linezolid

tedizolid es de 4-10 veces más activo que linezolid

conclusiones

Tedizolid es una alternativa a linezolid en:

1.- infecciones de piel y partes blandas en pacientes con:

a) insuficiencia renal (FG<30 mL/min)

b) alteraciones hematológicas (anemia, plaquetopenia)

2.- tratamientos prolongados (>21 días), como alternativa desde el inicio del tratamiento o a partir de la aparición de efectos adversos relacionados con linezolid:

a) infecciones sobre implantes (prótesis articulares)

b) osteomielitis-espondilodiscitis-artritis

c) infecciones por *Mycobacterium* spp (tuberculosis, atípicas)

3.- aquellas infecciones producidas por cepas resistentes a linezolid por la presencia del gen *cfr*.

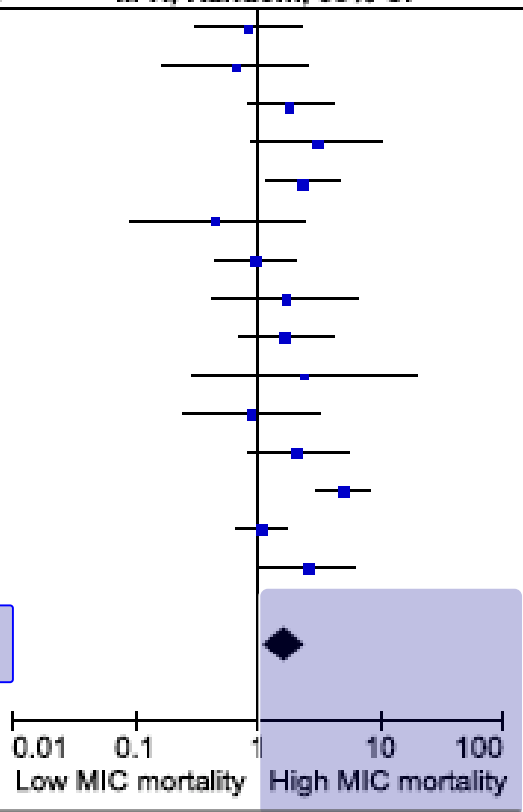
Lipoglicopéptidos: dalbavancin

Van Hal S, et al. The Clinical Significance of Vancomycin MIC in S. aureus Infections: A Systematic Review and Meta-analysis. *Clin Infect Dis 2012; 2012; 54: 755-71*

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

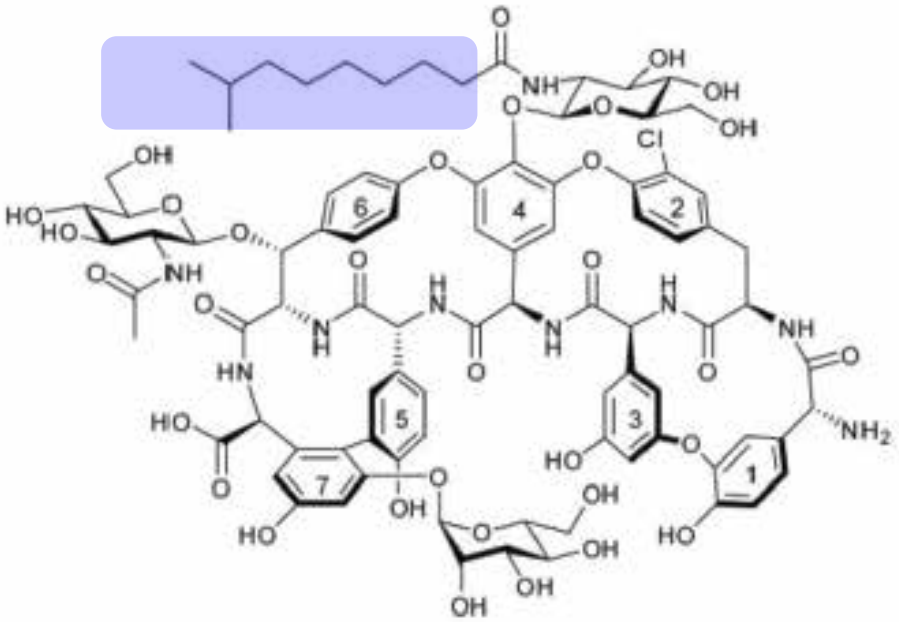
Test for overall effect: Z = 2.65 (P = .008)



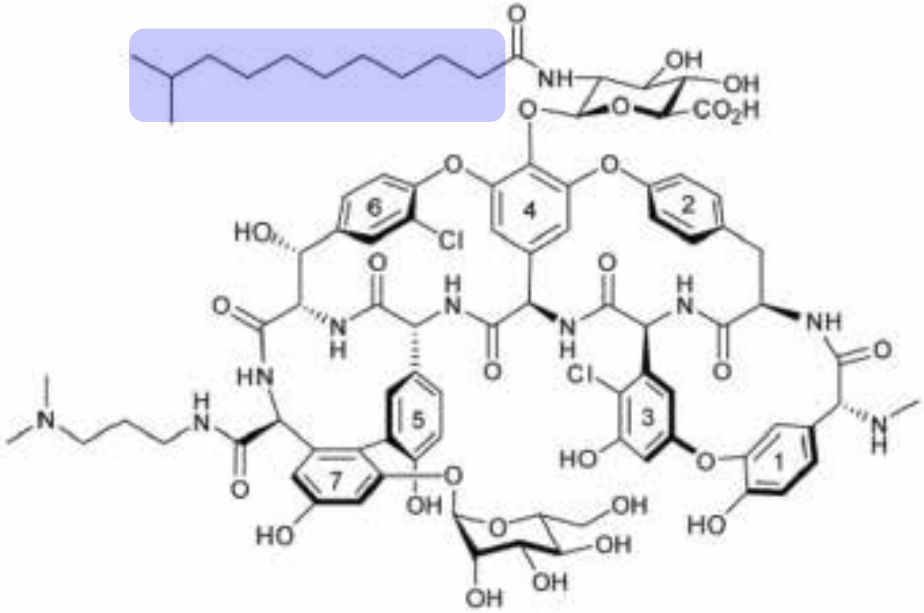
* High MIC ≥ 1.5 mg/L

Cheng M, et al. Anti-cooperative ligand binding and dimerisation in the glycopeptide antibiotic dalbavancin. *Org. Biomol. Chem 2014; 12: 2568*

teicoplanina



dalbavancina



Biedenbach DJ, et al. Activities of Dalbavancin against a Worldwide Collection of 81,673 Gram-Positive Bacterial Isolates. *Antimicrob Agents Chemother 2009; 53: 1260-3*

Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC (μg/ml)	
		50%	90%
S. aureus			
Oxacillin susceptible (27,052)	Dalbavancin	0.06	0.06
	Vancomycin	1	1
	Erythromycin	≤0.25	>2
	Clindamycin	≤0.25	≤0.25
	Levofloxacin	≤0.5	≤0.5
	Gentamicin	≤2	≤2
	Tetracycline	≤4	≤4
	Linezolid	2	2
Oxacillin resistant (19,721)	Dalbavancin	0.06	0.06
	Vancomycin	1	1
	Erythromycin	>2	>2
	Clindamycin	>2	>2
	Levofloxacin	>4	>4
	Gentamicin	≤2	>8
	Tetracycline	≤4	>8
	Linezolid	1	2

Biedenbach DJ, et al. Activities of Dalbavancin against a Worldwide Collection of 81,673 Gram-Positive Bacterial Isolates. *Antimicrob Agents Chemother 2009; 53: 1260-3*

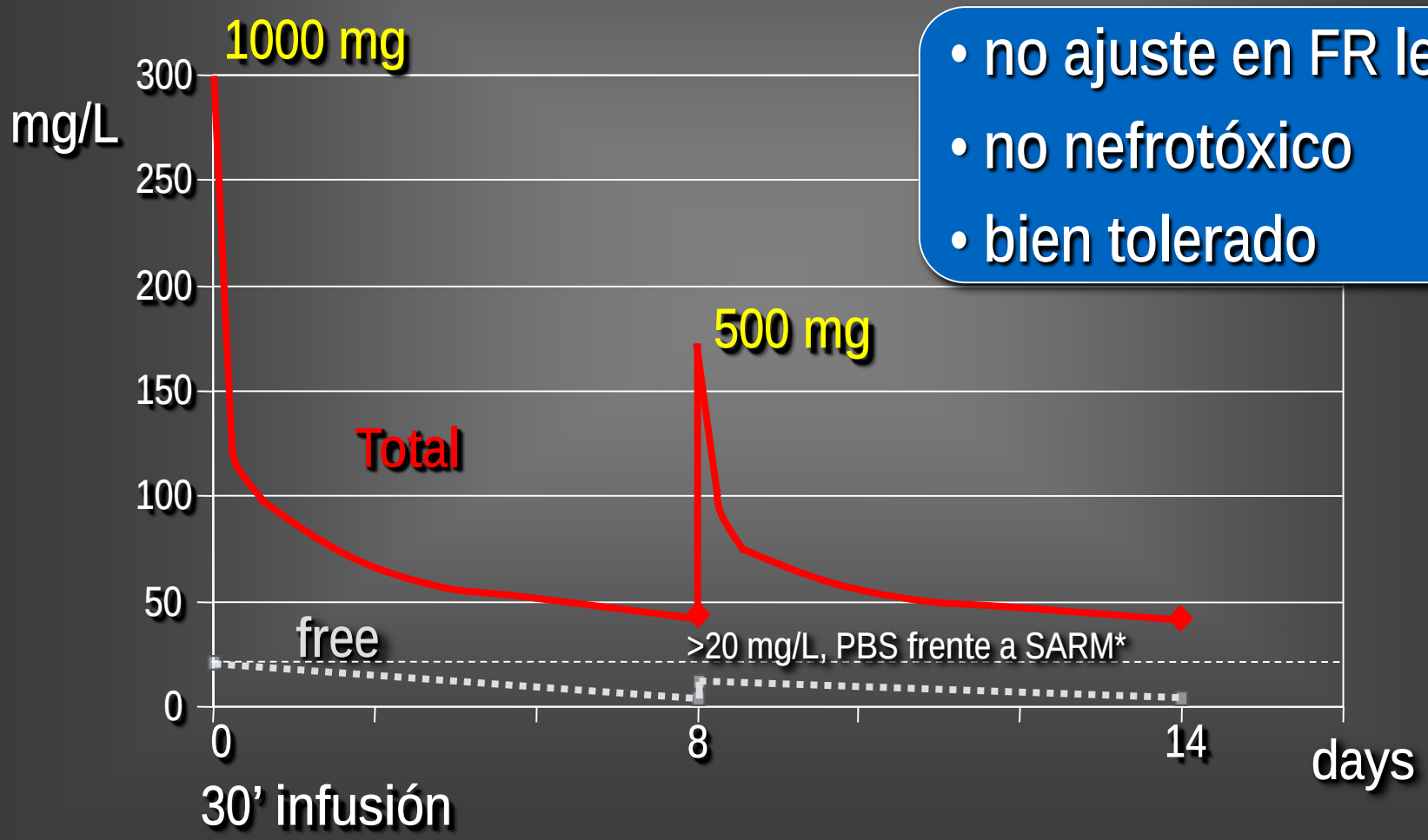
Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC (μg/ml)	
		50%	90%
CoNS			
Oxacillin susceptible (2,836)	Dalbavancin	≤0.03	0.06
	Vancomycin	1	2
	Erythromycin	≤0.25	>2
	Clindamycin	≤0.25	≤0.25
	Levofloxacin	≤0.5	4
	Gentamicin	≤2	≤2
	Tetracycline	≤4	>8
	Linezolid	1	1
Oxacillin resistant (9,472)	Dalbavancin	≤0.03	0.12
	Vancomycin	1	2
	Erythromycin	>2	>2
	Clindamycin	≤0.25	>2
	Levofloxacin	4	>4
	Gentamicin	4	>8
	Tetracycline	≤4	>8
	Linezolid	1	1

Biedenbach DJ, et al. Activities of Dalbavancin against a Worldwide Collection of 81,673 Gram-Positive Bacterial Isolates. *Antimicrob Agents Chemother 2009; 53: 1260-3*

Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC (μg/ml)	
		50%	90%
E. faecalis			
Vancomycin susceptible (10,025)	Dalbavancin	≤0.03	0.06
	Ampicillin	≤2	≤2
	Ciprofloxacin	1	>4
	Gentamicin (HL[c])	≤500	>1000
	Linezolid	1	2
Vancomycin nonsusceptible (349)	Dalbavancin	>4	>4
	Ampicillin	≤2	4
	Ciprofloxacin	>4	>4
	Gentamicin (HL)	>1000	>1000
	Linezolid	1	2
E. faecium			
Vancomycin susceptible (2,578)	Dalbavancin	0.06	0.12
	Ampicillin	>16	>16
	Ciprofloxacin	>4	>4
	Gentamicin (HL)	≤500	>1000
	Linezolid	1	2
Vancomycin nonsusceptible (2,176)	Dalbavancin	>4	>4
	Ampicillin	>16	>16
	Ciprofloxacin	>4	>4
	Gentamicin (HL)	≤500	>1000
	Linezolid	1	2

Dorr MB et al. Human pharmacokinetics and rationale for once-weekly dosing of dalbavancin, a semi-synthetic glycopeptide

J Antimicrob Chemother 2005;55 (Suppl2):25-30



- no ajuste en FR leve
- no nefrotóxico
- bien tolerado

* Leighton, et al. AACh 2004

Nicolau D et al. Pharmacokinetics of dalbavancin in plasma and skin blister fluid. *J Antimicrob Chemother 2007; 60: 681–684*

	Skin blister fluid			
Subject	C_{max} (mg/L)	$AUC_{Day\ 7}$ (mg·h/L)	Day 7 concentration (mg/L)	degree of penetration (%)
1	37	3984	19.7	44.4
2	77	7281	33.1	64.3
3	52	5453	29.7	62.8
4	77	6822	33.6	61.6
5	62	5926	30.1	61.3
6	59	6098	28.8	64.1
7	102	8237	30.5	55.0
8	67	7072	34.0	60.5
9	73	7071	33.4	62.3
Mean	67	6438	30.3	59.6
SD	18	1238	4.43	6.33

Boucher H et al. Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

N Engl J Med 2014;370:2169-79.

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

conclusiones

Dalbavancina es una alternativa a VNC/TEI/DAP en:

1.- infecciones de piel y partes blandas en pacientes con:

a) riesgo derivado del uso de catéteres vasculares (VC, MCP) o acceso vascular limitado (UDVP, flebitis recurrentes)

b) infección no grave que pueden tratarse en domicilio, pero no disponemos de alternativas p.o. (SARM) o no podemos garantizar el cumplimiento (ancianos, UDVP).

Raad I et al. Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

Clin Infect Dis 2005; 40:374–80

	Dalbavancin group	Vancomycin group
Study population		
ITT population	33	34
MicroITT population[a]	23 (70)	28 (82)
Evaluable population at EOT	17 (52)	21 (62)
Evaluable population at TOC	14 (42)	20 (59)

Estudio abierto y aleatorizado.
Pacientes con sospecha de BRC

Raad I et al. Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

Clin Infect Dis 2005; 40:374–80

	No. (%) of isolates	
1000 mg – 500 mg (8 d)*		1 g/12h*
Type of isolate	Dalbavancin group[a] (n = 26) (23)	Vancomycin group (n = 28)
Staphylococcus aureus	retirada inmediata del catéter	
All	11 (42.3)	12 (42.9)
MRSA[b]	5 (19.2)	9 (32.1)
CoNS	13 (50.0)	13 (46.4)
Enterococcus faecalis	2 (7.7)	3 (10.7)

Estudio abierto y aleatorizado en pacientes con sospecha de BRC

* En caso de BRC por CoNS con retirada del catéter, se administr ó dalbavancina en dosis única y vancomicina 7 días

Raad I et al. Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

Clin Infect Dis 2005; 40:374–80

Population and visit, response	Dalbavancin group	Vancomycin group
microITT population at EOT (8-14 días)		
Overall success	21/23 (91.3)	18/28 (64.3)
Clinical success	21/23 (91.3)	18/28 (64.3)
Microbiological success	22/23 (95.6)	26/28 (92.9)
microITT population at TOC (21 días)		
Overall success[a]	20/23 (87.0)[b]	14/28 (50.0)[c]
By catheter status		
Retained at baseline	6/8 (75.0)	4/10 (40.0)
Clinical success	20/23 (87.0)	14/28 (50.0)
Microbiological success	22/23 (95.7)	22/28 (78.6)

Belley A, et al. Oritavancin Kills Stationary-Phase and Biofilm Staphylococcus aureus Cells In Vitro

Antimicrob Agents Chemother 2009; 53: 918–925

Antimicrobial agent	MSSA ATCC 29213		MRSA ATCC 33591	
	MIC (μg/ml)	MBEC[a] (μg/ml)	MIC (μg/ml)	MBEC[a] (μg/ml)
Oritavancin[b]	2	2–4	0.5–4	0.5–4
Linezolid	8	>128	2–4	>128
Rifampin	<0.02	4	<0.03	0.25–4
Vancomycin	1	>128	1–2	≥128

[a] 24h biofilms (MBEC)

[b] without polysorbate 80 (decrease the biofilm formation)

Dunne MW, et al. Extended duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother 2015 in press*

Parameter	Cohort I (4th infusion) N=6	Cohort II (6th infusion) N=6	Cohort III (8th infusion) N=6
AUC 0-t (µg h/mL)	10203 (14.9%)	12292.79 (17.8%)	12173 (17.7%)
Cmax (µg/mL)	160.0 (14.0%)	187.0 (13.1%)	179.7 (11.0%)
Cmin (µg/mL)	33.0 (19.3%)	42.9 (17.4%)	40.2 (20.0%)
Tmax (h) (median, range)	0.5 (0.5 – 1.0)	0.5 (0.5-0.5)	0.5 (0.5 – 1.0)
Accumulation Ratio (R)	0.89 (10.7%)	0.96 (12.5%)	0.91 (17.0%)

On Day 1, subjects received 1000mg of dalbavancin IV over 30 minutes, followed by 500 mg IV over 30 minutes IV weekly for a total of 4 weekly infusions (Cohort 1), 6 weekly infusions (Cohort II) or 8 weekly infusions (cohort III).

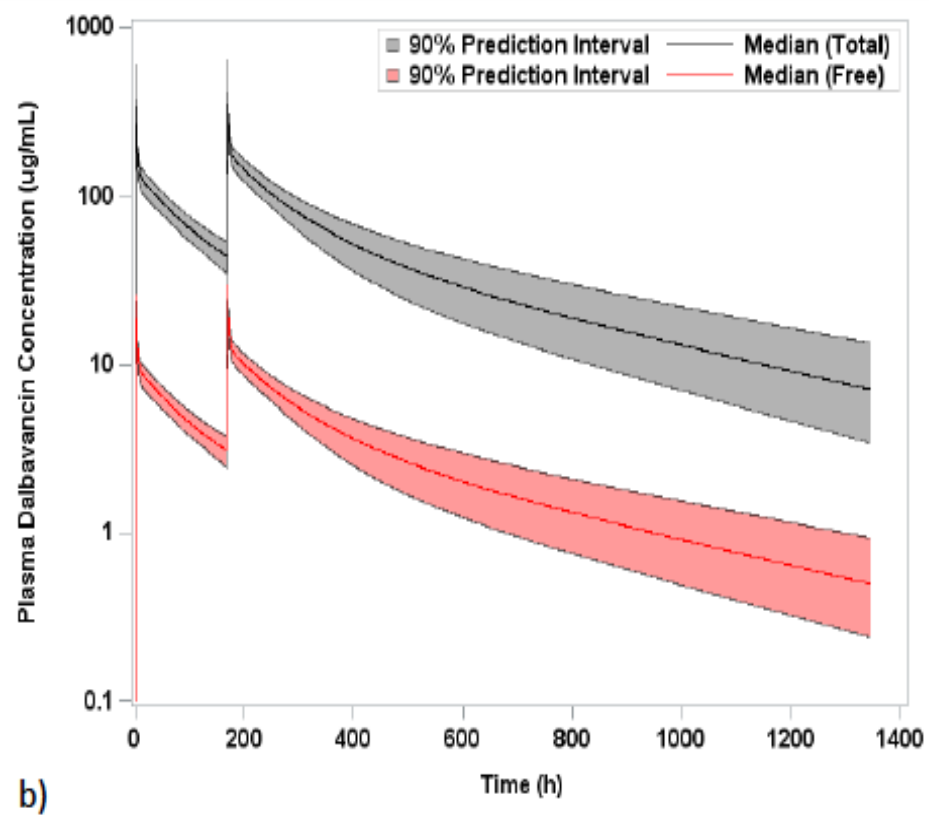
Two adverse events; transient urticaria and pain in the forearm.

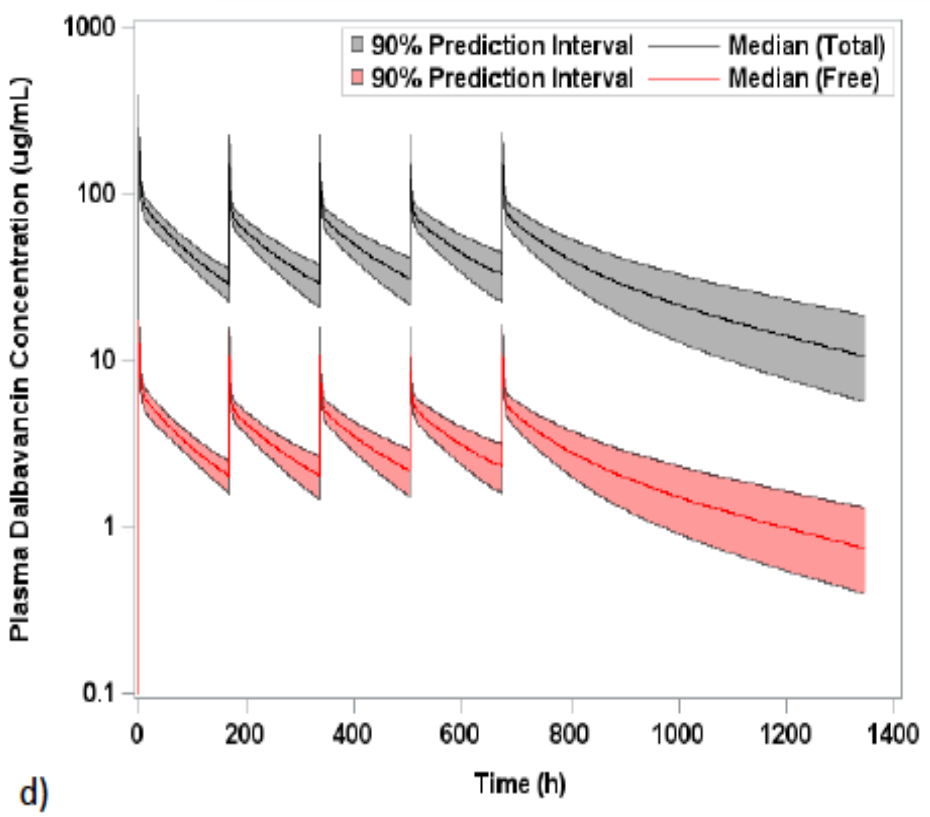
Dunne MW, et al. Extended duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother 2015 in press*

Mean (SD) Tissue Concentration		Hours (Days) postdose that samples were collected					
		12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (µg/ml)[a]	N	31	ND	ND	ND	ND	31
		85.3 (18.9)					15.3 (4.1)
Synovium[b] (µg/g)	N	3	3	3	4	2	3
		25.0 (0)	17.9 (7.8)	19.5 (4.9)	19.2 (8.9)	25.0 (0)	15.9 (7.9)
Synovial fluid[b] (µg/ml)	N	1	4	3	2	3	2
		22.9	27.4 (10.8)	19.2 (4.9)	11.6 (3.3)	13.9 (1.0)	6.2 (1.7)
Bone (µg/g)	N	5	5	5	5	5	5
		6.3 (3.1)	5.0 (3.5)	4.6 (3.8)	3.8 (2.7)	3.7 (2.2)	4.1 (1.6)
Skin[b] (µg/g)	N	2	3	2	2	1	2
		19.4 (7.9)	12.5 (6.5)	13.8 (1.4)	15.7 (1.0)	21.6	13.8 (2.1)

Administración de 1000 mg 0.5, 1,3,7,10 y 14 días antes de una artoplastia

Dunne MW, et al. Extended duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother 2015 in press*





Simultation of 1500 mg 2-doses 1 week apart.

Simultation of 1000 mg single dose and 500 mg weekly.

conclusiones

Dalbavancina es una alternativa a VAN/TEI/DAP en:

1.- infecciones de piel y partes blandas en pacientes con:

a) riesgo derivado del uso de catéteres vasculares (VC, MCP) o acceso vascular limitado (UDVP, flebitis recurrentes)

b) infección no grave que pueden tratarse en domicilio, pero la no disponemos de alternativas p.o. (SARM) o no podemos garantizar el cumplimiento (ancianos, UDVP).

2.- bacteriemia relacionada con un catéter vascular por un GP, particularmente en aquellos pacientes que no requieren un nuevo acceso vascular.

3.- bacteriemia/infección complicada por SARM (endocarditis, osteomielitis, espondilodiscitis, infecciones sobre implantes), para completar el tratamiento (4-6 semanas) reduciendo los días de cateterización.