I Jornada FarmUCI

Taller III:
Infecciones en el paciente crítico

Hospital Universitari de Bellvitge

y Hospital de Mataró

SCFC – I Jornada FarmUCI

Introducción

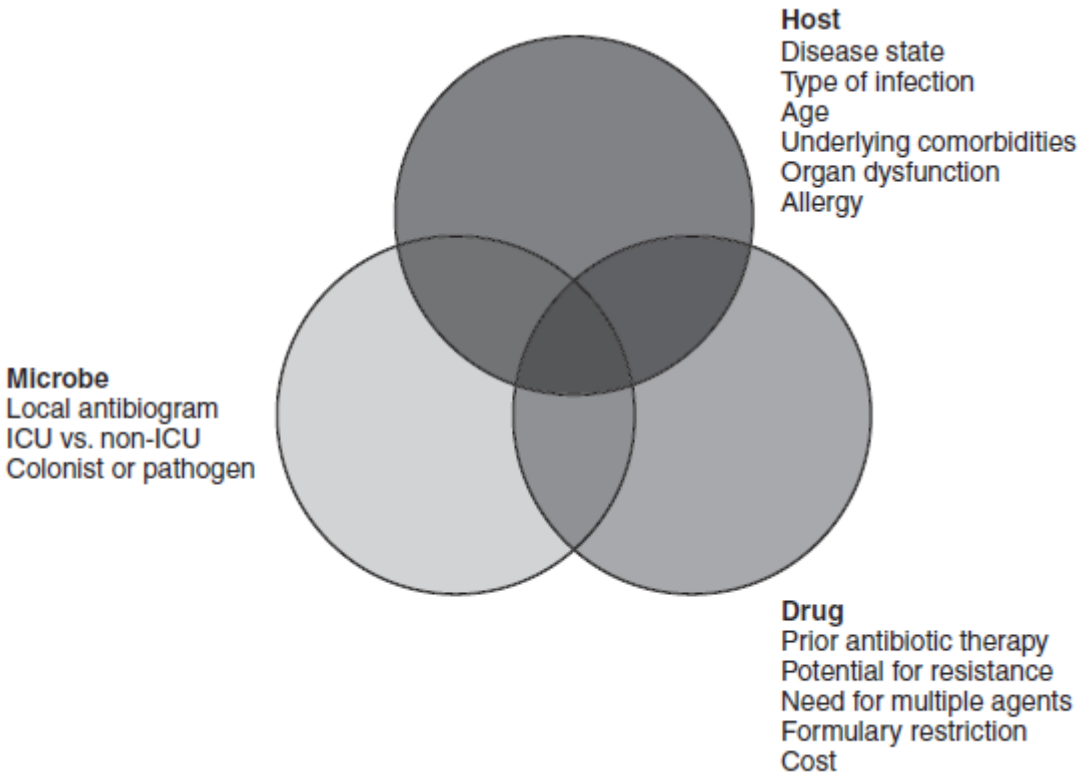
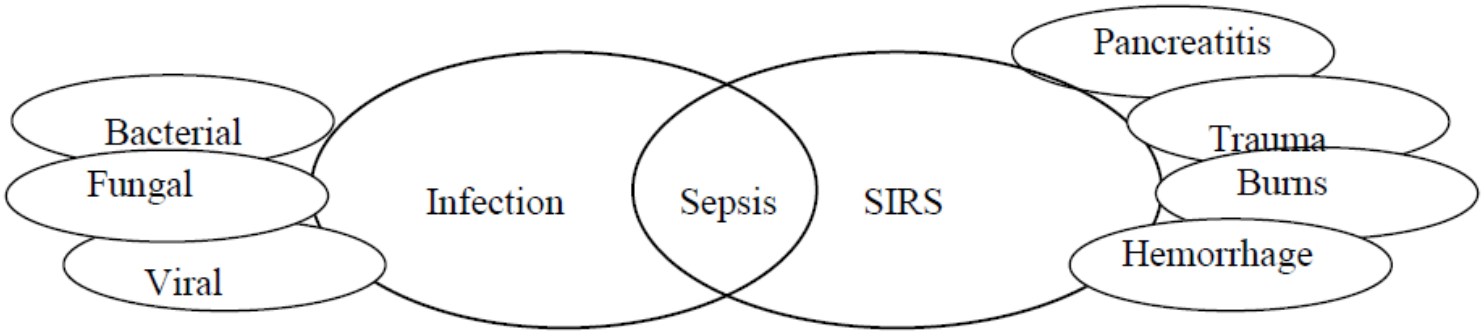


Figure 1 Host factors, microbe-specific factors, and drug-related factors all influence the selection of antibacterial agents. *ICU,* Intensive care unit.

Introducción

B. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2008. Crit Care Med 2008;36:296–327.



Sepsis = systemic response to infection (confirmed or suspected infection PLUS more than two systemic inflammatory response syndrome (SIRS) criteria)

Severe sepsis = sepsis associated with organ dysfunction or tissue hypoperfusion or hypotension (SBP less than 90 mm Hg or mean arterial pressure [MAP] less than 70 mm Hg or a drop in SBP of more than 40 mm Hg)

Septic shock = sepsis-induced hypotension persisting despite adequate fluid resuscitation

Sepsis-induced hypoperfusion is defined as septic shock, elevated lactate, or oliguria.

Hypoperfusion abnormalities include (but are not limited to):
Altered mental status
Hyperglycemia in the absence of diabetes mellitus
Cardiac index greater than 3.5 L/minute/m^2
Acute oliguria (more than 2 hours)

Increased SCr (more than 0.5 mg/dL over baseline)
Thrombocytopenia: platelets less than 100,000/cm^3
Hyperlactatemia (more than 4 mmol/L)

Edema or increased fluid balance
Decreased SvO_2
Arterial hypoxemia PaO_2/FiO_2 less than 300
Coagulopathy (INR more than 1.5 with no anticoagulant)
Ileus (absent bowel sounds)
Hyperbilirubinemia (more than 40 mg/dL)
Decreased capillary refill or mottling

Caso clínico

Paciente varón de 30 años con antecedentes personales de:

- Consumidor de cannabis y cocaína.
- Consumidor de 4 -6 UBE s al día.
- Síndrome depresivo y trastorno límite de la personalidad.
- Tratamiento habitual: Quetiapina 200mg 1c/d, Zolpidem 10mg 1c/d, Topiramato 100mg 1c/8h, Valproato 500mg/8h, Escitalopran 10mg/d

Politraumatizado

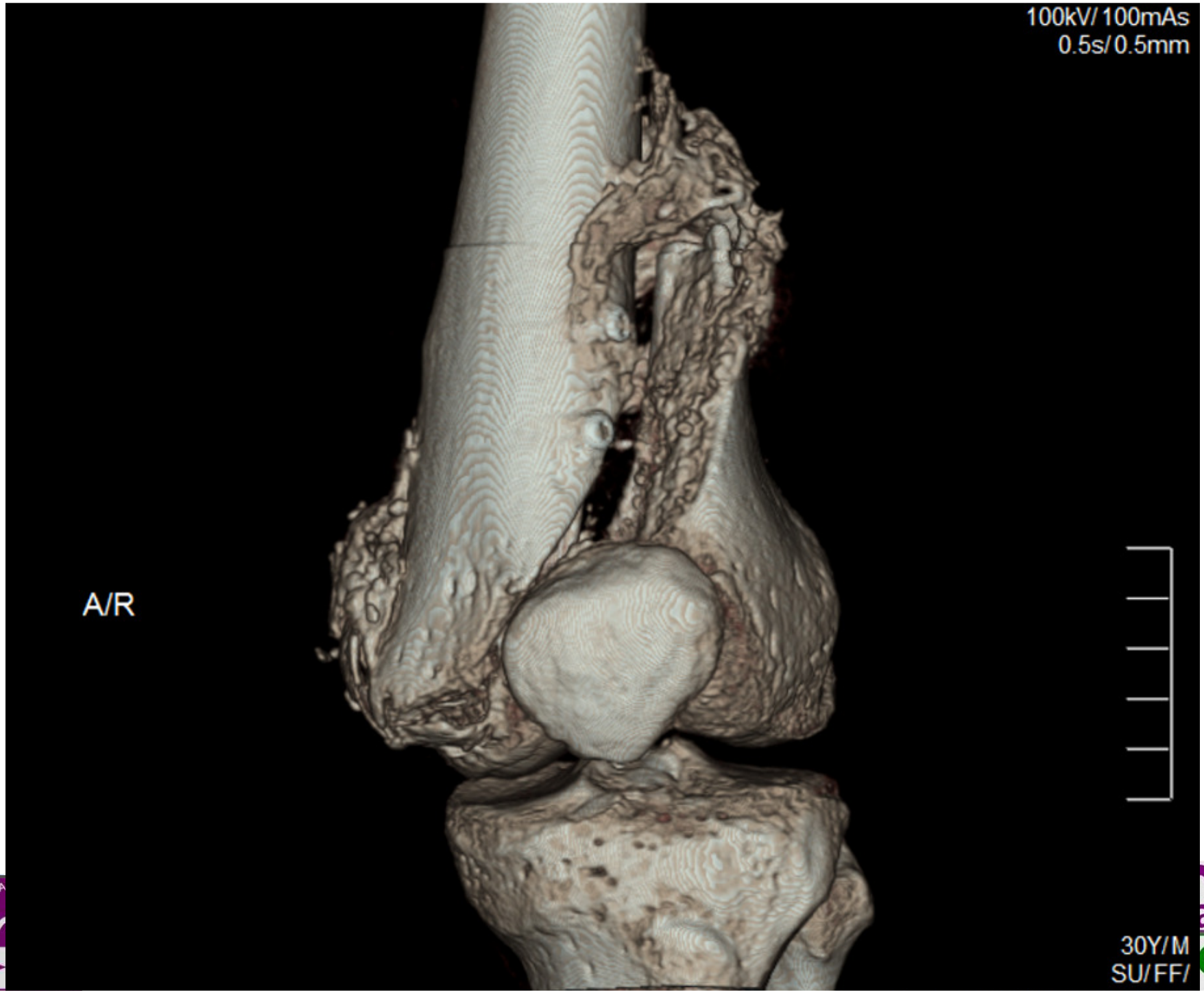
Otros antecedents: **PLT 2008**

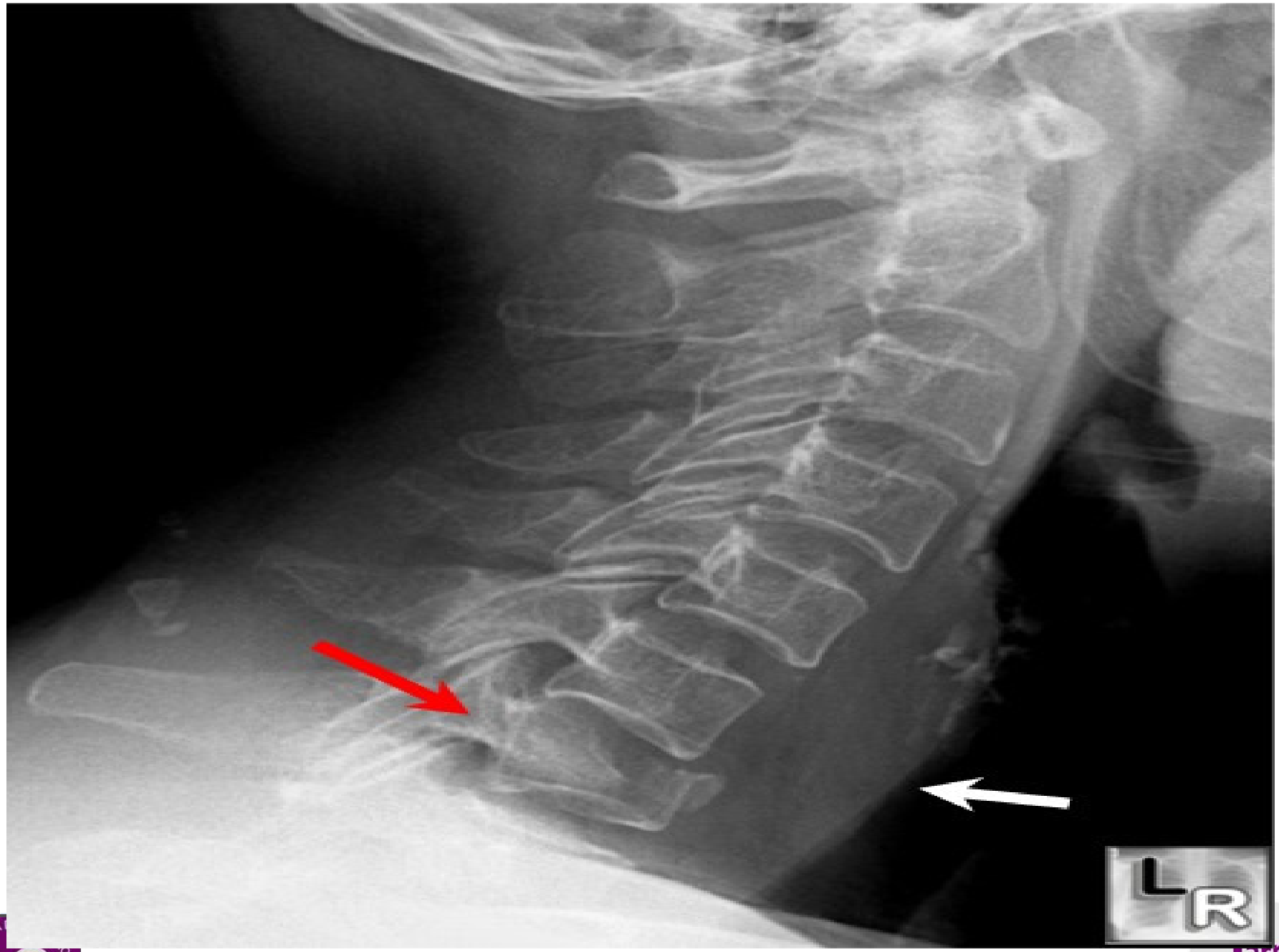
- TCE grave (GCS: 4 inicial)
- lesión axonal difusa
- esplenectomizado
- fractura fémur izquierda
- fractura cubital izquierda
- fractura costal del 10º arc
- escápula izquierda
- luxación articulación coraco-clavicular

ENFERMEDAD ACTUAL

POLITRAUMATISMO por 4º intento autolítico.

- Precipitado de 6 m, impactando craneo y hemicuerpo
- Fractura de la masa lateral derecha de C1
- Fractura en laminar y arco posterior de C5 (sin compromiso medular)
- Fractura de la pared posterior de cótil dret.
- Fractura supracondilia femur D.
- Fractura olecranon dret.
- Fractura supracondilia femur esquerre.
- Fractura anterior del hemisacre dret de S1.


100kV/100mAs
0.5s/0.5mm
A/R
30Y/M
SU/FF/



PLT

Evolució inicial

- Ingresa el 29/07/2014
- Sin insuficiencia respiratoria.
- Es realiza RMN por a descartar lesión medular.

A las 48 h de ingreso 31/07/2014. Presenta insuficiencia respiratoria.

- Broncoaspiración:
  - Tratamiento con **amoxicilina/clavulánico** de forma empírica

Tratamiento antimicrobiano empírico

Sospecha de **broncoaspiración**

- El diagnóstico suele ser clínico
- Se inicia tratamiento precoz

Cobertura para:
- *S.aureus*
- *Strep. pneumoniae*
- *Haemophillus influenza*
- Anaerobios

Tratamiento antimicrobiano empírico

Neumonia comunitaria

- Neumocócica
- Legionella
- Neumonía atípica

Ceftriaxona/cefotaxima

Levofloxacino/macrolidos

Tratamiento antimicrobiano empírico

En época epidemia.

Valorar tratamiento de la gripe A-B

No clear consensus has been reached about whether patients with obvious viral community-acquired pneumonia need to be treated with antibiotics

Oseltamivir

Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011 Apr 9;377(9773):1264-75.

Tratamiento antimicrobiano empírico

Neumonia extrahospitalaria de pacientes "cuidados sanitarios"

Conocer la epidemiologia de la zona

BMC Infect Dis. 2014 Oct 18;14(1):534. Validation of sputum Gram stain for treatment of community-acquired pneumonia and healthcare-associated pneumonia: a prospective observational study.

Polverino E1, Torres A, Menendez R, Cillóniz C, Valles JM, Capelastegui A, Marcos MA, Alfageme I, Zalacain R, Almirall J, Molinos L, Bello S, Rodríguez F, Blanquer J, Dorado A, Llevat N, Rello J; HCAP Study investigators. Microbial aetiology of healthcare associated pneumonia in Spain: a prospective, multicentre, case-control study. Thorax. 2013 Nov;68(11):1007-14. doi: 10.1136/thoraxjnl-2013-203828.

Tratamiento antimicrobiano empírico

Tratamiento en un **paciente inmunodeprimido**

Amplia cobertura
Bacterios / Hongos / Virus /Parásitos

Vehreschild JJ. Pneumonia and lung infiltrates in neutropenic patients: many stones unturned. Ann Am Thorac Soc. 2013 Oct;10(5):493-5.

Día +2 Ventilación mecánica no invasiva

- Inicialmente VMNI.

Dia +10 Caso clínico

- IQ trauma

  → Infección puntos de tracción femoral derecha

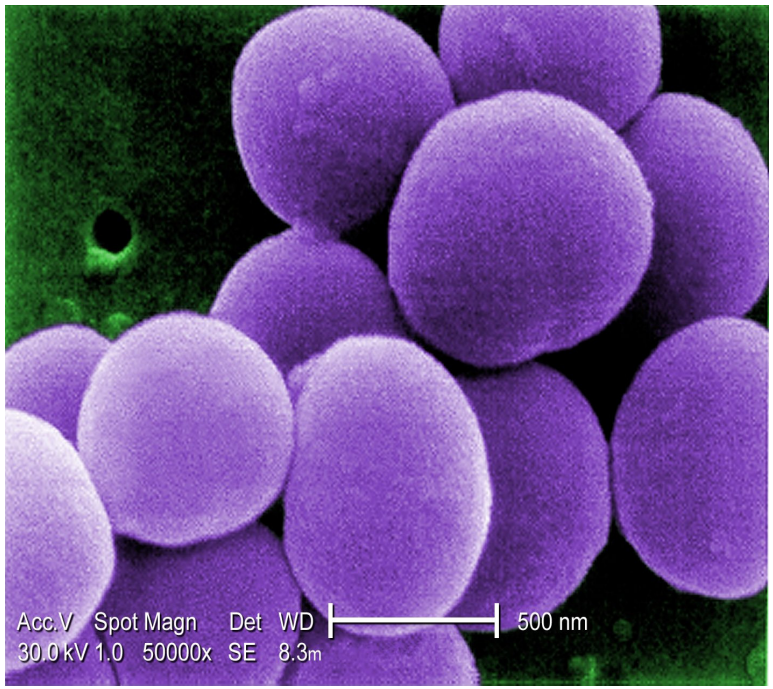
- Frotis de dia 08-10-11/08 → ***CGPs racimo***
  - bacteriemia asociada (HC positivos del dia 09 i 10/08)

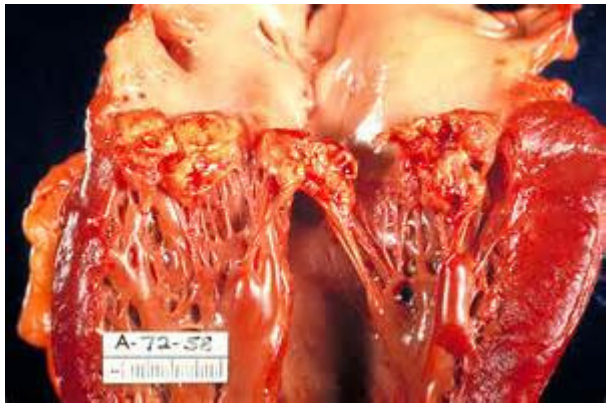
- 10/08: tratamiento antibiótico **Cloxacilina + vancomicina**

Holland TL1, Arnold C2, Fowler VG Jr1. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014 Oct 1;312(13):1330-41.

Sospecha clínica de endocarditis

- Endocarditis sobre válvula antiva
- Ecocardiografía transesofágica





¿Con qué pauta debemos iniciar el tto con Vancomicina en paciente crítico?

Recomendaciones TDM Vanco

Tabla 6. Recomendaciones de los niveles óptimos para vancomicina dependiendo de su régimen de administración y del tipo de infección[50,52,57,60,61]

	Vancomicina	
Tipo de infección	**Concentraciones séricas recomendadas**	
	Perfusión continua	**Régimen dosis múltiple**
Infección grave		
Neumonía	$\check{C}^{SS}$ = 20-25 mg/l	$C_{mín}^{SS}$ = 15-20 mg/l
Meningitis		$C_{máx}^{SS}$ = 30-40 mg/l*
Osteomielitis		
Infección herida/abcesos		
Bacteriemia	$\check{C}^{SS}$ = 15-20 mg/l	$C_{mín}^{SS}$ = 7-15 mg/l
		$C_{máx}^{SS}$ = 20-40 mg/l*

*Modelo farmacocinético bicompartimental; $C_{máx}$: concentración máxima; $C_{mín}$: concentración mínima; SS: *steady state*.

Appropriateness of vancomycin dosing in adult patients with normal renal function.

R. Juvany, E. Leiva, N. Méndez, M. E. Miquel, S. Cobo, A. Padullés, R. Jódar - Pharmacy, Hospital Universitari de Bellvitge

Abstract Submission for ESCP 2012 Symposium

- 117 pacientes y 144 determinaciones Cmin de vancomicina
- Cmin obtuvenidas 6 días de media (3-32) después del inicio de vancomicina

- Análisis de regresión lineal,

  Cmin se asociaron significativamente:
  - con la edad (B: 0,16, IC 95%: 0,12-0,21)
  - y BSA (B: -4,59, IC del 95%: -9,12-0,06).

UCI → 80% (n=8) Cmin <10

Cmin	Nº pacientes	Mediana (rango)
≤10 mg/L	72 (50%)	6,9 mg/L (1,5-10 mg/L)
<15 mg/L	113 (78,5%)	8,3 mg/L (1,5-14,9 mg/L)
>20 mg/L	5 (3,5%)	22,6 mg/L (20,6-26,8 mg/L)

- En función renal normal, una **dosis fija de 1 g cada 12 h de la vancomicina es insuficiente** para alcanzar los niveles deseados para evitar resistencias o para tratar infecciones complicadas.
- TDM de vancomicina debe ser realizado a pesar de la función renal normal.

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

Michael Rybak, Ben Lomaestro, John C. Rotschafer, Robert Moellering Jr., William Craig, Marianne Billeter, Joseph R. Dalovisio, and Donald P. Levine

Table 2.
Summary of Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring (TDM)[a]

Variable	Recommendation	Level of Evidence and Grade of Recommendation
Recommended TDM Parameters		
Optimal monitoring parameter	Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.	IIB
Timing of monitoring	Troughs should be obtained just prior to the next dose at steady-state conditions (approximately after the fourth dose).	IIB
Optimal trough concentration (see also Optimal trough concentration—complicated infections)	Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid development of resistance. For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC:MIC of 400.	IIIB
Optimal trough concentration—complicated infections (endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*)	Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.	IIIB
Dosing Regimen		
Dosing to achieve optimal trough concentrations	Daily doses of 15–20 mg/kg (as actual body weight) given every 8–12 hr are recommended for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. In patients with normal renal function, the targeted AUC:MIC of >400 is not achievable with conventional dosing methods if the MIC is ≥2 mg/L in a patient with normal renal function.	IIIB
Loading doses—complicated infections	In seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.	IIIB
Continuous vs. intermittent dosing	Continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing.	IIA
TDM for Vancomycin-Induced Nephrotoxicity		
Definition	A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.	IIB

Cmin

Cee → 4 dosis

Cmin >10 evitar ℞

Infx complicadas 15-20

Dm: 15-20mg/Kg c/8-12h para MIC ≤1

Infx serias D*20-30mg/Kg

Rybak M, Lomaestro B, Rotschafer JC et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009; 66: 82–98.

Adherence to the 2009 Consensus Guidelines for Vancomycin Dosing and Monitoring Practices: A Cross-Sectional Survey of U.S. Hospitals

Susan L. Davis,[1,2] Marc H. Scheetz,[3,4] John A. Bosso,[5] Debra A. Goff,[6,7] and Michael J. Rybak[1,*]

- A pesar de las recomendaciones de las guías de consenso, **no se aplican de forma amplia las prácticas para la dosificación y monitorización de vancomicina**.

Table 1. Frequency of Practices for Vancomycin Therapeutic Drug Monitoring in 163 Hospitals[a]

Therapeutic drug monitoring practice	Never	Sometimes	Always
Use of trough concentrations as optimal monitoring parameter, and no use of peak serum concentration monitoring	1 (0.6)	31 (19)	129 (79)
Trough concentrations obtained just before next dose at steady state, just before fourth dose	0 (0)	88 (54)	73 (45)
Maintenance of trough concentrations > 10 mg/L to avoid development of resistance	1 (0.6)	33 (20)	127 (78)
Targeting trough concentrations of 15–20 mg/L for complicated infections	0 (0)	28 (17)	133 (82)
No trough monitoring for patients with short courses of therapy and with stable renal function	32 (20)	102 (63)	22 (14)
Use of loading doses in seriously ill patients and complicated infections to facilitate rapid attainment of target serum concentrations **57%**	22 (14)	70 (43)	68 (42)
Doses based on actual body weight in normal-weight patients	1 (0.6)	29 (18)	131 (80)
Doses based on actual body weight in obese patients	9 (6)	65 (40)	85 (52)
Systematically monitoring nephrotoxicity in patients receiving vancomycin	56 (34)	63 (39)	31 (19)
Monitoring for ototoxicity in patients receiving concomitant ototoxic agents	77 (47)	57 (35)	14 (9)
Administration of vancomycin as a continuous infusion[b]	145 (89)	13 (8)	3 (2)

[a]Data are no. (%) of respondents. For each question, 2–13 respondents did not know the answer or declined to respond; percentages are based on the total of 163 responses.
[b]Not recommended by the consensus guidelines.[1]

Davis SL, Scheetz MH. et al. Adherence to the 2009 Consensus Guidelines for Vancomycin Dosing and Monitoring Practices: A Cross-Sectional Survey of U.S. Hospitals. PHARMACOTHERAPY Volume 33, Number 12, 2013

PKPD Vancomicina – paciente crítico

Number of patients	Age (years)	Weight (kg)	CLcr (ml/min)	CL (ml/min)	Vd (l/kg)	Reference
11	46.5 ± 16.6	67.8 ± 5.2	87.6 ± 22.3	62.7 ± 25.3	0.72 ± 0.35	20
50	37.3 ± 11.6	70.3 ± 16.0	76.9 ± 41.0	61.9 ± 22.3	0.55 ± 0.19	21
22	52.4 ± 14.7	71.0 ± 23.8	97.4 ± 35.7	79.2 ± 34.2	0.54 ± 0.22	22
704	44.5 ± 15.9	73.2 ± 17.2	80.2 ± 34.4	78.9 ± 37.1	0.64 ± 0.26	23
15	60.0 ± 9.0	79.0 ± 12.0	82.0 ± 27.1	78.3 ± 32.6	0.65 ± 0.15	24
107	53.4 ± 17.2	77.1 ± 23.1	89.5 ± 28.6	79.5 ± 33.3	0.60 ± 0.20	25
46	59.3 ± 16.9	71.5 ± 12.8	65.5 ± 48.1	60.0 ± 39.7	1.68 ± 2.19	This study

Pathogen	Vancomycin daily dose (mg)		
	1000	2000	3000
S. aureus	43.5	78	89.5
Coagulase-neg. staphylococci	28	61	79
S. epidermidis	24.5	55.5	75
S. haemolyticus	31	65	81
S. pneumoniae	86.5	97.5	99
Enterococcus faecalis	26	58	76.5
E. faecium	50	82	91.5

Equation 1 ($r^2 = 0.64$; $p < 0.01$):

$\mathbf{CL}(\text{ml/min/kg}) = 0.660 - 0.016*\text{age(years)} - 0.006*\text{ApII} + 0.380*\text{Ab} + 0.562*\text{CLcr}_i$ (ml/min/kg)

Equation 2 ($r^2 = 0.68$; $p < 0.01$):

$\mathbf{CL}(\text{ml/min/kg}) = 0.872 - 0.015*\text{age(years)} - 0.007*\text{ApII} + 0.234*\text{Ab} + 0.346\ \text{CLcr}_{\text{Levey}}$ (ml/min/kg)

Fernández de Gatta MM, RevillaN. Et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med (2007) 33:279–285

Nomograma dosificación paciente crítico

- **Kg** (actual) determina D* y Dm
- **eGFR** (MDRD) determina la ν

- Aumento de pacientes con Cmin inicial ≥15 mg/ml:
  39% (n=22) preimplantación a 72% (n=43) en el grupo posterior a la implementación (P = 0,0004).

- No diferencia en nefrotoxicidad:
  grupo post-implementación en comparación con grupo pre (18% vs 17,5%, P = 1,0).

Actual Body Weight	Loading Dose	Maintenance Dose based on estimated GFR (ml/min/1.73 m^2)			Actual Body Weight
		31-40	41-60	> 60	
40-49 kg	1000 mg x1	750 mg q24h	750 mg q12h	750 mg q8h	40-49 kg
50-59 kg	1250 mg x1	1000 mg q24h	1000 mg q12h	1000 mg q8h	50-59 kg
60-69 kg	1500 mg x1	1000 mg q24h	1000 mg q12h	1500 mg q8h	60-69 kg
70-79 kg	1750 mg x1	1250 mg q24h	1250 mg q12h	1500 mg q8h	70-79 kg
80-89 kg	2000 mg x1	1500 mg q24h	1250 mg q12h	1500 mg q8h	80-89 kg
90-99 kg	2250 mg x1	1500 mg q24h	1500 mg q12h	2000 mg q8h	90-99 kg
100-109 kg	2250 mg x1	1750 mg q24h	2000 mg q12h	2000 mg q8h	100-109 kg
110-119 kg	2250 mg x1	2000 mg q24h	2000 mg q12h	2000 mg q8h	110-119 kg
≥120 kg	2250 mg x1	2000 mg q24h	2000 mg q12h	2000 mg q8h	≥120 kg

Target trough: 15-20 mcg/ml

When to draw levels: **c/24h** **c/12h** **c/8h**

eGFR > 30 ml/min: Obtain trough immediately prior to 4th dose

If patient > 150 kg contact pharmacist for dosing recommendations

Fig. 1 Vancomycin dosing nomogram for ICU patients.

Golenia BS, Levine AR, Moawad IM, Yeh DD, Arpino PA. Evaluation of a vancomycin dosing nomogram based on the Modification of Diet in Renal Disease equation in intensive care unit patients. J Crit Care. 2013 Oct;28(5):710-6

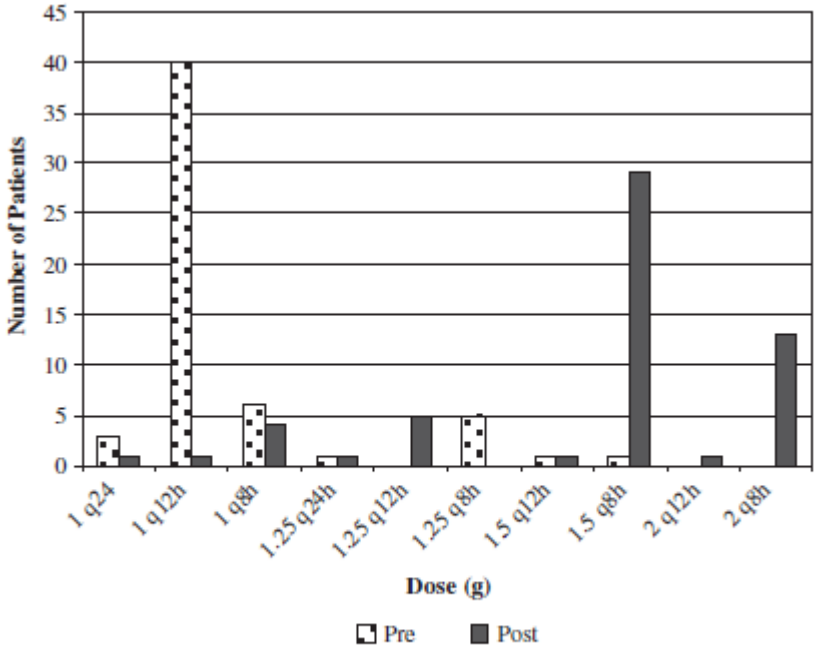


Fig. 4 Distribution of initial vancomycin regimens.

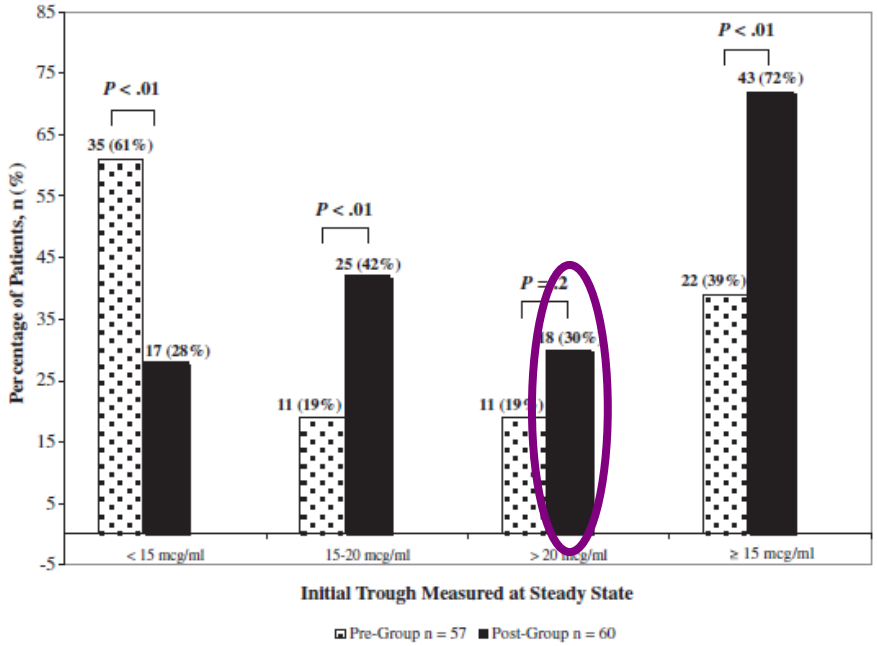


Fig. 3 Comparison of initial trough preimplementation vs postimplementation.

Vanco – Bacterièmia per MRSA

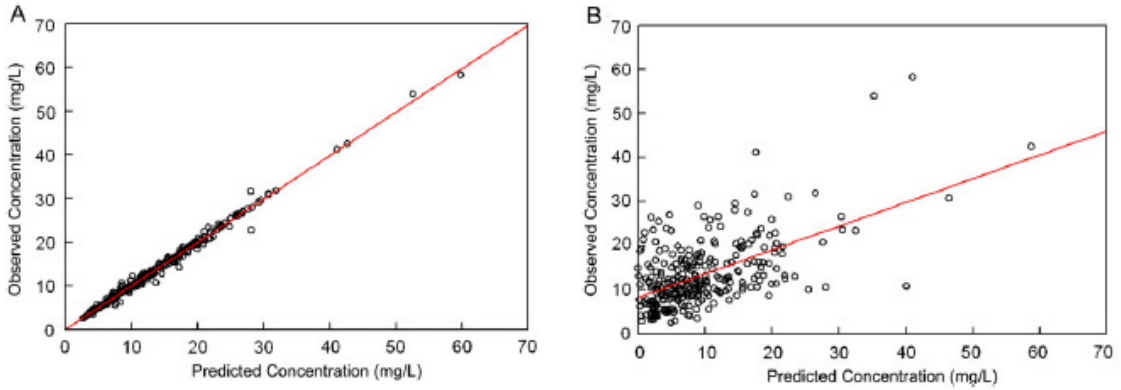


Figure 1. Observed vs predicted concentrations for Bayesian estimation approach (*A*) and formula-based approach (*B*).

Table 3. Association Between the Classification and Regression Tree Analysis–Derived Vancomycin Minimum Concentration and Area Under the Curve Exposure Variables and Overall Failure and 30-Day Mortality in the Poisson Regression Analyses

		Overall Failure[a]			30-d Mortality[b]		
	Exposure	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Day 1	$C_{min0-24\ h}/MIC_{BMD} \geq 14.9$	1.24	.67–2.29	.50	1.65	.77–3.56	.19
	$C_{min0-24\ h}/MIC_{ETEST} \geq 4.4$	0.63	.37–1.08	.09	0.43	.22–.87	.02
	$AUC_{0-24\ h}/MIC_{BMD} \geq 521$	0.54	.32–.91	.02	0.43	.20–.90	.03
	$AUC_{0-24\ h}/MIC_{ETEST} \geq 303$	0.48	.29–.78	.003	0.32	.16–.64	.001
Day 2	$C_{min24-48\ h}/MIC_{BMD} \geq 20.4$	1.47	.79–2.54	.24	1.38	.69–2.75	.36
	$C_{min24-48\ h}/MIC_{ETEST} \geq 11.2$	0.80	.44–1.44	.46	0.97	.46–2.03	.93
	$AUC_{24-48\ h}/MIC_{BMD} \geq 650$	0.58	.34–.99	.05	0.50	.25–1.02	.06
	$AUC_{24-48\ h}/MIC_{ETEST} > 320$	0.53	.32–.88	.01	0.49	.24–.98	.04

Lodise TP, Drusano GL, Zasowski E, et al. Vancomycin Exposure in Patients With Methicillin-Resistant Staphylococcus aureus Bloodstream Infections: How Much Is Enough? CID 2014:59 (1 September)

Estrategias optimización Vanco – críticos

- Pauta ajustada desde el inicio del ttm
  - Dosis de carga **20-30mg/Kg**
  - Mantenimiento: pauta **15-20mg/Kd c/8-12h**

- Monitorización niveles + Bayesiano
  - Pauta 1g/8h → monitorización 1º día
  - D*15-20mg/Kg + nivel → individualización

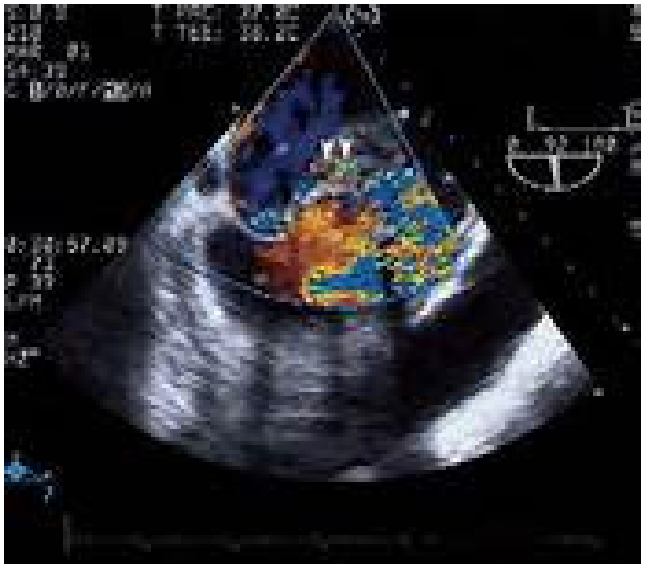
Optimizar pauta de VANCO según Cp (bayesiano PKS)
- Si bacteriemia: Cmin 10-15
- Si pneumonia: Cmin 15-20

Dia +12 Caso clínico

- 11/08 es confirma *S.aureus* sensible
- Se descarta endocarditis. Ecocardiografía

  – se retira vancomicina

  – Se continua con cloxacilina



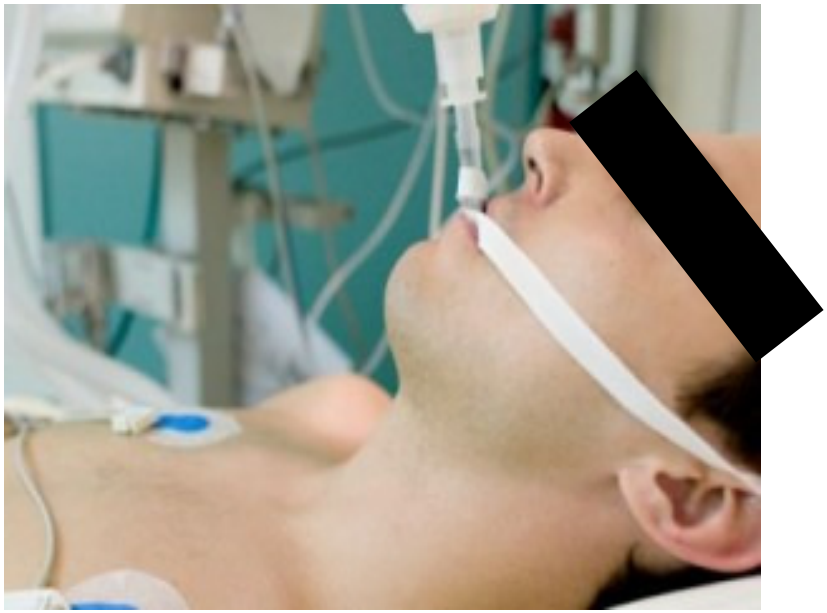
Si MRSA:

- **Optimizar pauta de VANCO** según Cp (bayesiano PKS)
- **Daptomicina**: 10mg/Kg/dia (NO pneumonia)
- **Linezolid**: precaución toxicidades/interacciones

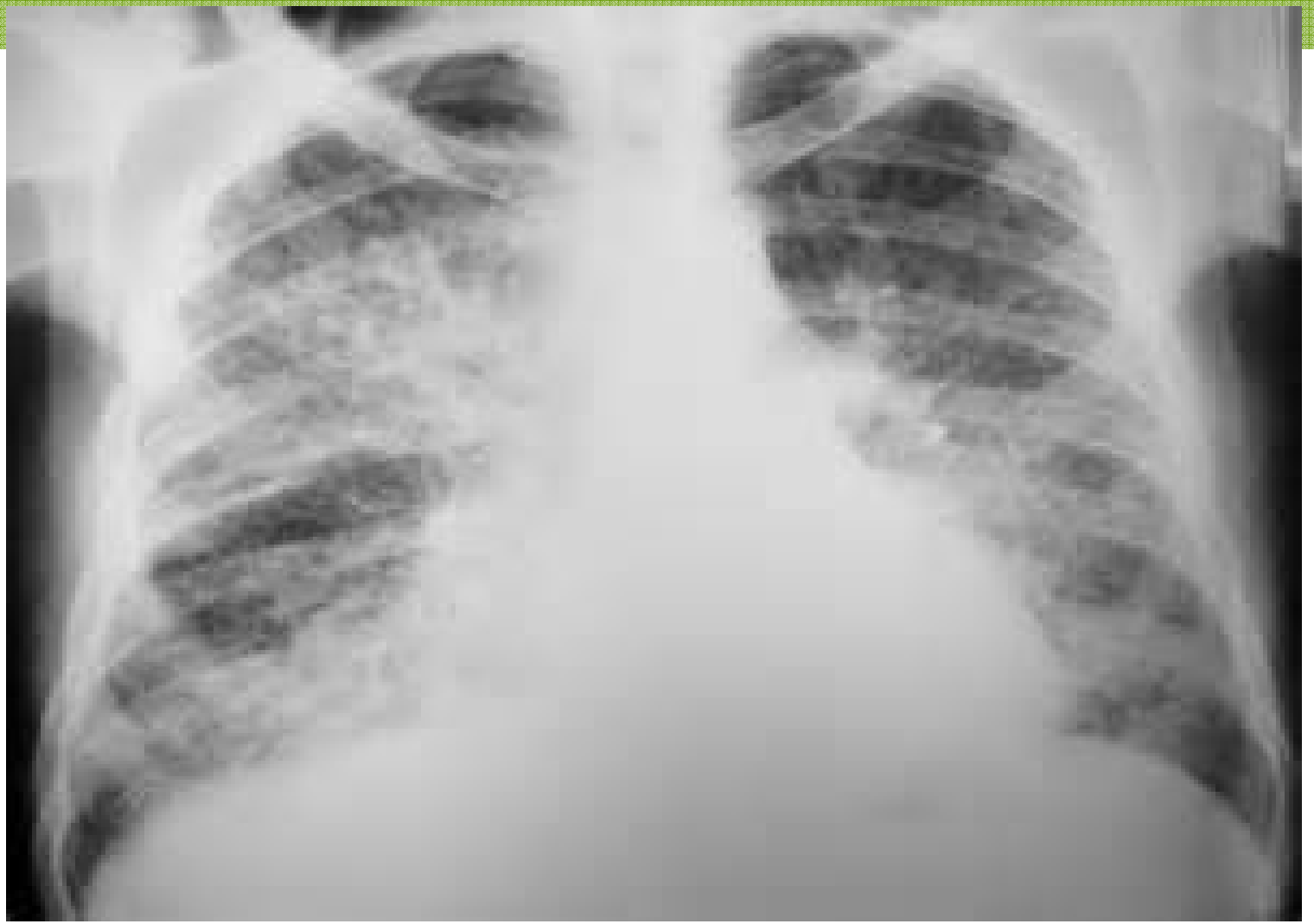
Dia +14 Empeoramiento clínico

- El día 14/08/2014 requiere reintubación orotraqueal

- Insuficiencia respiratoria importante requiriendo PEEP alta (PEEP +14 cmH2O i FiO2 70%).



Radiología de torax



Presenta infiltrado bilaterales y mala adaptación a la VMNI

Diagnóstico clínico pneumonia

Table 1 The clinical pulmonary infection score (CPIS)

Assessed Parameter	Result	Score
Temperature (°Celsius)	36.5–38.4 °C	0
	38.5–38.9 °C	1
	≤ 36 or ≥ 39 °C	2
Leukocytes in blood (cells/mm³)	4,000–11,000/mm³	0
	< 4,000 or > 11,000/mm³	1
	≥ 500 Band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/non-purulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diffuse/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth	1
	Moderate or florid growth AND pathogen consistent with Gram stain	2
Oxygenation status (defined by PaO_2:FiO_2)	> 240 or ARDS	0
	≤ 240 and absence of ARDS	2

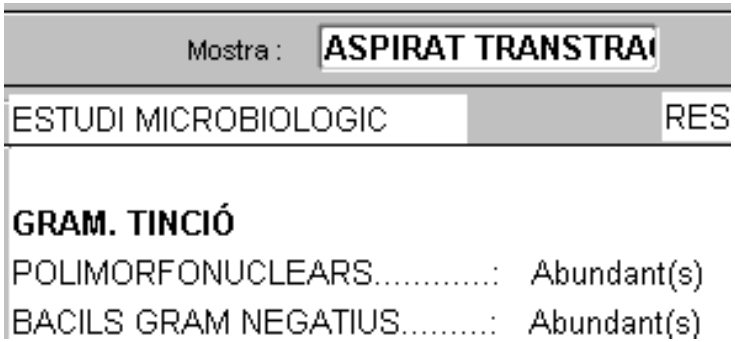
ARDS: acute respiratory distress syndrome; CHF: congestive heart failure

Diagnóstico microbiológico

B. Diagnóstico etiológico
N1. Muestra mínimamente contaminada:
- Lavado broncoalveolar ≥ 10^4 UFC/ml o ≥ 5% células con bacterias intracelulares
- Cepillo protegido ≥ 10^3 UFC/ml
- Aspirado distal protegido ≥ 10^3 UFC/ml
N2. Muestra posiblemente contaminada:
- Aspirado endotraqueal ≥ 10^6 UFC/ml
N3. Métodos microbiológicos alternativos:
- Hemocultivo positivo no relacionado con otro foco de infección
- Crecimiento patógeno en cultivo de líquido pleural
- Punción aspirativa positiva pleural o de absceso pulmonar
- Evidencia de neumonía en examen histológico pulmonar
- Diagnóstico positivo de neumonía por virus o microorganismos particulares (*Legionella*, *Aspergillus*, micobacteria, micoplasma, *Pneumocystis jiroveci*)
• Detección positiva de antígeno viral o anticuerpos a partir de secreciones respiratorias (EIA, FAMA, Shell vial assay, PCR)
• Examen directo positivo o cultivo positivo de secreciones bronquiales o tejido
• Seroconversión (p. ej., virus influenza, *Legionella*, *Chlamydia*)
• Detección de antígenos en orina (*Legionella* o neumococo)
N4. Cultivo positivo de esputo o no cuantitativo de muestra de tracto respiratorio
N5. Sin microbiología positiva

Dia +14 Muestras

- 14/08 BAL → BGN


Mostra : ASPIRAT TRANSTRA(

ESTUDI MICROBIOLOGIC RES

GRAM. TINCIÓ

POLIMORFONUCLEARS.....: Abundant(s)

BACILS GRAM NEGATIUS.....: Abundant(s)

- Cobertura neumonía tardía:
  - **Piperacilina+tazobactam + Colistina nebulizada**

Tratamiento

Table 2 Comparison of recommended initial empiric therapy for ventilator-associated pneumonia (VAP) according to time of onset [1], [34], [41]

Early-onset VAP	Late-onset VAP
Second or third generation cephalosporin: e. g., ceftriaxone: 2 g daily;	Cephalosporin
cefuroxime: 1.5 g every 8 hours;	e. g., cefepime: 1–2 g every 8 hours;
cefotaxime: 2 g every 8 hours	ceftazidime 2 g every 8 hours
OR	OR
Fluoroquinolones	Carbepenem
e. g., levofloxacin: 750 mg daily;	e. g., imipenem + cilastin: 500 mg every 6 hours or 1 g every 8 hours;
moxifloxacin: 400 mg daily	meropenem: 1 g every 8 hours
OR	OR
Aminopenicillin + beta-lactamase inhibitor e. g., ampicillin + sulbactam: 3 g every 8 hours	Beta-lactam/beta-lactamase inhibitor
OR	e. g., piperacillin + tazobactam: 4.5 g every 6 hours
Ertapenem	PLUS
1 g daily	Aminoglycoside
	e. g., amikacin: 20 mg/kg/day;
	gentamicin: 7 mg/kg/day;
	tobramycin: 7 mg/kg/day
	OR
	Antipseudomonal fluoroquinolone
	e. g., ciprofloxacin 400 mg every 8 hours;
	Levofloxacin 750 mg daily
+ / -	PLUS
	Coverage for MRSA
	e. g., vancomycin: 15 mg/kg every 12 hours
	OR
	linezolid: 600 mg every 12 hours

Optimal dosage includes adjusting for hepatic and renal failure. Trough levels for vancomycin (15–20 mcg/ml), amikacin (< 5 mcg/ml), gentamicin (< 1 mcg/ml) and tobramycin (< 1 mcg/ml) should be measured frequently to avoid untoward systemic side effects. All recommended doses are for intravenous infusion. Usual duration of therapy is 8 days unless treatment is for multidrug resistant organisms, in which case treatment will be for 14 days.

Tratamiento empírico NAV

Clin Microbiol Infect. 2001 Jan;7(1):32-3.
Therapy of ventilator-associated pneumonia: the Tarragona strategy.
Bodí M1, Ardanuy C, Olona M, Castander D, Diaz E, Rello J;
Department of Critical Care, Hospital Univeristari Joan XXIII, Tarragona, Spain.

-Med Klin Intensivmed Notfmed. 2014 Apr;109(3):156-61.
10.1007/s00063-013-0310-7. Epub 2014 Mar 22.
Tarragona strategy--appropriate antibiotic therapy in the ICU]
Engelmann L1, Schmitt DV.

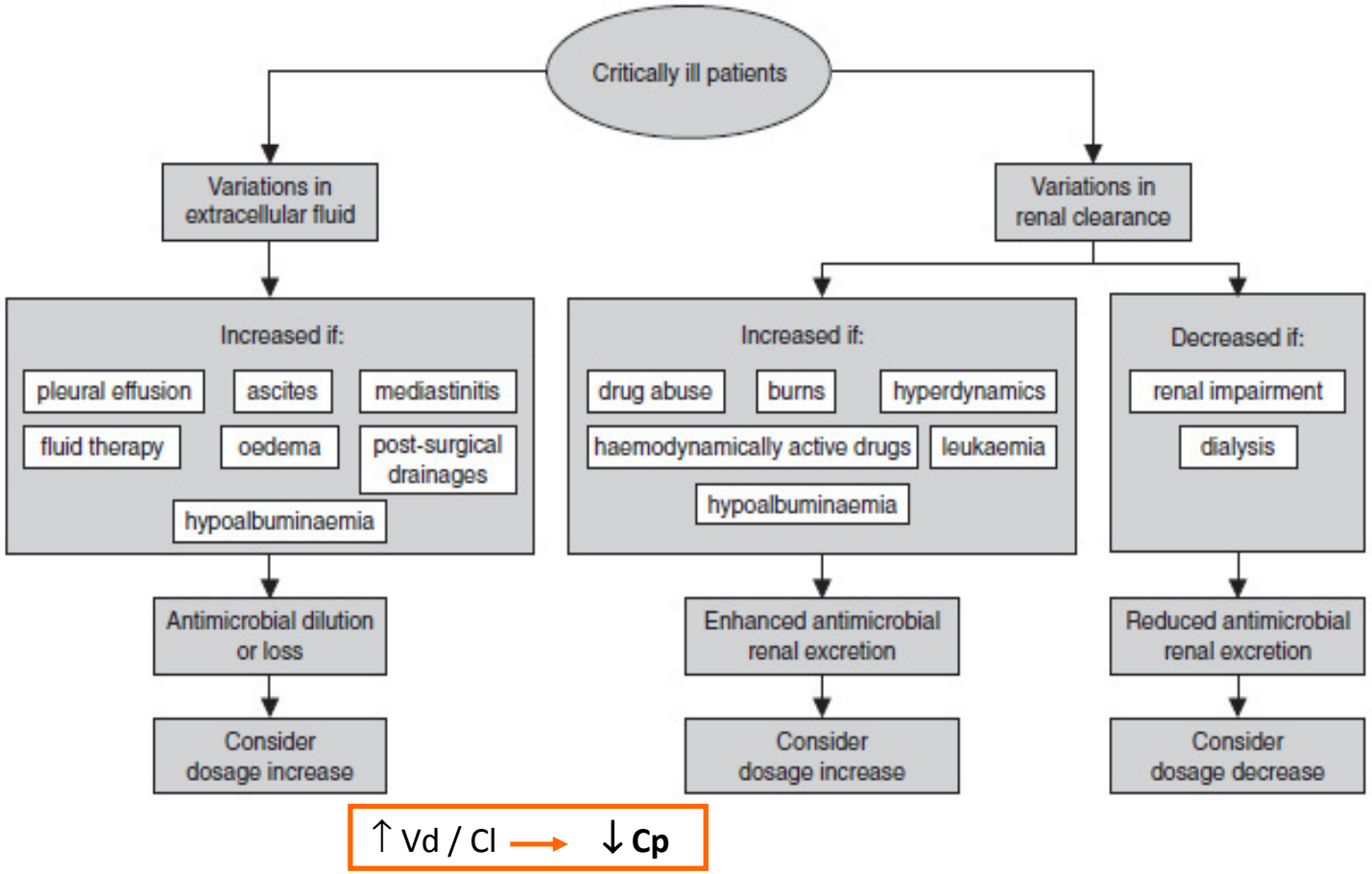
Monoterapia?

Un adecuado tratamiento antibiótico inicial disminuye la mortalidad a los 60 dias

Crit Care. 2013 Nov 7;17(6):R265. 10.1186/cc13095.
Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia**: impact on survival and bacterial resistance.**
Adrie C, Schwebel C, Garrouste-Orgeas M, Vignoud L, Planquette B, Azoulay E, Kallel H, Darmon M, Souweine B, Dinh-Xuan AT, Jamali S, Zahar JR, Timsit JF ; Article Was Written on behalf of the Outcomerea Study Group.

¿Podemos optimizar la administración de Piperacilina/tazobactam en neumonía asociada a VM?

Influencia de la fisiopatología sobre PK de los AB



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.

Fisiopatología sobre PK de los antibióticos

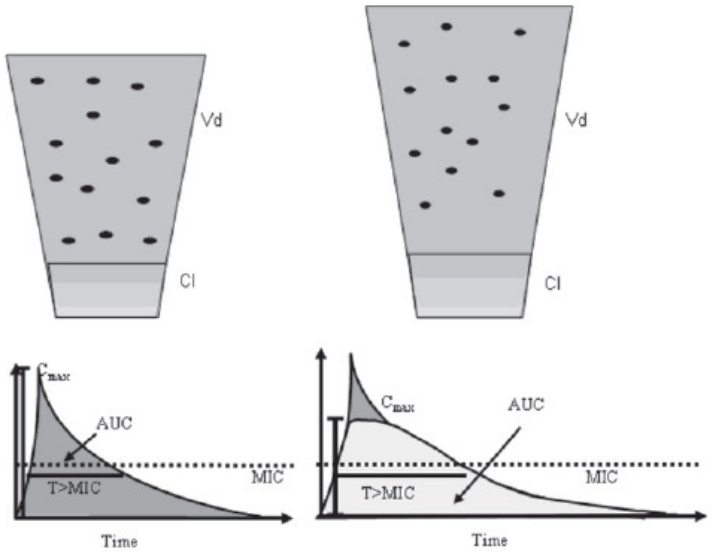
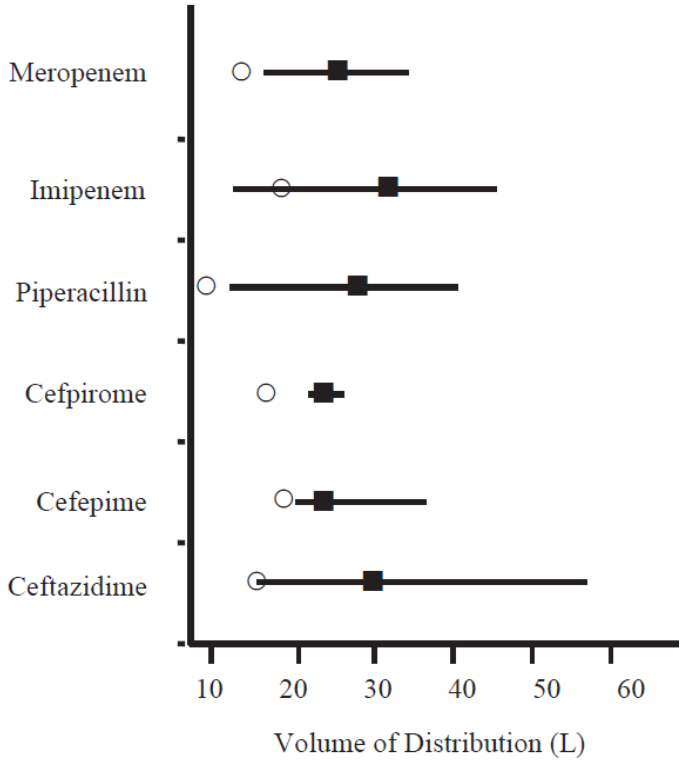


Figure 1 ICU patients present pharmacokinetic changes of antibiotics that may alte antibiotics in healthy volunteers (left panel). A large volume of distribution (V_d) (middle pane decreased maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$) and eventually higher bacteria minimum inhibitory 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*

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% $T_{>4\text{-}5\,MIC}$
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.*

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.*

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 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**

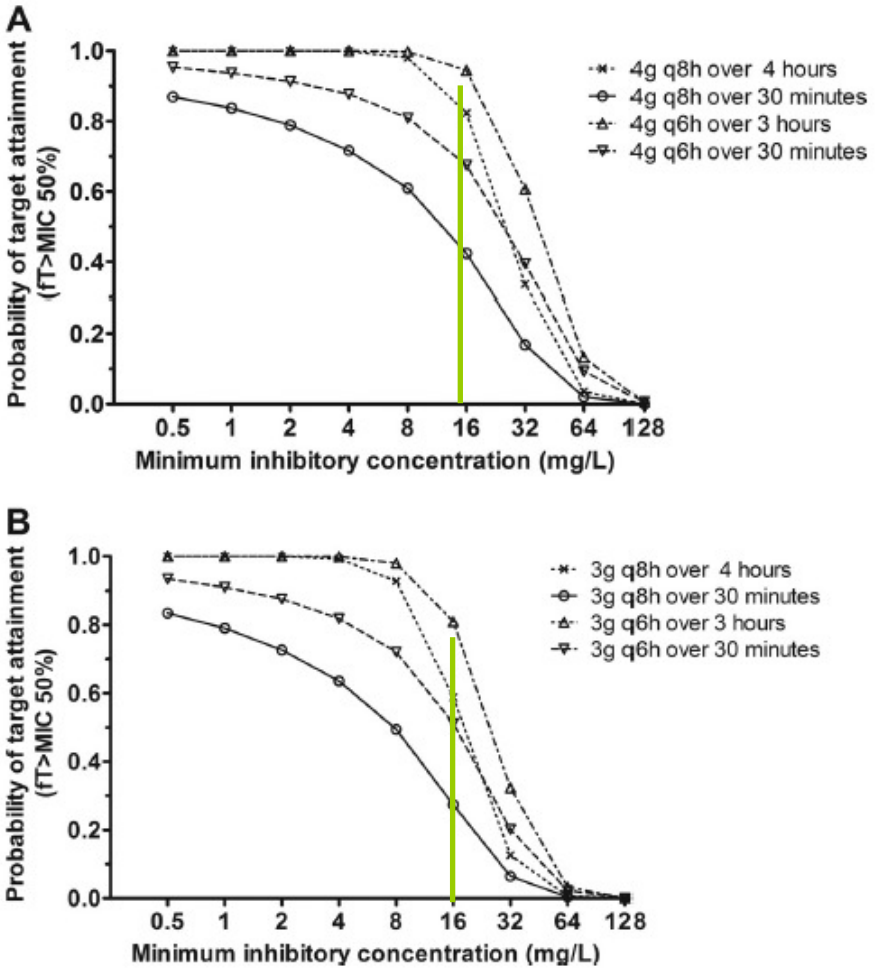


FIG 2 Results of the Monte Carlo simulation with the fractional target attainments against a range of MICs were determined for piperacillin administered intravenously (i.v.) for either 30 min or 4 h every 8 h as well as for 30 min or 3 h every 6 h (A), and 3 g pipe either 30 min or 4 h every 8 h as well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

Penetración pulmonar PiperTazo

- Gran variabilidad en las Cp piperacilina/tazobactam, con una **penetración alveolar de 40-50% para piperacilina** y 65-85% para tazobactam
  - asociación negativa entre las Cp o C-alveolares y ClCr

- Pacientes fx renal normal o con IR leve
  - **IC de 16/2 g permite alcanzar C. objetivo**,
  - NO con 12/1,5 g /día

Table 2. Individual P/T concentrations and outcomes in patients with no/mild renal failure

	Piperacillin Concentration					Tazobactam Concentration							
	Serum (mg/L)					Serum (mg/L)							Outcome
Patient No	8:00 a.m.	12:00 p.m.	6:00 p.m.	ELF (mg/L)	ELF/Serum	8:00 a.m.	12:00 p.m.	6:00 p.m.	ELF (mg/L)	ELF/Serum	Pathogen	MIC (mg/L)	Clinical	Microbiological
P/T 12/1.5 g														
1	33.7	52.0	42.9	14.8	.28	3.4	6.4	2.4	5.5	.86	*E. coli*	.25	Cure	Eradication
2	36.2	26.1	13.8	18.0	.69	4.8	3.5	3.5	6.9	1.97	*P. aeruginosa*	2	Cure	Eradication
3	37.0	32.6	32.3	17.0	.52	5.8	6.1	5.4	6.4	1.05	*P. aeruginosa*	1	Cure	Eradication
4	24.0	24.4	27.8	19.0	.78	5.0	2.8	6.1	1.4	.50	*S. aureus* oxa-R	>16	Cure	Eradication
5	20.0	20.7	17.6	10.7	.52	7.5	3.9	6.6	3.3	.85	*K. oxytoca*	.5	Cure	Eradication
6	32.2	45.5	35.4	18.2	.40	8.4	5.3	8.8	12.1	2.28	*S. aureus* oxa-R	>16	Cure	Eradication
7	33.0	30.5	32.8	6.1	.20	6.6	3.7	5.6	2.5	.68	*P. aeruginosa*	4	Failure	Persistence
8	11.8	7.8	15.3	4.8	.62	4.3	4.1	4.5	5.4	1.32	*P. aeruginosa*	2	Cure	Eradication
9	22.4	23.2	19.8	8.4	.36	5.4	6.2	5.8	4.3	.69	*E. coli*	.25	Cure	Eradication
10	20.5	23.1	24.3	6.7	.29	4.2	6.9	3.2	4.6	.67	*C. freundii*	.25	Cure	Eradication
Median	28.1	25.3	26.1	12.7	.46	5.2	4.7	5.5	5.0	.85	—	—	—	—
IQR range	20.5–33.7	23.1–32.6	17.6–32.8	6.7–18.0	.29–.62	4.3–6.6	3.7–6.2	3.5–6.1	3.3–6.4	.68–1.32	—	—	—	—
P/T 16/2 g														
11	32.6	32.9	35.7	12.5	.38	6.7	6.8	6.0	5.8	.85	*P. aeruginosa*	2	Cure	Eradication
12	31.3	12.7	19.8	18.7	1.47	3.6	4.9	5.6	4.1	.84	*S. aureus* oxa-R	>16	Cure	Eradication
13	41.2	48.4	55.5	14.5	.30	4.4	1.7	4.6	3.5	2.06	*S. aureus* oxa-R	>16	Cure	Eradication
14	26.5	15.7	22.3	14.0	.89	5.0	4.0	6.1	1.7	.43	*P. aeruginosa*	4	Failure	Superinfection
15	35.0	39.7	30.7	13.6	.34	11.0	2.6	7.8	3.7	1.42	*P. aeruginosa*	2	Death	NA
16	37.9	38.0	39.1	24.8	.65	19.0	18.8	25.5	17.0	.90	*P. aeruginosa*	1	Cure	Eradication
17	113.0	116.7	120.1	19.6	.17	22.8	24.4	26.8	12.2	.50	*E. coli*	.5	Cure	Eradication
18	86.5	78.2	88.3	20.2	.26	12.7	11.6	13.1	6.5	.56	*K. pneumoniae*	.25	Cure	Eradication
19	62.3	59.6	58.4	28.3	.47	13.4	14.5	11.7	7.2	.50	*P. aeruginosa*	1	Cure	Eradication
20	43.5	34.7	25.6	21.5	.62	4.1	3.8	4.6	4.0	1.05	*E. coli*	.5	Cure	Eradication
Median	39.6	38.9	37.4	19.1	.43	8.9	5.9	7.0	5.0	.84	—	—	—	—
IQR range	32.6–62.3	32.9–59.6	25.6–58.4	14.0–21.5	.30–.65	4.4–13.4	3.8–14.5	5.6–13.1	3.7–7.2	.50–1.05	—	—	—	—

P/T, piperacillin/tazobactam; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; IQR, interquartile range; oxa-R, oxacillin-resistant.

Boselli E, Breilh D, Rimmelé T, et al. Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia. Crit Care Med 2008 Vol. 36, No. 5

Penetración pulmonar PiperTazo

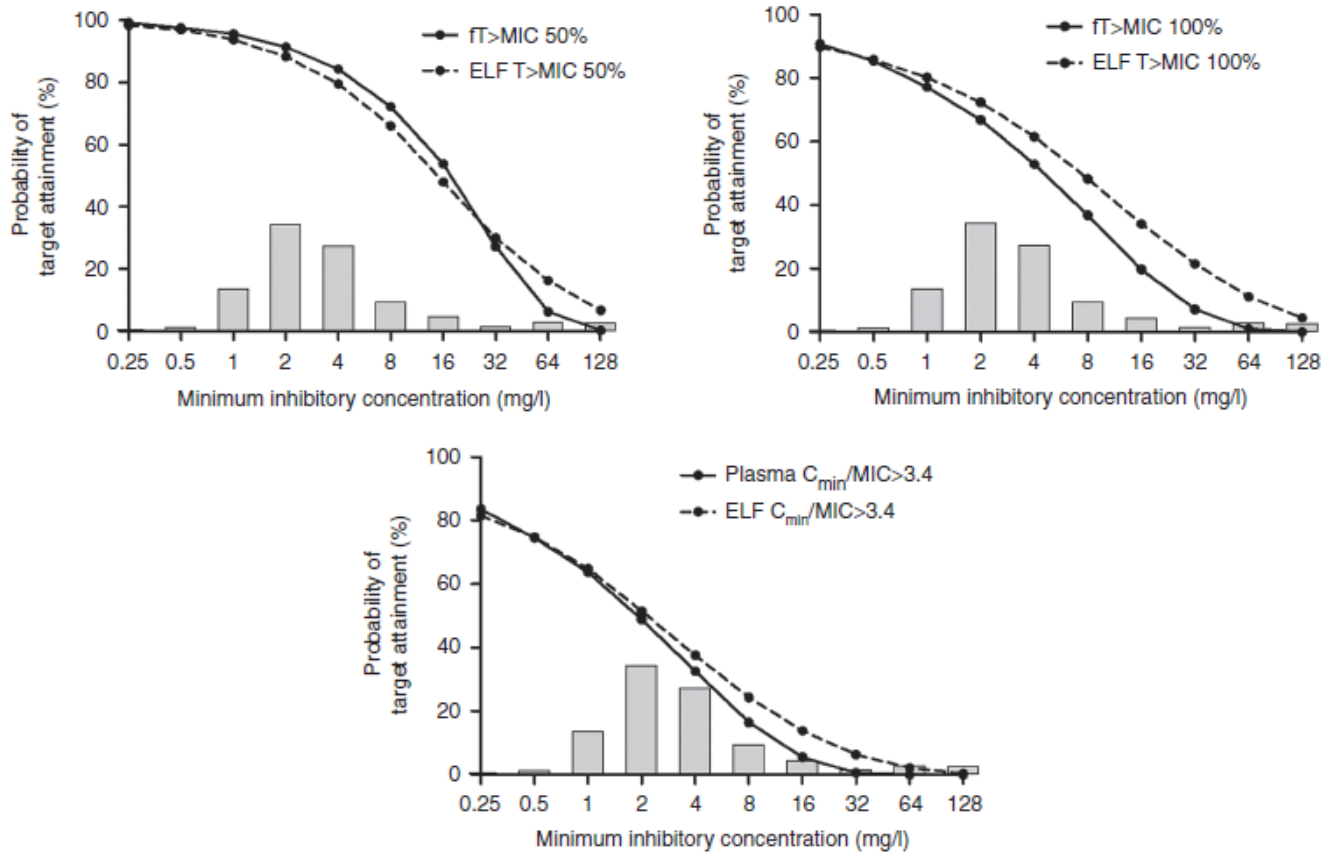


Figure 6 Results of the Monte Carlo simulation with the probability of target attainments, for unbound (solid line) and ELF (dashed line) piperacillin, against a range of MICs. The pharmacodynamic targets are the fraction of patients whose drug concentration was about the MIC for 50% (left panel) or 100% (middle panel) of the dosing interval and the fraction of patients whose trough piperacillin concentration to MIC ratio was ≥3.4. Histogram shows MIC distribution for organisms causing hospital-acquired and ventilator-associated pneumonia.[26] ELF, epithelial lining fluid; MIC, minimum inhibitory concentration.

Felton TW, McCalman K, Malagon I, et al. Pulmonary Penetration of Piperacillin and Tazobactam in Critically Ill Patients. Clinical pharmacology & Therapeutics Vol 96 N 4, October 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)

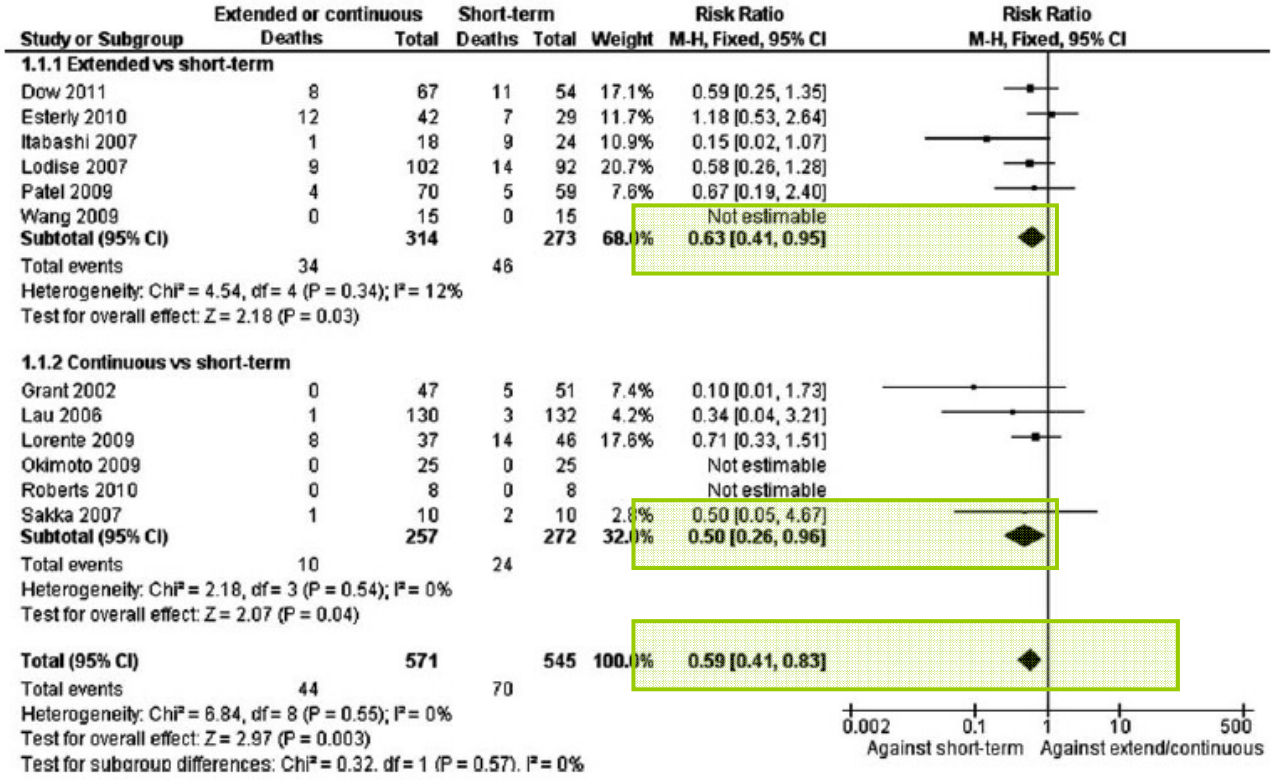
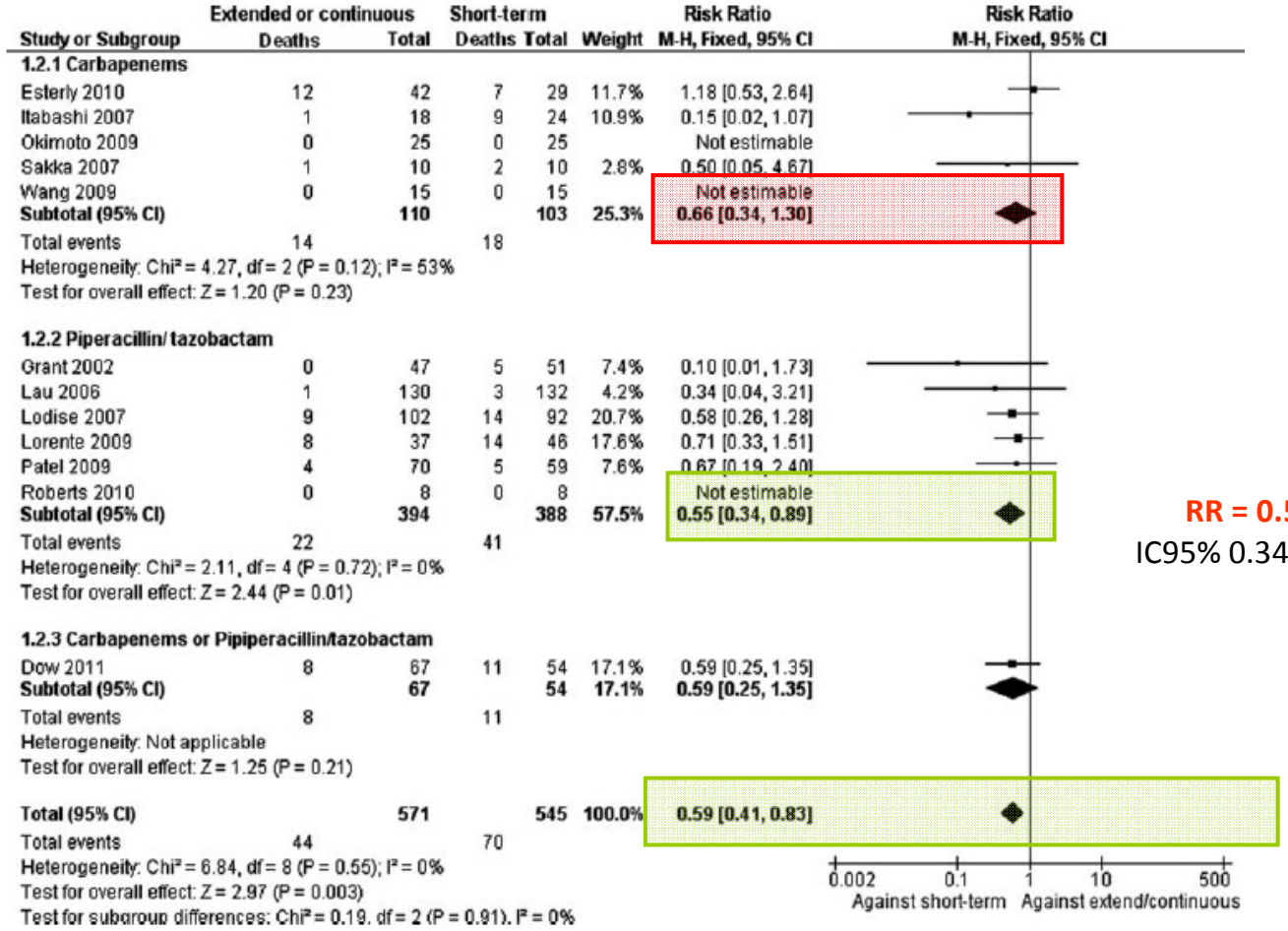


Figure 2. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios

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



RR = 0.55
IC95% 0.34–0.89

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

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

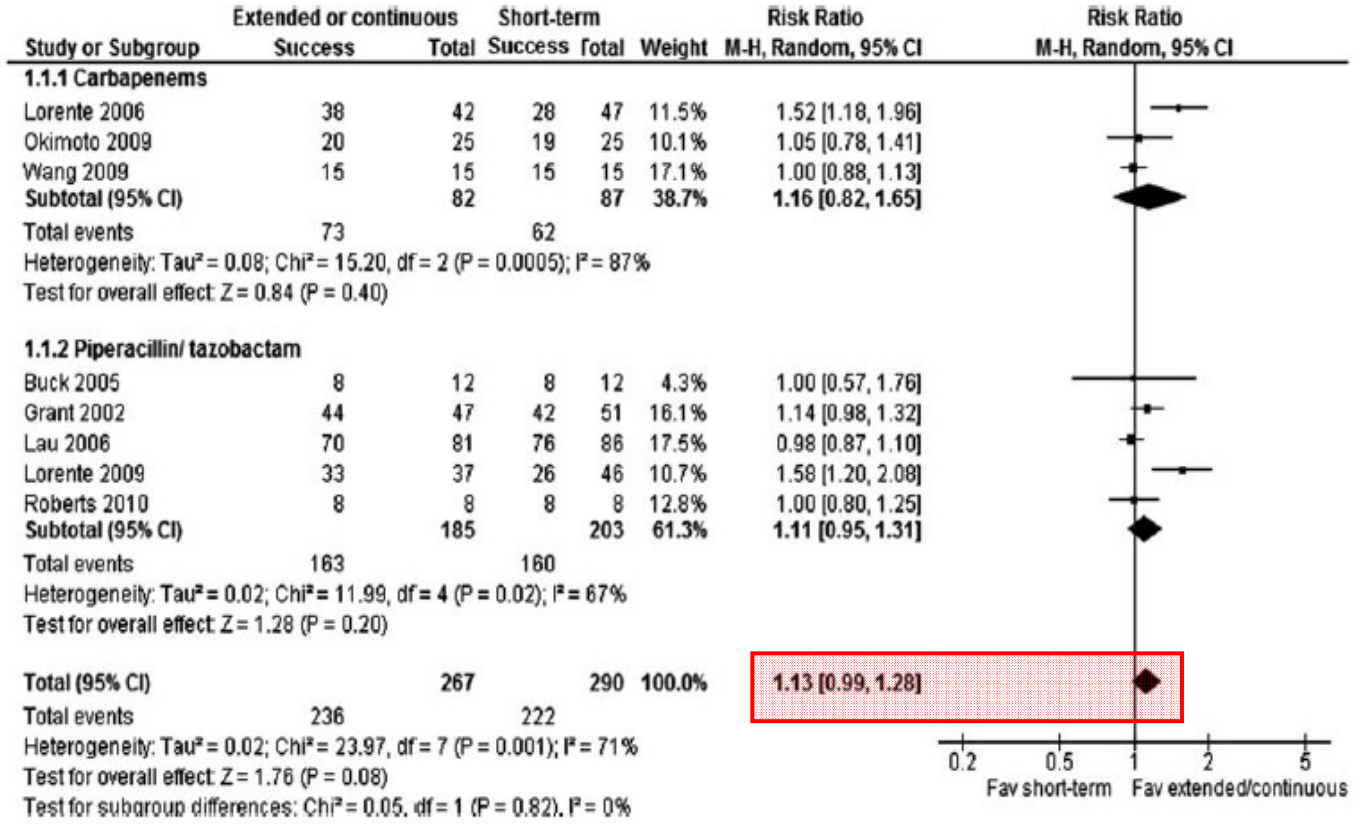


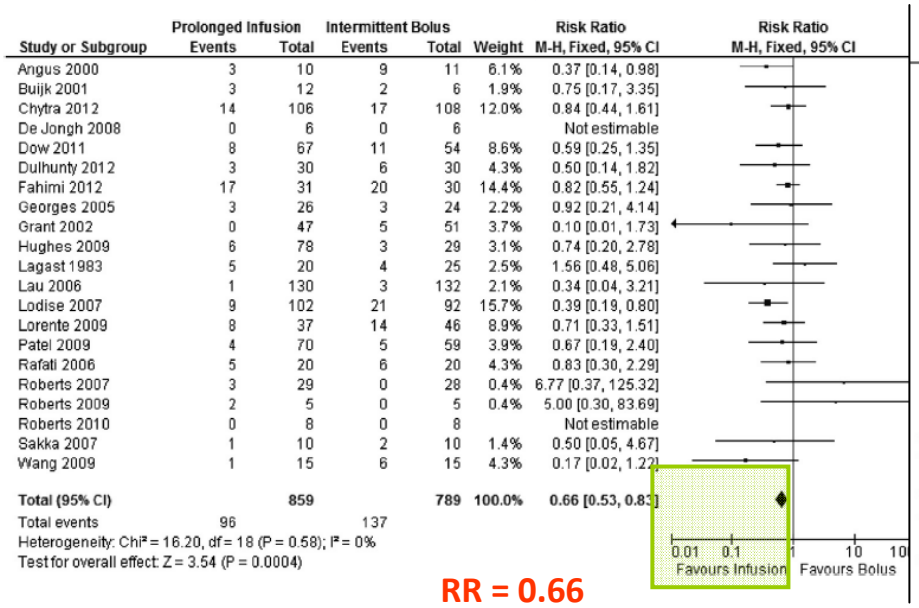
Figure 4. Forest plot depicting the risk ratios of clinical cure of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk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

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

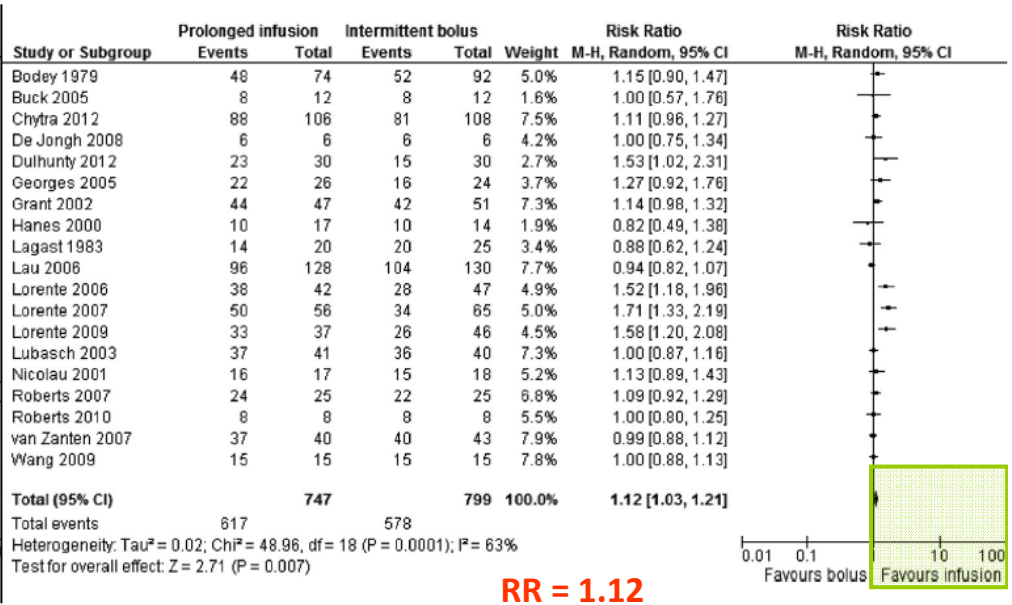
Mortality



RR = 0.66

IC95% 0.53–0.83

Clinical success



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.

Uso de IE o IC en práctica clínica

- Encuesta: Fceuticos hosp y Fceuticos miembros de la "Society of Infectious Diseases Pharmacists (SIDP)"
- La mayoría no hace uso de IC o IP de antibióticos:
  - 29 (11,2%) y 15 (5,8%) hospitales reportaron el uso de IC y IP, respectivamente.
- Motivos: mayor eficacia, igual o menor toxicidad, y ahorro de costes.
- La **PENICILINAS** son los ABL que se administran con mayor frecuencia como IC y IE.
- Los encuestados de la SIDP informaron con mayor frecuencia el uso de IP que los otros encuestados

Table 3.
Provision of ID and Pharmacokinetic Services Among Hospitals Using Continuous and Extended Infusions[a]

Characteristic	No. (%) Respondents: Random-Sample Survey, Using Continuous Infusions (n = 27)[b]	Random-Sample Survey, Using Extended Infusions (n = 14)	SIDP Survey, Using Continuous Infusions (n = 30)[b]	SIDP Survey, Using Extended Infusions (n = 21)
Provides ID consultation service	22 (82)	11 (79)	29 (97)	20 (95)
ID pharmacist participates on ID rounds	12 (44)	5 (36)	26 (87)	18 (86)
Offers pharmacokinetic services	25 (93)	14 (100)	27 (90)	20 (95)

[a]ID = infectious diseases, SIDP = Society of Infectious Diseases Pharmacists.
[b]A significantly greater percentage of SIDP survey respondents than random-sample survey respondents reported use of continuous infusions (30/59 [51%] versus 27/250 [11%], p = 0.001).

George JM, Colton BJ. and Rodvold KA. National survey on continuous and extended infusions of antibiotics. *Am J Health-Syst Pharm—Vol 69 Nov 1, 2012*

¿Experiencias de administración de infusión prolongada?

¿Uso de antibióticos nebulizados?

Objetivo nebulización de antibióticos

- Depósito del fármaco en el sitio de la infección, produciendo altas concentraciones en el sitio de la infección (eficacia).

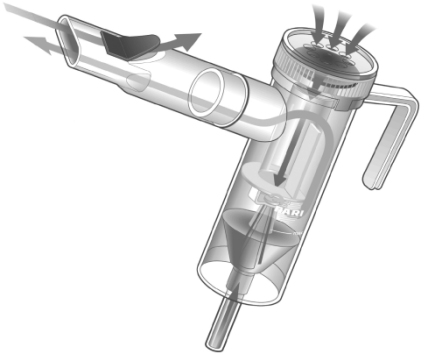
- Minimiza la toxicidad sistémica
  - Propia del fármaco (nefro y ototoxicidad de aminoglucósidos)
  - Infección *Clostridium difficile*

- Instilación traqueal de antibióticos
  - Distribución no homogénea

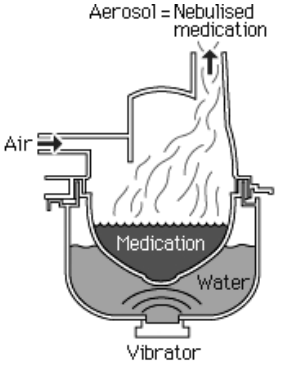
Aerosolized antibiotics for ventilator-associated pneumonia
Ruby et al Anesthesiology 2012; 117:1364-80

Factores afectan nebulización

- Tipo nebulizador
  - *Tipo jet*
    - Aerosol por atomización
    - Alto volumen residual
    - Menos eficientes . Depositan <15%



  - *Ultrasónicos*
    - Vibraciones cuarzo (aumenta la T)
    - Desnaturalización de antibióticos?
    - Tamaños entre 3-3.6 um
    - Eficiencia del 30-40%

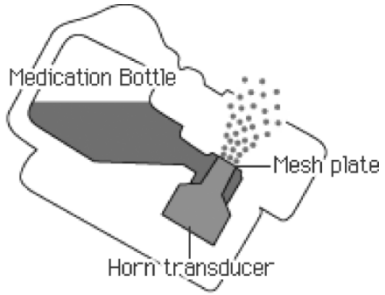


Luyt et al. Delivering antibiotics to the lungs of patients with ventilator associated pneumonia: an update. Expert Rev. Anti Infect Ther 11(5), 511-521 (2013)

Factores afectan nebulización

- Tipo nebulizador
  - *Malla*

    Nueva generación.
    No cambian la T
    Mayor deposición (40-60%)



Factores afectan nebulización

- Parámetros ventilatorios

  - *Modo ventilatorio*
    Recomendable controlado por volumen vs presión

  - *Tidal volume*
    > 500ml

  - *Flujo inspiratorio*
    Mejor lento

  - *Sincronización con la respiración*

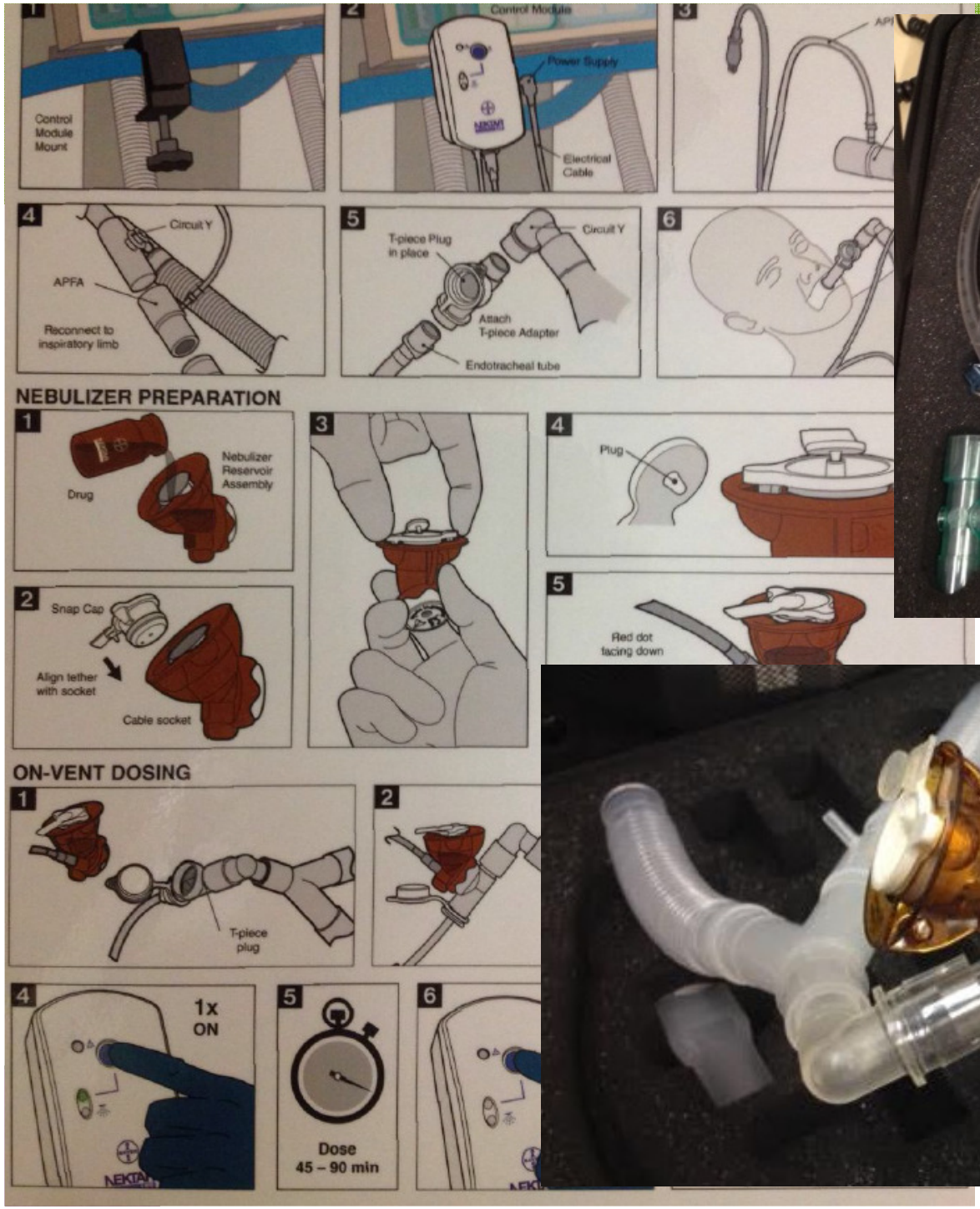
Factores afectan nebulización

- Circuito ventilatorio

Es necesario una humidificación para depositar bien las partículas
Nebulizador a 30-50 cm del tubo endotraqueal (15-20 de Y)

- Gas conductor

Deposición alveolar mejor con Helio-Oxígeno que con aire o oxígeno
Posible aumento del tamaño de partícula
Se necesitan más estudios


Control Module Mount
Control Module
Power Supply
Electrical Cable
Circuit Y
APFA
Reconnect to inspiratory limb
T-piece Plug in place
Attach T-piece Adapter
Endotracheal tube
NEBULIZER PREPARATION
Drug
Nebulizer Reservoir Assembly
Plug
Snap Cap
Align tether with socket
Cable socket
Red dot facing down
ON-VENT DOSING
T-piece plug
1x ON
Dose 45 – 90 min


NEKTAR

Factores afectan nebulización

- Tamaño de partícula

  - *Partículas < 1um*

    Son exhaladas durante la expiración

  - *Partículas > 5 um*

    Se depositan en orofaringe y se degluten

    Son atrapadas en el circuito ventilatorio

  - *Partículas entre 1 -5 um*

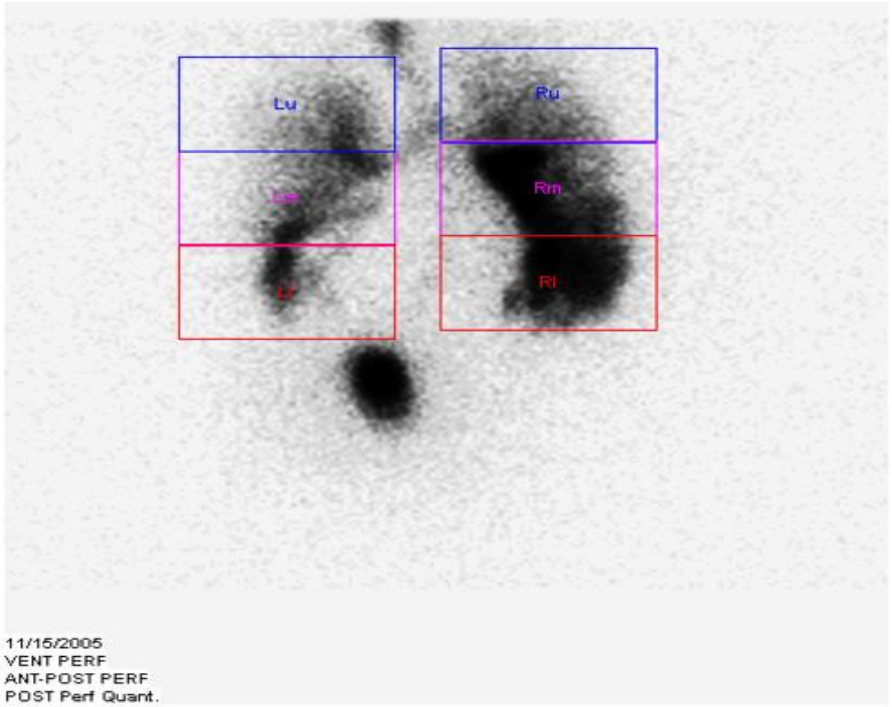
    Óptimo

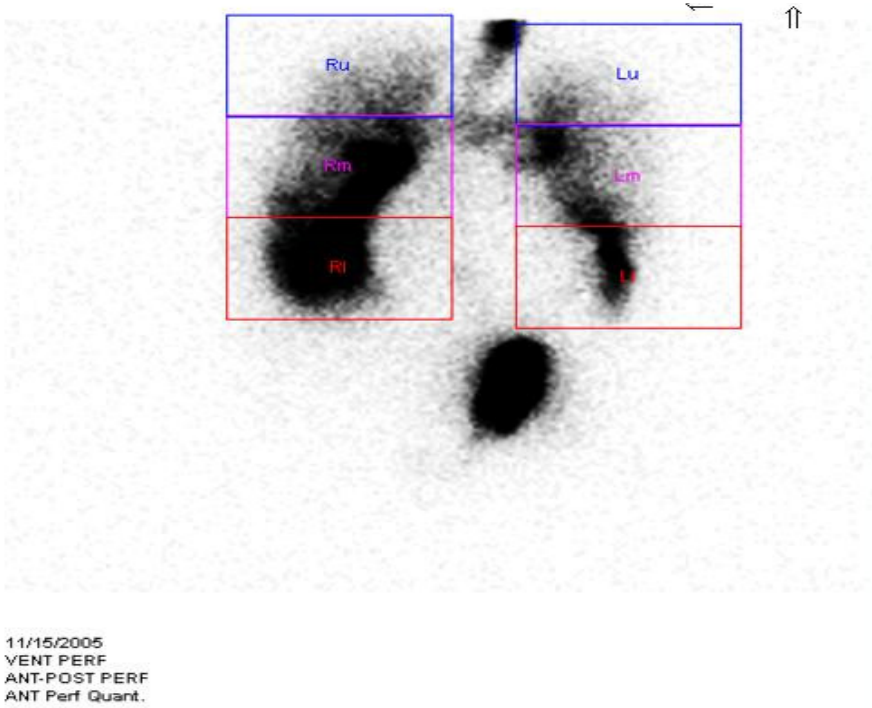
    Nebulizadores tipo jet, malla o ultrasónicos dan este tamaño

Particle Diameter (μ)	Site of Retention
< 1	Alveoli
1- < 8	Bronchioles
8-16	Trachea
> 16	Oral Cavity

Eisenberg, RS and Oatway, WH Am Rev of Resp Disease 1971; 103:289-92

Luyt et al. Delivering antibiotics to the lungs of patients with ventilator associated pneumonia: an update. Expert Rev. Anti Infect Ther 11(5), 511-521 (2013)





	Posterior Kct				Geometric Mean Kct				Anterior Kct			
	Left		Right		Left Lung		Right Lung		Right		Left	
	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct
Upper Zone:	7.0	9.41	10.0	13.44	6.2	7.88	8.3	10.64	6.9	8.43	5.4	6.61
Middle Zone:	11.3	15.20	39.3	52.76	12.3	15.74	36.9	47.03	34.2	41.92	13.3	16.30
Lower Zone:	6.6	8.89	25.8	34.62	7.6	9.64	28.7	36.67	31.7	38.84	8.5	10.45
Total Lung:	24.9	33.49	75.1	100.82	26.1	33.26	73.9	94.34	72.8	89.19	27.2	33.35

Nebulización ANFOTERICINA

Nebulizadores

Efectos adversos nebulización

- **Tos y Broncoespasmo**

Depende de viscosidad, tensión superficial, osmolalidad, tonicidad y pH del preparado farmacéutico

- Osmolalidad: 150-1200 mOsm/Kg
- Sodio: 77-154 mEq/l
- pH: 2.6-10

Muchos preparados contienen conservantes tipo sulfatos y/o fenoles que contribuyen a la broncoconstricción

Dosis antibióticos nebulizados

Antibiotic	Therapeutic Use	Common Dosage	Adverse Effects and Monitoring Parameters
Aminoglycosides			Tinnitus, hoarseness, voice alteration, wheezing, cough, dyspnea, bronchospasm (consider pretreatment with albuterol), systemic effects (nephrotoxicity and hearing loss); baseline and periodic audiometric evaluations for auditory and vestibular ototoxicity in special populations (e.g., cystic fibrosis) or where systemic exposure is suspected; BUN and S_{cr} for renal function in patients receiving long-term therapy; serum trough concentrations in patients for those whom systemic accumulation is suspected (e.g., renal dysfunction)
Amikacin	Acute exacerbation of non–cystic fibrosis bronchiecstasis, nontuberculosis mycobacterial infection	500 mg nebulized b.i.d.	
Gentamicin	Acute exacerbation of non–cystic fibrosis bronchiecstasis	80 mg nebulized b.i.d.	
Tobramycin	Chronic suppressive therapy, prevention, or eradication of cystic fibrosis; treatment of hospital-acquired pneumonia; suppression therapy for non–cystic fibrosis bronchiecstasis	300 mg nebulized b.i.d. with Pari LC Plus	
	Acute exacerbation of non–cystic fibrosis bronchiecstasis	80 mg nebulized b.i.d.	
β-Lactams			
Aztreonam lysine	Chronic suppressive therapy of cystic fibrosis	75 mg nebulized t.i.d. for 28-day periods with eFlow device	Cough, nasal congestion, wheezing
Cefotaxime or ceftazidime	Treatment of hospital-acquired pneumonia, suppression therapy for non–cystic fibrosis bronchiecstasis	250 mg q12h–500 mg q6h nebulized	Well-tolerated in limited studies

Dosis antibioticos nebulizados

Antifungal agents			
Amphotericin B deoxycholate	Proposed for prophylaxis against invasive aspergillosis in patients with hematologic malignancies or lung transplantation	20–25 mg/day nebulized in 1 or 2 divided doses (use 50 mg/day for mechanically ventilated patients)	Cough, chest tightness, taste disturbance, nausea and vomiting; more adverse effects reported with amphotericin B deoxycholate compared with lipid-based amphotericin B
Lipid-based amphotericin B	Proposed for prophylaxis against invasive aspergillosis in patients with lung transplantation	50 mg nebulized q.d. (use 100 mg q.d. for mechanically ventilated patients)	
Liposomal amphotericin B	Proposed for prophylaxis against invasive aspergillosis in patients with hematologic malignancies	12.5 mg nebulized twice/wk on 2 consecutive days	
Others			
Colistin	Prevention or eradication of cystic fibrosis, treatment of hospital-acquired pneumonia, suppression therapy for non–cystic fibrosis bronchiectasis	1–2 million units (≈ 80–160 mg) nebulized b.i.d.[a]	Serious adverse effects including nephrotoxicity and bronchospasm; higher rate and severity of pulmonary effects compared with aminoglycosides; colistimethate sodium (parenteral formulation) associated with fewer respiratory adverse effects compared with colistin sulfate (oral formulation); colistin should be compounded immediately before use to avoid potentially fatal pulmonary toxicity
Pentamidine	Prevention of *Pneumocystis jiroveci* pneumonia	300 mg every 4 wks with Respirgard II nebulizer	Respiratory symptoms including cough, wheezing, shortness of breath, and bronchospasm; other effects include fatigue, dizziness or lightheadedness, fever, throat irritation, conjunctivitis, decreased appetite, nephrotoxicity, glucose intolerance, and allergic reactions

Le J, et al. Consensu summary of aerosolized antimicrobial agents: Application of guideline criteria (Society of Infectious diseases Pharmacists). Pharmacotherapy 2010;30(6):562-584

Estudios de ATB nebulizados en NAVM

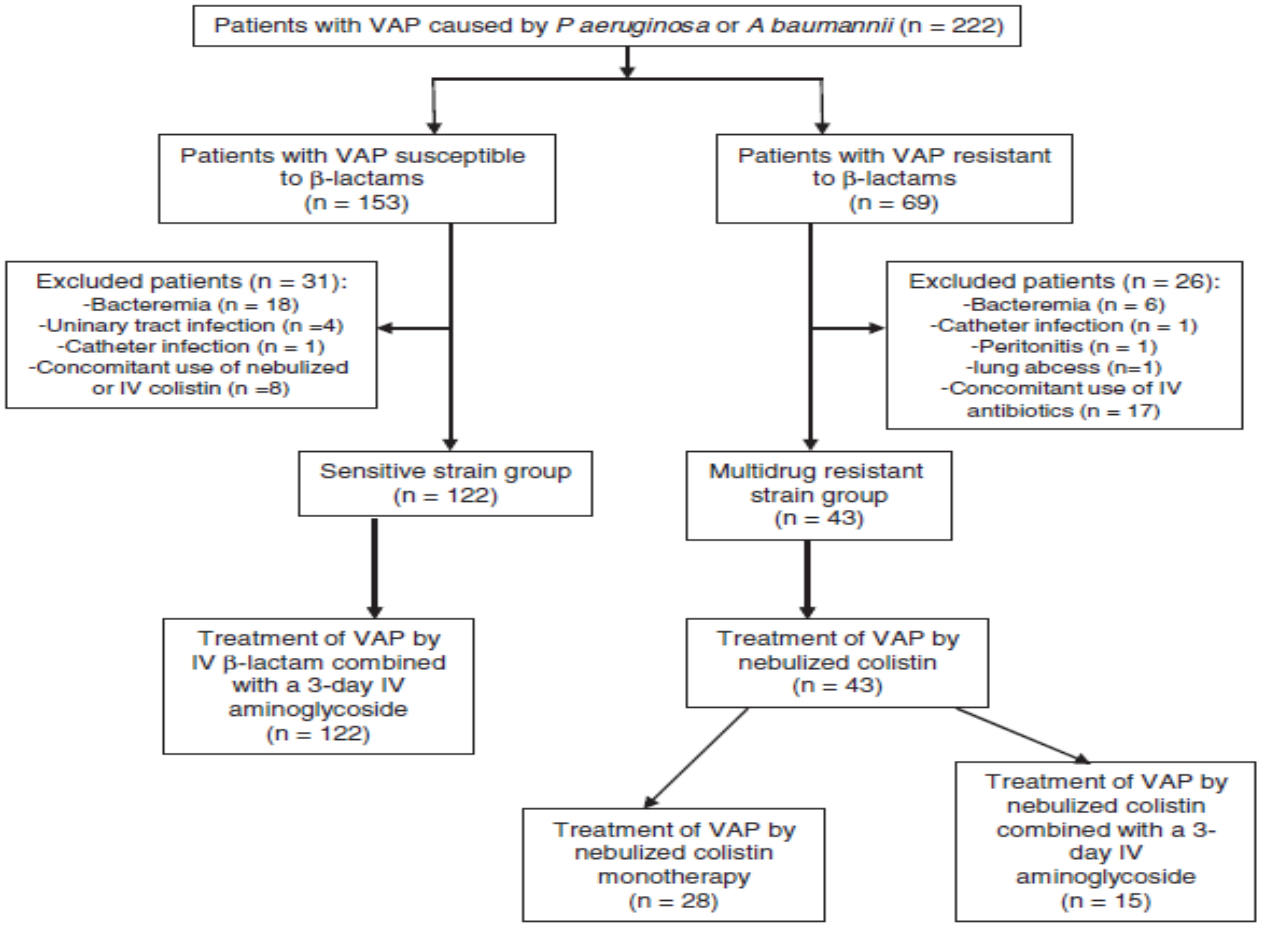
Table 2. Recent clinical trials of aerosolized antibiotics in patients with ventilator-associated pneumonia

Reference	Design	Number of patients	Treatment	Outcomes (aerosol vs. control)
Arnold *et al.* [32▪▪]	Retrospective, single-center, cohort	93	Adjunct aerosolized colistin or tobramycin vs. intravenous antibiotics	30-day mortality: 0 vs. 18%
Lu *et al.* [19]	Prospective, randomized	40	Aerosolized ceftazidime and amikacin vs. intravenous ceftazidime and amikacin	Success: 70 vs. 55%; superinfection: 15 vs. 15%; day-28 mortality: 10 vs. 5%
Lu *et al.* [33▪▪]	Prospective, observational, comparative (not randomized)	165	Aerosolized colistin ± IV aminoglycosides vs. IV β-lactams plus aminoglycosides or quinolones	Clinical cure: 67 vs. 66%; superinfection: 6 vs. 13%; mortality: 16 vs. 23%
Niederman *et al.* [17▪▪]	Double blind, randomized	69	Aerosolized amikacin (q12 h, q24 h) or placebo, each with IV antibiotics	Target concentration: 50 vs. 17%; clinical cure: 94 vs. 75 vs. 88%
Montgomery *et al.* [26]	Double-blind, randomized, phase 1	4	Escalating doses of aerosolized amikacin and fosfomycin	Amikacin: ≥98-fold higher than *P. aeruginosa* MIC_{90}; fosfomycin: ≥68-fold higher than MRSA MIC_{90}

Kollef M, Hamilton C, Montgomery B. Aerosolized antibiotics: de they add to the treatment of pneumonia? Curr Opin Infect Dis December 2013, 26(6):538-544

Estudios de ATB nebulizados en NAVM

Efficacy of high-dose nebulizer collision in ventilator-associated pneumonia caused by multidrug-resistant P*seudomonas aeruginosa* and *Acinetobacter baumannii*
Lu Q, Luo R, Bodin L, Yang J, Zahr N, Aubry A, Golmard JL, Rouby JJ
Anesthesiology December 2012; 117(6):1335-47

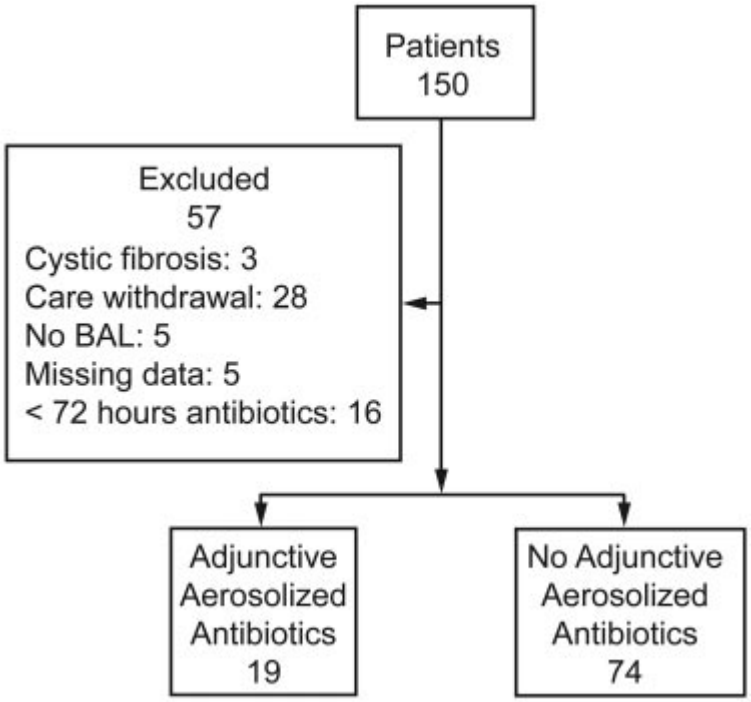


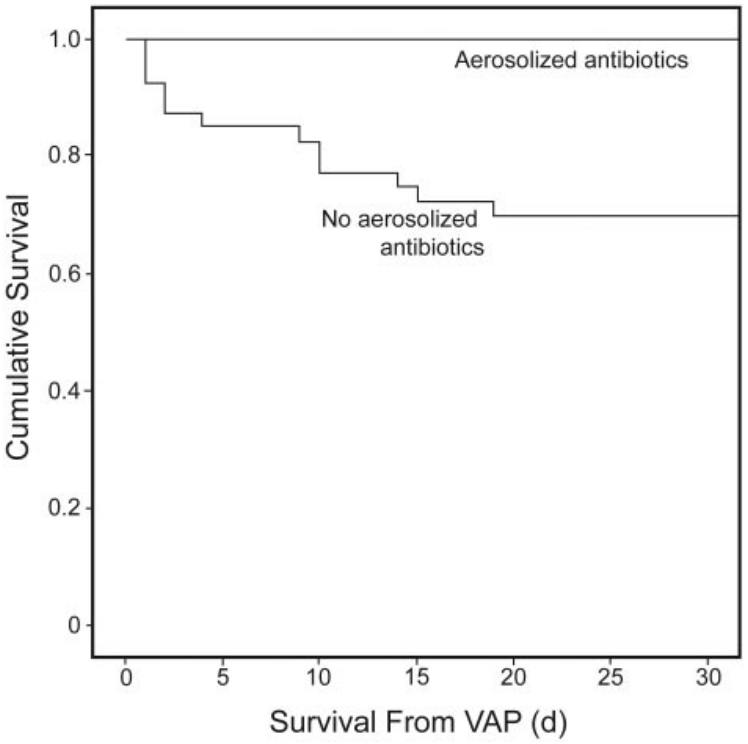
Estudios de ATB nebulizados en NAVM

	Sensitive Strain Group (n = 122)	Multidrug-resistant Strain Group (n = 43)	*P* Value
Cure of VAP at day 14, overall	81/122 (66.4%)	29/43 (67.4%)	
Cure of VAP caused by *P. aeruginosa*	72/113 (64%)	19/32 (59.3%)	0.654
Cure of VAP caused by *A. baumannii*	9/9 (100%)	10/11 (91%)	0.353
Persisting VAP at day 14, n (%)			
VAP caused by *P. aeruginosa*	21/113 (19%)	10/32 (31%)	0.122
VAP caused by *A. baumannii*	0/9	0/11	
VAP caused by superinfection at day 14, n (%)	16/122 (13%)	2/43 (6%)	0.126
Per-treatment death, n (%)	4/122 (3%)	2/43 (5%)	0.679
Recurrence of VAP after day 14, n (%)			
VAP caused by *P. aeruginosa*	11/113 (10%)	6/32 (26%)	0.162
VAP caused by *A. baumannii*	1/8 (11%)	0/11 (0)	
VAP caused by superinfection after day 14, n(%)	8/122 (6.6%)	4/43 (9%)	0.551
Duration of MV after inclusion, media (IQR)	8 (2–21)	15 (6–24)	0.031
Duration of MV, median (IQR)	18 (12–33)	38 (23–54)	<0.001
Length of stay in ICU, median (IQR)	25 (16–46)	54 (32–73)	<0.001
All-cause ICU mortality	28 (23%)	7 (16%)	0.357

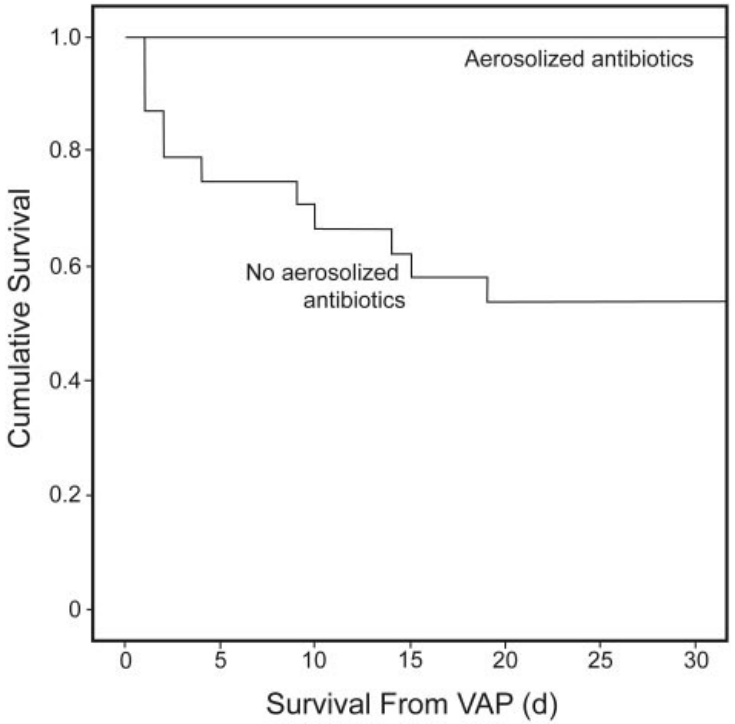
Estudios de ATB nebulizados en NAVM

Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa and Acinetobacter baumannii* Ventilator-Associaated pneumonia
Arnold HM, Sawyer A, Kollef M
Respiratory Care August 2012 vol 57 nº8





Kaplan-Meier curves depicting the probability of survival from ventilator-associated pneumonia (VAP) in patients receiving adjunctive aerosolized antibiotics and patients who did not receive
adjunctive aerosolized antibiotics (*P .030 by log rank test).*



Kaplan-Meier curves depicting the probability of survival from ventilator-associated pneumonia (VAP) in patients receiving adjunctive aerosolized antibiotics and patients who did not receive adjunctive aerosolized antibiotics (*P .004 by log rank test) for*
the subgroup of patients having Acute Physiology and Chronic Health Evaluation II scores > 16.

- Tobramicina
- Colistina
- Aztreonam lysinato
- Gentamicina
- Amikacina
- Levofloxacino (MP-376)
- Fosfomicina
- Amfotericina B
- Claritromicina
- Azitromicina
- Rifampicina
- Isoniazida
- Doxiciclina
- Clindamicina
- Telitromicina
- Squalamina

Zarogoulidis et at. Clinical experimentation with aerosol antibiotics: current and future methods of administration. Drug Design, Development and Therapy 2013:7 1115-1134

Dia +14 Muestras

- 14/08 BAL → BGN
- 16/08 se confirma Pseudomonas spp

- Desescalada antibiótica:
  - **Cefalosporina + Colistina nebulizada**

BITERAPIA

¿Qué evidencia hay sobre la biterapia o monoterapia en el tto de la neumonía asociada a VM?

Biterapia vs Monoterapia

Surviving Sepsis Campaign

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM

International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
Table of Contents

Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient's presenting illness and local patterns of infection. We suggest combination empiric therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp. (grade 2B). **For selected patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an ami- noglycoside or a fluoroquinolone** is suggested for P. aeru- ginosa bacteremia (**grade 2B**). Similarly, a more complex combination of beta-lactam and a macrolide is suggested for patients with septic shock from bacteremic Streptococ- cus pneumoniae infections (grade 2B).

Biterapia vs Monoterapia

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2004 AND THE IDSA GUIDELINE COMMITTEE, OCTOBER 2004

Major Points and Recommendations for Optimal Antibiotic Therapy

1. Empiric therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses, to ensure maximum efficacy (**Level I**) (240, 242–247). Initial therapy should be administered to all patients intravenously, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable agents, such as the quinolones and linezolid, may be easily switched to oral therapy in such patients (**Level II**) (248, 253, 254).
2. Aerosolized antibiotics have not been proven to have value in the therapy of VAP (**Level I**) (256). However, they may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy (**Level III**) (255).
3. Combination therapy should be used if patients are likely to be infected with MDR pathogens (**Level II**) (21, 205). No data have documented the superiority of this approach compared with monotherapy, except to enhance the likelihood of initially appropriate empiric therapy (**Level I**) (262).
4. If patients receive combination therapy with an aminoglycoside-containing regimen, the aminoglycoside can be stopped after 5–7 days in responding patients (**Level III**) (235).
5. Monotherapy with selected agents can be used for patients with severe HAP and VAP in the absence of resistant pathogens (**Level I**) (240, 242–247). Patients in this risk group should initially receive combination therapy until the results of lower respiratory tract cultures are known and confirm that a single agent can be used (**Level II**).

Biterapia vs Monoterapia

A FAVOR	EN CONTRA
Ampliar espectro de acción	Aumento toxicidad
Provocar sinergia	Riesgo sobrecrecimiento fúngico
Disminuir aparición de resistencias	Infecciones cateter

Combination therapy for treatment of infections with gram-negative bacteria
Tamma PD, Cosgrove S, Maragakis L
Clinical Microbiology reviews July 2012, 25 (3) 450-470

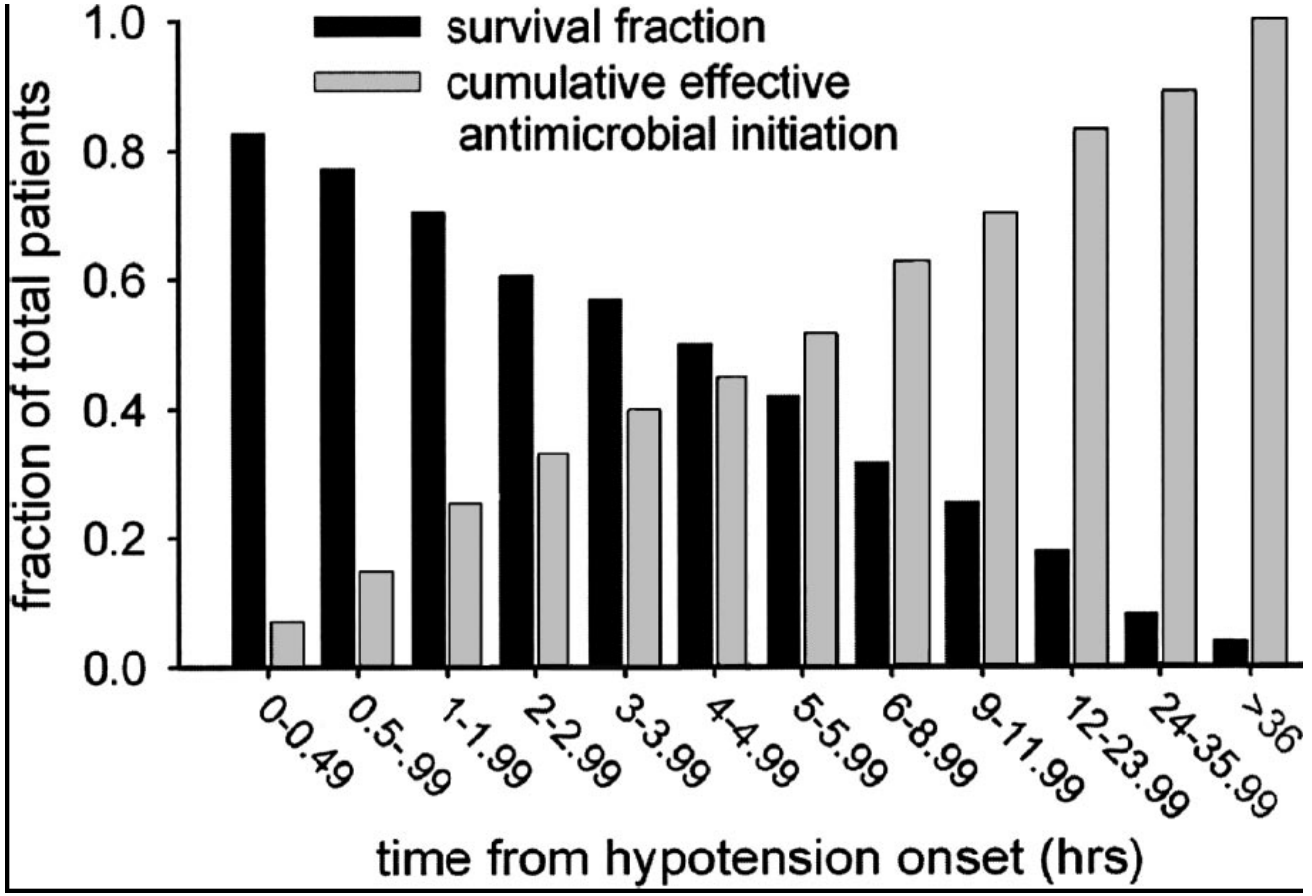
Ampliar el espectro de acción

	B-lactam monotherapy	Empiric combination	*p*
Mortality 28 days	36%	29%	*0.0002*
Ventilation free days	10 (0-25)	17 (0-26)	*0.008*

Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis.
Kumar A1, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, Laporta D, Lapinsky S, Ellis P, Mirzanejad Y, Martinka G, Keenan S, Wood G, Arabi Y, Feinstein D, Kumar A, Dodek P, Kravetsky L, Doucette S; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group.
Crit Care Med. 2010 Sep;38(9):1773-85.

Biterapia vs Monoterapia

Acertar el antibiótico y rápido



Kumar A. Crit Care Med 2006;34(6): 1589-96

Biterapia vs Monoterapia

Provocar sinergias

B-lactamicos y aminuglucósidos	*B-lactamicos y fluorquinolonas*
Demostrada in-vitro excepto cuando el inóculo es muy grande	Variable in-vitro (17%-82%)
Pocos estudios demuestran reducción de mortalidad	Metanálisis comparando biterapia con aminoglucósido vs fluorquinolona Sin diferencias en mortalidad ni curación clínica. Menos toxicidad con flourquinolonas
Sólo beneficios en pacientes neutropénicos	

Ciprofloxacin vs an aminoglycoside in combination with a beta-lactam for the treatment of febrile neutropenia: a meta-analysis of randomized controlled trials.
Bliziotis IA1, Michalopoulos A, Kasiakou SK, Samonis G, Christodoulou C, Chrysanthopoulou S, Falagas ME.
Mayo Clin Proc. 2005 Sep;80(9):1146-56.

Biterapia vs Monoterapia

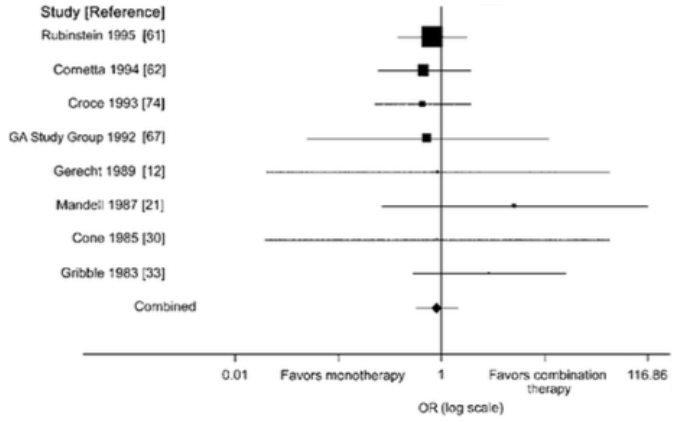
Minimizar resistencias

Prospective randomized trial of piperacillin monotherapy versus carboxypenicillin-aminoglycoside combination regimens in the empirical treatment of serious bacterial infections.
M J Gribble, et al Antimicrob Agents Chemother. Sep 1983; 24(3): 388–393.

TABLE 4. Emergence of resistance during therapy

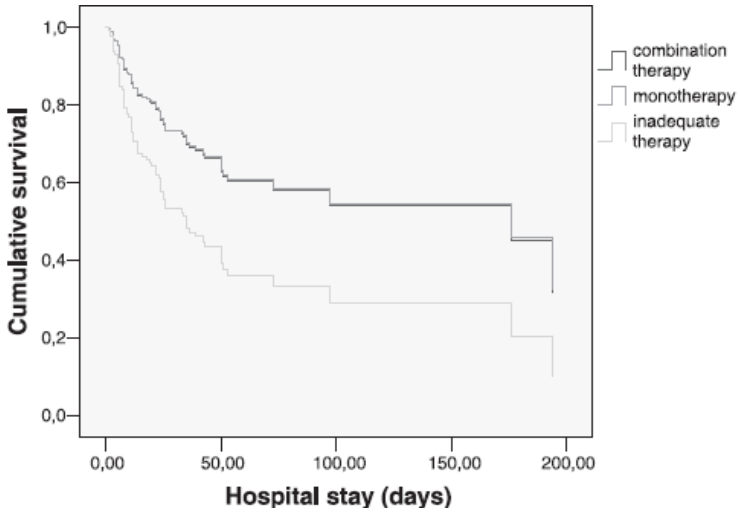
Resistance	No. (%) in following treatment group: Piperacillin (n = 26)	Combination (n = 24)	P^a
Emergence of resistant isolates during therapy	11 (42)	4 (17)	0.0465
Original organism	6	2	
New organism	8	2	
Treatment failure, superinfection, or both due to emergence of resistance	5 (19)	2 (8)	0.2437
Proportion of all patients with treatment failure, superinfection, or both due to resistance	5/9	2/10	0.1299
Treatment failure	3/6	0/6	
Superinfection	4/5	2/4	

Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials.
Bliziotis IA1, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME. Clin Infect Dis. 2005 Jul 15;41(2):149-58. Epub 2005 May 31.



Conclusiones Biterapia o Monoterapia

	Survivors (n = 38)	Nonsurvivors (n = 52)	p
Age, yrs[a]	50.8 (19.9)	63.4 (14.3)	<.001
Gender (male)	29 (76.3)	39 (75)	1
APACHE II score[a]	21.1 (9.7)	20.9 (11.4)	.6
Type of patients			.12
Medical	13 (34.2)	28 (53.8)	
Surgical	17 (44.7)	19 (36.5)	
Trauma	8 (21.1)	5 (9.6)	
Underlying diseases			
Hepatic cirrhosis	0 (0)	2 (3.8)	.5
Immunosuppression	3 (7.9)	6 (11.5)	.73
End-stage renal disease	4 (10.5)	4 (7.7)	.72
Chronic cardiac failure	0 (0)	13 (25)	<.0001
COPD	3 (7.9)	8 (15.4)	.34
Diabetes mellitus	7 (18.4)	16 (30.8)	.22
Alcoholism	5 (13.2)	12 (23.1)	.28
Smoking habit	11 (28.9)	12 (23.1)	.63
HIV infection	0 (0)	1 (1.9)	1
Bacteremia	3 (7.9)	6 (11.5)	.73
Recurrent VAP	4 (10.5)	2 (3.8)	.2
Prescribed empirical therapy			.38
Monotherapy	11 (28.9)	20 (38.5)	
Combination therapy	27 (71.1)	32 (61.5)	
Effective empirical therapy			.028
Inappropriate	4 (10.5)	18 (34.6)	
Monotherapy	13 (34.2)	11 (21.2)	
Combination therapy	21 (55.3)	23 (44.2)	
Definitive therapy			.78
Monotherapy	7 (18.4)	8 (15.4)	
Combination therapy	31 (81.6)	44 (84.6)	



Optimal mangement therapy for Pseodomna aeruginosa venitalor associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy
Garnacho J, Borges M, Sole-Violan J, Barcenilla F, Escoresca-Ortega A, Ochoa M, Cayuela A, Rello J
Crit Care Med. 2007 35(8).

Conclusiones Biterapia o Monoterapia

A single beta lactam antibiotic versus a beta lactam-aminoglycoside combination for patients with severe infection

Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L
7 January 2014

We searched the literature until November 2013. We included in the review 69 trials that randomly assigned 7863 participants . Participants were hospitalized with urinary tract, intra-abdominal, skin and soft tissue infections, pneumonia and infections of unknown source. One set of studies compared a broad-spectrum beta lactam versus a different, generally narrower-spectrum beta lactam combined with an aminoglycoside (47 studies). No clear difference in all-cause deaths was observed, but treatment failures were fewer with single beta lactam antibiotic treatment. A significant survival advantage was seen with single therapy in studies that involved infections of unknown source. The other studies compared one beta lactam versus the same beta lactam combined with an aminoglycoside antibiotic (22 studies). In these trials, no differences between single and combination antibiotic treatments were seen. Overall, adverse event rates did not differ between the study groups, but renal damage was more frequent with the combination therapy. Combination therapy did not prevent the development of secondary infection.

The review authors concluded that beta lactam-aminoglycoside combination therapy does not provide an advantage over beta lactams alone. Furthermore, combination therapy was associated with an increased risk of renal damage. The limited number of trials comparing the same beta lactam in both study arms and the fact that more than a third of the studies did not report on all-cause deaths may limit these conclusions. **The subgroup of *Pseudomonas aeruginosa* infections was underpowered to examine effects.**

Experiencias tratamiento dirigido

Experiència clínica:

- Biterapia en pneumonias (según guias clínicas)

- “Monoterapia igual efectiva”

¿¿¿ Porqué no se usa monoterapia???

Experiencia en MONOTERAPIA NEBULIZADA

CONCLUSIONES