I Jornadas de Actualización en PROA
Hospital Universitari Mútua Terrassa
22-23 de noviembre de 2023

¿Bactericida o Bacteriostático?

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REAL ACADEMIA ESPAÑOLA

-cida

Del lat. *–cīda*, de la raíz de *caedĕre* 'matar'.

1. elem. compos. Significa 'matador' o 'exterminador'. *Herbicida, insecticida.*

estático, ca

Del lat. mod. *staticus*, y este del gr. στατικός *statikós*; la forma f., del lat. mod. *statica*, y este del gr. στατική *statikḗ* 'arte de pesar'.

1. adj. Perteneciente o relativo a la **estática.**

2. adj. Que permanece en un mismo estado, sin mudanza en él.

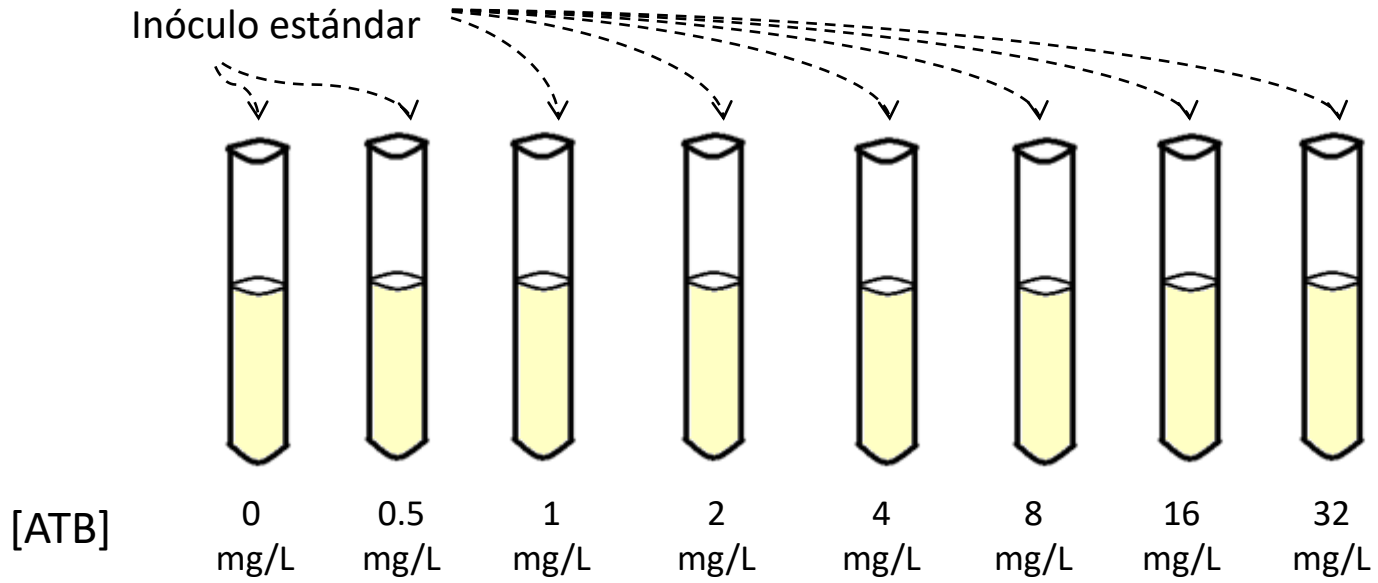
3. adj. Dicho de una persona: Que se queda parada de asombro o de emoción.

4. f. *Fís.* Rama de la mecánica que estudia las leyes del equilibrio.

5. f. *Fís.* Conjunto de leyes que estudia la **estática.**

CMI Concentración mínima inhibitoria

(µg/mL ó mg/L)



Balouiriret al. J Pharmac Analysis. 2016

CMI Concentración mínima inhibitoria

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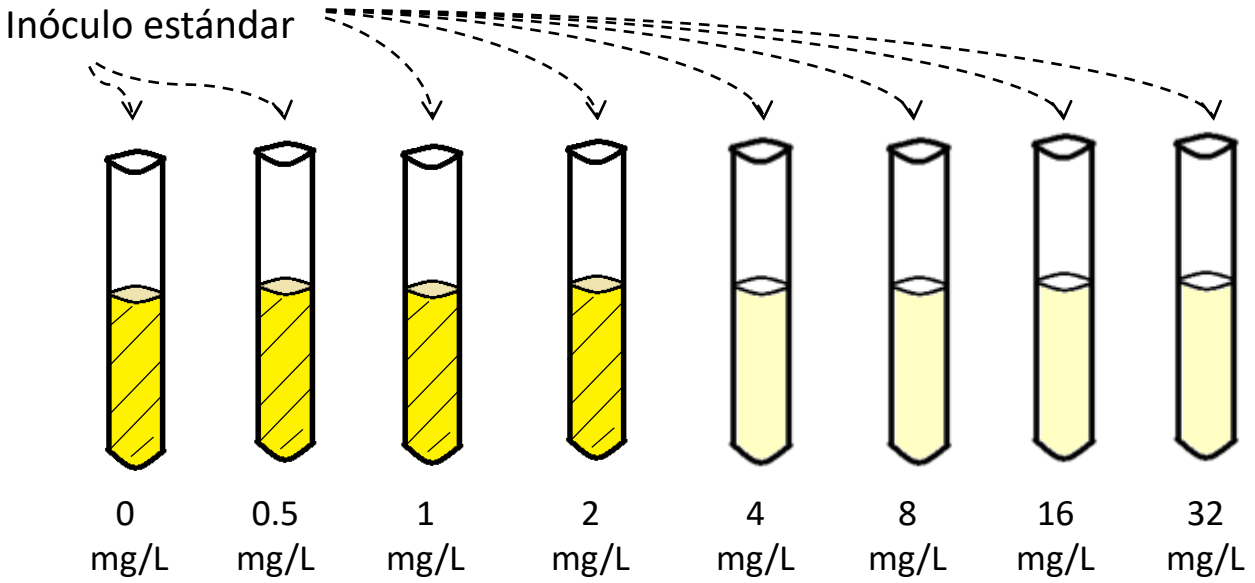
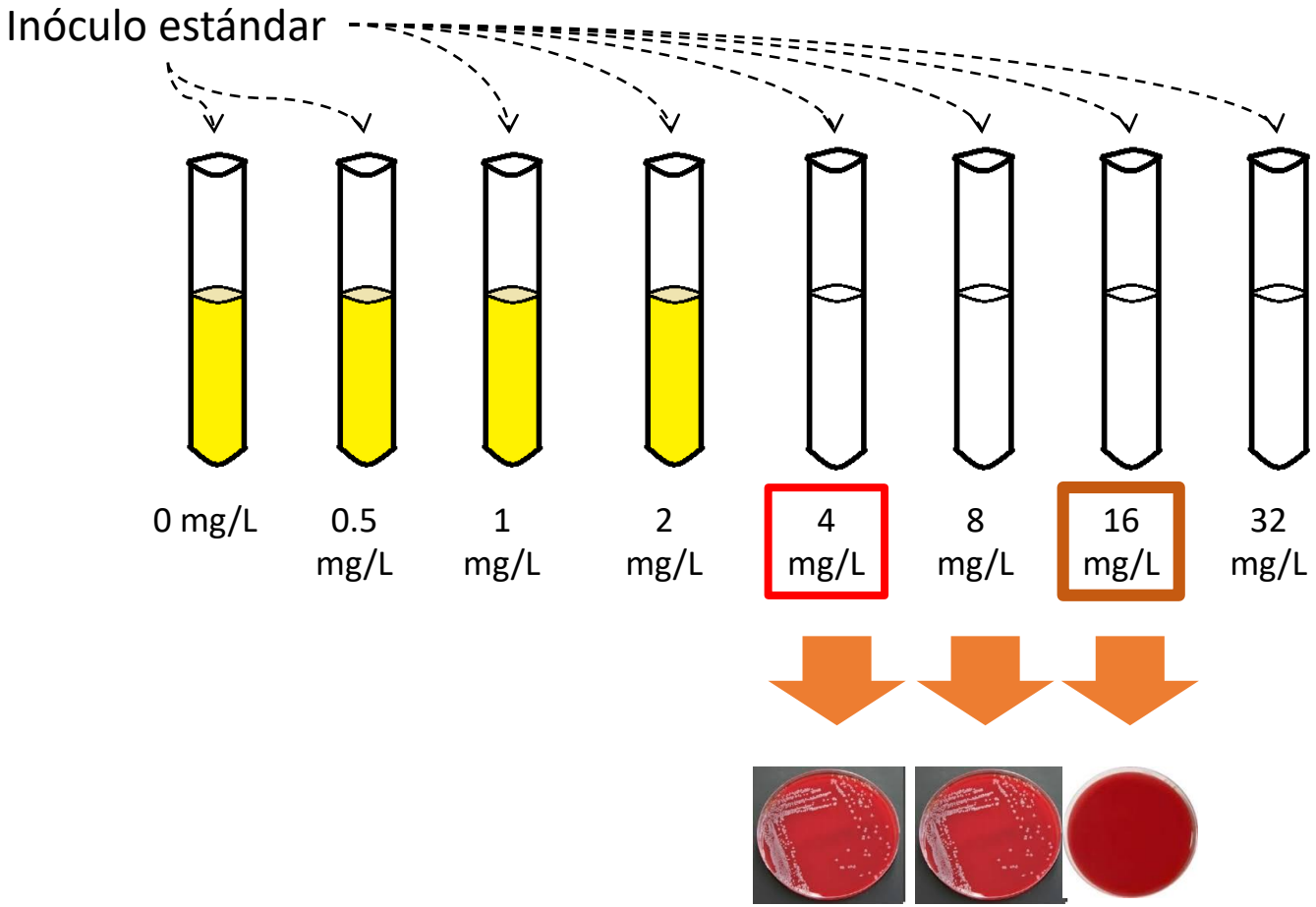
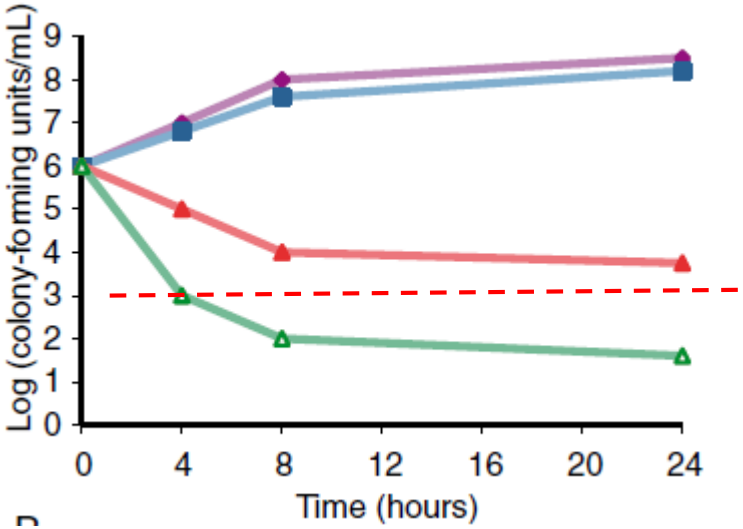


Balouiriret al. J Pharmac Analysis. 2016

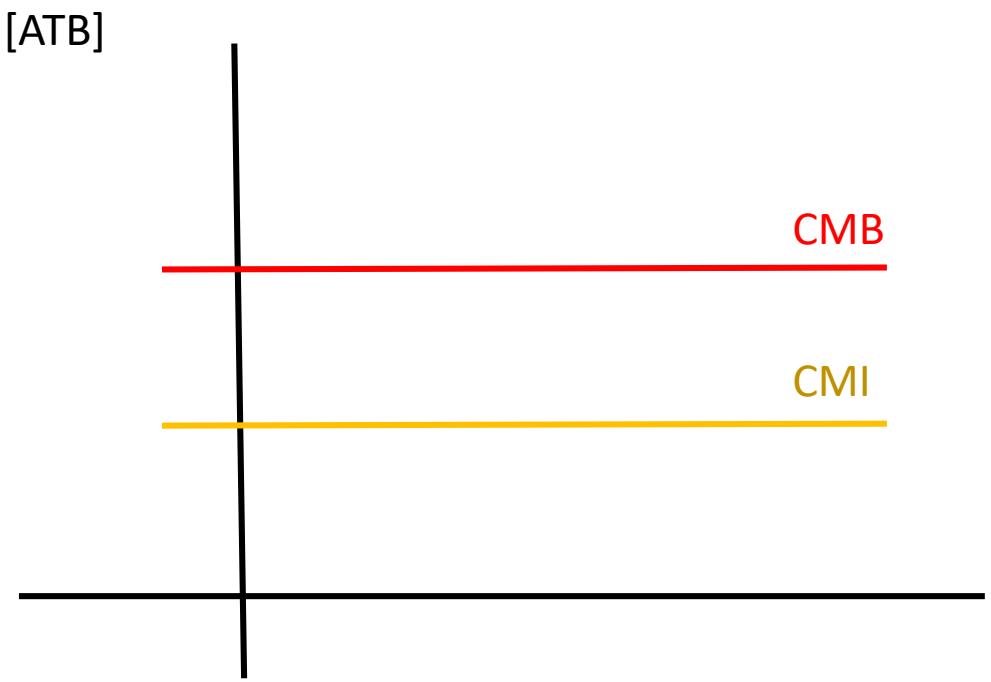
Concentración mínima bactericida (CMB)



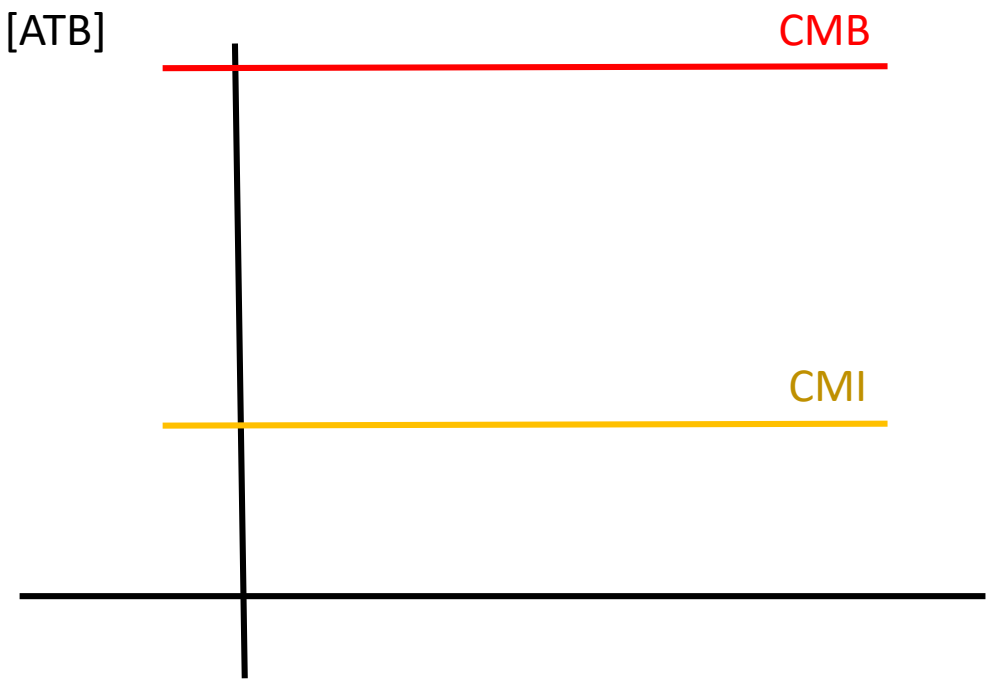


Balouiriret al. J Pharmac Analysis. 2016

CMB/CMI ≤4 → bactericida



CMB/CMI > 4 → bacteriostático



Panley & Sabath. CID 2004
Dickler et al. CID 2018

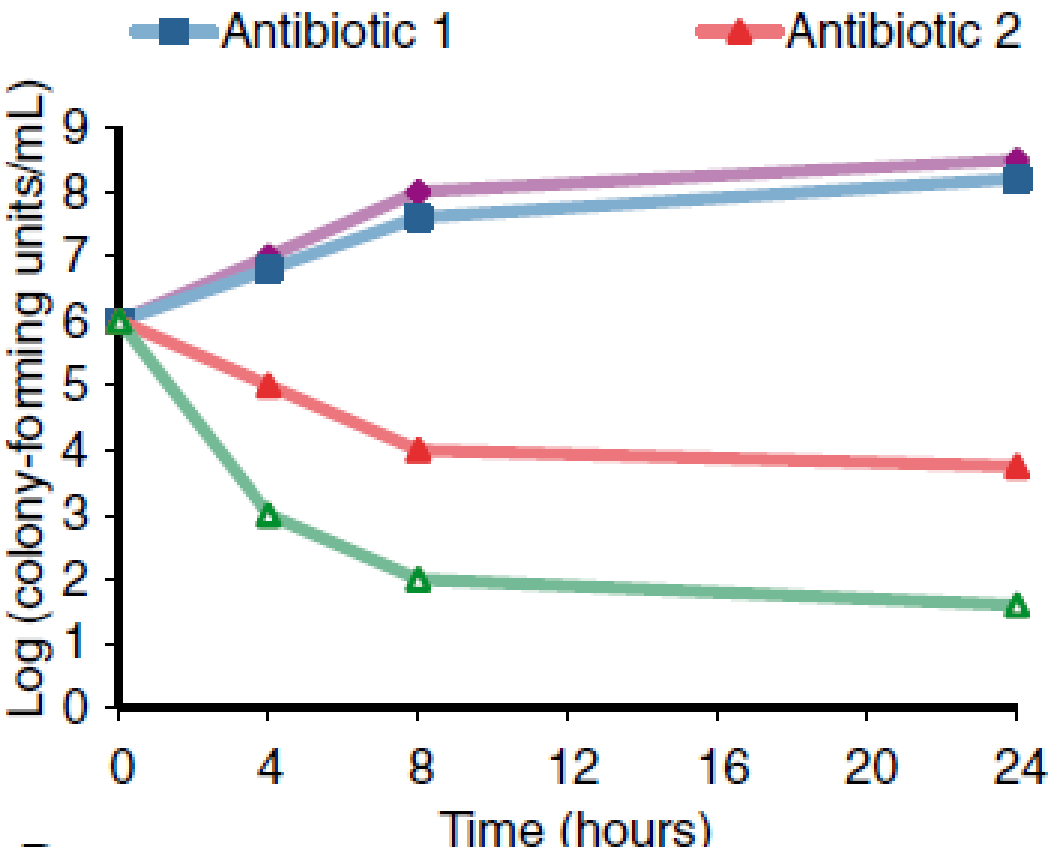
The Importance of Bactericidal Drugs: Future Directions in Infectious Disease

Robert W. Finberg,[1] Robert C. Moellering,[2] Francis P. Tally,[3] William A. Craig,[4] George A. Pankey,[5] E. Patchen Dellinger,[6] Michael A. West,[7] Manjari Joshi,[8] Peter K. Linden,[9] Ken V. Rolston,[10] John C. Rotschafer,[11] and Michael J. Rybak[12]

Table 1. Bactericidal activity of several classes of antimicrobial agents.

Class	Mechanism of action	Bactericidal activity
β-Lactams and glycopeptides	Inhibition of cell wall synthesis	Yes; see text for exceptions [6]
Fluoroquinolones	Inhibition of DNA replication	Yes [10]
Macrolides, lincosamides, streptogramins, chloramphenicol, and aminoglycosides	Inhibition of protein synthesis	Aminoglycosides: yes; others: no; see text for exceptions [6, 9]
Oxazolidinones	Inhibition of protein synthesis	In general, no [14]; may be slowly bactericidal against *Staphylococcus aureus* [15]
Polymyxins and lipopeptides	Cell membrane binding	Yes [7, 8]
Rifamycins	Inhibition of DNA-dependent RNA polymerase	Sometimes [13]
Tetracyclines	Inhibition of protein synthesis	No [12]
Trimethoprim and sulfonamides	Inhibition of folate synthesis	No; see text for exceptions [11]

Finberg et al. CID 2004



CURRENT STATUS OF THERAPY IN BACTERIAL ENDOCARDITIS

Maxwell Finland, M.D., Boston

mycin-resistant strains that may appear to be somewhat sensitive to them in vitro.

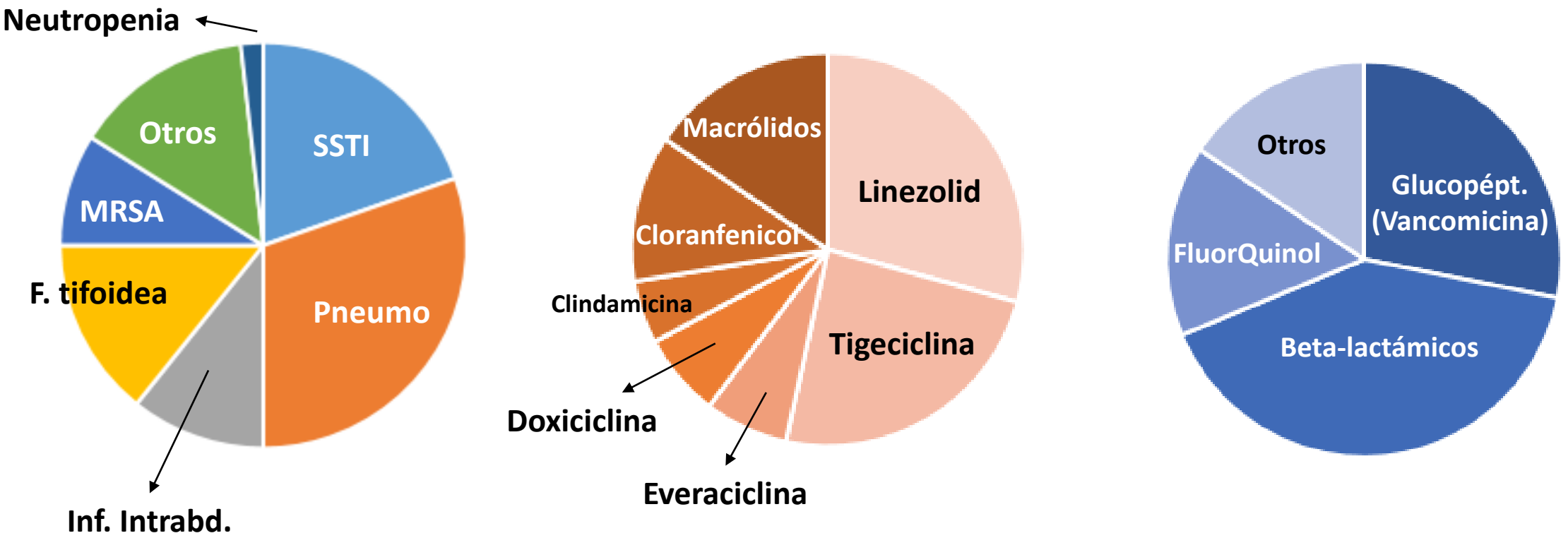
Hunter [4] has emphasized the importance of determining the bactericidal concentration of antibiotic agents individually and in certain combinations. He has also demonstrated the value of strepto-

Finland et al. JAMA 1958

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

Revisan resultados de 56 ensayos clínicos comparando agentes bacteriostáticos contra bactericidas.



Dickler et al. CID 2018

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

- **49 ensayos (81%) no encuentran diferencia en el endpoint primario → bactericida = bacteriostático.**
- **5 ensayos (9%) hay mejor actividad del ATB bacteriostático → bactericida < bacteriostático**

Itani *et al*, 2010 [5]	Phase 4, open-label, multicenter	Complicated SSTI	Linezolid	Vancomycin	Linezolid (static) superior.
Sharpe *et al*, 2005 [45]	Open-label, single center	MRSA complicated SSTI	Linezolid	Vancomycin	Linezolid (static) superior.
Lin *et al*, 2008 [49]	Double-blind, multicenter	Gram-positive infections (nosocomial pneumonia or complicated SSTI)	Linezolid	Vancomycin	Linezolid (static) superior.
San Pedro *et al*, 2002 [52]	Open-label, multicenter	Pneumococcal pneumonia	Linezolid	Ceftriaxone/ cefpodoxime	Linezolid (static) superior.
Wunderink *et al*, 2012 [47]	Double-blind, multicenter	MRSA pneumonia	Linezolid	Vancomycin	Linezolid (static) superior.

Dickler et al. CID 2018

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

- **1 ensayo (2%) hay mejor actividad del ATB bactericida → bactericida > bacteriostático**

Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia☆

Antonio T. Freire[a], Vasyl Melnyk[b], Min Ja Kim[c], Oleksiy Datsenko[d], Oleksandr Dzyublik[e], Felix Glumcher[f], Yin-Ching Chuang[g], Robert T. Maroko[h], Gary Dukart[h], C. Angel Cooper[h], Joan M. Korth-Bradley[h], Nathalie Dartois[i,*], Hassan Gandjini[i]
for the 311 Study Group

Tigeciclina: carga 100 mg, seguido de 50 mg/12h

Clinical response at TOC

CE population

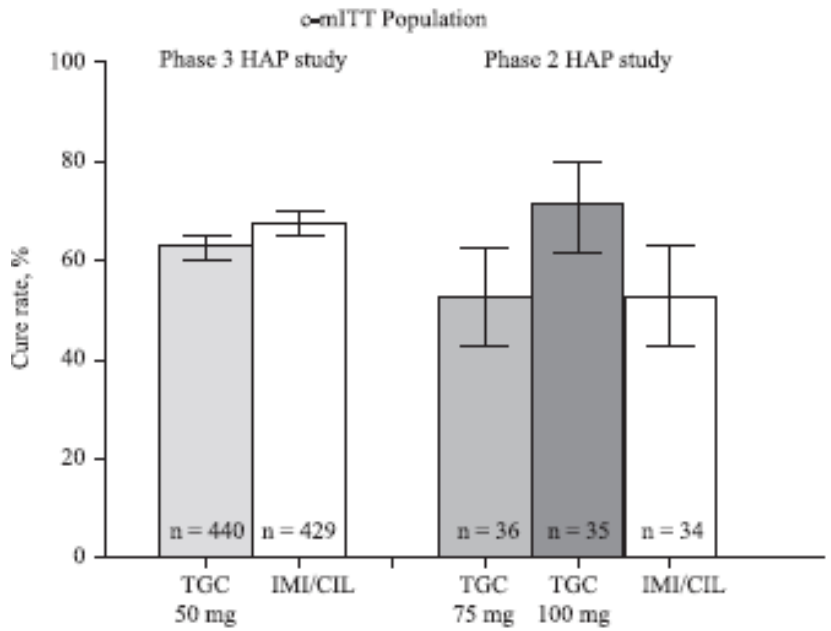
Clinical response	Tigecycline (n = 268)	Imipenem/cilastatin (n = 243)	Absolute difference (95% CI)	Test for noninferiority
P				
Cure	182 (67.9)	190 (78.2)	−10.4 (−17.8 to −3.0)	0.120
Failure	86 (32.1)	53 (21.8)		

Randomized Phase 2 Trial To Evaluate the Clinical Efficacy of Two High-Dosage Tigecycline Regimens versus Imipenem-Cilastatin for Treatment of Hospital-Acquired Pneumonia

Julio Ramirez,[a] Nathalie Dartois,[b] Hassan Gandjini,[b*] Jean Li Yan,[c] Joan Korth-Bradley,[c] Paul C. McGovern[c]

Tigeciclina:

- carga 150 mg, seguido de 75 mg/12h
- Carga 200 mg, seguido de 100 mg/12h



Freire et al. DMID 2010
Ramírez et al. AAC 2013
Dickler et al. CID 2018

Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis

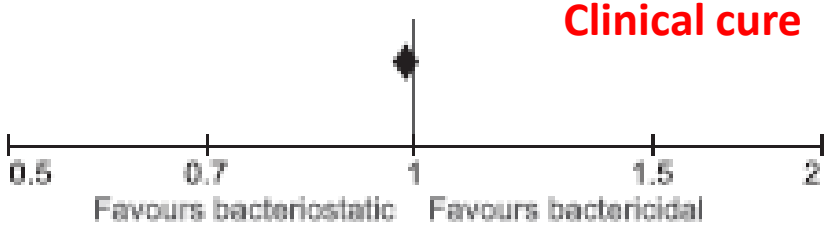
Johannes Nemeth[1]*†, Gabriela Oesch[2]† and Stefan P. Kuster[1]†

Metanálisis de 33 RCT

Clinical cure

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

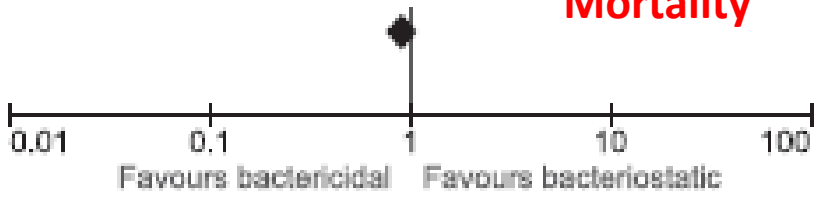
Heterogeneity: Tau² = 0.00; Chi² = 41.83, df = 32 (P = 0.11); I² = 24%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Chi² = 7.34, df = 3 (P = 0.06), I² = 59.1%



Mortality

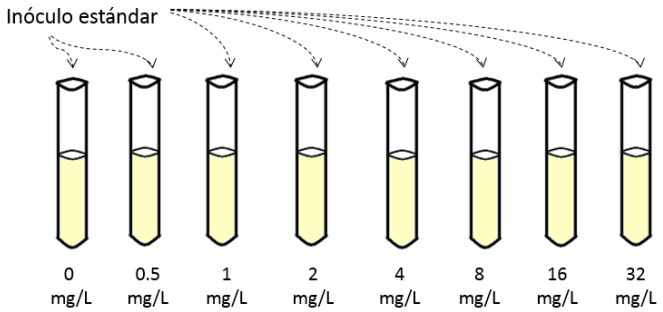
Total (95% CI)	6548	6550	100.0%	0.91 [0.76, 1.08]
Total events	208	255		

Heterogeneity: Tau² = 0.00; Chi² = 16.65, df = 24 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Chi² = 4.56, df = 3 (P = 0.21), I² = 34.2%



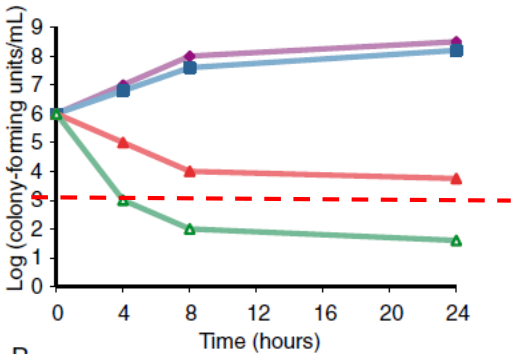
Nemeth et al. JAC 2015

Limitaciones de la CMI y la CMB – Limitaciones de la definición de antibiótico bactericida.



i. Condiciones de laboratorio muy precisas

- Temperatura 35-37ºC
- pH específico ≈ 7,2
- Medición a las 18-24h
- Inóculo estándar $5 \cdot 10^5$ ufc/mL
- Medio de cultivo específico, [CO_2] específica
- Fase de crecimiento exponencial



ii. Arbitrariedad en las definiciones

- Arbitrariedad en la definición de CMB (99.9%??)
- Arbitrariedad en la definición de bactericida: CMI/CMB ≤4
- Los ATB bacteriostáticos también eliminan bacterias – aumentar dosis hasta CMB

Levinson. Inf Dis North Am 1995
Pankey & Sabath. CID 2004
Dickler et al. CID 2018

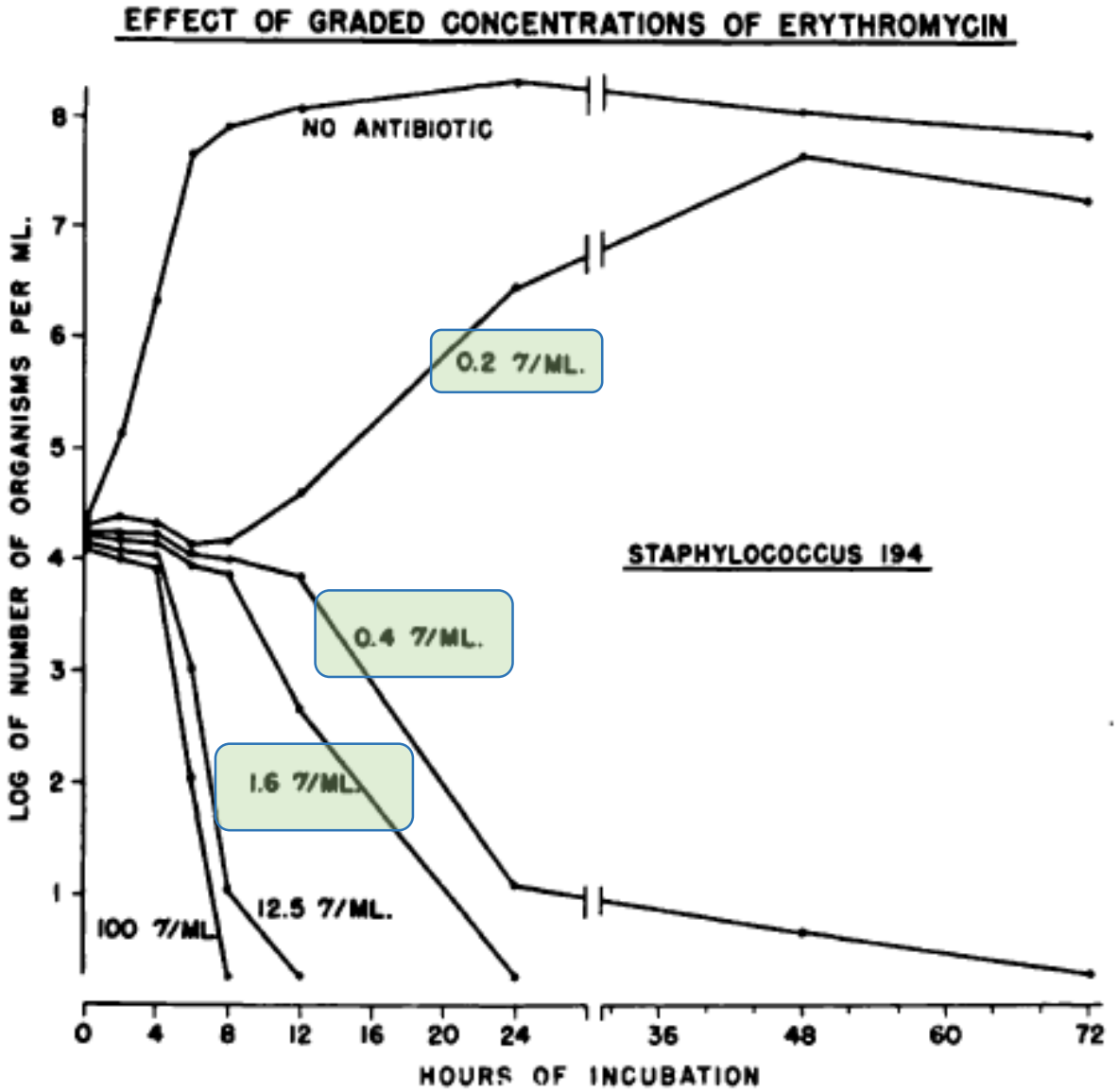
iii. Inconsistencia de la definición :

- Variabilidad de conducta en función del microorganismo:
  - Penicilina es estática frente a *Enterococcus* spp.
  - Los macrólidos son bactericidas frente a estreptococos (*S. pyogenes, S. pneumoniae*)

Observations on Mode of Action of Erythromycin.* (19817)

THOMAS H. HAIGHT AND MAXWELL FINLAND.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.



Haight & Finland. Proc Soc Exp Biol Med 1952

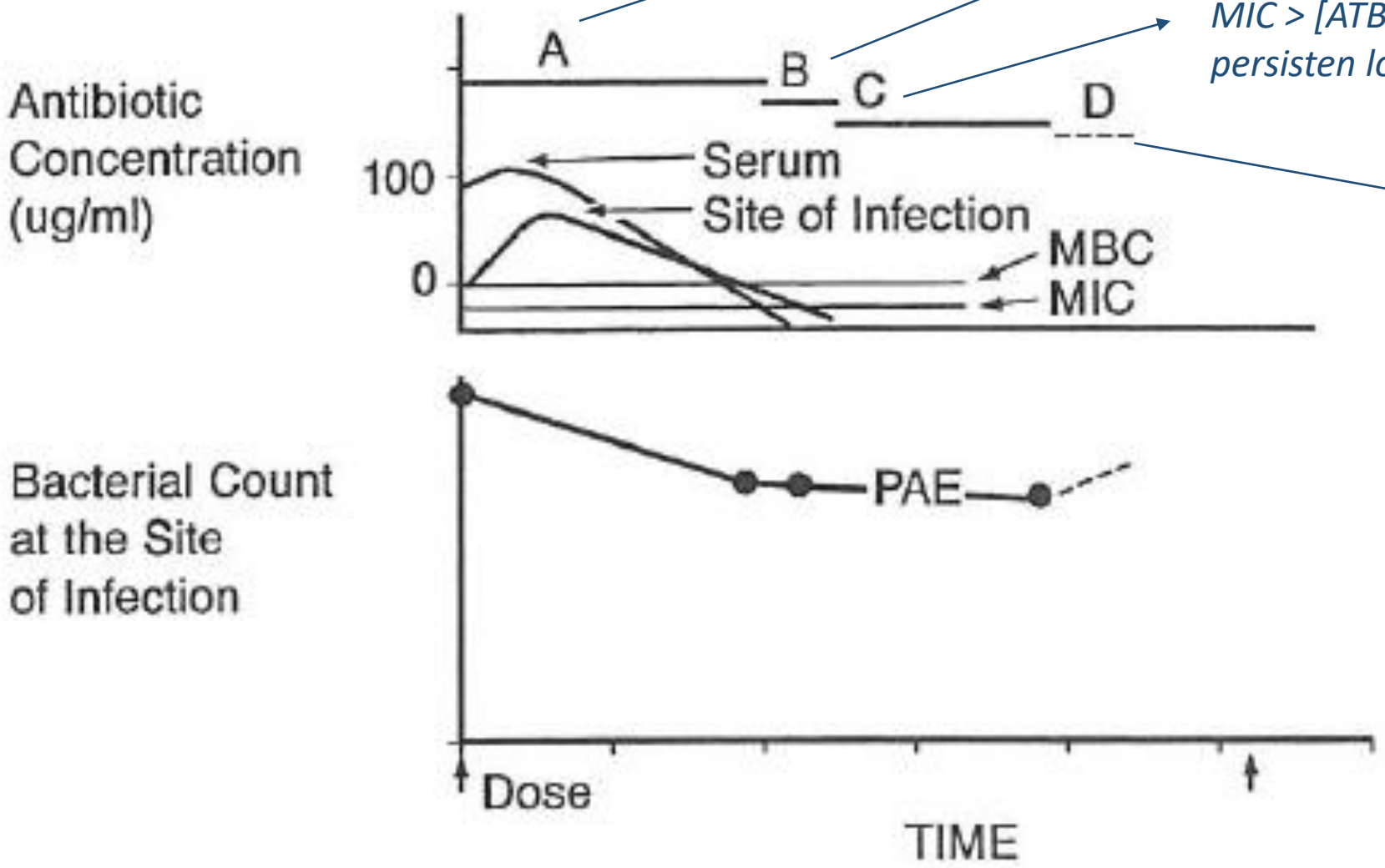
iv. Traslación al mundo *in vivo* – importancia del sistema inmune

[ATB] > MBC en el lugar de la inf.

MBC > [ATB] > MIC en el lugar de la inf.

MIC > [ATB] en el lugar de la inf, pero persisten los efectos del ATB

recrecimiento



Bush & Levinson. Crit Care Clin 1988

Levinson. Inf Dis North Am 1995

iii. Importancia del inóculo

Efecto inóculo: incremento de la MIC al usar inóculos > $5 \cdot 10^5$ ufc/mL

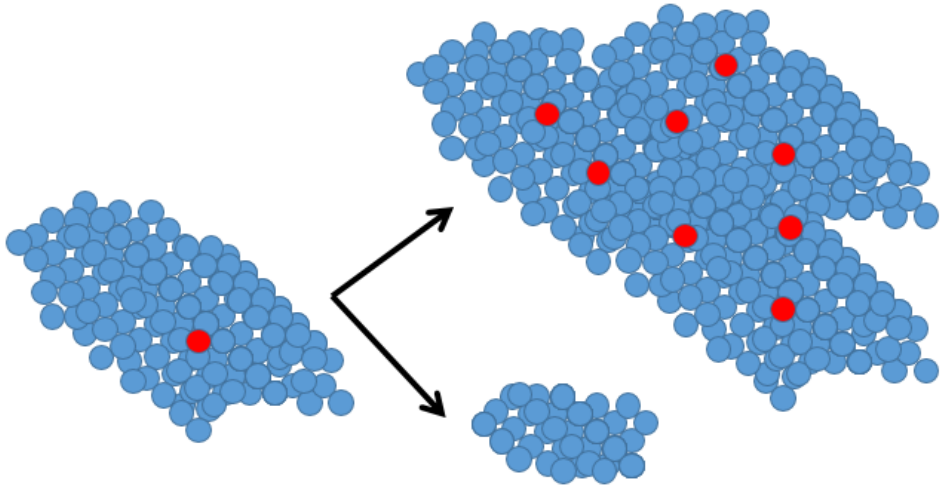
Table 2. Summary of inoculum effect of various antibiotics against common Enterobacteriaceae and *Pseudomonas aeruginosa*.

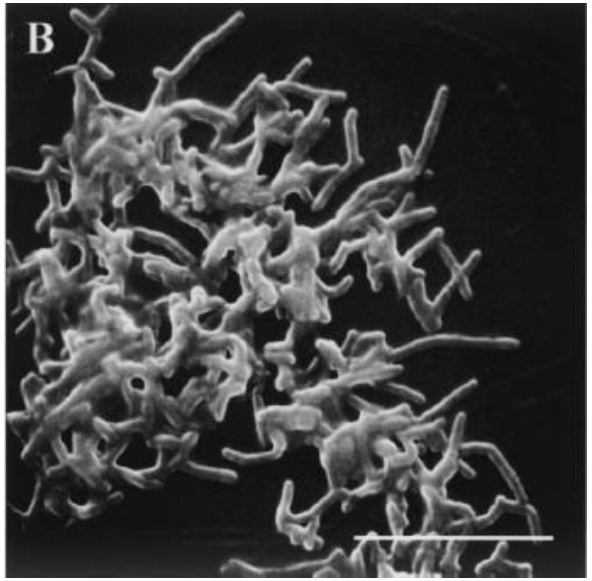
Antibiotic	*Escherichia coli*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Salmonella typhi*
Moxalactam	+	+	+	ND	ND
Cefotaxime	+	+	+	+	+
Ceftizoxime	+	+	+	+	+
Cefoperazone	+	+	+	+	+
Ceftazidime	+	+	+	+	+
Cefoxitin	±	±	−	−	−
Cefotetan	−	−	+	ND	ND
Aztreonam	+	+	ND	+	+
Azlocillin	ND	ND	ND	+	ND
Chloramphenicol	±	−	ND	−	−
Carbenicillin	−	ND	ND	−	ND
Piperacillin	ND	ND	+	+	ND
Ticarcillin	ND	ND	ND	−	ND
Imipenem	−	−	−	−	+
Kanamycin	±	ND	ND	±	ND
Gentamicin	±	−	ND	±	−
Ciprofloxacin*	−	−	−	−	ND
Norfloxacin*	−	−	−	−	ND
Tetracycline	−	ND	ND	ND	ND

Brook. Rev Inf Dis 1989

Motivos que justifican el efecto inóculo

- Mecanicismo – hay que repartir las moléculas de ATB entre mayor número de bacterias /dianas
- Emergencia de mutantes resistentes
- Consumo nutrientes – cambio metabólico
- Ralentización de la tasa de crecimiento – menor expresión de dianas (PBPs)
- Formación de micro-agregados – cambio metabólico
- Mayor densidad de enzimas hidrolíticas (ej. beta-lactamasas)



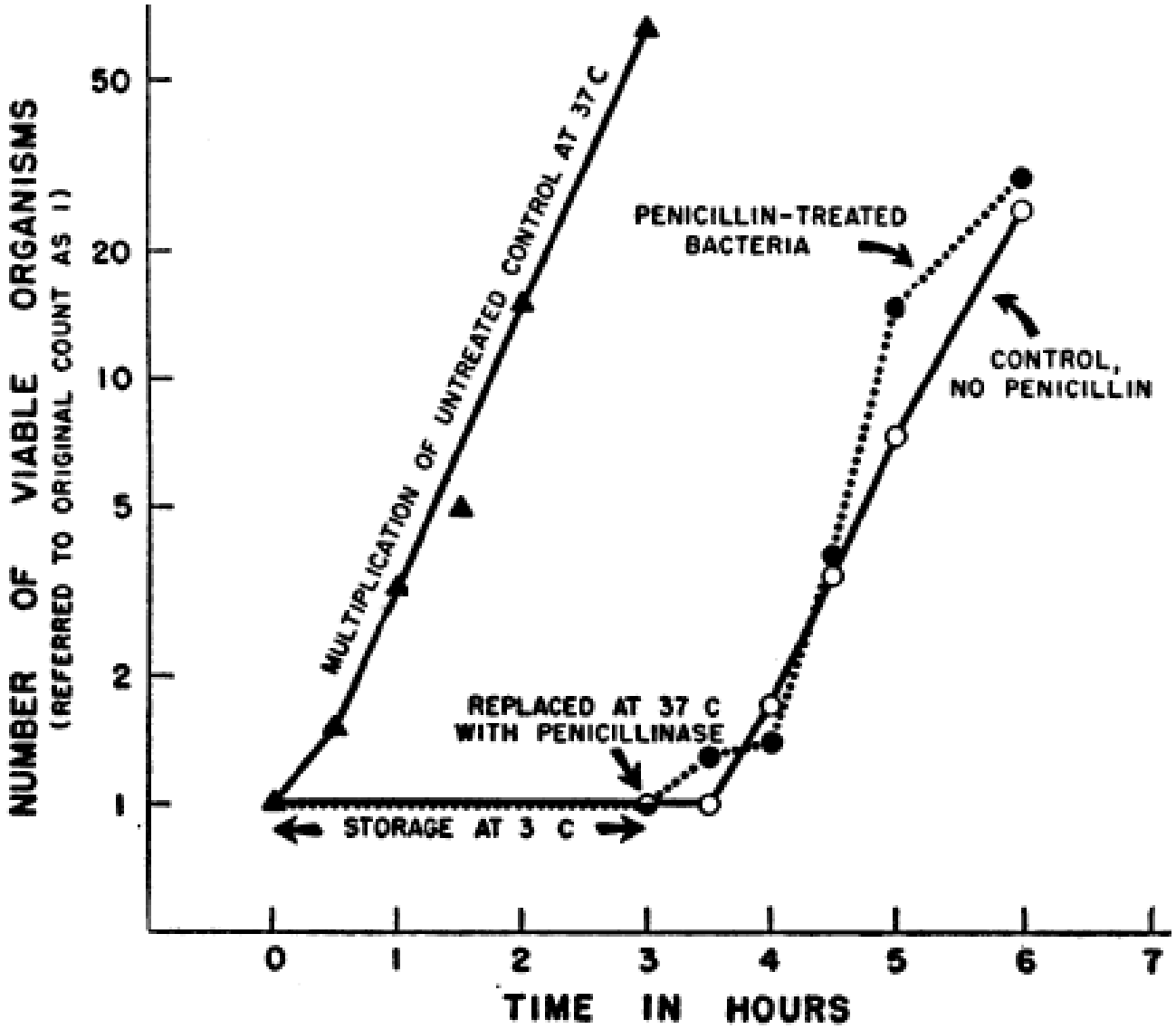


Brook. Rev Inf Dis 1989
Bardouniotis, et al. Curr Microb, 2003
Lenhard & Bulman. JAC 2019

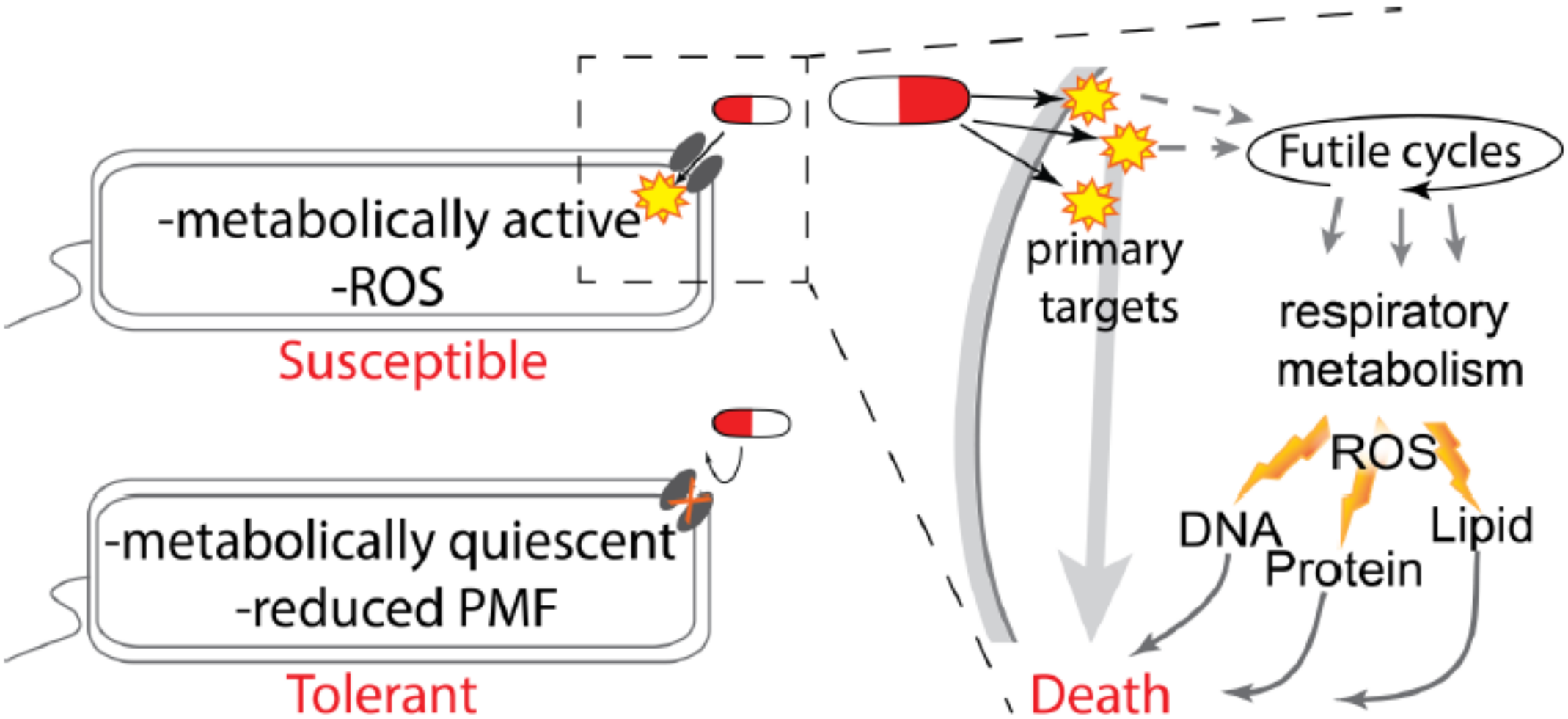
iv. Importancia de la fase metabólica del microorganismo

THE SLOW RECOVERY OF BACTERIA FROM THE TOXIC EFFECTS OF PENICILLIN

HARRY EAGLE AND ARLYNE D. MUSSELMAN

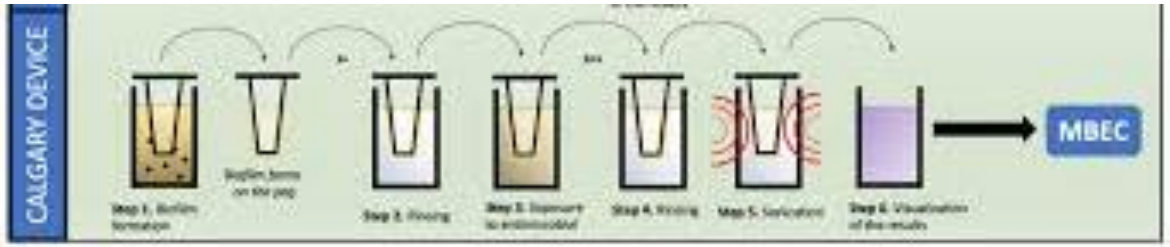


Eagle & Musselman. J Bacteriol 1948



Rowan et al. Microb Cell 2016
Yang et al . Curr Opin Microbiol 2017

iv-bis. Importancia de la fase metabólica del microorganismo – el biofilm

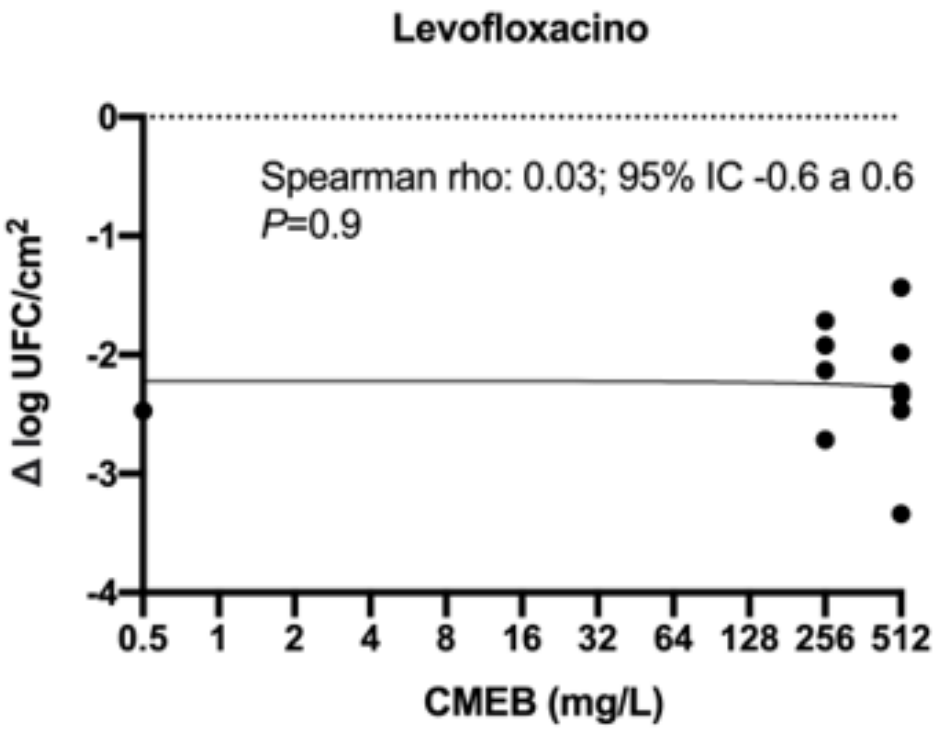


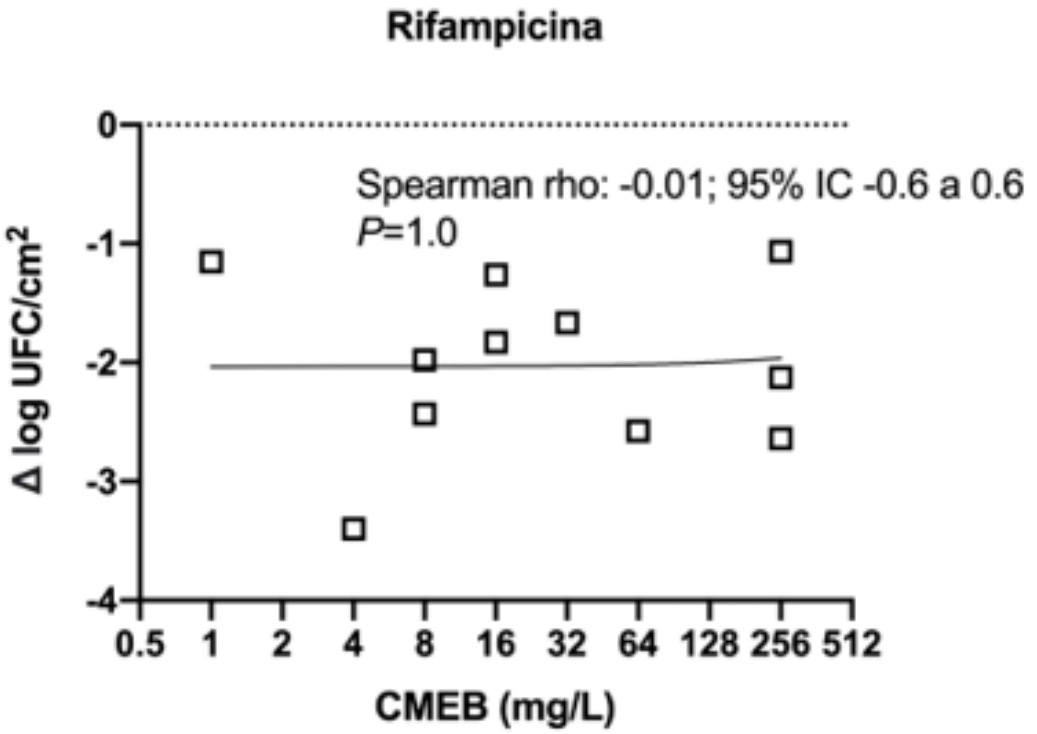
Antibiotic	MIC (μg/ml)		MBEC (μg/ml)	
	NCCLS assay[a]	Assay with CBD[a]	A_{650}[a]	0 CFU/peg[b]
Cefazolin	0.5	0.5	>1,024	>1,024
Ciprofloxacin	0.25	0.5	512	512
Clindamycin	0.12	0.25	128	256
Gentamicin	0.5	0.5	2	2
Oxacillin	0.12	0.25	>1,024	>1,024
Penicillin	1	4	128	128
Vancomycin	1	1	>1,024	>1,024

Ceri et al. J Clin Microbiol 1999

Strain-to-strain variability among *Staphylococcus aureus* causing prosthetic joint infection drives heterogeneity in response to levofloxacin and rifampicin

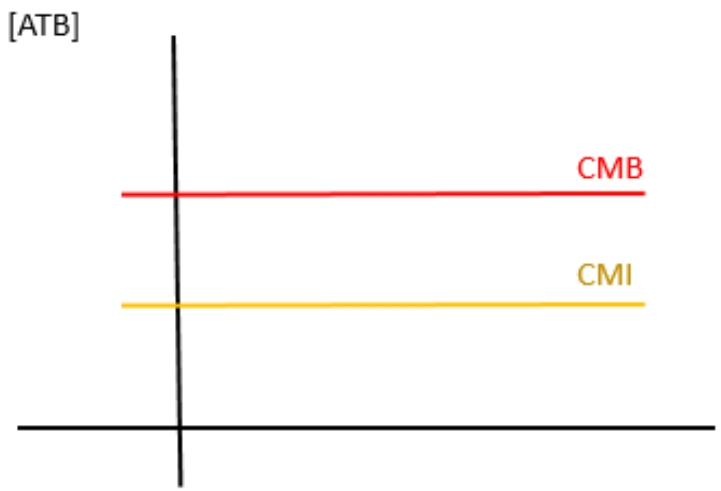
María Ángeles Meléndez-Carmona [1], Mikel Mancheño-Losa [2*], Albert Ruiz-Sorribas [3], Irene Muñoz-Gallego [1], Esther Viedma [1], Fernando Chaves [1], Françoise Van Bambeke [3] and Jaime Lora-Tamayo [2,4]



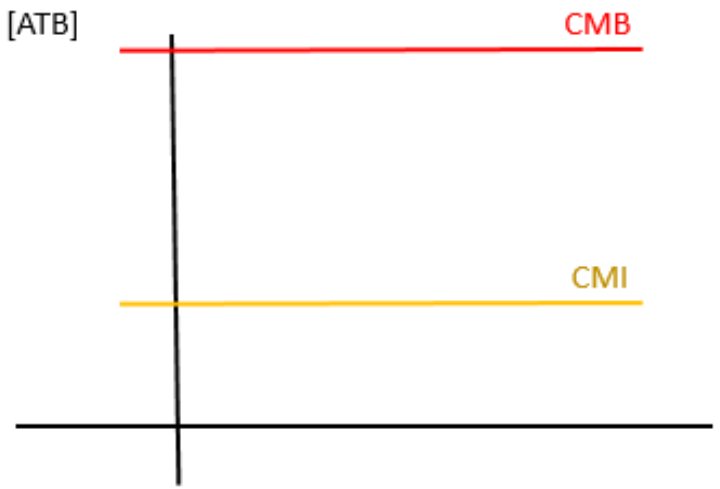


Meléndez-Carmona et al. JAC 2022
Lora-Tamayo & Meléndez-Carmona. EIMC 2022

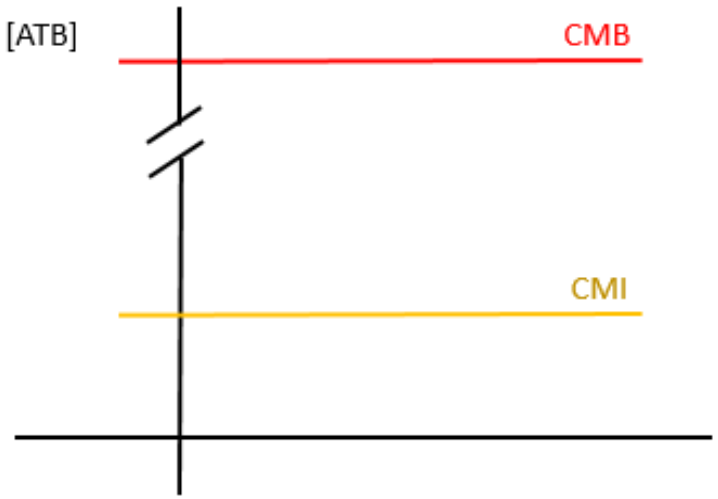
CMB/CMI ≤4 → bactericida

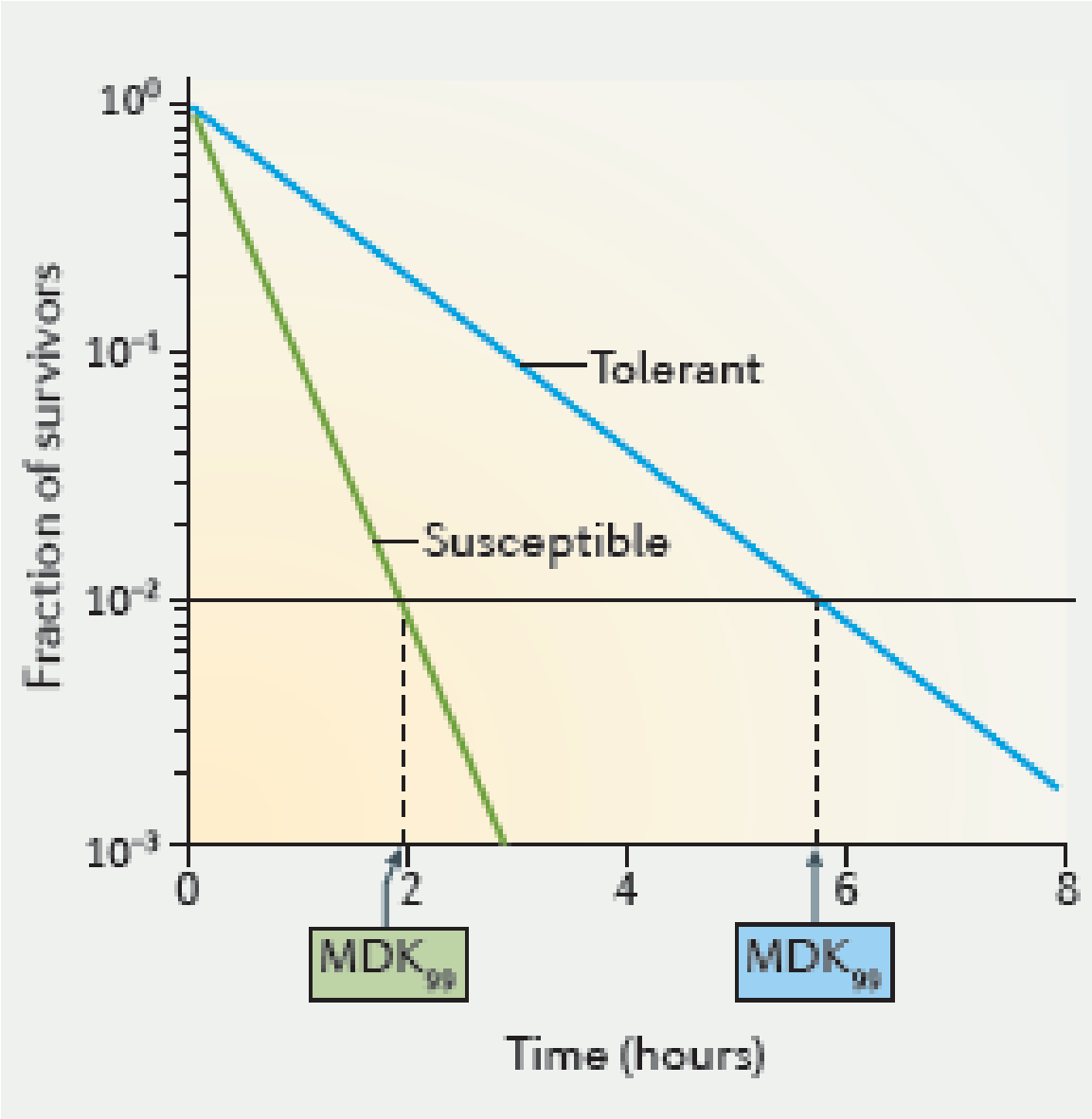


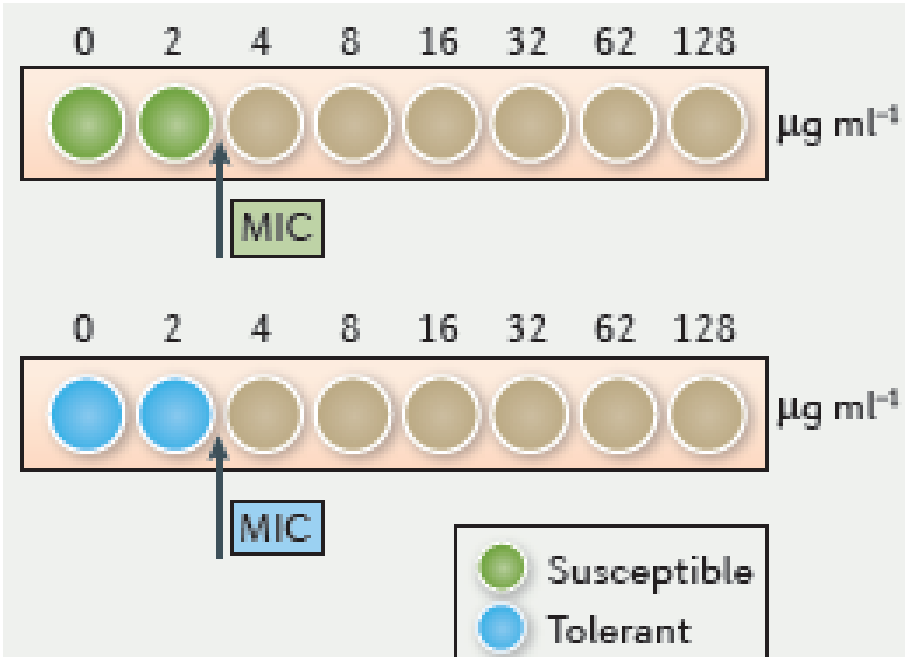
CMB/CMI > 4 → bacteriostático



CMB/CMI > 32 → tolerancia







MIC vs MDK (minimal duration killing)

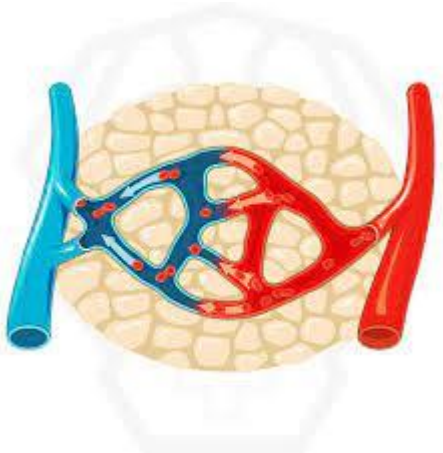
Biofilm → Tolerancia → Necesidad de **más tiempo**

Brauner et al. Nat Rev Microbiol 2016

Importancia de la exposición real al antibiótico – Importancia del PK

- Concentración sérica libre (fracción no unida a proteínas)

- Superficie capilar
  - Elevada en tejidos irrigados (pulmón, riñón…)
  - Baja en un absceso



- Permeabilidad vascular (barrera hemato-encefálica – SNC/ojo)

- Permeabilidad tisular – permeabilidad de la membrana y carriers

- Acumulación intracelular

- Condiciones físico-químicas del tejido (índices pKa)

- Hidrosolubilidad / liposolubilidad de la molécula

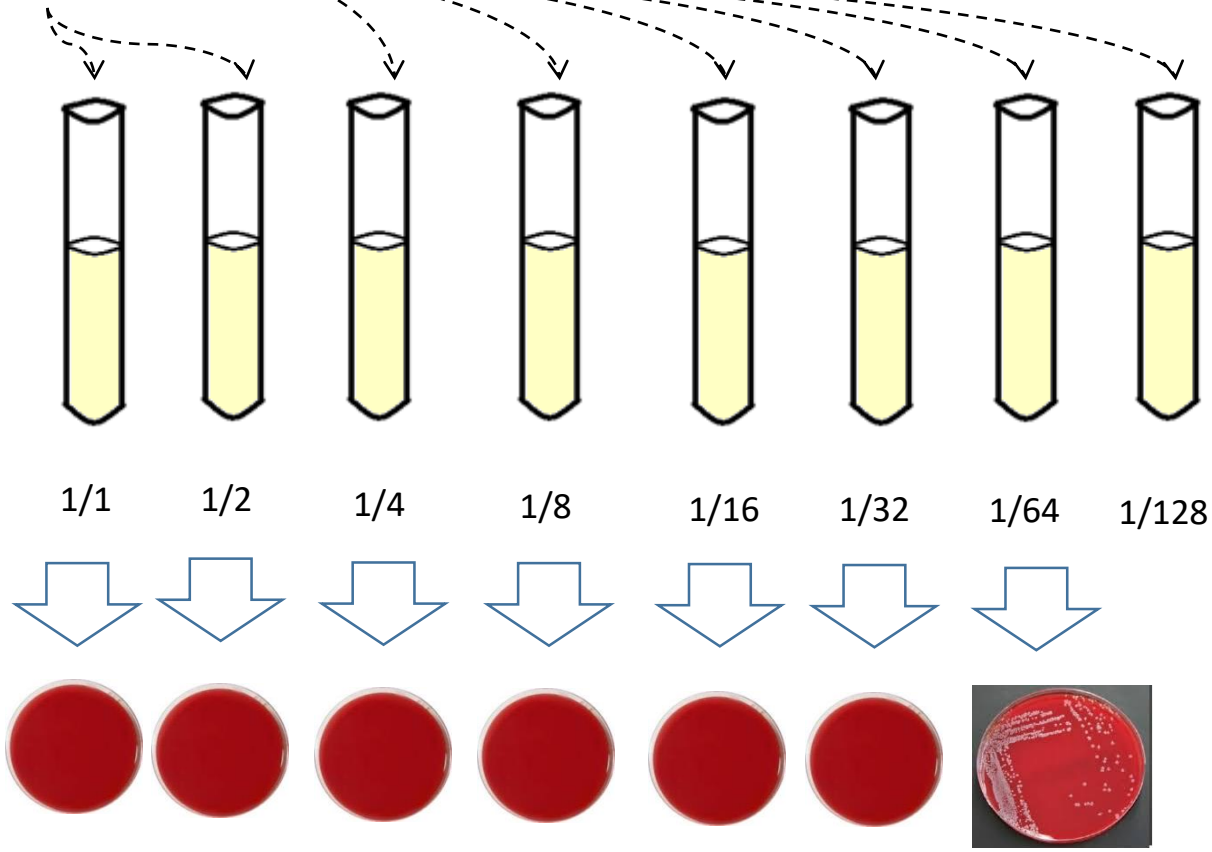
Levinson. Inf Dis North Am 1995

- Aprox. 30-60 min tras infusión de ATB (≈C_{max})
- Antes de la infusión de la sig. dosis (≈C_{min})

Serum Bactericidal Activity

Inóculo estándar

Suero del paciente



Poder bactericida = última dilución capaz de eliminar el 99.9% del inóculo administrado

Sculier & Klastersky. Am J Med 1984

Significance of Serum Bactericidal Activity in Gram-Negative Bacillary Bacteremia in Patients with and without Granulocytopenia

TABLE II **Relation between Granulocytosis, Peak Serum Bactericidal Activity, and Clinical Outcome**

Serum Bactericidal Titer	Granulocyte Count <100/mm³		Granulocyte Count >1,000/mm³	
	Success	Failure	Success	Failure
<1:2	1	2	—	1
1:2	—	1	—	—
1:4	—	2	—	3
1:8	—	1	5	—
1:16	5	1	5	—
1:32	2	1	7	—
1:64	1	1	2	—
≥1:128	12	—	25	1
Total	21	9	44	5

Sculier & Klastersky. Am J Med 1984

Management of Ventriculoperitoneal Shunt Infections in Adults: Analysis of Risk Factors Associated With Treatment Failure

Iván Pelegrín,[1] Jaime Lora-Tamayo,[1,2] Joan Gómez-Junyent,[1] Nuria Sabé,[1] Dolors García-Somoza,[3] Andreu Gabarrós,[4] Javier Ariza,[1] Pedro Fernández Viladrich,[1] and Carmen Cabellos[1]

108 episodios de inf. Shunt en pacientes adultos entre 1980 y 2014

¿Necesitamos ATB bactericidas en SNC?

- Mala experiencia en la asociación de tetraciclinas o cloranfenicol a los beta-lactámicos en meningitis
- Ampicilina es bacteriostático frente a *Listeria monocytogenes,* pero demuestra aclarar LCR en modelos animales
  - ¿asociación con gentamicina?
  - ¿uso de cotrimoxazol?

Finberg et al. CID 2004
Pelegrín et al. CID 2017

¿Necesitamos antibióticos bactericidas en endocarditis infecciosa?

Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence

Matthew E. Falagas[1–3]*, Katerina G. Manta[1], Fotinie Ntziora[1] and Konstantinos Z. Vardakas[1]

- Análisis de reports de uso de LNZ en endocarditis
- N =56, evaluable = 33 (MRSA, MRSE, otros GP, valv. nativas y protésicas)
- Tasa global de curación 64%...

Linezolid for endocarditis: a case series of 14 patients

Carlo Tascini[1]*, Maria Grazia Bongiorni[2], Roberta Doria[1], Marina Polidori[1], Riccardo Iapoce[1], Serena Fondelli[1], Enrico Tagliaferri[1], Ezio Soldati[2], Antonello Di Paolo[3], Alessandro Leonildi[1] and Francesco Menichetti[1]

- N=14 casos, serie heterogénea, uso mayoritario como rescate
- Tasa global de curación 88%
  - MRSA, válvulas protésicas…
  - Pacientes no operables…

Falagas et al. JAC 2006
Tascini et al. JAC 2011

¿Necesitamos antibióticos bactericidas en pacientes neutropénicos?

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

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

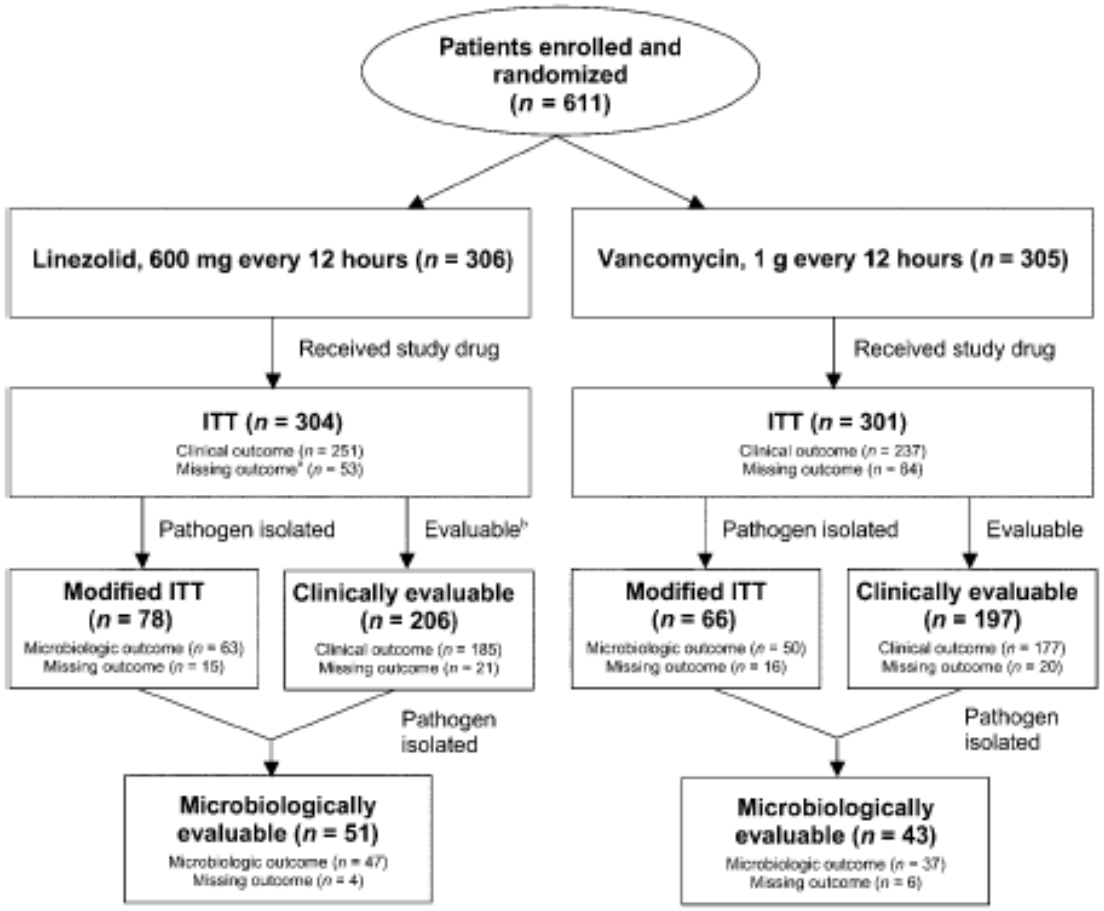


Table 3. Clinical outcome at 7 days after the completion of therapy (i.e., at the test of cure assessment).

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

Jaksic et al. CID 2006

REFLEXIONES FINALES

- La definición de antibiótico bactericida o bacteriostático tiene limitaciones significativas
  - Las condiciones de realización de CMI y CMB pueden ser muy distintas a la realidad clínica
  - Los antibióticos bacteriostáticos sí eliminan bacterias – cuestión de dosis y concentración

- Con frecuencia, esta distinción no tiene una traducción clínica significativa

- Es probable que la eficacia de los antibióticos (PD) tenga más que ver con aspectos farmacocinéticos (PK)
  - Concentraciones reales y activas de los antibióticos en tejidos
  - Concentraciones intracelulares
  - Actividad intrínseca del antimicrobiano
  - ¿Papel del poder bactericida del suero / LCR / otros?

muchas gracias

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