II Jornada del Comité Español del Antibiograma (CoEsAnt)

Madrid, 12 de febrero de 2026

Papel del PK/PD en la lectura del antibiograma. ¿Cuándo es indispensable su aplicación?

Dr. Andrés Canut Blasco
Servicio de Microbiología
Hospital Universitario Araba. Vitoria-Gasteiz.

Conflicto de Intereses

El ponente ha participado en foros científicos patrocinados por :

MSD, Pfizer, Shionogi, Menarini, Meiji, ERN, bioMérieux, Thermo Fisher,

Becton Dickinson, Werfen, Beckman, etc.

Guion

1. Criterios PK/PD: indispensables para establecer y revisar los puntos de corte de sensibilidad

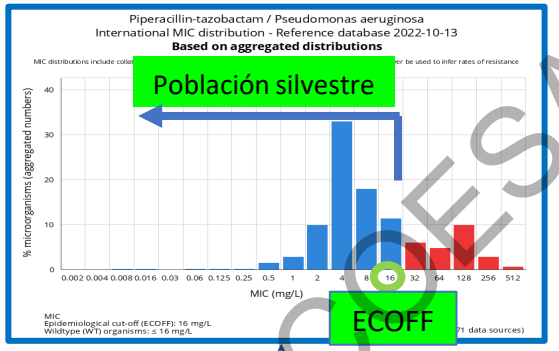
2. Discrepancias puntos de corte *vs* exposición a los antimicrobianos

3. Utilidad del análisis PK/PD en infecciones de difícil tratamiento: algunos ejemplos

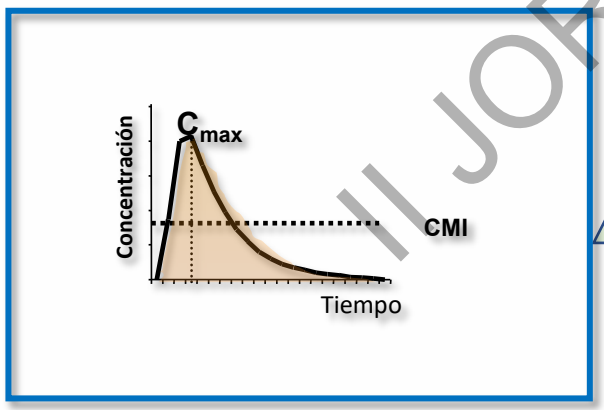
Establecimiento de los puntos de corte:

Criterios microbiológicos + Criterios farmacocinéticos/farmacodinámicos (PK/PD) + Criterios de evolución clínica

Criterios microbiológicos

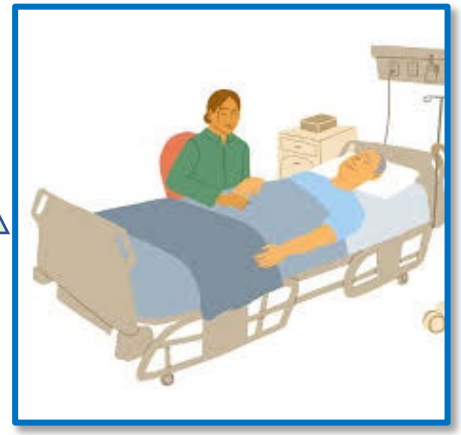


Criterios PK/PD



Puntos de corte de sensibilidad actualizados y **en revisión periódica**

Resultados clínicos



Establecimiento de los puntos de corte:
Criterios microbiológicos + Criterios farmacocinéticos/farmacodinámicos (PK/PD) + Criterios de evolución clínica

Criterios microbiológicos

1. Distribuciones de CMI (≥ 500 cepas clínicas de una especie frente a un antibiótico)
2. Aislados de la población silvestre y aislados con diferentes niveles de resistencia adquirida
3. EUCAST define el concepto de ECOFF (población silvestre o wild type). Semejante al ECV (epidemiological cutoff value) de CLSI
4. EUCAST remarca que los puntos de corte clínicos no deben dividir las distribuciones de CMI de la población silvestre (“wild type”)

Comité Español del Antibiograma

- *Morosini MI. Mesa 3. XIX Congreso SEIMC Sevilla 2015*
- *Turnidge J. et al. Clin Microbiol Infect. 2006; 12: 418-25*
- *www.eucast.org*
- *https://coesant-seimc.org/*
- CLSI M100 35th. 2025

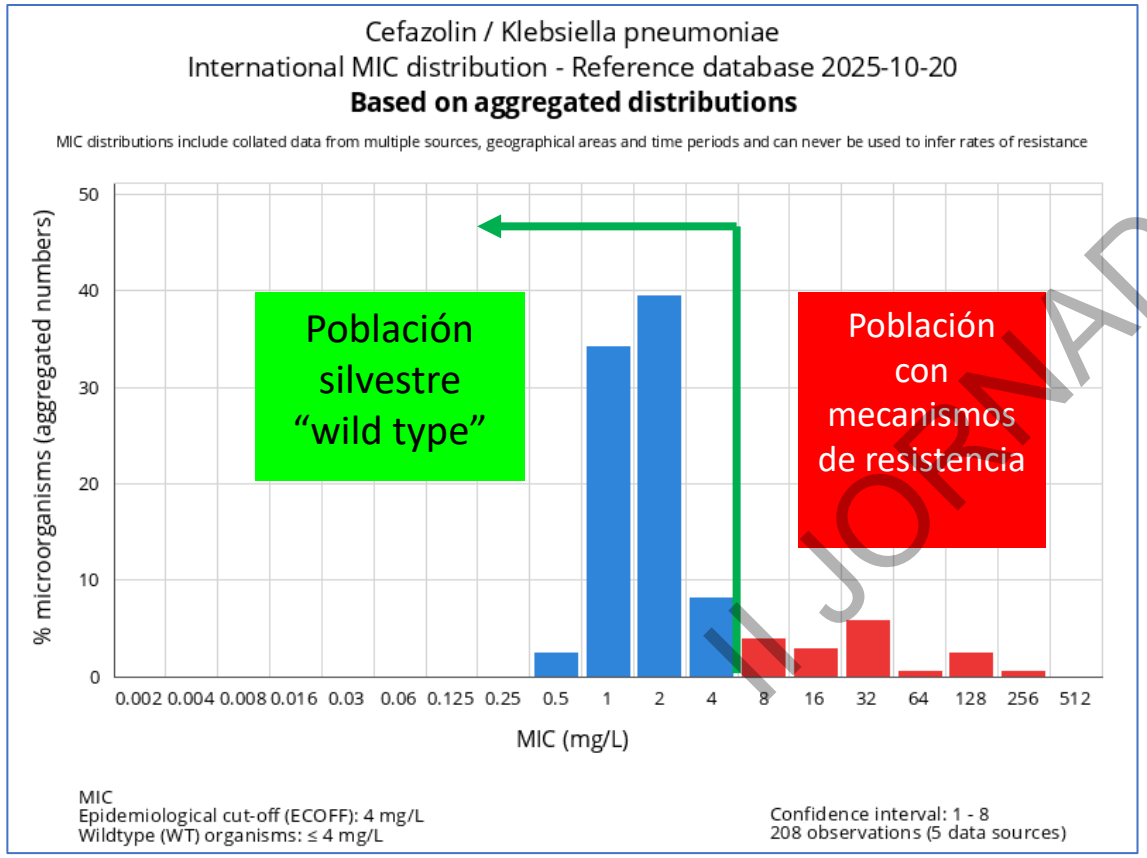
Criterios microbiológicos

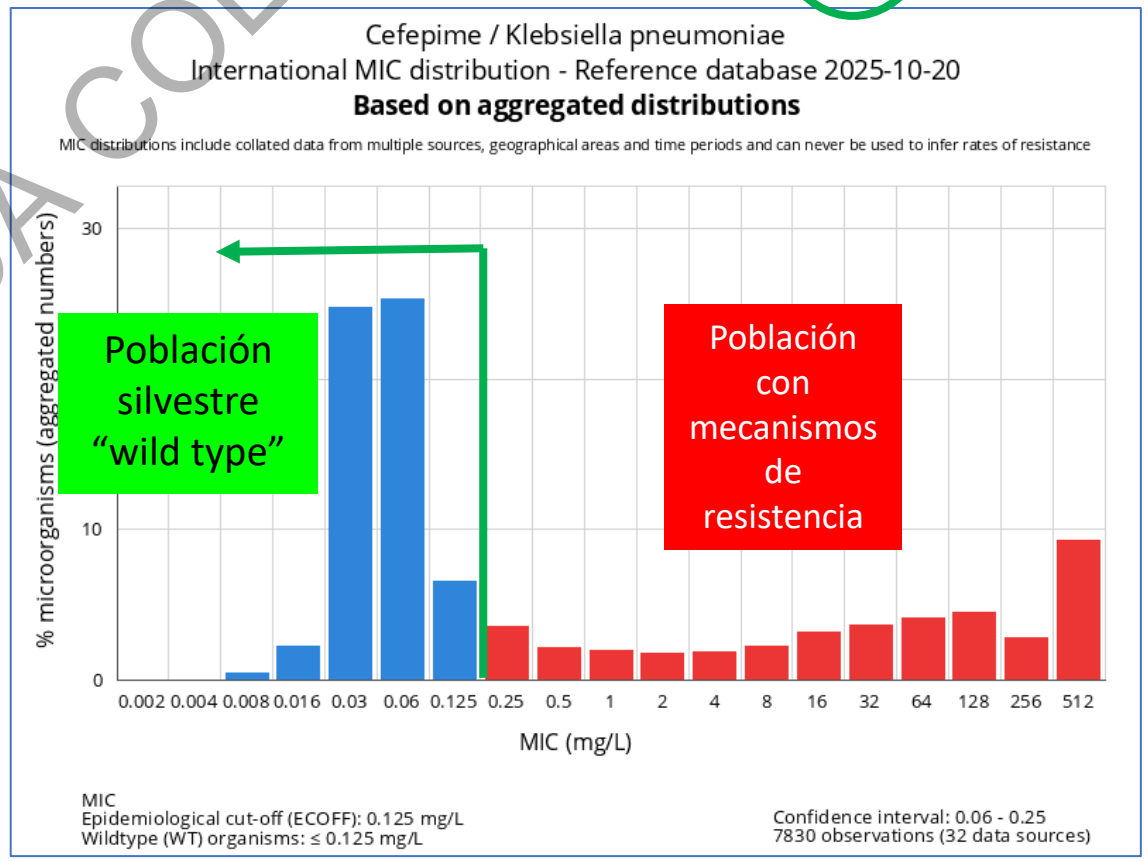
www.eucast.org

MIC distributions for Klebsiella pneumoniae, 2025-10-20

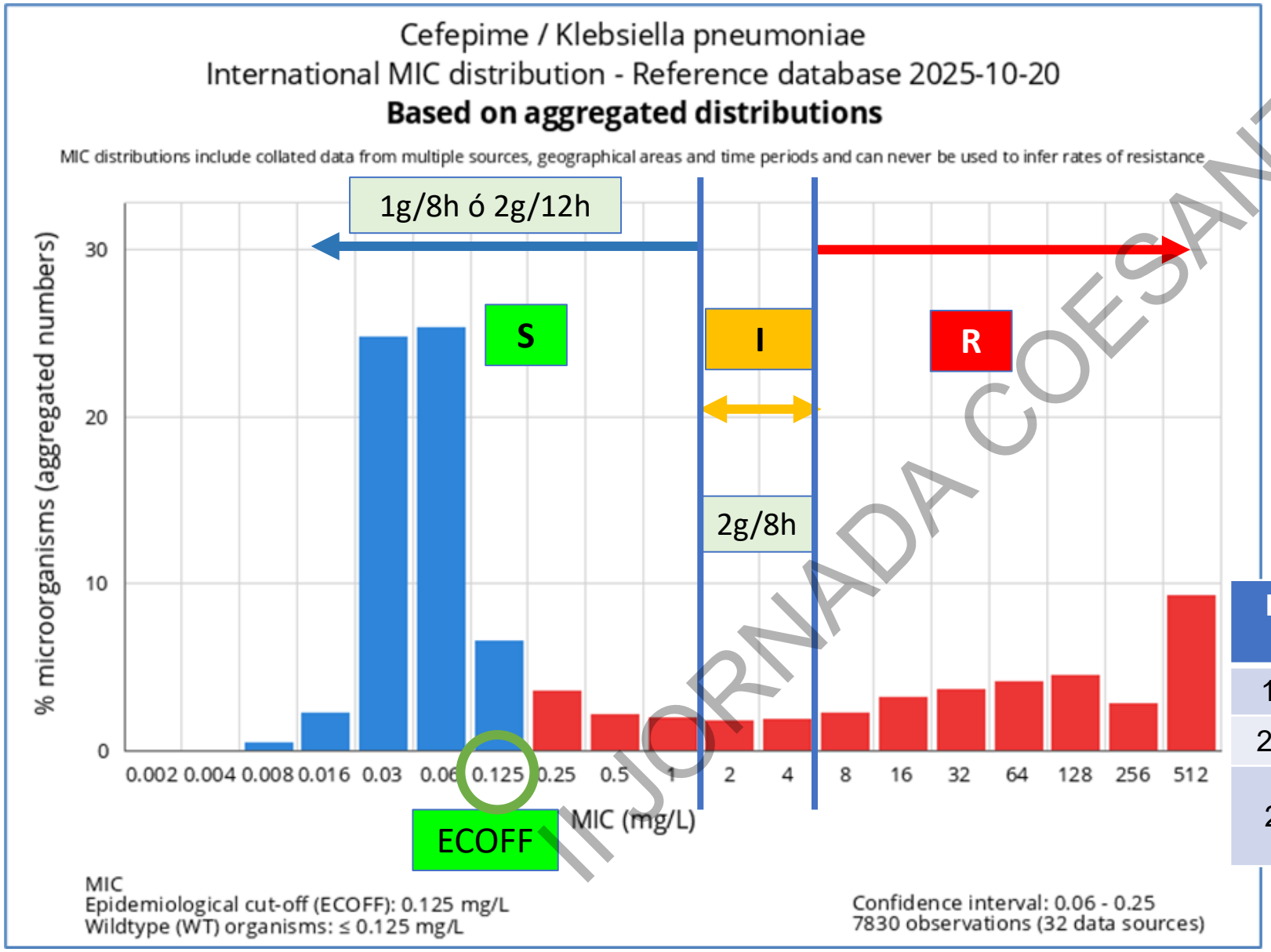
Species: Klebsiella pneumoniae (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF
Cefazolin	0	0	0	0	0	0	0	0	5	71	82	17	8	6	12	1	5	1	0	5	208	4
Cefepime	0	0	35	170	1940	1980	513	278	168	150	138	143	176	243	283	323	352	215	723	32	7830	0.125





Criterios microbiológicos [Exposición/CMI]



www.eucast.org

Cociente inhibitorio = C_{min}/CMI

C_{min} 6,2 ± 3,8 mg/L con 1g/12h

en 12 pacientes adultos con neumonía (Aitken SL et al. Int J Antimicrob Agents 2015; 45:541-544)

Dosis	C_{min} mg/L	CMI mg/L	% tiempo > CMI
1 g/ 8h	3,5 mg/L	1	100
2 g/12h	1,7 mg/L		100
2 g/8h	7 mg/L	2	100
		4	100

Guía Mensa. Utilidades. Betalactámicos IV.

Cefepima y *Enterobacterales*
Tres categorías sensibilidad (S, I, R)
Dos dosificaciones (estándar e incrementada)

Criterios PK/PD

Cefepima y *P. aeruginosa*
Dos categorías sensibilidad (I, R)
Siempre dosis incrementada (2g/8h)

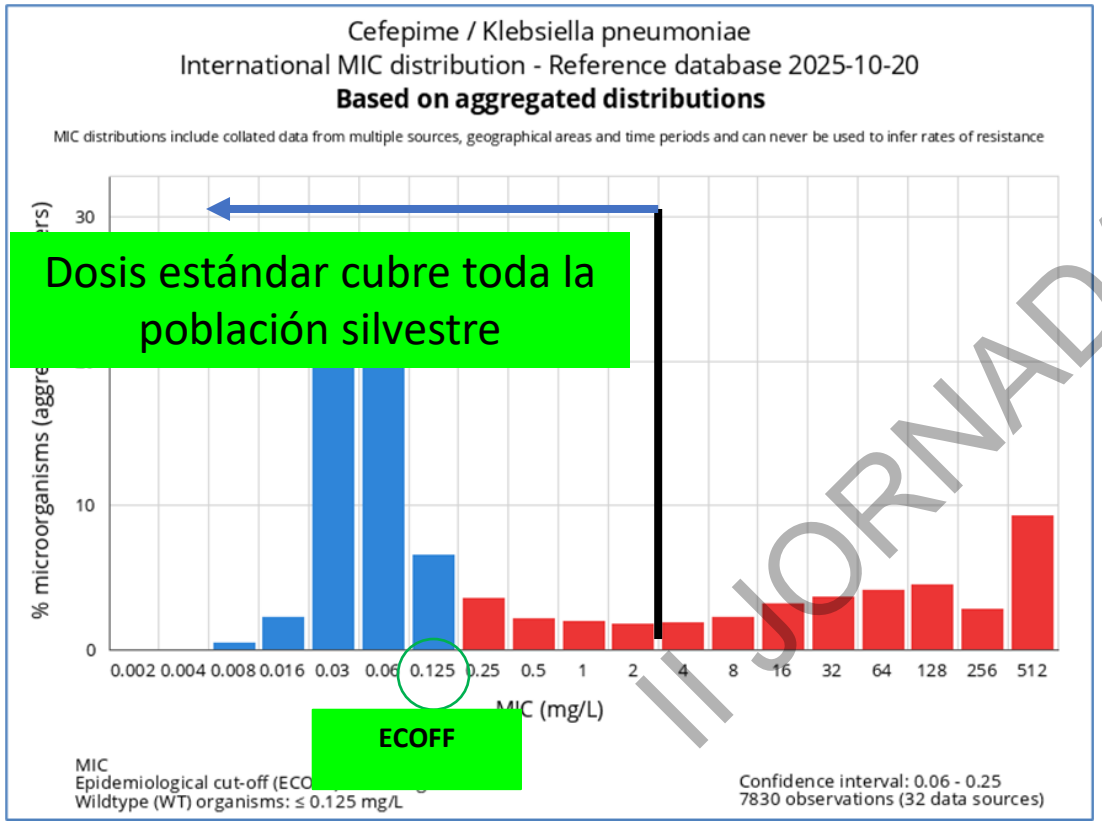
1g/8h (Dosis estándar)
∫ T>CMI ≥ 60%

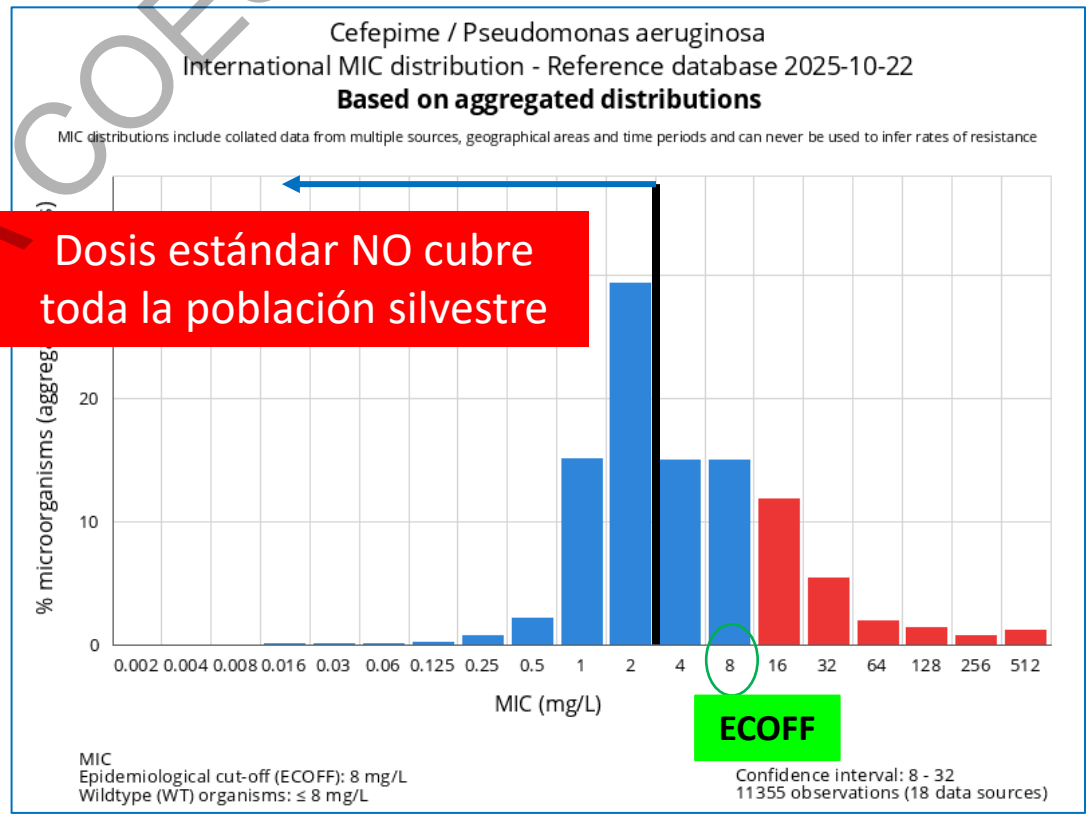
1 mg/L PTA 100%
2 mg/L PTA 99%
4 mg/L PTA 84%
8 mg/L PTA 20%

2g/8h IE 4h (Dosis elevada)
∫ T>CMI ≥ 60%

4 mg/L PTA 100%
8 mg/L PTA 100%

C_{min} 16 mg/L

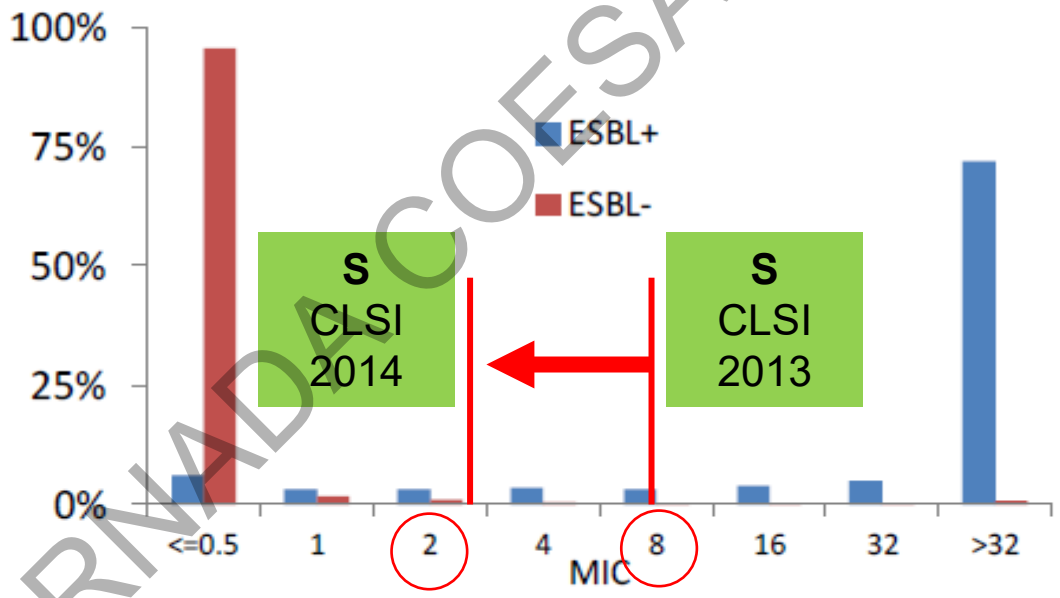




- Frei CR et al.. J Antimicrob Chemother. 2008 Mar;61(3):621-8. doi:10.1093/jac/dkm536.
- www.eucast.org

Criterios de evolución clínica

Cefepima			CMI ≥ 8 mg/L	CMI < 8 mg/L	p
Bhat SV et al 2007	BGN 1-2 g/12h	Mortalidad a 28 días	54,8%	24,1%	<0,01



Asociadas a exposiciones bajas < 3 g/día

Cefepima Puntos de corte		BGN Enterobacterias Según dosis	BGN *Pseudomonas* 1g/8h ó 2g/12h
CLSI 2014-2024	BGN	≤ 2 S (1g/12h) 4-8 SDD ≥ 16 R	≤ 8 S 16 I ≥ 32 R

- CLSI M100 35th. 2025
- Bhat SV et al. Antimicrob Agents Chemother 2007

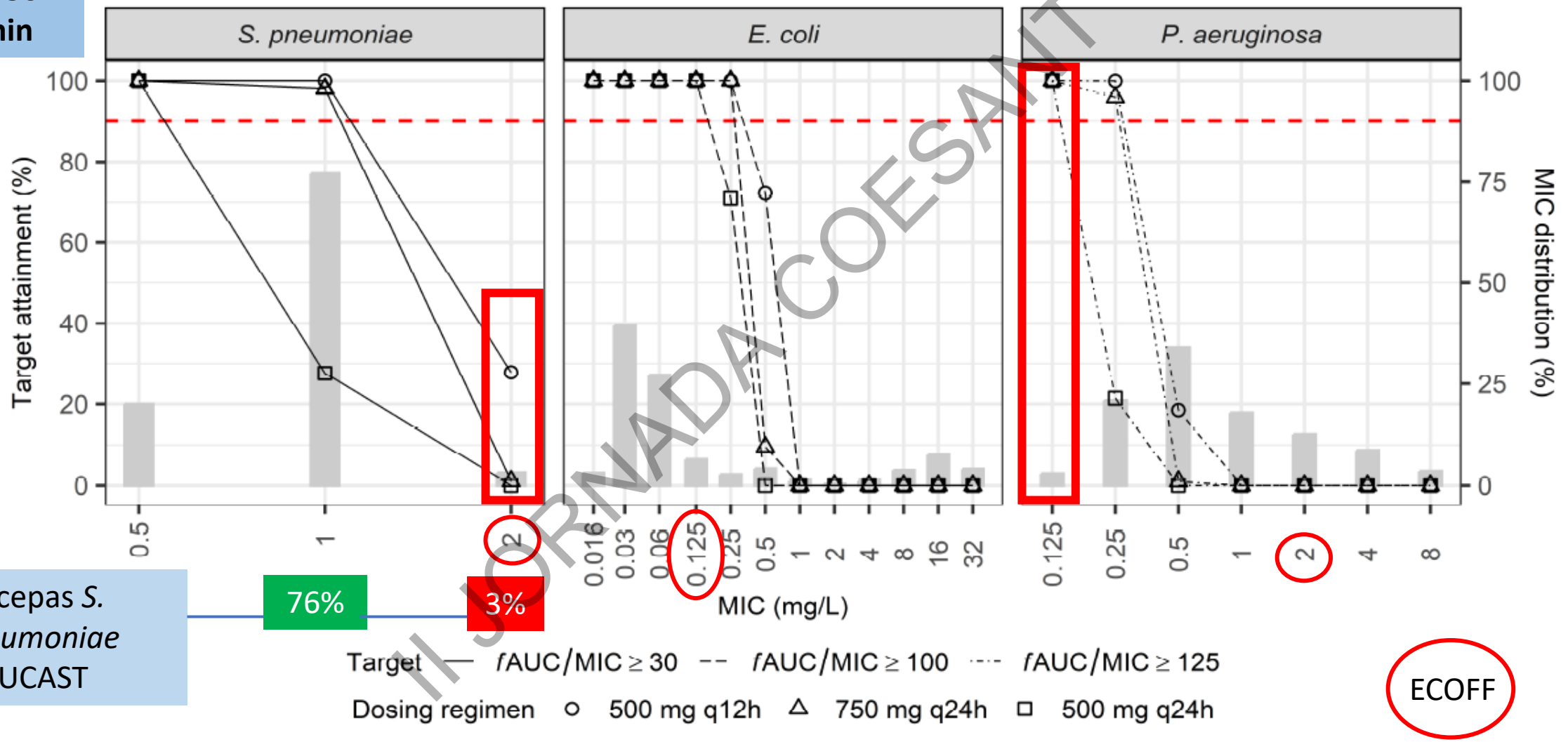
Puntos de corte sensibilidad *vs* exposición por PK/PD (levofloxacino)

Pacientes CrCl ≥ 50 mL/min

Levofloxacino I ≤ 2 mg/L

Levofloxacino S ≤ 0,5 mg/L

Levofloxacino I ≤ 2 mg/L



% cepas *S. pneumoniae* EUCAST

76%

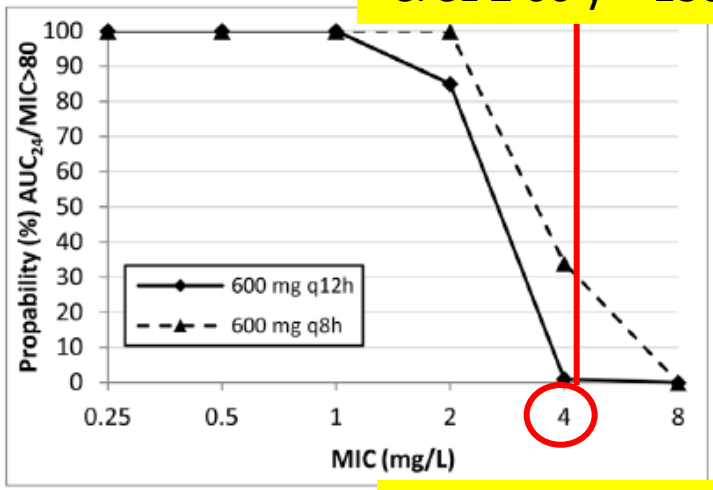
3%

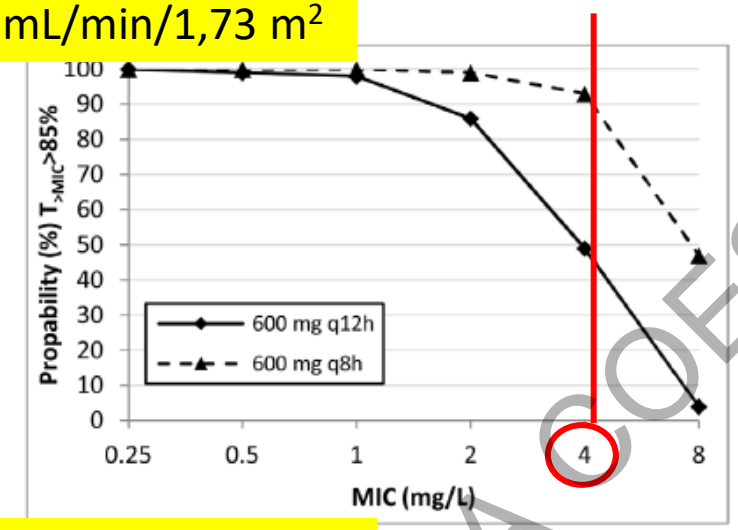
ECOFF

Lee YJ, Kang G, Zang DY, Lee DH. Development of a Population Pharmacokinetic Model of Levofloxacin in Healthy Adults and Identification of Optimal Dosing Regimens. Pharmaceuticals (Basel). 2025 Apr 25;18(5):621. doi: 10.3390/ph18050621.

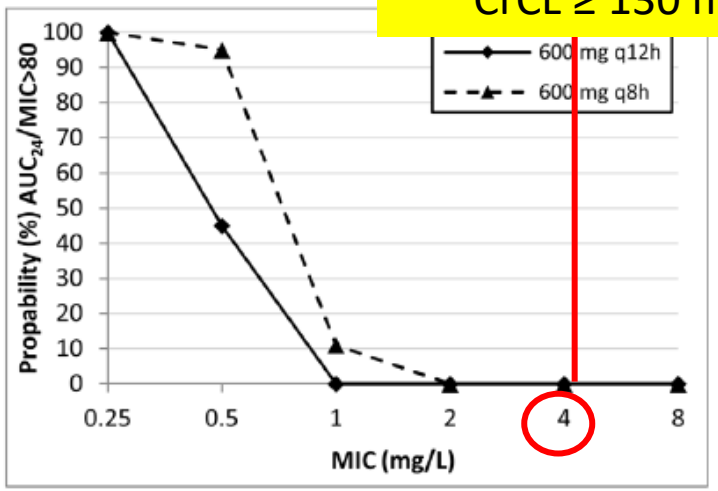
Puntos de corte sensibilidad *vs* exposición por PK/PD (linezolid)

CrCL ≥ 60 y < 130 mL/min/1,73 m^2





CrCL ≥ 130 mL/min/1,73 m^2



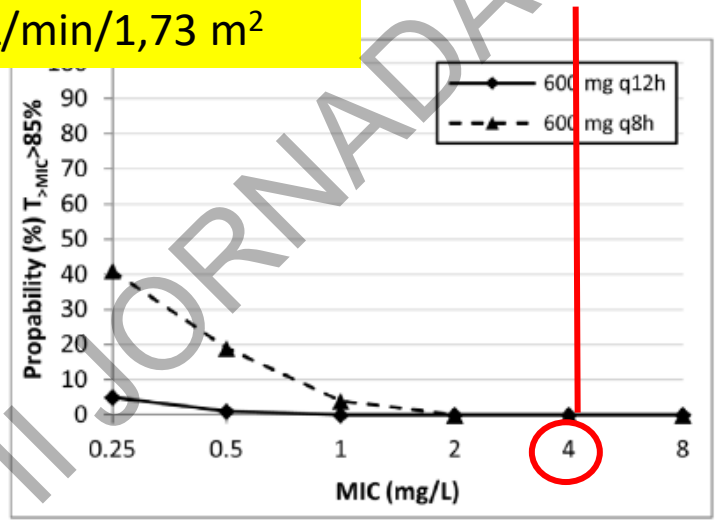


Figure 2. Estimated probability of target attainment (PTA) values with the four dose regimens in each group of simulated patients.

***Staphylococcus* S ≤ 4 mg/L**
Punto de corte = ECOFF

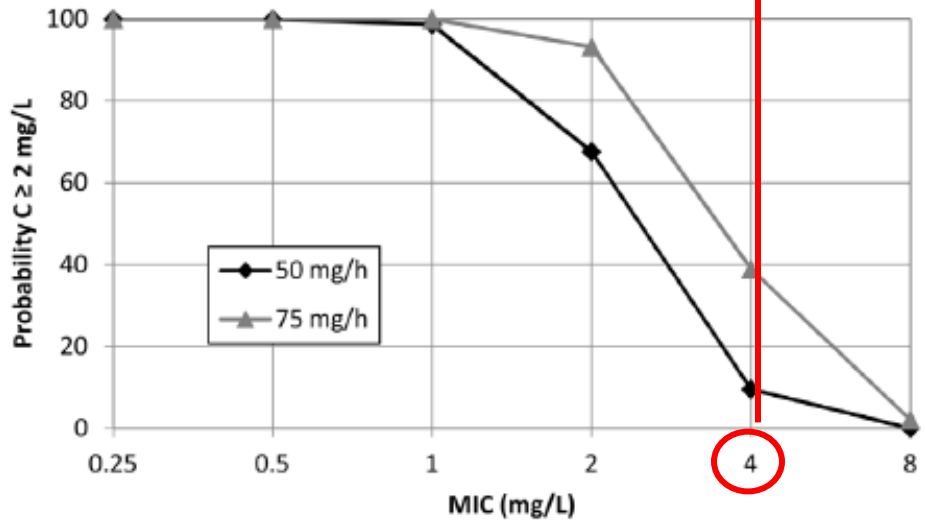


Figure 4. Estimated probability of target attainment (PTA) values with the continuous infusion of linezolid at rates of 50 mg/h and 75 mg/h.

***S. aureus* con CMI 2 mg/L (58%) y 4 mg/L (8%)**
EUCAST

Barrasa H, Soraluce A, Usón E, Sainz J, Martín A, Sánchez-Izquierdo JÁ, Maynar J, Rodríguez-Gascón A, Isla A. Impact of augmented renal clearance on the pharmacokinetics of linezolid: Advantages of continuous infusion from a pharmacokinetic/pharmacodynamic perspective. Int J Infect Dis. 2020 Apr;93:329-338. doi: 10.1016/j.ijid.2020.02.044.

Linezolid

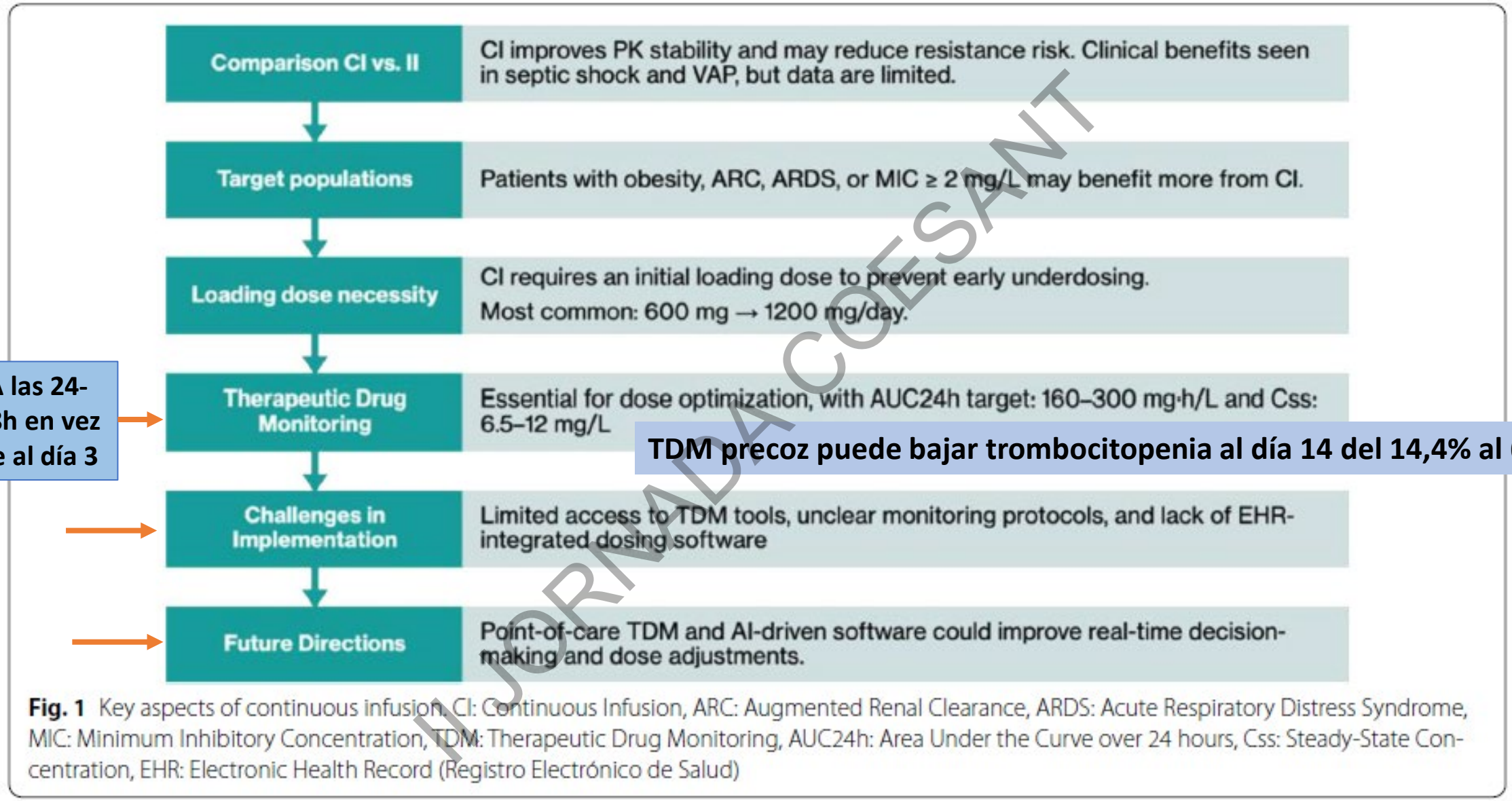


Fig. 1 Key aspects of continuous infusion. CI: Continuous Infusion, ARC: Augmented Renal Clearance, ARDS: Acute Respiratory Distress Syndrome, MIC: Minimum Inhibitory Concentration, TDM: Therapeutic Drug Monitoring, AUC24h: Area Under the Curve over 24 hours, Css: Steady-State Concentration, EHR: Electronic Health Record (Registro Electrónico de Salud)

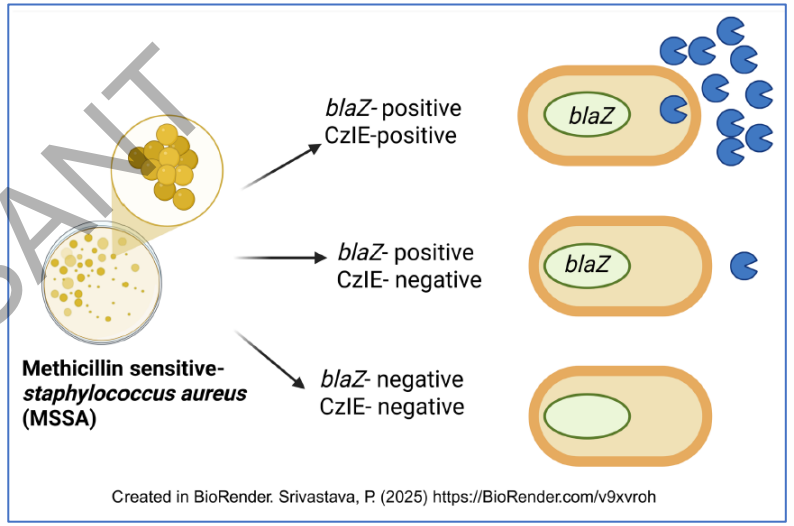
A las 24-48h en vez de al día 3

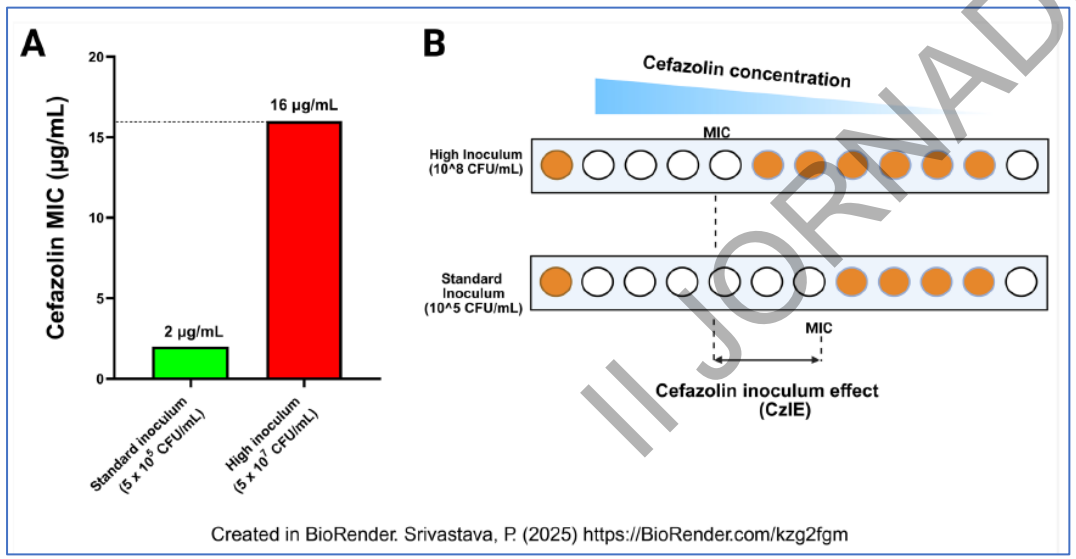
TDM precoz puede bajar trombocitopenia al día 14 del 14,4% al 6,3%

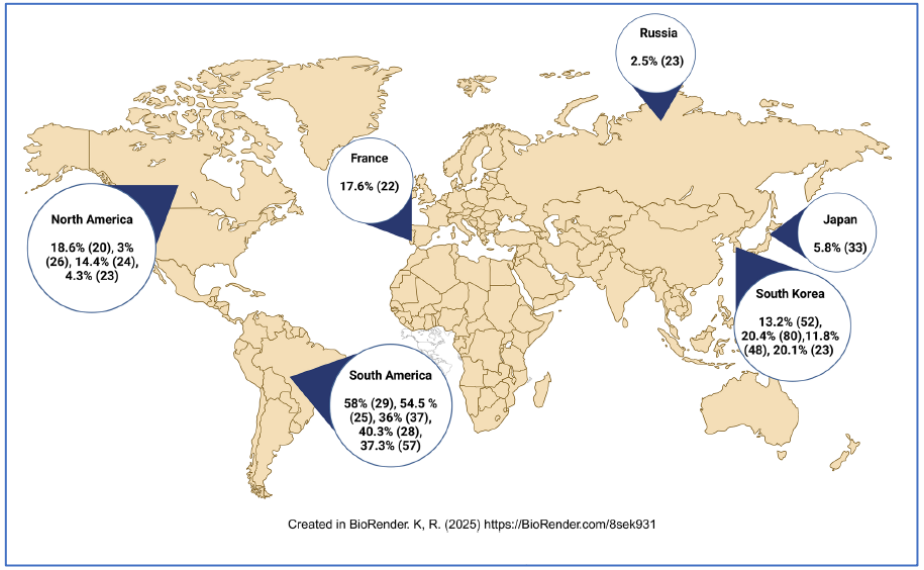
1. Barrasa H, Valdazo C, Martín A. Continuous infusion of linezolid for critically ill patients: toward a new standard of care. Intensive Care Med. 2025 Jun;51(6):1157-1160. doi: 10.1007/s00134-025-07889-y. Epub 2025 Apr 12. Erratum in: Intensive Care Med. 2025 Sep;51(9):1747. doi: 10.1007/s00134-025-08004-x. 2. Wicha SG, et al. Population pharmacokinetics and toxicodynamics of continuously infused linezolid in critically ill patients. Int J Antimicrob Agents. 2022 May;59(5):106572. doi: 10.1016/j.ijantimicag.2022.106572.

Efecto inóculo en betalactámicos: el caso de cefazolina en *S. aureus* sensible a meticilina (SASM)

1. Infecciones por SASM nosocomiales aumentan 3,9% anual *vs* SARM disminuyen un 6,9% anual (EEUU)
2. Bacteriemia por cualquier foco y EI comparada con cloxacilina
   a. Comparable en duración y tasas de curación clínica
   b. Mejor tolerabilidad
   c. Menor incidencia de IR
3. Las cepas portadoras de *blaZ* presentan efecto inóculo frente a cloxacilina y cefazolina
4. Betalactamasa variante A se asocia a mayor riesgo de fracaso terapéutico



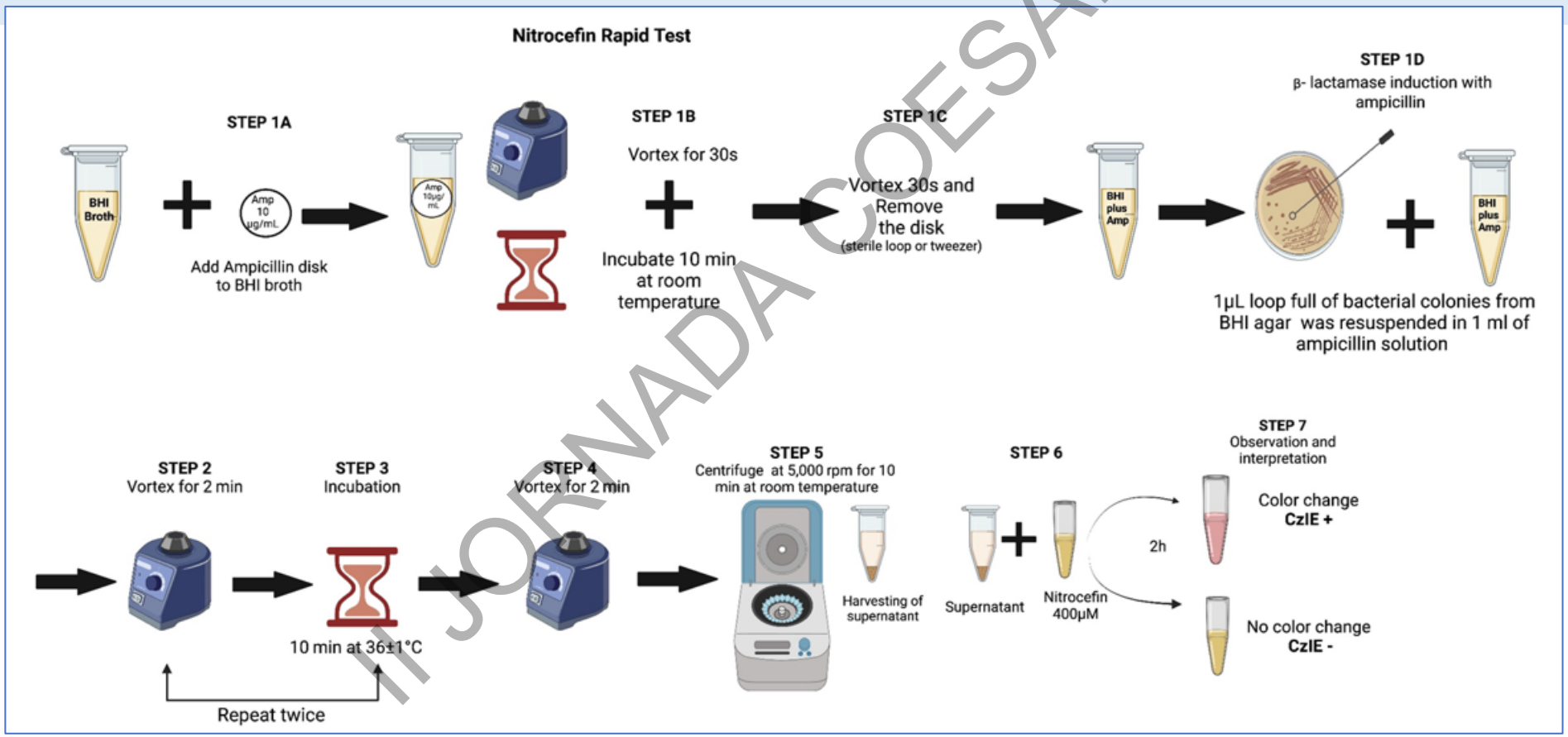




1. Srivastava P et al. The Cefazolin Inoculum Effect: An Underappreciated Factor in MSSA Treatment Strategies. Infect Dis Ther. 2025 Dec 20. doi: 10.1007/s40121-025-01283-3. 2. Jean B et al. β-Lactam Inoculum Effect in Methicillin-Susceptible *Staphylococcus aureus* Infective Endocarditis. JAMA Netw Open. 2024 Dec 2;7(12):e2451353. doi: 10.1001/jamanetworkopen.2024.51353.

Efecto inóculo en betalactámicos: el caso de cefazolina en *S. aureus* sensible a meticilina (SASM)

1. No se suele estudiar el efecto inóculo en la rutina del laboratorio.
2. Se han descrito métodos rápidos para detectar en SASM (Gómez-Villegas SI et al, 2025)
3. Marcadores subrogados con especificidad elevada: clindamicina R (92,9%) y eritromicina R (90,9%). VPN > 82% (Song KH et al, 2017)



1. Gomez-Villegas SI et al. Validation of a modified rapid test to detect the cefazolin inoculum effect in methicillin-susceptible *Staphylococcus aureus* from bloodstream infections in hospitals from North and Latin America. J Antimicrob Chemother. 2025 May 2;80(5):1437-1444. doi: 10.1093/jac/dkaf093.2. Song KH, et al; Korea INfectious Diseases (KIND) study group. Characteristics of cefazolin inoculum effect-positive methicillin-susceptible *Staphylococcus aureus* infection in a multicentre bacteraemia cohort. Eur J Clin Microbiol Infect Dis. 2017 Feb;36(2):285-294. doi: 10.1007/s10096-016-2799-1.

Efecto inóculo en betalactámicos: el caso de cefazolina en *S. aureus* sensible a meticilina (SASM)

1. La sensibilidad de *Staphylococcus* a cefazolina se infiere de la sensibilidad a cefoxitina.
2. Si se reporta para SASM se debe informar como **I "Sensible, con incremento de exposición". 2 g/8 h**

MIC distributions for *Staphylococcus aureus*

AGENT	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	(T)ECOFF
Cefazolin	0	0	0	0	0	18	359	3277	7870	4718	878	250	181	157	1343	0	0	0	201	5	2

Cefazolin **[ECOFF = 2]**

Patients. PB(%): 91.6 ± 6.7; Vd (L): 13.01 ± 4.4; $t_{½\beta}$ (h): 1.8 ± 0.38

Conclusions

Available clinical data and PK/PD analyses support the use of cefazolin and cefepime with the currently listed dosage regimens. PK/PD analysis support the use of cefuroxime iv, but published experience with its use is limited and high dosages are required. PK/PD analyses suggest that cefotaxime may not be a reliable agent, especially in serious infections. This is also the case for ceftriaxone, although there is ongoing controversy in the literature about is role and efficacy [Appendix-32].

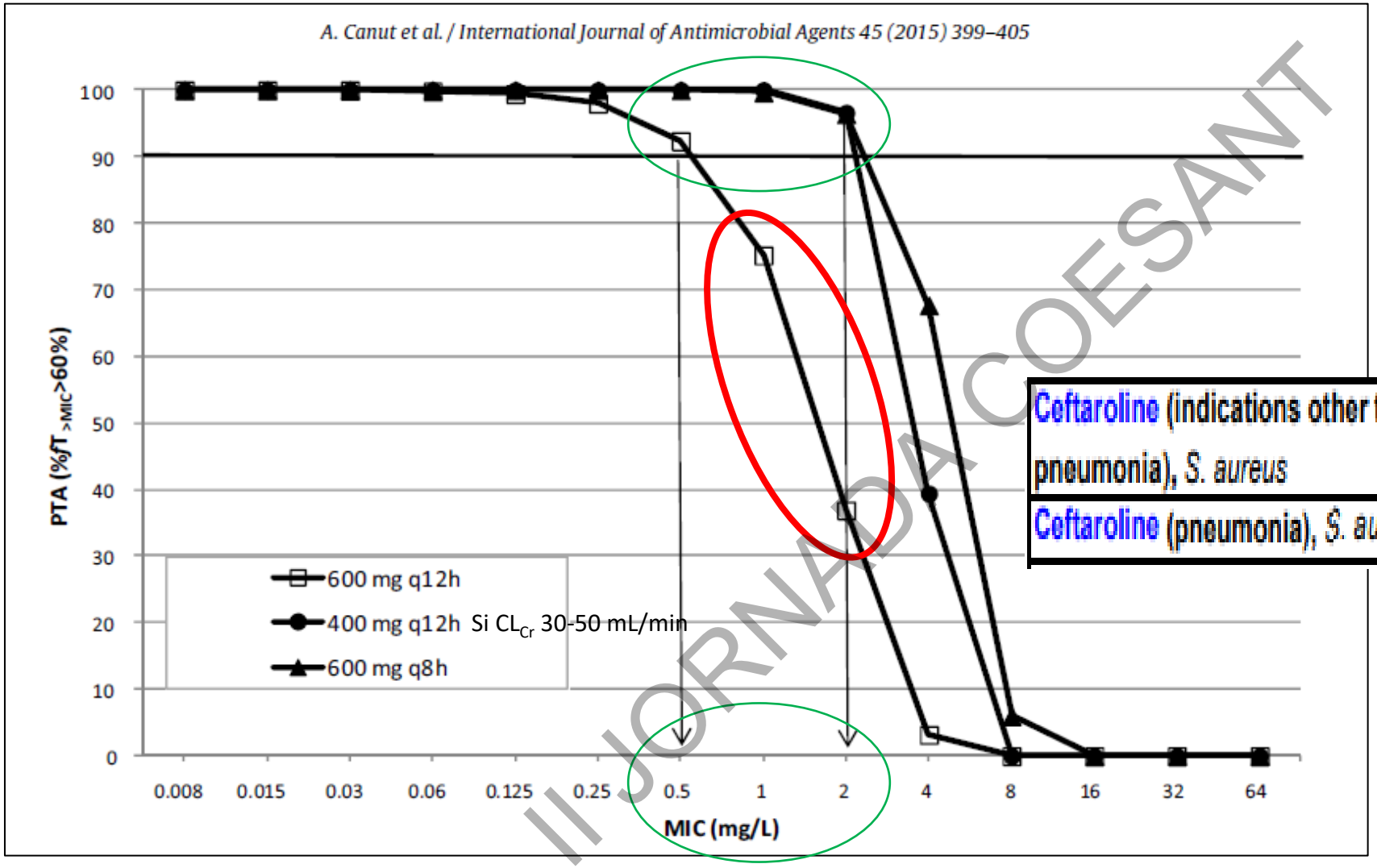
PTAs **f%T>MIC 35%**

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	98	99	99	99
2	89	95	97	99
4	61	77	90	95
8	17	31	60	77

1. https://www.eucast.org/fileadmin/eucast/pdf/guidance_documents/Cephalosporins_for_Staphylococcus_aureus_Infections_20250224.pdf

Ceftarolina

***S. aureus* in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.



	S ≤ ECOFF	R >	ATU
Ceftaroline (indications other than pneumonia), *S. aureus*	1[7]	2[7,8]	1
Ceftaroline (pneumonia), *S. aureus*	1[7]	1[7]	1

13% CMI 1 mg/L
4% CMI 2 mg/L
EUCAST

1. Canut A, Isla A, Rodríguez-Gascón A. Pharmacokinetic/pharmacodynamic analysis to evaluate ceftaroline fosamil dosing regimens for the treatment of community-acquired bacterial pneumonia and complicated skin and skin-structure infections in patients with normal and impaired renal function. Int J Antimicrob Agents. 2015 Apr;45(4):399-405. doi: 10.1016/j.ijantimicag.2014.12.023.
2. Sunzel, M., Kujacic, M., Broadhurst, H., Li, J., & Edeki, T. (2014). Phase I, randomised single-and multiple-dose study of ceftaroline fosamil 600 mg every 12 h (60-min infusion) and every 8 h (120-min infusion). In *24th European Congress of Microbiology and Infectious Diseases* (pp. 10-13).

Cefazolina en profilaxis quirúrgica

CFR %

2 g antes de la incisión y redosificación intermitente vs infusión continua

3 g si > 120 kg
C_{min} 9,5 mg/L

Body weight (kg)	Dose	Creatinine clearance (ml min^{-1})	Pathogen		
			Staphylococcus aureus (%)	*Staphylococcus epidermidis* (%)	Escherichia coli (%)
60	2000 mg intermittent 4-hourly	50	91	81	96
		80	90	74	92
		120	86	59	77
80		50	91	81	96
		80	91	76	93
		120	89	64	84
100		50	91	81	96
		80	91	81	96
		120	89	67	87
60	2000 mg intermittent 3-hourly	50	92	84	97
		80	91	80	95
		120	92	84	97
80		50	92	83	97
		80	91	80	95
		120	90	75	92
100		50	92	83	97
		80	91	80	95
		120	90	75	92
60	1000 mg continuous dose after 2 g loading dose	50	92	87	98
		80	92	83	97
		120	91	79	95
80		50	92	86	98
		80	91	83	97
		120	91	80	95
100		50	98	98	99
		80	91	83	97
		120	91	80	96

C_{min} 10 mg/L
CMI_{90} CoNS MS 1-4 mg/L

C sérica 2 mg/L

Naik BI, Roger C, Ikeda K, Todorovic MS, Wallis SC, Lipman J, Roberts JA. Comparative total and unbound pharmacokinetics of cefazolin administered by bolus versus continuous infusion in patients undergoing major surgery: a randomized controlled trial. Br J Anaesth. 2017 Jun 1;118(6):876-882. doi: 10.1093/bja/aex026.

El VALOR DE LA CMI Y EL ANÁLISIS PK/PD COMO SOPORTE DEL REGIMEN DE DOSIFICACIÓN

Table 1. Pneumonia

Pathogens	ESCMID recommendations	Comments and practical approach
Ventilator-associated pneumonia caused by AmpC-producing Enterobacterales	No specific recommendations for AmpC-producing Enterobacterales pneumonia For 3GCephRE infections: piperacillin-tazobactam or quinolones for non-severe infections; carbapenems for severe infections	**Cefepime as first-line treatment** Cefepime as monotherapy when MIC ≤2 mg/L Higher mortality was only found in ESBL-producing Enterobacterales infections with high cefepime MIC For AmpC-producing Enterobacterales infections, cefepime performed at least as well as comparators in observational studies, including in ICUs

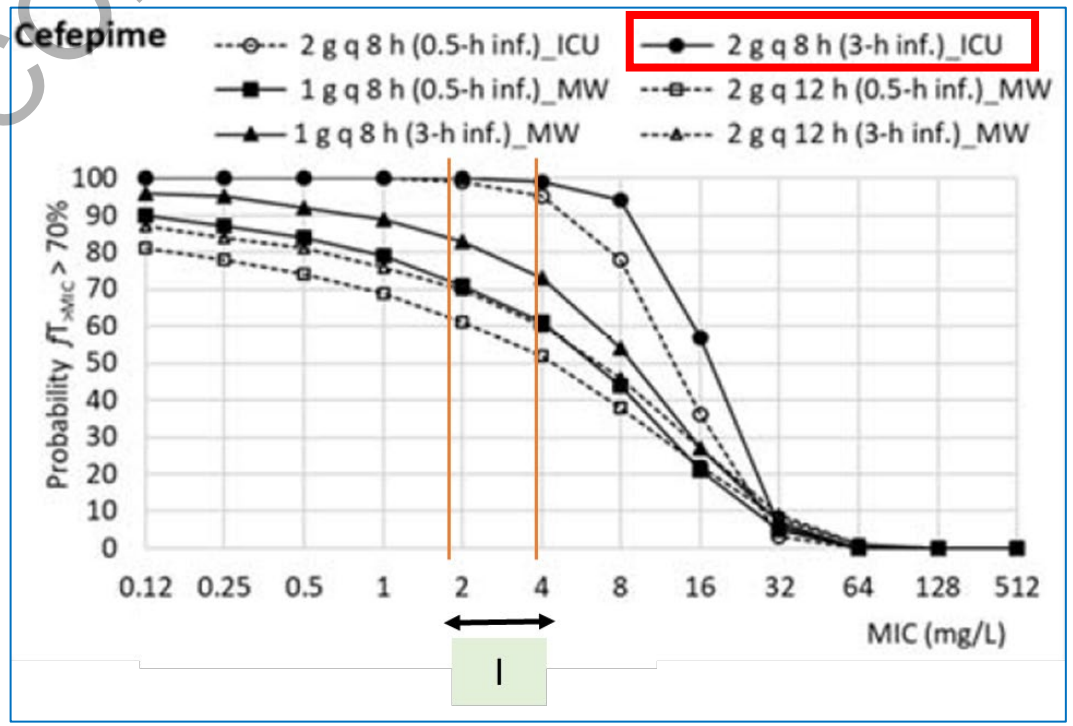
Table 2
Severe complicated urinary tract infections.

AmpC-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) No recommendations for organisms with moderate to high likelihood of AmpC production due to inducible AmpC gene (e.g. *Enterobacter cloacae, Citrobacter freundii*) Conditional recommendation against the use of cefepime for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to AmpC-producing Enterobacterales with cefepime MIC ≤2 mg/L: high-dose cefepime (2 g t.i.d.) cUTIs due to AmpC-producing Enterobacterales with cefepime MIC >2 mg/L: new BLBLIs may be considered, instead of carbapenems, based on local resistance rates

Cefepima

I = Sensible, cuando se incrementa la exposición

CMI	Dosis	Cmin	% T > CMI
2 mg/L	2 g/12h	1,7 mg/L	96
2 mg/L	**2 g/8h**	**7,1 mg/L**	**100**
4 mg/L	2 g/12h	1,7 mg/L	79
4 mg/L	**2 g/8h**	**7,1 mg/L**	**100**



1. Meschiari M, Asquier-Khati A, Tiseo G, Luque-Paz D, Murri R, Boutoille D, Falcone M, Mussini C, Tattevin P; Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF). Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases. Int J Antimicrob Agents. 2024 Jul;64(1):107186. doi: 10.1016/j.ijantimicag.2024.107186.
2. Mensa J et al.Guía de Terapéutica Antimicrobiana. Utilidades. Administración betalactámicos. Concentración sérica y T > CMI. Guía disponible en app para móviles.
3. Valero A, Rodríguez-Gascón A, Isla A, Barrasa H, Del Barrio-Tofiño E, Oliver A, Canut A, Solinís MÁ. *Pseudomonas aeruginosa* Susceptibility in Spain: Antimicrobial Activity and Resistance Suppression Evaluation by PK/PD Analysis. Pharmaceutics. 2021 Nov 8;13(11):1899. doi: 10.3390/pharmaceutics13111899.

El VALOR DE LA CMI Y EL ANÁLISIS PK/PD COMO SOPORTE DEL REGIMEN DE DOSIFICACIÓN

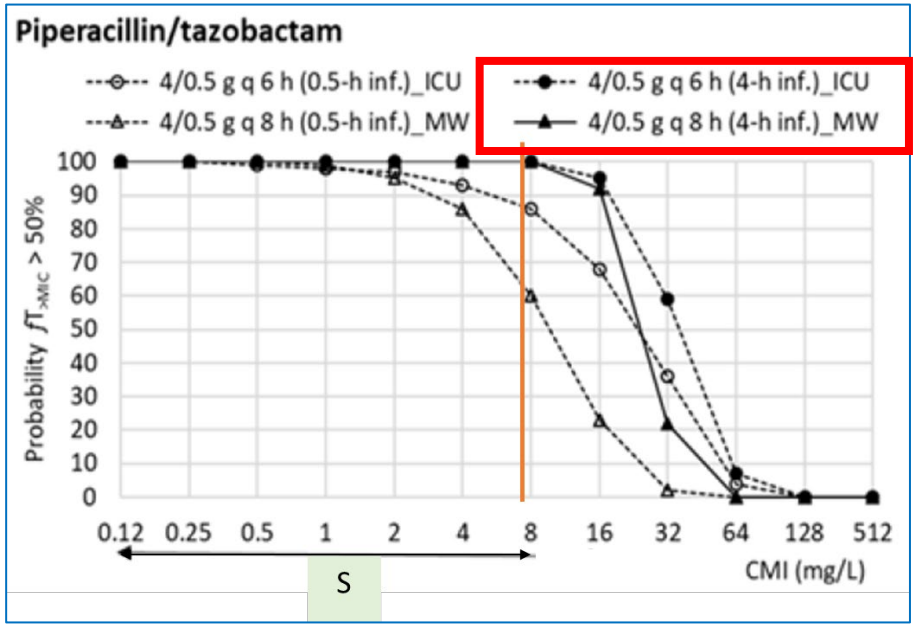
Table 2
Severe complicated urinary tract infections.

Pathogens	ESCMID recommendations	Comments and practical approach
ESBL-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) Under AMS consideration, piperacillin-tazobactam can be used as the first-line therapy in low-inoculum, non-severe 3GCephRE infections, and as a step-down therapy for severe infections Conditional recommendation/ good practice statement against the use of new BLBLIs for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to ESBL-producing Enterobacterales with piperacillin-tazobactam MIC ≤8 mg/L: high-dose piperacillin-tazobactam, with loading dose and continuous infusion cUTIs due to ESBL-Enterobacterales with piperacillin-tazobactam MIC >8 mg/L, aminoglycosides or intravenous fosfomycin are alternatives alone or in combination strategies due to high urinary concentrations and low prevalence of resistance Cefoxitin may be an option for ESBL-producing *Escherichia coli*, as well as temocillin, based on drug-susceptibility testing studies New BLBLIs should be reserved for settings with concomitant high rates of resistance to piperacillin-tazobactam and carbapenems

Piperacilina-tazobactam

S

CMI	Dosis	Cmin	% T > CMI
8 mg/L	**4,5 g/6h inf 4 h**	**12 mg/L**	**100**
	4,5 g/6h inf 30 min	2,7 mg/L	74



1. Meschiari M, Asquier-Khati A, Tiseo G, Luque-Paz D, Murri R, Boutoille D, Falcone M, Mussini C, Tattevin P; Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF). Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases. Int J Antimicrob Agents. 2024 Jul;64(1):107186. doi: 10.1016/j.ijantimicag.2024.107186.
2. Mensa J et al.Guía de Terapéutica Antimicrobiana. Utilidades. Administración betalactámicos. Concentración sérica y T > CMI. Guía disponible en app para móviles.
3. Valero A, Rodríguez-Gascón A, Isla A, Barrasa H, Del Barrio-Tofiño E, Oliver A, Canut A, Solinís MÁ. *Pseudomonas aeruginosa* Susceptibility in Spain: Antimicrobial Activity and Resistance Suppression Evaluation by PK/PD Analysis. Pharmaceutics. 2021 Nov 8;13(11):1899. doi: 10.3390/pharmaceutics13111899.

Piperacilina-tazobactam en hematológicos con neutropenia febril

PTA 100% *f* T>CMI durante las 48 horas iniciales de tratamiento

CrCL	0.5	1	2	4	8	16	32	64
4 g q6h 3 h infusion								
60 mL/min	99.4	99.1	97.7	95.8	79.9	23.9	0.6	0
90 mL/min	98.7	97.5	95.8	90.5	66.5	14.8	0.2	0
120 mL/min	96.7	93.1	88.5	77.8	52.8	6.3	0	0
150 mL/min	93.4	89.7	84.2	74.6	44.5	4	0	0
2 g LD + 4 g q6h 3 h infusion								
60 mL/min	99.4	99.1	97.7	96.2	91.1	74.5	27.4	0.5
90 mL/min	98.7	97.5	95.8	91.3	78.8	55.1	12.7	0.3
120 mL/min	96.7	93.1	88.5	78.9	64	37.7	6.1	0.1
150 mL/min	93.4	89.7	84.2	75.6	57.9	30.4	4.3	0
2 g LD + 12 g 24 h continuous infusion								
60 mL/min	100	100	100	100	100	97.1	51.6	2.4
90 mL/min	100	100	100	100	100	93.2	33.3	0.8
120 mL/min	100	100	100	100	99.9	85.5	18.5	0.2
150 mL/min	100	100	100	100	99.7	80.5	13.9	0
2 g LD + 16 g 24 h continuous infusion								
60 mL/min	100	100	100	100	100	97.8	65.5	6.5
90 mL/min	100	100	100	100	100	97.1	55.5	2.9
120 mL/min	100	100	100	100	100	95.7	37.2	1.2
150 mL/min	100	100	100	100	99.9	93.1	29.6	0.6

Sólo infusión continua 12-16 g/día obtiene exposición adecuada en:

- ✓ Pacientes con CrCL > 90 mL
- ✓ Microorganismos con CMI 8-16 mg/L

1. Laporte-Amargos J, Ulldemolins M, Hernández-Mitre MP, Roberts JA, Rigo-Bonnin R, Carmona-Torre F, Huguet M, Puerta-Alcalde P, Arnan M, Del Pozo JL, Torrent A, García-Vidal C, Sureda A, Bergas A, Sastre-Escolà E, Carratalà J, Gudiol C. Population pharmacokinetics and optimized dosing of piperacillin-tazobactam in hematological patients with febrile neutropenia. Antimicrob Agents Chemother. 2026 Jan 7;70(1):e0125325. doi: 10.1128/aac.01253-25.

Análisis PK/PD

Table 1
PK/PD index and target magnitude for each antimicrobial agent.

Antibiotic	PK/PD index	Magnitude
β-lactams		
Penicillins	f % $T_{>MIC}$	50–60
Cephalosporins	f % $T_{>MIC}$	60–70
Carbapenems	f % $T_{>MIC}$	40–50
Amynoglicosides	C_{max}/MIC	10
Quinolones	AUC/MIC	125
Tetracyclines		
Tetracycline	AUC/MIC	25
Glucopeptides		
Vancomycin	AUC/MIC	400
Teicoplanin	C_{min}/MIC	≥10 for serious Gram-positive infections ≥20 for deep-seated infections
Macrolides		
Clarithromycin	f AUC/MIC	25
Azithromycin	f AUC/MIC	25
Daptomycin	AUC/MIC	666
Tigecycline	AUC/MIC	17.9
Linezolid	AUC/MIC	100
Colistin	f AUC/MIC	27.6–45.9

***f* % $T_{>MIC}$**: percentage of time that the antimicrobial free serum concentration remained above the MIC. **C_{max}/MIC**: Maximum concentration divided by the MIC. **C_{min}/MIC**: Minimum concentration divided by the MIC. **AUC/MIC**: The area under the concentration-time curve over 24 h in steady-state divided by the MIC. ***f* AUC/MIC**: The area under the free concentration-time curve over 24 h in steady-state divided by the MIC.

Índices en pacientes NO críticos

Índices en pacientes críticos

Índices conservadores

Índices exigentes

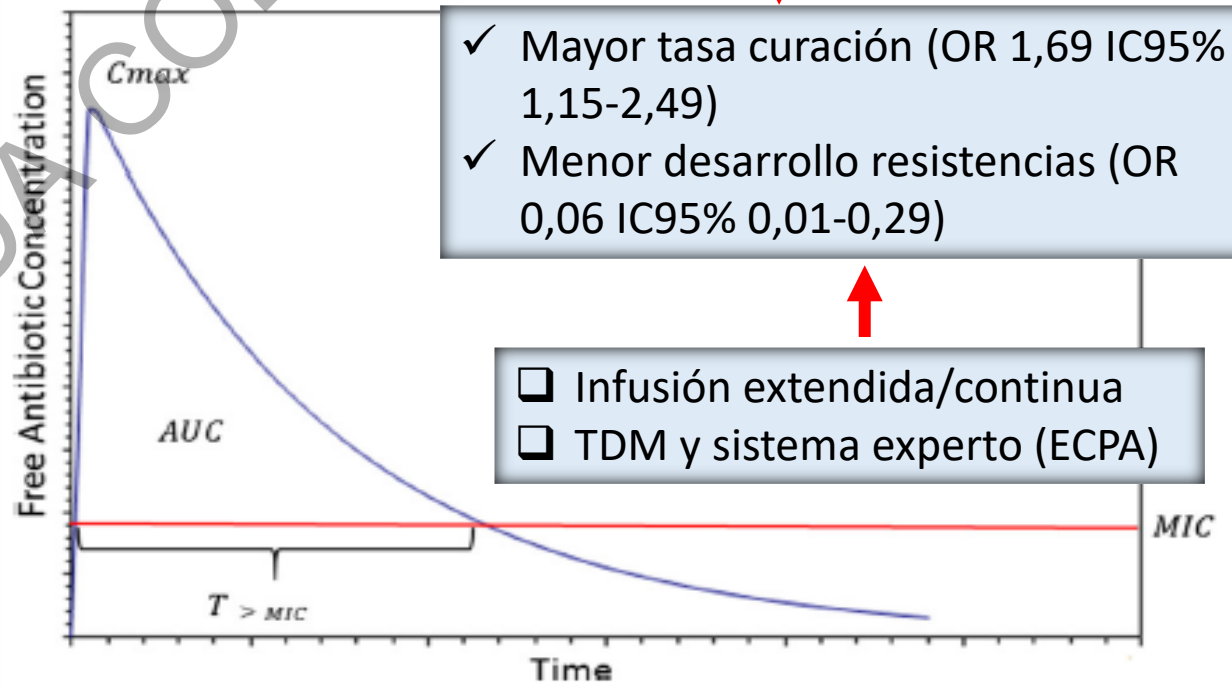
≥ 100% *f* $T_{>1\text{-}4 \times CMI}$

≥ 100% *f* $T_{>4 \times CMI}$ = *f* C_{min} /CMI> 4

RS y metaanálisis

- ✓ Mayor tasa curación (OR 1,69 IC95% 1,15-2,49)
- ✓ Menor desarrollo resistencias (OR 0,06 IC95% 0,01-0,29)

- ❑ Infusión extendida/continua
- ❑ TDM y sistema experto (ECPA)



1. Asín-Prieto E et al. / J Infect Chemother 21 (2015) 319e329; 2. Gatti M, Cojutti PG, Pea F. Crit Care. 2024 Apr 16;28(1):123. doi: 10.1186/s13054-024-04911-5; 3. Gatti M et al. Utility of a TDM-Guided Expert Clinical Pharmacological Advice Program for Optimizing the Use of Novel Beta-Lactam/Beta-Lactamase Inhibitor Combinations and Cefiderocol in a Tertiary University Hospital: An Interim Analysis. Ther Drug Monit. 2025 Dec 1;47(6):809-819. doi: 10.1097/FTD.0000000000001334.

OPTIMIZAR DOSIFICACIÓN MEROPENEM: COMBINACIÓN DE PK Y SENSIBILIDAD LOCAL CEPAS DE UCI

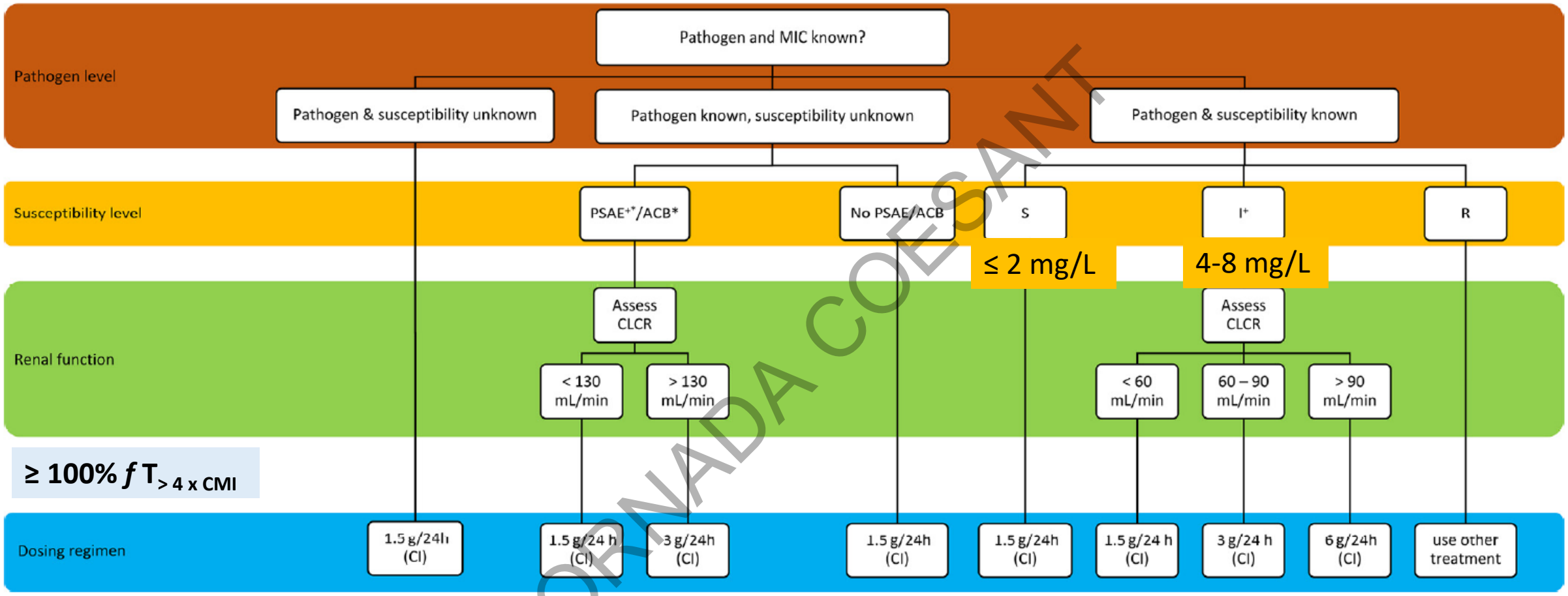


FIG 3 Dosing algorithm based on intensive care unit-specific pathogen information of a tertiary care hospital for meropenem in critically ill patients with Gram-negative infections. *, Resistance rate of ≥10%, consider combination therapy. +, Target of 100% time above 1× MIC. CI, continuous infusion; PSAE, *Pseudomonas aeruginosa*; ACB, *Acinetobacter baumannii*; S, susceptible; I, susceptible with increased exposure; R, resistant.

1,5g/día C_{min} 5 mg/L

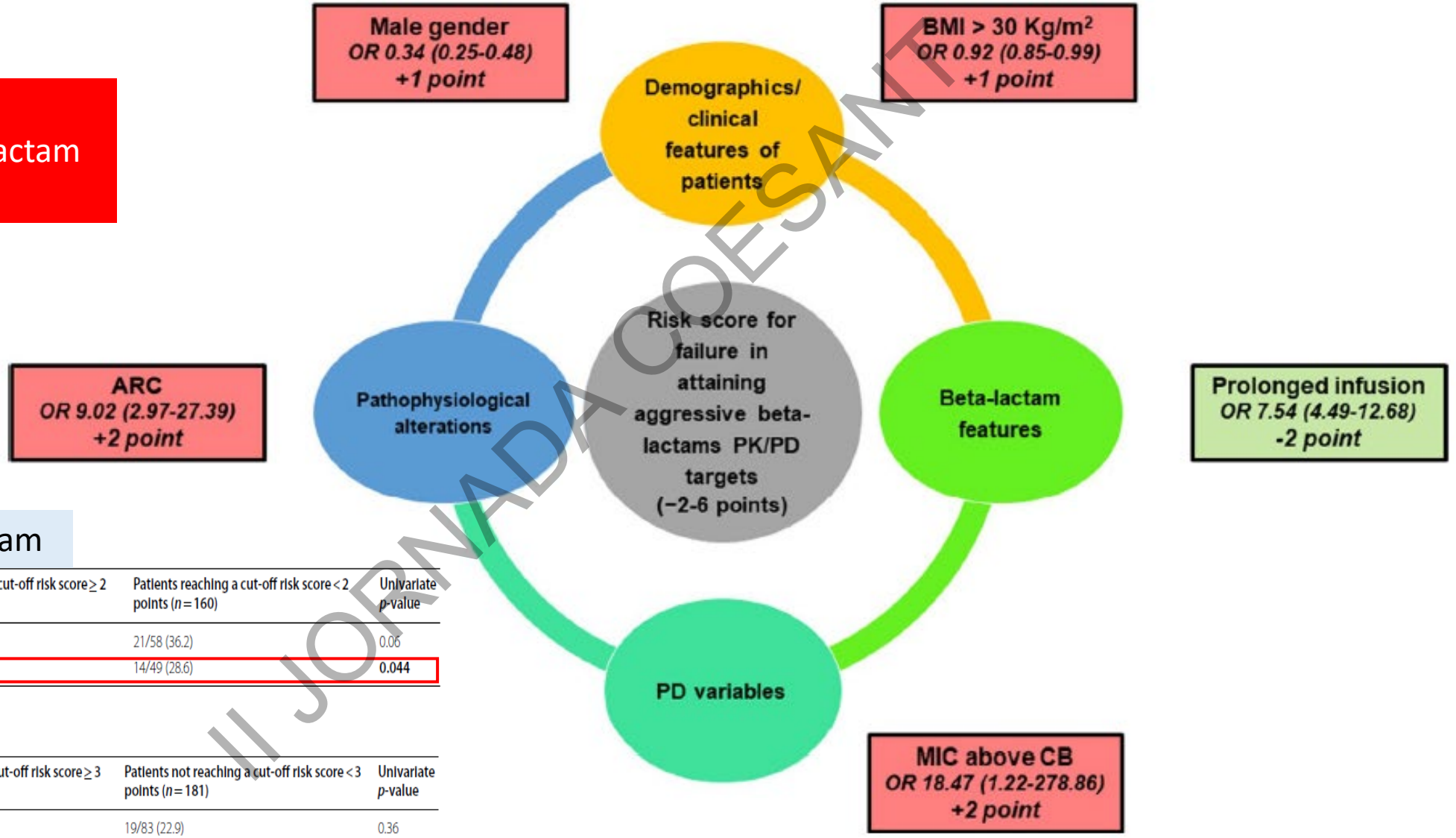
3 g/día C_{min} 10 mg/L

6 g/día C_{min} 20 mg/L

Liebchen U, Weinelt F, Scharf C, Schroeder I, Paal M, Zoller M, Kloft C, Jung J, Michelet R. Combination of Pharmacokinetic and Pathogen Susceptibility Information To Optimize Meropenem Treatment of Gram-Negative Infections in Critically Ill Patients. Antimicrob Agents Chemother. 2022 Feb 15;66(2):e0183121. doi: 10.1128/AAC.01831-21.

PREDICTORES INDEPENDIENTES DE FRACASO EN ALCANZAR EXPOSICIONES EXIGENTES (≥ 100%f $T_{> 4 \times CMI}$ = f C_{min} /CMI> 4)

Puntuación de riesgo
≥ 2 piperacilina-tazobactam
≥ 3 meropenem



Piperacilina-tazobactam

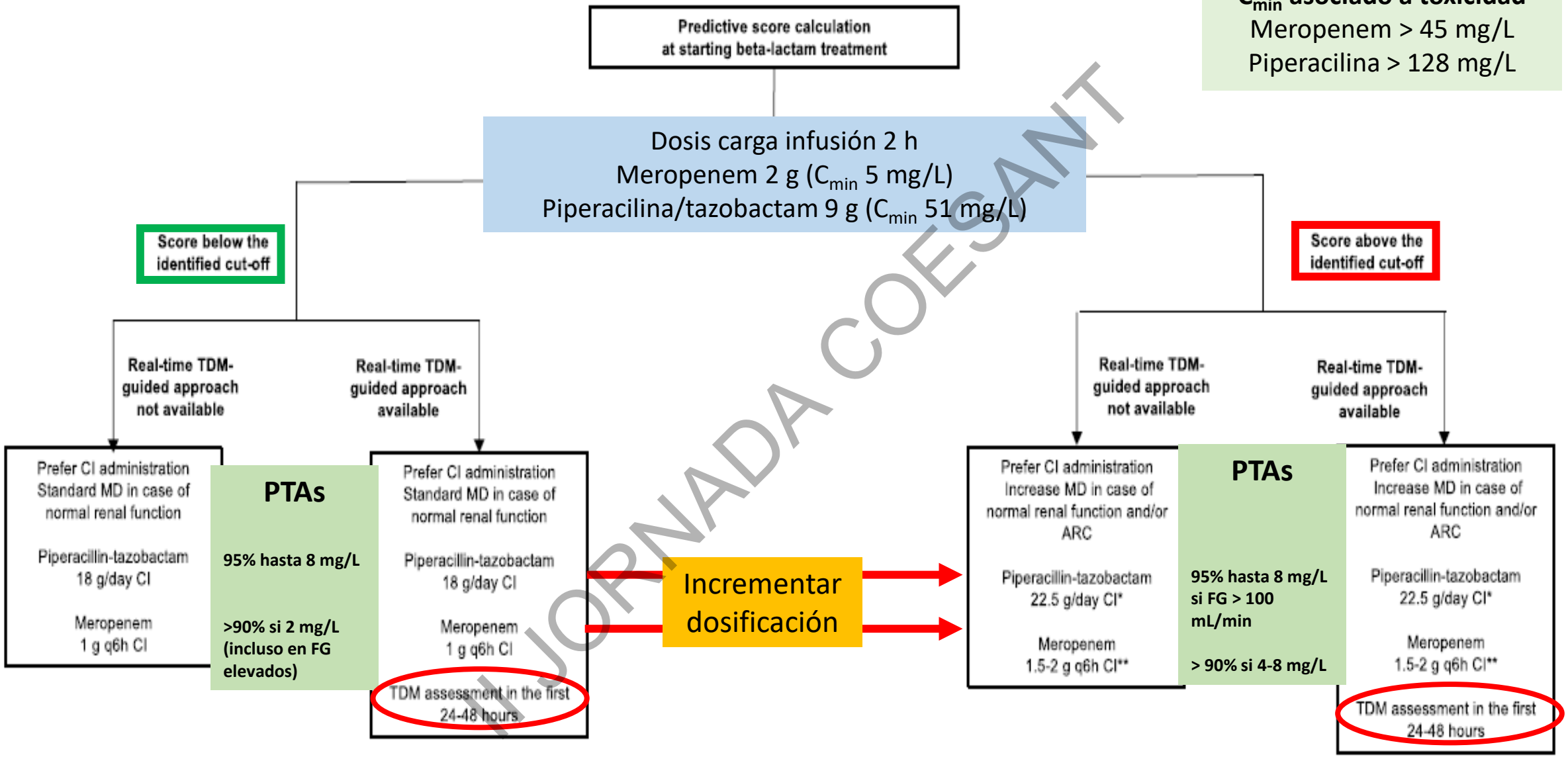
Variables	Patients reaching a cut-off risk score ≥ 2 points (n = 49)	Patients reaching a cut-off risk score < 2 points (n = 160)	Univariate p-value
Clinical failure*	12/20 (60.0)	21/58 (36.2)	0.06
Microbiological failure**	9/16 (56.3)	14/49 (28.6)	**0.044**

Meropenem

Variables	Patients reaching a cut-off risk score ≥ 3 points (n = 22)	Patients not reaching a cut-off risk score < 3 points (n = 181)	Univariate p-value
Clinical failure*	3/7 (33.3)	19/83 (22.9)	0.36
Microbiological failure**	3/6 (50.0)	8/77 (10.4)	**0.028**

1. Gatti M, Cojutti PG, Pea F. Crit Care. 2024 Apr 16;28(1):123. doi: 10.1186/s13054-024-04911-5;

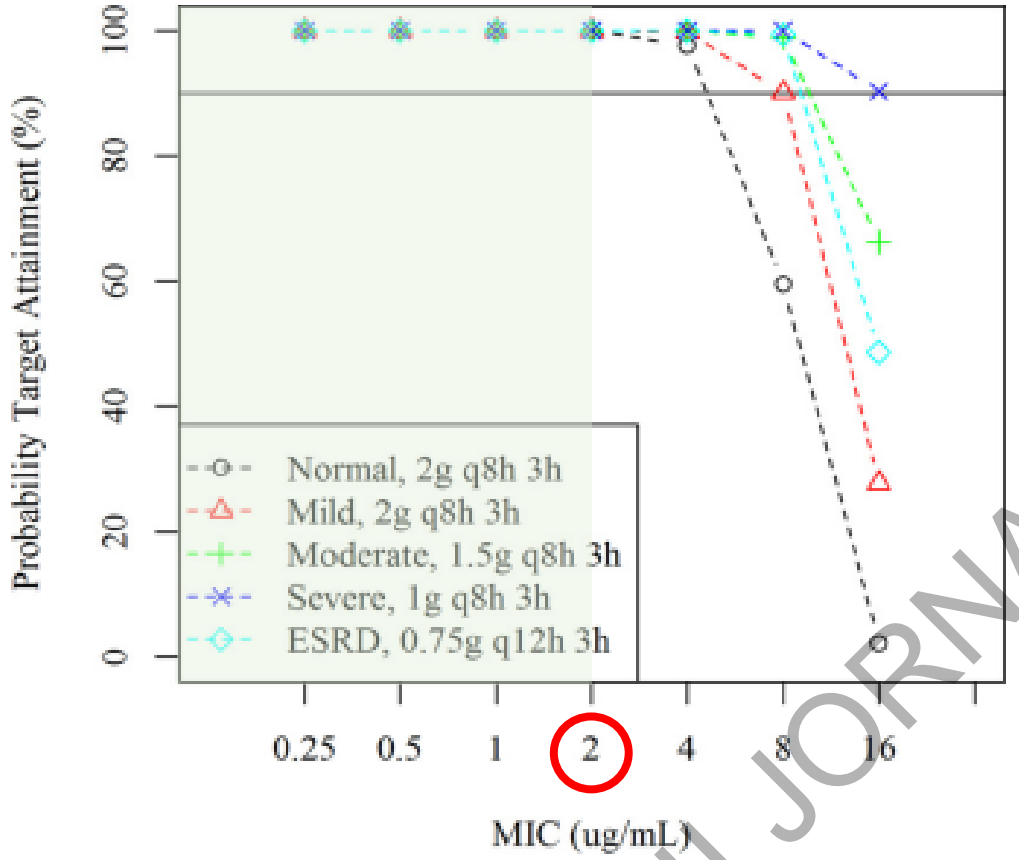
C_{min} asociado a toxicidad
Meropenem > 45 mg/L
Piperacilina > 128 mg/L



1. Gatti M, Grimaldi P, Rinaldi M, Siniscalchi A, Tonetti T, Viale P, Pea F. Validation of a predictive risk score of aggressive PK/PD target non-attainment with continuous infusion piperacillin/tazobactam or meropenem in critically ill patients having documented Gram-negative infections. J Anesth Analg Crit Care. 2025 Dec 4;6(1):4. doi: 10.1186/s44158-025-00324-0.
2. Delattre IK, Hites M, Laterre PF, Dugernier T, Spapen H, Wallemacq PE, Jacobs F, Taccone FS. What is the optimal loading dose of broad-spectrum β-lactam antibiotics in septic patients? Results from pharmacokinetic simulation modelling. Int J Antimicrob Agents. 2020 Oct;56(4):106113. doi: 10.1016/j.ijantimicag.2020.106113.

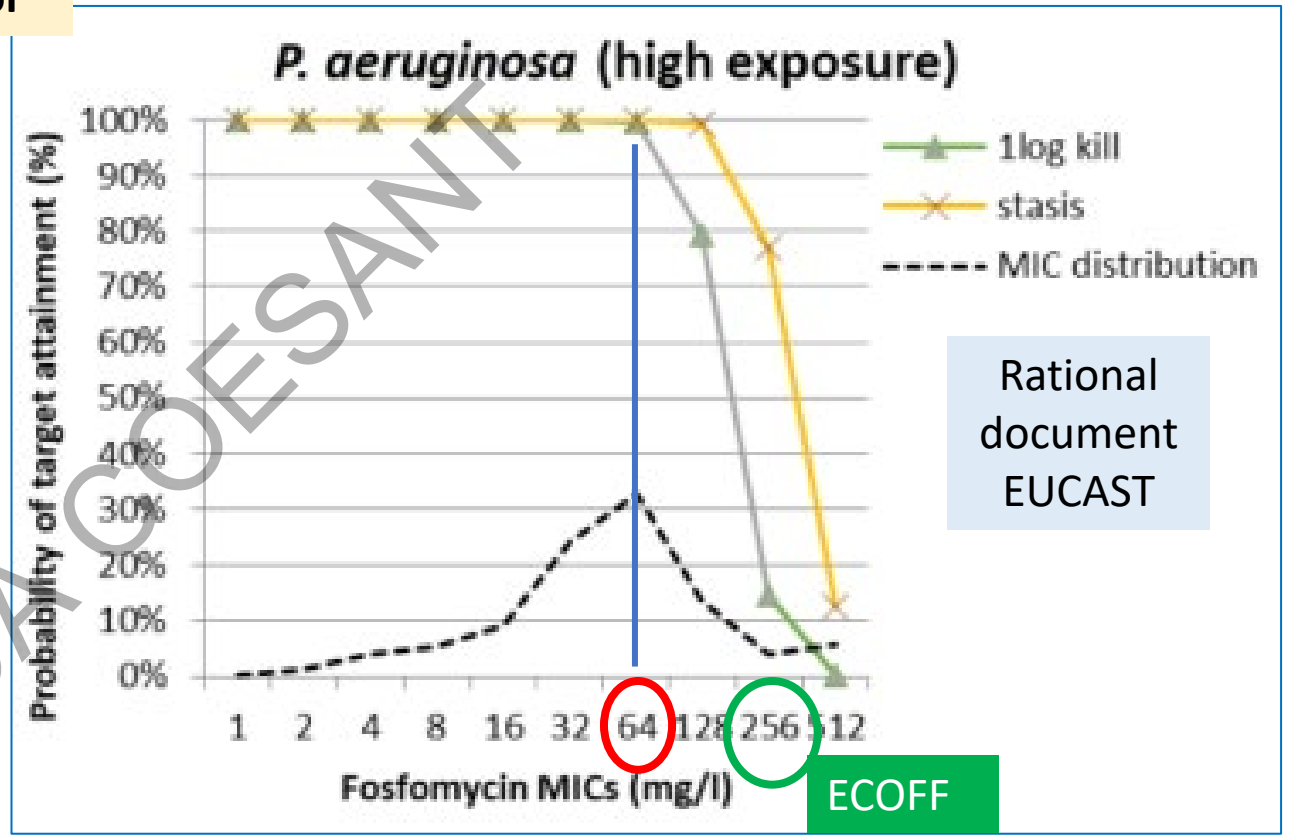
Neumonía grave *P. aeruginosa* ceftolozano-tazobactam-R MBL: Combinado, por lo menos uno activo *in vitro* + ATB en aerosol

Ajuste de dosis de **cefiderocol** según función renal 75% *f* T>CMI



C_{min} 13,6 mg/L 100% T > CMI

Fosfomicina IV 16 g/día 40,8 *f* AUC0-24/MIC for 1-log10 kill



Rational document EUCAST

Continuous infusion	12 g/day	16 g/day
Probability C_{ss} > 32 mg/L	100	100
Probability C_{ss} > 64 mg/L	70	98
Probability C_{ss} > 128 mg/L	0	4

1. Katsube T et al. Pharmacokinetic/Pharmacodynamic Modeling and Simulation of Cefiderocol, a Parenteral Siderophore Cephalosporin, for Dose Adjustment Based on Renal Function. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e01381-16. doi: 10.1128/AAC.01381-16. 2. https://www.eucast.org/fileadmin/eucast/pdf/rationale_documents/bacteria/Fosfomycin_iv_Rationale_Document_v1.0_20231123.pdf. 3. Rodríguez-Gascón A, Canut-Blasco A. Deciphering pharmacokinetics and pharmacodynamics of fosfomycin. Rev Esp Quimioter. 2019 May;32 Suppl 1(Suppl 1):19-24. 4. Meschiari M, Asquier-Khati A, Tiseo G, Luque-Paz D, Murri R, Boutoille D, Falcone M, Mussini C, Tattevin P; Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF). Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases. Int J Antimicrob Agents. 2024 Jul;64(1):107186. doi: 10.1016/j.ijantimicag.2024.107186.

Pacientes graves/críticos: antibioterapia rápida y exposición adecuada

Al inicio de la antibioterapia

1. Identificación (MALDI-TOF) y antibiograma (CMI) 24/7
2. Predicción del antibiótico apropiado
   - ✓ Según antecedentes paciente
   - ✓ Informe sensibilidad local
3. Dosis/régimen dosificación
   - ✓ Dosis de carga
   - ✓ IE/perfusión continua

Equipo multidisciplinar con estrategias PROA

Durante la antibioterapia

1. Monitorizar niveles (TDM) en primeras 24-48 h (modelos poblacionales PK) en pacientes:
   - ✓ Fallo renal (agudo, crónico, hiperfiltradores)
   - ✓ Con técnicas depuración extrarrenal (TDE)
   - ✓ Jóvenes (hiperfiltradores) y ancianos
   - ✓ Infecciones por bacterias multirresistentes
   - ✓ Infecciones de tratamiento difícil
2. Ajuste dosis mantenimiento
3. Desescalar si foco controlado y buena evolución clínica
4. Duración antibioterapia

Muchas gracias

andres.canutblasco@osakidetza.eus