Jornada
Grupo AFINF:
Actualización en Atención Farmacéutica en Enfermedades Infecciosas

NOVEDADES TERAPÉUTICAS: ACTUALIZACIÓN TRATAMIENTO G-

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Servicio Navarro de Salud
Osasunbidea

Madrid 22 junio 2016

Conflictos de interés:

- Sistema Navarro de Salud.
- Sistema Extremeño de Salud.
- Sistema Andaluz de Salud.
- He recibido financiación de Roche, Fresenius-Kabi, Novartis, MSD, Astellas, Grifols, Pfizer.

Metodología

Revisión

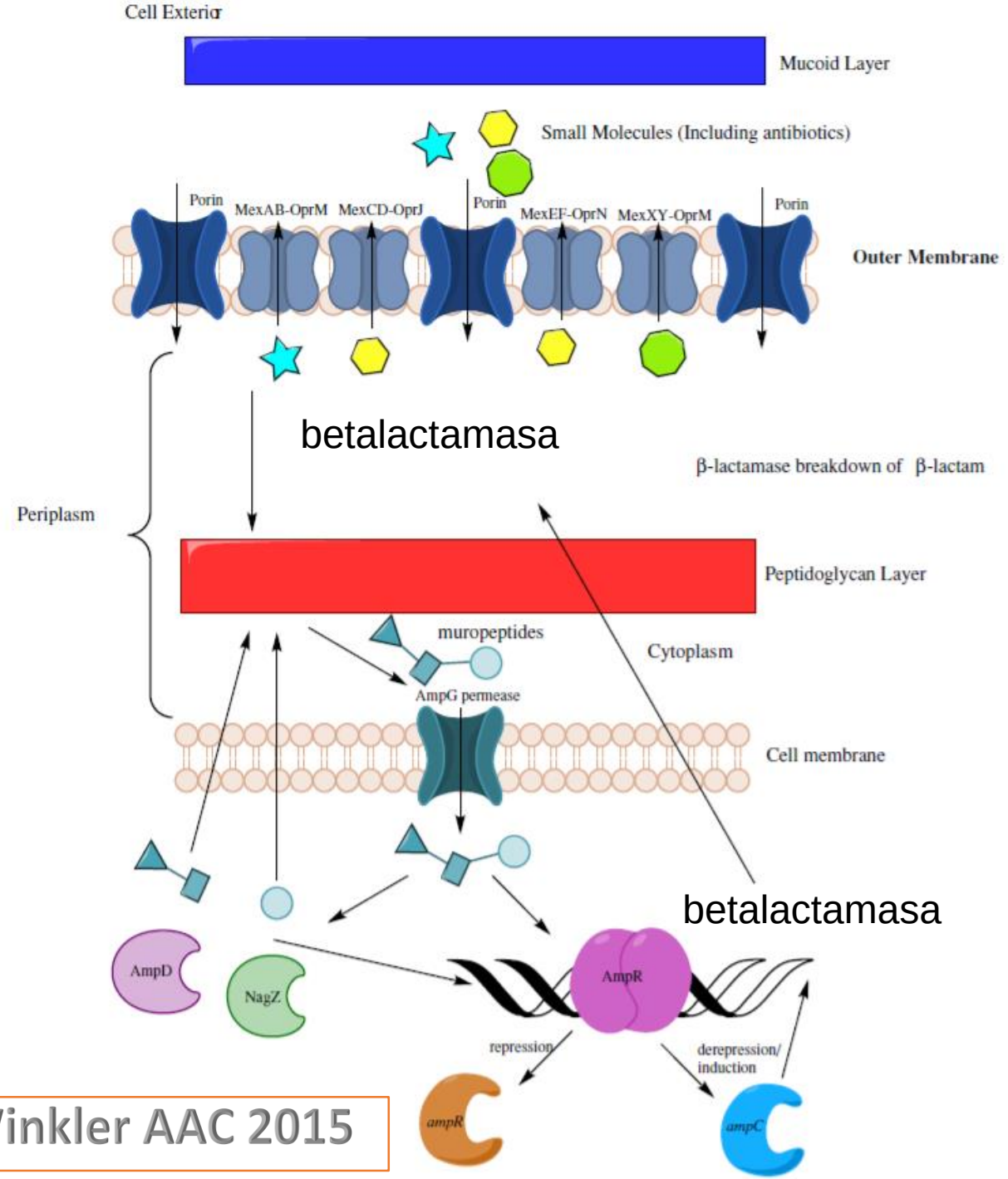
CID, JAC, AAC, CMI, IJAA…

Periodo

Enero 2015- Junio2016

Gram negativos tienen variedad de mecanismos de resistencia adquirida e intrínseca:

- Pérdida de porinas.
- Bombas expulsión.
- Cambios en la PBP.
- **Producción de betalactamasas**



Winkler AAC 2015

Ambler classification	Bush–Jacoby classification	Structure and function	Genetics	Common species	Common examples
Class A	Group 2 (2be includes "classical" ESBLs)	Contain serine residues at active site. Key feature of ESBL producers is resistance to third-generation cephalosporins (e.g., ceftriaxone) and monobactams, but not cephamycins. Inhibited by clavulanate or tazobactam in vitro (except KPC)	ESBLs arise from mutations in "parent" narrow-spectrum β-lactamase. Highly transmissible on mobile genetic elements (e.g., plasmids) often carrying multiple resistance determinants	ESBLs most common in *E. coli*, *Klebsiella* spp., and *Proteus* spp. but have been described in most Enterobacteriaceae and *Pseudomonas* spp. KPC seen in *Klebsiella pneumoniae*	ESBLs: TEM and SHV variants, CTX-M Carbapenemase: KPC
Class B	Group 3	Contain metal ions (e.g., Zn^{2+}). Carbapenemase activity, not inhibited by clavulanate/tazobactam. Aztreonam not hydrolyzed	Highly transmissible on plasmids carrying multiple other resistance determinants	*E. coli*, *Klebsiella* spp. But described in many Enterobacteriaceae	Carbapenemase: IMP, NDM (Often called "metallo-β-lactamases")
Class C	Group 1	Contain serine residues at active site. Also known as "AmpC" enzymes. Broad cephalosporinase activity including hydrolysis of third-generation cephalosporins and cephamycins, but cefepime usually stable. Not inhibited well by clavulanate, and only limited tazobactam effect	Chromosomally encoded in several species, and may be inducible by exposure to β-lactams. Expression regulated by complex systems; mutations in key regulatory genes can lead to "derepression" and high-level AmpC production. Increasing plasmid transmission seen	*Enterobacter cloacae*, *E. aerogenes*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia* spp. and *Morganella morganii* all contain inducible AmpC enzymes. Plasmid mediated AmpC increasing in *E. coli*, *Klebsiella* spp.	Cephalosporinase: CMY, DHA, ACT
Class D	Group 2d	Contain serine residues at active site. Oxacillinases that may have carbapenemase activity. Only weakly inhibited by clavulanate	May be acquired or naturally occurring chromosomal genes. May be co-located on plasmids with other β-lactamases (e.g., OXA-48 and CTX-M-15)	Increasingly described in Enterobacteriaceae (e.g., *K. pneumoniae* and OXA-48)	Carbapenemase: OXA-types

Abbreviation: ESBLs, extended-spectrum β-lactamases.

BLEE

CARBAPENEM ASAS TIPO KPC

CARBAPENEMASAS TIPO METALOBETALACTAM ASAS : **NDM, IMP**

AMPc

CARBAPENEMASAS TIPO OXA

Semin Respir Crit Care Med 2015;36:56–73

ENTEROBACTERIAS PRODUCTORAS DE CARBAPENEMASAS

REGÍMENES AHORRADORES CARBAPENÉMICOS

NUEVOS ATM

ENTEROBACTERIAS PRODUCTORAS DE CARBAPENEMASAS

COMBINACIONES & G- MR

Reference	Regimen	N	Pathogens	Outcome
Kontopidou CMI 2014	Monotherapy (colistin, aminoglycoside, tigecycline) vs. combinations	127	*Klebsiella* KPC (ICU)	Mortality colistin 23.1%; aminoglycoside 22.7%; tigecycline 31.3%; tigecycline + aminoglycosides, 18.1%; colistin + aminoglycosides, 11.7%; colistin + tigecycline, 44.4%.
Qureshi ZA CMI 2012	Monotherapy vs. combinations (colistin or tigecycline + carbapenem)	41	*Klebsiella* KPC	Mortality 57.8% vs. 13.3%
Tumbarello CID 2012	Monotherapy vs. combinations	125	*Klebsiella* KPC	Mortality 54.3 vs. 34.1%
Zarkotou O, CID 2011	Monotherapy vs. combinations (colistin + tigecycline or tigecycline + gentamicin)	53	*Klebsiella* KPC	Mortality 47 vs. 0%
Batirel A EJCID 2014	Colistinmonotherapy ($N=36$) vs. combination ($N=214$)	250	XDR *A. baumannii*	Mortality 72 vs. 52%, microbiological eradication 56 vs. 80%
Daikos AAC 2014	Colistin monotherapy ($N=37$) vs. combination with carbapenem or aminoglycosydes ($N=12$)	67	*Klebsiella* MBL	Mortality 27 vs. 8.3%
Durante-Mangoni E, CID 2013	Colistin monotherapy vs. colistin + rifampin	210	XDR *A. baumannii*	Microbiological eradication 45 vs. 61%

KPC, *Klebsiella pneumonia* carbapenemase; MBL, metallo-beta-lactamases; XDR, extensively drug-resistant.

Basetti CO Critical Care 2016

Diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant *Enterobacteriaceae*.

Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology

Rodríguez-Baño JR Enferm Infecc Microbiol Clin. 2015 May;33(5):337

Treatment of invasive infections caused by carbapenemase-producing *Enterobacteriaceae*

KPC-producing K. pneumoniae carbapenemase-producing Enterobacteriaceae

Monotherapy with a carbapenem is not recommended (CIII)

Combination therapy (CII),

May be considered in cases of mild invasive infections

Carbapenem <8mg/ml (BII)

+

tigecycline, aminoglycoside or fosfomycin

Sepsis from the urinary tract, without urinary tract obstruction nor severe sepsis or septic shock

CEFTA/AVIBACTAM?

Rodriguez-Baño JR et al Enfermedades Infecciosas y Microbiología Clínica 2015

Treatment of invasive infections caused by carbapenemase-producing *Enterobacteriaceae*

No recommendation combination of ertapenem + doripenem /meropenem for KPC-producers (unresolved issue)

>8 mg/ml CMI carbapenem <16 mg/ml + 2 two fully active (CIII)

tigecycline, aminoglycoside or fosfomycin

CEFTA/AVIBACTAM?

Rodriguez-Baño JR et al Enfermedades Infecciosas y Microbiología Clínica 2015

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

- **Objetivo**:

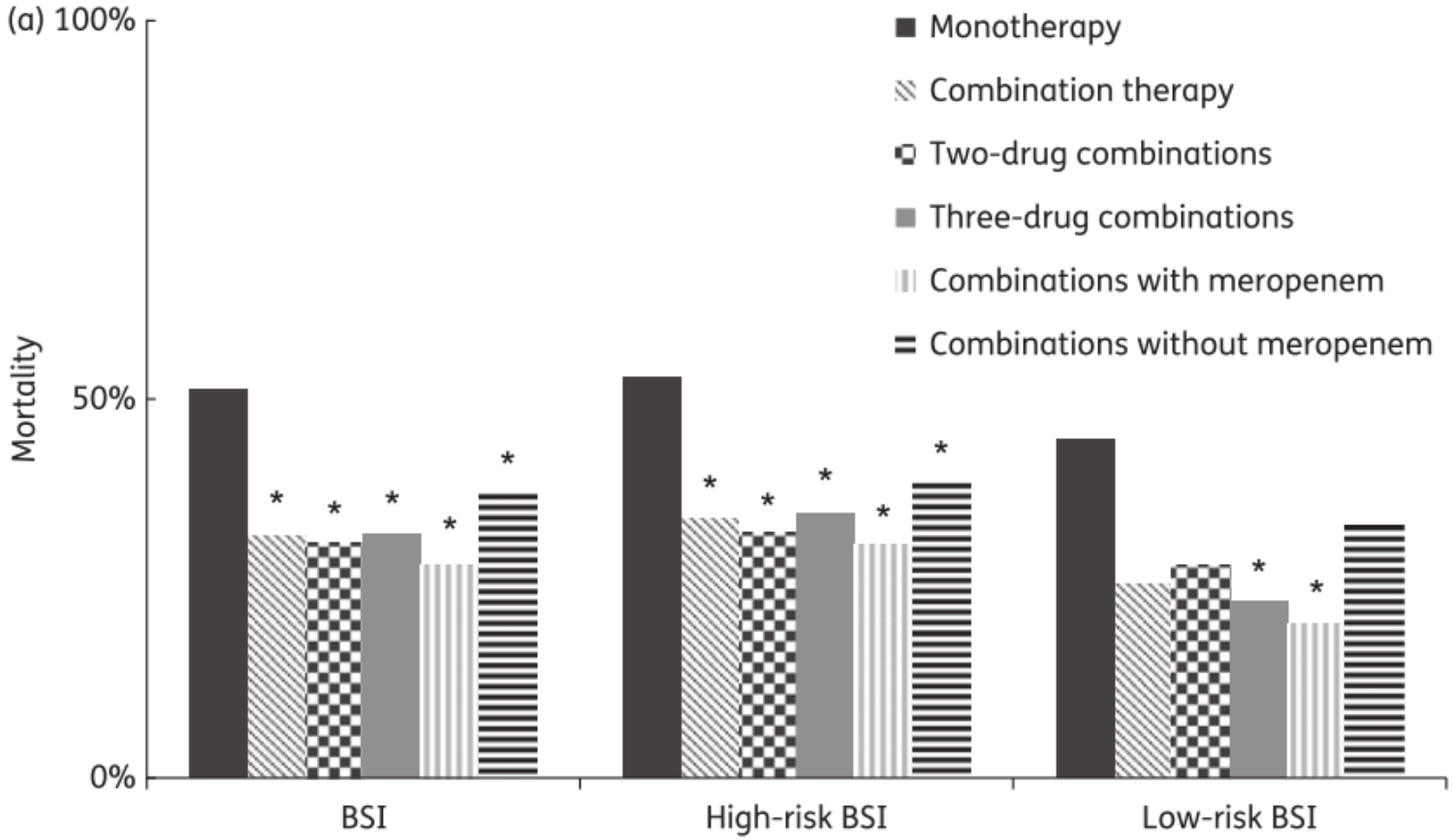
Assess their outcomes and identify risk factors for 14 day mortality. 2010–13 retrospective cohort study in five large Italian teaching hospitals

- **Pacientes**
  - MIC EUCAST
  - 75.2% blaKPC-3 gene;
  - 24.8% blaKPC-2 gene.
  - Half produced ESBLs (CTX-M in most cases)

Meropenem MICs
≥16mg/L 63.2%
4-8 mg/ml 35.2% intermediate
≤2mg/L 1.5% susceptible .

Tumbarello M J Antimicrob Chemother. 2015 Oct;70(10):2922

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

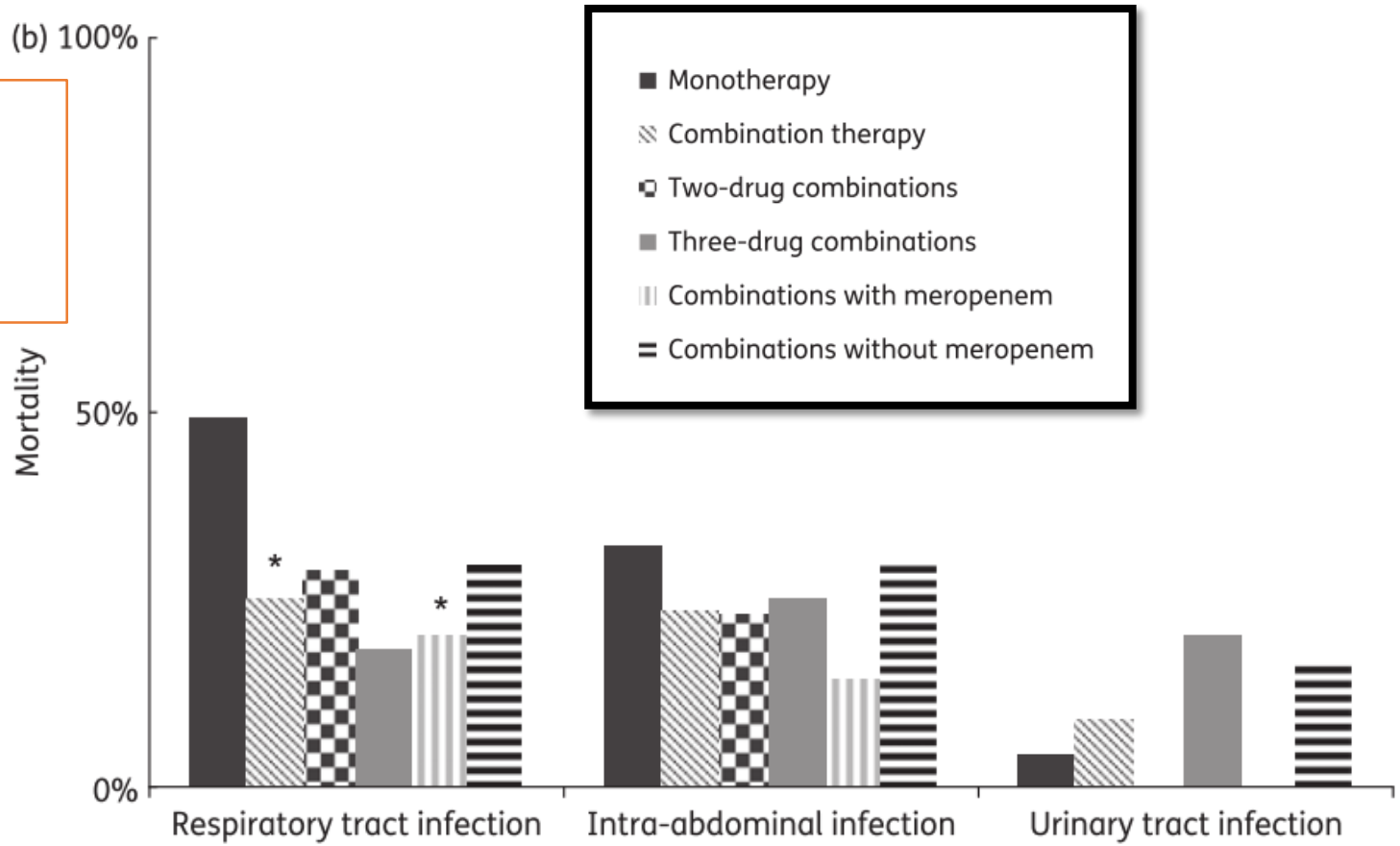


BSIs 447/661, 67.6%

Tumbarello M J Antimicrob Chemother. 2015 Oct;70(10):2922

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

No-BSIs 214/661, 32,4%



COMBINACIÓN ASOCIADA MENOR MORTALIDAD EN INFECCIONES GRAVES
CMI<8 mg/ml

Figure 2. Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs (a) or non-bacteraemic infections (b). *Statistically significant differences ($P<0.05$) among different types of combination therapy and monotherapy.

Tumbarello M J Antimicrob Chemother. 2015 Oct;70(10):2922

AHORRADORES DE CARBAPENÉMICOS

Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter*, *Citrobacter* or *Serratia* species: a systematic review with meta-analysis

The objectives

To compare the efficacy of broad-spectrum BLBLI agents (e.g. piperacillin/tazobactam), cefepime or fluoroquinolones with carbapenems (standard therapy)

Patients

Adult patients with BSI caused by AmpC-producing Enterobacteriaceae;
empirical or definitive monotherapy

- -Carbapenems
- -Broad-spectrum BLBLI agents (piperacillin/tazobactam or ticarcillin/clavulanate), -
- -Cefepime
- -Fluoroquinolones

Outcome: all-cause mortality

Result

11 estudios observacionales
N=2039

Harris P J Antimicrob Chemother 2016; 71: 296–306

Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter*, *Citrobacter* or *Serratia* species: a systematic review with meta-analysis

Sin diferencias mortalidad cruda BLBLIs or cefepime empírico o definitivo

Sin diferencias: carbapenemémicos vs no carbapenémicos tto definitivo.

Menor mortalidad tto definitivo FQ-> atenuado tras ajuste factores de confusión

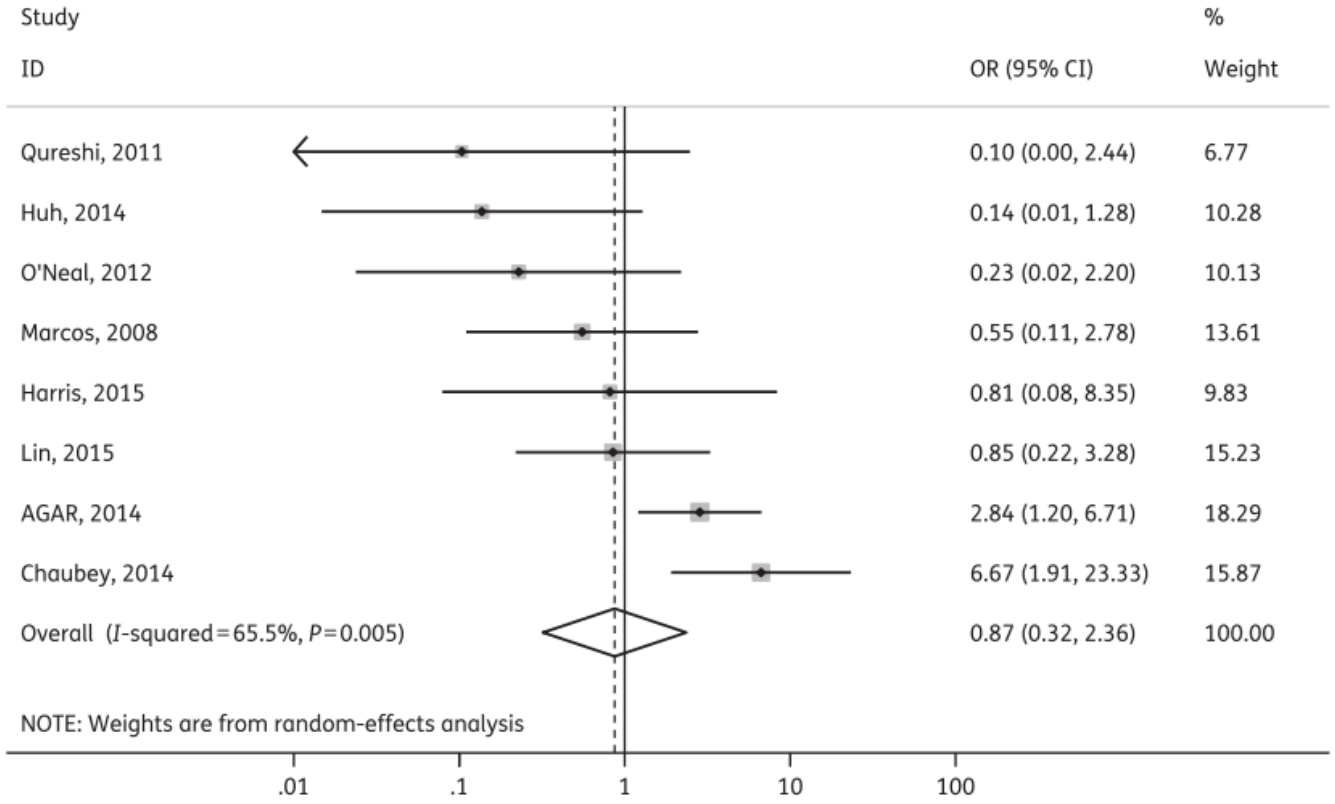


Figure 2. Forest plot of unadjusted ORs for mortality in patients given definitive therapy with BLBLIs versus carbapenems.

Harris P J Antimicrob Chemother 2016; 71: 296–306

AHORRADOR DE CARBAPENÉMICOS

β-Lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: a multinational, pre-registered cohort study.

Methods:
A multi-national (12 countries, 37 hospitals), retrospective cohort study including patients with monomicrobial BSI.

Outcome variables:
Cure rate at day 14 and 30-day mortality.

B. Gutiérrez-Gutiérrez Antimicrob Agents Chemother. 2016

AAC Journals.ASM.org

β-Lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: a multinational, pre-registered cohort study.

ETC N=365

- 170 BLBLIs (123 PTZ-73,2% S; 45 AMC-60,3% S)
- 195 CARBAPENEMS (MEROP 128, ERTA 32, IMP 35)

TTC N=601

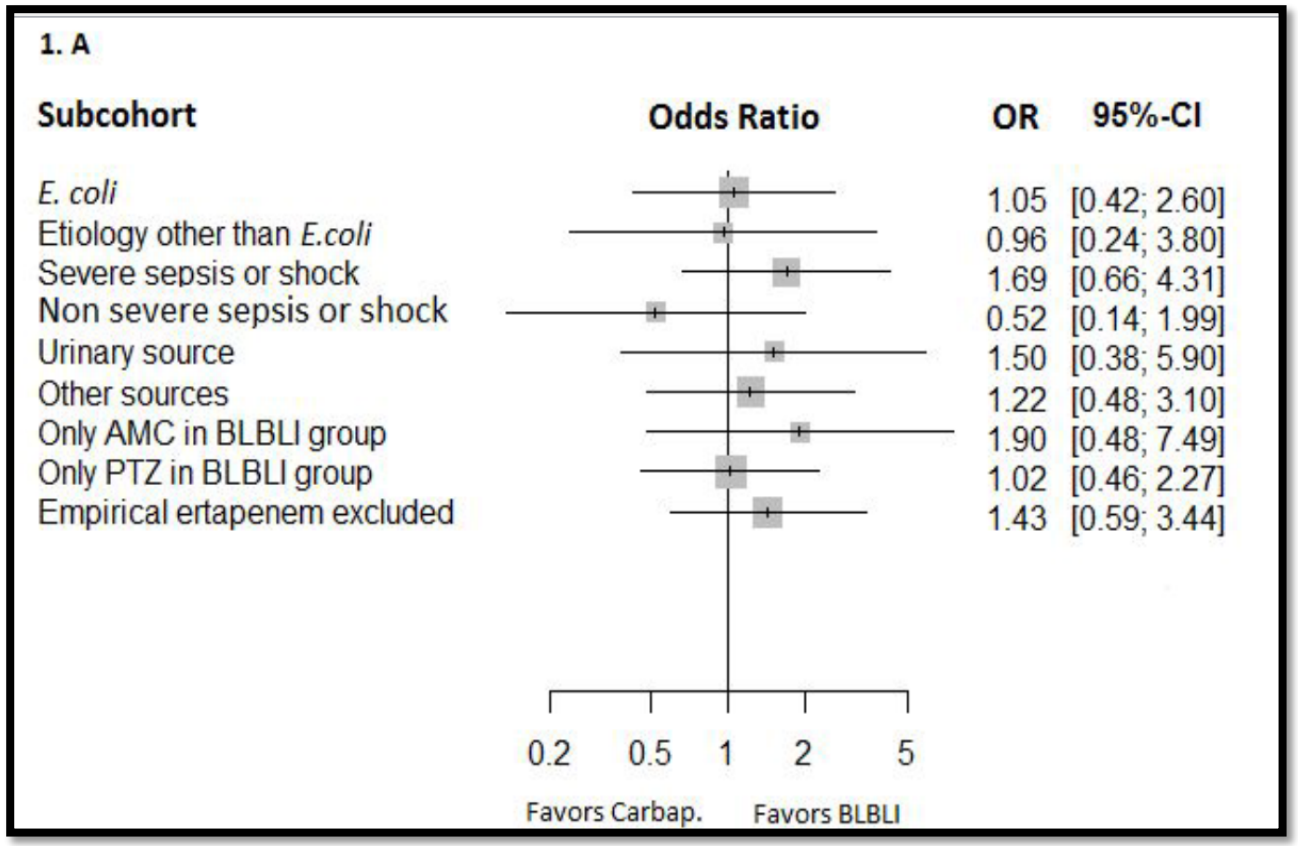
- 92 BLBLIs (60 PTZ; 32 AMC)
- 509 CARBAPENEMS (MEROP 185, ERTA 205, IMP 118, DORI 1)

GC N=627

- 157 BLBLI empirical
- 156 carbapenem empirical
- 63 BLBLI empirical and targeted
- 225 empirical no BLBLI/carbap and targeted carabap
- 31 empirical no BLBLI/carbap and targeted BLBLIs

B. Gutiérrez-Gutiérrez Antimicrob Agents Chemother. 2016

β-Lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: a multinational, pre-registered cohort study.



- Cure/improvement rates with BLBLI and carbapenems
  - ETC 80.0% vs 78.9%
  - TTC 90.2% vs 85.5%
- 30-day mortality
  - ETC 17.6% vs 20% Adjusted OR (95% CI) 0,55 (0.69–2.76);
  - TTC 9.8% vs 13.9% Adjusted OR (95% CI) 0,59 (0.69–2.76);

“BLBLI, if active in vitro, appear as effective as carbapenems for ET and TT of BSI due to ESLB-E regardless of the source and specific species”

B. Gutiérrez-Gutiérrez Antimicrob Agents Chemother. 2016

Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study

ETC N=365

- 170 BLBLIs (123 PTZ-73,2% S; 45 AMC-60,3% S)
- **195 CARBAPENEMS (MEROP 128, ERTA 32, IMP 35)**

TTC N=601

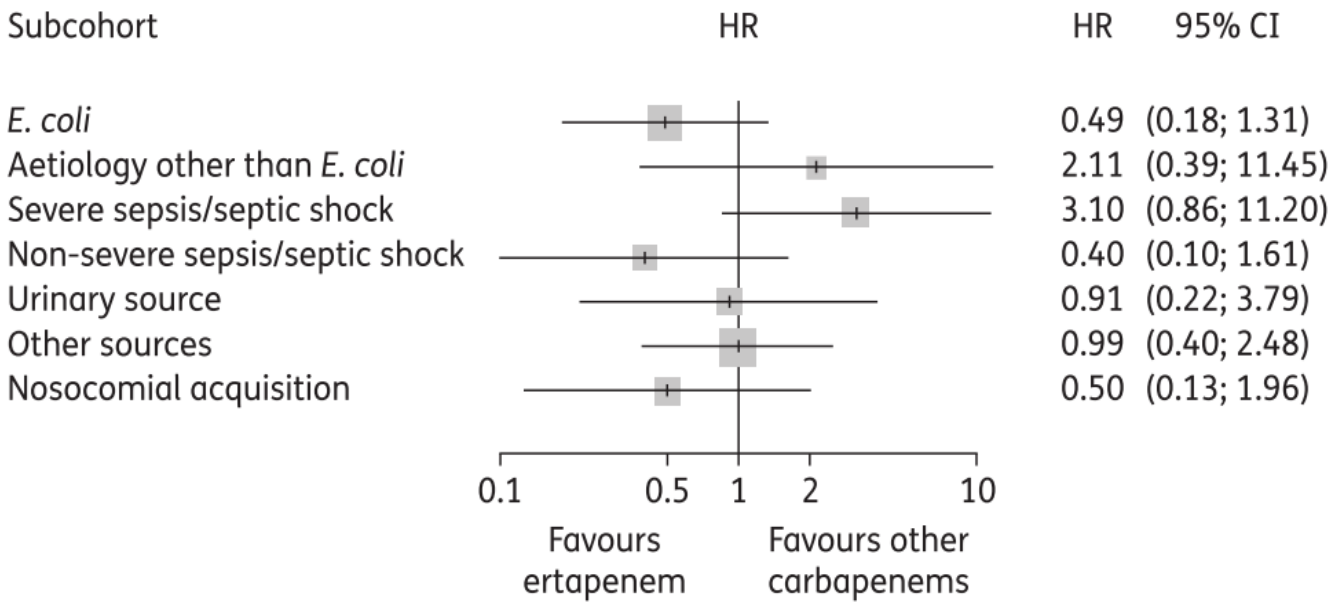
- 92 BLBLIs (60 PTZ; 32 AMC)
- **509 CARBAPENEMS (MEROP 185, ERTA 205, IMP 118, DORI 1)**

GC N=627

- 157 BLBLI empirical
- 156 carbapenem empirical
- 63 BLBLI empirical and targeted
- 225 empirical no BLBLI/carbap and targeted carabap
- 31 empirical no BLBLI/carbap and targeted BLBLIs

B. Gutiérrez-Gutiérrez Journal of Antimicrobial Chemotherapy Advance. 2016

Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study



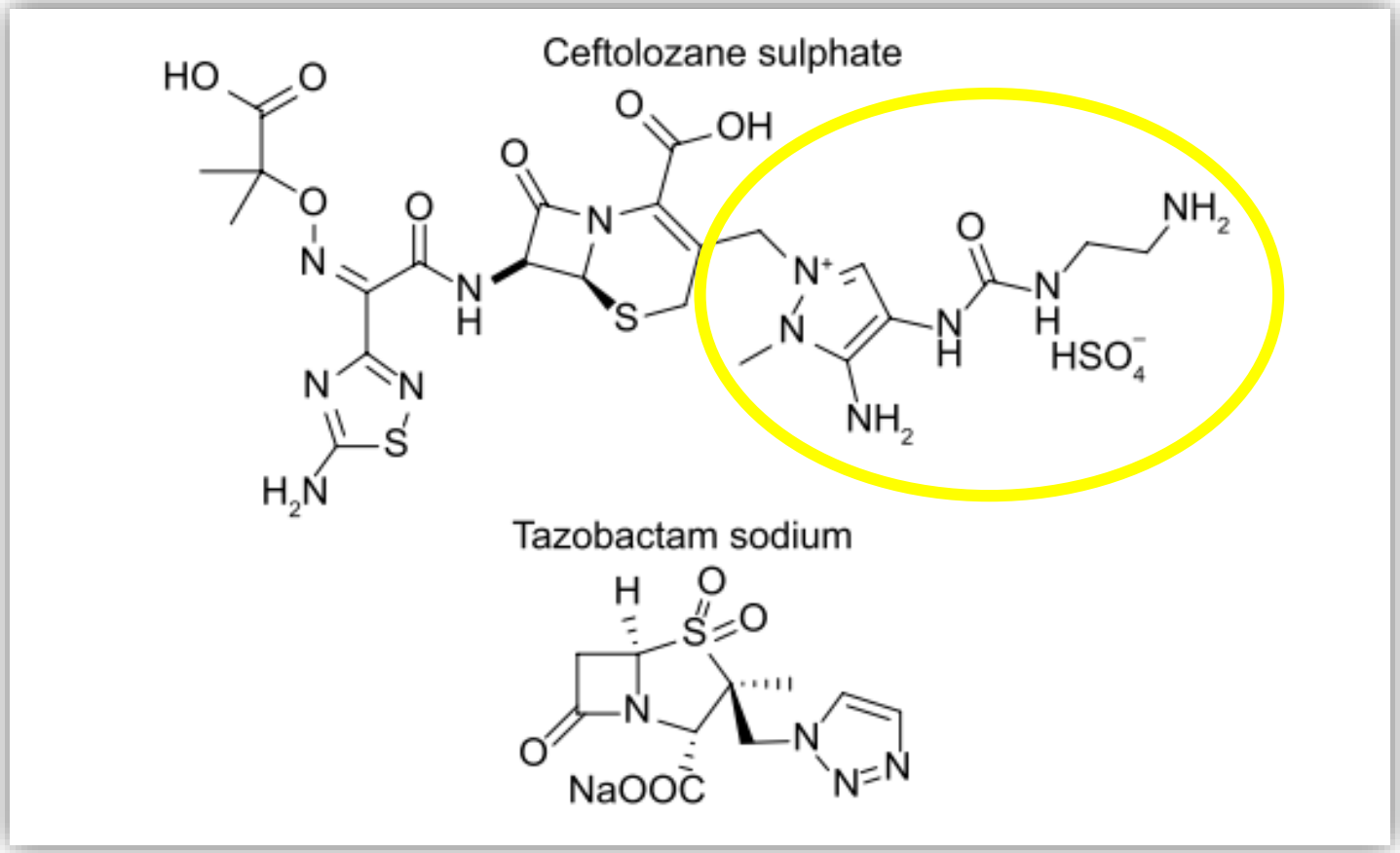
gure 3. Sensitivity analyses for mortality in the definitive therapy cohort.

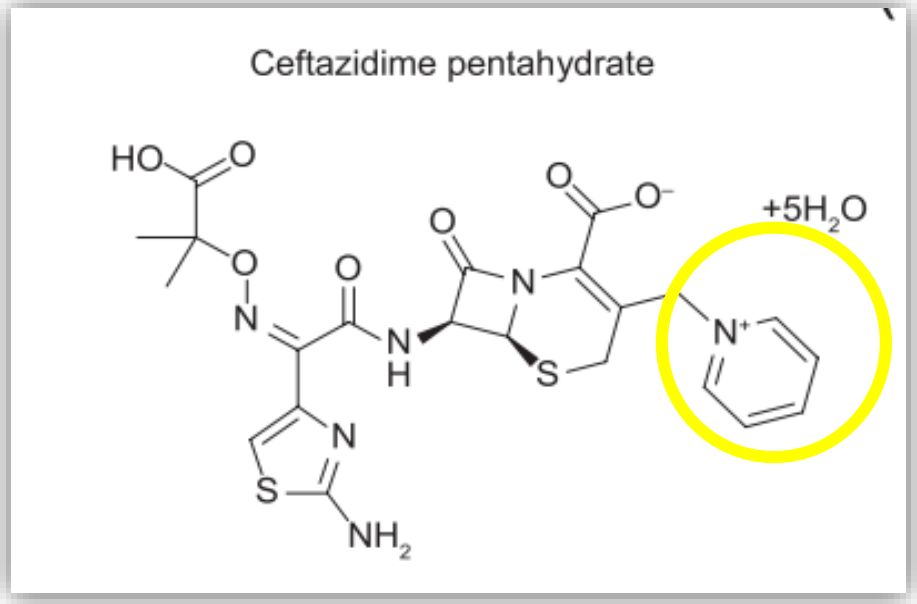
- Ertapenem no inferior ET o TT
- Baja potencia estadística en análisis por subgrupos (shock séptico)
- No se evaluó CMI

B. Gutiérrez-Gutiérrez Journal of Antimicrobial Chemotherapy. 2016

NUEVOS AB PARA G-

CEFTOLOZANO/TAZOBACTAM (Zerbaxa®)





Activa frente PBP 1b, 1c y 3 nula sobre PBP4-reponsable de la inducción tipo AmpC

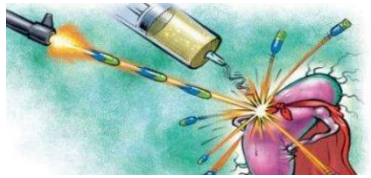
Van Duin Clin Infect Dis. 2016

@Amonterodel

In vitro activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* and Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study

M Tato. International Journal of Antimicrobial Agents 46 (2015) 502–510

- El **87.2%** de los Enterobacterias eran sensibles
- Más activo que PTZ, ceftazidima o cefotaxima para las cepas hiperproductoras de AmpC β-latamasas
- El más activo frente a Pseudomonas incluidas aquellas cepas MR

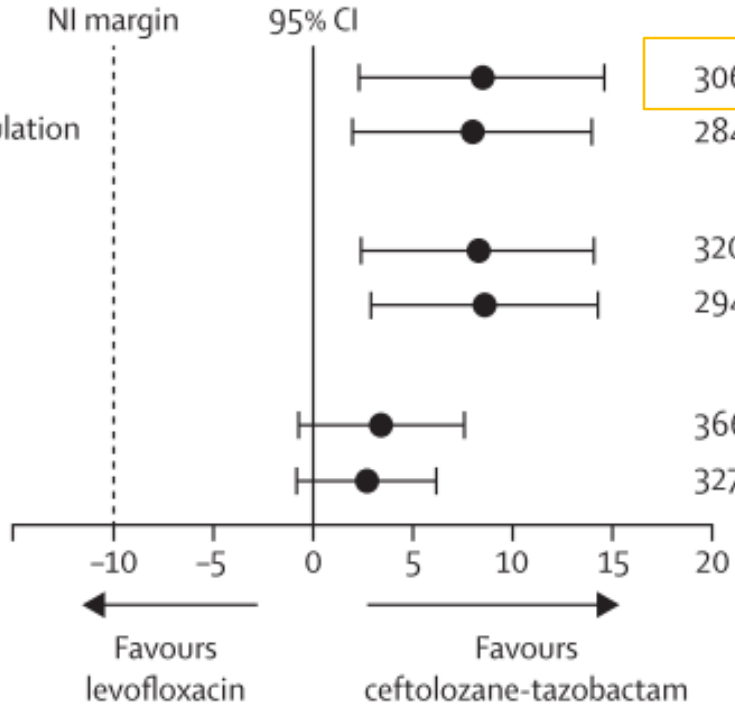


Resistance to ceftolozane in clinical isolates -hyperproduction of the pseudomonal AmpC cephalosporinase

Castanheira M. Antimicrob Agents Chemother 2014;58:6844–50.
Cabot G. Antimicrob Agents Chemother 2014;58:3091–9.

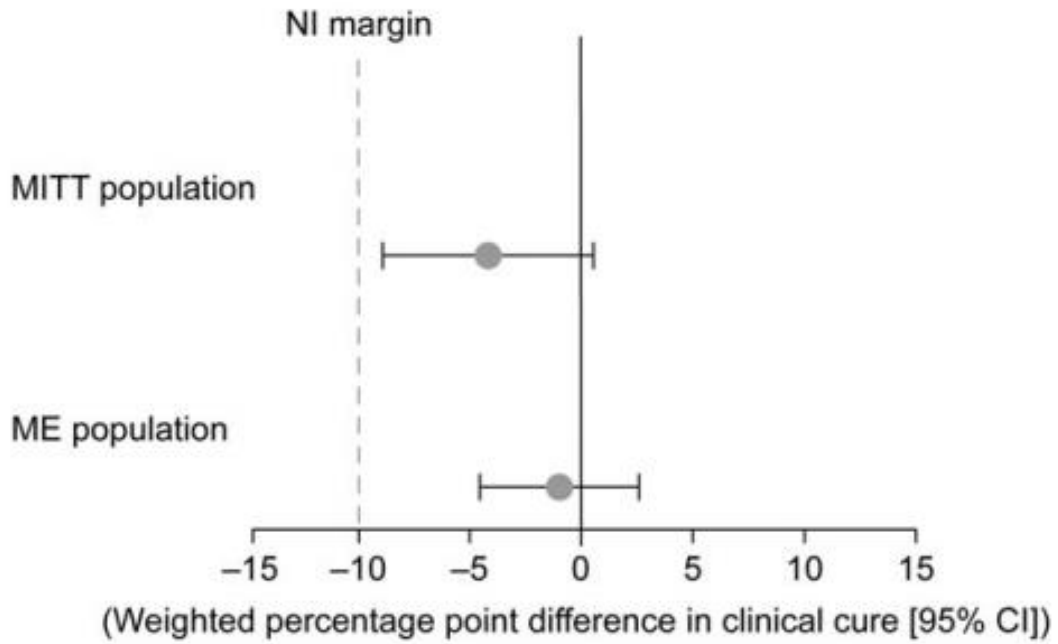
ASPECT ITUc

	Difference (%)	Number of patients/total (%)		Percentage difference	
		Ceftolozane-tazobactam	Levofloxacin	(95% CI)	(99% CI)
Composite cure					
Primary endpoint mMITT population		306/398 (76·9%)	275/402 (68·4%)	8·5 (2·3 to 14·6)	8·5 (0·4 to 16·5)
Secondary endpoint per-protocol population		284/341 (83·3%)	266/353 (75·4%)	8·0 (2·0 to 14·0)	8·0 (0·01 to 15·8)
Microbiological eradication					
mMITT population		320/398 (80·4%)	290/402 (72·1%)	8·3 (2·4 to 14·1)	..
Per-protocol population		294/341 (86·2%)	274/353 (77·6%)	8·6 (2·9 to 14·3)	..
Clinical cure					
mMITT population		366/398 (92·0%)	356/402 (88·6%)	3·4 (–0·7 to 7·6)	..
Per-protocol population		327/341 (95·9%)	329/353 (93·2%)	2·7 (–0·8 to 6·2)	..



Wagenlehner FM, ASPECT- cUTI. Lancet 2015; 385: 1949–56.

ASPECT- IAIc



	Ceftolozane/ tazobactam plus metronidazole No. (%)	Meropenem No. (%)	Percentage difference (95% CI)
MITT population	n = 389	n = 417	
Cure	323 (83.0)	364 (87.3)	–4.2 (–8.91 to .54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n = 275	n = 321	
Cure	259 (94.2)	304 (94.7)	–1.0 (–4.52 to 2.59)
Failure	16 (5.8)	17 (5.3)	

Figure 2. Primary and secondary analysis endpoints at the test-of-cure visit. In the microbiological intent-to-treat (MITT) population, a treatment failure approach was used, where indeterminate clinical responses were imputed as failures. In the microbiologically evaluable (ME) population, a data-as-observed approach was used, where indeterminate clinical responses were excluded from the analysis. Abbreviations: CI, confidence interval; NI, non-inferiority margin.

SOLOMONKIN J Clin Infect Dis. 2015 May 15;60(10):1462-71

NN-NAVM

- **Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008) (ASPECT-NP)**
  - **2,5g/8h**
  - **Comparación con meropenem**
  - **Fin de estudio febrero 2018**
- **NAVM- comparador piperacilina/tazobactam**
  - **2,5g/8h**
  - **Finalizado reclutamiento enero 2016**

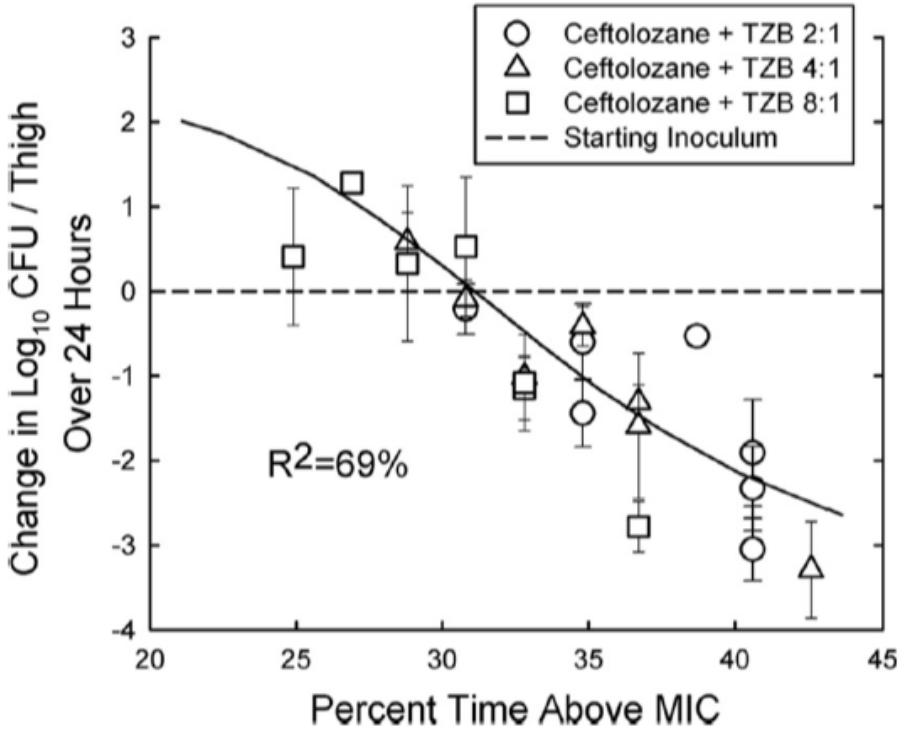


FIG 5 Relationship between the percent T>MIC and the change in CFU/thigh over 24 h for five ESBL-producing *Enterobacteriaceae* after 6-hourly therapy with 400 and 800 of ceftolozane mg/kg in combination with tazobactam (TZB) at 2:1, 4:1, and 8:1 ratios. Each point represents the mean of three mice, and the error bar represents the SD. R^2 represents the percentage of variance in CFU/thigh that can be attributed to the percent T>MIC.

	VOLUMEN DE DISTRIBUCIÓN	UPP
CEFTOLOZANO	13,5 L	16-21%
TAZOBACTAM	18,2L	30%

Craig Antimicrob Agents Chemother. 57(4):1577-82 2013

CEFTOLOZANO/TAZOBACTAM

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT-CEFTOLOZANO-TAZOBACTAM/V1/23022016

- **<u>Ceftolozano/tazobactam ha sido financiado:</u>**
  - Pacientes en elevado riesgo de infección por bacterias gram negativas multirresistentes y especialmente con mayor probabilidad de aislamiento de Pseudomonas aeruginosa, enfocándose principalmente en los casos más complicados por la comorbilidad del paciente
    - ingresados en UCI, inmunodeprimidos, neutropénicos, o por la gravedad de la infección (sepsis urinaria, infección de orina relacionada con la sonda, peritonitis secundarias o terciarias).

CEFTOLOZANO/TAZOBACTAM

Empírico	Unidades alta tasa de *Pseudomonas* MR en pacientes recogidos IPT
Dirigido en BGN	Resistencia a primera línea de fármacos. Fracaso a líneas previas

New β-Lactamase Inhibitors in the Clinic

DIAZABICYCLOOCTANONES,

BORONIC ACID b-LACTAMASE INHIBITORS

PHOSPHONATES

NOVEL SULFONES

METALLO-b-LACTAMASE-SPECIFIC INHIBITORS IN PRECLINICAL DEVELOPMENT: BISTHIAZOLIDINES AND ME1071

Papp-Wallace K Infect Dis Clin N Am 30 (2016) 441–4

AVIBACTAM

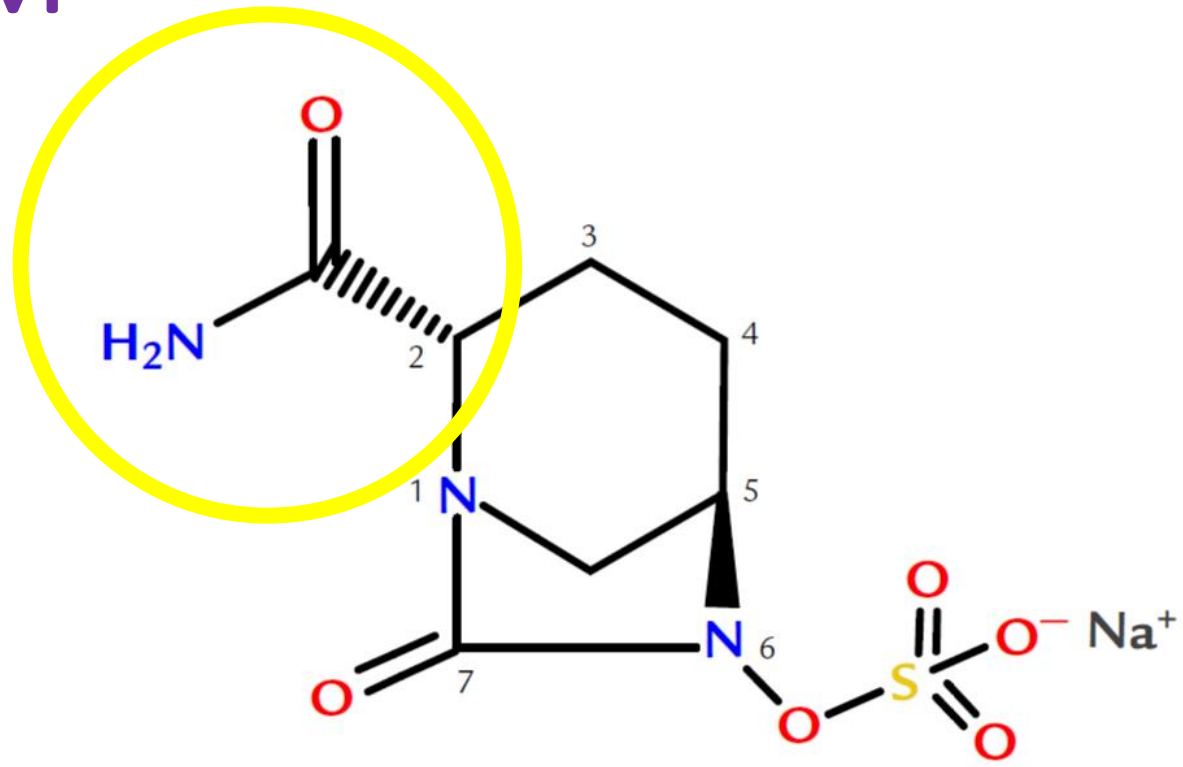


Figure 2. Chemical structure of avibactam sodium.

AVIBACTAM

IBL	ESTRUCTURA	UNIÓN	ACTIVIDAD
1ºG -CLÁVULÁNICO -TAZOBACTAM - SULBACTAM	ANILLO BETALACTÁMICO	**IRREVERSIBLE** (INHIBICIÓN SUICIDA) -**OCUPACIÓN TRANSITORIA COMPETITIVA** DEL SITIO ACTIVO (Acilación del IBL)	CLAV- 50% TEM recupera actividad em 7MIN
2ªG: -AVIBACTAM -RELABACTAM	DBO	OCUPACIÓN TRANSITORIA COMPETITIVA DEL SITIO ACTIVO (Sin degradación del IBL)	AVI-50% TEM 7 DÍAS, **RECUPERA SU ACTIVIDAD**

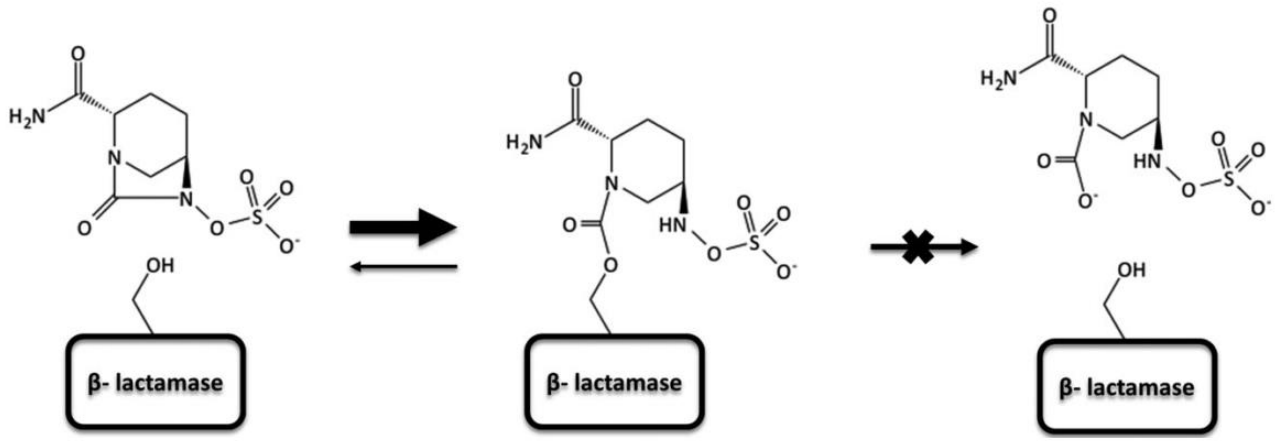
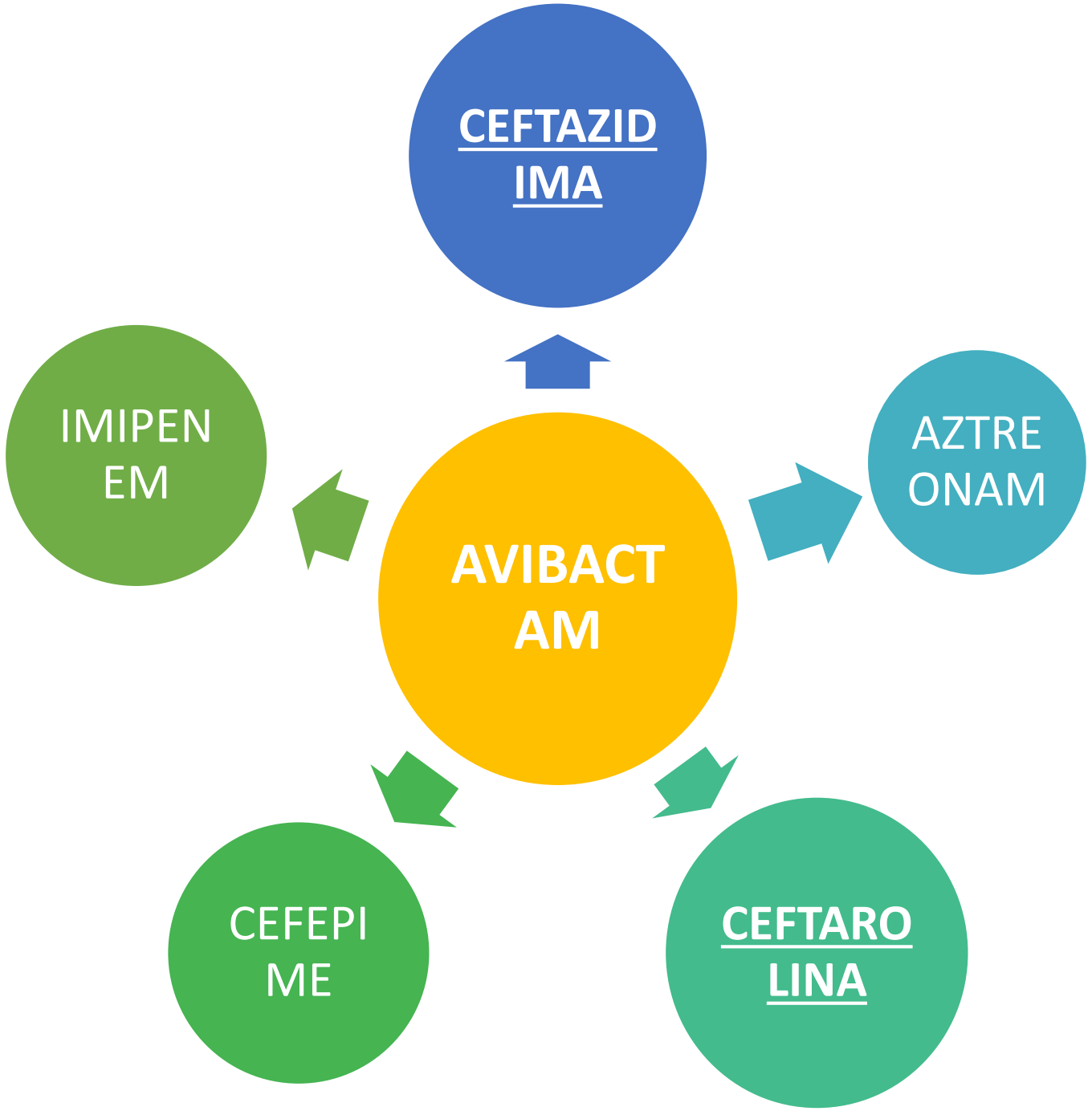


Figure 4. Acetylation of β-lactamases by avibactam.

ZASOWKI PHARMACOTHERAPY 2015


CEFTAZIDIMA
IMIPENEM
AZTREONAM
AVIBACTAM
CEFEPIME
CEFTAROLINA

CEFTAZIDIMA-AVIBACTAM (Zavicefta®)

- ESPECTRO
  - Betalactamasas de clase A (**BLEE (CTX-M-14 y CTX-M-15)** y **carbapenemasas de *Klebsiella pneumoniae***)
  - Betalactamasas clase C (AmpC)
  - Algunas betalactamasas clase D (ej OXA-48)
  - **NO ACTIVIDAD METALOBETALACTAMASAS (NDM, VIM, IMP)**
  - Actividad frente *Pseudomonas aeruginosa* (descritas tasas 18%-R)
  - **NO** frente *Acinetobacter* spp.
  - Poca actividad frente anaerobios.

CEFTAZIDIMA-AVIBACTAM (Zavicefta®)

- Improves susceptibility to ceftazidime by 16- to 1024-fold in:
  - E. coli, Enterobacter spp., and Klebsiella spp. that are carbapenem resistant or express extended-spectrum β-lactamases, AmpC, OXA-48, KPC, and other resistance mechanisms

Zhanel GG. Drugs 2013

CEFTAZIDIMA/AVIBACTAM RESISTENCIAS

First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing *Klebsiella pneumoniae* Isolate

Romney M. Humphries,[a] Shangxin Yang,[a] Peera Hemarajata,[a] Kevin W. Ward,[a] Janet A. Hindler,[a] Shelley A. Miller,[a] Aric Gregson[b]

Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, California, USA[a]; Department of Medicine, Division of Infectious Diseases, University of California, Los Angeles, Los Angeles, California, USA[b]

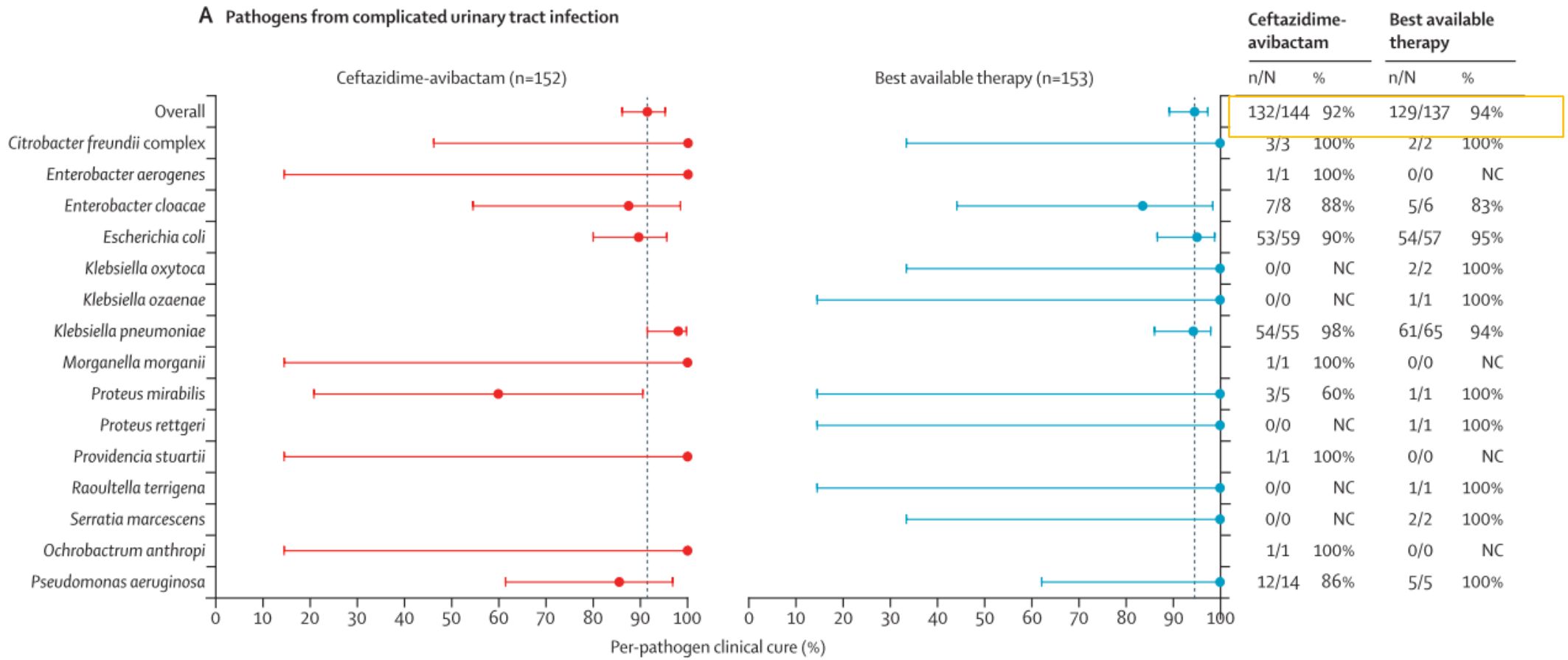
Ceftazidime-avibactam is the first antimicrobial approved by the U.S. FDA for the treatment of carbapenem-resistant *Enterobacteriaceae*. Avibactam, a non-β-lactam β-lactamase inhibitor, inactivates class A serine carbapenemases, including *Klebsiella pneumoniae* carbapenemase (KPC). We report a KPC-producing *K. pneumoniae* isolate resistant to ceftazidime-avibactam (MIC, 32/4 μg/ml) from a patient with no prior treatment with ceftazidime-avibactam.

Antimicrob Agents Chemother 2015;59(10):6605–7.

CEFTAZIDIMA/AVIBACTAM

- APROBADO FDA 2015
- PREVISIÓN ESPAÑA 2017
- AEMPS Abril 2016
  - **IIAc C/A + METRO**
  - **ITUc**
  - **NN, NAVM**
  - Infecciones causadas por organismos Gram-negativos aerobios en pacientes adultos con opciones de tratamiento limitadas
- RA más comunes observadas durante el desarrollo clínico fueron test de Coombs directo positivo, náuseas y diarrea.

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

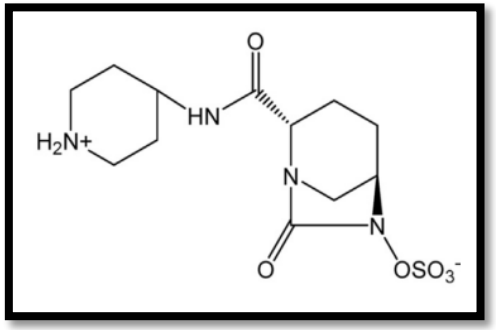


Carmeli Y. Lancet Infect Dis. 2016 Jun;16(6):661-73

CEFTAZIDIMA-AVIBACTAM

Empírico	Sepsis grave en unidades con alta prevalencia de enterobacterias productoras carbapenemasas (>10%)

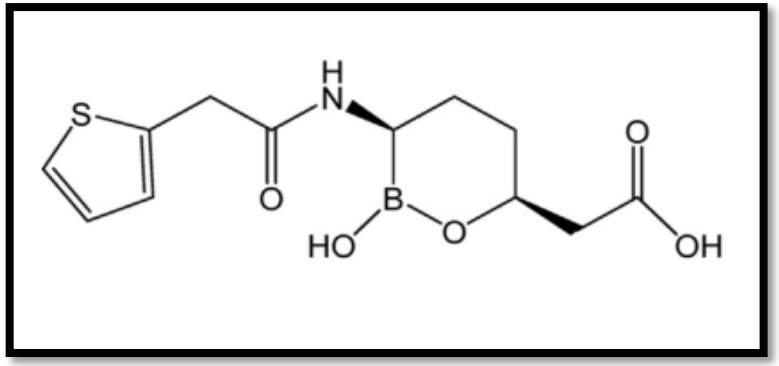
RELEBACTAM+ IMIPENEM/CILASTATIN



- Relebactam DBO
- Activity against class A and C carbapenemasas.
- Relebactam has been granted qualified infectious disease product (QIDP) fast-track status for the treatment of cUTIs, cIAIs, and hospital-acquired/ventilator-associated bacterial pneumonia phase III

D.M. Martirosov, T.P. Lodise / Diagnostic Microbiology and Infectious Disease 85 (2016) 266–275 273

RPX7009+MEROPENEM



- Mimics the β-lactam ring using a novel cyclic boronic acid structure.
- Designated as a QIDP and is currently undergoing phase 3 studies
  - cUTI and AP (TANGO1)
  - cUTI, AP, nosocomial pneumonia, and bacteremia (TANGO 2)

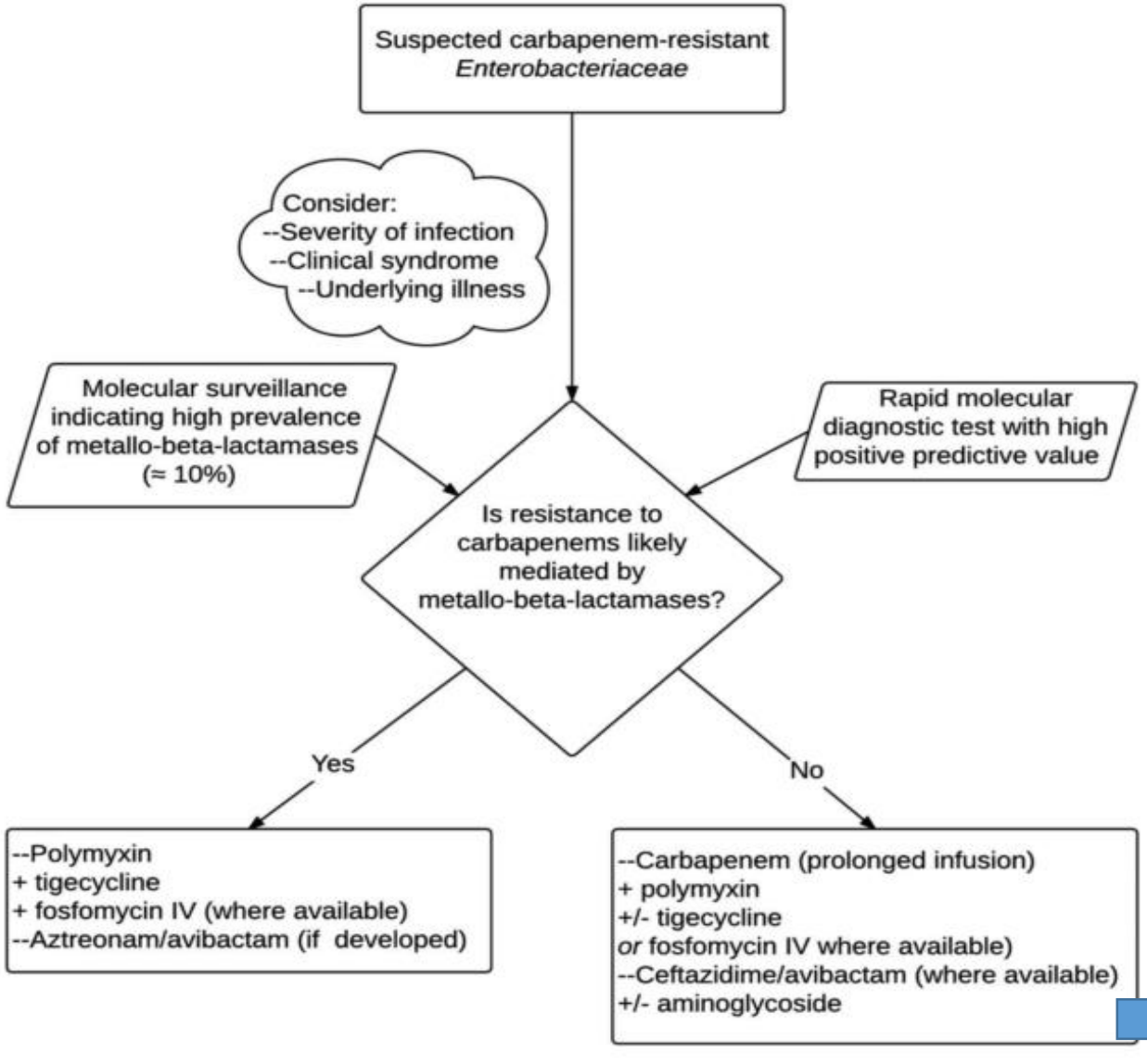
D.M. Martirosov, T.P. Lodise / Diagnostic Microbiology and Infectious Disease 85 (2016) 266–275 273

NUEVAS TETRACICLINAS

FÁRMACO	ACTIVIDAD IN VITRO	OBSERVACIONES
ERAVACICLINA	MDR gram-negative, gram-positive, and anaerobic organisms. -Acinetobacter spp resist carbapenémicos. -ESBL-producing Enterobacteriaceae -KPC K.pneumoniae -MLB Enterobacterias. -**Sin actividad P.aeruginosa MR**	-Fase III **IGNITE:** cIAI cITU -Formulación oral en desarrollo. -May be associated with an 11–22% incidence of mild to moderate nausea
OMADACYCLINE	-G+ y G-	-Fase II -Neumonia comunitaria -ITU -IPPB

AMINOGLUCÓSIDOS

FÁRMACO	ACTIVIDAD IN VITRO	OBSERVACIONES
Plazomicin	-Amplio espectro G+ y G- -Resistencia enzimas hidrolizan AMG -No activos metiltransferasas ribosomicas como mec de resistencias. -**Enterobact BLEE** -Enterob AmpC -**KPC Klebsiella** -No activo frente NMD -Pseudomonas y Acinetobacter MR	-Phase IIImulticenter, randomized, open-label **superiority** study comparing it to colistin+ meropenem or tigecycline blood- streaminfections and pneumonia caused by CRE (ClinicalTrials.gov identifier: NCT01970371- -Limited information available, but as with other aminoglycosides**, therapy may result in neurotoxicity, ototoxicity, and nephrotoxicity**, and **close monitoring of plasma drug levels** may be necessary



AZTREONAM +
CEFTAZIDIMA/AVIBACTAM

CMI >8 mg/L
OXA-48, SME

Figure 7. Guide for the empiric treatment of infections where carbapenem-resistant *Enterobacteriaceae* is suspected, based on the local prevalence of metallo-beta-lactamases and results of rapid molecular diagnostics.

Pérez F et al Expert Opinion on Pharmacotherapy, 2016 vol. 17, no. 6, 761–781

Selva de Irati (Navarra)

MUCHAS GRACIAS

AAC
Journals.ASM.org

Preliminary Clinical Study of the Effect of Ascorbic Acid on Colistin-Associated Nephrotoxicity

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Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand[a]; Department of Biochemistry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand[b]; Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia[c]

MONOTERAPIA?

ntimicrob Chemother 2015; **70**: 905–913
i:10.1093/jac/dku432 Advance Access publication 25 October 2014

Journal of Antimicrobial Chemotherapy

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Marcelino Gonzalez-Padilla[1]†, Julián Torre-Cisneros[1,2]*†, Francisco Rivera-Espinar[3], Antonio Pontes-Moreno[3], Lorena López-Cerero[2,4,5], Alvaro Pascual[2,4,5], Clara Natera[1], Marina Rodríguez[3], Inmaculada Salcedo[6], Fernando Rodríguez-López[2,7], Antonio Rivero[1] and Jesús Rodríguez-Baño[2,4,5]

Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

Wentao Ni, MD, Yuliang Han, MD, Jie Liu, MD, Chuanqi Wei, MD, Jin Zhao, MD, Junchang Cui, MD, Rui Wang, PhD, and Youning Liu, MD

Abstract: Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are prevalent worldwide; they have few effective treatments and this jeopardizes public health. Clinicians often use tigecycline to combat CRE, but its clinical efficacy remains controversial. Therefore, to compare the efficacy and safety of tigecycline in treating CRE infections compared with that of other antimicrobial agents, and to evaluate whether combination therapy and high-dose regimens are beneficial, we performed a systematic review and meta-analysis.

PubMed and Embase were searched for controlled trials or cohort studies reporting the efficacy and/or safety of tigecycline-based regimens to treat CRE infections. Statistical analyses were performed using the Comprehensive Meta-Analysis V2.2. All meta-analyses were performed based on fixed- or random-effects model, and the I^2 method was

Our results indicated that the efficacy of tigecycline in treating CRE infections is similar to that of other antibiotics. Tigecycline combination therapy and high-dose regimens may be more effective than monotherapy and standard-dose regimens, respectively. Nonetheless, considering that the current available evidence is limited, well-designed randomized controlled trials are urgently needed to clarify the comparative efficacy of tigecycline in treating CRE infections.

(*Medicine* 95(11):e3126)

Abbreviations: CI = confidence interval, CRE = carbapenem-resistant *Enterobacteriaceae*, ICU = intensive care unit, NOS = Newcastle–Ottawa scale, OR = odds ratio, RCT = randomized controlled trial.

DOSIS ELIMINACIÓN URINARI

De Pascale *et al. Critical Care* 2014, **18**:R90
http://ccforum.com/content/18/3/R90

CRITICAL CARE

RESEARCH Open Access

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

Gennaro De Pascale[1*], Luca Montini[1], Mariano Alberto Pennisi[1], Valentina Bernini[1], Riccardo Maviglia[1], Giuseppe Bello[1], Teresa Spanu[3], Mario Tumbarello[2] and Massimo Antonelli[1]

J Antimicrob Chemother 2014; **69**: 2606–2610
doi:10.1093/jac/dku189 Advance Access publication 30 May 2014

Journal of Antimicrobial Chemotherapy

Tigecycline in treatment of multidrug-resistant Gram-negative bacillus urinary tract infections: a systematic review

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2011, p. 3002–3004 Vol. 55, No. 6
0066-4804/11/$12.00 doi:10.1128/AAC.01420-10

Double-Carbapenem Therapy for Carbapenemase-Producing *Klebsiella pneumoniae*▽

Catharine C. Bulik[1] and David P. Nicolau[1,2]*

- Overall, results have been mixed and, at best, demonstrate a “static” effect that commonly led to bacterial regrowth after an initial killing phase in in vitro studies. Because inhibitors that neutralize the effect of common β-lactamases (such as KPCs) are now available, the use of antibiotics as competitive substrates may be unnecessary

Hagihara et al., 2013; Hong et al., 2013;Wiskirchen et al., 2013)

ión

Ertapenem-containing double-carbapenem therapy for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae*: a case series

OBJETIVO

Outcomes in patients with infections with carbapenem-resistant Klebsiella 15 pneumoniae (CRKP) who received ertapenem-containing double-carbapenem therapy

DISEÑO

non-interventional, retrospective October 2013 to November 2014.

PACIENTES

ERTAPENEM (AS **IBL**) 1H BEFORE + FIRST DOSE MEROPENEM O DORIPENEM carbapenem-resistant *Klebsiella pneumoniae* N=18

RESUTADOS

Clinical success 7/18 (39%) patients: Mortality 5/18 (28%) ≈ 40% BSI (7/18)

Two patients (11%) developed seizures during ECDCT

CONCLUSIONES

Our laboratory did not report actual MICs of the organism when they were above 4 mcg/mL. **CMI para carbapenémicos???**

Cprek JB Antimicrob Agents Chemother. 2015 Nov 9;60(1):669-73

FOREST

A phase 3, randomized, controlled, multicentric, open-label clinical

Non-inferiority of fosfomycin (4g/6h) vs meropenem (1g/8h)

Targeted treatment of **bacteraemic** urinary tract infection **UTI due to Escherichia coli producing extended- spectrum beta-lactamases** (ESBLs).

JR-Baño

MERINO-TRIAL

- Desing Multicentre randomised controlled non-inferiority (5%) open-label phase III trial
- **Meropenem 1 g/8h vs piperacillin-tazobactam 4.5 grams /6 h**.
- Bacteraemia caused by E. coli or Klebsiella spp ESBL
- N=454
- Primary outcome mortality at 30 days.

Harris et al. Trials 2015 16:24

TABLE 3. Range of MICs of carbapenems for clinical *Enterobacteriaceae* expressing the main carbapenemases

	MIC (mg/L)		
	Imipenem	Meropenem	Ertapenem
KPC	0.5 to >32	0.5 to >32	0.5 to >32
IMP/VIM/NDM	0.5 to >32	0.5 to >64	0.38 to >32
OXA-48/OXA-181	0.25 to 64	0.38 to 64	0.38 to >32

P. Nordmann et al. Clin Microbiol Infect 2012; 18: 432–438