Con: Tigeciclina

E. Maseda

Que buena es la tigeciclina…
Que buena es la tigeciclina…
Que buena es la tigeciclina…
Que buena es la tigeciclina…
Que buena es la tigeciclina…
Que buena es la tigeciclina..

No funciona en NVM

No funciona en bacteriemias

10 min

Selecciona cepas resistentes de *Acinetobacter* spp.

Induce sobreinfecciones por *P. aeruginosa* o *Proteae*.

10 min

Bergallo C, et al.

Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin.

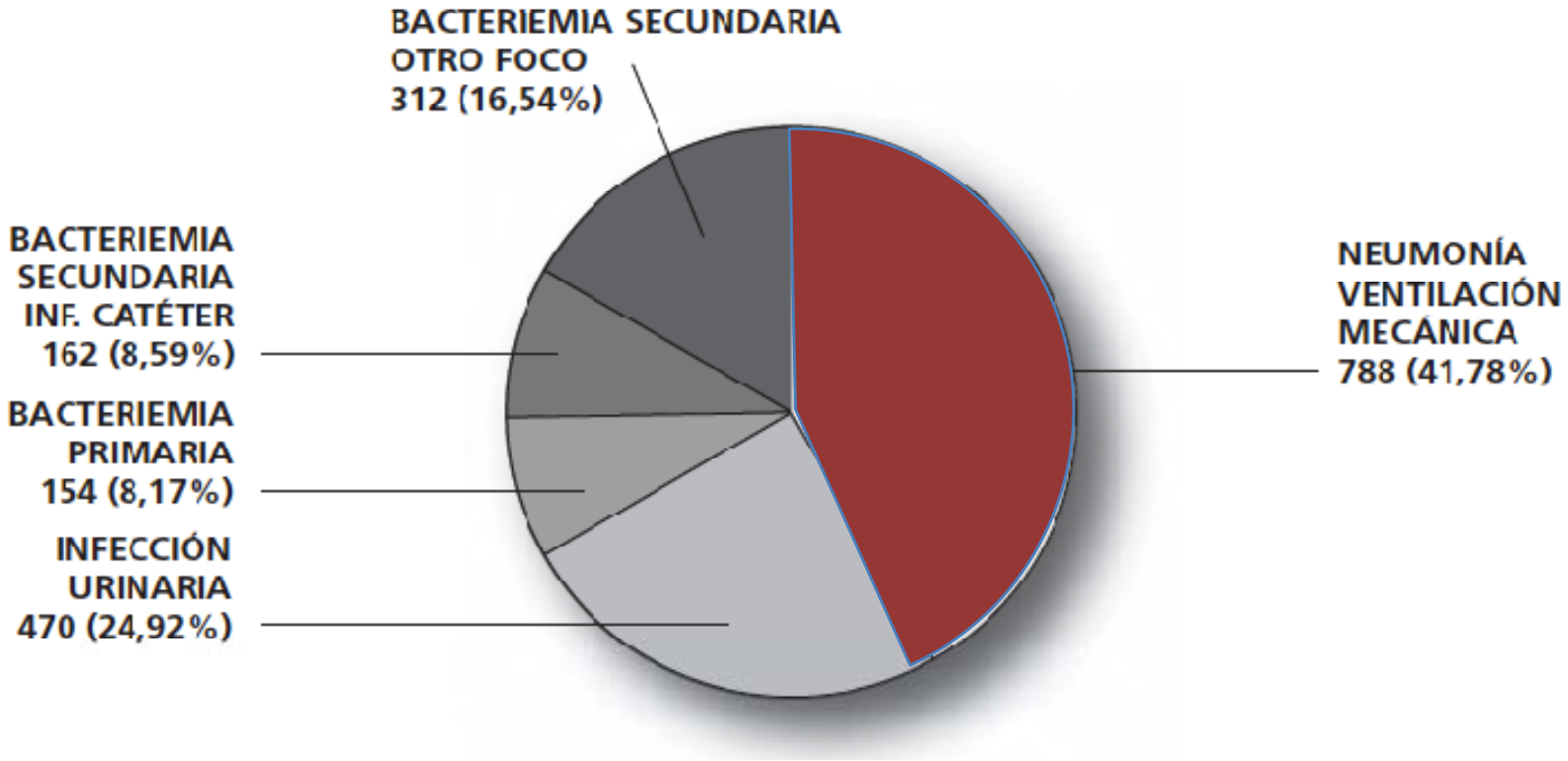
Diagn Microbiol Infect Dis 2009; 63:52-61

N= 418 pacientes; Fine IV = 18,4 %

Estudio de no inferioridad: 95% IC -15%

Population	Tigecycline		Levofloxacin		TGC versus LEVO, % (95% CI for difference)	*P* value for test for noninferiority
	n/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)		
CE	125/138	90.6 (84.4 to 94.9)	136/156	87.2 (80.9 to 92.0)	3.4 (−4.4 to 11.2)	<0.001
c-mITT	149/191	78.0 (71.5 to 83.7)	158/203	77.8 (71.5 to 83.3)	0.2 (−8.5 to 8.9)	<0.001
ME	70/75	93.3 (85.1 to 97.8)	84/93	90.3 (82.4 to 95.5)	3.0 (−6.4 to 12.5)	<0.001
Monomicrobial[b]	52/56	92.9 (82.7 to 98.0)	61/66	92.4 (83.2 to 97.5)	0.4 (−11.5 to 11.5)	
Polymicrobial[b]	17/18	94.4 (72.7 to 99.9)	22/26	84.6 (65.1 to 95.6)	9.8 (−16.1 to 30.8)	
m-mITT	84/100	84.0 (75.3 to 90.6)	95/115	82.6 (74.4 to 89.0)	1.4 (−9.5 to 12.3)	0.0012
Monomicrobial[b]	64/78	82.1 (71.7 to 89.8)	70/86	81.4 (71.6 to 89.0)	0.7 (−12.3 to 13.2)	
Polymicrobial[b]	18/20	90.0 (68.3 to 98.8)	23/27	85.2 (66.3 to 95.8)	4.8 (−20.4 to 26.3)	

Distribución de las infecciones controladas en UCI



Freire AT, et al.

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

Diagn Microbiol Infect Dis 2010; 68:140-51

Estudio RCT, no inferioridad (95% IC -15%)

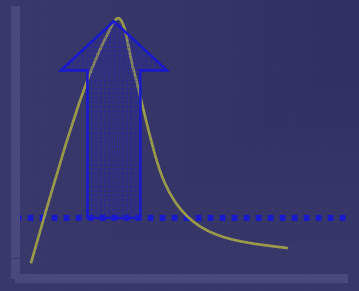
N = 945 pacientes; APACHE II > 15 = 25%

	n/N	Tigecycline (95% CI) (%)	*n/N*	Imipenem/cilastatin (95% CI) (%)	Difference (95% CI)
CE population					
VAP					
Cure	35/73	47.9 (36.1–60.0)	47/67	70.1 (57.7–80.7)	−22.2 (−37.8 to −4.9)
Failure	38/73	52.1	20/67	29.9	
Non-VAP					
Cure	147/195	75.4 (68.7–81.3)	143/176	81.3 (74.7–86.7)	−5.9 (−14.5 to 3.0)
Failure	48/195	24.6	33/176	18.8	
c-mITT population					
VAP					
Cure	59/127	46.5 (37.6–55.5)	67/116	57.8 (48.2–66.9)	−11.3 (−24.6 to 2.0)
Failure	57/127	44.9	32/116	27.6	
Indeterminate	11/127	8.6	17/116	14.6	
Non-VAP					
Cure	217/313	69.3 (63.9–74.4)	223/313	71.2 (65.9–76.2)	−1.9 (−9.4 to 5.6)
Failure	65/313	20.8	59/313	18.9	
Indeterminate	31/313	9.9	31/313	9.9	

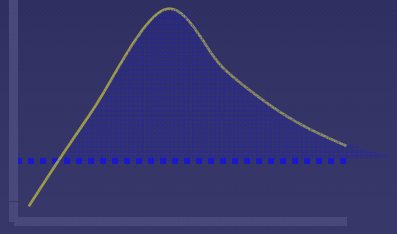
- aminoglucósidos

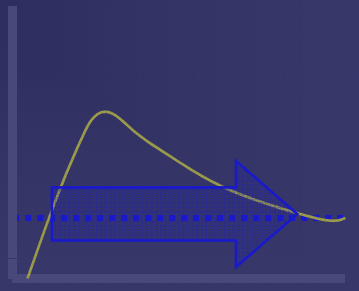
- fluorquinolonas
- metronidazol
- rifamicinas
- cetólidos
- daptomicina
- glucopéptidos
- macrólidos
- clindamicina
- tetraciclinas
- linezolid

- betalactámicos



ABC / CIM





ABC

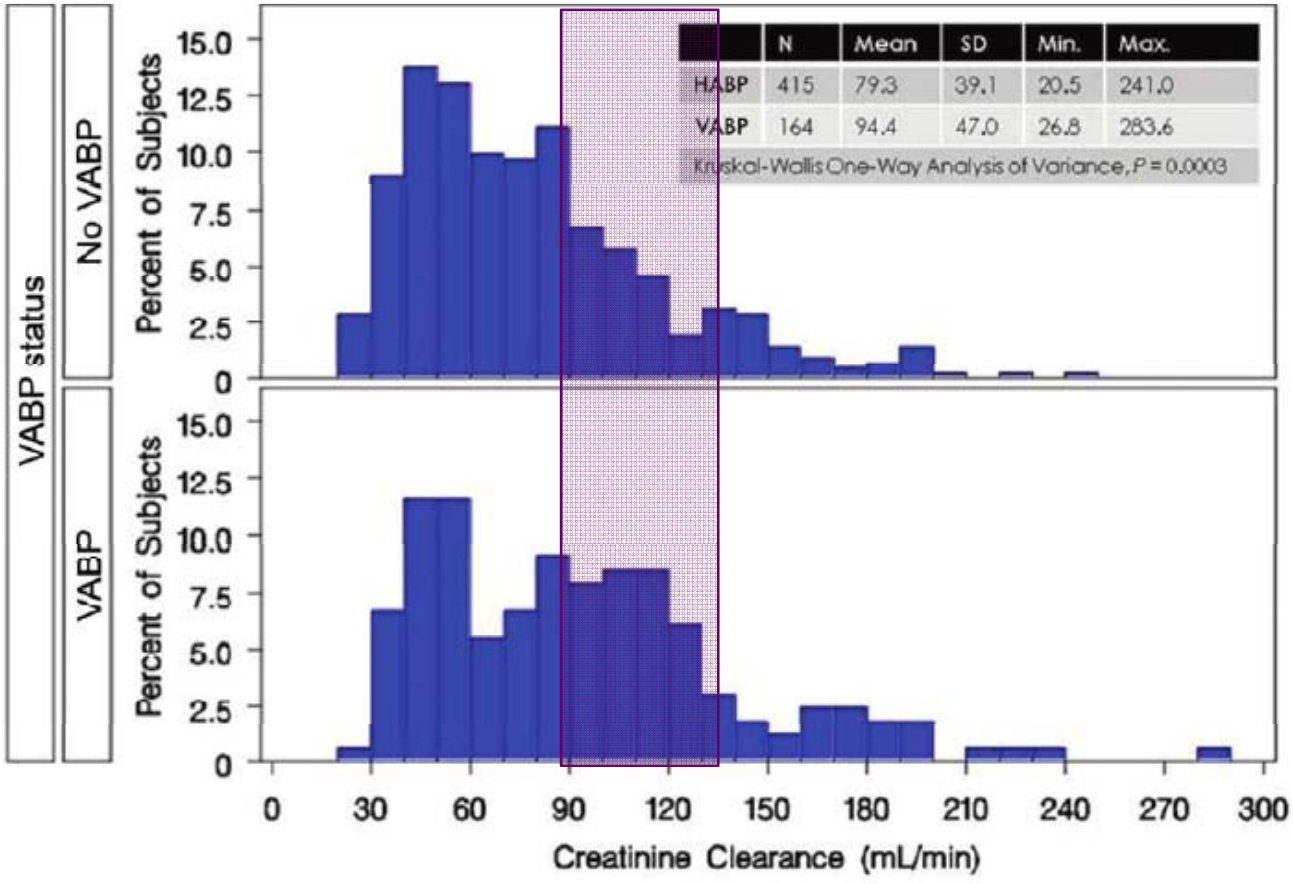
- dosis
- aclaramiento
- penetración en el tejido

CIM

Institute for Clinical Pharmacodynamics, Ordway Research Institute Demographic Database.- 579 pacientes

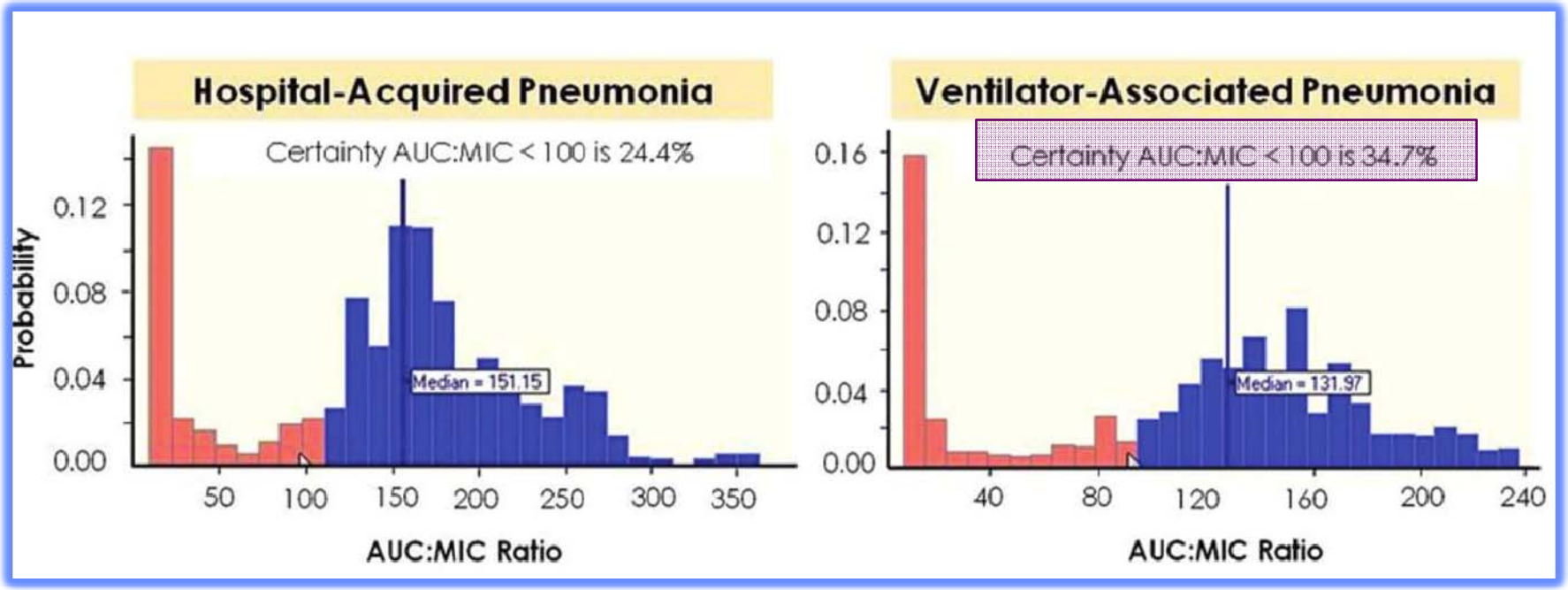
Aclaramiento de creatinina

N = 579 pacientes



Institute for Clinical Pharmacodynamics, Ordway Research Institute Demographic Database.

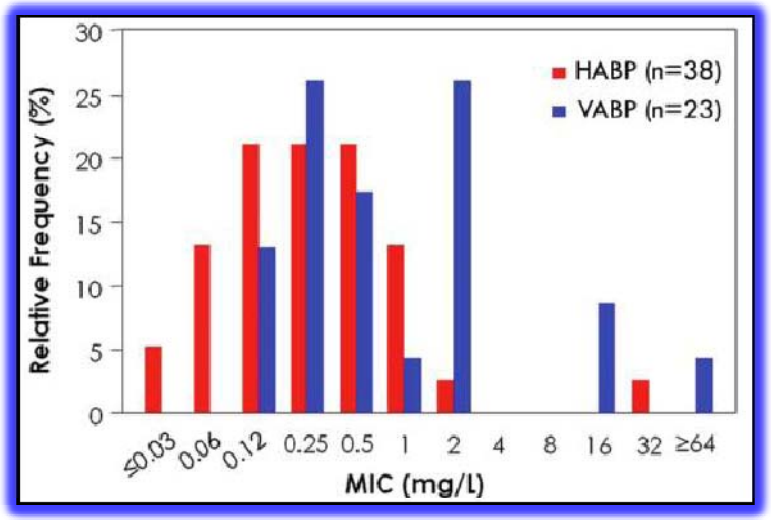
Modelo PK (Montecarlo) levofloxacino 750 mg para *K.pneumoniae*
ABC/CIM ≈ 100



Ambrose PG, et al.

Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: Look before you leap!.

Clin Infect Dis 2010; 51(S1):S103–S110



		Free-drug AUC_{0-24}:MIC		
Types of pneumonia	No. of patients	Mean ± SD	Median (range)	Proportion of patients cured (%)
HABP	38	9.45 ± 12.0	5.69 (0.0490–54.1)	31/38 (82)
VABP	23	3.10 ± 4.03	1.14 (0.00557–16.1)	12/23 (52)

Kett DH, et al

Candida bloodstream infections in intensive care units: Analysis of the extended prevalence of infection in intensive care unit study

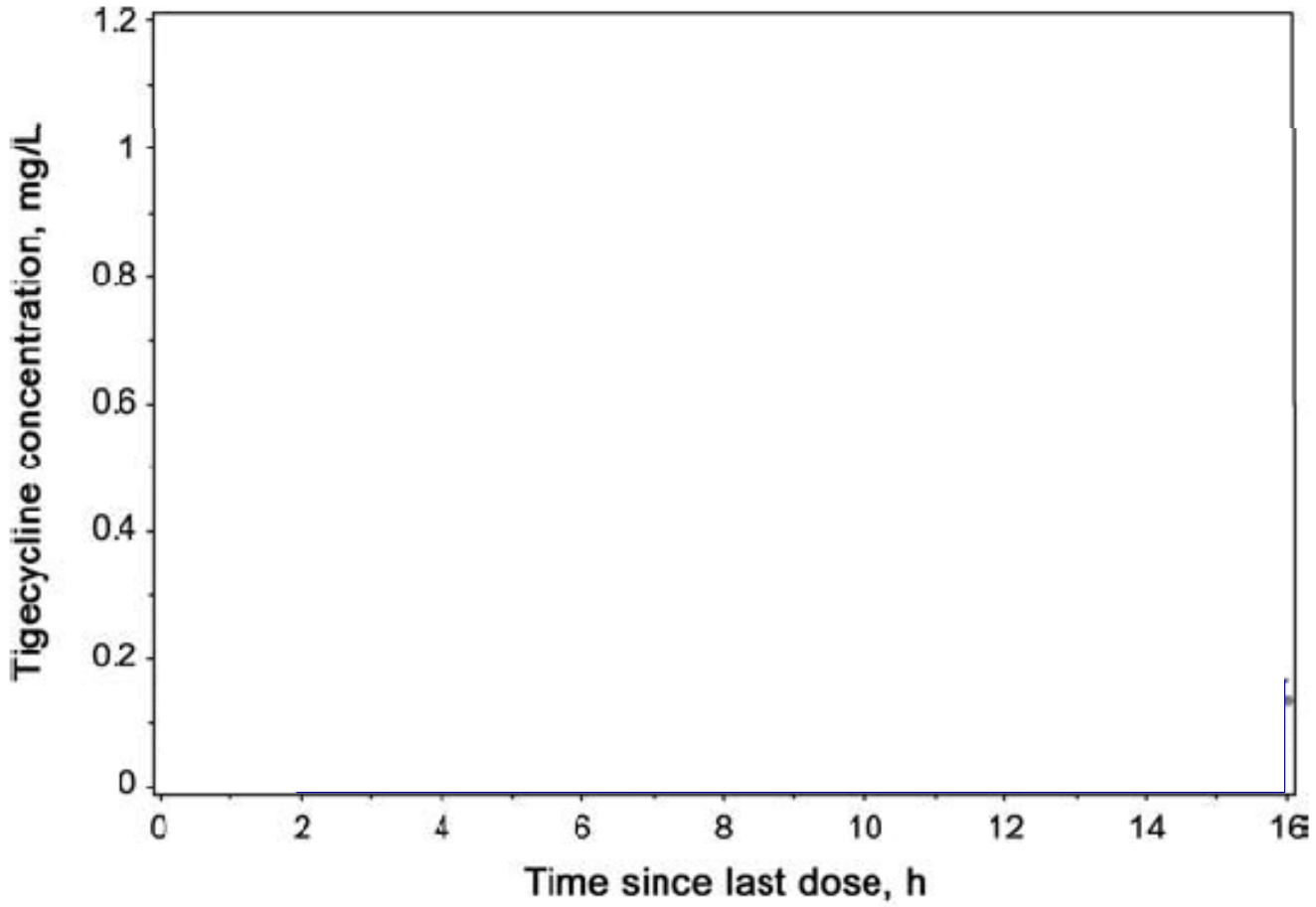
Crit Care Med 2011;39:665-70

	Candida BSI (n = 61)	Gram-Positive BSI (n = 420)	Gram-Negative BSI (n = 264)	Combination BSI (n = 38)
Patient characteristics				
Age, yrs (mean [IQR])	61 [46–71]	62 [48.5–72]	63 [47.5–72]	60.5 [46–69]
Male sex (no., %)	36 (59)	267 (63.7)	154 (58.3)	52 (59.1)
SAPS II score (mean [IQR])	38 [31–50]	37 [29–49.5]	37.5 [29.5–52]	38.5 [27–52]
SOFA total score (mean [IQR])	9 [6–13]	7 [5–10]	7 [4–10]	7.5 [5–12]
Prior days in ICU (mean [IQR])	14 [5–25]	8 [3–20]	10 [2–23]	11.5 [4–24]
Pre-existing conditions				
COPD (no., %)	8 (13.1)	52 (12.4)	44 (16.7)	11 (12.5)
Solid organ cancer (no., %)	15 (24.6)	40 (9.5)[a]	28 (10.6)[a]	13 (14.8)
Heart failure (no., %)	1 (1.6)	48 (11.4)	24 (9.1)	6 (6.8)
Diabetes mellitus (no., %)	4 (6.6)	49 (11.7)	36 (13.6)	9 (10.2)
Chronic renal failure (no., %)	6 (9.8)	46 (11)	33 (12.5)	6 (6.8)
Cirrhosis (no., %)	1 (1.6)	19 (4.5)	5 (1.9)	5 (5.7)
Hematologic cancer (no., %)	2 (3.3)	19 (4.5)	14 (5.3)	4 (4.5)
ICU-related interventions				
Mechanical ventilation (no., %)	44 (72.1)	307 (73.1)	175 (66.5)	64 (72.7)
Vasopressor use (no., %)	23 (37.7)	148 (35.2)	94 (35.6)	35 (39.8)
Hemodialysis/filtration (no., %)	17 (27.9)	67 (16)	55 (20.9)	16 (18.2)
Venous catheter (no., %)	54 (88.5)	361 (86.2)	227 (86)	79 (89.8)
Right heart catheter (no., %)	1 (1.6)	11 (2.6)	6 (2.3)	1 (1.1)
Arterial catheter (no., %)	39 (63.9)	269 (64.4)	173 (65.5)	64 (72.7)
Outcomes				
ICU mortality (no., %)	26 (42.6)	101 (25.3)	75 (29.1)	27 (31.4)
Hospital mortality (no., %)	26 (42.6)	135 (33.8)	91 (35.3)	33 (38.4)
ICU LOS (median [IQR])	33 [18–44]	20 [9–43]	21 [8–46]	24.5 [11–49]
Hospital LOS (median [IQR])	39 [26–62]	35 [17–62]	37 [17–66]	37 [23–69]

Meagher AK, et al.

The pharmacokinetic and pharmacodynamic profile of tigecycline

Clin Infect Dis 2005; 41:S333–40



CIM

Rodvold KA, et al.

Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose.

J Antimicrob Chemther 2006; 58:1221–9

Distribución tisular tras 100 mg de tigeciclina

Tissue or body fluid group	Site AUC_{0-24} (mg·h/L or mg·h/kg)[b]	Serum AUC_{0-24} (mg·h/L)	AUC_{0-24} ratio (site:serum)
Bile	2815/1787	5.24/4.86	537/368
Gall bladder	119.99/65.96	5.24/4.86	23/14
Colon	17.30/9.83	6.58/5.46	2.6/1.8
Lung	9.19/8.02	4.48/3.99	2.0/2.0
Bone	2.05/1.26	4.95/4.49	0.41/0.28
Synovial fluid	1.68/1.58	5.35/4.86	0.31/0.32
CSF	0.460/0.426	4.18/3.59	0.11/0.12

MacGowan AP, et al.

Tigecycline pharmacokinetic/pharmacodynamic update

J Antimicrob Chemoter 2008; 62(S1):i11–i16

Pharmacokinetic parameter	Healthy subjects ($n = 5$) mean (%CV)	cIAI ($n = 83$) mean (%CV)	cIAI ($n = 24$) mean (%CV)	cSSSI ($n = 43$) mean (%CV)
C^{ss}_{max} (mg/L)	0.621 (15)	0.794 (60)	0.837 (47)[a]	0.40 (45)[b]
C^{ss}_{min} (mg/L)	0.145 (16)	0.152 (47)	0.192 (47)	0.140 (52)
AUC^{ss}_{12} (mg·h/L)	3.07 (12)	3.16 (46)	3.16 (46)	2.24 (40)
CL (L/h)	16.5 (12)	18.3 (37)	15.9 (36)	—
CL (L/h/kg)	0.204 (9)	—	—	0.313 (40)

Análisis PK-PD de estudios sobre ITPB

Cohort	Pathogens	Tigecycline MIC range (mg/L)	Number of patients (number of pathogens)	Microbiological outcome (% eradication)	Clinical outcome (% cure)
1	monomicrobial *S. aureus* only	0.12–0.5	20 (20)	75	85
2[a]	monomicrobial *S. aureus* or streptococci	0.12–0.5	29 (29)	83	83
3	polymicrobial Gram-positive pathogens	0.06–0.5	7 (12)	92	86
4	polymicrobial Gram-positive pathogens (>2) and/or Gram-negative	0.06–16	14 (39)	79	71
5	other (monomicrobial Gram-negative or anaerobe)	0.25–1	8 (8)	100	100

Gardiner D, et al.
Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials
Clin Infect Dis 2010; 50:229-38

N=170 pac.

Characteristic	No. of cured subjects/no. of subjects in group (%)		P
	Tigecycline arm (n = 91)	Comparator arm (n = 79)	
Overall bacteremia	74/91 (81.3)	62/79 (78.5)	.703
Age, years			
<55	44/57 (77.2)	34/46 (73.9)	.818
≥55	30/34 (88.2)	28/33 (84.9)	.734
≥65	17/21 (81.0)	9/13 (69.2)	.680
≥75	6/7 (85.7)	3/4 (75.0)	>.99
Sex			
Male	46/56 (82.1)	46/55 (83.6)	>.99
Female	28/35 (80.0)	16/24 (66.7)	.362
APACHE score			
<10	23/30 (76.7)	30/35 (85.7)	.523
≥10	15/18 (83.3)	4/8 (50.0)	.149
Fine score			
< III	13/15 (86.7)	6/9 (66.7)	.326
≥ III	12/14 (85.7)	8/11 (72.7)	.623
Creatinine clearance			
<90 mL/min	40/49 (81.6)	34/44 (77.3)	.618
≥90 mL/min	34/42 (81.0)	28/35 (80.0)	>.99
Diabetes			
Yes	8/13 (61.5)	10/13 (76.9)	.673
No	66/78 (84.6)	52/66 (78.8)	.392
Infection site			
Complicated skin/skin-structure	19/23 (82.6)	14/17 (82.4)	>.99
Complicated intra-abdominal	30/39 (76.9)	34/42 (81.0)	.786
Community-acquired pneumonia	25/29 (86.2)	14/20 (70.0)	.279

David Gardiner, Gary Dukart, Angel Cooper, and Timothy Babinchak
Pfizer, Collegeville, Pennsylvania

Autores empleados de Pfizer

Ningún ensayo pivotal fue diseñado para valorar la eficacia de tigeciclina en pacientes bacteriémicos

En muchos casos el antibiótico comparador no es el de elección para el tipo de microorganismo o la dosis no fue la adecuada, lo que explicaría una baja tasa de curación:

- *SASM: vancomicina en lugar de cloxacilina*
- *Neumococo: levofloxacino 500 mg/d en lugar de 750 mg/d*

Bacteriemia por SARM tratadas con vancomicina no se determinaron nivles: ¿dosis subterapéuticas?

Vincent JL, et al
International Study of the Prevalence and Outcomes of Infection in Intensive Care Units
JAMA 2009; 302: 2323-2329

1.265 UCIs (75 países)
13.796 pac. (>18 a)
7.087 (51%) con infec.
9.084 (70%) reciben atb

No. (%)		7087 (51.4)
Microorganisms		
Positive isolates		4947 (69.8)
Gram-positive		2315 (46.8)
Staphylococcus aureus		1012 (20.5)
MRSA		507 (10.2)
S epidermidis		535 (10.8)
Streptococcus pneumoniae		203 (4.1)
VSE		352 (7.1)
VRE		186 (3.8)
Other		319 (6.4)
Gram-negative		3077 (62.2)
Escherichia coli		792 (16.0)
Enterobacter		345 (7.0)
Klebsiella species		627 (12.7)
2º	*Pseudomonas* species	984 (19.9) 22%
	Acinetobacter species	435 (8.8) 12%
	Other	840 (17.0)
	ESBL-producing	93 (1.9)
Anaerobes		222 (4.5)
Other bacteria		76 (1.5)
Fungi		
Candida		843 (17)
Aspergillus		70 (1.4)

Navon-Venezia S, et al.

High tigecycline resistance in multidrug-resistant Acinetobacter baumannii

J Antimicrob Chemoter 2007; 59:772–4

82 aislados de *A. baumanii*	***A. baumanii* R-Tigeciclina (%)**	***p***
***A. baumanii* R-imipenem**	**95**	**0,0038**
***A. baumanii* S-imipenem**	**60**	

Anthony KB, et al.

Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline.

Clin Infect Dis 2008; 46:567–70

18 pacientes

Causative organism	Resistance mechanism	Initial TIG MIC, μg/mL	Therapy duration, days	Coadministered antibiotics	Response		Final disposition[b]
					Clinical	Microbiological	
Acinetobacter baumannii							
…	…	3.00 (I)	7	FEP[a]	Negative	ND	Died (related)
…	…	1.00 (S)	15	VAN[a]	Positive	Positive	Alive
…	…	3.00 (I)	28	AMK, COL	Negative	Negative	Died (related)
…	…	3.00 (I)	10	COL (inhaled)	Negative	ND	Died (related)
…	…	2.00 (S)	49	None	Positive	Positive	Alive
…	…	ND	8	TOB (inhaled)	Positive	ND	Alive
		3.00 (I)/ 2.00 (S)	8	TOB	Negative	ND	Died (related)
…	…	1.00 (S)	17	None	Positive	Positive	Alive
…	…	3.00 (I)	17	LEV[a]	Positive	ND	Alive
…	…	2.00 (S)	42	None	Uncertain	ND	Alive
Enterobacteriaceae							
Enterobacter cloacae	AmpC	3.00 (I)	8	None	Uncertain	ND	Died (unrelated)
E. cloacae	AmpC	ND	7	None	Uncertain	Negative	Died (unrelated)
Klebsiella pneumoniae	ESBL, KPC (confirmed)	1.00 (S)	16	GEN	Negative	Negative	Died (related)
K. pneumoniae	Data unavailable	0.75 (S)	11	None	Positive	ND	Alive
K. pneumoniae	ESBL	0.75 (S)	15	TOB (inhaled)[c]	Positive	ND	Alive
K. pneumoniae	ESBL	ND	11	None	Negative	Positive	Died (unrelated)
K. pneumoniae	ESBL	1.50 (S)	23	None	Negative	Negative	…
K. pneumoniae	ESBL	1.00 (S)	18	MEM, COL	Negative	Negative	Died (related)
Escherichia coli	KPC (inferred)	0.75 (S)	133	None	Uncertain	Negative	Alive

Hornsey M, et al.

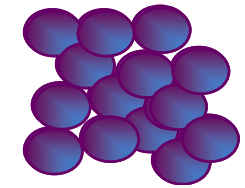
Whole-genome comparison of two Acinetobacter baumannii isolates from a single patient, where resistance developed during tigecycline therapy

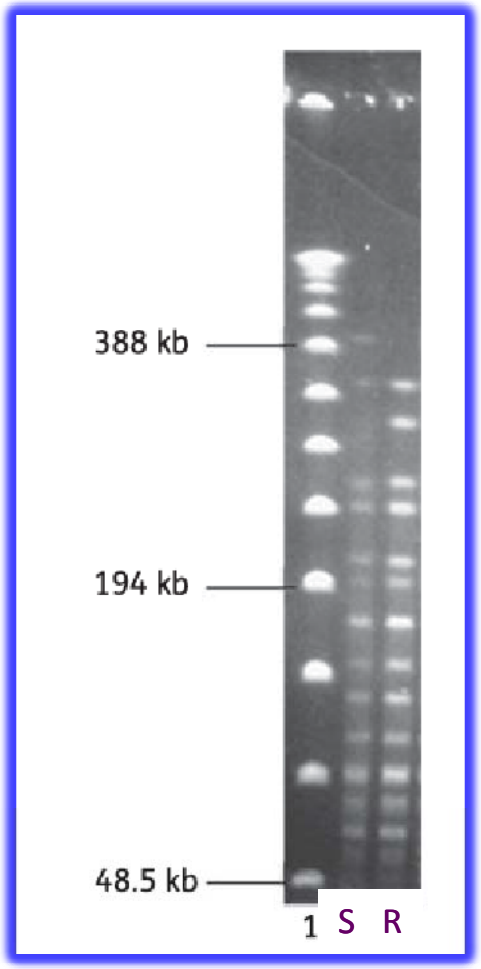
J Antimicrob Chemoter 2011; 00:000–00

Acinetobacter baumannii

resistente tigeciclina

tigeciclina
7 días





Peleg AY, et al.

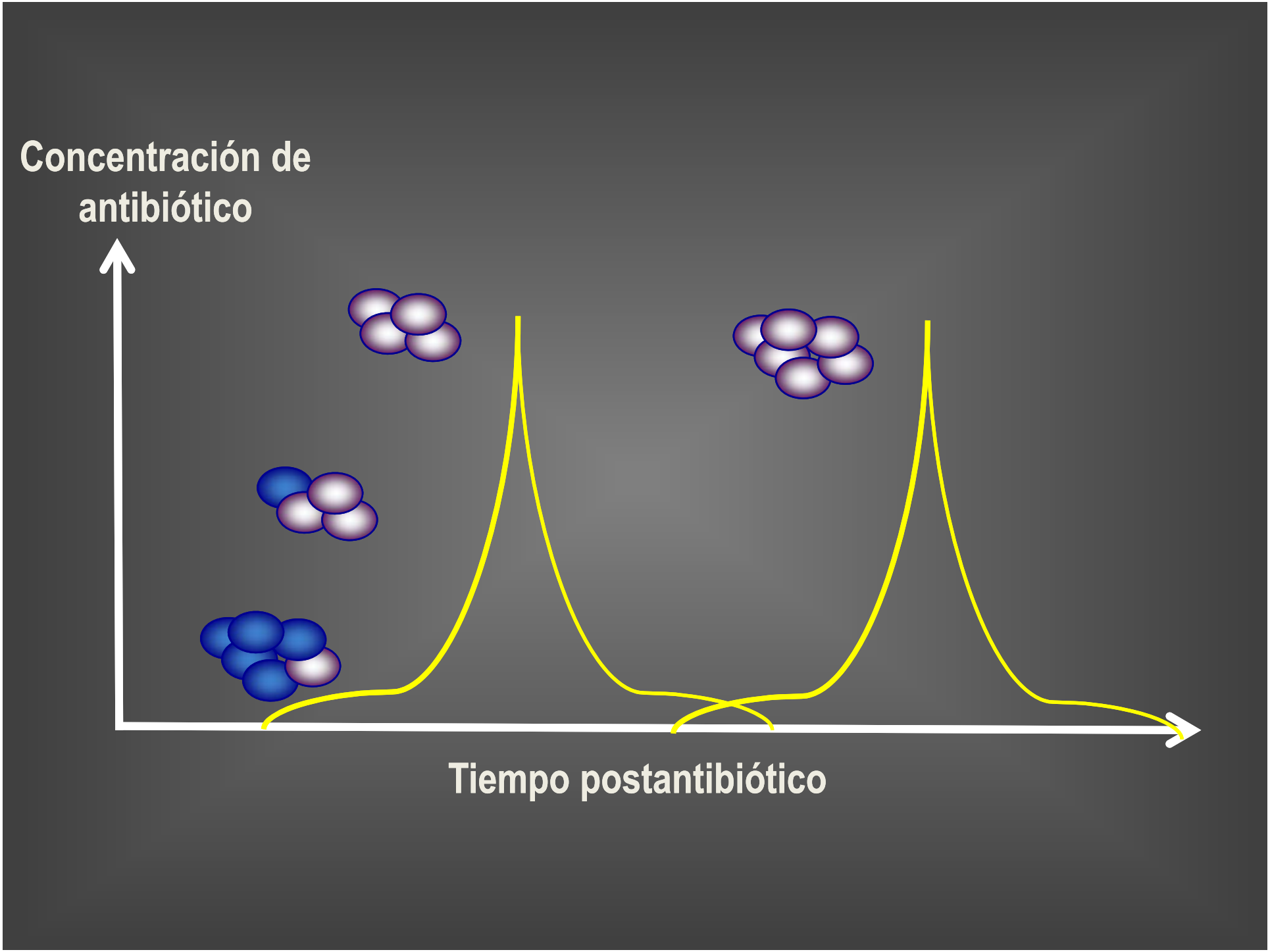
Acinetobacter baumannii bloodstream infection while receiving tigecycline: a cautionary report

J Antimicrob Chemoter 2007; 59:128–31

Descripción de 2 casos con aparición de bacteriemia por *A. baumanii* R-tigeciclina durante el tratamiento con tigeciclina por otro tipo de infecciones.

mecanismo posible: "bomba de achique"

		MIC (mg/L)									
Strains	TGC	MIN	GEN	TOB	CIP	CHL	PIP	CAZ	FEP	IPM	MEM
Case 1 isolate	4.0	0.25 S	8.0 I	24 R	>32 R	32 R	256 R	96 R	>256 R	1.5 S	4.0 I
+PAβN	1.0	0.25 S	4.0 S	16 R	32 R	8.0 S	256 R	8.0 S	128 R	0.25 S	0.25 S
Case 2 isolate	16	2.0 S	128 R	16 R	>32 R	32 R	48 I	192 R	>256 R	1.5 S	4.0 I
+PAβN	4.0	1.0 S	16 R	6 I	32 R	8.0 S	8.0 S	8.0 S	16 I	0.125 S	0.125 S


Concentración de antibiótico
Tiempo postantibiótico

CONTROL EPIDEMIOLÓGICO DE LA MICROBIOTA HALLADA EN LOS PACIENTES INGRESADOS EN REA 3ª (HOSPITAL GENERAL)

Infección de herida quirúrgica tratada 7 días con tigeciclina

- Frotis faríngeo: 10^5 cols. de ***Proteus mirabilis*** sensible. 10^3 cols. de ***Candida albicans***. Microbiota alterada.
- Frotis rectal: 10^5 cols. de ***E coli*** sensible ; ***Strept faecalis*** ; ***Proteus mirabilis*** resistente a Colimicina. 10^3 cols. de ***Klebsiella pneumoniae*** resistente a Levofloxacino y Cefalotina ; ***Ps aeruginosa*** resistente a Cotrimoxazol y Cefalotina. Microbiota normal.
- Frotis nasal: 10^3 cols. de ***Staph epidermidis***. Microbiota normal.
- Frotis axilar: 10^7 cols. de ***Klebsiella pneumoniae*** resistente a Levofloxacino y Cefalotina ; ***Staph epidermidis***. Microbiota alterada.
- A.bronquial: 10^5 cols. de ***Proteus mirabilis*** resistente a Colimicina. Valorar por clínica.
- Orina: 10^3 ufc/ml. de ***Ps aeruginosa*** resistente a Cotrimoxazol y Cefalotina.

García-Cabrera E, et al. *Superinfection during treatment of nosocomial infections with tigecycline* *Eur J Clin Microbiol Infect Dis 2010; 29:867-71*

Clinical cure/ microbial eradication[a]	Duration of treatment with tigecycline	Bacteria causing superinfection. Clinical syndrome	Clinical cure/ microbial eradication[b]	Final Outcome
Yes/yes	7 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	Yes/yes	Cure
Yes/yes	10 days	*Pseudomonas aeruginosa* Burn infection	Yes/yes	Cure
Yes/yes	14 days	*Pseudomonas aeruginosa* Intra-abdominal abscess	Yes/yes	Cure
Yes/yes	8 days	*Pseudomonas aeruginosa* Surgical site infection	Yes/yes	Cure
Yes/yes	8 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	Yes/ yes	Cure
No/yes	26 days	*Pseudomonas aeruginosa* Intra-abdominal abscess	No/no	Death
Yes/yes	7 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	No/yes	Death
Yes/yes	7 days	*Providencia stuartii* Pleural empyema	Yes/yes	Cured
No/yes	7 days	*Morganella morganii* Intra-abdominal infection	No/no	Death
Yes/yes	12 days	*Enterococcus faecalis* Surgical site infection	Yes/yes	Cured
Yes/yes	7 days	*Proteus mirabilis* intra-abdominal infection	Yes/yes	Non-related death
Yes/yes	14 days	*Enterobacter cloacae* Tracheobronchitis	No/no	Non-related death

Algunas cosas que recordar…

Es necesario diseñar ensayos clínicos para determinar:

- **La eficacia y seguridad de tigeciclina en NVM utilizando dosis elevadas (200 mg inicial y 100 mg/12 h)**
- **El papel de tigeciclina en combinación con otros antibióticos**
- **El papel inductor sobre cepas resistentes (*Acinetobacter* spp) o sobre la aparición de sobreinfecciones por *P.aeruginosa* o *Proteae***


That's all Folks!