SEICAV

Sociedad Española de Infecciones Cardiovasculares

Novedades en el tratamiento antibiótico de las infecciones postquirúrgicas por bacilos Gram negativos multirresistentes.

Enrique Navas

Barcelona, 29 de Septiembre de 2017

VI Congreso SEICAV

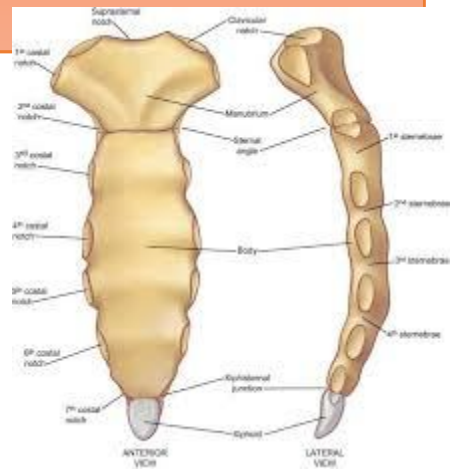
Sociedad Española de Infecciones Cardiovasculares

SEICAV

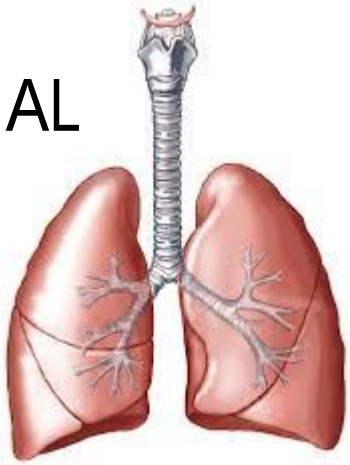
Facultat de Medicina
Campus Clínic
Universitat de Barcelona

Barcelona
29 y 30 Septiembre 2017

Infecciones en Cirugía Cardiovascular

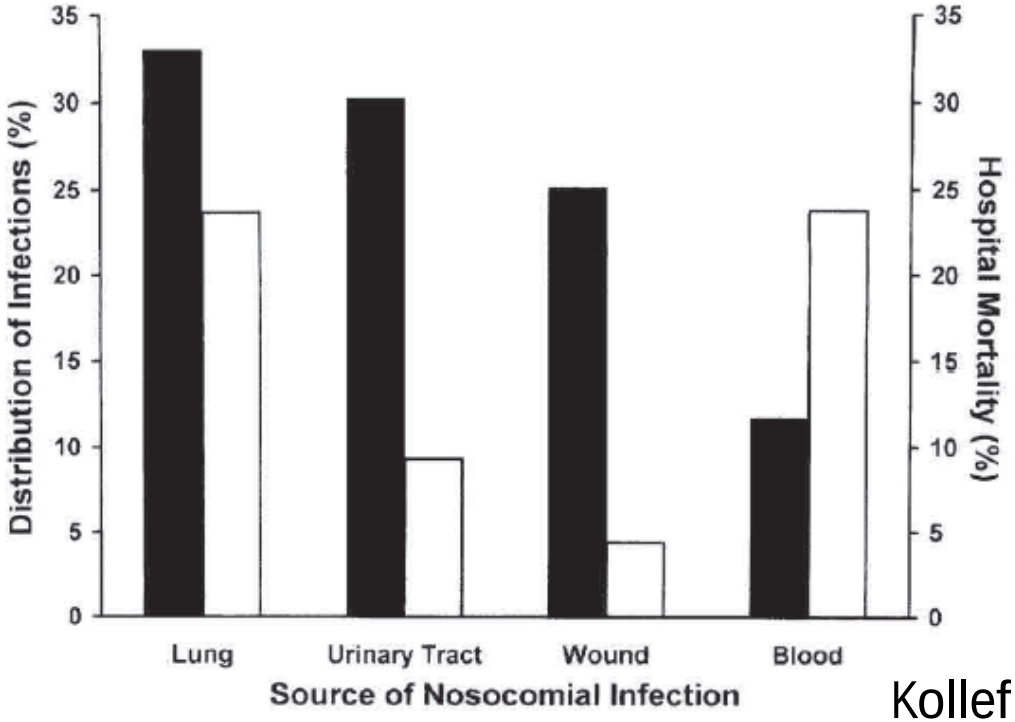


- INFECCION DE LA ESTERNOTOMIA /HERIDA QUIRURGICA (“SSI”)
- BACTERIEMIA PRIMARIA/CATETER/ENDOCARDITIS
- NEUMONIA NOSOCOMIAL
- ITU/OTRAS



The Impact of Nosocomial Infections on Patient Outcomes Following Cardiac Surgery

- 131 (21,7%) desarrolla una IRAS
- OR mortalidad: 4. 0 (IC 2.7-5.8)
- Estancia hospitalaria: 20.1±13.0 d vs 9.7±4.5 d



Kollef et al, *CHEST 1997; 112:666-75*

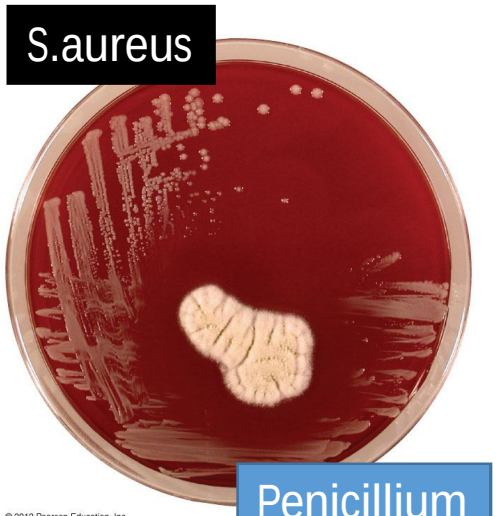
Etiología de las infecciones del sitio quirúrgico en pacientes intervenidos de cirugía cardíaca

	Cirugía valvular (n = 86)		Bypass coronario (n = 94)		p
	Frecuencia	%	Frecuencia	%	
Cocos grampositivos					
SASM	14	16,3	14	14,7	0,797
SARM	4	4,7	8	8,4	0,299
SCN	34	39,5	33	34,7	0,539
Streptococcus grupo viridans	0	0	1	1,1	0,522
Streptococcus spp.	1	1,2	1	1,1	0,949
Enterococcus faecalis	5	5,8	4	4,2	0,631
Enterococcus spp.	0	0	2	2,1	0,271
Bacilos grampositivos					
Propionibacterium spp.					0,522
Corynebacterium spp.					0,213
Cocos gramnegativos, enterobacterias					
Escherichia coli					0,206
Klebsiella pneumoniae					0,466
Enterobacter aerogenes					0,477
Enterobacter cloacae					0,555
Proteus mirabilis					0,949
Citrobacter freundii					0,477
Serratia marcescens					0,41
Serratia spp.					0,949
Morganella morgagni	1	1,2	1	1,1	0,949
Bacilos gramnegativos, no enterobacterias					
Pseudomonas aeruginosa	3	3,5	3	3,2	0,615
Acinetobacter baumannii	1	1,2	2	2,1	
Acinetobacter spp.	1	1,2	1	1,1	0,949
Bacilos anaeróbicos					
Bacteroides grupo fragilis	1	1,2	0	0	0,477
Prevotella spp.	0	0	1	1,1	0,522
Otras bacterias	1	1,2	2	2,1	0,533

30% Infecciones por BGN

- 5% *E.coli*
- 5% *Klebsiella*, *Enterobacter*
- 4,4% *Serratia*
- 5% *Pseudomonas aeruginosa* y BGNNF

Muñez et al, Cir Cardiov. 2013;20(3):139-143



Penicillium

E.coli
TEM1
SHV1

Enterobacterias
BLEEs (CTXm)
P.aeruginosa MDR
Acinetobacter MDR

40´s 50´s 60´s 70´s 80´s 90´s 2000 10´s

Penicilina
Sulfamidas
Estreptomicina
Neomicina

Tetraciclinas
Vancomicina
Colistina
Tianfenicol
Metronidazol

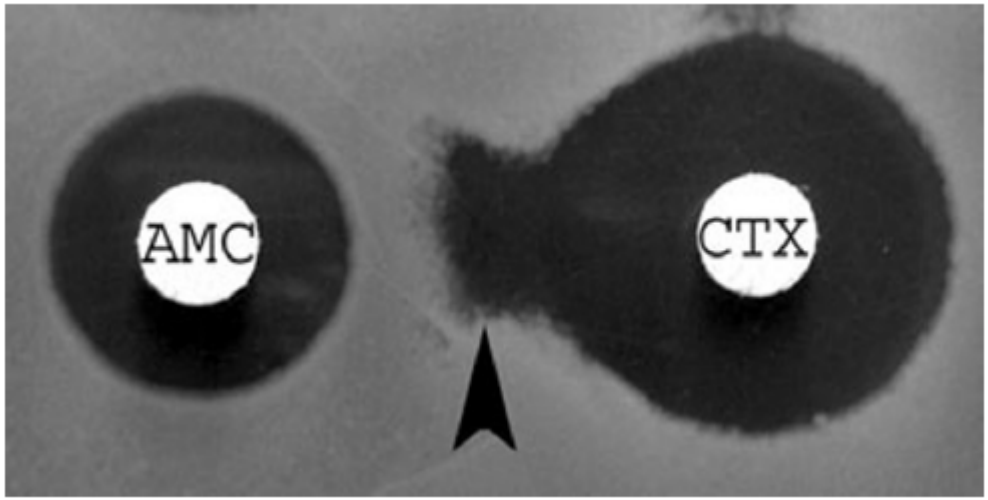
Ampicilina
Carbenicilina
Clindamicina
Rifampicina
Gentamicina

Cefalosporinas
Tobramicina
Amikacina

Ceftazidima
Ceftriaxona
F-quinolonas
Imipenem
Clavulánico
Sulbactam
Azitromicina

Meropenem
Pip-tazobactam
Linezolid
Cefepima
Synercid

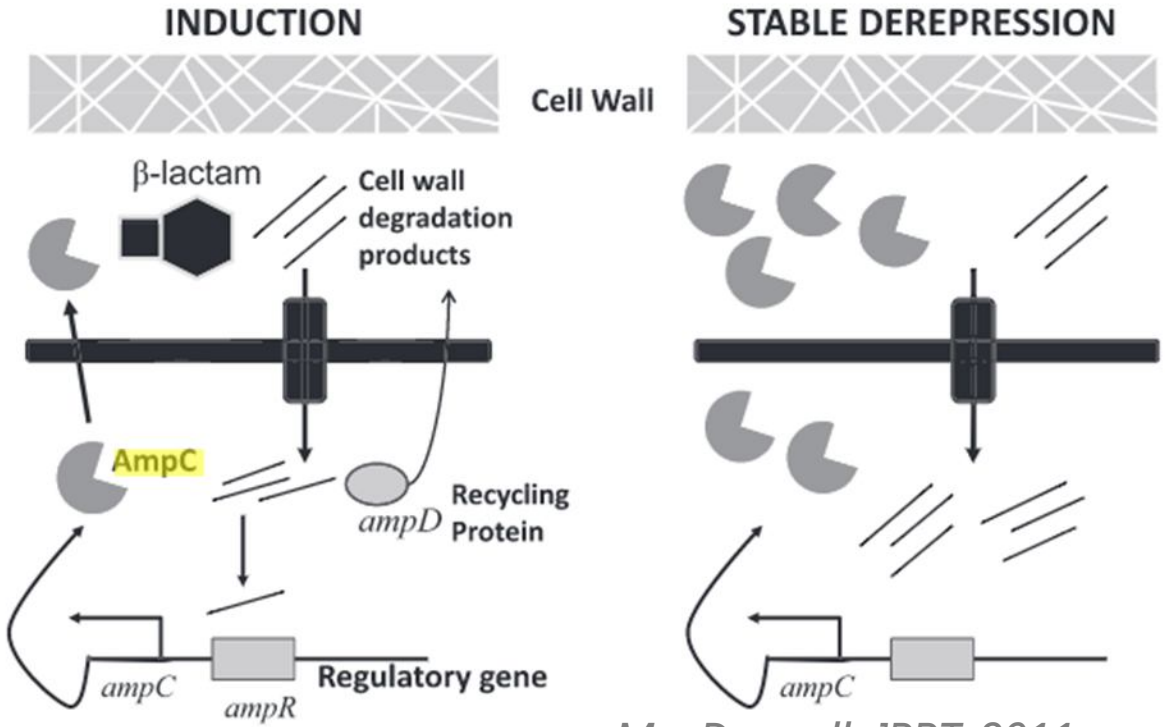
Daptomicina
Tigeciclina
Doripenem
Telavancina
Bedaquilina



BLEE *clase A*

- *E.coli, Klebsiella…*
- Variantes TEM-SHV
- CTX-M

	Amoxicilina	Amoxi-Clav	Cefazolina	Cefuroxima	Cefoxitina	Cefotaxima Ceftazidima	Imipenem
E.coli TEM-1	R	S	R	S	S	S	S
E.Coli BLEE CTX-M	R	S	R	R	S	CTX R CAZ I/S/R	S

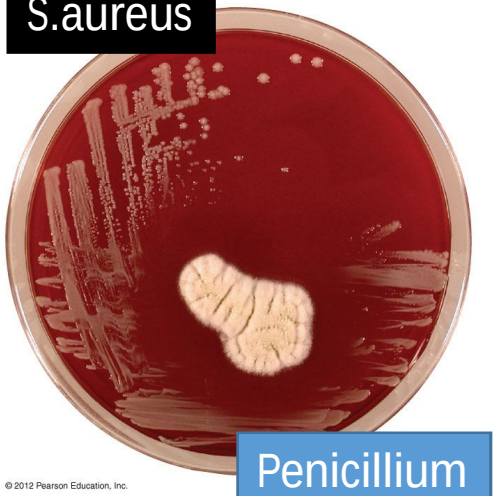


MacDougall, JPPT, 2011

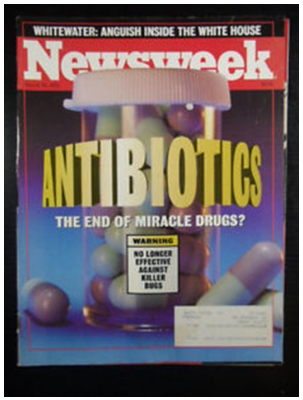
Enterobacter, Serratia, Citrobacter, Morganella (Pseudomonas aeruginosa)

	Cefazolina	Cefoxitina	Pip-Tzb	Ceftriaxona	Cefepima	Imipenem
Wild-type	R	R	S	S	S	S
Desreprimido	R	R	R	R	S/I/R	S

S.aureus



Penicillium



E.coli
TEM1
SHV1

Enterobacterias
BLEEs (CTXm)
P.aeruginosa MDR
Acinetobacter MDR

Carbapenemasas

40´s 50´s 60´s 70´s 80´s 90´s 2000 10´s

Penicilina
Sulfamidas
Estreptomicina
Neomicina

Tetraciclinas
Vancomicina
Colistina
Tianfenicol
Metronidazol

Ampicilina
Carbenicilina
Clindamicina
Rifampicina
Gentamicina

Cefalosporinas
Tobramicina
Amikacina

Ceftazidima
Ceftriaxona
F-quinolonas
Imipenem
Clavulánico
Sulbactam
Azitromicina

Meropenem
Pip-tazobactam
Linezolid
Cefepima
Synercid

Daptomicina
Tigeciclina
Doripenem
Telavancina
Bedaquilina

Figura 1: Mecanismos de resistencia de *E. coli* (%)

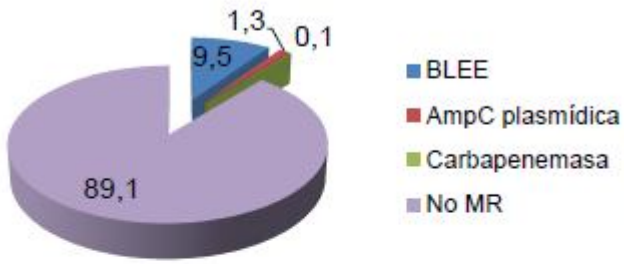


Figura 2: Mecanismos de resistencia de *K. pneumoniae* (%)

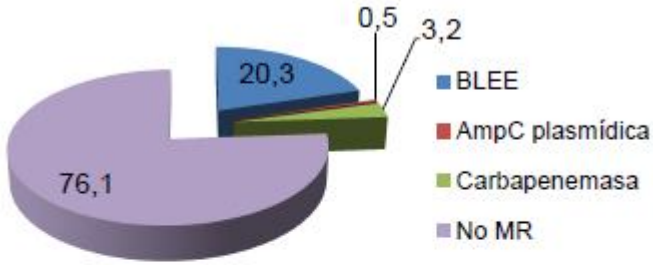
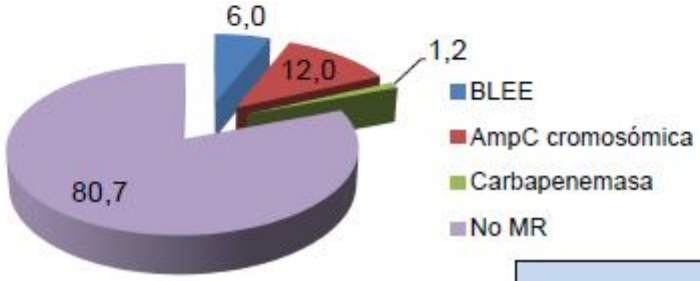


Figura 3: Mecanismos de resistencia de *E. cloacae* (%)



Prevalencia de microorganismos multirresistentes en hemocultivos Salmerón P et al, SEIMC, 2017

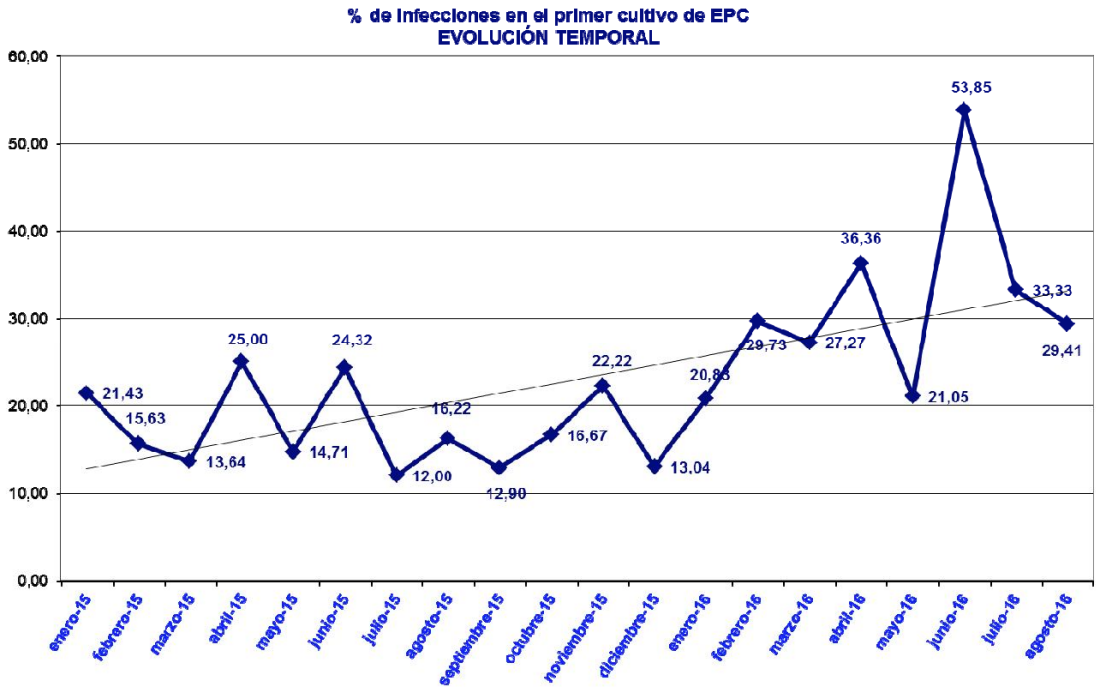
Hospital Vall d´Hebron
2015-2016

MICROORGANISMO	Nº	Multirresistentes (MR) Nº (%)
Klebsiella pneumoniae	222	53 ( )
Enterobacter aerogenes	24	5 ( )
Enterobacter cloacae	83	16 ( )
Staphylococcus aureus	249	45 (18,1)
Pseudomonas aeruginosa	198	34 ( )
Escherichia coli	785	86 ( )
Morganella morganii	23	2 (8,7)
Citrobacter freundii	12	1 (8,3)
Acinetobacter baumannii	16	1 (6,2)
Klebsiella oxytoca	41	2 (4,9)
Serratia marcescens	32	1 (3,1)

EB-Carbapenemasas Hospital Ramón y Cajal: enero15-agosto16
López-Fresneña N, S. Med. Preventiva

	Frecuencia	Porcentaje
COLONIZACIÓN	126	71,2%
INFECCIÓN	47	26,6%
COLONIZACIÓN + INFECCIÓN	4	2,3%
Total	177	100

Mortalidad global: 14,7% (21% en casos de infección)



Localización del primer cultivo		
	TOTAL	Porcentaje
RECTAL	**123**	**69,5**
UROCULTIVO	**27**	**15,3**
M RESPIRATORIA	8	4,5
HEMOCULTIVO	6	3,4
HERIDA	1	0,6
EXUDADO FARÍNGEO	4	2,3
LÍQUIDO ORGÁNICO	5	2,8
ABSCESO	5	1,4
Total	177	100

	n	%
K. pneumoniae	**131**	**72,38**
E. coli	**24**	**13,26**
P. aeruginosa	12	7,53
E. cloacae	10	6,23
K. oxytoca	7	1,82
C. koserii	1	0,26
	181	100

70% asocian BLEE
(88% en *Klebsiella* spp, 25% en *E. coli*

Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012–2013

Journal of Hospital Infection (2015)

Crude and attributable mortality of CRKP at six and 30 days

Mortality	CRKP patients ($N = 49$)	CSKP patients ($N = 49$)	Attributable mortality[a]
At six days	12 ( )	4 (8%)	
At 30 days	30 ( )	10 (20%)	

Outcomes of mortality at 30 days after isolation of the pathogen

Variable	Crude mIRR		Adjusted mIRR	
	mIRR (95% CI)	*P*-value	mIRR (95% CI)	*P*-value
CRKP (resistant infection)	(1.5–6.1)	0.003	(1.3–7.1)	0.012

CARBAPENEMASAS

CLASE MOLECULAR	ENZIMAS	INHIBICION IN VITRO	RESISTENCIA CARBAPENEM	AZTREONAM	MICROORGANISMO
A (ser)	KPC	CLAV	Heterogéneo	R	*Enterobacterias (Klebsiella) P.aeruginosa*
B (metalo)	VIM IMP NDM	EDTA	Heterogéneo	S	*P.aeruginosa Enterobacterias*
D (ser)	OXA-48	CLAV	Bajo	S	*A.baumanii Enterobacterias*

Infección por enterobacteria productora de carbapenemasa

- CMI ≤ 8 mg/L:
  - Meropenem en infusión extendida 3h
  - Asociar 1-2 abcos activos:

  Colistina, Aminoglucósido, Fosfomicina, Tigeciclina…

- *CMI >8 mg/L*

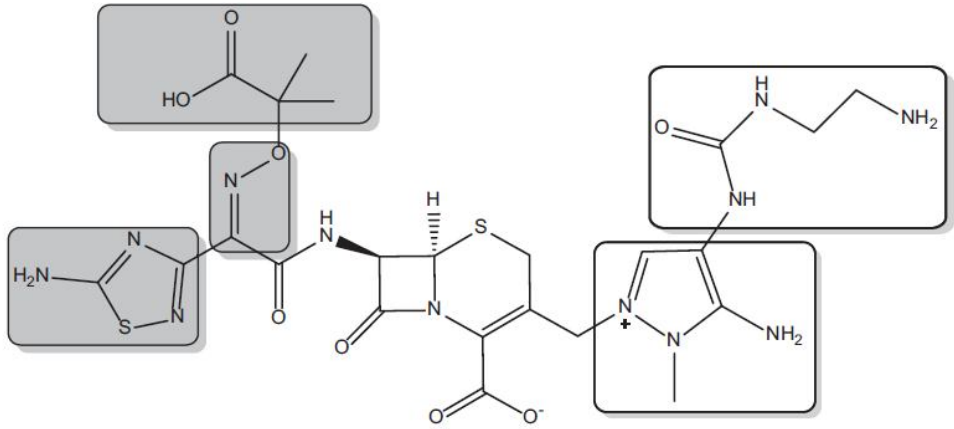
Pipeline abcos para BGN multirresistentes

- CEFTOLOZANO-Tazobactam
- Nuevos Inhibidores de betalactamasas:
  - AVIBACTAM (+ Ceftazidima, Aztreonam)
  - Relebactam (+ Imipenem)
  - Vaborbactam (+ Meropenem)
  - Zidebactam (+Cefepima)
- Sideróforo-Abco:
  - Sideróforo-Sulfactam (BAL 30072)
  - Sideróforo-Cefiderocol (S-649266)
- Nueva Tetraciclina: Eravaciclina
- Nuevo aminoglucósido: Plazomicina
- Nuevas quinolonas: Delafloxacino, Finafloxacino

Pipeline abcos para BGN multirresistentes

- [redacted]
- Nuevos Inhibidores de betalactamasas:
  - AVIBACTAM (+ Ceftazidima, Aztreonam)
  - Relebactam (+ Imipenem)
  - Vaborbactam (+ Meropenem)
- Zidebactam (+Cefepima)
- Sideróforo-Abco:
  - Sideróforo-Sulfactam (BAL 30072)
  - Sideróforo-Cefiderocol (S-649266)
- Nueva Tetraciclina: Eravaciclina
- Nuevo aminoglucósido: Plazomicina
- Nuevas quinolonas: Delafloxacino, Finafloxacino

Ceftolozano



- Cefalosporina:
  - Gran afinidad por PBPs
  - Estable frente a ampC
  - ↑ actividad frente a *P.aeruginosa*
  - ↑ permeabilidad membrana externa
  - No se afecta por expresión de bombas
- Asociación a Tazobactam:
  - Actividad frente a serina-betalactamasas (clase A)
  - NO activa frente a OXA (clase D), ni frente a carbapenemasas (MBL/Clase A)

Pseudomonas aeruginosa
Mecanismos de resistencia

- Inactivación: betalactamasas:
  - ampC inducible
  - Transferible: Betalactamasas plasmídicas
- Sobreexpresión de MexA-MexB-OprM (bombas)
- Mutaciones de OprD (permeabilidad)

Tazobactam:
- Inactiva ßl clase A (no Carbapenemasa)

Avibactam:
- Inactiva ampC
- Inactiva ßl clase A, C y algunas D

Ceftolozano:
- Débil sustrato de bombas MexAB
- No se afecta por la pérdida de OprD
- Baja hidrólisis por ampC

Ceftolozano-Tazobactam

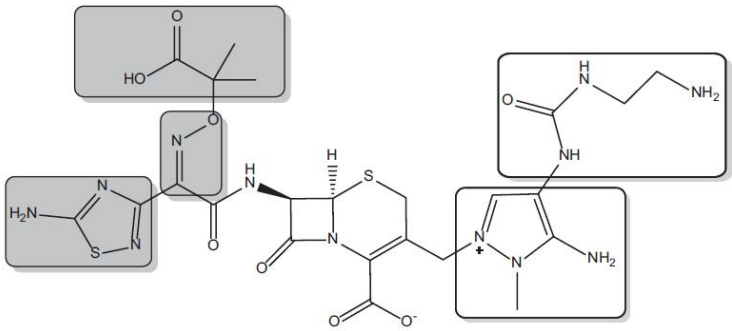


Table 3. Antimicrobial activity of ceftolozane/tazobactam, ceftazidime and meropenem against *P. aeruginosa* strains stratified by country (2011–12)

Country (no. tested)	Ceftolozane/tazobactam $MIC_{50/90}$ (%S at ≤8 mg/L)	Ceftazidime $MIC_{50/90}$ (%S at ≤8 mg/L)[a]	Meropenem $MIC_{50/90}$ (%S at ≤2 mg/L)[a]
Belgium (53)	2/>32 (64.2)	16/>32 (47.2)	8/>8 (34.0)
France (299)	1/4 (98.0)	4/32 (74.5)	0.5/8 (78.6)
Germany (124)	0.5/2 (95.2)	2/32 (81.5)	0.5/4 (80.6)
Greece (90)	0.5/>32 (80.0)	4/>32 (67.8)	1/>8 (65.6)
Ireland (122)	0.5/2 (100.0)	2/32 (85.2)	0.5/4 (86.1)
Israel (100)	0.5/2 (97.0)	4/>32 (71.0)	0.5/4 (81.0)
Italy (266)	0.5/4 (92.1)	2/32 (78.9)	0.5/8 (80.5)
Poland (90)	>32/>32 (25.6)	32/>32 (16.7)	>8/>8 (17.8)
Portugal (96)	1/>32 (81.3)	4/>32 (56.3)	2/>8 (57.3)
Russia (189)	2/>32 (60.3)	32/>32 (33.3)	4/>8 (33.3)
Spain (260)	0.5/2 (98.1)	2/32 (72.3)	0.5/8 (74.6)
Sweden (52)	0.5/2 (100.0)	2/16 (84.6)	0.5/4 (75.0)
Turkey (262)	1/8 (90.1)	4/>32 (74.0)	1/8 (64.1)
UK (107)	1/4 (99.1)	2/16 (86.0)	0.5/4 (86.0)
Ukraine (81)	4/>32 (54.3)	32/>32 (33.3)	4/>8 (39.5)
Five major countries (1056)[b]	0.5/4 (99.2)	2/32 (77.4)	0.5/8 (79.4)
Overall (2191)			

[a]According to the susceptible breakpoints established by CLSI (2014)[19] and EUCAST (2014).[20]
[b]Includes isolates from the five most populated Western European countries, i.e. France, Germany, Italy, Spain and the UK.

Sader et al, J Antimicrob Chemother 2014; 69: 2713–2722

Ceftolozano tazobactam: desarrollo ensayos clínicos

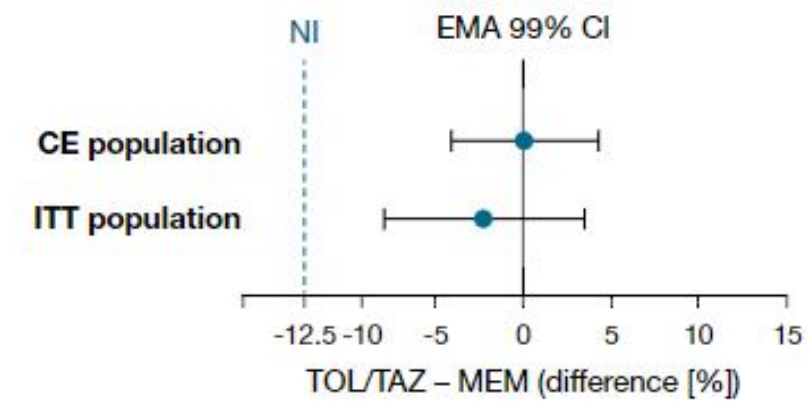
- ASPECT-cIAI *Infección intraabdominal*
  - CFT-TZB 1,5g + MDZ vs Meropenem
- ASPECT-cUTI *Infección Urinaria*
  - CFT-TZB 1,5g vs Levofloxacino 750 mg qd
- ASPECT-NP *Neumonía asociada a Ventilación mecánica*
  - CFT-TZB 3g vs Meropenem

  cierre estimado en Junio 2018

Globalmente no inferior al comparador en IAI/UTI
Tasas de respuesta clínica y erradicación microbiológica superiores en infecciones por enterobacterias BLEE

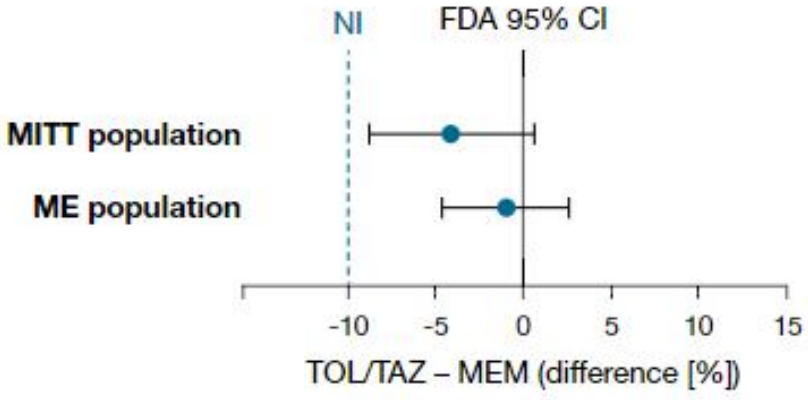
ASPECT-cIAI

24th ECCMID, 2014
Clin Infect Dis. 2015



TOL/TAZ+MTZ n/N (%)	MEM n/N (%)	Percentage difference (99% CI)
353/375 (94.1)	375/399 (94.0)	0.0 (-4.2 to 4.3)
399/476 (83.8)	424/494 (85.8)	-2.2 (-8.0 to 3.4)

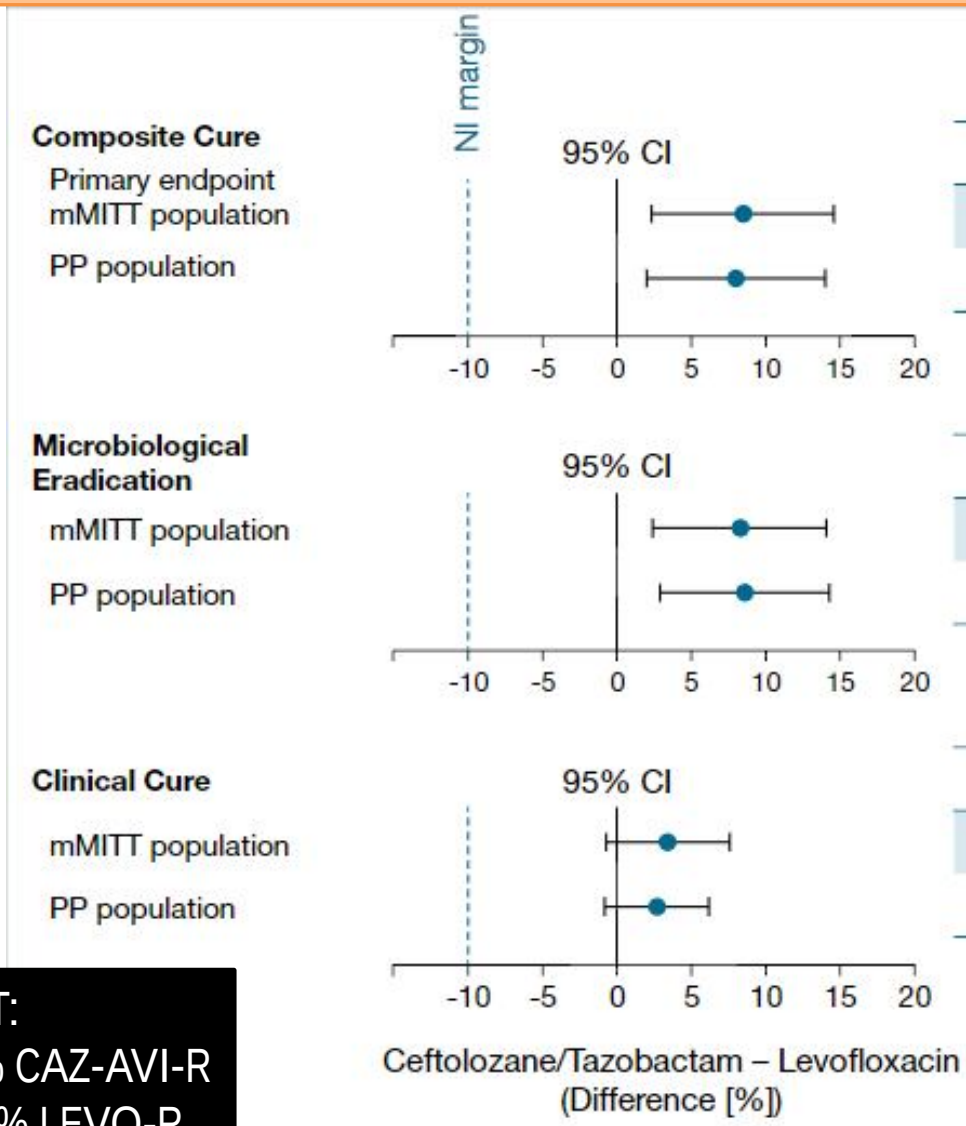
No inferioridad



TOL/TAZ+MTZ n/N (%)	MEM n/N (%)	Percentage difference (95% CI)
323/389 (83.0)	364/417 (87.3)	-4.2 (-8.9 to 0.5)
259/275 (94.2)	304/321 (94.7)	-1.0 (-4.5 to 2.6)

ASPECT-cUTI

IDWeek, 2014
Lancet, 2015



	Ceftolozane/ Tazobactam	Levofloxacin	Percentage Difference
Composite Cure	*No. of patients/total No. (%)*		(95% CI)
Primary endpoint mMITT population	306/398 (76.9)	275/402 (68.4)	8.5 (2.3 to 14.6)
PP population	284/341 (83.3)	266/353 (75.4)	8.0 (2.0 to 14.0)

Microbiological Eradication	*No. of patients/total No. (%)*		(95% CI)
mMITT population	320/398 (80.4)	290/402 (72.1)	8.3 (2.4 to 14.1)
PP population	294/341 (86.2)	274/353 (77.6)	8.6 (2.9 to 14.3)

Clinical Cure	*No. of patients/total No. (%)*		(95% CI)
mMITT population	366/398 (92.0)	356/402 (88.6)	3.4 (-0.7 to 7.6)
PP population	327/341 (95.9)	329/353 (93.2)	2.7 (-0.8 to 6.2)

MITT:
2,7% CAZ-AVI-R
26,7% LEVO-R

No inferior curación
Superior Erradicación microbiológica

ASPECT-NP

Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008) (ASPECT-NP)

This study is currently recruiting participants.

See ▶ **Contacts and Locations**

Verified September 2017 by Cubist Pharmaceuticals LLC

Sponsor:
Cubist Pharmaceuticals LLC

Information provided by (Responsible Party):
Cubist Pharmaceuticals LLC

ClinicalTrials.gov Identifier:
NCT02070757

First received: February 19, 2014
Last updated: September 11, 2017
Last verified: September 2017
History of Changes

Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer | How to Read a Study Record

Estimated Enrollment:	726
Actual Study Start Date:	September 23, 2014
Estimated Study Completion Date:	June 19, 2018
Estimated Primary Completion Date:	May 28, 2018 (Final data collection date for primary outcome measure)

¿Ahorrador de carbapenemes?

- Tratamiento dirigido: EB-BLEE, EB-ampC, *Pseudomonas aeruginosa*
- Tratamiento empírico: asociado a metronidazol en Infección Intraabdominal

Precio unitario (PVL+IVA)	Ceftolozano-Tazobactam vial 1g/0,5g
Precio unitario	64,16 €
Pauta	1/0,5g/8h
Coste día	192,48 €
Coste tratamiento 10 días	1924,80 €
Coste incremental (diferencial) respecto a la terapia de referencia	-

Piperacilina-Tazobactam 4,5g EFG:	6-7 €/VIAL
Meropenem 1 g EFG:	14 €
Cefepima 2 g EFG:	14€

Pipeline abcos para BGN multirresistentes

- CEFTOLOZANO-Tazobactam
- [redacted]
  - AVIBACTAM (+ Ceftazidima, Aztreonam, Ceftarolina)
  - Relebactam (+ Imipenem)
  - Vaborbactam (+ Meropenem)
- Zidebactam (+Cefepima)
- Sideróforo-Abco:
  - Sideróforo-Sulfactam (BAL 30072)
  - Sideróforo-Cefiderocol (S-649266)
- Nueva Tetraciclina: Eravaciclina
- Nuevo aminoglucósido: Plazomicina
- Nuevas quinolonas: Delafloxacino, Finafloxacino

A resurgence of ß-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. AAC 2015

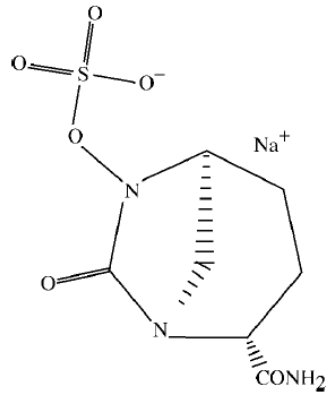
- Nuevos inhibidores de estructura no beta-lactámica que inhiben las serina-betalactamasas
- La principal diana de los nuevos inhibidores son las serina-CARBAPENEMASAS y el objetivo principal de los nuevos antimicrobianos son las enterobacterias resistentes a carbapenémicos
- No disponemos aún de inhibidores selectivos de METALOBETALACTAMASAS

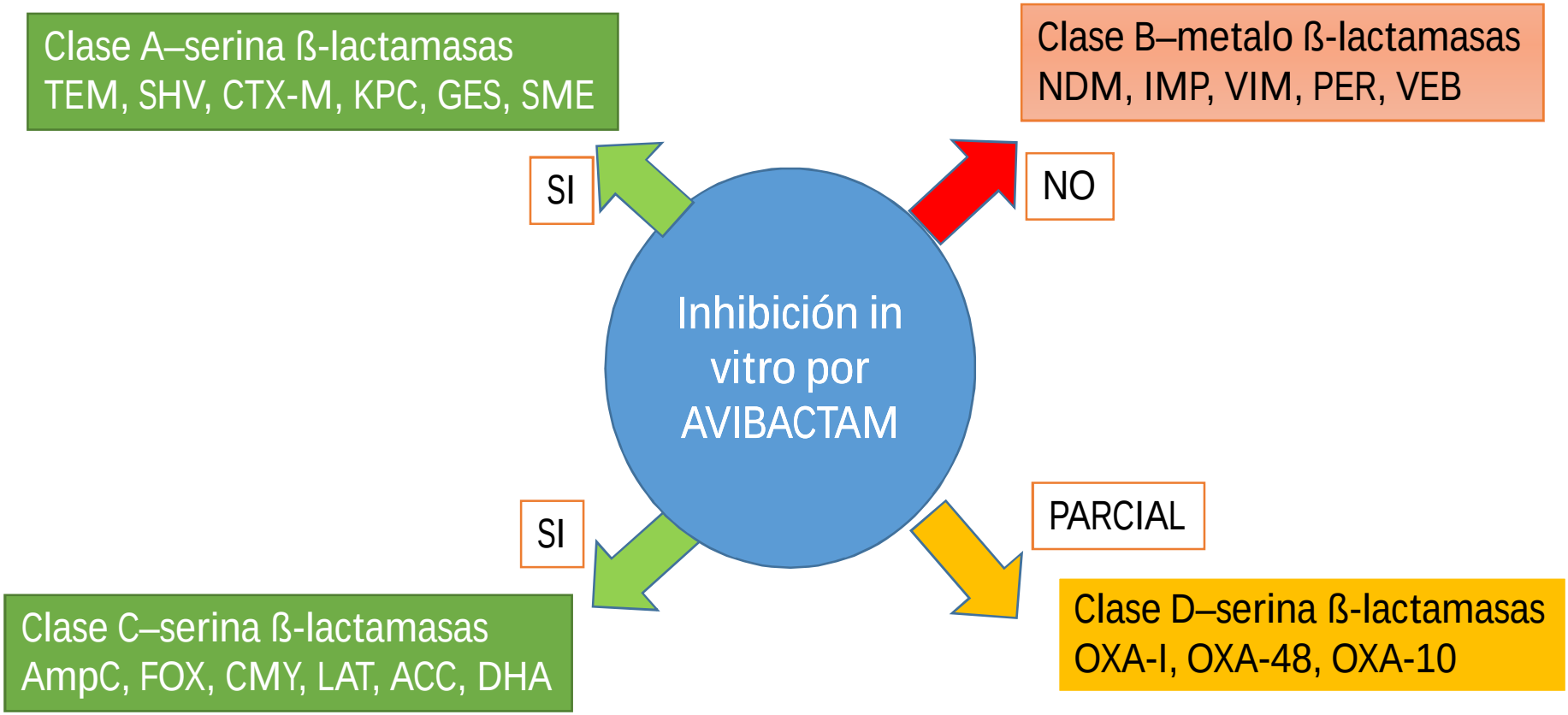
In vitro activity of AVE1330A (AVIBACTAM), an innovative broad-spectrum non-b-lactam b-lactamase inhibitor

Journal of Antimicrobial Chemotherapy (2004) 54, 410–417

Efecto inhibidor de *betalactamasas* ***in vitro*** ***más potente y duradero*** **que clavulánico/tazobactam**

Enzyme and inhibitor	IC_{50}, mg/L (nM)	Tn	Recovery of β-lactamase activity (%)
TEM-1			
AVE1330A	0.0023 (8)	2	30% after 7 min (50% after 7 days)
clavulanic acid	0.027 (130)	214	50% after 7 min (75% after 7 days)
tazobactam	0.013 (40)	ND	ND
P99			
AVE1330A	0.023 (80)	5	50% after 7 days
clavulanic acid	205.1 (1×10^6)	ND	ND
tazobactam	1.6 (5000)	55	50% after 290 min (100% after 24 h)





Ceftazidima-Avibactam:

- Enterobacterias productoras de serina BLEE clase A, hiperproductoras de ampC, carbapenemasas clase A (KPC) y **algunas** clase D (OXA-48); NO ACTIVA FRENTE A METALOBETALACTAMASAS (VIM, NDM, IMP)
- Pseudomonas aeruginosa resistente a ceftazidima por hiperproducción de ampC
- NO ACTIVA EN Acinetobacter ni anaerobios.

Ceftazidima-Avibactam
Actividad frente a *Pseudomonas aeruginosa*

Mejora la actividad respecto a cetazidima en cepas hiperproductoras de ampC
(no en resistencia mediada por porinas/bombas de expulsión)

TABLE 1 Summary of ceftazidime-avibactam activity tested against *P. aeruginosa* isolates from U.S. hospitals (2012 to 2013), including antimicrobial-resistant subsets

Organism (no. tested)[a]	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/ml) of:									MIC	
	≤0.25	0.5	1	2	4	8	16	32	>32	50%	90%
All isolates (3,902)	60 (1.5)	194 (6.5)	1,523 (45.5)	1,217 (76.7)	563 (91.2)	223 (96.9[b])	74 (98.8)	23 (99.4)	25 (100.0)	2	4
[redacted] (634)		1 (0.2)	41 (6.6)	149 (30.1)	181 (58.7)	[redacted]	73 (92.4)	23 (96.1)	25 (100.0)	4	16
MEM-NS (702)		8 (1.1)	63 (10.1)	172 (34.6)	218 (65.7)	146 (86.5[b])	54 (94.2)	18 (96.7)	23 (100.0)	4	16
P-T-NS (837)		4 (0.5)	62 (7.9)	189 (30.5)	267 (62.4)	196 (85.8[b])	72 (94.4)	22 (97.0)	25 (100.0)	4	16
MER-NS, CAZ-NS, and P-T-NS (330)		1 (0.3)	4 (1.5)	45 (15.2)	87 (45.1)	100 (71.8[b])	53 (87.9)	17 (93.0)	23 (100.0)	8	32
MDR (580)	1 (0.2)	3 (0.7)	31 (6.0)	113 (25.5)	174 (55.5)	148 (81.0[b])	64 (92.1)	21 (95.7)	25 (100.0)	4	16
XDR (338)		1 (0.3)	8 (2.7)	51 (17.8)	88 (43.8)	101 (73.7[b])	46 (87.3)	18 (92.6)	25 (100.0)	8	32

[a] CAZ, ceftazidime; MEM, meropenem; P-T, piperacillin-tazobactam; NS, nonsusceptible; MDR, multidrug resistant; XDR, extensively drug-resistant.
[b] Percent susceptible according to the U.S. FDA breakpoint criteria (11).

Ceftazidima-Avibactam
Ensayos clínicos Fase III

cUTI: *RECAPTURE*

AVYCAZ vs Doripenem (n=1020)

No Inferior

cIAI: *RECLAIM*

AVYCAZ plus metronidazole vs meropenem (n=1058)

No Inferior

Ceftazidima-Avibactam
Ensayos clínicos

cNP: *REPROVE*

AVYCAZ vs meropenem (n=879)

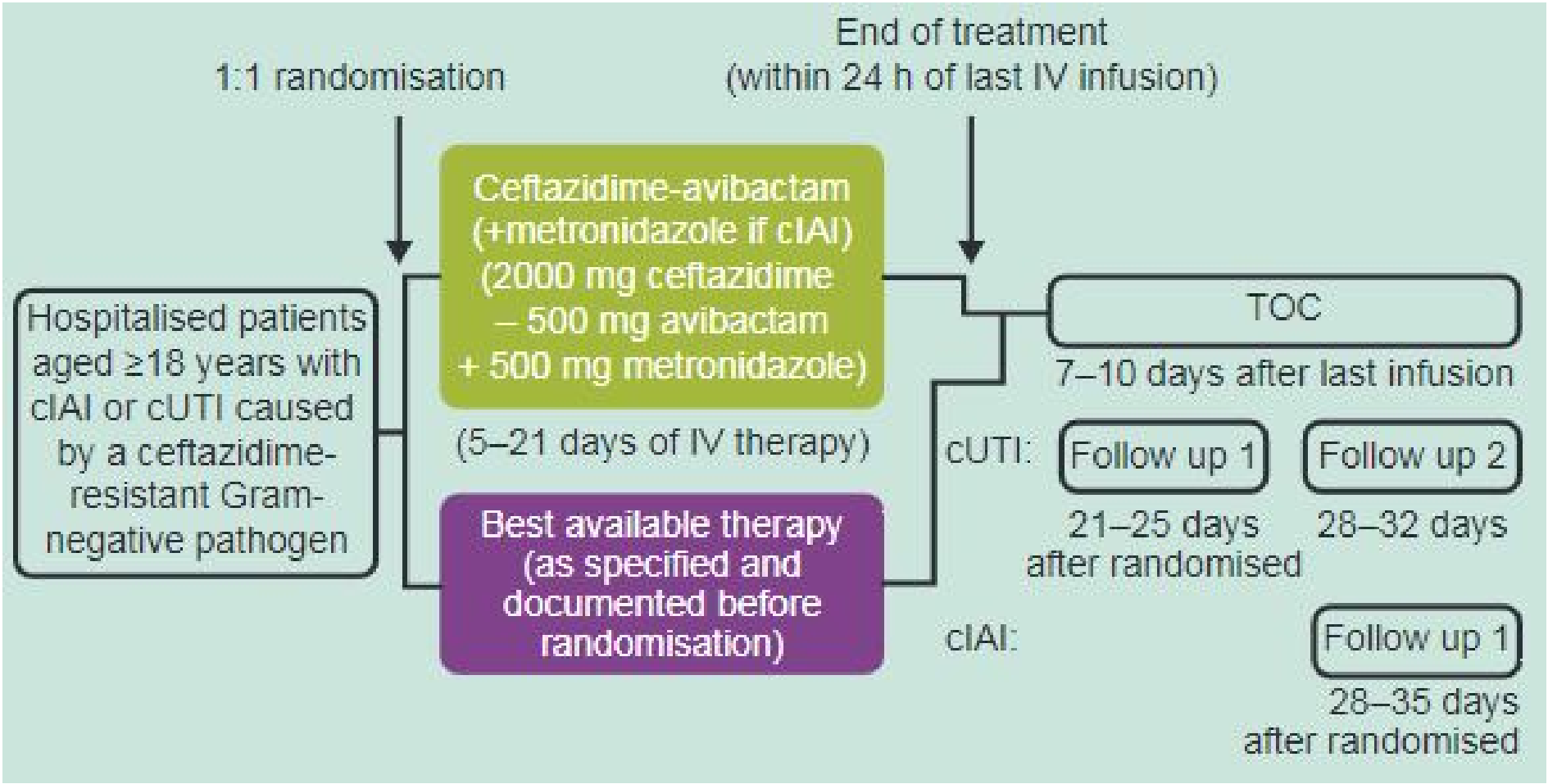
No Inferior

cUTI-cIAI: *REPRISE*

AVYCAZ vs best available therapy (BAT; n=305)

No Inferior
mejor respuesta microbiológica

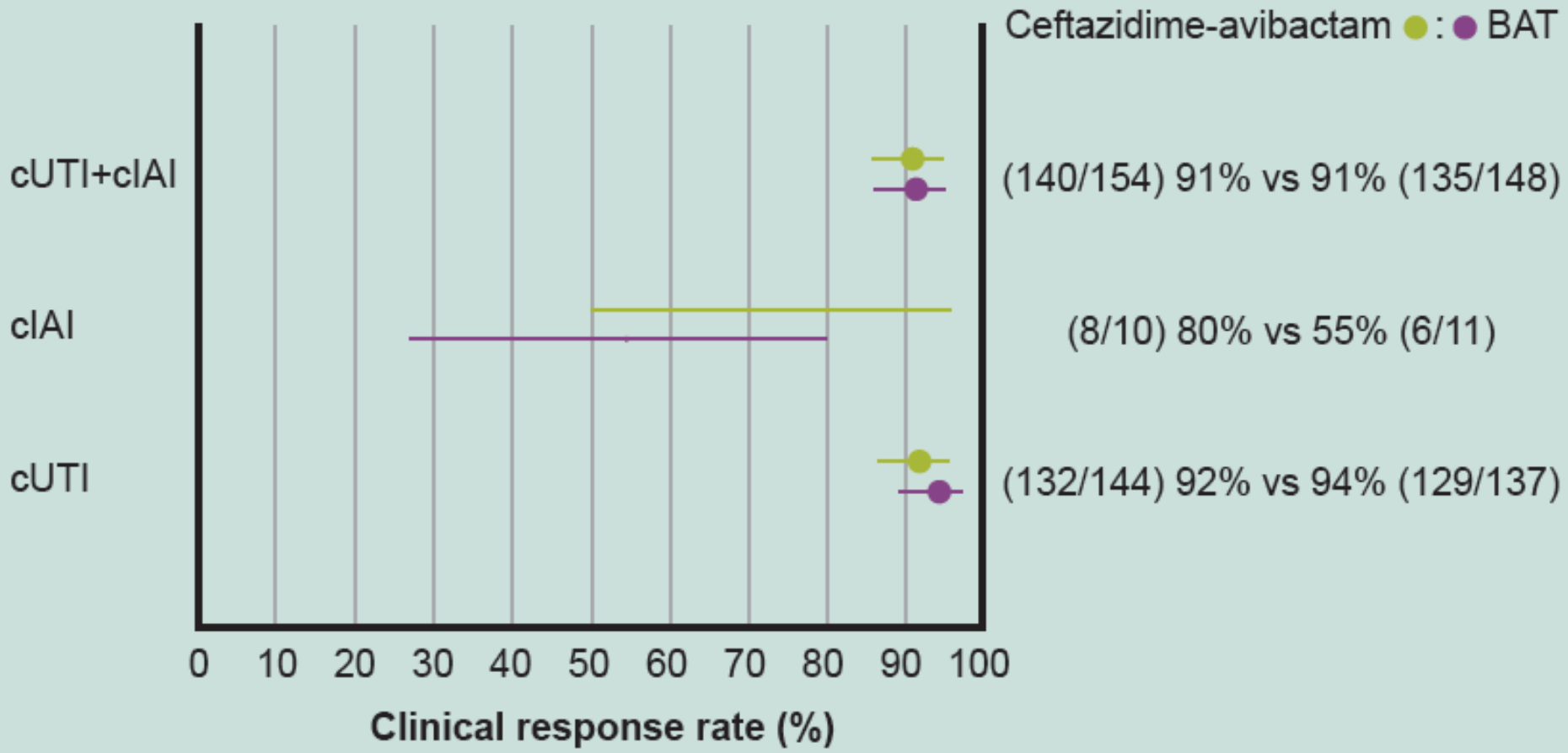
CAZ-AVI *Reprise (IAI/UTI CAZ-R)*



Carmeli et al, ECCMID 2015

CAZ-AVI *Reprise*

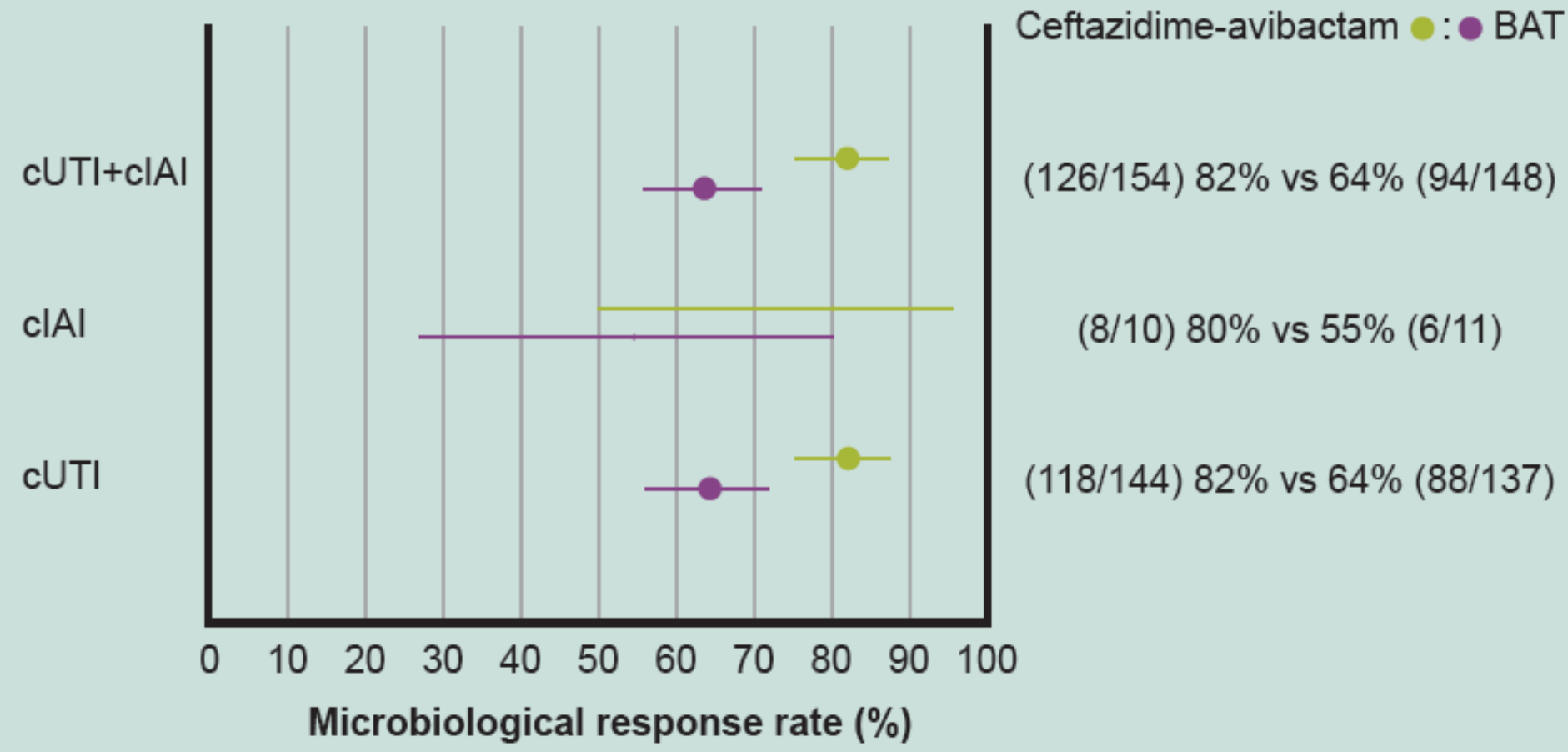
Figure 2. *Clinical response rate (95% CI) at TOC (mMITT population)*



Carmeli et al, ECCMID 2015

CAZ-AVI *Reprise*

Figure 3. *Per-patient favourable microbiological response rate (95% CI) at TOC (mMITT population)**



Carmeli et al, ECCMID 2015

Ceftazidima-Avibactam Seguridad

	AVYCAZ plus metronidazole* % (N=529)	Meropenem† % (N=529)
Nervous system disorders		
Headache	3%	2%
Dizziness	2%	1%
Gastrointestinal disorders		
Diarrhea	8%	3%
Nausea	7%	5%
Vomiting	5%	2%
Abdominal pain	1%	1%

	AVYCAZ‡ % (N=511)	Doripenem§ % (N=509)
Gastrointestinal disorders		
Nausea	3%	2%
Diarrhea	3%	1%
Constipation	2%	1%
Upper abdominal pain	1%	<1%

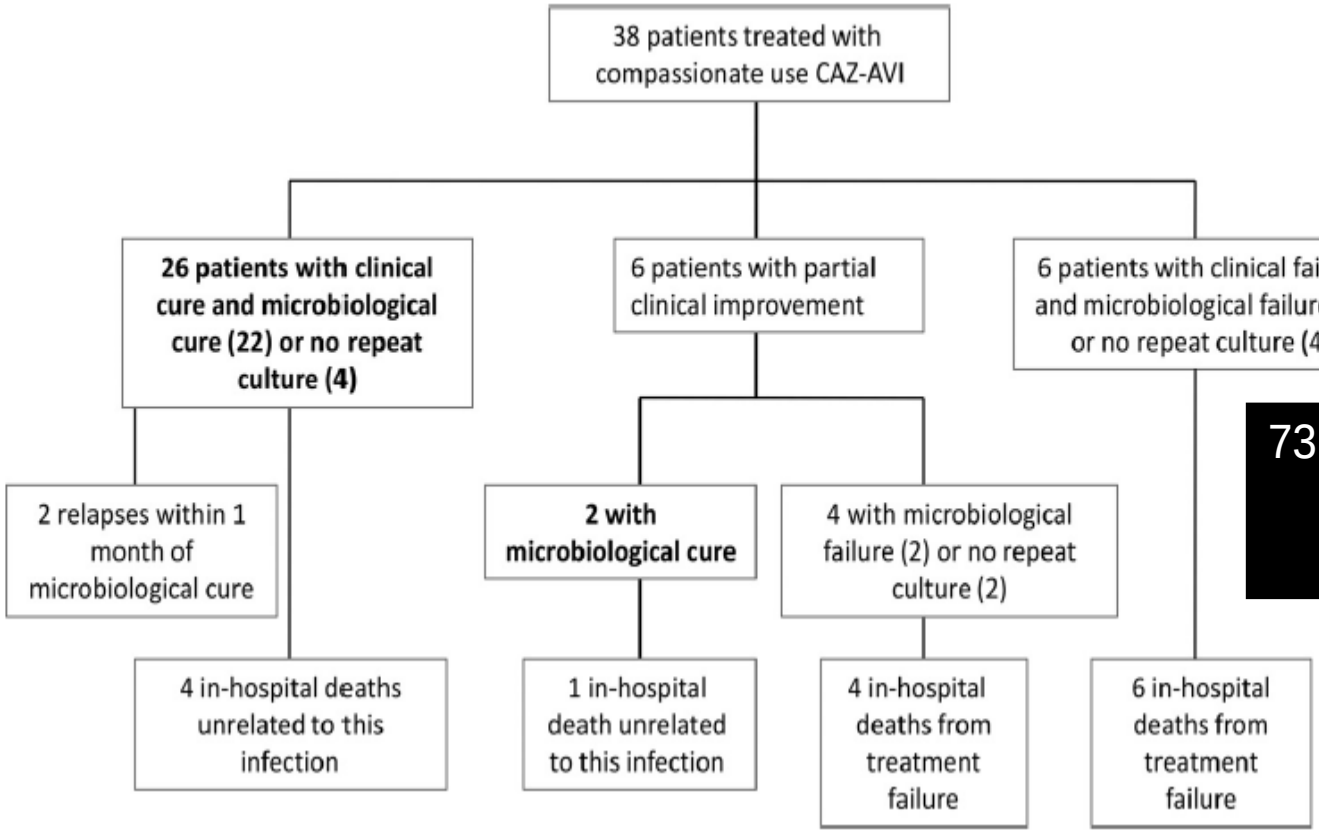
Important identified risks	*Clostridium difficile*-associated diarrhoea Anaphylaxis and other severe hypersensitivity reactions
Important potential risks	Hepatotoxicity Superinfection (bacterial or fungal) Bacterial resistance development In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced
Missing information	Pregnancy exposure Lactation exposure Pre-existing significant hepatic impairment Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy Immunocompromised population exposure

Assessment report
EMEA/H/C/004027/0000

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

Elizabeth Temkin,[a] Julian Torre-Cisneros,[i,j] Bojana Beovic,[b] Natividad Benito,[c,d] Maddalena Giannella,[e] Raúl Gilarranz,[f] Cameron Jeremiah,[g] Belén Loeches,[h] Isabel Machuca,[i,j] María José Jiménez-Martín,[k] José Antonio Martínez,[l] Marta Mora-Rillo,[h] Enrique Navas,[m] Michael Osthoff,[n] Juan Carlos Pozo,[o] Juan Carlos Ramos Ramos,[h] Marina Rodriguez,[o] Miguel Sánchez-García,[k] Pierluigi Viale,[p] Michel Wolff,[q,r] Yehuda Carmeli[a,s]

Klebsiella pneumoniae	
KPC	22
OXA-48	12
Klebsiella oxytoca (KPC)	1
Escherichia coli (OXA-48)	1
Pseudomonas aeruginosa	2



73.7% (IC95% 56.9 to 86.6%)
Respuesta clínica y/o microbiológica

Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia

Shields et al, AAC 2017

Characteristics	C-A (n=13)	CB + AG (n=25)	CB + COL (n=30)	Other[1] (n=41)	P-value
Patient Demographics					
Male, n (%)	7 (54)	16 (64)	18 (60)	21 (51)	0.75
Median age (range)	66 (32 – 91)	57 (32 – 87)	59 (26 – 84)	62 (25 – 90)	0.63
ICU at time of bacteremia, n (%)	6 (46)	13 (52)	12 (40)	25 (61)	0.36
Renal replacement therapy, n (%)	2 (15)	7 (28)	7 (23)	8 (20)	0.79
Median Pitt Bacteremia score (range)	4 (1 – 6)	4 (0 – 9)	4 (0 – 9)	4 (0 – 9)	0.74
Median APACHE II score (range)	20 (16 – 33)	17 (8 – 38)	16 (7 – 36)	19 (4 – 34)	0.46
Strain Characteristics					
Presence of KPC, n (%) • KPC-2 • KPC-3	13 (100) 9 4	24 (96) 19 5	30 (100) 24 6	39 (95) 29 10	0.56
Primary bacteremia, n (%)	3 (23)	6 (24)	5 (17)	14 (34)	0.41
Secondary bacteremia, n (%) • Abdominal • Respiratory • Urinary tract • Soft tissue	10 (77) 2 3 5 0	19 (76) 12 2 2 3	25 (83) 16 6 2 1	27 (66) 20 3 4 0	0.41
Treatment characteristics					
2 or more active agents*, n (%)	5 (38)**	10 (40)***	9 (30)	8 (20)	0.28
Median time to active treatment (IQR)	55.7 (25 – 67)	52.5 (28 – 64)	67.9 (30 – 133)	65.0 (35 – 95)	0.23
Median duration of treatment in days (range)	13 (5 – 23)	12 (3 – 28)	14 (3 – 96)	10 (3 – 47)	0.31
Patient outcomes					
Clinical success, n (%)					

Clinical outcomes, drug toxicity and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections

Shields, CID 2016

- Estudio retrospectivo (Pittsburgh):
  - 37 pacientes con EB-CR tratados con CAZ-AVI (70% monoterapia/30% combi)
  - 11/37 trasplantados
  - 31 K. pneumoniae. 3 E.coli, 3 Enterobacter spp
  - 29/37 KPC (no MBL ni OXA)
- 15 fracasos (9 exitus, 4 recurrencias, 2 no respuesta)

Fracaso microbiológico. 10/37
RESISTENCIA ADQUIRIDA A CAZ-AVI (CMI > 8): 3/10 casos

Resistencia a CAZ-AVI

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne bla_{KPC-3} Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,[a,b] Liang Chen,[c] Shaoji Cheng,[a] Kalyan D. Chavda,[c] Ellen G. Press,[a] Avin Snyder,[a] Ruchi Pandey,[c] Yohei Doi,[a] Barry N. Kreiswirth,[c] M. Hong Nguyen,[a,b] Cornelius J. Clancy[a,b,d]

Variantes mutacionales: algunas causan reversión de la resistencia a meropenem

Ceftolozano tazobactam ZERBAXA ®

- Infección intraabdominal
- Infección Urinaria

Muy activo en ampC, antipseudomónico más acivo. Activo frente a BLEEs

[redacted]

Escasa actividad anti-anaerobia

1000/500 mg (1,5g) cada 8 h
64,16 € /1,5g

Ceftazidima avibactam AVYCAZ/ZAVICEFTA®

- Infección intraabdominal
- Infección Urinaria
- Neumonía (incl. NAV)
- *"Tratamiento de infecciones por microorganismos aerobios Gram-negativos en pacientes adultos con opciones terapéuticas limitadas"*

Activo frente a ßL clase A (BLEEs), ampC, y carbapenemasas [redacted]

Escasa actividad anti-anaerobia

1000/250 – 2000/500 mg (1,5-2,5g) cada 8 h

AZTREONAM-AVIBACTAM

Trial record **2 of 2** for: aztreonam avibactam

◂ Previous Study | Return to List | Next Study

Determine the PK and Safety and Tolerability of ATM-AVI for the Treatment of cIAIs in Hospitalized Adults (REJUVENATE)

This study is currently recruiting participants.

See ▶ **Contacts and Locations**

Verified September 2017 by Pfizer

Sponsor:
Pfizer

Information provided by (Responsible Party):
Pfizer

ClinicalTrials.gov Identifier:
NCT02655419

First received: December 1, 2015
Last updated: September 6, 2017
Last verified: September 2017
History of Changes

Fase IIa

CEFTAROLINA-AVIBACTAM

Comparative Study of Coadministered Ceftaroline Fosamil and NXL104 vs. Intravenous Doripenem in Adult Subjects With Complicated Urinary Tract Infections

This study has been completed.

Sponsor:
Forest Laboratories

Information provided by (Responsible Party):
Forest Laboratories

ClinicalTrials.gov Identifier:
NCT01281462

First received: January 13, 2011
Last updated: January 2, 2014
Last verified: January 2014
History of Changes

Fase II

Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer | How to Read a Study Record

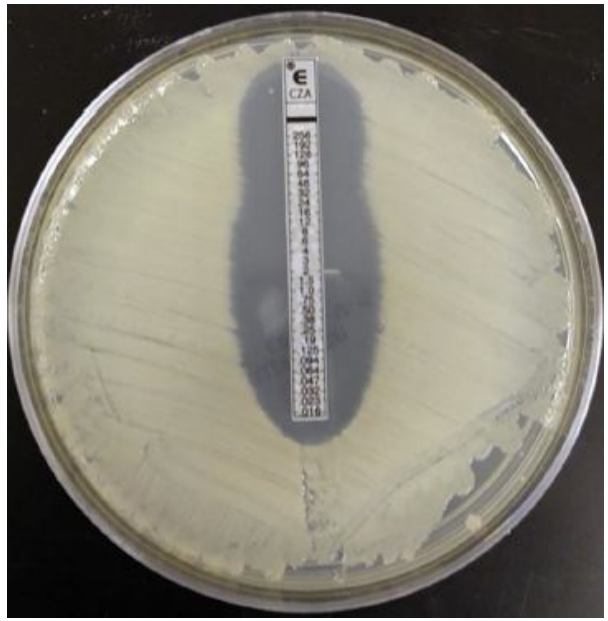
Wenzler et al. Synergistic activity of ceftazidime-avibactam and aztreonam against serine and metallo β-lactamase-producing Gram negative pathogens

Diagnostic Microbiology and Infectious Disease (2017)

Table 2. Synergistic activity assessed via Etest MIC:MIC ratio method

	Ceftazidime + Aztreonam		Ceftazidime + Ceftazidime-avibactam		Aztreonam + Ceftazidime-avibactam	
Organism	FIC	Interpretation	FIC	Interpretation	FIC	Interpretation
E. coli NDM	2	I	2	I	0.016	S
P. aeruginosa IMP	0.5	S	2	I	1.5	I
C. freundii VIM	0.5	S	2	I	0.031	S
E. cloacae KPC	0.125	S	0.011	S	0.009	S
K. pneumoniae KPC	0.125	S	0.039	S	0.011	S
A. baumannii OXA	0.094	S	0.063	S	1	A
K. pneumoniae ATCC[a]	0.25	S	0.078	S	0.0094	S

FIC, fractional inhibitory concentration; I, indifferent; S, synergistic; A, additive



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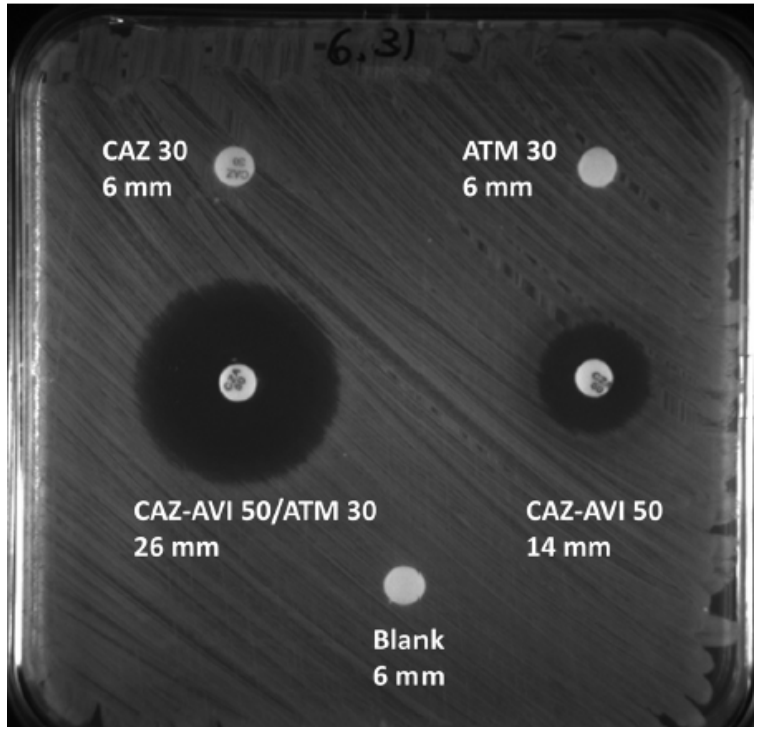
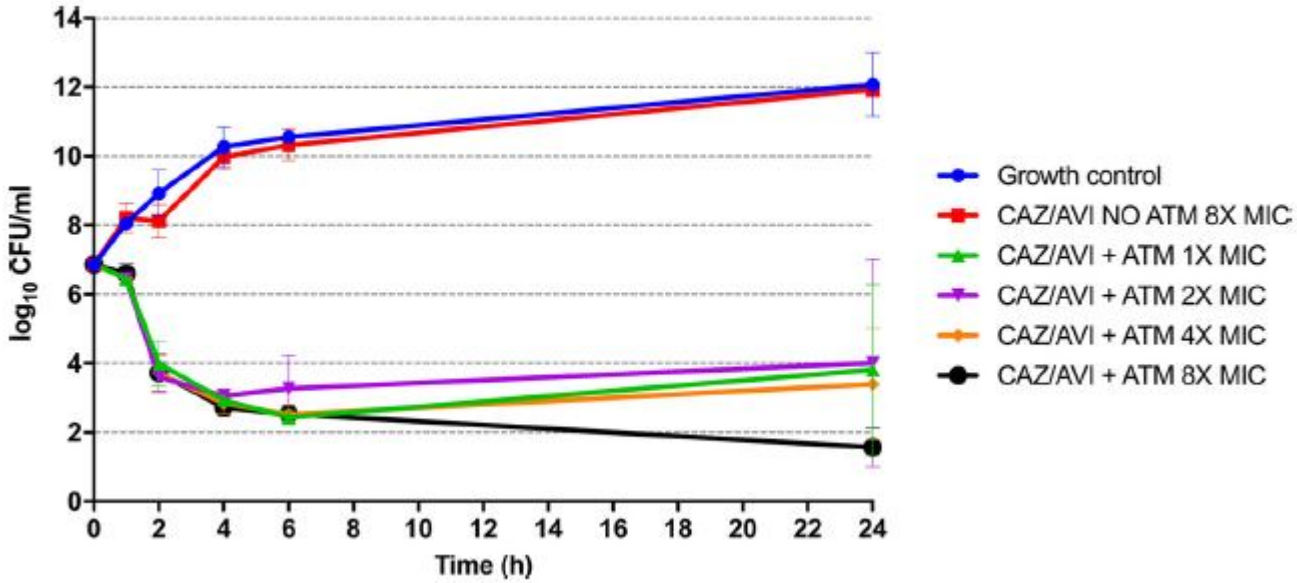


Can Ceftazidime-Avibactam and Aztreonam Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae*?

Steven Marshall,[a] Andrea M. Hujer,[a,b] Laura J. Rojas,[a,b,c] Krisztina M. Papp-Wallace,[a] Romney M. Humphries,[d] Brad Spellberg,[e] Kristine M. Hujer,[a,b] Emma K. Marshall,[a] Susan D. Rudin,[a,b] Federico Perez,[a,b] Brigid M. Wilson,[a] Ronald B. Wasserman,[f] Linda Chikowski,[g] David L. Paterson,[h] Alejandro J. Vila,[i] David van Duin,[j] Barry N. Kreiswirth,[k] Henry F. Chambers,[l] Vance G. Fowler, Jr.,[m] Michael R. Jacobs [illegible] Robert A. Bonomo[a,b,c,p]

Louis Stokes Cleveland Department of Veterans Affair: Medicine, Case Western Reserve University School of M Molecular Biology and Microbiology, Case Western Re USA[c]; Department of Pathology and Laboratory Medi California, USA[d]; Division of Infectious Diseases, Keck S USC Medical Center, Los Angeles, California, USA[e]; Infe California, USA[f]; John Muir Health, Walnut Creek, Calif Clinical Research, Brisbane, Queensland, Australia[h]; Ins Nacional de Investigaciones Científicas y Técnicas de A Argentina[i]; Division of Infectious Diseases, University o Health Research Institute Center, New Jersey Medical University of California, San Francisco, and San Francis Division of Infectious Diseases, Department of Medici Medical Center, Durham, North Carolina, USA[m]; Depar School of Medicine, Cleveland, Ohio, USA[n]; University USA[o]; Departments of Pharmacology, Biochemistry, a University School of Medicine, Cleveland, Ohio, USA[p]



April 2017 Volume 61 Issue 4 e02243-16 Antimicrobial Agents and Chemotherapy

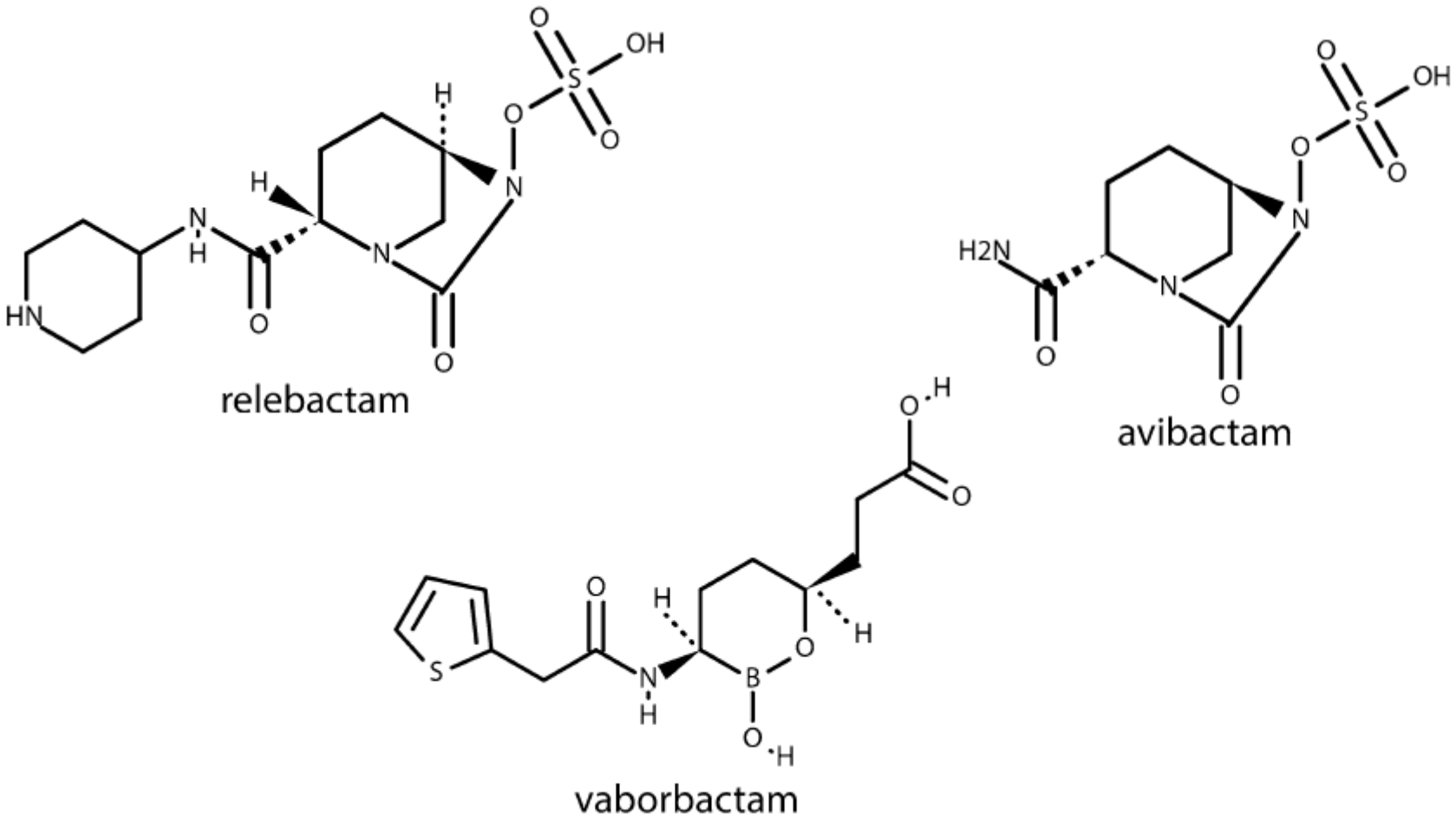
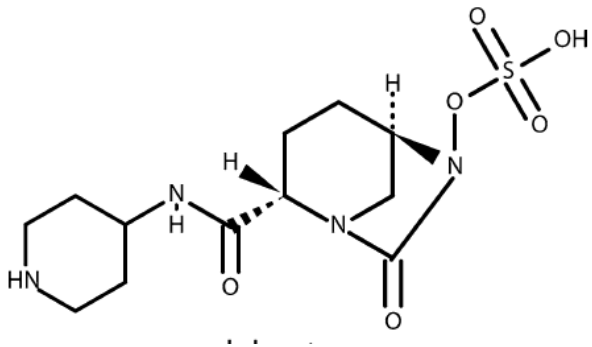


Table 1 Activities of avibactam, vaborbactam and relebactam against various classes of β-lactamases

	TEM/SHV (class A)	CTX-M (class A)	AmpC (class C)	KPC (class A)	OXA (class D)	IMP/VIM (class B)
Avibactam	Yes	Yes	Yes	Yes	Yes	[illegible]
Vaborbactam	Yes	Yes	Yes	Yes	[illegible]	[illegible]
Relebactam	Yes	Yes	Yes	Yes	TBD	[illegible]

OXA oxacillinase, *KPC Klebsiella pneumoniae* carbapenemase, *VIM* Verona integron-encoded metallo-β-lactamases, *TBD* to be determined

Imipenem-Relebactam



- Relebactam:

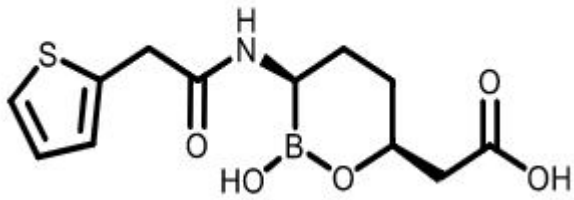
- Inhibidor de estructura no betalactámico.
- Actividad similar a Avibactam: serina betalactamasas clase A y C; no actividad frente a MBL. Peor actividad en OXA-48 que avibactam
- Imipenem –Relebactam puede ser activo en infecciones por cepas con mutaciones de oprD.

Imipenem-Cilastatina-RELEBACTAM

Row	Saved	Status	Study Title	Conditions	Interventions
3	☐	Recruiting	Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014)	Bacterial Pneumonia **RESTORE-IMI 2** **Fase III**	Drug: Imipenem; Drug: Relebactam; Drug: Cilastatin; Drug: Piperacillin; Drug: Tazobactam; Drug: Linezolid
4	☐	Completed	Study of the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone to Treat Complicated Intra-Abdominal Infection [cIAI] (MK-7655-004)	Intra-abdominal Infections Fase II	Drug: MK-7655 250 mg with imipenem/cilastatin; Drug: MK-7655 125 mg with imipenem/cilastatin; Drug: imipenem/cilastatin with placebo; Drug: Matching placebo to MK-7655
5	☐	Completed	Study of the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone for the Treatment of Complicated Urinary Tract Infection (cUTI) (MK-7655-003)	Urinary Tract Infections; Pyelonephritis Fase II	Drug: MK-7655 250 mg; Drug: MK-7655 125 mg; Drug: imipenem/cilastatin 500 mg; Drug: Placebo to MK-7655; Drug: Ciprofloxacin
2	☐	Active, not recruiting	Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection (MK-7655A-013)	Bacterial Infections **RESTORE-IMI 1** **Fase III**	Drug: Imipenem+Cilastatin/Relebactam; Drug: Colistimethate sodium (CMS); Drug: Imipenem+Cilastatin; Drug: Placebo to CMS

MEROPENEM-VABORBACTAM CARBAVANCE®

Hecker et. al. J Med Chem 2015;58:3682-92



- VABORBACTAM (RPX7009):
  - Estructura cíclica de ácido borónico
  - Inhibidor de serina-betalactamasas: A y C
    particularmente activo frente a *KPC; no frente a OXA-48/MBL*

Tango-I

Inf. urinaria / Pielonefritis Aguda

Meropenem-Vaborbactam vs Pip-Tazobactam.

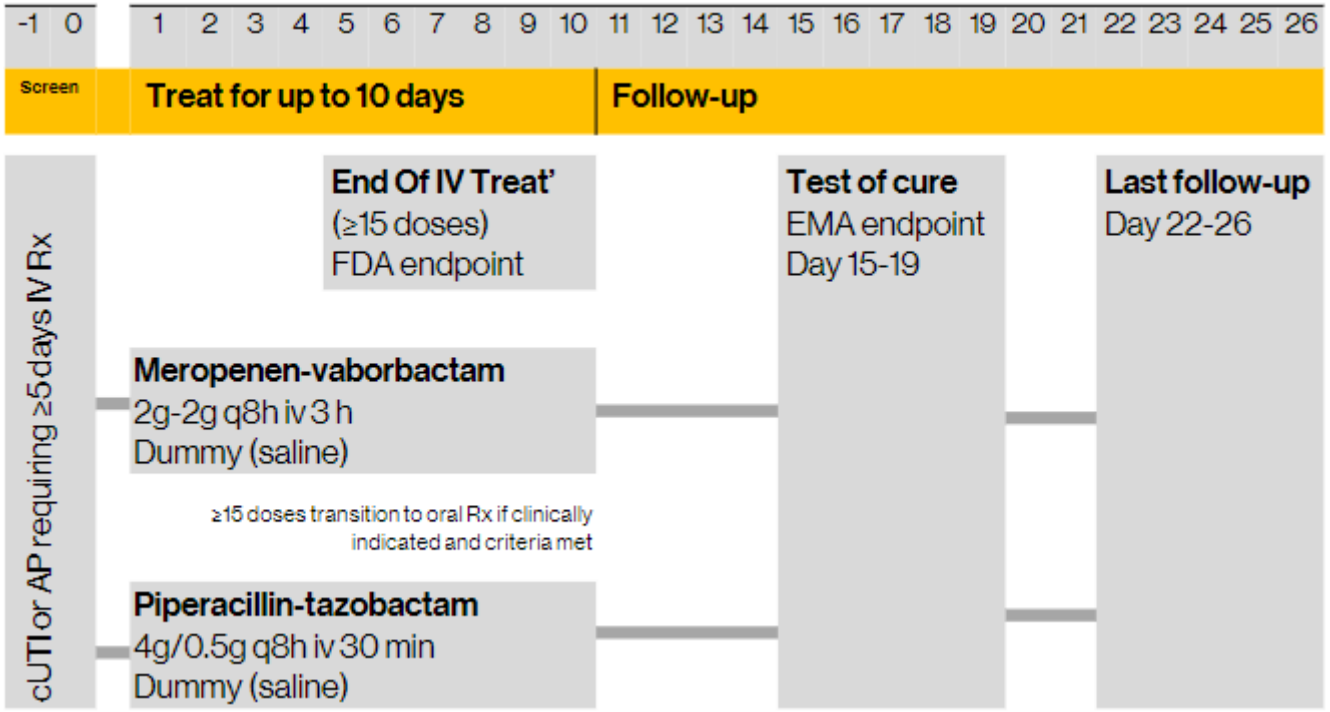
Doble ciego 1:1

Tango-II

Inf. urinaria /Neumonía/ Inf. intraabdominal con o sin bacteriemia con sospecha o confirmación de enterobacteria productora de carbapenemasa frente a la "mejor terapia disponible". Abierto 2:1

MEROPENEM-VABORBACTAM (TANGO-1)
Infección Urinaria complicada

IDWeek 2016



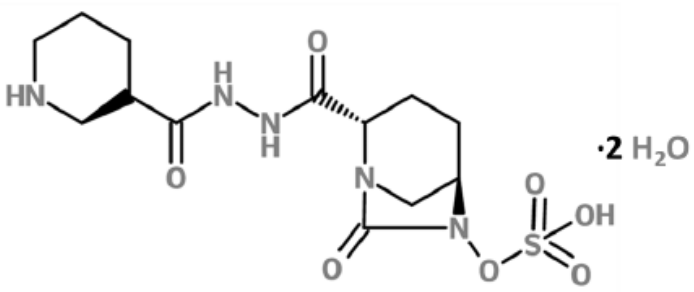
FDA Primary Endpoint mMITT Population	Meropenem-Vaborbactam	Piperacillin-Tazobactam
Overall Success[1] at EOIVT	188/192 (98.4%)	171/182 (94.0%)
Difference (95% CI)	4.5% (0.7%, 9.1%)	

No inferioridad

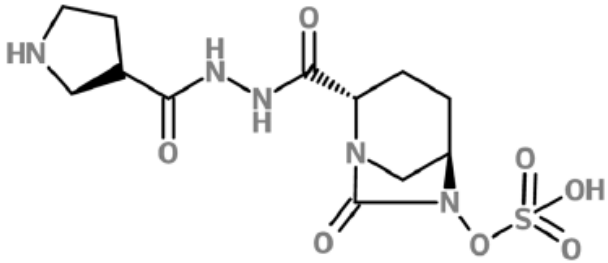
Investors

The Medicines Company announces TANGO-2 trial of meropenem-vaborbactam (formerly, Carbavance) stopped early for superior benefit-risk compared to best available therapy for CRE

CEFEPIMA-ZIDEBACTAM



zidebactam dihydrate (WCK 5107)



WCK 5153

<u>Zidebactam y WCK 5153</u>

Potentes Inhibidores de PBP2 "potenciadores" de betalactámicos: restauran la actividad de otros betalactámicos en cepas resistentes

Potencia Cefepima (inhibidor de PBP1a y PBP3) aún en presencia de hiperproducción de ampC e hiperexpresión de bombas, e incluso en presencia de MBL

Moya et al, AACh 2017

ZIDEBACTAM

- No actividad en *Acinetobacter* y *Stenotrophomonas*
- Menor actividad en *Proteae*
- No evade totalmente los mecanismos de R mediados por hiperexpresión de bombas de expulsión

CMI Zidebactam

	Number of isolates with indicated MIC (mg/L)										
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
E. coli ($n = 50$)	3	28	12	5	1				1		
Klebsiella spp. ($n = 58$)		3	17	17	2	1	1	1		13	3
Enterobacter and *Citrobacter* spp. ($n = 52$)		11	20	10	2		1			1	7
Serratia spp. ($n = 10$)			1	1				1		7	
Proteeae ($n = 6$)											6
P. aeruginosa ($n = 50$)											
β-lactam-susceptible controls ($n = 10$)						3[a]	5	1			1
AmpC derepressed ($n = 10$)							2	5	3		
MBL producers ($n = 10$)								6	2	1	1
up-regulated efflux ($n = 10$)								3	2	5	
cystic fibrosis, mixed mechanisms ($n = 10$)						1[a]	2	2	3	1	1
A. baumannii ($n = 30$)											30
S. maltophilia ($n = 10$)											10

Livermore et al, JAC 2016

Specimen ID	Species and mechanism	MIC of zidebactam (mg/L)	Cefepime MIC (mg/L) with zidebactam at:								
			0	0.06	0.12	0.25	0.5	1	2	4	8
SE01046	*S. marcescens*, AmpC	>32	2	1	0.25	0.25	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
H053420099	*K. pneumoniae*, CTX-M 9 group	>32	64	32	16	8	0.125	≤0.03	≤0.03	≤0.03	≤0.03
NCTC 13465	*K. pneumoniae*, CTX-M-25	>32	16	1	0.5	0.06	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
Mei 1	*K. pneumoniae*, ESBL	>32	2	0.06	0.125	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
SE06031	*M. morganii*, CTX-M 1 group	>32	4	0.25	0.06	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
H053460141	*Proteus* spp., ESBL	>32	>256	32	8	2	1	0.5	0.25	0.125	0.06
LN09056	*Proteus mirabilis*, ESBL	>32	>256	1	0.25	0.125	0.06	≤0.03	≤0.03	≤0.03	≤0.03
H092260700	*Klebsiella* spp., OXA-48 + ESBL	>32	64	8	2	0.25	0.06	≤0.03	≤0.03	≤0.03	≤0.03
H112860135	*Klebsiella* spp., OXA-48 + ESBL	>32	>256	8	2	0.125	0.06	≤0.03	≤0.03	≤0.03	≤0.03
H131480242	*M. morganii*, ESBL	>32	>256	>256	>256	256	128	≤0.03	≤0.03	≤0.03	≤0.03
H124240625	*K. pneumoniae*, KPC + SHV	>32	256	128	64	64	32	0.125	0.06	≤0.03	≤0.03
H114600525	*Enterobacter aerogenes*, KPC	>32	64	16	8	4	0.06	≤0.03	≤0.03	≤0.03	≤0.03
H113980340	*K. pneumoniae*, NDM, ATM-R	>32	256	64	32	8	0.25	0.25	0.25	0.25	0.25
H112240413	*K. pneumoniae*, VIM, ATM-R	>32	4	2	2	1	0.5	0.5	0.5	0.5	0.25
H130680324	*E. coli*, NDM, ATM-R	16	>256	256	256	256	256	256	256	256	256
H092540314	*M. morganii*, NDM, ATM-I	>32	64	8	8	4	1	1	1	1	1
H123140552	*P. rettgeri*, NDM, ATM-R	>32	>256	>256	256	256	256	256	256	256	256
H123560843	*P. rettgeri*, NDM, VEB, CMY-14 ATM-R	>32	>256	256	256	256	256	256	256	256	256
H124880510	*P. stuartii*, NDM, ATM-S	>32	16	16	16	16	2	2	2	2	2
H124880511	*P. rettgeri*, NDM, ATM-S	>32	64	64	64	64	64	64	64	64	64

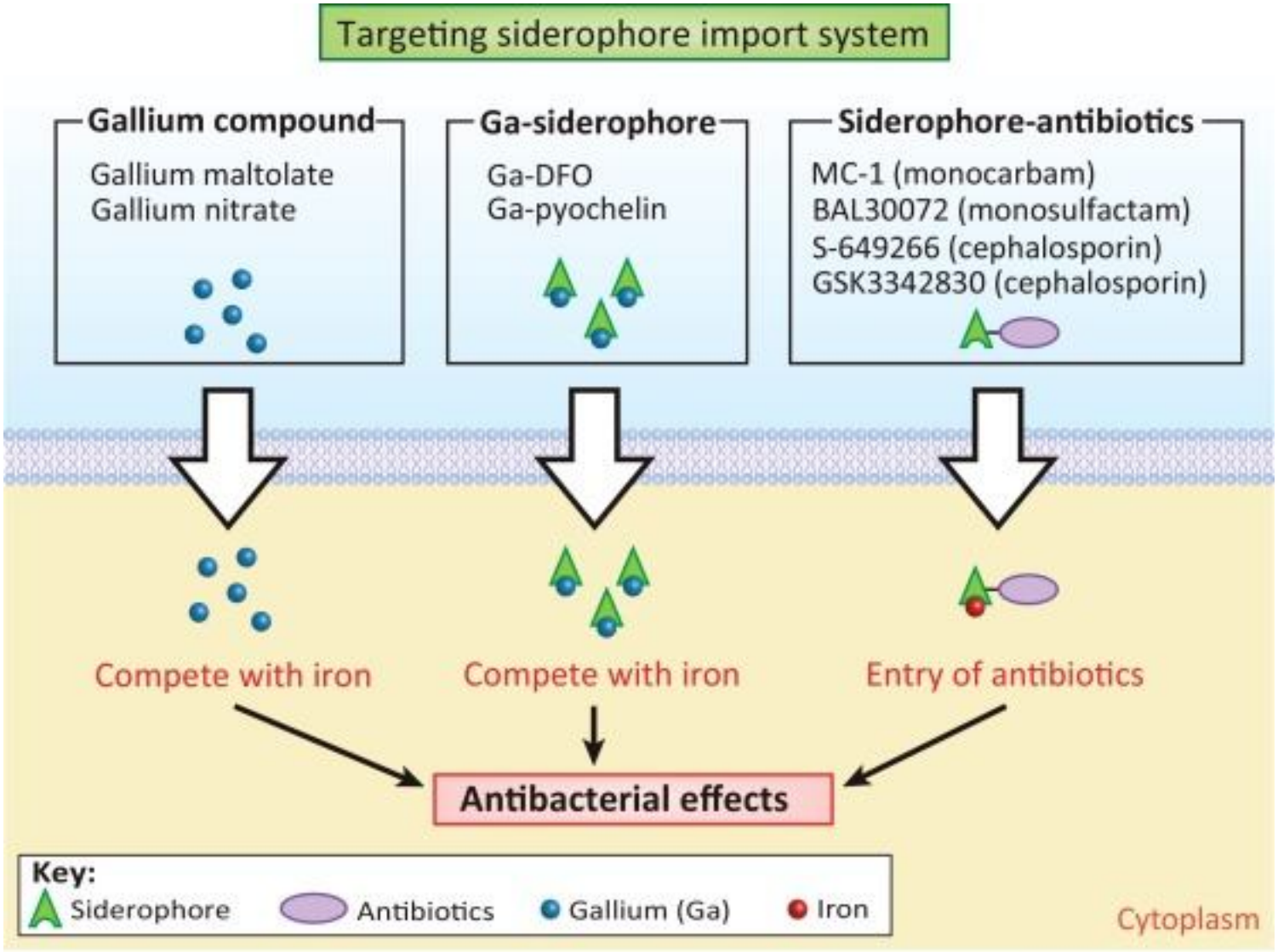
CMI Cefepima-Zidebactam

Livermore et al, JAC 2016

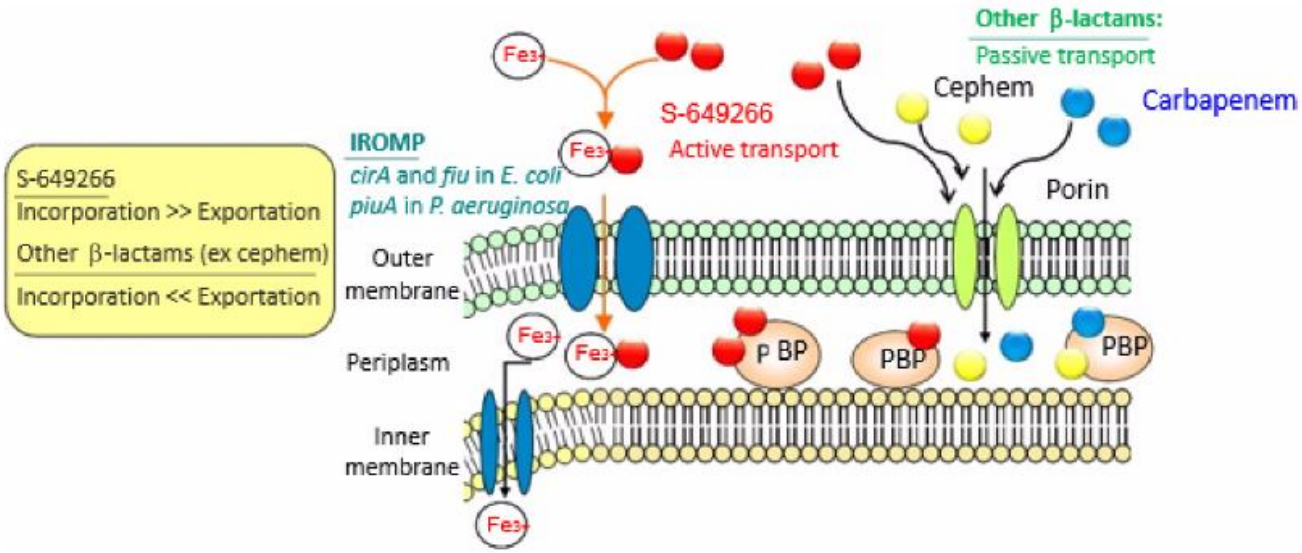
Pipeline abcos para BGN multirresistentes

- CEFTOLOZANO-Tazobactam
- Nuevos Inhibidores de betalactamasas:
  - AVIBACTAM (+ Ceftazidima, Aztreonam)
  - Relebactam (+ Imipenem)
  - Vaborbactam (+ Meropenem)
- Zidebactam (+Cefepima)
- [redacted]
  - Sideróforo-Sulfactam (BAL 30072)
  - Sideróforo-Cefiderocol (S-649266)
- Nueva Tetraciclina: Eravaciclina
- Nuevo aminoglucósido: Plazomicina
- Nuevas quinolonas: Delafloxacino, Finafloxacino

Antibióticos conjugados con sideróforos



Trends in Molecular Medicine



ORGANISM (NO. OF ISOLATES)	MIC_{90} (µg/mL)			
	S-649266	CEFEPIME	PIPERACILLIN/TAZOBACTAM	MEROPENEM
ESBL producers				
E. coli (50)	0.25	>64	128	0.063
K. pneumoniae (50)	0.5	>64	>256	0.125
E. cloacae (10)	4	>64	128	0.5
MBL producing *P. aeruginosa* (33)	4	>64	256	>32
Multidrug resistant				
P. aeruginosa (30)	1	>64	>256	>32
A. baumannii (30)	4	>64	>256	>32
NDM-1 producers (50)	4	>32	–	>16
KPC producers (47)	0.5	>64	>256	>32

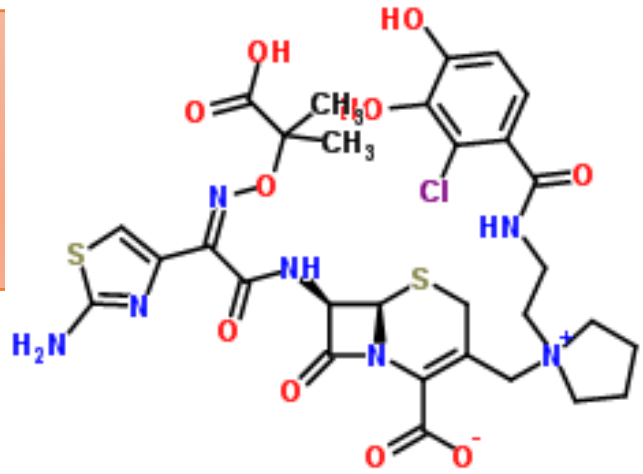
In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, Against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem Non-Susceptible Isolates: The SIDERO-WT-2014 Study

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]			MIC interpretation[b]		
		Range	MIC_{50}	MIC_{90}	% Susceptible	% Intermediate	% Resistant
Meropenem-non-susceptible Enterobacteriaceae (139)	[redacted]	0.008-8	1	4			
	Cefepime	0.25->64	>64	>64	6.5	1.4	92.1
	Ceftazidime-avibactam	≤0.06->64	1	>64	71.9	0	28.1
	Ceftolozane-tazobactam	0.5->64	>64	>64	5.0	2.2	92.8
	Ciprofloxacin	≤0.12->8	>8	>8	10.8	1.4	87.8
	Colistin	≤0.25->8	1	>8	72.7	0	27.3
	Meropenem	2->64	16	>64	0	10.1	89.9
Meropenem-non-susceptible *Pseudomonas aeruginosa* (202)	[redacted]	0.008-4	0.25	1			
	Cefepime	1->64	16	>64	47.5	18.3	34.2
	Ceftazidime-avibactam	1->64	8	64	68.3	0	31.7
	Ceftolozane-tazobactam	0.5->64	1	>64	67.3	5.9	26.7
	Ciprofloxacin	≤0.12->8	8	>8	34.7	5.0	60.4
	Colistin	≤0.25-4	1	1	99.0	1.0	0
	Meropenem	4->64	8	16	0	19.8	80.2
Meropenem-non-susceptible *Acinetobacter baumannii* (595)	[redacted]	0.004-64	0.12	1			
	Cefepime	4->64	64	>64	2.4	13.6	84.0
	Ceftazidime-avibactam	1->64	32	>64			
	Ceftolozane-tazobactam	1->64	16	>64			
	Ciprofloxacin	≤0.12->8	>8	>8	0.2	0	99.8

Hackel et al, Antimicrob. Agents Chemother. 2017

Cefiderocol

Shionogi Inc



Row	Saved	Status	Study Title	Conditions	
1	☐	Completed Fase II	A Study of Efficacy/Safety of Intravenous S-649266 Versus Imipenem/Cilastatin in Complicated Urinary Tract Infections	Urinary Tract Infections	Drug: S-649266; Drug: Imipenem/cilastatin
2	☐	Recruiting Fase III	Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens	Healthcare-associated Pneumonia (HCAP); Bloodstream Infections (BSI); Hospital Acquired Pneumonia (HAP); Complicated Urinary Tract Infection (cUTI); Sepsis; Ventilator Associated Pneumonia (VAP)	Drug: S-649266; Drug: Best Available Therapy
3	☐	Recruiting Fase III	Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens	Healthcare-associated Pneumonia (HCAP); Hospital Acquired Pneumonia (HAP); Ventilator Associated Pneumonia (VAP)	Drug: S-649266; Drug: Meropenem; Drug: Linezolid

Pipeline abcos para BGN multirresistentes

- CEFTOLOZANO-Tazobactam
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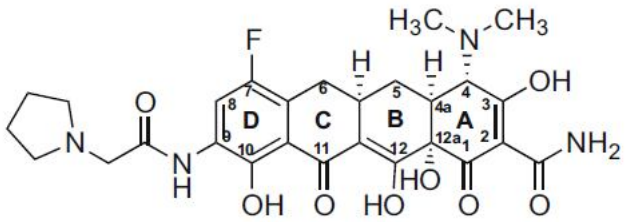
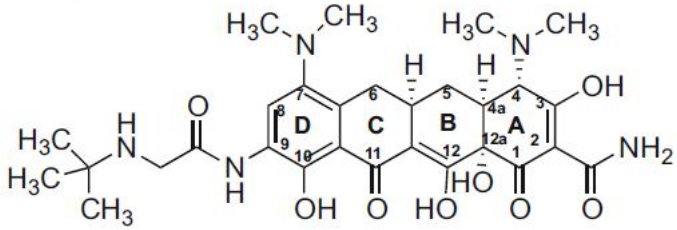
- [redacted]
- Nuevo aminoglucósido: Plazomicina
- Nuevas quinolonas: Delafloxacino, Finafloxacino

Eravacycline



Tigecycline

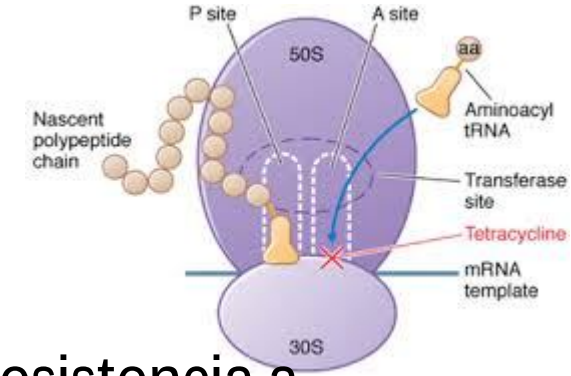


ERAVACICLINA

Tetraphase®

(TP-271, TP-6076)

- Fluorociclina estructuralmente relacionada con TIGECICLINA; 2-8 x más potente. Inhibe la síntesis proteica en la subunidad 30S ribosomal
- 28% biodisponibilidad oral
- Espectro actividad similar a Tigeciclina: (Strep., Staph, Enterobacterias BLEE; etc.)
- Más activa que tigeciclina (4X) en cepas con resistencia a tetraciclinas mediada por bombas Tn1721 tet(A)



ERAVACICLINA

Ensayos clínicos

- IGNITE-1: fase III cIAI ERV *bid* vs Ertapenem — No Inferioridad
- IGNITE -2: fase III cUTI ERV qd vs Levo — No Inferioridad
- IGNITE-3: fase III cUTI ERV *qd* vs Ertapenem — Pdte análisis
- IGNITE-4: fase III cIAI ERV *bid* vs Meropenem — No Inferioridad

	Eravacycline n/N (%)	Meropenem n/N (%)	95% Confidence Interval (CI)
Microbiological intent-to-treat (micro-ITT) population; 12.5% non-inferiority margin (FDA)	177/195 (90.8%)	187/205 (91.2%)	-6.3, 5.3
Modified intent-to-treat (MITT); 12.5% non-inferiority margin (EMA)	231/250 (92.4%)	228/249 (91.6%)	-4.1, 5.8
Clinically evaluable (CE); 12.5% non-inferiority margin (EMA)	218/225 (96.9%)	222/231 (96.1%)	-2.9, 4.5

Pipeline abcos para BGN multirresistentes

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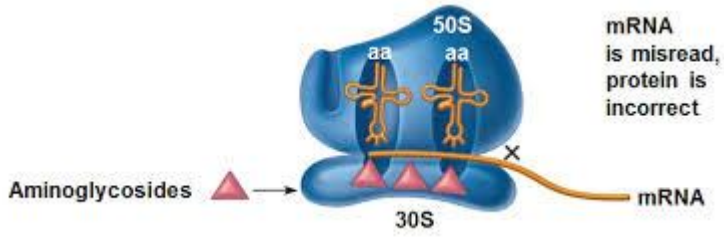
- Nueva Tetraciclina: Eravaciclina
- [redacted]
- Nuevas quinolonas: Delafloxacino, Finafloxacino

RESISTENCIA A AMINOGLUCOSIDOS



- Mutación en la diana ribosomal: 16S rRNA
- Modificación ribosomal: metil-transferasas

  NpmA, ArmA, RmtA,B1,B2,C,D1,D2,E,F,G,H

- Enzimas modificadores:

  - AG *N*-acetiltransferasas (AACs)
  - AG *O*-nucleotidiltransferasas (ANTs)
  - AG *O*-fosfotransferasas (APHs)

- Delección de Porinas
- Bombas de expulsión: AcrAD

Plazomicina (Achaogen®)

- Aminoglucósido; 15 mg/kg *qd*
- Resiste a la mayoría de enzimas modificadores, incluyendo AAC(6′), con la excepción de AAC (2´)-I (cromosoma de *Providencia stuartii*)
- No activo frente a bacterias productoras de metil-transferasas ArmA, RmtC (se asocian a plásmidos que contienen MBL NDM-I).
  - NCT01096849: PLZ vs Levo en UTI (PNA)
  - NCT02486627: PLZ vs Mero en cUTI *EPIC*
  - NCT01970371: PLZ vs Colis en Infección por CPE *CARE*
    (+ Meropenem/Tigeciclina)

Plazomicina (Achaogen®)

- NCT02486627: PLZ vs Mero en cUTI *EPIC*

	Plazomicin n/N (%)	Meropenem n/N (%)	Difference (%)[a] (95% CI)
Composite endpoint at Day 5, mMITT (FDA)	168/191 (88.0%)	180/197 (91.4%)	-3.4% (-10.0, 3.1%)
Composite endpoint at TOC, mMITT (FDA)	156/191 (81.7%)	138/197 (70.1%)	11.6% (2.7, 20.3%)*
Microbiological eradication at TOC, mMITT (EMA)	167/191 (87.4%)	142/197 (72.1%)	15.4% (7.5, 23.2%)*
Microbiological eradication at TOC, ME (EMA)	162/179 (90.5%)	134/175 (76.6%)	13.9% (6.3, 21.7%)*

Fase III

No inferioridad

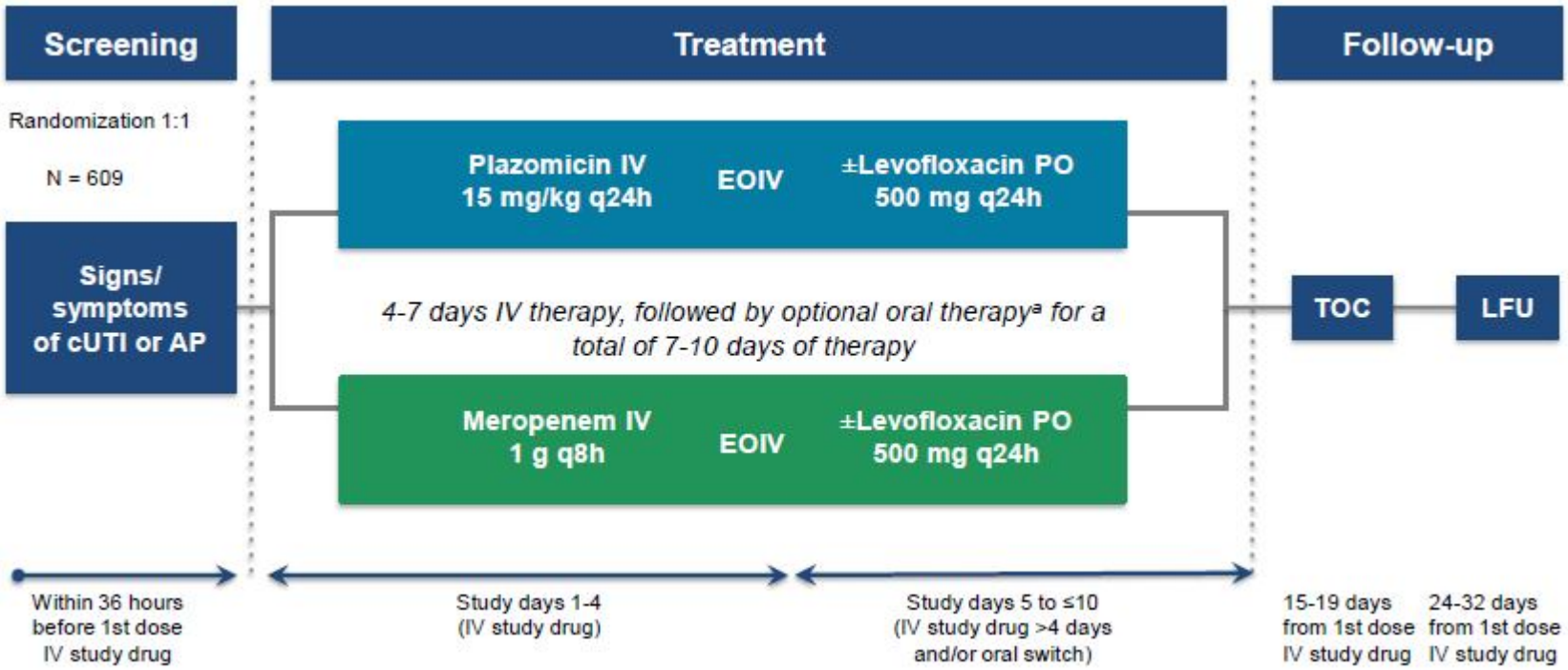
Superioridad

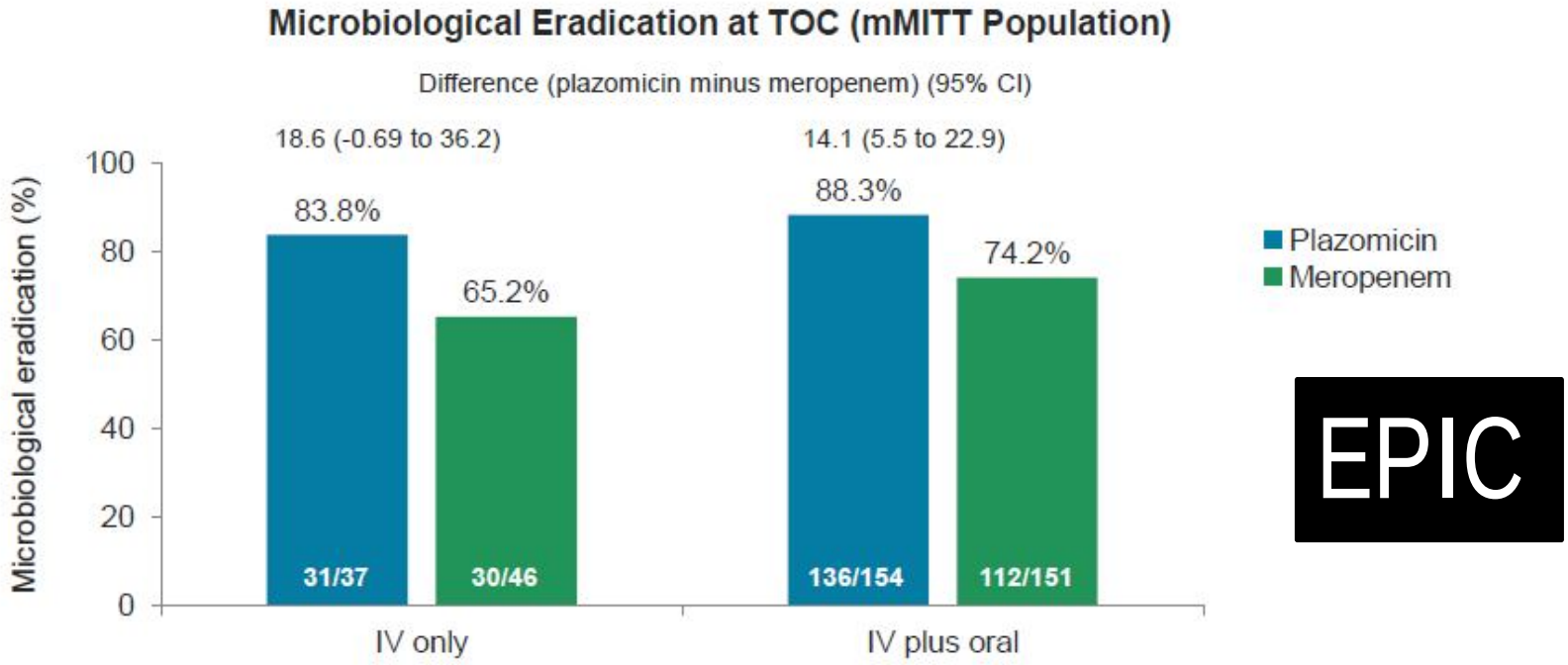
- NCT01970371: PLZ vs Colis en Infección por CPE *CARE*

	Plazomicin n/N (%)	Colistin n/N (%)	Difference[a] (90% CI)	Relative Reduction
Day 28 all-cause mortality or significant disease-related complications	4/17 (23.5%)	10/20 (50.0%)	26.5% (-0.7, 51.2%)	53.0%
Day 28 all-cause mortality	2/17 (11.8%)	8/20 (40.0%)	28.2% (0.7, 52.5%)	70.5%

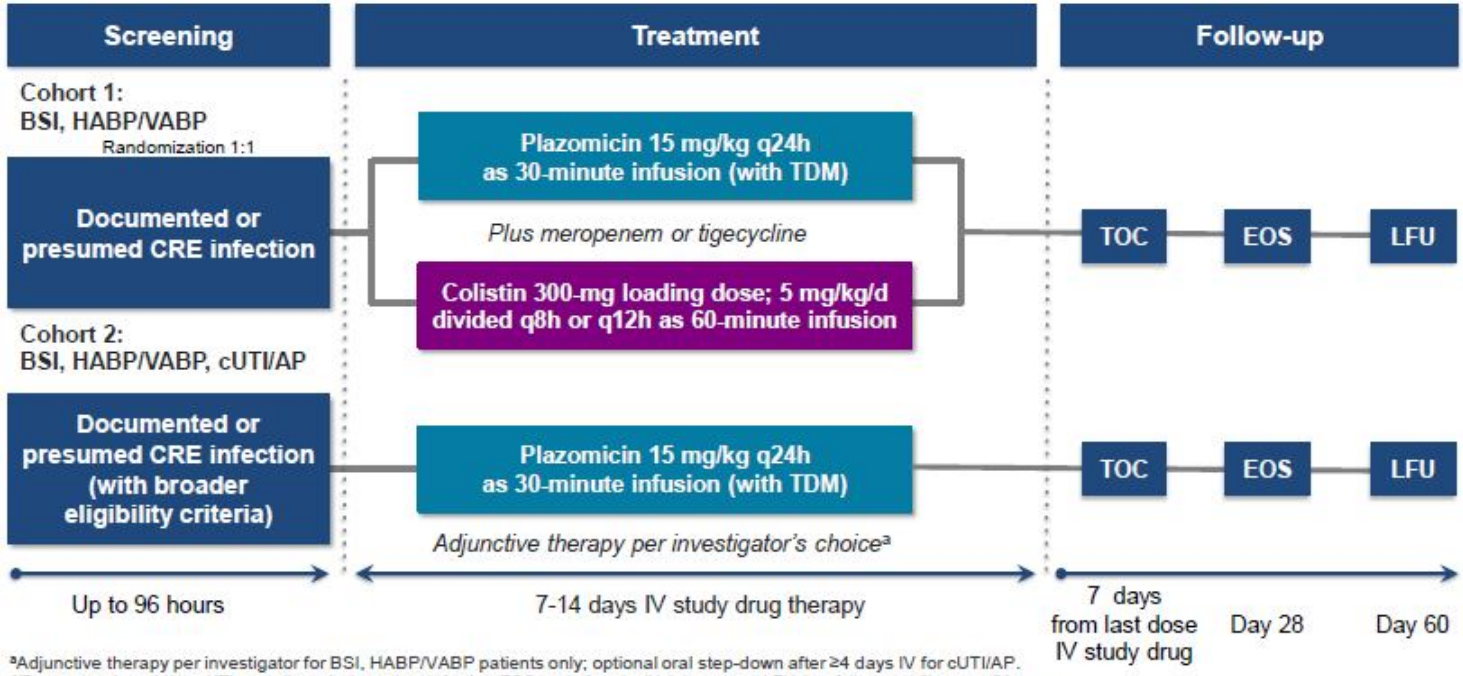
Fase III

Aes renales: PLZ 16.7% vs Colistina 38.1%

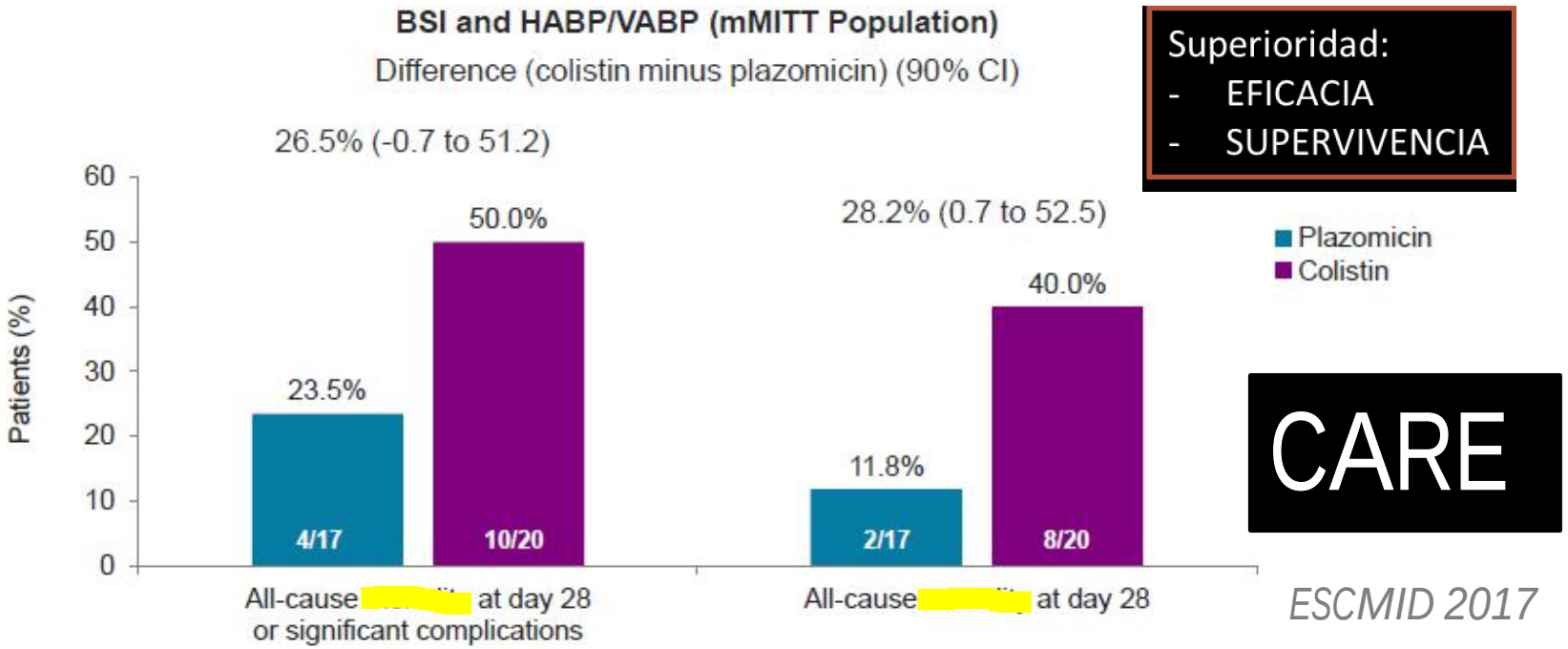

Screening
Treatment
Follow-up
Randomization 1:1
N = 609
Signs/ symptoms of cUTI or AP
Plazomicin IV 15 mg/kg q24h
EOIV
±Levofloxacin PO 500 mg q24h
4-7 days IV therapy, followed by optional oral therapy[a] for a total of 7-10 days of therapy
Meropenem IV 1 g q8h
EOIV
±Levofloxacin PO 500 mg q24h
TOC
LFU
Within 36 hours before 1st dose IV study drug
Study days 1-4 (IV study drug)
Study days 5 to ≤10 (IV study drug >4 days and/or oral switch)
15-19 days from 1st dose IV study drug
24-32 days from 1st dose IV study drug


Microbiological Eradication at TOC (mMITT Population)
Difference (plazomicin minus meropenem) (95% CI)
18.6 (-0.69 to 36.2)
14.1 (5.5 to 22.9)
Microbiological eradication (%)
100
80
60
40
20
0
83.8%
65.2%
88.3%
74.2%
31/37
30/46
136/154
112/151
IV only
IV plus oral
Plazomicin
Meropenem

EPIC



[a]Adjunctive therapy per investigator for BSI, HABP/VABP patients only; optional oral step-down after ≥4 days IV for cUTI/AP. AP, acute pyelonephritis; cUTI, complicated urinary tract infection; EOS, end of study; IV, intravenous; LFU, late follow up; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; TDM, therapeutic drug management; TOC, test of cure.



Superioridad:
- EFICACIA
- SUPERVIVENCIA

CARE

ESCMID 2017

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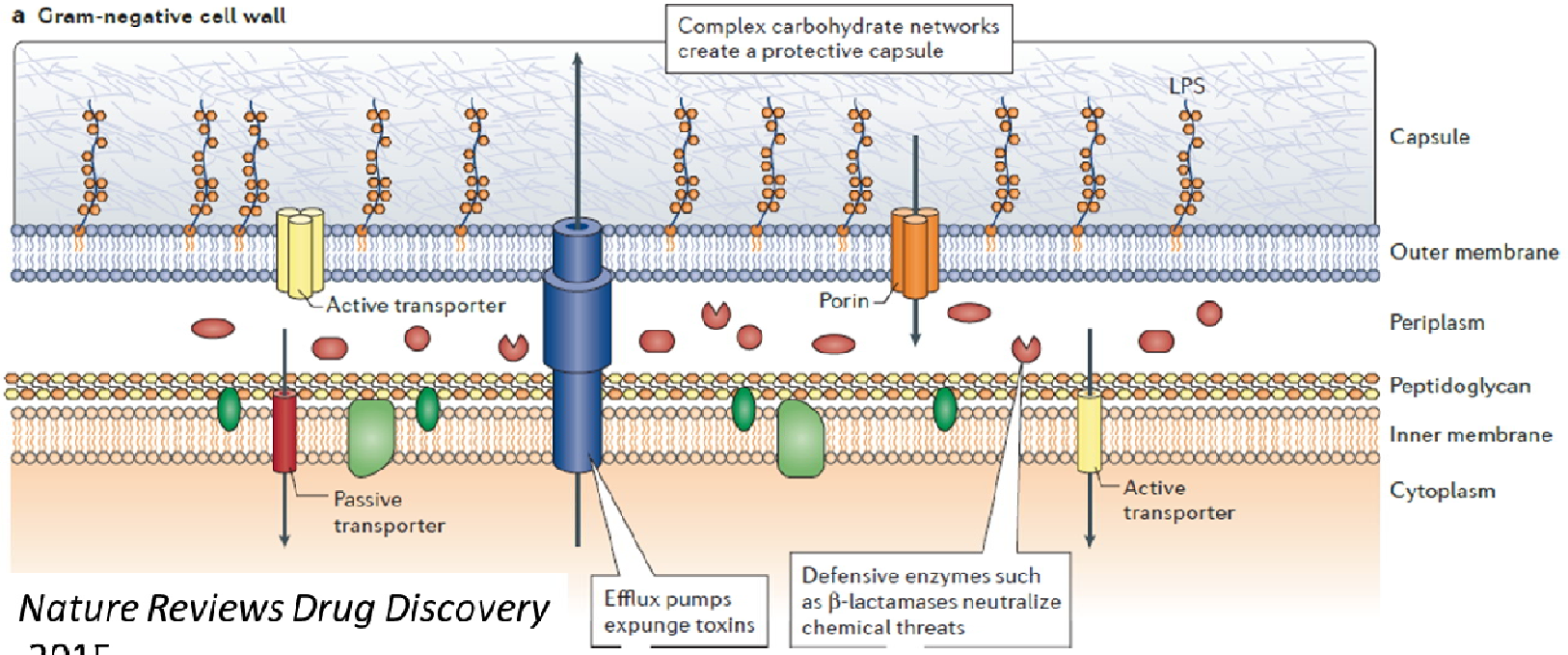
  - Sideróforo-Cefiderocol (S-649266)
- Nueva Tetraciclina: Eravaciclina
- Nuevo aminoglucósido: Plazomicina
-

Nuevas fluorquinolonas

- **Delafloxacino** (BAXDELA®)
  - Infección de piel y partes blandas
  - Buena actividad en SAMR
- **Finafloxacino** (MerlionPharma):
  - Se activa a pH ácido
  - Xtoro® formulación ótica para otitis externa
  - En desarrollo para Inf respiratoria, partes blandas, ITU, Infección abdominal y *H.pylori*
- Avarofloxacino (JNJ-Q2), zabofloxacino (DW224a), nemonoxacino (TG-873870)
- *AZD0914: Inhibidor de DNA girasa/topisomerasa* "spiropirimidinetriona" Activa frente a cepas resistentes a quinolonas (gram positivos, *Legionella*, gonococo, *H.influenzae, C difficile*....)

¿NUEVAS DIANAS?



Nature Reviews Drug Discovery
2015

- Conocer mejor los mecanismos de entrada (porinas) de los antimicrobianos a través de la membrana externa y de funcionamiento de las bombas de expulsión.
- Nuevas dianas: enzimas bacterianas o vías de síntesis no exploradas previamente (e.j. FabI- enoil -Acil carrier protein (ACP) reductasa (elongación de ac grasos de gram+)