AMPLIANDO HORIZONTES
BROADENING HORIZONS
del 4 al 7 de octubre 2016
4-7 October 2016
Gijón

Gram-: Perfusión extendida de ß-lactámicos

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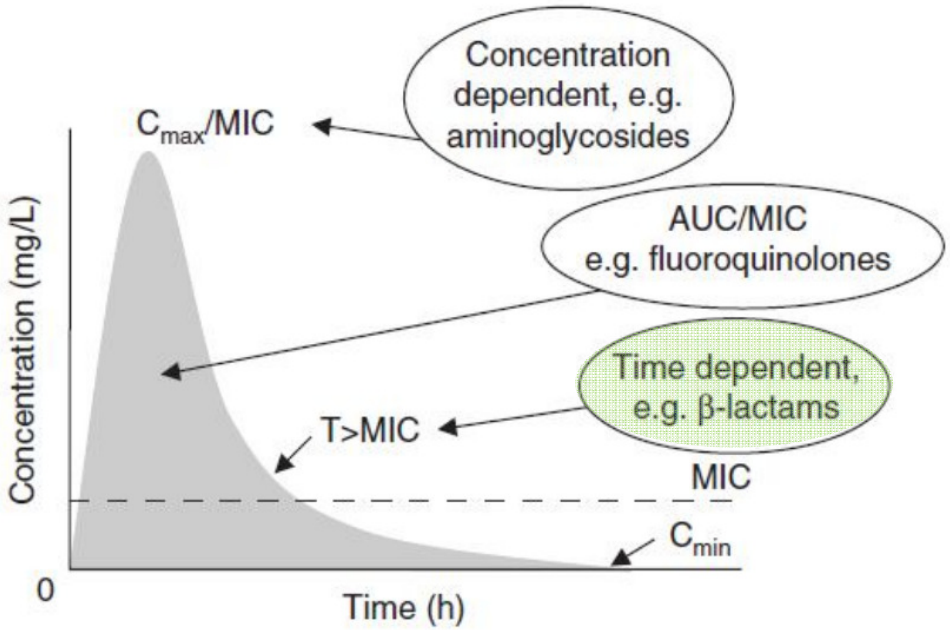
Características AB beta-lactámicos

- Semividas plasmáticas cortas
  - (escasas excepciones) por lo que se administran en dosis múltiples
- Mínimo efecto post-antibiótico
- Actividad bactericida tiempo dependiente
- Índice PK/PD que más se correlaciona con su eficacia es el **T>CMI**



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

Cambios en parámetros farmacocinéticos

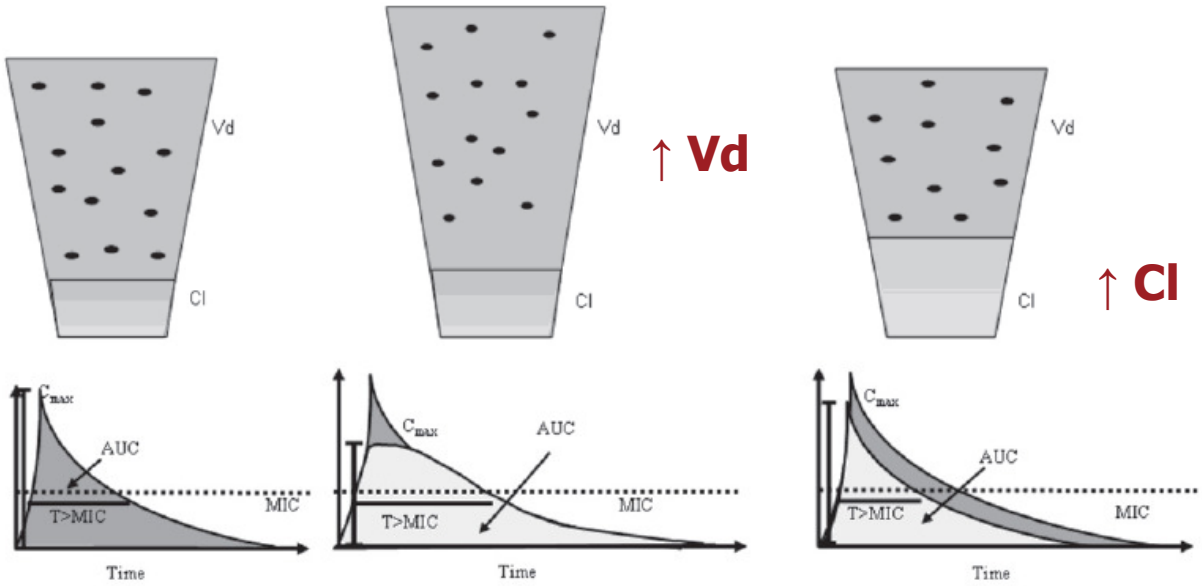
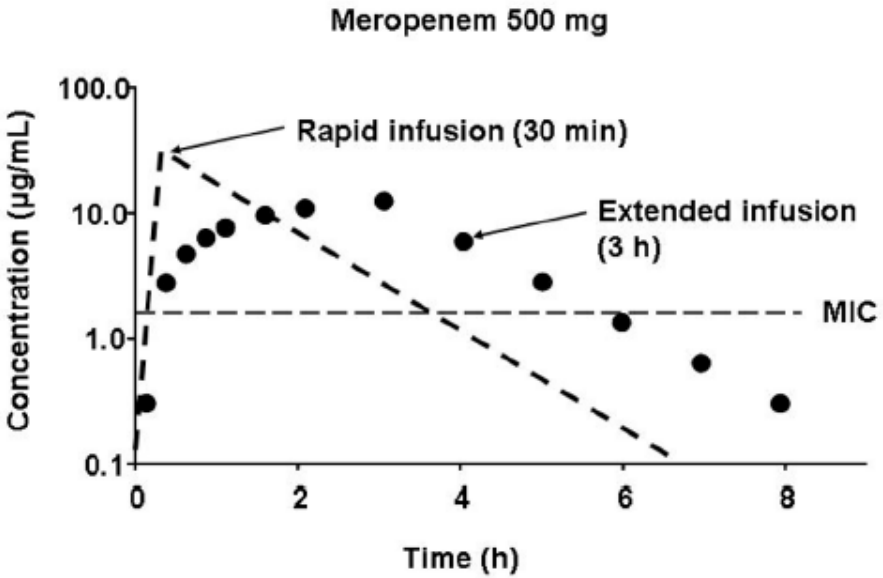


Figure 1 ICU patients present pharmacokinetic changes of antibiotics that may alter bacterial exposure. Concentration-time curve of antibiotics in healthy volunteers (left panel). A large volume of distribution (V_d) (middle panel) is often present in ICU patients, leading to decreased maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$) and eventually higher time that the antibiotic concentration is above the bacteria minimum inhibitory concentration (T > MIC). The antibiotic area under the concentration time curve (AUC) remains virtually the same. An increase in drug clearance (Cl) (right) is associated with decreases in AUC, $T_{1/2}$ and T > MIC. Straight dotted lines-bacteria minimum inhibitory concentration.

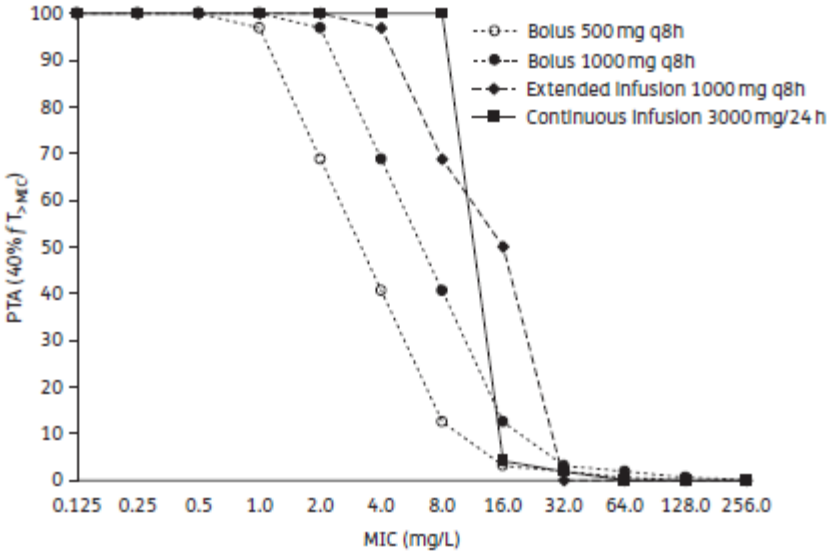
Gonçalves-Pereira J and Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. ***Critical Care 2011, 15:R206***

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.*

Pharmacodynamic Profiling of Piperacillin in the Presence of Tazobactam in Patients through the Use of Population Pharmacokinetic Models and Monte Carlo Simulation

Thomas P. Lodise Jr., Ben Lo
Larry H. Danziger and George

2004

Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients

2006

Mohammad Reza Rafati [a], Mohammad Reza Rouini [b,*], Mojtaba Mojtahedzadeh [c], Atabak Najafi [d], Has

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

2007

Thomas P. Lodise, Jr.,[1,2] Ben Lomaestro,[3] and George L. Drusano[2]

Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock

2010

Fabio Silvio Taccone[1], Pierre-François Laterre[2], Thierry Dugernier[3], Herbert Spapen[4], Isabelle Delattre[5], Vincent[1] and Frédérique Jacobs*[6]

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Joel M. Dulhunty,[1] Jason A. Roberts,[1] Joshua S. Davis,[2] Steven A. R. Webb,[3] Charudatt Shirwadkar,[6] Glenn M. Eastwood,[4] John Myburgh,[7] David L. Paters

Impact of Bolus Dosing versus Continuous Infusion of Piperacillin and Tazobactam on the Development of Antimicrobial Resistance in Pseudomonas aeruginosa

2013

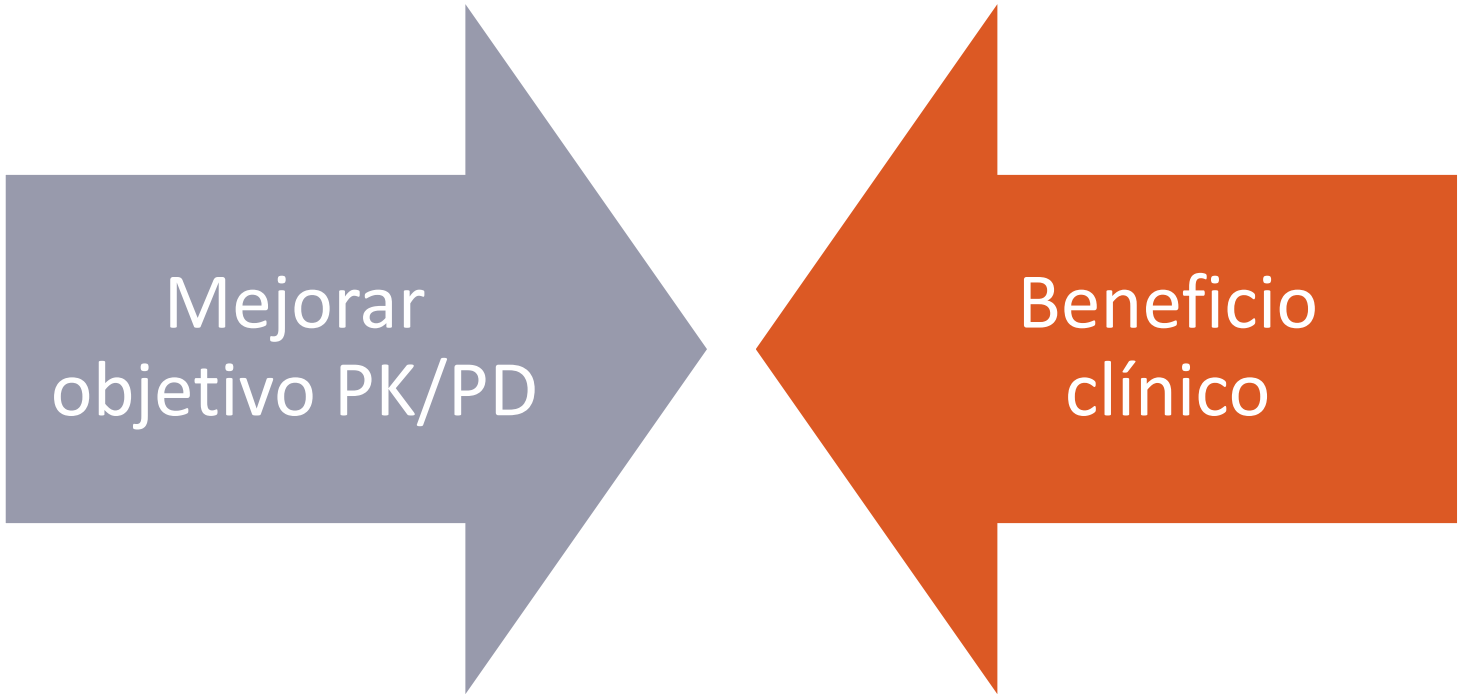
T. W. Felton, J. Goodwin, L. O'Connor, A. Sharp, L. rd, M. N. Neely and W. W.

Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients

De Waele

2014

Estudios sobre perfusiones extendidas de ABL



Piperacilina/Tazobactam: **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**
  - Simulacions 2000 pacients
  - IC permite mayor probabilidad de alcanzar objetivo 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.

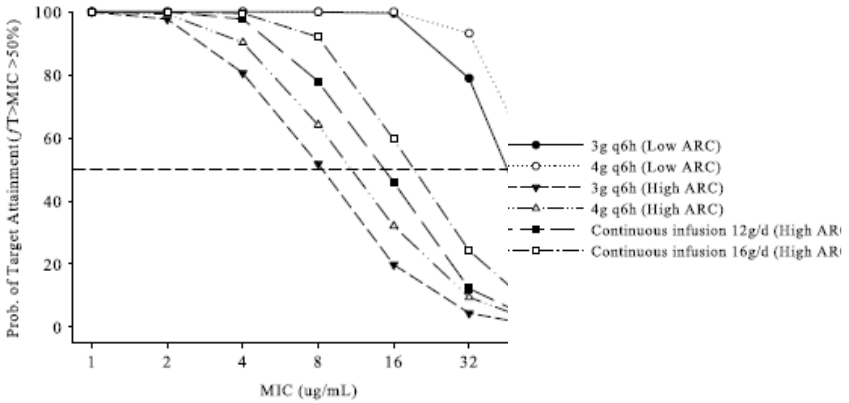
Roberts JA et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *International Journal of Antimicrobial Agents 35 (2010) 156–163*

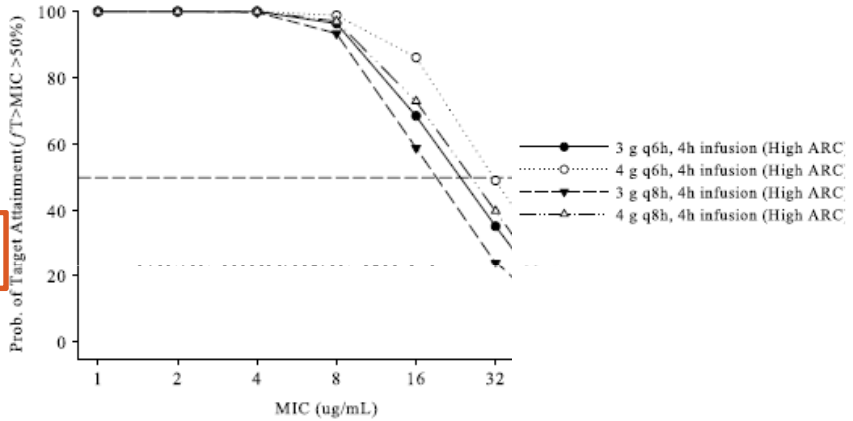
Piper/Tazo IE o IC

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

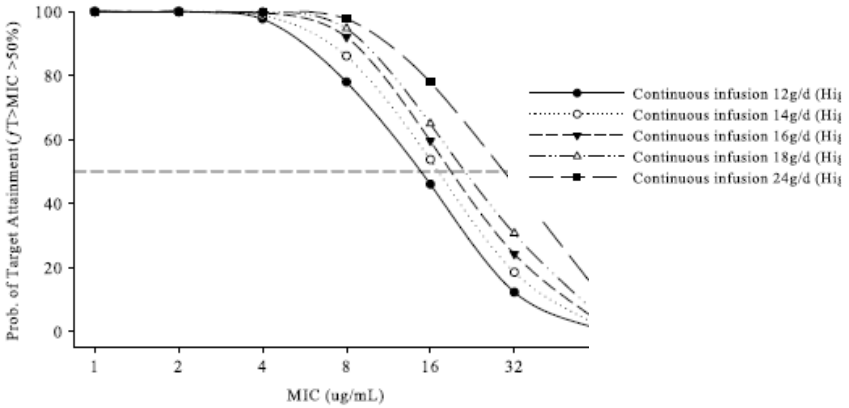
	Free Piperacillin		
	ARC Score ≤ 6 (n = 5)	ARC Score ≥ 7 (n = 8)	*p*
Volume of distribution, L/kg	0.37 (0.29–0.52)	1.23 (0.77–2.23)	0.008
Clearance, mL/kg/min	2.5 (1.7–4.5)	12.3 (5.3–17.5)	0.003
AUC, h·µg/mL	233.9 (176.9–453.0)	76.4 (50.3–101.7)	0.003
Peak, µg/mL	80.8 (65.0–157.9)	35.0 (29.2–54.7)	0.003
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 usode **IP permitiría superar el rápido Cl de fármaco**
- Se requieren de 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*

Penetración pulmonar Meropenem

- N=55 pacientes UCI con Meropenem 1 g/8h por neumonía intrahospitalaria grave:
  - N=30 assignats a II de 0,5 h i N=25 a IE de 3 h.
  - Determinación de Cp y de líquido de revestimiento epitelial (ELF)
- Se obtuvo **mejor penetración pulmonar con la IE que con II**.

- Patógenos susceptibles MIC=2 mg/L éxito con 1 g/8h II para alcanzar 40-100% fT>MIC
- Necesarias dosis mayores para alcanzar objetivo PK/PD para patógenos con sensibilidad intermedia (CIM=8mg/L) o para targets más elevados (40%, 54% i 100% fT>MIC).

- Utilizar empíricamente dosi **2g IE 3 h c/8 h** para **tto de neumonía nosocomial grave**

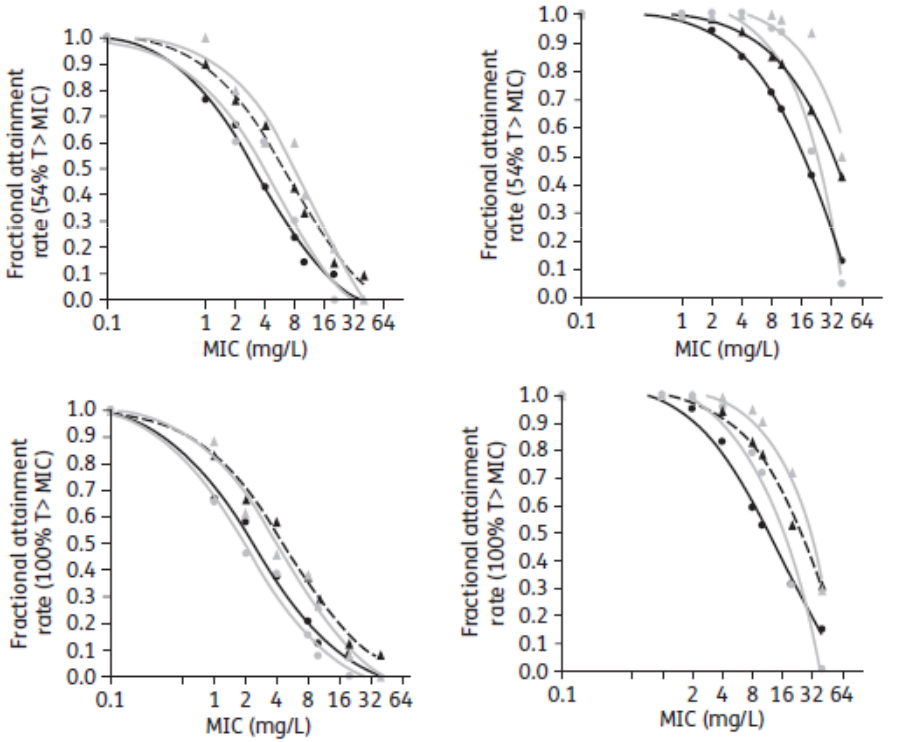


Figure 3. Target attainment rates in ELF (left) and plasma (right) after different dosing regimens: continuous black line with black circles: 1 g, 0.5 h infusion; continuous light grey line with light grey circles: 1 g, 3 h infusion; broken black line with black triangles, 2 g, 0.5 h infusion; and continuous grey line with grey triangles, 2 g, 3 h infusion.

Frippiat F, Musuamba FT, Seidel L, et al. Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study. J Antimicrob Chemother. 2015 Jan;70(1):207-16.

Paciente crítico
+/- aclaramiento renal aumentado

Microorganismos MICs elevadas

Concentraciones en el lugar de la infx

Mejora de la curación clínica y menor mortalidad

¿?

Revisiones/metanálisis

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

A Systematic Review of Pharmacokinetic and Pharmacodynamic Parameters

Sofia K. Kasiakou,[1,2] Kenneth R. Lawrence,[3] Nicolaos Choulis[4] and Matthew E. Falagas[1,5,6]

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. Ho, FJFICM, PhD; Jeffrey Lipman, FJFICM, MD

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*], Nirupama Putcha[2], Yong D Suh[3], Kyle J Van Arendonk[4] and Michael L Rinke[5]

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

Greg T Mah, Vincent H Mabasa, Ivy Chow, and Mary HH Enson

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

Shiu JR, Wang E, Tejani AM, Wasdell M

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]

EXPERT REVIEWS

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

Expert Rev. Anti Infect. Ther. 11(6), 585–595 (2013)

Ioanna P Korbila[1,2],

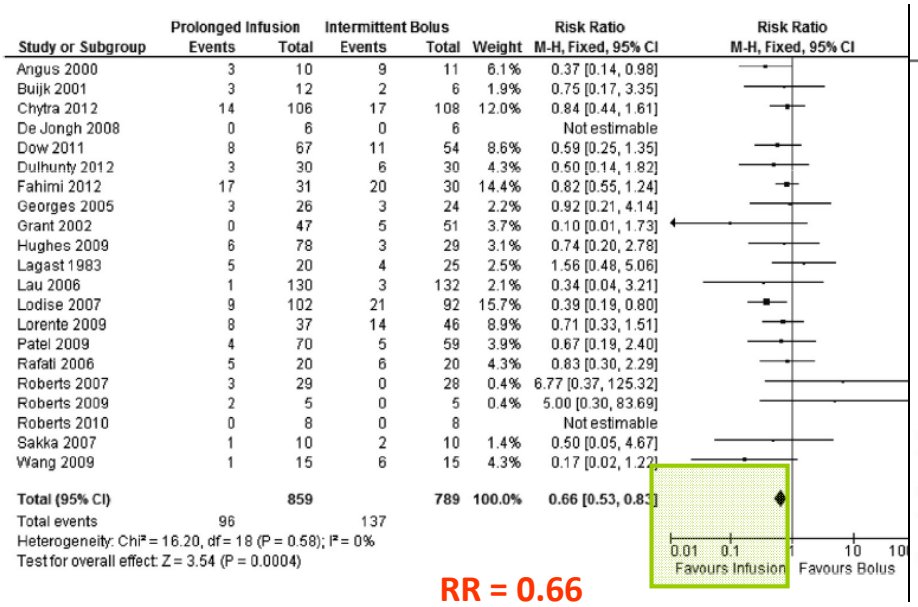
The authors sought to study whether extended or continuous infusion of cephalosporins is

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)

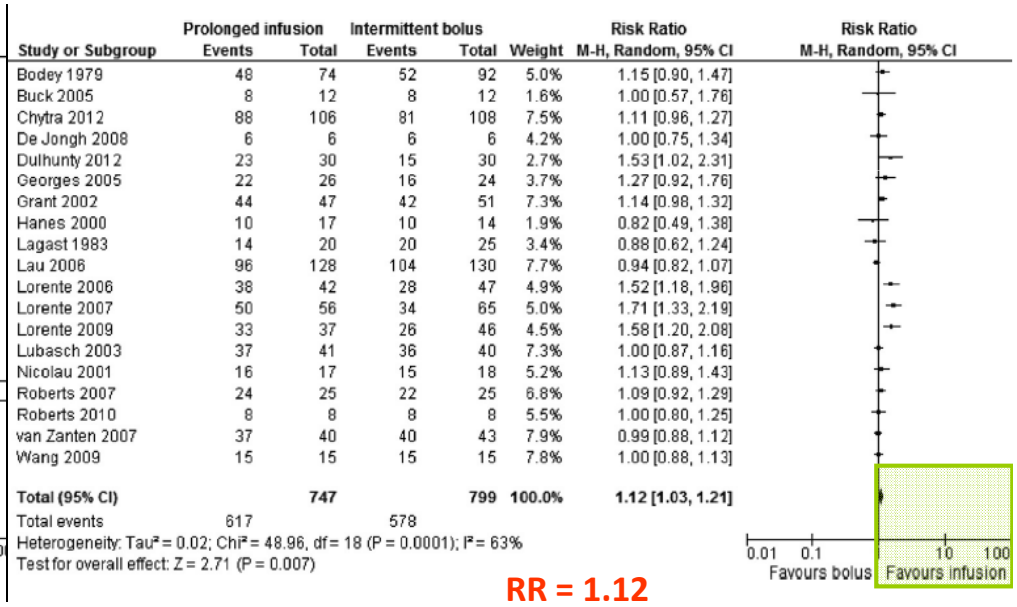
Risk Ratio M-H, Fixed, 95% CI

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.

A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

BLING II Investigators

Joel M. Dulhunty[1,2], Jason A. Roberts[1,2,3], Joshua S. Davis[4,5], Steven A. R. Webb[6,7], Rinaldo Bellomo[8,9], Charles Gomersall[10,11], Charudatt Shirwadkar[12], Glenn M. Eastwood[8], John Myburgh[13,14], David L. Paterson[15,16], Therese Starr[1,2], Sanjoy K. Paul[17], and Jeffrey Lipman[1,2]; for the BLING II Investigators for the ANZICS Clinical Trials Group*

- Ensayo multicentrico, aleatorizado, en **<u>432 pacientes críticos con sepsis severa</u>**
- <u>Comparación de IC vs II</u> de AB:
  - Ticarcilina-àcid clavulànic, Piperacilina-tazobactam o Meropenem

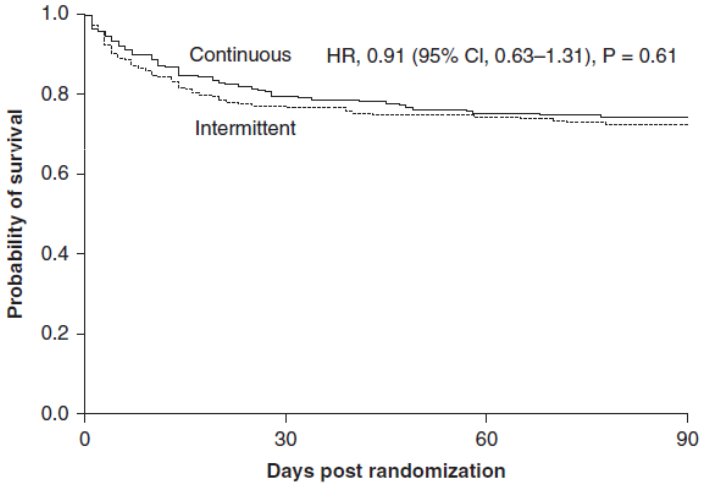


Figure 2. Kaplan-Meier plot for intention-to-treat population. CI = confidence interval; HR = hazard ratio.

Table 3. Primary and Secondary Outcomes, Clinical Results, and Adverse Events

	Continuous (*n* = 212)	Intermittent (*n* = 220)	*P* Value
Alive ICU-free days	18 (2–24)	20 (3–24)	0.38
ICU survivors	21 (12–24)	22 (14–25)	0.12
Day-90 survival*†	156 (74.3)	158 (72.5)	0.67
ICU survival†	180 (84.9)	182 (82.7)	0.54
Hospital survival†‡	168 (79.2)	164 (74.9)	0.28
Clinical cure	111 (52.4)	109 (49.5)	0.56
Organ failure–free days	6 (0–10)	6 (0–11)	0.27
Duration of bacteremia, d§	0 (0–0)	0 (0–1)	0.24
ICU length of stay, d‖	7 (3–13)	6 (3–11)	0.042
Hospital length of stay, d‖	16 (8–32)	14 (8–27)	0.25
Adverse events	20 (9.4)	28 (12.7)	0.28
Serious adverse events	19 (9.0)	25 (11.4)	0.41

- **NO diferencias en curación clínica** (14 días) después suspensión de AB
  - OR=1,12; IC95%: 0,77 -1,63; p=0,56.
- **NO diferencia en supervivencia** a 90 días entre IC e II
  - HR=0,91; IC95% 0,63 a 1,31; p=0,61

Study drug

¿Diferencias?

Meropenem

Piperacillin-tazobactam

Ticarcillin-clavulanate

Dulhunty et al, 2015

Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

Intensive Care Med
DOI 10.1007/s00134-015-4188-0

- **N=140 pacientes** (n=70 IC vs n=70 II) con cefepime, meropenem o piper/tazo
- Las tasas de logro objetivo PK 100%fT >MIC fueron mayores en IC vs II (97 vs 70%, p =0,001).

Table 2 Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

Primary endpoint	Intervention (n = 70)	Control (n = 70)	Absolute difference (95 % CI)	Significance (p value)[a,b]
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, n (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
Meropenem	14 (67)	8 (38)	29 (−0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (−0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, n (%)[d]				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, n (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, n (%)[f]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

Secondary endpoints	Intervention (n = 70)	Control (n = 70)	Absolute difference (95 % CI)	Significance (p value)[a,b]
PK/PD target attainment, n (%)[g]				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (−0.4 to −0.1)	**<0.001**
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (−0.4 to −0.1)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	21 (19–23)	21 (14–24)	0 (−3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (−2 to 18)	**0.043**
ICU survivors[i]	23 (21–25)	21 (0–25)	2 (−3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (−0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (−0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	**<0.001**

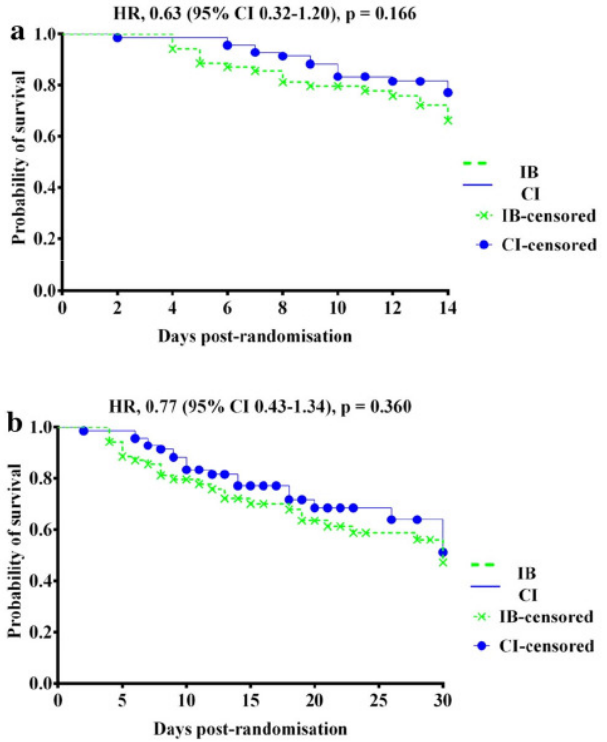


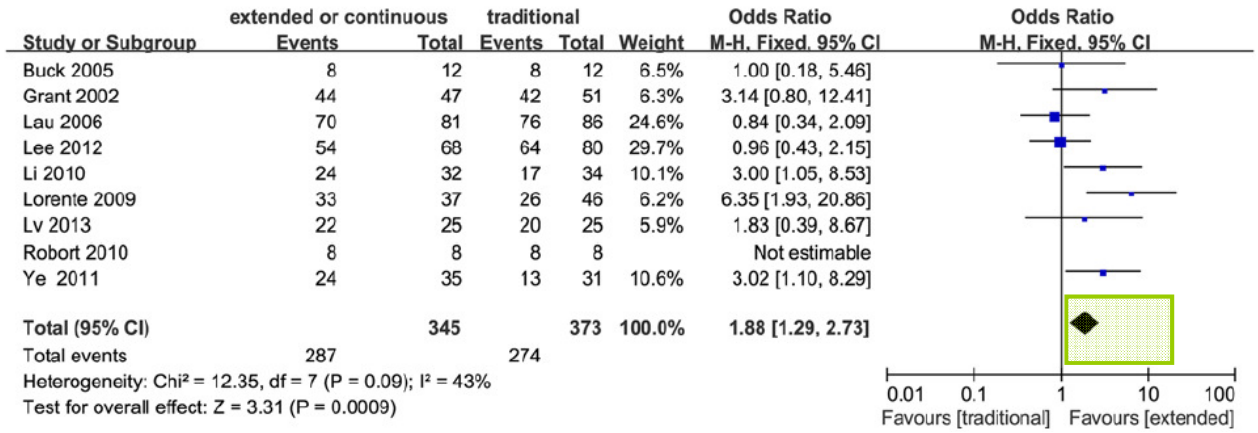
Fig. 1 Kaplan–Meier survival curves for the intention-to-treat population censored at **a** 14 days and **b** 30 days post-randomisation. *HR* hazard ratio, *CI* confidence interval

- **SI diferencias en curación clínica** (56 vs 34%, p = 0,011) y **días sin VM** (22 vs a 14 días, p=0,043) que con II.
- **NO diferencia en supervivencia** a 14 o 30 días

Abdul-Aziz et al, 2015

Clinical Outcomes with Alternative Dosing Strategies for Piperacillin/Tazobactam: A Systematic Review and Meta-Analysis

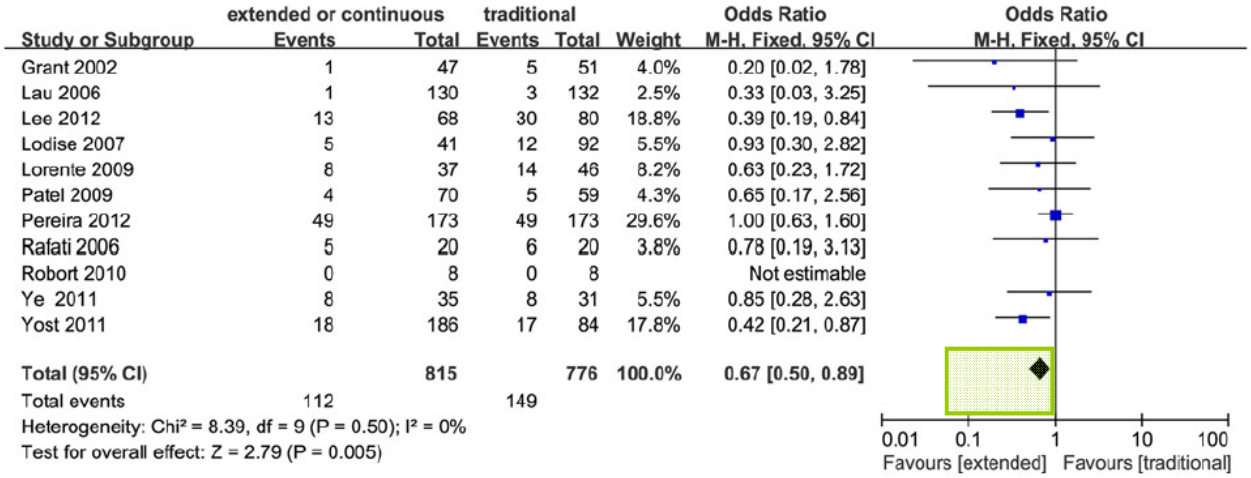
Hui Yang[1,2], Chao Zhang[1]*, Quanyu Zhou[3], Yike Wang[2], Lujia Chen[2]



Study or Subgroup	extended or continuous Events	Total	traditional Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Buck 2005	8	12	8	12	6.5%	1.00 [0.18, 5.46]
Grant 2002	44	47	42	51	6.3%	3.14 [0.80, 12.41]
Lau 2006	70	81	76	86	24.6%	0.84 [0.34, 2.09]
Lee 2012	54	68	64	80	29.7%	0.96 [0.43, 2.15]
Li 2010	24	32	17	34	10.1%	3.00 [1.05, 8.53]
Lorente 2009	33	37	26	46	6.2%	6.35 [1.93, 20.86]
Lv 2013	22	25	20	25	5.9%	1.83 [0.39, 8.67]
Robort 2010	8	8	8	8		Not estimable
Ye 2011	24	35	13	31	10.6%	3.02 [1.10, 8.29]
Total (95% CI)		**345**		**373**	**100.0%**	**1.88 [1.29, 2.73]**
Total events	287		274			

Heterogeneity: Chi² = 12.35, df = 7 (P = 0.09); I² = 43%
Test for overall effect: Z = 3.31 (P = 0.0009)

Figure 2. Forest plot depicting the odds ratios of clinical cure of patients receiving extended or continuous versus conventional inte infusion of piperacillin/tazobactam.



Study or Subgroup	extended or continuous Events	Total	traditional Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Grant 2002	1	47	5	51	4.0%	0.20 [0.02, 1.78]
Lau 2006	1	130	3	132	2.5%	0.33 [0.03, 3.25]
Lee 2012	13	68	30	80	18.8%	0.39 [0.19, 0.84]
Lodise 2007	5	41	12	92	5.5%	0.93 [0.30, 2.82]
Lorente 2009	8	37	14	46	8.2%	0.63 [0.23, 1.72]
Patel 2009	4	70	5	59	4.3%	0.65 [0.17, 2.56]
Pereira 2012	49	173	49	173	29.6%	1.00 [0.63, 1.60]
Rafati 2006	5	20	6	20	3.8%	0.78 [0.19, 3.13]
Robort 2010	0	8	0	8		Not estimable
Ye 2011	8	35	8	31	5.5%	0.85 [0.28, 2.63]
Yost 2011	18	186	17	84	17.8%	0.42 [0.21, 0.87]
Total (95% CI)		**815**		**776**	**100.0%**	**0.67 [0.50, 0.89]**
Total events	112		149			

Heterogeneity: Chi² = 8.39, df = 9 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)

Figure 3. Forest plot depicting the odds ratios of mortality of patients receiving extended or continuous versus conventional intermi of piperacillin/tazobactam.

El grupo de IC o IP:

- **Mayor curación clínica**
(**OR 1.88**, IC95%: 1,29-2,73; p=0,0009)

- **Menor mortalidad**
(**OR 0,67**; IC95%: 0.50- 0,89, p=0,005)

-No se observó diferencia estadística para la curación bacteriológica
(OR 1.40 IC95%: 0,82-2,37; p=0,22)

Yang et al, 2015

Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/ pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort

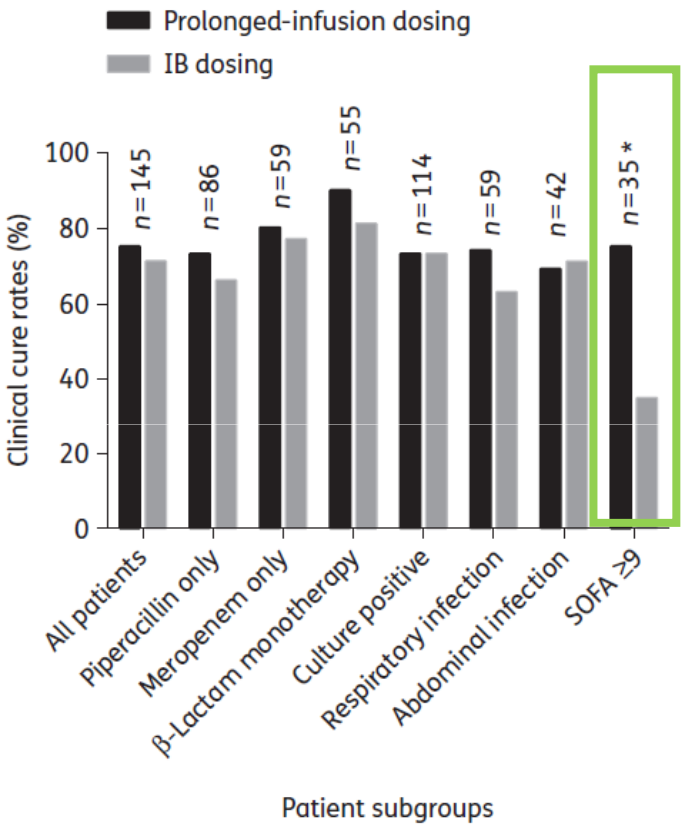
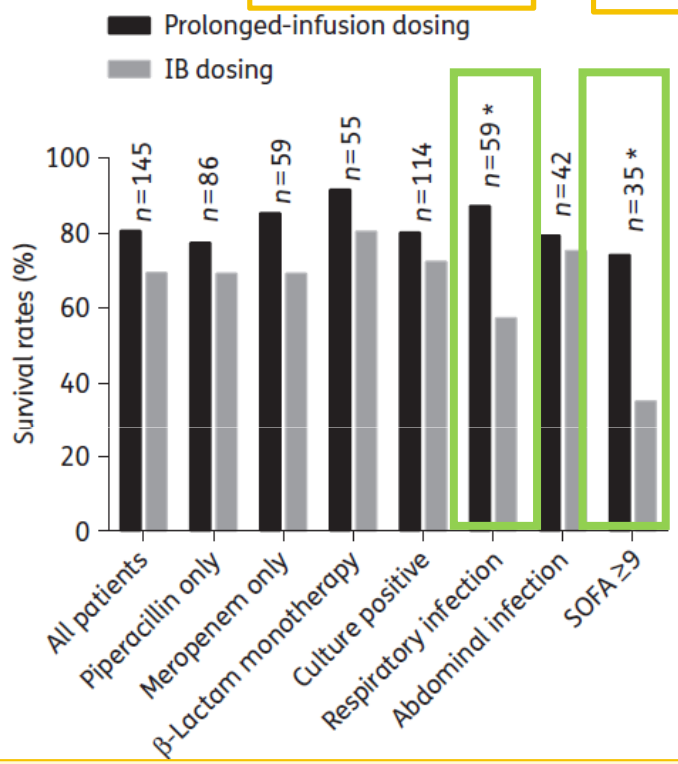


Figure 3. Clinical cure rate comparison between prolonged-infusion and IB dosing for patients who received antibiotics for treatment of infections, stratified according to subgroups. An asterisk indicates a significant difference between prolonged-infusion and IB dosing ($P<0.05$). *n*, number of patients in the subgroup.

86,2% vs 56,7%

73,3% vs 35%



Infx respiratoria o SOFA >9 **mayor supervivencia**

Figure 4. Comparison of 30 day survival between prolonged-infusion and IB dosing for patients who received antibiotics for treatment of infections, stratified according to subgroups. An asterisk indicates a significant difference between prolonged-infusion and IB dosing ($P<0.05$). *n*, number of patients in the subgroup.

Abdul-Aziz et al, JAC 71 - 2016

Prolonged versus Intermittent Infusion of β-Lactams for the Treatment of Nosocomial Pneumonia: A Meta-Analysis

Ashima Lal[1,2], Philippe Jaoude[1,2], and Ali A. El-Solh[1,2,3]

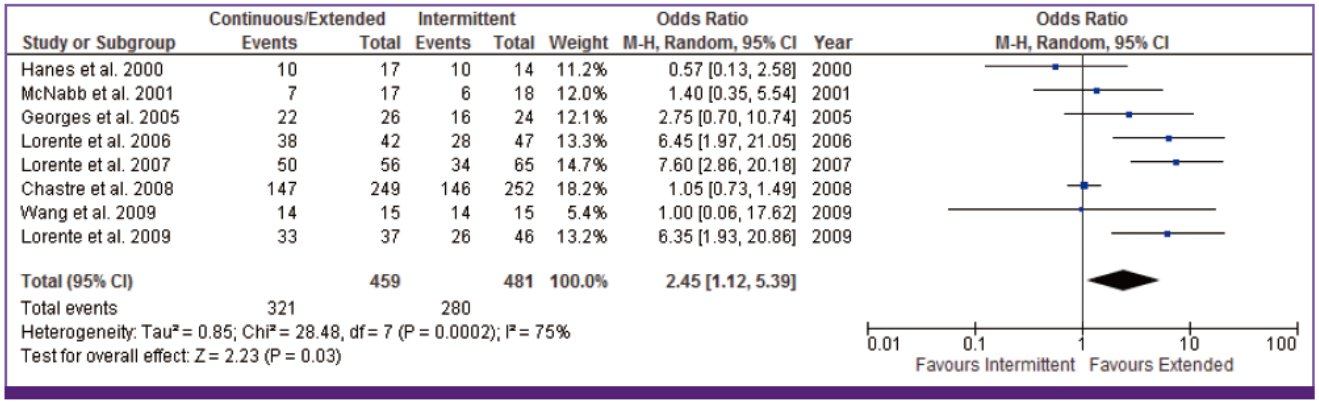


Figure 4. Forest plot comparing clinical cure rates in patients with nosocomial pneumonia receiving prolonged infusion and intermittent boluses.

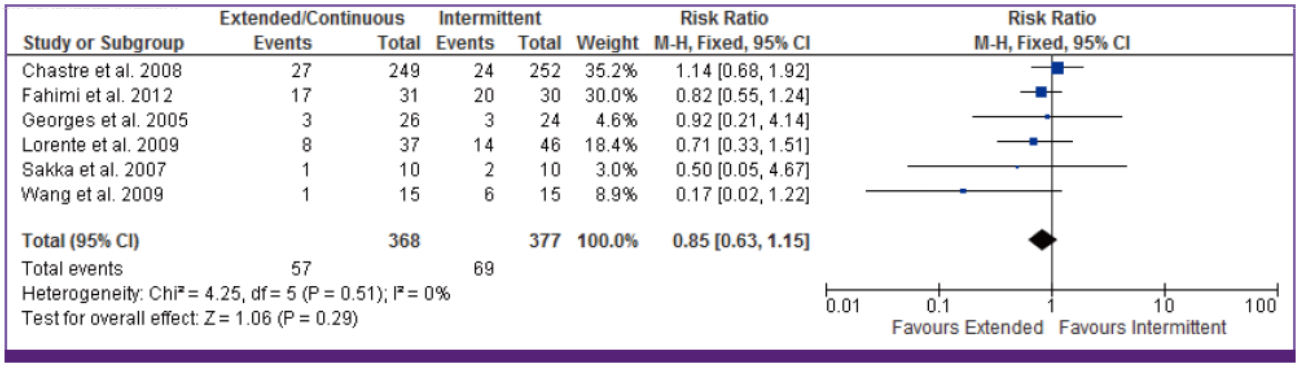


Figure 2. Forest plot comparing mortality rates in patients with nosocomial pneumonia receiving prolonged infusion and intermittent boluses.
CI, continuous infusion.

Table 3. Subgroup analysis of selected studies

	Clinical cure				Mortality			
	Number of studies	Number of patients	Odds ratio (95% CI)	I^2	Number of studies	Number of patients	Odds ratio (95% CI)	I^2
RCTs	5	647	1.09 (0.79-1.51)	0%	3	571	1.07 (0.66-1.73)	0%
Cephalosporins	4	237	2.21 (0.71-6.86)	68%	1	50	0.92 (0.21-4.14)	-
Carbapenems	3	620	2.01 (0.48-8.37)	76%	3	551	0.92 (0.57-1.47)	47%
APACHE II ≥ 15	5	824	3.45 (1.08-11.01)	85%	4	634	0.86 (0.57-1.28)	29%

IP de betalactámicos:

-**Mayor curación clínica**
(OR 2,45; IC95%, 1,12-5,37)

-**No diferencia mortalidad**
(OR 0,85, IC95% 0,63-1,15).

-No diferencias por ABL
-**SI mayor curación con APACHE II ≥ 15**
(OR 3,45, IC del 95%: 1.8 a 11.1).

Lal et al, 2016

Mejorar objetivo PK/PD

Beneficio clínico

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1] Sara E. Cosgrove,[2] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8]

X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum ß-Lactams and Vancomycin?

Recommendation

11. In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs *(weak recommendation, low-quality evidence)*.

Comment: Although data for improved outcomes for broad-spectrum β-lactam dosing with this approach are still limited, these interventions are associated with antibiotic cost savings. ASPs should consider implementation but must take into account logistical issues such as nursing and pharmacy education and need for dedicated IV access. Considering the limited evidence, we cannot give any recommendation about the utility of alternative dosing strategies for vancomycin.

Evidence Summary

Dosing strategies based on PK/pharmacodynamic (PK/PD) principles for aminoglycosides, such as once-daily dosing, have been shown to be effective in reducing nephrotoxicity and, in some studies, improve clinical outcomes [100, 101]. The effectiveness of alternative dosing schemes for β-lactam antibiotics and vancomycin based on PK/PD principles is unclear.

For β–lactam antibiotics, one meta-analysis showed decreased mortality (risk ratio, 0.59; 95% CI, .41–.83) among patients receiving continuous infusions of carbapenems or piperacillin-tazobactam vs standard infusions. This meta-analysis included 3 randomized controlled trials (RCTs) that comprised only 25% of the patient outcomes analyzed [102]. In contrast, another meta-analysis that included 14 RCTs did not support improved outcomes using prolonged infusions of broad-spectrum β-lactam antibiotics (either extended or continuous infusion) [103]. A Cochrane review [104] and a recent randomized trial [105] in critically ill patients of continuous infusions of β-lactam antibiotics compared with standard intermittent dosing also did not demonstrate benefits in outcome.

Práctica extendida?

DOCUMENTO DE CONSENSO

Programas de optimización de uso de antimicrobianos (PROA) en hospitales españoles: documento de consenso GEIH-SEIMC, SEFH y SEMPSPH☆,☆☆

J. Rodríguez-Baño[a,•], J.R. Paño-Pardo[b,•], L. Alvarez-Rocha[c], Á. Asensio[d], E. Calbo[e], E. Cercenado[f], J.M. Cisneros[g], J. Cobo[h], O. Delgado[i], J. Garnacho-Montero[j], S. Grau[k], J.P. Horcajada[l], A. Hornero[m], J. Murillas-Angoiti[n], A. Oliver[o], B. Padilla[f], J. Pasquau[p], M. Pujol[m], P. Ruiz-Garbajosa[q], R. San Juan[r] y R. Sierra[s]

Velocidad de la infusión intravenosa. Deben seguirse las indicaciones para la administración (en bolo, en perfusión extendida o en perfusión continua). En caso de indicarse la administración en perfusión extendida o continua debe comprobarse la estabilidad del fármaco.

Should β-lactam antibiotics be administered by continuous infusion in critically ill patients? A survey of Australia and New Zealand intensive care unit doctors and pharmacists

Menino O. Cotta [a,b,c,*], Joel M. Dulhunty [b,d], Jason A. Roberts [a,b,c], John Myburgh [e,f], Jeffrey Lipman [a,b]

International Journal of Antimicrobial Agents 47 (2016) 436–438

Current practice for the administration of meropenem and piperacillin/tazobactam (TZP) ($n = 111$).

Characteristic	Frequency [n (%)]	
	Meropenem	TZP
Standard practice is intermittent infusion	82 (73.9)	91 (82.0)
Standard practice is extended infusion (i.e. over 1–4 h)	6 (5.4)	4 (3.6)
Standard practice is continuous infusion (i.e. over 24 h)	2 (1.8)	2 (1.8)
Administration is determined on a case-by-case basis	19 (17.1)	12 (10.8)
Not stated	2 (1.8)	2 (1.8)

24.3% 16.3%

Table 3
Perceived benefit of β-lactam antibiotics administered by continuous versus intermittent infusion.

Statement	Perception	Frequency [n (%)]		Between-group difference (P-value)
		Medical staff ($n = 67$)	Pharmacists ($n = 41$)	
Continuous infusion is a more effective method of administering β-lactam antibiotics than intermittent infusion	Agree	23 (34.3)	35 (85.4)	<0.001
	Neither agree nor disagree	36 (53.7)	5 (12.2)	
	Disagree	8 (11.9)	1 (2.4)	
There is uncertainty as to whether continuous infusion of β-lactam antibiotics results in better patient-centred outcomes than intermittent infusion	Agree	50 (74.6)	27 (65.9)	0.85
	Neither agree nor disagree	8 (11.9)	2 (4.9)	
	Disagree	9 (13.4)	12 (29.3)	
I would be prepared to enrol patients with severe sepsis into a RCT comparing whether there is a difference in survival between continuous and intermittent infusion of β-lactam antibiotics	Agree	63 (94.0)	38 (92.7)	0.87
	Neither agree nor disagree	2 (3.0)	2 (4.9)	
	Disagree	2 (3.0)	1 (2.4)	

RCT, randomised controlled trial.

Fuerte justificación PK/PD para la elección de IE o IC → CASO A CASO

- patógenos con **MICs elevadas**
- cambios fisiopatológicos como en la **sepsis grave**
- mayor **gravedad** de la enfermedad

Cotta et al, 2016

Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/ pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort

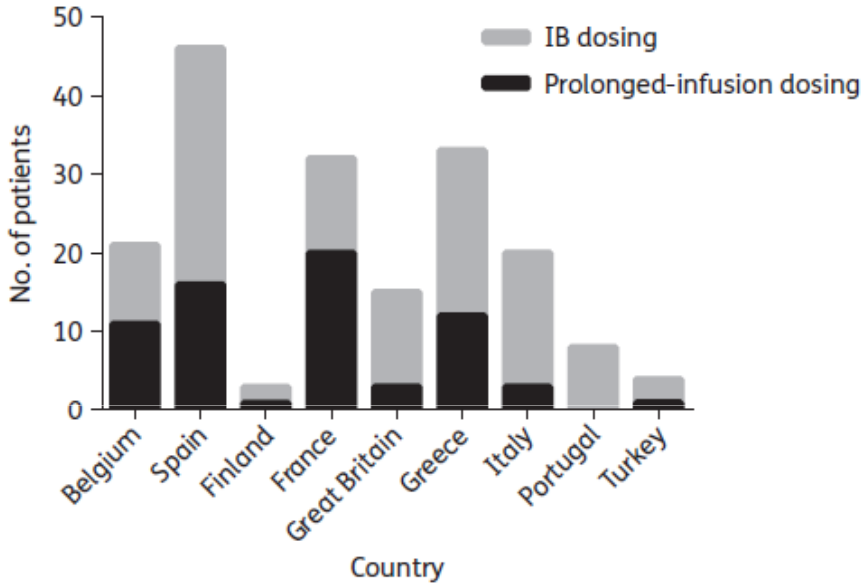


Figure 2. Method of piperacillin/tazobactam and meropenem administration according to participating countries.

- **<u>Estudio UCIs de 9 países europeos</u>** encontró administraron mediante IC e IE:
  - el **12,6%** de meropenem
  - y el **24,1%** de TZP.

- **Más de la mitad** de los pacientes observados en Francia y Bélgica recibieron ABL en IP o IC

Abdul-Aziz et al, JAC 71 - 2016

TDM β-lactàmicos

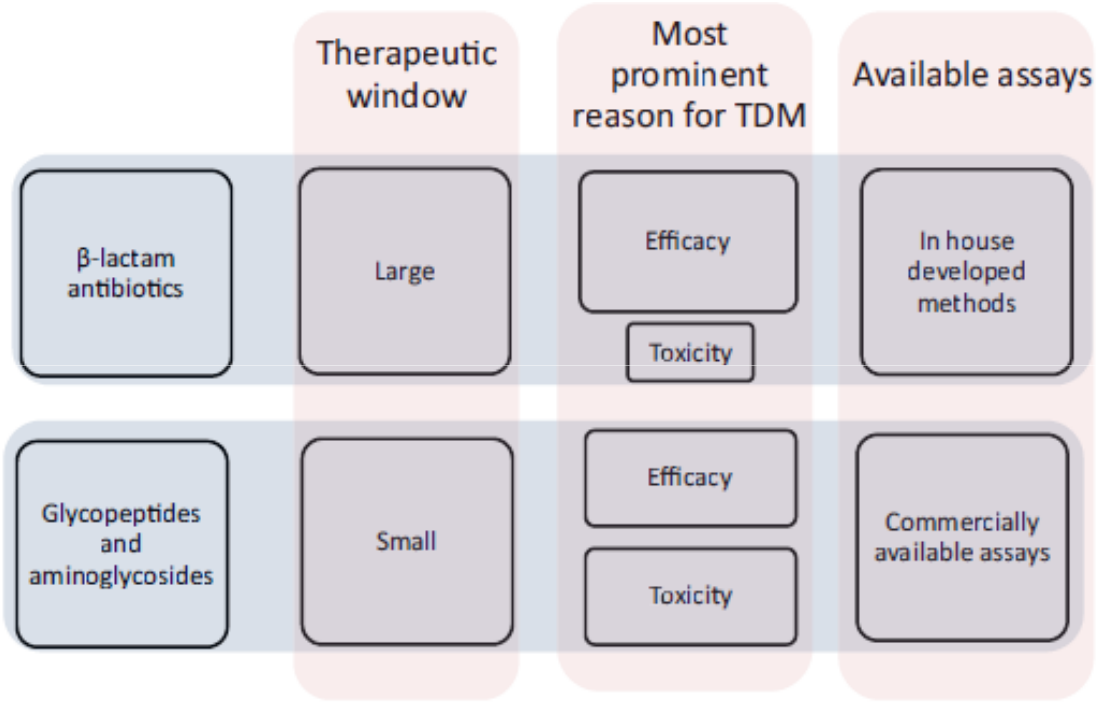
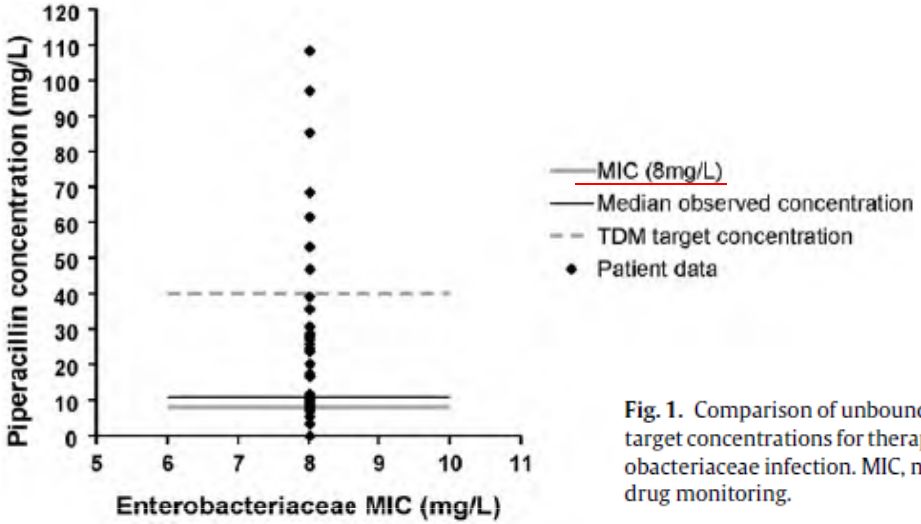


Fig. 1. Comparison of therapeutic drug monitoring (TDM) of β-lactam antibiotics with that of aminoglycosides and glycopeptides.

M. Carlier et al. / International Journal of Antimicrobial Agents Jul (2015)

TDM β-lactámicos pacientes críticos



- **63 %** de los pacientes obtenían una Cmin 8 mg/L
- Sólo el **35 % alcanzaba conc diana** (32-40 mg/l).

Fig. 1. Comparison of unbound piperacillin concentrations with pharmacodynamic target concentrations for therapy in patients ($n = 49$) with known or suspected Enterobacteriaceae infection. MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

Effect of antibiotic prescribed on the need for β-lactam antibiotic dose adjustment at the first therapeutic drug monitoring (TDM) level.

Antibiotic	Standard initiation dose[a]	Patients	Dose maintained	Dose increased[b]	Dose decreased
PIP/TAZ[c]	4.5 g q6h	116	27 (23%)	57 (49%)	32 (28%)
Ampicillin	2 g q6h	4	0 (0%)	1 (25%)	3 (75%)
Meropenem	1 g q8h	51	8 (16%)	29 (57%)	14 (27%)
Penicillin G	2.4 g q4h	9	3 (33%)	3 (33%)	3 (33%)
Flucloxacillin	2 g q4h	16	1 (6%)	15 (94%)	0 (0%)
Cefazolin	1 g q8h	6	0 (0%)	6 (100%)	0 (0%)
Ceftriaxone	1 g q12h	33	22 (67%)	7 (21%)	4 (12%)
Cefalothin	1 g q6h	1	0 (0%)	1 (100%)	0 (0%)
Total		236	61 (25.8%)	119 (50.4%)	56 (23.7%)

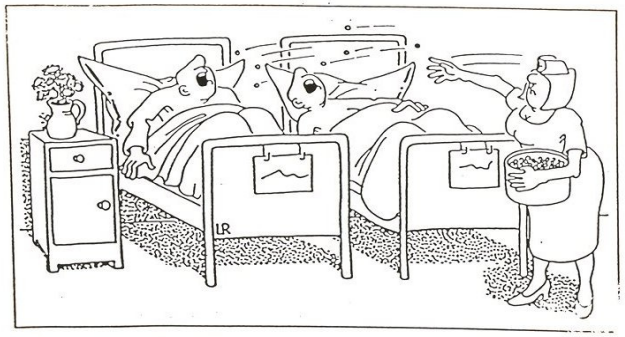
PIP/TAZ, piperacillin/tazobactam; q6h, every 6 h; q8h, every 8 h; q4h, every 4 h, q12h, every 12 h.

[a] Dose for a patient with 'normal' renal function (serum creatinine concentration <90 μmol/L). Different doses may be administered at the discretion of the clinician if the patient has moderate-to-severe renal dysfunction or is receiving continuous renal replacement therapy.

[b] Dose increase includes increased dose, increased dosing frequency, or administration by continuous or extended infusion. Dose adjustments at direction of pharmacist dependent on discrepancy between TDM and minimum inhibitory concentration (MIC) information as per Table 1.

[c] Dosing for PIP/TAZ was based on piperacillin levels only.

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



Pilule et épidémiologie.

INDIVIDUALIZAR

SELECCIONAR PACIENTES CANDIDATOS

Paciente crítico sepsis severa

Microorg. menor susceptibilidad

Penetración en el lugar de la infección

Ajustes por PK/PD

TDM

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