59 CONGRESO NACIONAL
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Betalactámicos en paciente crítico

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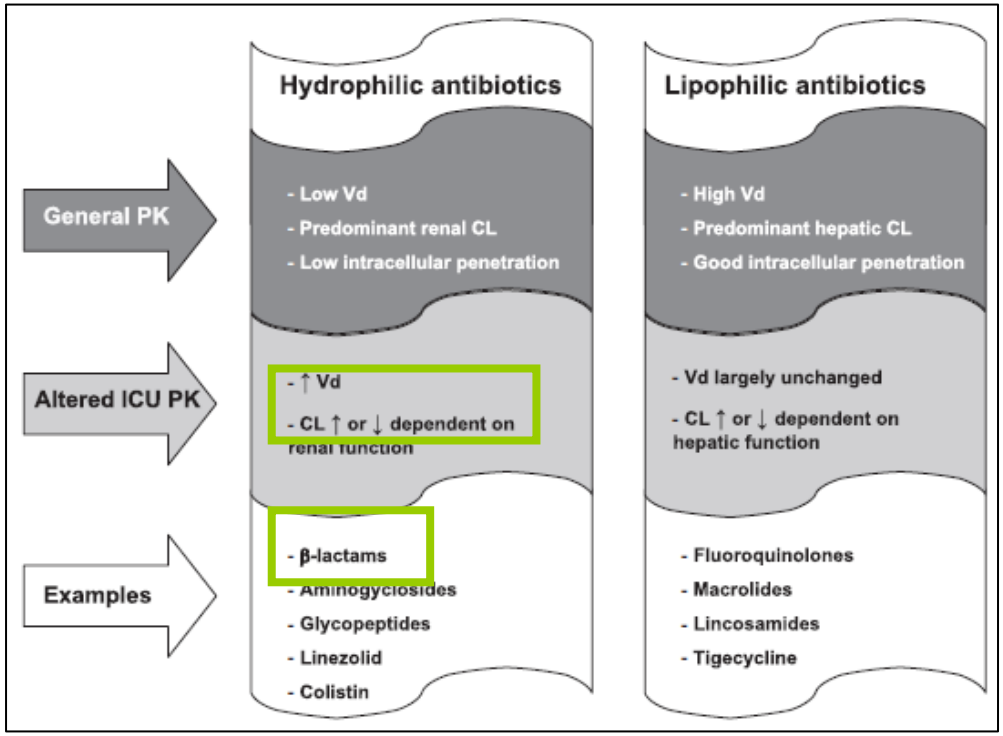
Introducción

- Uso racional de los antibióticos es una medida siempre deseable
  - importante en últimos años dado el incremento de microorganismos multiresistentes

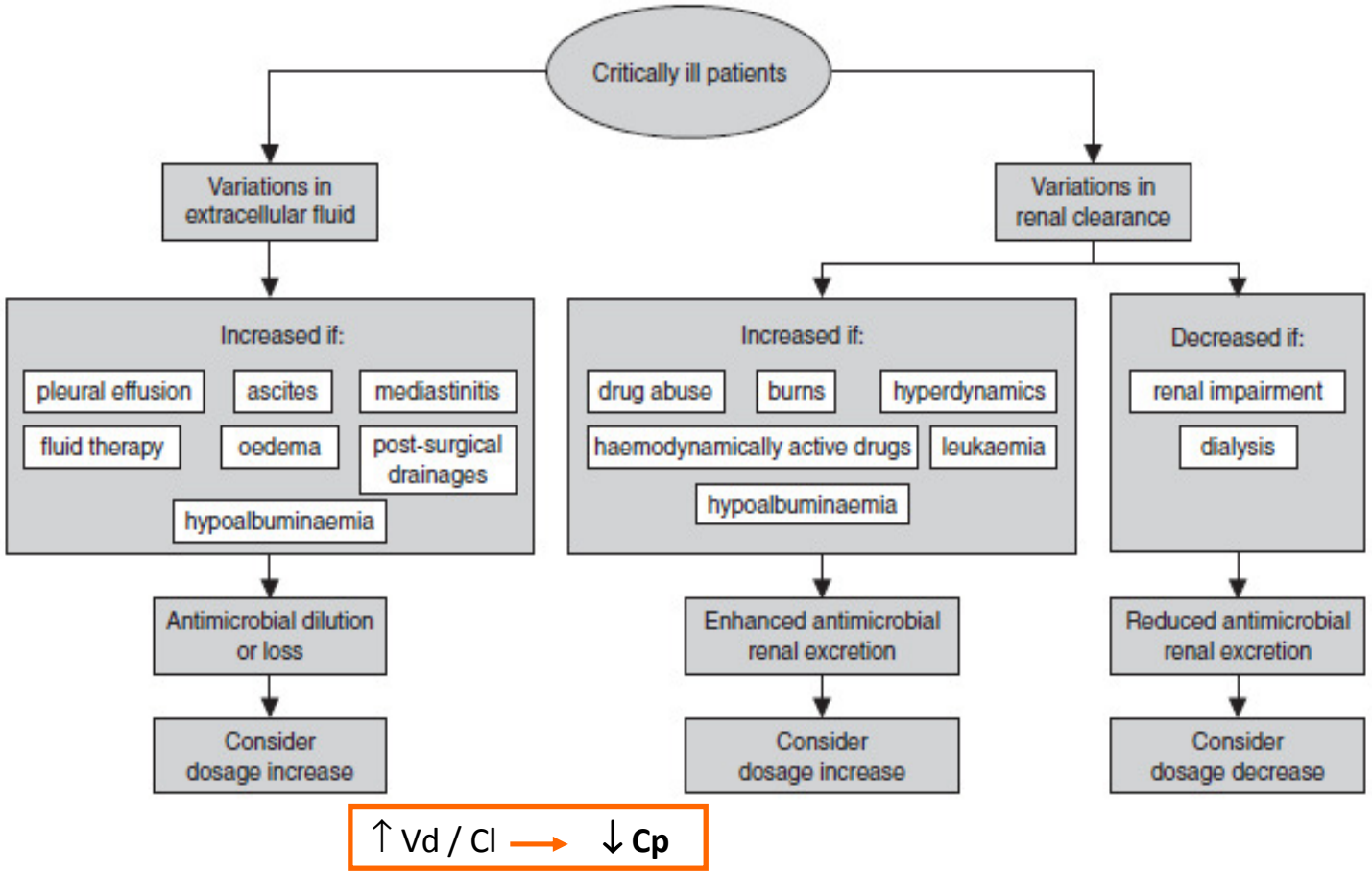
- Optimización de ABL especial interés en pacientes críticos
  - características fisio-patológicas diferenciales que implican un comportamiento PK diferente

- Presentan cambios:
  - volumen de distribución (Vd),
  - eliminación (semivida - t1/2),
  - penetración y distribución tejidos,
  - hipoalbuminemia y disfx orgánica



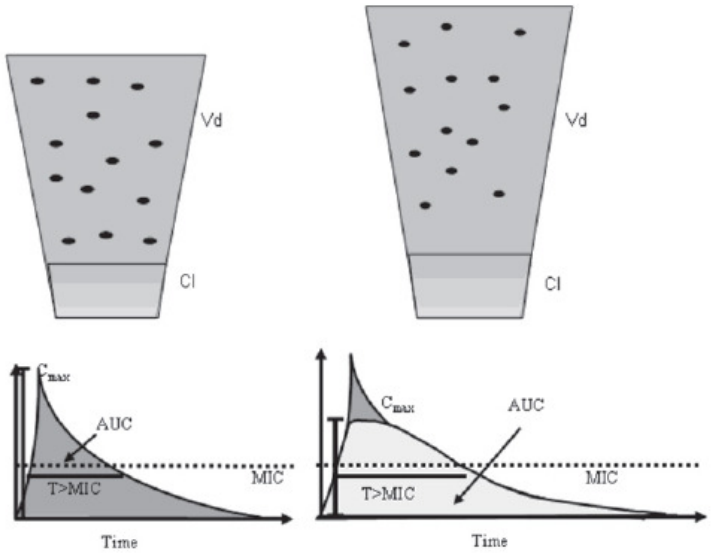
Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med 2009;37(3):840-51.*

Influencia de la fisiopatología sobre PK de los antibióticos



Pea F, Viale P et al. Antimicrobial therapy in critically ill patients. A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. *Clin Pharmacokinet 2005;44(10):1009-1034.*

Volumen de distribución β-lactámicos



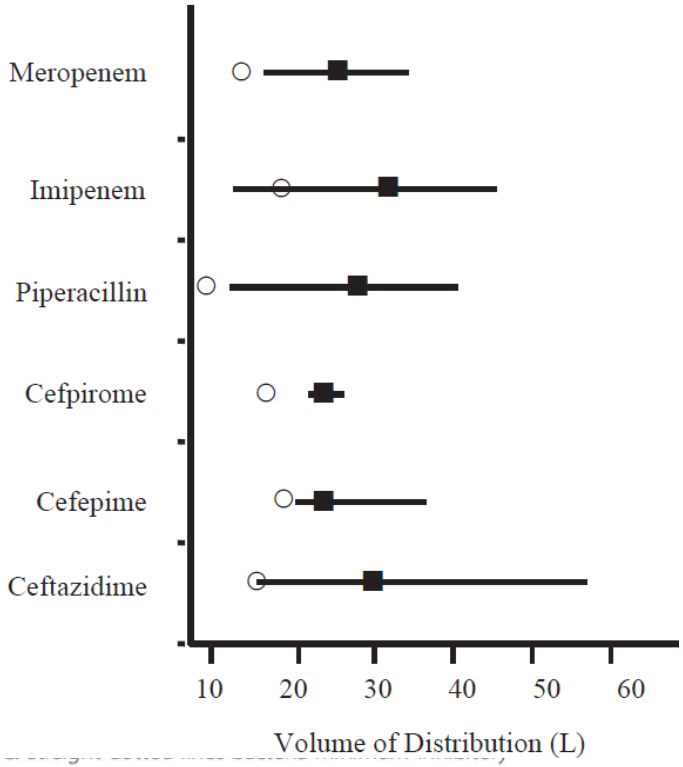
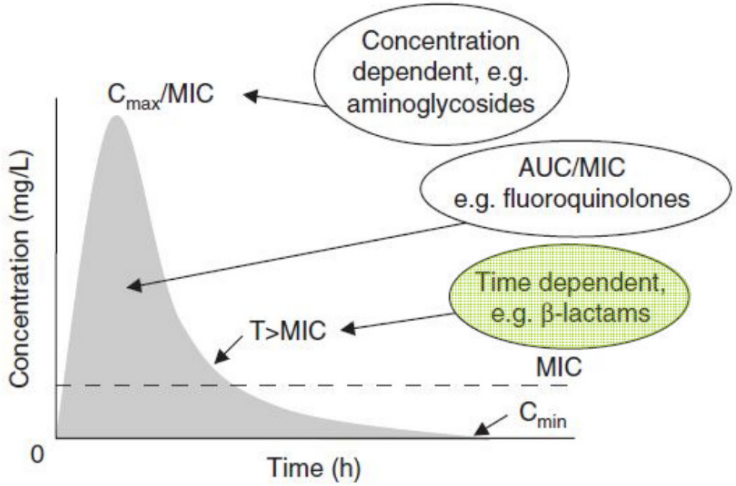


Figure 1 ICU patients present pharmacokinetic changes of antibiotics that may alte antibiotics in healthy volunteers (left panel). A large volume of distribution (V_d) (middle pane decreased maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$) and eventually higher bacteria minimum inhibitory concentration (T > MIC). The antibiotic area under the concent An increase in drug clearance (Cl) (right) is associated with decreases in AUC, $T_{1/2}$ and T > M concentration.

Gonçalves-Pereira J and Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. *Critical Care 2011, 15:R206*

Antibióticos beta-lactámicos

- **Antibióticos beta-lactámicos:**
  - semividas plasmáticas cortas
    (con escasas excepciones) por lo que se administran en múltiples dosis
  - actividad bactericida tiempo dependiente
  - y el índice PK/PD que más se correlaciona con su eficacia es el **T>CMI**



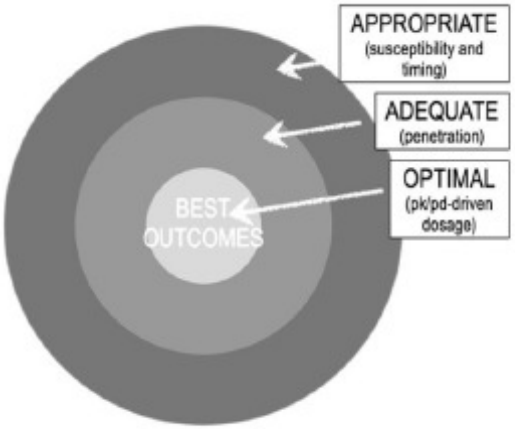


Fig. 1. The components of appropriate, adequate, and optimal antibiotic therapy.

- Enfoque individualizado de dosificación en paciente crítico
  - ÓPTIMO: según criterios PK/PD

Ulldemolins M, Nuvials X, Palomar M, Masclans JR, Rello J. Appropriateness is critical. *Crit Care Clin. 2011 Jan;27(1):35-51*

Pregunta 1

¿Target PKPD beta-lactámicos paciente crítico?

- 100% tiempo > MIC — 35%
- 100% tiempo > 4 x MIC — 50%
- 40-70% tiempo > MIC — 15%

Target PK/PD β-lactámicos

- In-vitro e in-vivo de animales, objetivo PD **general** β-lactámicos:

% fT>MIC	Bacteriostático	Bactericida
Carbapenémicos	20%	40%
Penicilinas	30%	50%
Aztreonam	50%	60%
Cefalosporinas	35-40%	60-70%

40-70%
fT> MIC

- Deben ser considerados como los criterios PD mínimos

  → pueden NO ser adecuados para el tratamiento de infecciones graves y para prevenir el desarrollo de resistencia a los antibióticos

  → **Paciente crítico**: beneficios clínicos con exposiciones más altas y largas

Roberts JA, Lipmana J et al. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? *Current Opinion in Critical Care 2008, 14:390–396*

Abdul-Aziz MH, Dulhunty JM, et al. Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Annals of Intensive Care 2012, 2:37

Target PK/PD β-lactámicos – pacientes críticos

	Preclinical studies		Clinical studies	
Time-dependent				
Carbapenems	Maximum killing[88]	40% $T_{>MIC}$	Clinical cure[89]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[90,91]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[17]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[11]	60–70% $T_{>MIC}$	Clinical cure[92]	100% $T_{>MIC}$
	Resistance suppression	--	Microbiological cure[16,93]	60–100% $T_{>MIC}$; 95% $T_{>4·3×MIC}$
Penicillins	Maximum killing[11]	40–50% $T_{>MIC}$	Clinical cure	--
	Resistance suppression[94]	40–50% $T_{>MIC}$	Microbiological cure[95]	40–50% $T_{>MIC}$

- El re-crecimiento bacteriano se producirá tan pronto como la Cp β-lactámico cae por debajo de la MIC
- La actividad bactericida máxima se produce a Cp 4-5 × MIC
  - especialmente con microorganismos menos susceptibles
- Paciente sepsis: reducción de la penetración de AB en tejidos
  - Cp elevadas aumentan la PB de [ ] eficaces en tejido

Objetivo PD en paciente crítico

100% fT>CIM

100% fT> 4-5× MIC

(elegido para maximizar la probabilidad de curación clínica)

Roberts JA, Ulldemolinsa M, Robertse MS, et al. Therapeutic drug monitoring of -lactams in critically ill patients: proof of concept. *International Journal of Antimicrobial Agents 36 (2010) 332–339*

Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis. 2014 Jun;14(6):498-509 Review.*

Antibiotics	PD targets	Percentage of patients achieving targets	References
Meropenem, 1 g tid or 3 g/day CI	40% *f* T > MIC, with *f* assumed to be 98%. CFR according to Mystic database	PTA for MIC = 2 mg/L: bolus 100%, CI 100% PTA for MIC = 8 mg/L: bolus 70%, CI 100% CFR for EC: bolus 100%, CI 100% CFR for PA: bolus 40.6%, CI 100%	Roberts *et al.*, 2009 [24]
Ceftazidime, 2 g	70% T > 4 × EUCAST breakpoint of PA	28%	Taccone *et al.*, 2010 [23]
Cefepime, 2 g	70% T > 4 × EUCAST breakpoint of PA	16%	
Meropenem, 1 g	40% T > 4 × EUCAST breakpoint of PA	75%	
Piperacillin/tazobactam, 4.5 g	50% T > 4 × EUCAST breakpoint of PA	44%	
Imipenem 1 g tid or 2 g/day CI	40% *f* T > MIC, with *f* assumed to be 80%	MIC = 2 mg/L bolus dosing 88%, CI 100% MIC = 4 mg/L bolus 75%, CI 86%	Sakka *et al.*, 2007 [31]
Piperacillin/tazobactam 4.5 g qid or 13.5 g CI	50% *f* T > MIC. CFR according to Mystic database	PTA for MIC = 0.25 mg/L bolus 79.2%, CI 100% PTA for MIC = 1 mg/L bolus 60%, CI 100% CFR for 18 g/day: bolus 53.4%, CI 92.5% CFR for 13.5 g/day: bolus 40%, CI 92.4%	Roberts *et al.*, 2009 [46]
Cefpirome 2 g bid	60% T > MIC	PTA for MIC = 4 mg/L: bolus 60%, CI (4 g/day) 100% PTA for MIC = 16 mg/L: bolus 10%, CI (4 g/day) 50%	Lipman *et al.*, 2001 [48]
Cefepime 2 g	65% *f* T > MIC, with *f* assumed to be 90%. CFR according to Queensland Health Pathology Service	CFR for EC: 2 g bid 78.9%, CI (4 g/day) 96.9% CFR for PA: 2 g bid 54%, CI (4 g/day) 91.7%	Roos *et al.*, 2006 [60]
Ceftazidime 1 g every 4 hours	100% T > 4 × MIC (isolated pathogens; if negative cultures 100% T > 16 mg/L)	Ceftazidime 47.8% PTA with 1 g every 3 hours 88.2%	Conil *et al.*, 2007 [54]

Estudio DALI

(Defining antibiotic levels in intensive care unit patients)

- N=361 pacientes y 2 mediciones Cp: 50 y 100% tau.
  - Correlacionar PK/PD observado con resultados clínicos.

Table 3. Antibiotic Data for Achievement of Pharmacokinetic/Pharmacodynamic Targets[a] in Critically Ill Patients

	Antibiotic (No. of Patients)								
Dosing and PK/PD Data	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)	Total (N = 361)
Dosage per 24 h[b], g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	6.0 (5.0–6.0)	2.0 (2.0–4.0)	1.75 (1.50–3.0)	12.0 (12.0–16.0)	3.0 (3.0–4.0)	
50% $fT_{>MIC}$ achieved	52.1%	55.6%	100.0%	78.6%	97.0%	100.0%	80.6%	95.0%	78.9%
50% $fT_{>4\times MIC}$ achieved	16.9%	27.8%	50.0%	50.0%	93.9%	69.2%	48.9%	68.8%	48.9%
100% $fT_{>MIC}$ achieved	18.3%	33.3%	78.6%	78.6%	93.9%	76.9%	67.0%	69.7%	60.4%
100% $fT_{>4\times MIC}$ achieved	11.3%	22.2%	14.3%	71.4%	87.9%	30.8%	30.3%	41.6%	35.0%

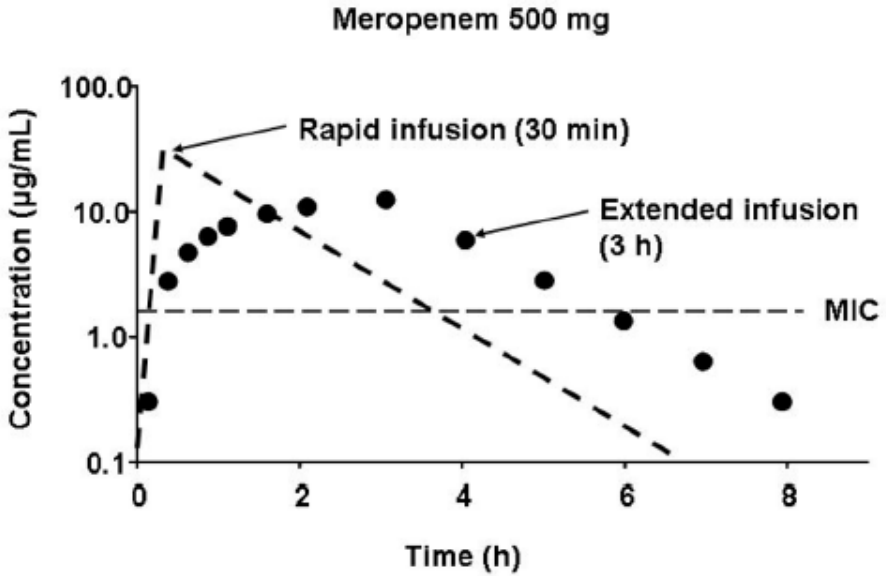
- De los 248 pacientes tratados por infecciones, **el 16% NO alcanzaron 50% fT>MIC**
  - estos pacientes eran 32% menos propensos a tener un resultado clínico positivo
  - No alcanzaron el 50% ft>MIC: 20% II vs 7% IP

- **Resultados clínicos positivos directamente relacionados con ↑↑ 50 y 100 %T>CIM**, con una interacción significativa con el estado de gravedad de la enfermedad:
  - **OR=1,02** aumento de los ratios 50% f T> MIC y **OR=1,56** el 100% f T> MIC es (p<0,03)

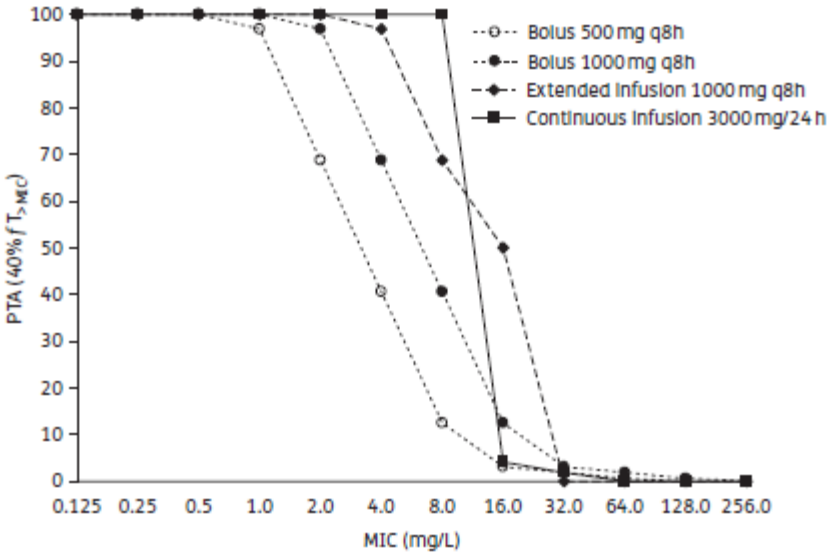
Roberts JA, Paul SK, Akova M, Bassetti M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis. 2014 Apr;58(8):1072-83.*

Estrategias optimización PK beta-lactámicos

- β-lactámicos más eficaces cuando se administran en IC → >MIC durante todo ttm
- La infusión extendida o prolongada (IE) también ha sugerido maximizar la fT> MIC sin los inconvenientes asociados a la IC
- **IC y IE** particularmente ventajosas en el **tto de infecciones graves.**



David P Nicolau. Pharmacodynamic optimization of β-lactams in the patient care setting. Review. *Critical Care 2008, 12(Suppl 4):S2*



Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. *J Antimicrob Chemother. 2011 Feb;66(2):227-31.*

Caso clínico

Hombre, 59 años

- 15/04: Ingresa en otro centro para estudio de epigastralgia y sd tóxico 2 meses evolución
  Eco abdominal: colecistitis aguda.
- 30/04: Colangiografia per CPRE

Dx: Adenocarcinoma colédoco pancreático y neoplasia colon transverso.

- 06/05 via CTPH coloca drenaje biliar int-ext.
  Durante el ingreso presenta shock séptico por colangitis:
  - HC → E.coli cobertura con Ceftriaxona
  - TC (09/05) áreas en s.VI compatibles con áreas flegmonosas/abscesos en fase de organització 6x4cm localizadas cerca del trayecto del drenaje int-ext.

Hospital Universitari de Bellvitge

- 26/05 revisión del drenaje (vía biliar intra y extrahepática hasta la oclusión a nivel de colédoco medio no está dilatada) y se recambia
- 27/05: SHOCK SÉPTICO:
  - TC ABDOMINAL presencia de colecciones-abscesos peribiliars en segmento VI
  - Colangitis. Abscesos hepáticos. Empiema pleural.

- **28/05: Traslado a UCI**

- Empeoramiento clínico
  - Insuficiencia respiratoria, posiblemente por distress + componente de atelectasia pasiva por empiema derecho

  - Acidosis metabólica con anion GAP elevado de causa multifactorial que compensa respiratoriamente

  - Sepsis: de momento hemocultivos negativos, cambio de vías y recultivo

28/05: Cultivo de BILIS → cocos G+ y de BNGs

PIPER/TAZO + TEICOPLANINA
+ METRONIDAZOL para cubrir anaerobios.

Pregunta 2

¿Optimización administración PIPERACILINA/TAZOBACT en paciente crítico?

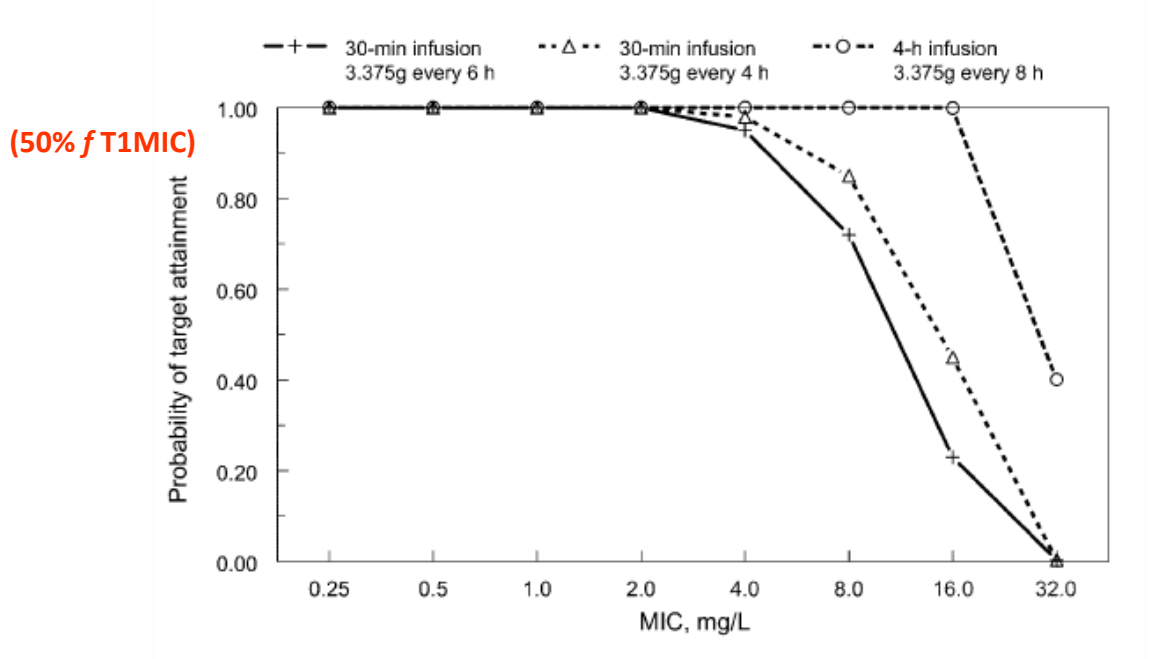
- Se debe administrar siempre en IE de 4 horas — 10%
- PiperTazo no ha demostrado ventaja alguna con la administración en IC o IE — 20%
- Paciente crítico la IC o IE permite alcanzar los objetivos PK/PD — 70%

Estudios PK en pacientes hospitalizados - PiperTazo

• PopPK piperacillin-tazobactam: pacientes hospitalizados

• Sujetos: cirugía abdominal, torácica y colorrectal y pacientes con neutropenia e infecciones bacterianas.

•Datos completos de **128 pacientes, y 873 muestras de Cp**



Lodise TP Jr, Lomaestro B, and Drusano GL. Piperacillin-Tazobactam for Pseudomonas aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy. *Clinical Infectious Diseases 2007; 44:357–63*

PK PTZ pacientes críticos: **II vs IE**

- Simulaciones de Cp en 5000 pacientes, de modelos PopPK descritos

- Piperacillin/tazobactam: **n=56** (complicated intra-abdominal infections)

  Li C, Kuti JL, Nightingale CH et al. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. JAC 2005; 56: 388–95.

		>50% $fT_{>MIC}$		>75% $fT_{>MIC}$		100% $fT_{>MIC}$	
Antibiotic	Dose	CTA (excluding MRSA)	effect	CTA (excluding MRSA)	effect	CTA (excluding MRSA)	effect
Meropenem	**1 g every 8 h (t' 0.5 h)**	**0.82 (0.88)**		**0.75 (0.80)**		**0.62 (0.66)**	
	1 g every 8 h (t' 3 h)	0.85 (0.91)	+	0.80 (0.86)	+ (++)	0.73 (0.78)	+++
	2 g every 8 h (t' 0.5 h)	0.85 (0.91)	+	0.79 (0.84)	+	0.69 (0.74)	++
	2 g every 8 h (t' 3 h)	0.87 (0.93)	+	0.83 (0.89)	++	0.77 (0.82)	+++
Piperacillin/tazobactam	**3.375 g every 6 h (t' 0.5 h)**	**0.79 (0.84)**		**0.60 (0.64)**		**0.36 (0.39)**	
	3.375 g every 6 h (t' 3 h)	0.84 (0.90)	+ (++)	0.79 (0.84)	+++	0.63 (0.67)	++++
	4.5 g every 6 h (t' 0.5 h)	0.80 (0.86)	+	0.65 (0.70)	+ (++)	0.42 (0.45)	++
	4.5 g every 6 h (t' 3 h)	0.84 (0.90)	+ (++)	0.81 (0.87)	++++	0.67 (0.72)	++++
Cefepime	**2 g every 12 h (t' 0.5 h)**	**0.81 (0.87)**		**0.74 (0.79)**		**0.62 (0.66)**	
	2 g every 12 h (t' 3 h)	0.82 (0.88)	+	0.77 (0.82)	+	0.68 (0.73)	++
	2 g every 8 h (t' 0.5 h)	0.85 (0.91)	+	0.81 (0.87)	++	0.78 (0.83)	+++
	2 g every 8 h (t' 3 h)	0.86 (0.92)	+	0.83 (0.89)	++	0.80 (0.86)	+++

Zelenitsky SA1, Ariano RE, Zhanel GG. Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data. ***J Antimicrob Chemother. 2011 Feb;66(2):343-9.***

PTZ PopPK críticos: **IE**

- Modelo PK poblacional
- n=11 pacientes críticos

- Piper/Tazo **3.375g/8h IE de 4h**

- Simulación de Monte Carlo sugiere que PiperTazo **4,5 g/6 h infusión de 3 h puede ser utilizado con éxito para tratar organismos con una MIC de 16 mg/L**

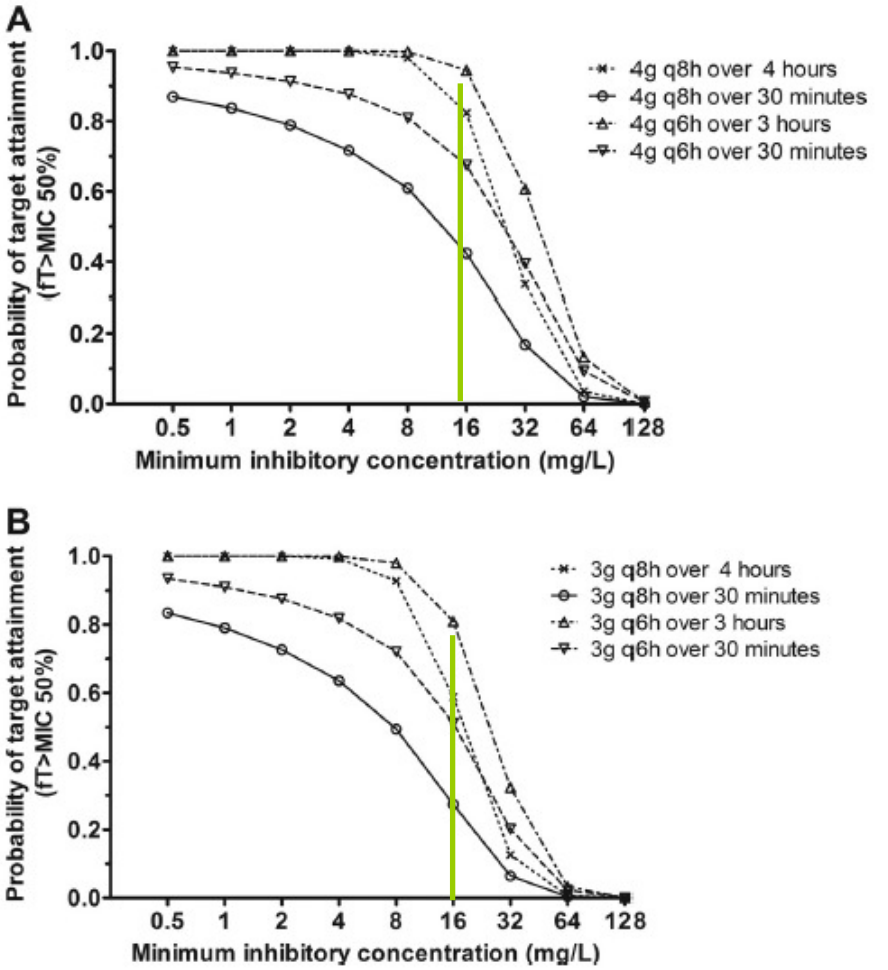


FIG 2 Results of the Monte Carlo simulation with the fractional target attainments against a range of MICs were determined for piperacillin administered intravenously (i.v.) for either 30 min or 4 h every 8 h as well as for 30 min or 3 h every 6 h (A), and 3 g pipe either 30 min or 4 h every 8 h as well as 4 g piperacillin administered i.v. for 30 min or 3 h every 6 h (B).

Felton TW, Hope WW, Roberts JA. How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it? *Diagn Microbiol Infect Dis. 2014 Aug;79(4):441-7.*

PTZ pacientes críticos: **II vs IC**

- Modelo PopPK, 16 pacientes críticos con fx renal normal
- Dosis: **12g/dia en grupo de IC; 4g/6-8h en grupo de II**.
- **Concentraciones > en grupo de IC**
  - Simulaciones 2000 pacientes
  - IC permite mayor probabilidad de alcanzar objectivo PD 50%ft>MIC (**93% vs 53%)**

Table 3
Probability of target attainment by minimum inhibitory concentration (%) for various bolus, extended and continuous dosing strategies of piperacillin in critically ill patients with sepsis.

MIC (mg/L)	% frequency from MYSTIC database [41]	Bolus dosing				Extended infusion		Continuous Infusion		
		3 g q4h	3 g q6h	4 g q8h	4 g q6h	4 g q8h	4 g q6h	8 g/day	12 g/day	16 g/day
0.125	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	54.58	47.76	31.82	25.58	34.11	42.63	50.05	54.58	54.58	54.58
2	21.84	16.38	10.92	8.87	11.83	15.70	18.19	21.84	21.84	21.84
4	9.51	5.94	3.97	3.27	4.36	6.24	7.13	9.51	9.51	9.51
8	5.48	2.74	1.82	1.54	2.06	3.26	3.66	1.89	5.48	5.48
16	1.75	0.66	0.44	0.38	0.51	0.93	1.02	0.44	0.49	0.66
32	2.05	0.51	0.34	0.32	0.43	0.00	1.03	0.32	0.39	0.39
64	0.63	0.08	0.06	0.06	0.08	0.00	0.00	0.06	0.07	0.07
128	4.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CFR		74.07	49.37	40.03	53.38	68.75	81.08	88.64	92.35	92.52

The target chosen was 50% $f_{T>MIC}$. Data for piperacillin susceptibility includes various pathogens isolated. MIC, minimum inhibitory concentration; q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; CFR, cumulative fraction of response.

Roberts JA et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *International Journal of Antimicrobial Agents 35 (2010) 156–163*

PTZ pacientes críticos: **II vs IC**

- n=40 pacientes críticos sépticos
- **Piperacilina IC** (**2 g D* + 8 g en 24 h** (n = 20)) o **II** (**3 g/6 h durante 0,5 h** (n = 20))
- Eficacia clínica de piperacilina en IC > II en pacientes críticos.
  - Cambios en APACHE II desde el inicio hasta el final del segundo, tercer y cuarto día, respectivamente, fueron 4.1, 5.1 y 5.2 para IC y 2,0, 2,6 y 2,8 para la II (P <= 0,04).
  - Mortalidad debida a infección: menor en IC vs II (40% (2 de 5 pacientes) y 67% (4 de 6 pacientes), respectivamente, P = 0,38).

- Se aislaron 10 patógenos de 8 pacientes en el grupo IC y 6 patógenos de 4 pacientes en el grupo II.

IC proporciona Cp medias superiores que la II

MIC patógenos	% T>MIC	
	IC	II
16 mg/L	100%	62%
32 mg/L	65%	39%

Rafati MR, Rouini MR, Mojtahedzadeh M, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents. 2006 Aug;28(2):122-7

Augmented Renal Clearance (ARC)

- N=61 pacientes críticos
- **48% NO alcanzó la PK/PD 100% fT> MIC,** casi el 80% tenían ClCr> 130ml/min
  - 7 de 19 pacientes (37%) que presentan un aclaramiento de creatinina> 130 ml / min no alcanzaron la PK/PD mínimo del 50% fT> MIC.

- Análisis multivariante → ClCr fue un predictor independiente de no alcanzar el objetivo PK/PD

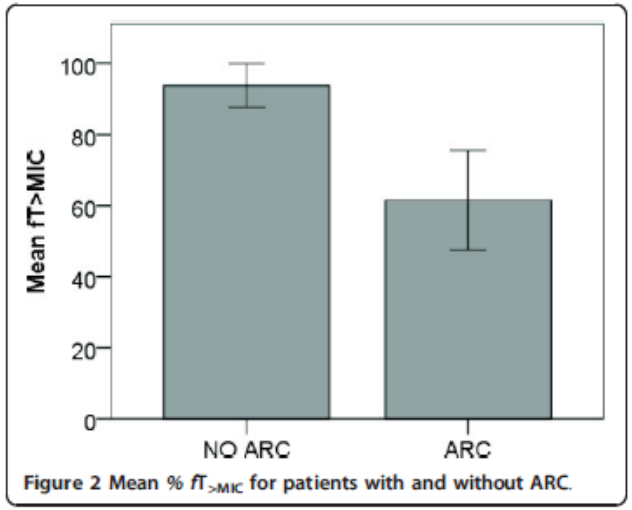


Figure 2 Mean % $fT_{>MIC}$ for patients with and without ARC.

Table 2 Multivariate regression model with attainment of 100% $fT_{>MIC}$ as dependent variable.

	Attainment of 100 % $fT_{>MIC}$ as dependent variable				
	B	*P* value	Exp(B)	95% CI for Exp(B)	
		Lower	Upper		
Creatinine clearance (mL/min)	-0.028	0.002	0.972	0.955	0.990
Weight (kg)	-0.040	0.114	0.961	0.915	1.010
Age (years)	0.020	0.331	1.020	0.980	1.063
Constant	5.788	0.033	326.34		

Carlier M, Carrette S, Roberts JA et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Critical Care 2013, 17:R84*

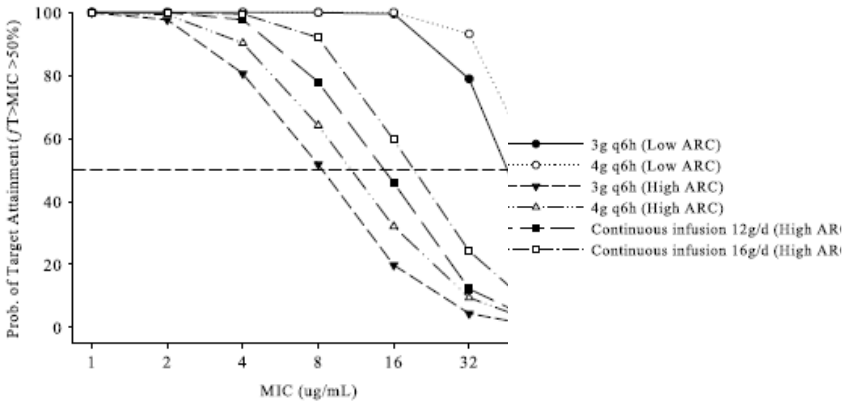
Piper/Tazo IE o IC

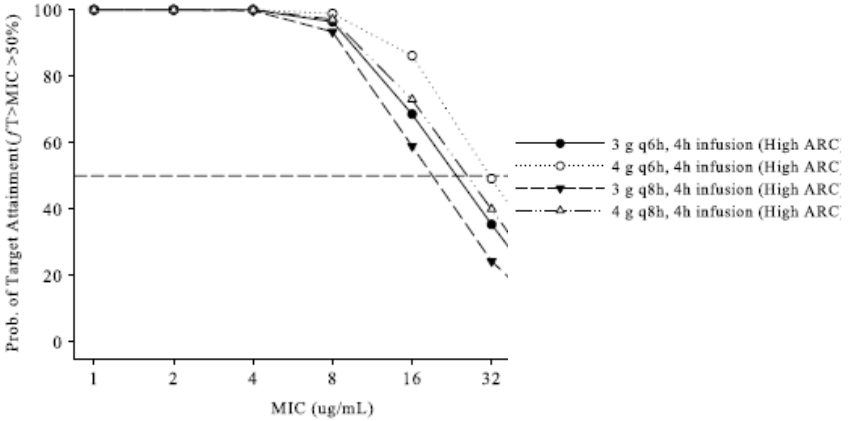
- **Augmented Renal Clearance (ARC)**
  - Factores: edad <50, trauma y SOFA<4
    6 p 3 p 1p

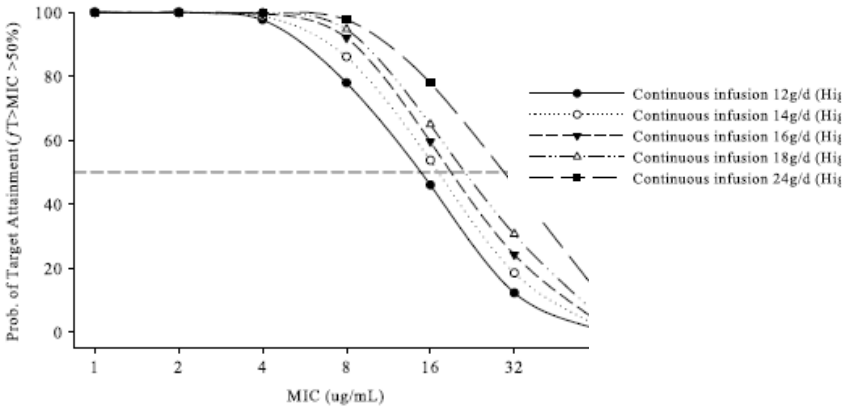
	Free Piperacillin		
	ARC Score ≤ 6 (n = 5)	ARC Score ≥ 7 (n = 8)	*p*
Volume of distribution, L/kg	0.37 (0.29–0.52)	1.23 (0.77–2.23)	0.00
Clearance, mL/kg/min	2.5 (1.7–4.5)	12.3 (5.3–17.5)	0.00
AUC, h·µg/mL	233.9 (176.9–453.0)	76.4 (50.3–101.7)	0.00
Peak, µg/mL	80.8 (65.0–157.9)	35.0 (29.2–54.7)	0.00
Trough, µg/mL	11.7 (4.5–28.8)	2.7 (0.8–5.6)	0.11

Data are presented as mean (SD) or median (IQR).

- Simulaciones sugieren que el uso de **IP permitiría superar el rápido Cl de fármaco**
- Se necesitan estudios prospectivos para determinar ajustes de dosis adecuados







Akers KS, Niece KL. Et al. Modified Augmented Renal Clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. *J Trauma Acute Care Surg 2014 Vol 77, Number 3, Supplement 2*

Pregunta 3

¿Beneficios clínicos con la IC o IE?

- La IP de todos los β-lactámicos ha demostrado menor mortalidad — 25%
- La IP de todos los β-lactámicos ha demostrado mayor curación clínica — 15%
- En el subgrupo de pacientes críticos se ha demostrado mayor beneficio clínico con IC o IE — 60%

Revisiones/metanálisis

Ceftalops/ vanco/tobra - IC vs II	- 9 estudios (pocos pacientes) - Críticos o neutrop QT	Fracaso clínico menor (No E.S) →Subanálisis de ABL: favorable a la IC (pero no E.S)

Continuous versus Intermittent Intravenous Administration of Antibacterials with Time-Dependent Action 2005

A Systematic Review of Pharmacokinetic and Pharmacodynar

Sofia K. Kasiakou,[1,2] K
Matthew E. Falagas[1,5]

A systematic review on clinical benefits of continuous administration of β-lactam antibiotics* 2009

Jason A. Roberts, PhD; Steven Webb, FJFICM, PhD; David Paterson, FRACP, PhD; Kwok M.

Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials 2011

Pranita D Tamma[1*]

Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections (Review) 2013

THE COCHRANE COLLABORATION®

Shiu JR, Wang E, Tejani AM, Wasdell M

Cefalosp/ PipeTaz/ Carbapen - IC+IP vs II	- 14 ECA - UCI + no UCI	No DIF en mortalidad, curación clínica o incidencia de EA.
Betalact, AMG, linez, vanco - IC vs II	- 21 ECA	

Revisiones/metanálisis

Evaluating Outcomes Associated with Alternative Dosing Strategies for Piperacillin/Tazobactam: A Qualitative Systematic Review 2012

Greg T Mah, Vincen

12 estudios: - 7 resultados clínicos y 5 de PK/PD - **UCI + no UCI**	-IP o IC alcanza más los criterios PD que la infusión tradicional. - Asociación con mejora resultados clínicos no está clara.

EXPERT REVIEWS

Extended or continuous versus short-term intravenou infusion of cephalosporins: a meta-analysis 2013

Expert R

Ioanna P Korbila[1,2], The aut

11 estudios n=1250	- No diferencia en curación clínica o mortalidad IE/IC vs II - **Grupo IE/IC Dtotal más baja**

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis 2013

Matthew E. Falagas,[1,2,4] Giannoula S. Tansarli,[1] Kazuro Ikawa,[3] and Konstantinos Z. Vardakas[1,2]

Carbapenems: Lorente 2006, (n=89), Esterly 2010, (n=71)...

Piper/tazo: Grant 2002 (n=98), Lodise 2007 (n=194), Lorente 2009 (n=83), Patel 2009 (n=129)...

-Incorporan estudios no EC
-**SI beneficios clínicos**

Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis

Jocelyn Teo, Yixin Liew, Winnie Lee, Andrea Lay-Hoon Kwa* 2014

Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: A narrative and systematic review ☆

Erlangga Yusuf, MD, PhD[a], Herbert Spapen, MD, PhD[b], Denis Piérard, MD, PhD[a] 2014

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

IC y IP vs II	-Carbap/PiperTaz - UCI y no UCI	-14 estudios – 1229 pacientes (Carbap 3 estud n=302, Piper/Tazo 7 estud n=806) -Pacientes tratados con IP (≥3 horas) o IC (24 horas) vs II (20-60 minutos)

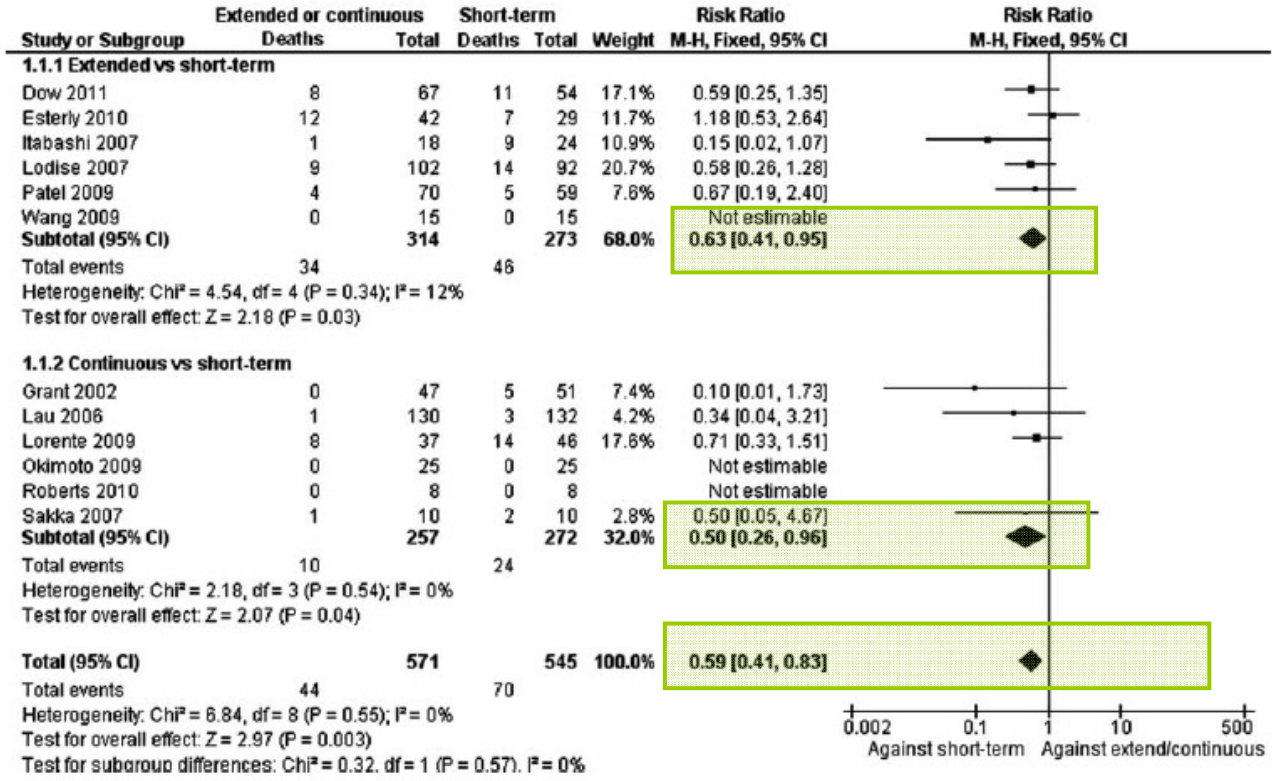


Figure 2. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

Falagas ME, Tansarli GS, Ikawa K and Vardakas KZ. Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis. *CID 2013:56 (15 January)*

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

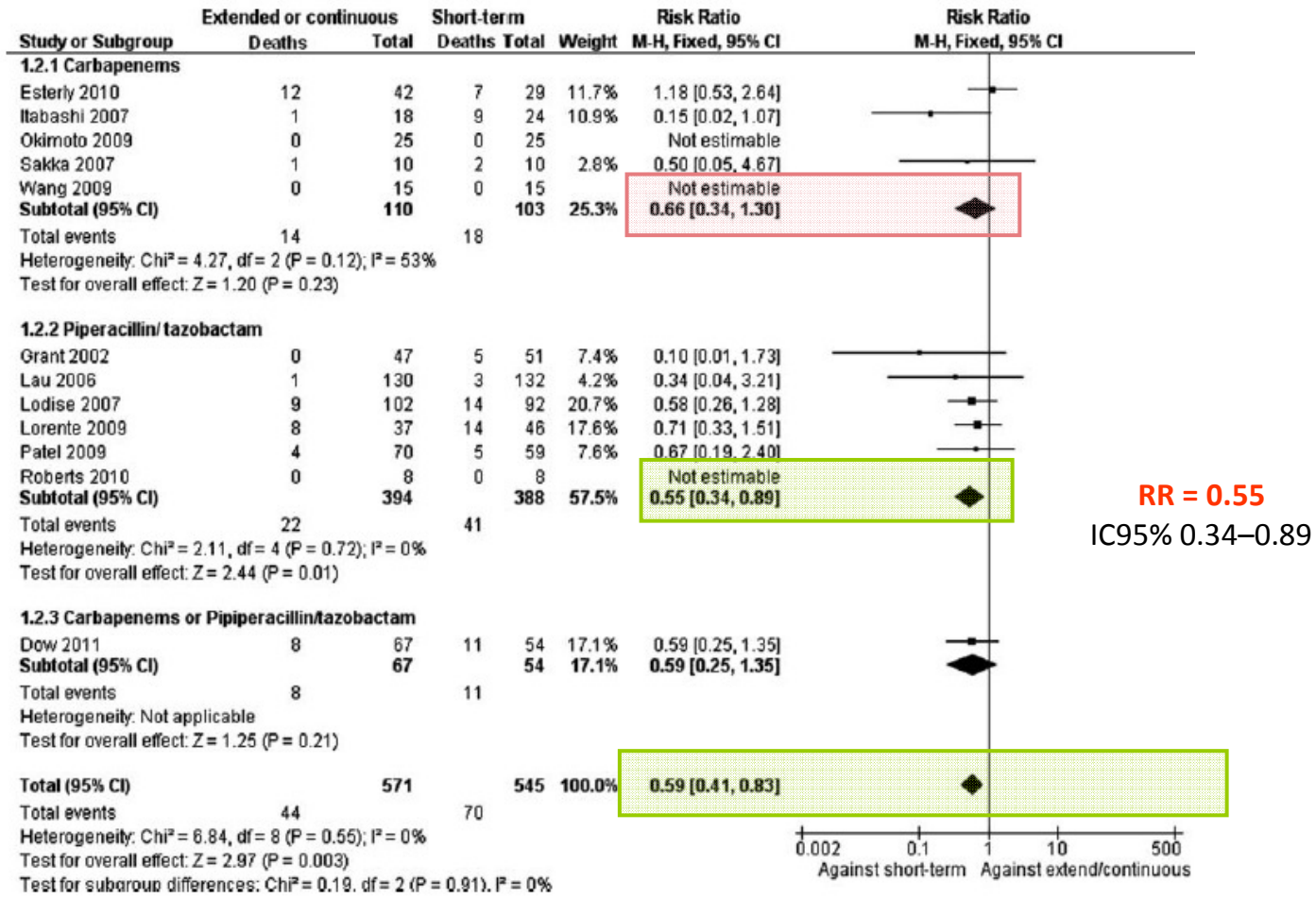


Figure 3. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems ar

Falagas ME, Tansarli GS, Ikawa K and Vardakas KZ. Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis. *CID 2013:56 (15 January)*

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/ Tazobactam: A Systematic Review and Meta-analysis

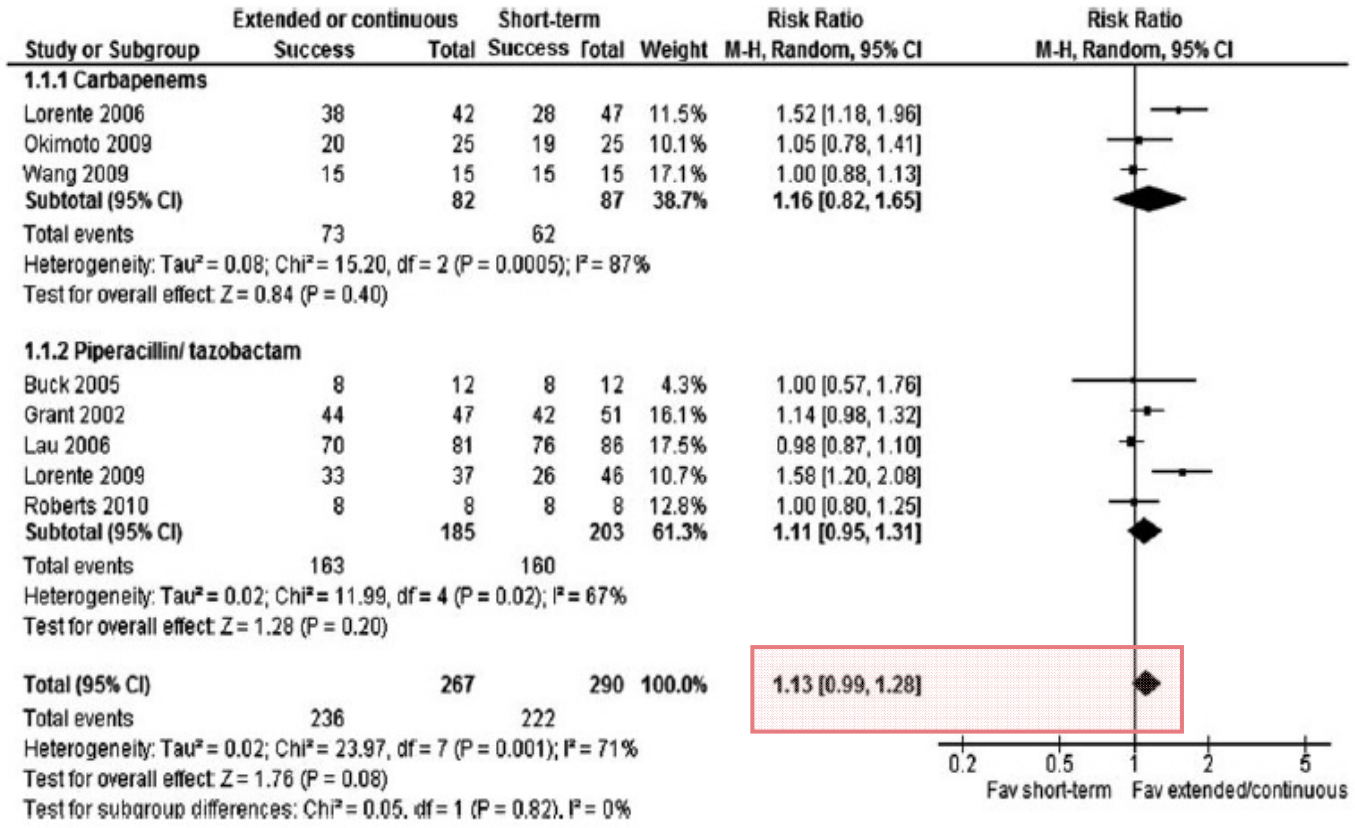


Figure 4. Forest plot depicting the risk ratios of clinical cure of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

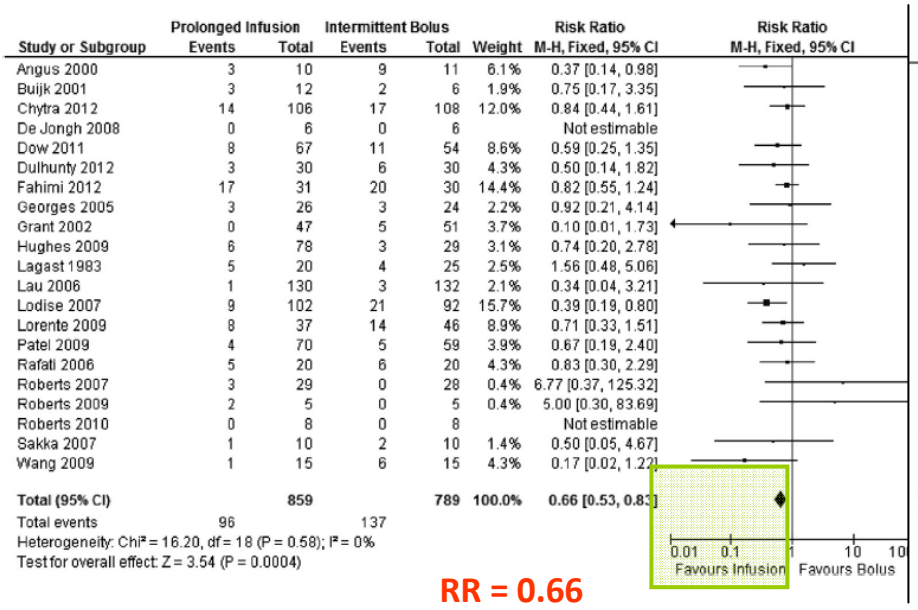
Falagas ME, Tansarli GS, Ikawa K and Vardakas KZ. Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis. *CID 2013:56 (15 January)*

Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis

Jocelyn Teo, Yixin Liew, Winnie Lee, Andrea Lay-Hoon Kwa*

IC+IP vs II	-Cefalosp/ PipeTaz/ Carbapenems	-29 estudios – 2206 pacientes (1620 pacientes para análisis de mortalidad, 1546 para curación clínica) - Críticos o no críticos

Mortality



Study or Subgroup	Prolonged Infusion Events	Total	Intermittent Bolus Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Angus 2000	3	10	9	11	6.1%	0.37 [0.14, 0.98]
Buijk 2001	3	12	2	6	1.9%	0.75 [0.17, 3.35]
Chytra 2012	14	106	17	108	12.0%	0.84 [0.44, 1.61]
De Jongh 2008	0	6	0	6		Not estimable
Dow 2011	8	67	11	54	8.6%	0.59 [0.25, 1.35]
Dulhunty 2012	3	30	6	30	4.3%	0.50 [0.14, 1.82]
Fahimi 2012	17	31	20	30	14.4%	0.82 [0.55, 1.24]
Georges 2005	3	26	3	24	2.2%	0.92 [0.21, 4.14]
Grant 2002	0	47	5	51	3.7%	0.10 [0.01, 1.73]
Hughes 2009	6	78	3	29	3.1%	0.74 [0.20, 2.78]
Lagast 1983	5	20	4	25	2.5%	1.56 [0.48, 5.06]
Lau 2006	1	130	3	132	2.1%	0.34 [0.04, 3.21]
Lodise 2007	9	102	21	92	15.7%	0.39 [0.19, 0.80]
Lorente 2009	8	37	14	46	8.9%	0.71 [0.33, 1.51]
Patel 2009	4	70	5	59	3.9%	0.67 [0.19, 2.40]
Rafati 2006	5	20	6	20	4.3%	0.83 [0.30, 2.29]
Roberts 2007	3	29	0	28	0.4%	6.77 [0.37, 125.32]
Roberts 2009	2	5	0	5	0.4%	5.00 [0.30, 83.69]
Roberts 2010	0	8	0	8		Not estimable
Sakka 2007	1	10	2	10	1.4%	0.50 [0.05, 4.67]
Wang 2009	1	15	6	15	4.3%	0.17 [0.02, 1.22]
Total (95% CI)		**859**		**789**	**100.0%**	**0.66 [0.53, 0.83]**
Total events	96		137			

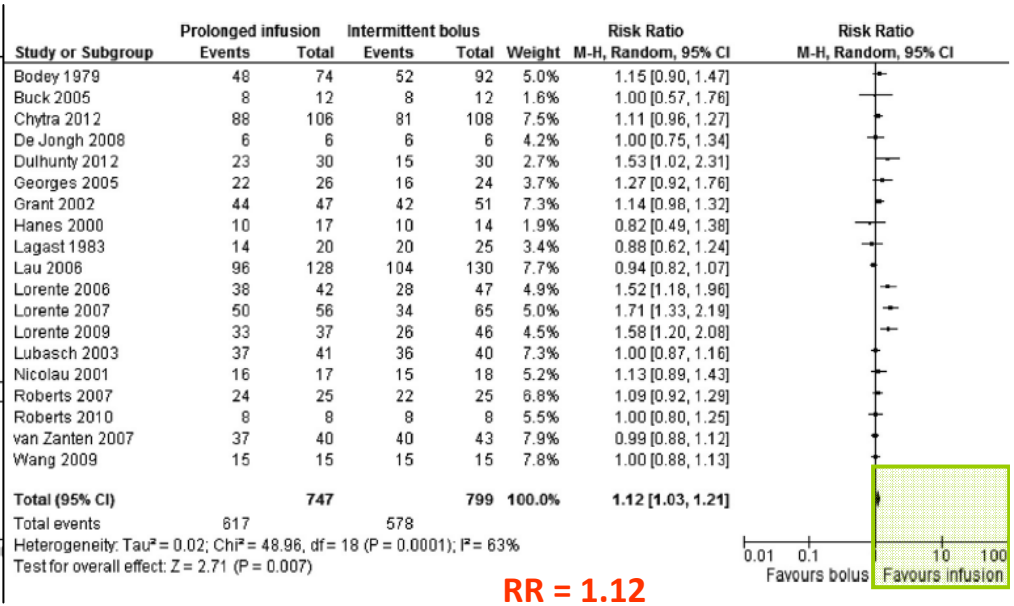
Heterogeneity: Chi² = 16.20, df = 18 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.54 (P = 0.0004)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours Infusion Favours Bolus

RR = 0.66

IC95% 0.53–0.83

Clinical success



Study or Subgroup	Prolonged infusion Events	Total	Intermittent bolus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bodey 1979	48	74	52	92	5.0%	1.15 [0.90, 1.47]
Buck 2005	8	12	8	12	1.6%	1.00 [0.57, 1.76]
Chytra 2012	88	106	81	108	7.5%	1.11 [0.96, 1.27]
De Jongh 2008	6	6	6	6	4.2%	1.00 [0.75, 1.34]
Dulhunty 2012	23	30	15	30	2.7%	1.53 [1.02, 2.31]
Georges 2005	22	26	16	24	3.7%	1.27 [0.92, 1.76]
Grant 2002	44	47	42	51	7.3%	1.14 [0.98, 1.32]
Hanes 2000	10	17	10	14	1.9%	0.82 [0.49, 1.38]
Lagast 1983	14	20	20	25	3.4%	0.88 [0.62, 1.24]
Lau 2006	96	128	104	130	7.7%	0.94 [0.82, 1.07]
Lorente 2006	38	42	28	47	4.9%	1.52 [1.18, 1.96]
Lorente 2007	50	56	34	65	5.0%	1.71 [1.33, 2.19]
Lorente 2009	33	37	26	46	4.5%	1.58 [1.20, 2.08]
Lubasch 2003	37	41	36	40	7.3%	1.00 [0.87, 1.16]
Nicolau 2001	16	17	15	18	5.2%	1.13 [0.89, 1.43]
Roberts 2007	24	25	22	25	6.8%	1.09 [0.92, 1.29]
Roberts 2010	8	8	8	8	5.5%	1.00 [0.80, 1.25]
van Zanten 2007	37	40	40	43	7.9%	0.99 [0.88, 1.12]
Wang 2009	15	15	15	15	7.8%	1.00 [0.88, 1.13]
Total (95% CI)		**747**		**799**	**100.0%**	**1.12 [1.03, 1.21]**
Total events	617		578			

Heterogeneity: Tau² = 0.02; Chi² = 48.96, df = 18 (P = 0.0001); I² = 63%
Test for overall effect: Z = 2.71 (P = 0.007)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours bolus Favours infusion

RR = 1.12

IC95% 1.03–1.21

Teo J, Liew Y, Lee et al. Prolonged infusion versus intermittent boluses of beta -lactam antibiotics for treatment of acute infections: a meta-analysis. *International Journal of Antimicrobial Agents 43 (2014) 403–411*

Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis

Jocelyn Teo, Yixin Liew, Winnie Lee, Andrea Lay-Hoon Kwa*

Subgroup analyses of included studies.

Study subgroup	Mortality				Clinical success			
	No. of studies	No. of patients	Summary risk ratio (95% CI)	I^2 (%)	No. of studies	No. of patients	Summary risk ratio (95% CI)	I^2 (%)
RCTs	10	779	0.83 (0.57–1.21)	0	14	1125	1.05 (0.99–1.12)	0
Non-RCTs	9	841	**0.57 (0.43–0.76)**	0	5	421	**1.34 (1.02–1.76)**	90
Penicillins	8	974	**0.60 (0.45–0.82)**	0	6	491	1.08 (0.94–1.25)	60
Cephalosporins	5	191	0.92 (0.52–1.63)	33	9	662	1.11 (0.98–1.25)	65
Carbapenems	4	274	0.74 (0.42–1.28)	28	3	333	1.16 (0.93–1.46)	83
Equivalent daily dose	10	813	0.82 (0.56–1.20)	0	10	934	**1.22 (1.05–1.43)**	75
APACHE II score ≥15	10	861	**0.63 (0.48–0.81)**	9	8	663	**1.26 (1.06–1.50)**	83
All studies	19	1620	**0.66 (0.53–0.83)**	0	19	1546	**1.12 (1.03–1.21)**	63

CI, confidence interval; RCT, randomised controlled trial; APACHE, Acute Physiology and Chronic Health Evaluation.
Numbers in bold denote statistically significant results.

Mortalidad más baja con IP:
- UCI patients with APACHEII ≥15
- Penicilinas (incluye PiperTazo)

Mejor curación clínica con IP:
- UCI patients with APACHEII ≥15

- Las diferencias en mortalidad y curación clínica se detectaron solo en estudios observacionales, no en ECA.
- En el subanálisis de los estudios que utilizan dosis equivalentes en las dos administraciones no se observó mejora en la mortalidad pero si en curación clínica.

Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: A narrative and systematic review *

Erlangga Yusuf, MD, PhD[a], Herbert Spapen, MD, PhD[b], Denis Piérard, MD, PhD[a]

Solo estudios de **pacientes UCI** en ttm con **PiperTazo**	-2 EC -6 retrospectivos

- Análisis de estudiós PK/PD → beneficio de IP

Estudios PK/PD proporcionan un sólido fundamento para preferir IP vs II de PTZ

- Estudios de beneficio clínico:
  - 2 ECA no mostraron diferencias
    - *Rafati* – mortalidad → Problemas metodológicos ¿?
    - *Lau* – curación clínica y microb
  - De 6 estudios de cohortes retrospectives:
    - 2 no mostraron diferencias en mortalidad (*Fahimi; Gonçalves*)
    - 4 mostraron beneficio clínico con IP:
      - *Lee* – menor mortalidad a los 30 días
      - *Lodise* – menor mortalidad a los 14 días en pacientes con APACHE >17
      - *Lorente* - tasa de curación clínica superior y menor duración de la estancia hospitalaria
      - *Waxler* - menor duración VMI

EVIDENCIA:
Strong/**moderate**/limited/conflicting/no evidence

Evidencia **moderada** de un mejor resultado en los pacientes críticos con IP

Yusuf E, Spapen H, Piérard D. Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: A narrative and systematic review. *J Crit Care. 2014 Aug 7.*

Crit Care Resusc. 2013 Sep;15(3):179-85.

A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study.

Dulhunty JM[1], Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Udy AA, Paul SK, Lipman J; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australasian Society for Infectious Diseases Clinical Research Network.

- **Actualmente en curso** Ensayo multicéntrico, aleatorizado - **Beta-lactam Infusion Group [BLING]**
  - Comparación de IC vs II en pacientes críticos, independiente de la dosis controlada.
  - N=420 pacientes de UCI con sepsis severa
  - En ttm con ticarcilina-ácido clavulánico, piperacilina-tazobactam o meropenem
  - Variable principal: UCIfree a los 28 días
  - Secundarias: supervivencia 90 días, curación clínica 14 días, días sin insuficiencia órganos en el día 14 y la duración de la bacteriemia.

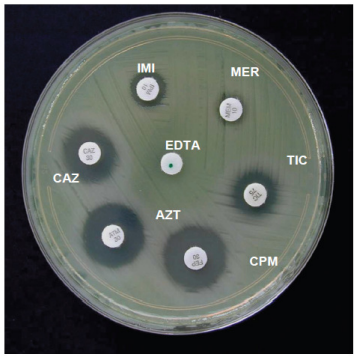
28/05 → Pipertacilina/Tazobactam **4g/6h II 30 min** **+** Metronidazol + Teicoplanina.

Cultivo de BILIS → **Pseudomonas aeruginosa** + **Enterococcus faecium**

ANTIBIOGRAMA (Pseudomonas aeruginosa)
PIPERACIL.LINA
PIPERACIL.LINA-TAZOBACTAM
TICARCIL.LINA
CEFTAZIDIMA
AZTREONAM
CEFEPIME
GENTAMICINA
TOBRAMICINA
AMIKACINA

CMI (Enterococcus faecium)
PENICIL.LINA
AMPICIL.LINA
TEICOPLANINA
VANCOMICINA
LEVOFLOXACINO
CLINDAMICINA
FOSFOMICINA
DAPTOMICINA
SYNERCID

Pseudomonas aeruginosa multirresistente



30/05

- **Ceftazidima en perfusión contínua**
- + Ciprofloxacino a dosis plena (completar 3 dias)
- Mantener **Metronidazol + Teicoplanina**.

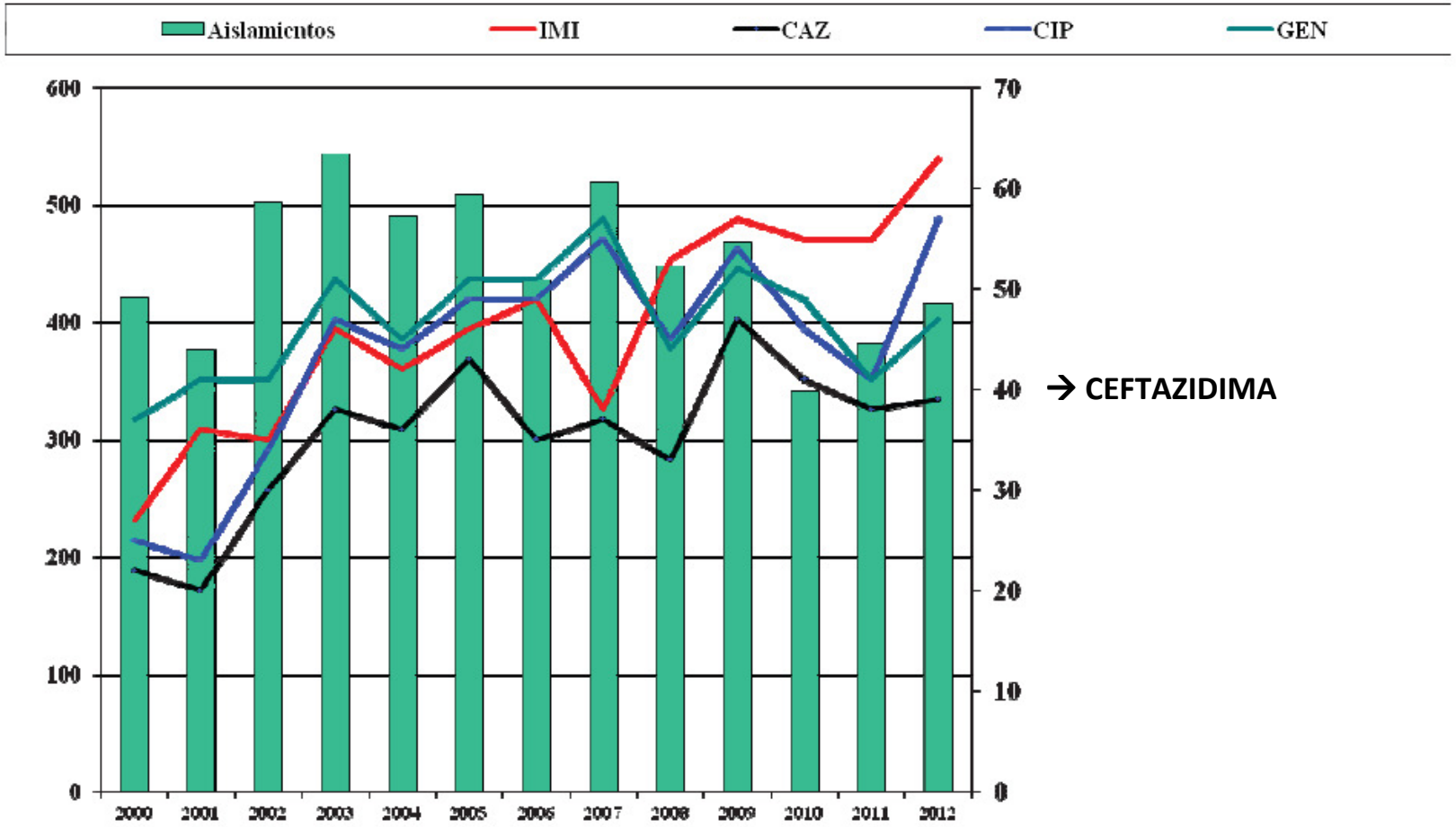
Evolución de los patrones de resistencia

UCI

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
n° Pacients	(140)	(155)	(165)	(166)	(173)	(186)	(149)	(146)	(137)	(135)	(132)	(112)	(167)	(132)
IM MEQUI AG ß-L														
S S S S S	48 %	35 %	39 %	35 %	34%	24%	23%	23%	20%	15%	23%	31%	34%	27%
S S S S I/R	8 %	10 %	6 %	8 %	7%	9%	7%	4%	5%	6%	5%	2%	7%	4%
S S S R S/I/R	15 %	14 %	12 %	9 %	8%	8%	7%	6%	7%	4%	5%	1%	4%	2%
S S R S S/I/R	4%	6%	3%	5%	5%	9%	6%	4%	3%	10%	8%	2%	3%	4%
S S R R S/I/R	1 %	5 %	4 %	9 %	5%	9%	9%	11%	15%	9%	4%	7%	2%	2%
R S S S S	2 %	6 %	7 %	6 %	5%	3%	5%	3%	3%	2%	1%	4%	4%	3%
R R R R I/R	5 %	12 %	11 %	13 %	23%	29%	32%	28%	30%	30%	39%	36%	26%	43%
R Otros patrones	17%	12%	18%	15%	14%	9%	11%	21%	17%	39%	15%	16%	20%	15%

Cedido por Dra. Fe Tubau

P. aeruginosa: Resistencia antibiotica en UCI HUB, 2000-2012



→ **CEFTAZIDIMA**

Cedido por Dra. Fe Tubau

Pregunta 4

¿Dosificación de CEFTAZIDIMA en perfusión continua?

- 4g / 24h — 30%
- Dosis carga 2g + 6g / 24h — 60%
- Según función renal y hepática — 10%

PD target CEFTAZIDIMA

- Modelo PK in vitro: simula concentraciones de fármaco en suero

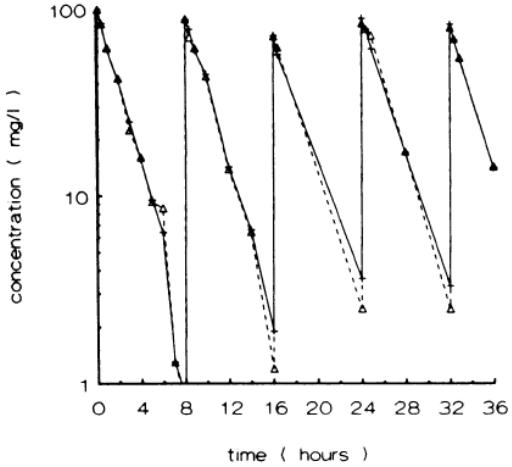


FIG. 2. Typical example of concentration-time curves of ceftazidime during intermittent bolus injection at every eighth hour (300 mg/liter/24 h). Crosses, central compartment; triangles, peripheral compartment.

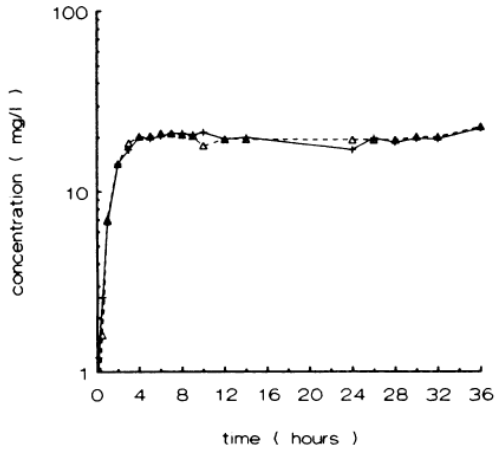


FIG. 3. Typical example of concentration-time curves of ceftazidime during continuous infusion (300 mg/liter/24 h). Crosses, central compartment; triangles, peripheral compartment.

- Cp sostenidas alrededor o ligeramente > MIC no son suficientes para mantener la eficacia

- Para alcanzar **Cp > 4 x MIC** → la administración **IC es más eficaz que II**

Mouton JW, den Hollander JG. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. *AAC 1994 May;38(5):931-6.*

CEFTA: Pacientes alcanzan target PD y tiempo > MIC

Antibiotics	PD targets	Percentage of patients achieving targets	References
Ceftazidime, 2 g	70% T > 4 × EUCAST breakpoint of PA	28%	Taccone *et al.*, 2010 [23]
Ceftazidime 1 g every 4 hours	100% T > 4 × MIC (isolated pathogens; if negative cultures 100% T > 16 mg/L)	Ceftazidime 47.8% PTA with 1 g every 3 hours 88.2%	Conil *et al.*, 2007 [54]
Ceftazidime 2 g tid	100% T > 5 × MIC MIC = 8 mg/L (PA break point)	10% PTA for CI (6 g/day) 60%	Young *et al.*, 1997 [65]
Ceftazidime 2 g tid or 6 g/day CI	100% T > 5 × MIC MIC = 8 mg/L (PA break point)	Bolus 20% CI 100%	Lipman *et al.*, 1999 [68]
Ceftazidime 1.5 g tid or 4.5 g/day CI	T > 4 × MIC plasma and peritoneum (isolated pathogens)	Plasma: bolus dosing 100%, CI 100% Peritoneum: bolus 88%, CI 100%	Buijk *et al.*, 2002 [74]
Ceftazidime 2 to 6 g/day CI	100% T > 5 × MIC MIC = 8 mg/L (PA break point) Target concentration 40 ± 10 mg/L	35.9%	Aubert *et al.*, 2010 [72]
		Percentage of time on target (mean)	
Ceftazidime 2 g tid or 3 g/day CI	T > MIC MIC = 4 mg/L (MIC of one isolated PA)	Bolus T = 92%; CI T = 100%	Benko *et al.*, 1996 [67]
Ceftazidime 2 g tid or 60 mg/kg/day CI	T > MIC (isolated pathogens)	Bolus T = 92.9%; CI T = 100%	Hanes *et al.*, 2000 [70]

Gonçalves-Pereira J. and Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of b-lactams. ***Critical Care 2011, 15:R206***

PopPK Ceftazidima pacientes UCI

- N=72 pacier
- 443 muestra
- 3 grupos pos
  - 2g/8h II 3(
  - 6 g IC
  - D* 2g + 6g IC

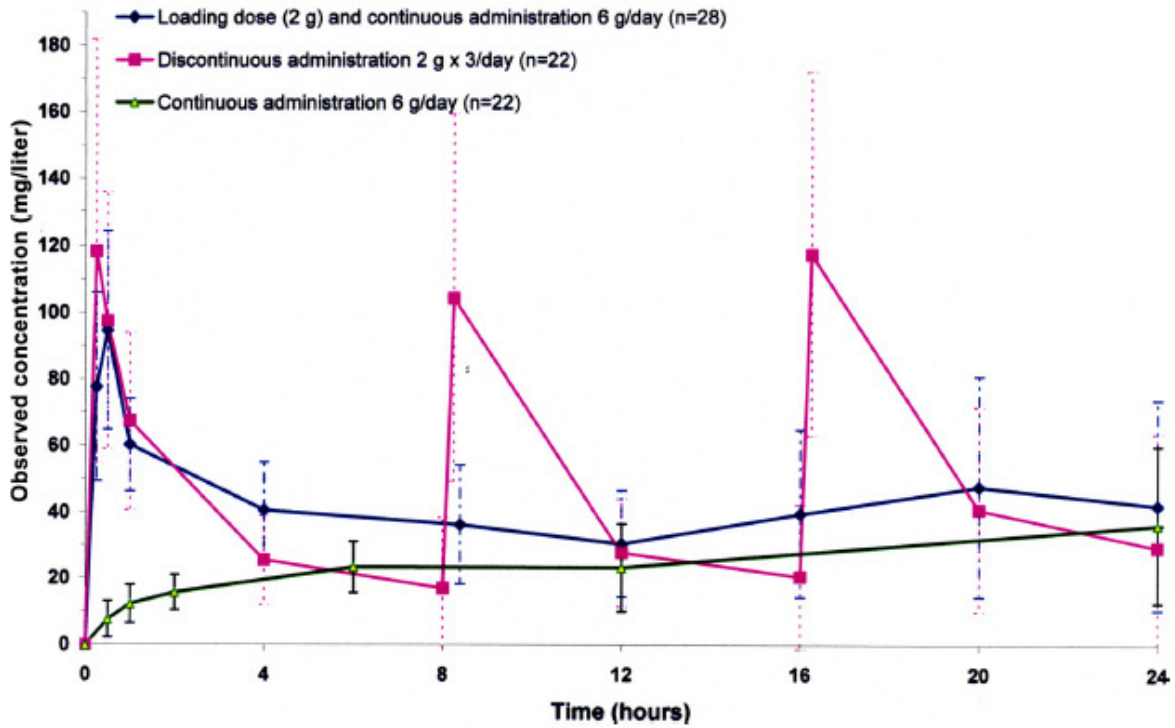


FIG. 1. Mean (±SD) ceftazidime concentrations (mg/liter) versus time in 72 ICU patients.

Georges B, Conil JM, et al. Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission. *AAC, Oct. 2009, p. 4483–4489*

PopPK Ceftazidima pacientes UCI

Covariables:

- ✓**Tasa de filtrado glomerular**
- ✓**Ventilación mecánica**
- ✓**Motivo de ingreso UCI**

TV**CL**=THETA(1)+THETA(2)***MDRD**
CL=TVCL*EXP(ETA(1))

V1=TVV1*EXP(ETA(2))
Ventilación mecánica NO → TVV1=THETA(3)
SI → TVV1=THETA(4)

TV**Q**=THETA(5)

V2=TVV2*EXP(ETA(4))
Paciente politrauma → TVV2=THETA(6)
Paciente postIQ → TVV2=THETA(7)
Paciente médico → TVV2=THETA(8)

TABLE 2. Objective function, pharmacokinetic parameter thetas, interindividual variability omegas, and intraindividual variability sigma (CV%) in the basic, intermediate and total model[a]

Parameter	Value		
	Basic model (n = 49)	Intermediate model (n = 49)	Final model (n = 72)
Objective function	1,818	1,730	2,588
Theta 1 (liters/h)	4.62 (10%)	2.20 (21%)	2.24 (27%)
Theta 2		0.023 (18%)	0.024 (23%)
Theta 3 (liters)	10.70 (13%)	22.30 (15%)	18.90 (10%)
Theta 4 (liters)		9.24 (13%)	9.02 (9%)
Theta 5 (liters/h)	12.80 (14%)	14.20 (13%)	15.20 (13%)
Theta 6 (liters)	44.90 (22%)	77.40 (14%)	57.10 (12%)
Theta 7 (liters)		27.50 (17%)	25.70 (18%)
Theta 8 (liters)		15.50 (20%)	13.60 (26%)
Interindividual variability			
Omega CL	0.23 (30%)	0.08 (28%)	0.09 (24%)
Omega V1	0.22 (95%)	0.19 (74%)	0.12 (86%)
Omega Q	0.56 (80%)	0.51 (68%)	0.50 (38%)
Omega V2	0.84 (47%)	0.17 (133%)	0.11 (116%)
Intraindividual variability			
Sigma	0.05 (18%)	0.05 (12%)	0.05 (13%)
PEs			
Mean PE	−0.5%	0.04%	−2%
Mean APE	39%	32%	30%
Median PE	−11%	−4%	−6%
Median APE	31%	27%	26%
AFE	1.15	1.09	1.11

[a] See the text for the equation describing the total model.

Georges B, Conil JM, et al. Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission. *AAC, Oct. 2009, p. 4483–4489*

D* 2g + 6g PC **2g/8h**

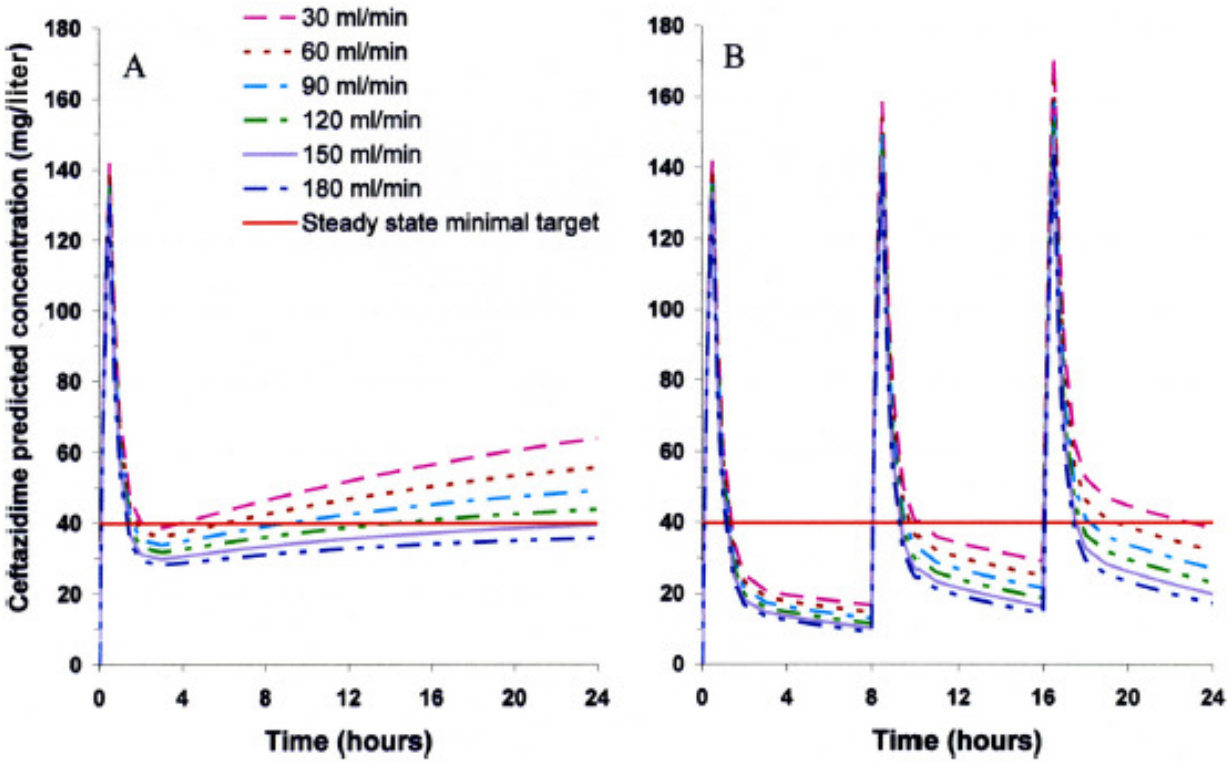


FIG. 3. Simulated concentrations of ceftazidime for polytrauma patients with mechanical ventilation as a function of creatinine clearance as estimated by MDRD and ranging from 30 to 180 ml/min after a 2-g loading dose followed by a 6-g/day continuous infusion (A) or discontinuous administration of 2 g every 8 h (B). The solid red lines correspond to the steady-state target concentration calculated as five times the new European breakpoint of 8 mg/liter.

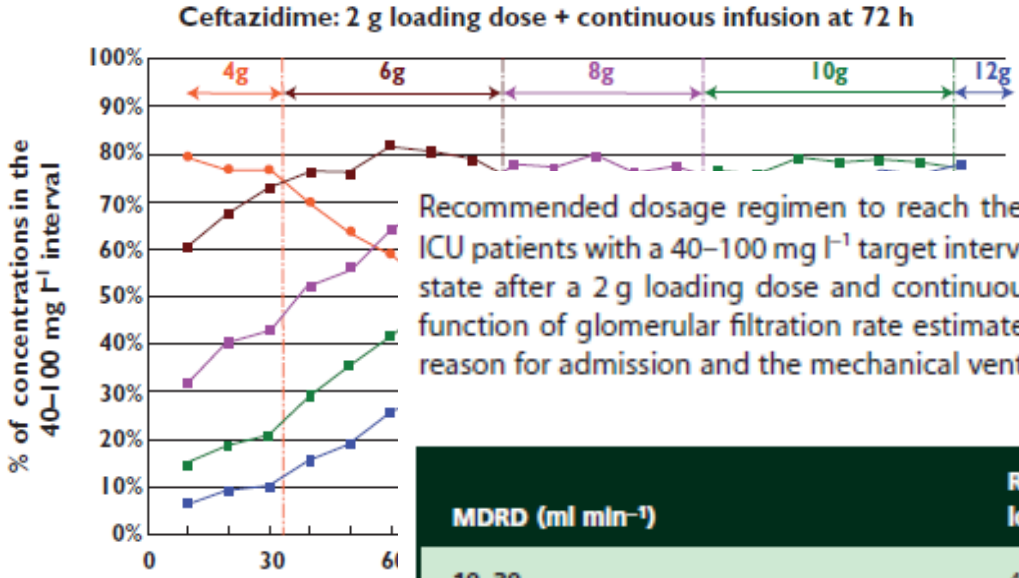
Target PD = 40mg/L → fT>5xMIC (=8)

Simulación POLITRAUMA + VMI

- No se alcanza el 100% fT>5xMIC con la administración discontinua.
- **100% fT>5MIC SI se alcanza con una dosis de 6 g/día** → sólo para pacientes MDRD <150 ml/min

Georges B, Conil JM, et al. Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission. *AAC, Oct. 2009, p. 4483–4489*

Simulaciones MonteCarlo Ceftazidima



Recommended dosage regimen to reach the maximum percentage of ICU patients with a 40–100 mg l^{-1} target interval concentration at steady-state after a 2 g loading dose and continuous infusion expressed as a function of glomerular filtration rate estimated by MDRD whatever the reason for admission and the mechanical ventilation status

MDRD (ml min^{-1})	Recommended dosage: 2 g loading dose followed by
10–30	4 g day^{-1}
40–80	6 g day^{-1}
90–110	8 g day^{-1}
120–190	10 g day^{-1}
≥200	12 g day^{-1}

Figure 2

Percentage of simulated patients with 72 h ceftazidime concentr
continuous infusion doses as a function of glomerular filtration ra
ventilation status. The coloured arrows present the recommended

Optimización Ceftazidima

- Dosis de carga: 2g + IC según función renal: 4-6g/24h

Georges B, Conil JM, et al. Ceftazidime dosage regimen in intensive care unit patients: from a population pharmacokinetic approach to clinical practice via Monte Carlo simulations. Br J Clin Pharmacol / 73:4 / 588–596

30/05

- Inicio **CEFTAZIDIMA IC → D*2g + 6g IC**

Estabilidad de la dilución:
- Reconst 2 g en 10 ml API.
- Diluir en SSF hasta conc de 10 o 20 mg/ml.
- Estable 24 h PROTEGIDO DE LA LUZ

28/05: Cultivo de BILIS → crecimiento de **Pseudomonas aeruginosa** + **Enterococcus faecium**

ANTIBIOGRAMA (Pseudomonas aeruginosa)		
PIPERACIL.LINA	S	
PIPERACIL.LINA-TAZOBACTAM	S	
TICARCIL.LINA	S	
CEFTAZIDIMA	S	**MIC=4**
AZTREONAM	S	
CEFEPIME	S	
GENTAMICINA	S	
TOBRAMICINA	S	
AMIKACINA	S	

- 01/06: Se mantiene perfusión de **CEFTAZIDIMA 6g IC**
- **02/06: Hemocultivos negativos**
- 03/06: BQ -> muestra

Concentraciones plasmáticas CEFTA

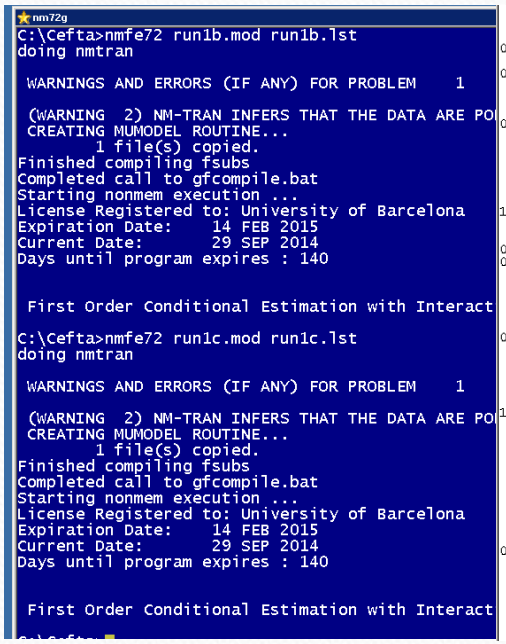
03/06/2014 → Extracción de niveles plasmáticos de Ceftazidima

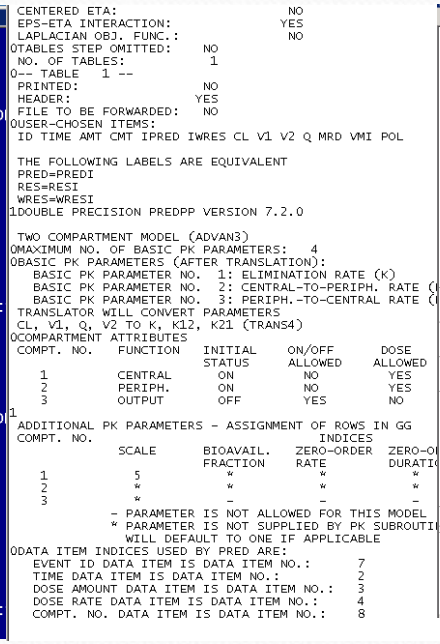
- Cr 46 µmol/L i GFR (MDRD)=162

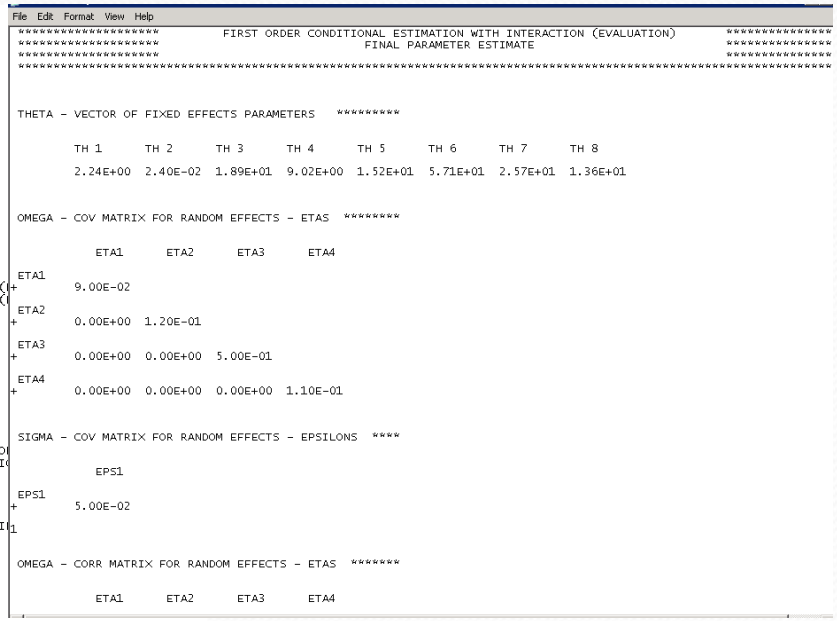
Cp Ceftazidima	**43,1 mg/L**

PAS: S≤8

fT> 4-5 x MIC = 32-40 mg/L







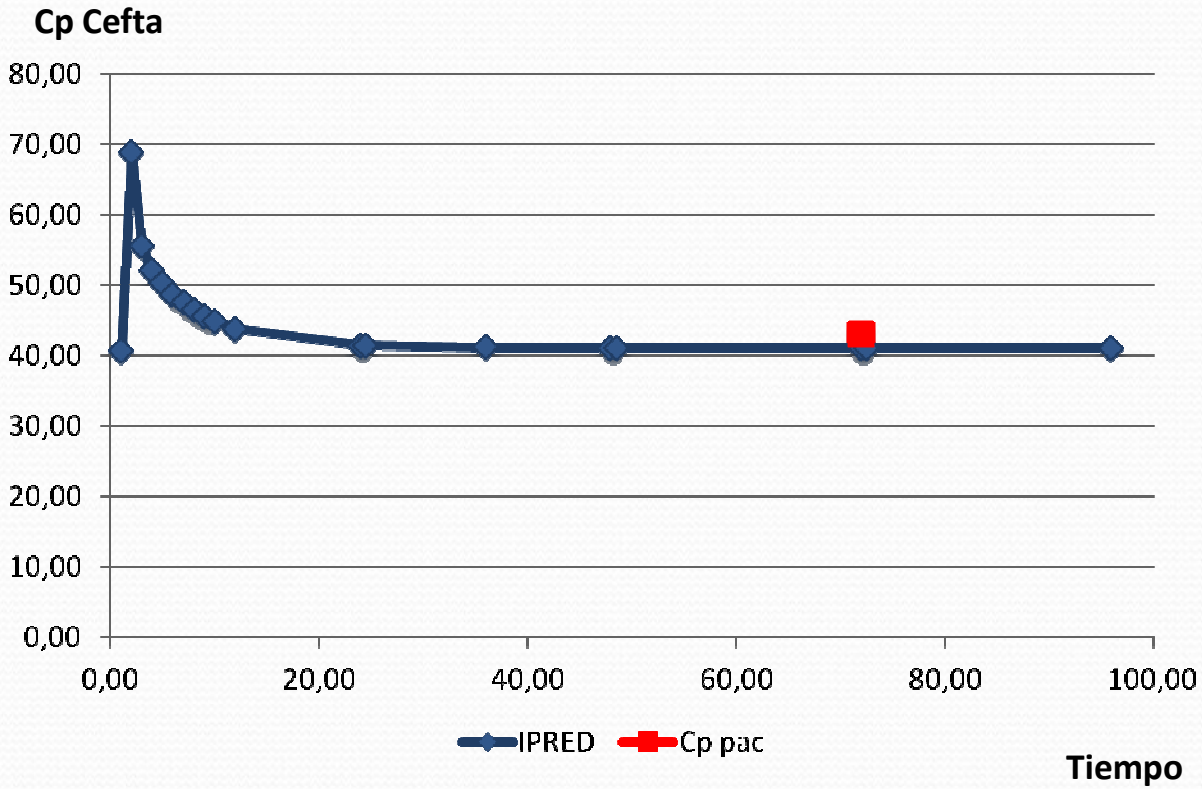
Cedido por Dra. Helena Colom

Predicción bayesiana

- Parámetros PK paciente

CL	V1	V2	Q
6.08	18.90	13.60	15.20

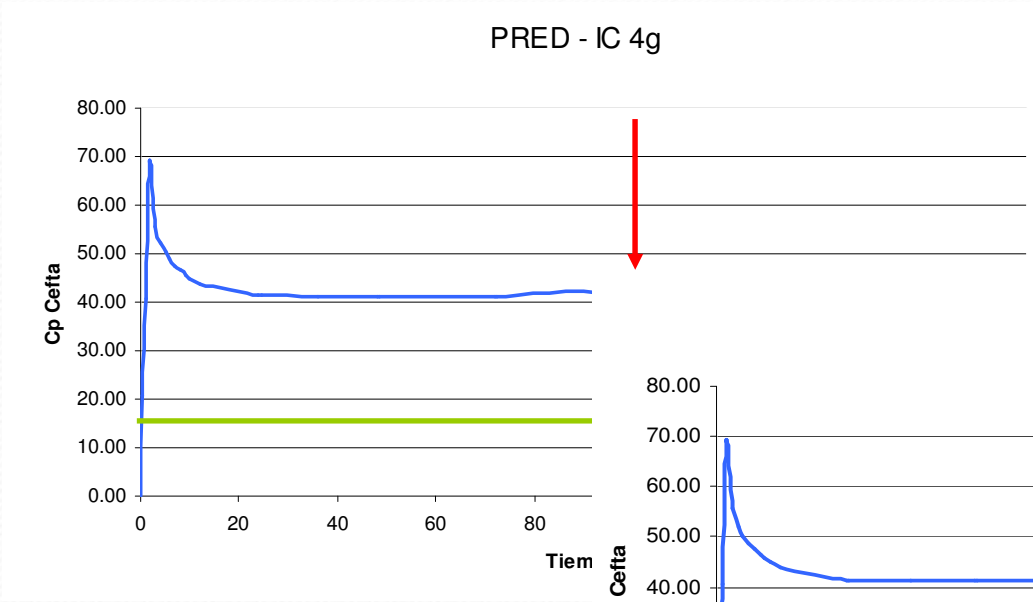
TIME	AMT	IPRED	DV	PRED
0.00	2.00	0.00	0.00	0.00
0.50	6.00	20.89	0.00	20.89
1.00	0.00	40.62	0.00	40.62
2.00	0.00	68.90	0.00	68.90
3.00	0.00	55.55	0.00	55.55
4.00	0.00	52.13	0.00	52.12
5.00	0.00	50.23	0.00	50.22
6.00	0.00	48.76	0.00	48.75
7.00	0.00	47.54	0.00	47.53
8.00	0.00	46.52	0.00	46.51
9.00	0.00	45.66	0.00	45.65
10.00	0.00	44.94	0.00	44.93
12.00	0.00	43.82	0.00	43.81
24.00	0.00	41.47	0.00	41.45
24.50	6.00	41.44	0.00	41.43
36.00	0.00	41.17	0.00	41.16
48.00	0.00	41.14	0.00	41.12
48.50	6.00	41.14	0.00	41.12
72.00	0.00	41.13	43.10	41.12
72.50	6.00	41.13	0.00	41.12
96.00	0.00	41.13	0.00	41.12

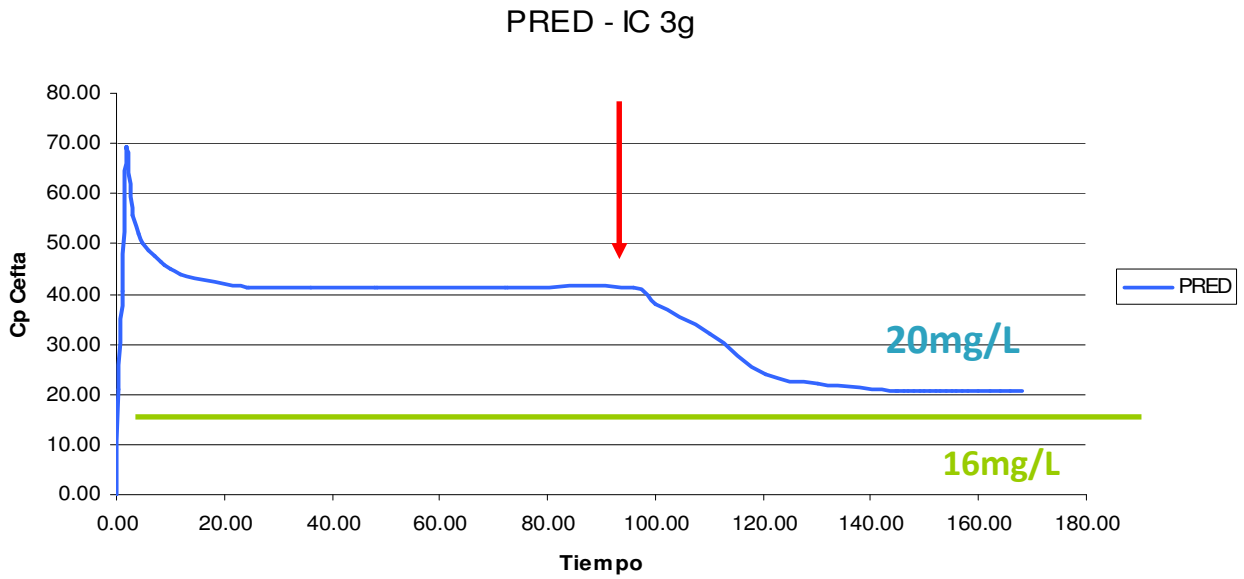


Estimación de la dosis

MIC=4

fT> 4-5x MIC = 16-20 mg/L





Target PD
100% ft>MIC
100% ft>4xMIC

IE o IC
mejor perfil PK/PD
que II

Beneficios clínicos
con IE/IC
(evidencia moderada)
+ Críticos y Piper/Tazo

Importancia
de individualizar
en paciente crítico

Determinación Cp
¿TDM?
¿Dosis inferiores?