CEFTOLOZANO-TAZOBACTAM

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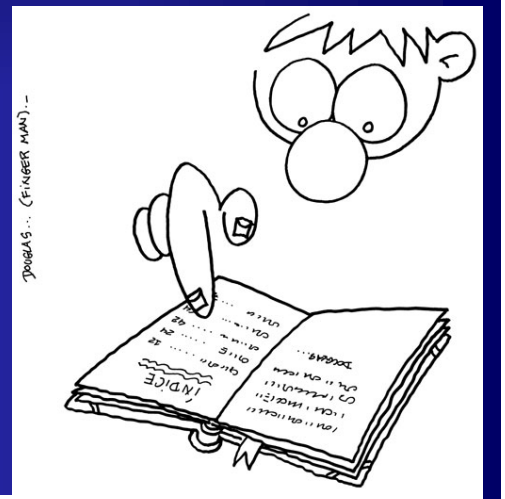
CEFTOLOZANO-TAZOBACTAM

- Método de búsqueda
- ¿Qué es?
- ¿Para qué sirve?
- Dimensión del problema: ¿importa?
  - ✓ GAME
- ¿Qué tenemos? …Nuevos fármacos
- Actividad *in vitro* y resistencias
- *In vivo*
- ¿Qué aporta en EI e infecciones endovasculares?



METODOLOGÍA

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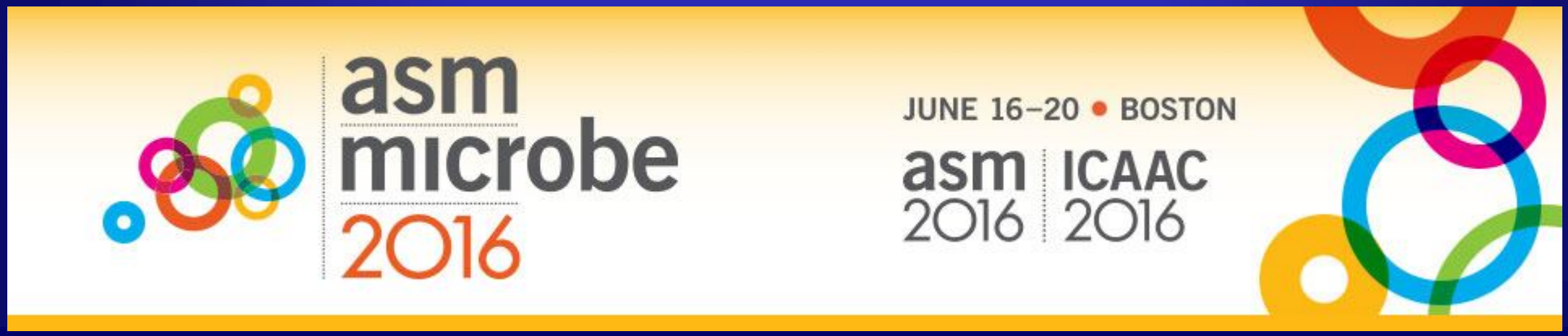
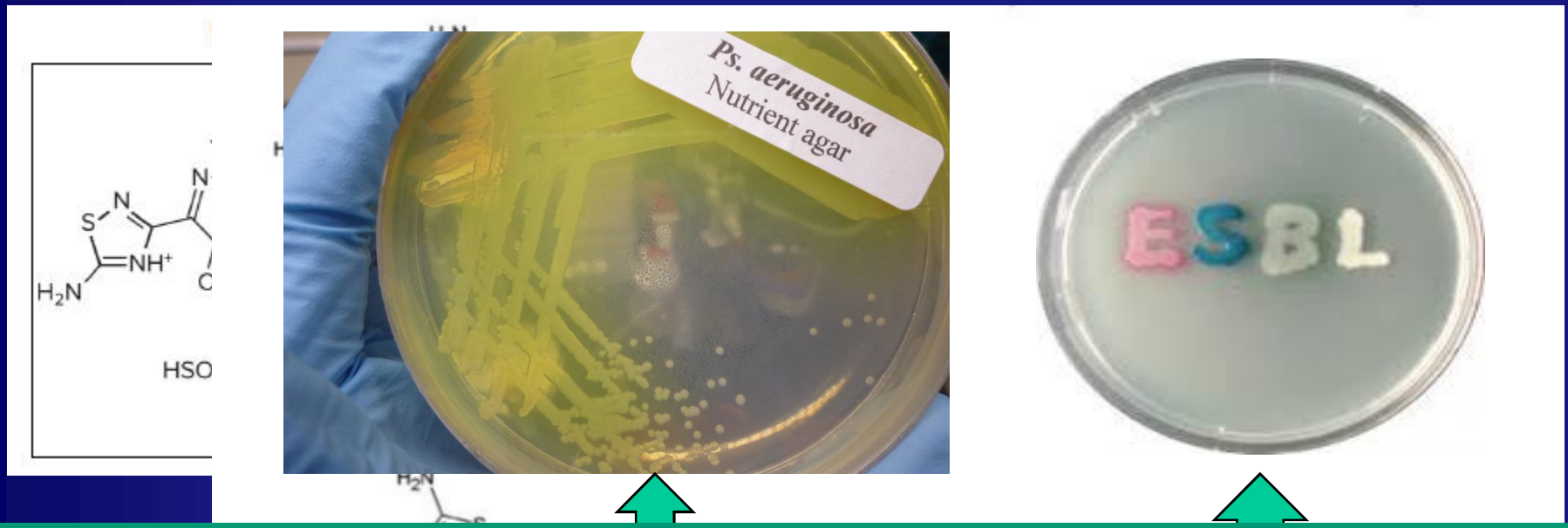
Sociedad Española de Infecciones Cardiovasculares

PubMed



¿Qué es?



Más activa que ceftazidima frente a *P. aeruginosa

***MICs para *P. aeruginosa* :**

- ✓ **4 mg/L AmpC *vs* 16 mg/L ceftazidima**
- ✓ **<2 mg/L bombas exp. vs 8-16 mg/L cfz**
- ✓ **>128 mg/L MBL**

¿Para que sirve?

- *P. aeruginosa** R
  - -Carbapenem
  - -Piper-tazo
  - -Ceftazidima
  - -Fluorquinolonas
  - -AG
  - -MDR

- Enterobacterias productoras de BLEE

- ANAEROBIOS *Bacteroides* spp.

*AmpC, PBP, B-lactamasas, bombas de expulsión, porinas…

¿Para que sirve?

- *P. a*
  - -Carb
  - -Pipe
  - -Ceft
  - -Fluo
  - -AG
  - -MDR

E

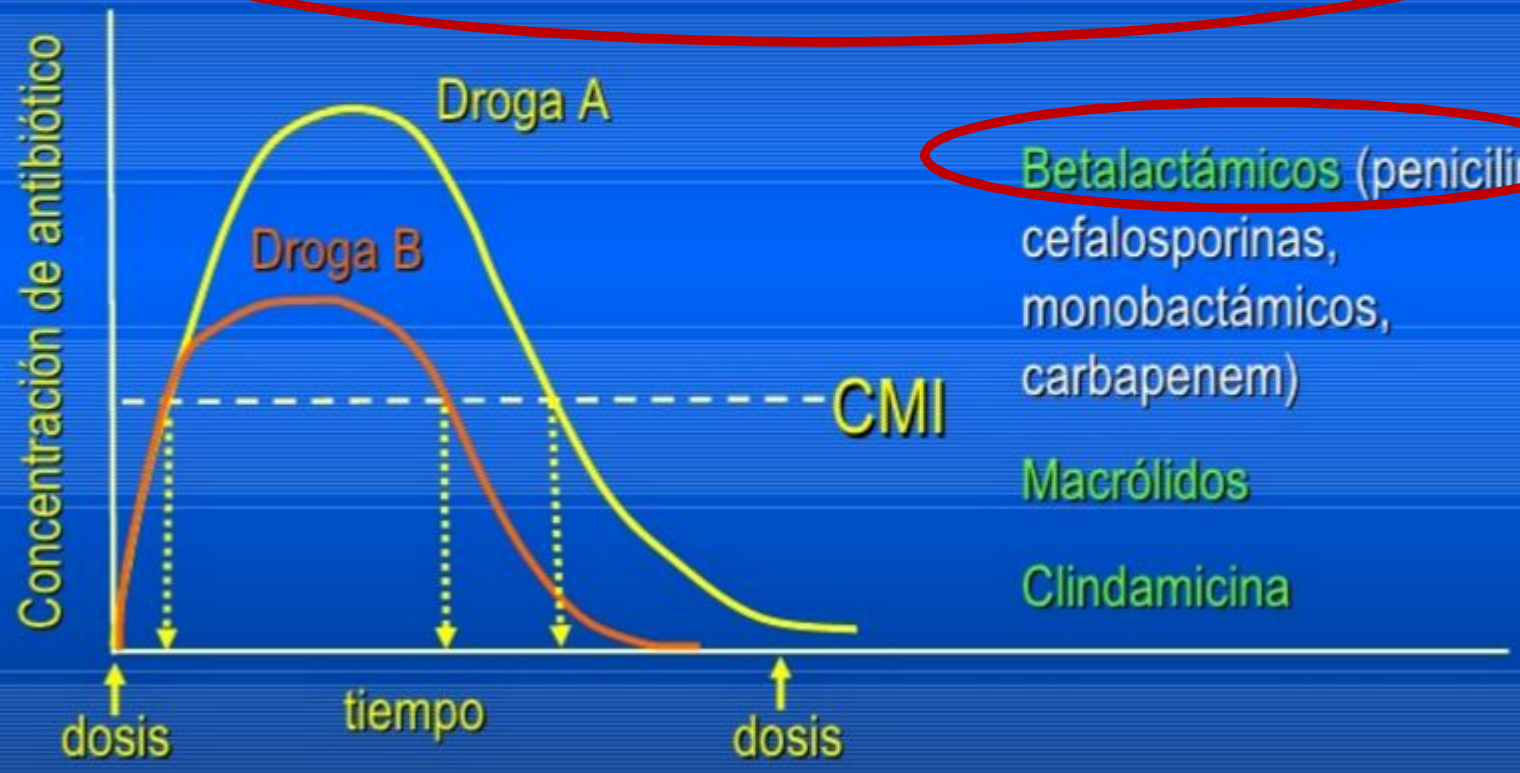
- BAJ
- >90
- Farm

n)

Farmacocinética

Antibióticos Tiempo Dependientes

mayor eficacia a > tiempo mantengan concentraciones > CMI



Betalactámicos (penicilinas, cefalosporinas, monobactámicos, carbapenem)

Macrólidos

Clindamicina

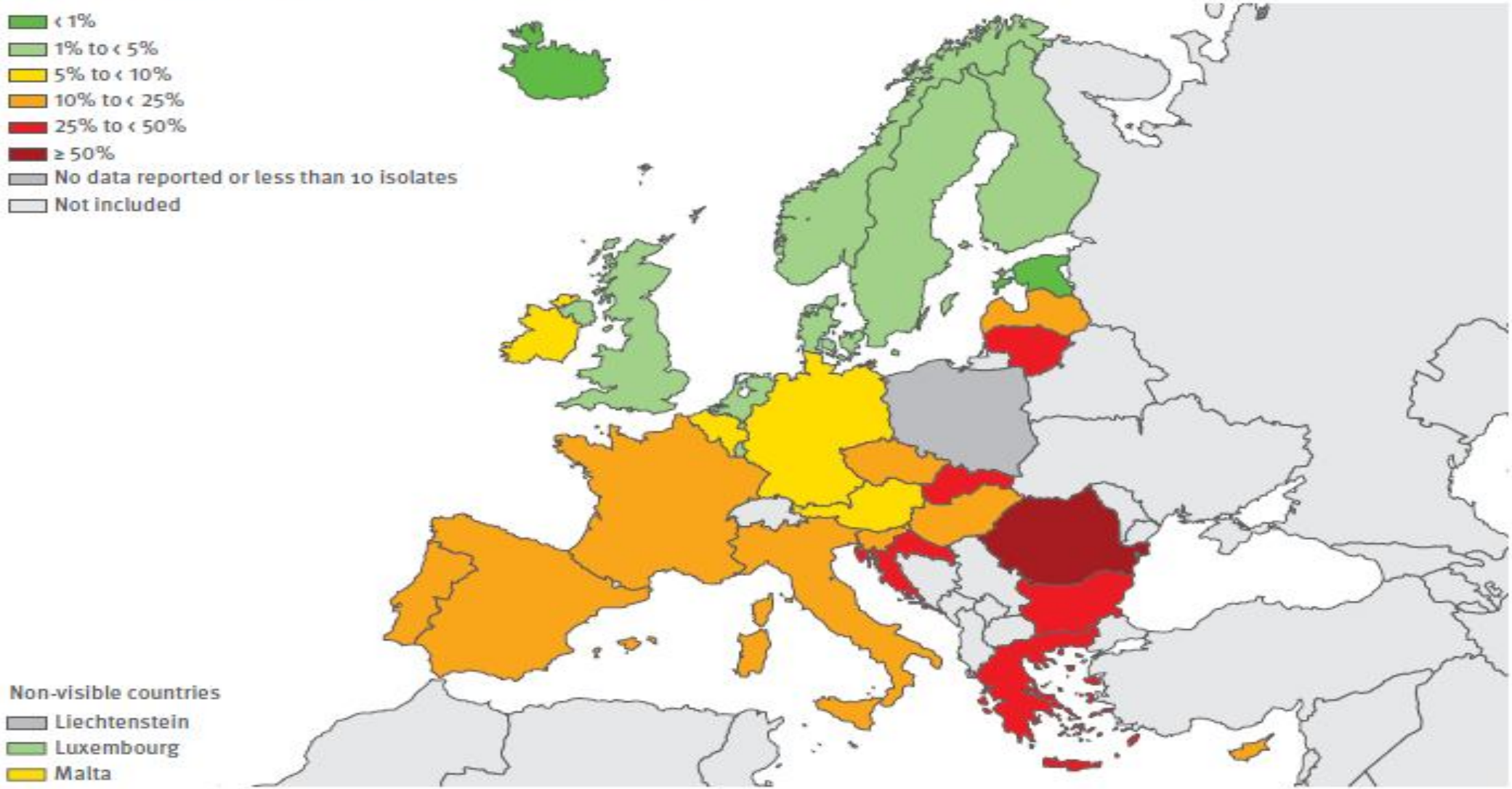
T > CMI al menos el 40-50% del intervalo entre dosis

*AmpC, B-lactamasas, bombas de expulsión, porinas…

DIMENSIÓN DEL PROBLEMA

DIMENSIÓN DEL PROBLEMA

Figure 3.16. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2014



DIMENSIÓN DEL PROBLEMA

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Table 3.22. *Pseudomonas aeruginosa*. Total number of tested isolates and resistance combinations among invasive isolates tested against at least three antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems (n=11649), EU/EEA countries, 2014

Resistance pattern	Number of isolates	% of total*
Fully susceptible (to tested antibiotics)	7630	65.5
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**1462**	**12.6**
Carbapenems	532	4.6
Fluoroquinolones	435	3.7
[Piperacillin + tazobactam]	217	1.9
Aminoglycosides	199	1.7
Ceftazidime	79	0.7
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**834**	**7.3**
[Piperacillin + tazobactam] + ceftazidime	292	2.5
Fluoroquinolones + aminoglycosides	185	1.6
Fluoroquinolones + carbapenems	126	1.1
[Piperacillin + tazobactam] + carbapenems	76	0.7
Aminoglycosides + carbapenems	50	0.4
[Piperacillin + tazobactam] + fluoroquinolones	43	0.4
Fluoroquinolones + ceftazidime	21	0.2
Ceftazidime + carbapenems	20	0.2
[Piperacillin + tazobactam] + aminoglycosides	13	0.1
Ceftazidime + amonoglycosides	8	0.1
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**621**	**5.4**
Fluoroquinolones + aminoglycosides + carbapenems	186	[illegible]
[Piperacillin + tazobactam] + ceftazidime + carbapenems	114	1.0
[Piperacillin + tazobactam] + fluoroquinolones + cefatzidime	83	0.7
[Piperacillin + tazobactam] + fluoroquinolones + aminoglycosides	82	
[Piperacillin + tazobactam] + fluoroquinolones + carbapenems	41	
[Piperacillin + tazobactam] + ceftazidime + aminoglycosides	40	
Fluoroquinolones + ceftazidime + aminoglycosides	27	
Fluoroquinolones + ceftazidime + carbapenems	21	
[Piperacillin + tazobactam] + aminoglycosides + carbapenems	18	0.2
Ceftazidime + amonoglycosides + carbapenems	9	0.1
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**467**	**4.0**
[Piperacillin + tazobactam] + fluoroquinolones + aminoglycosides + carbapenems	141	1.2
[Piperacillin + tazobactam] + fluoroquinolones + cefatzidime + carbapenems	116	1.0
Fluoroquinolones + ceftazidime + aminoglycosides + carbapenems	93	0.8
[Piperacillin + tazobactam] + fluoroquinolones + cefatzidime + aminoglycosides	69	0.6
[Piperacillin + tazobactam] + ceftazidime + aminoglycosides + carbapenems	48	0.4
Resistance to five antimicrobial groups		
[Piperacillin + tazobactam] + fluoroquinolones + cefatzidime + aminoglycosides+ carbapenems	35	5.5

3 AB

4 AB

5 AB

DIMENSIÓN DEL PROBLEMA

Table 3.15. *Klebsiella pneumoniae*. Total number of tested invasive isolates* and resistance combinations against third-generation cephalosporins, fluoroquinolones, aminoglycosides and carbapenems (n=18 180), EU/EEA countries, 2014

Resistance pattern	Number of isolates	% of total**
Fully susceptible	11820	65.0
Single resistance (to indicated antimicrobial group)		
Total (all single resistance)	1131	6.1
Fluoroquinolones	532	2.9
Third-generation cephalosporins	460	2.5
Aminoglycosides	134	0.7
Carbapenems	5	‹0.1
Resistance to two antimicrobial groups		
Total (all two-group combinations)	1256	6.8
Third-generation cephalosporins + fluoroquinolones	498	2.7
Third-generation cephalosporins + aminoglycosides	463	2.5
Fluoroquinolones + aminoglycosides	258	1.4
Third-generation cephalosporins + carbapenems	33	0.2
Fluoroquinolones + carbapenems	3	0.0
Aminoglycosides + carbapenems	1	0.0
Resistance to three antimicrobial groups		
Total (all three-group combinations)	2929	16.1
Third-generation cephalosporins + fluoroquinolones + aminoglycosides	2766	15.2
Third-generation cephalosporins + fluoroquinolones + carbapenems	142	0.8
Third-generation cephalosporins + aminoglycosides + carbapenems	18	0.1
Fluoroquinolones + aminoglycosides + carbapenems	3	‹ 0.1
Resistance to four antimicrobial groups		
Third-generation cephalosporins + fluoroquinolones + aminoglycosides + carbapenems	1044	5.7

1 AB

2 AB

3 AB

4 AB

* Only data from isolates tested against all four antimicrobial groups were included in the analysis.

** Not adjusted for population differences in the reporting countries.

DIMENSIÓN DEL PROBLEMA

Table 3.8. *Escherichia coli.* Total number of tested isolates* and resistance combinations among invasive isolates tested against aminopenicillins, third-generation cephalosporins, fluoroquinolones, aminoglycosides and carbapenems (n=52788), EU/EEA countries, 2014

Resistance pattern	Number of isolates	% of total**
Fully susceptible	21857	41.4
Single resistance (to indicated antimicrobial group)		
Total	**18044**	**34.1**
Aminopenicillins	16707	31.6
Fluoroquinolones	1210	2.3
Aminoglycosides	121	0.2
Carbapenems	6	<0.1
Resistance to two antimicrobial groups		
Total	**6508**	**12.4**
Aminopenicillins + fluoroquinolones	4427	8.4
Aminopenicillins + third-generation cephalosporins	1209	2.3
Aminopenicillins + aminoglycosides	783	1.5
Fluoroquinolones + aminoglycosides	87	0.2
Aminopenicillins + carbapenems	2	<0.1
Resistance to three antimicrobial groups		
Total	**3853**	**7.3**
Aminopenicillins + fluoroquinolones + third-generation cephalosporins	1897	3.6
Aminopenicillins + fluoroquinolones + aminoglycosides	1718	3.3
Aminopenicillins + third-generation cephalosporins + aminoglycosides	231	0.4
Aminopenicillins + third-generation cephalosporins + carbapenems	3	<0.1
Aminopenicillins + fluoroquinolones + carbapenems	3	<0.1
Aminopenicillins + aminoglycosides + carbapenems	1	<0.1
Resistance to four antimicrobial groups		
Total	**2514**	**4.7**
Aminopenicillins + fluoroquinolones + third-generation cephalosporins + aminoglycosides	2498	4.7
Aminopenicillins + fluoroquinolones + third-generation cephalosporins + carbapenems	9	<0.1
Aminopenicillins + fluoroquinolones + aminoglycosides + carbapenems	4	<0.1
Aminopenicillins + third-generation cephalosporins + aminoglycosides + carbapenems	3	<0.1
Resistance to five antimicrobial groups		
Aminopenicillins + fluoroquinolones + third-generation cephalosporins + aminoglycosides + carbapenems	**19**	**<0.1**

1 AB

2 AB

3 AB

4 AB

* Only data from isolates tested against all five antimicrobial groups were included in the analysis.

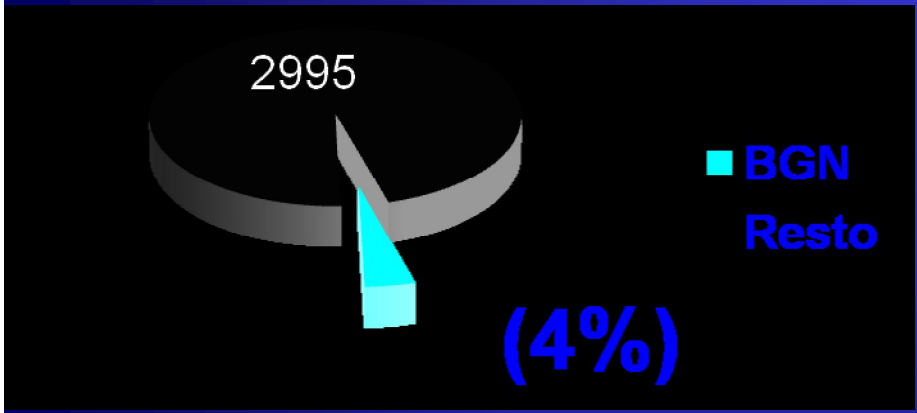
** Not adjusted for population differences in the reporting countries.

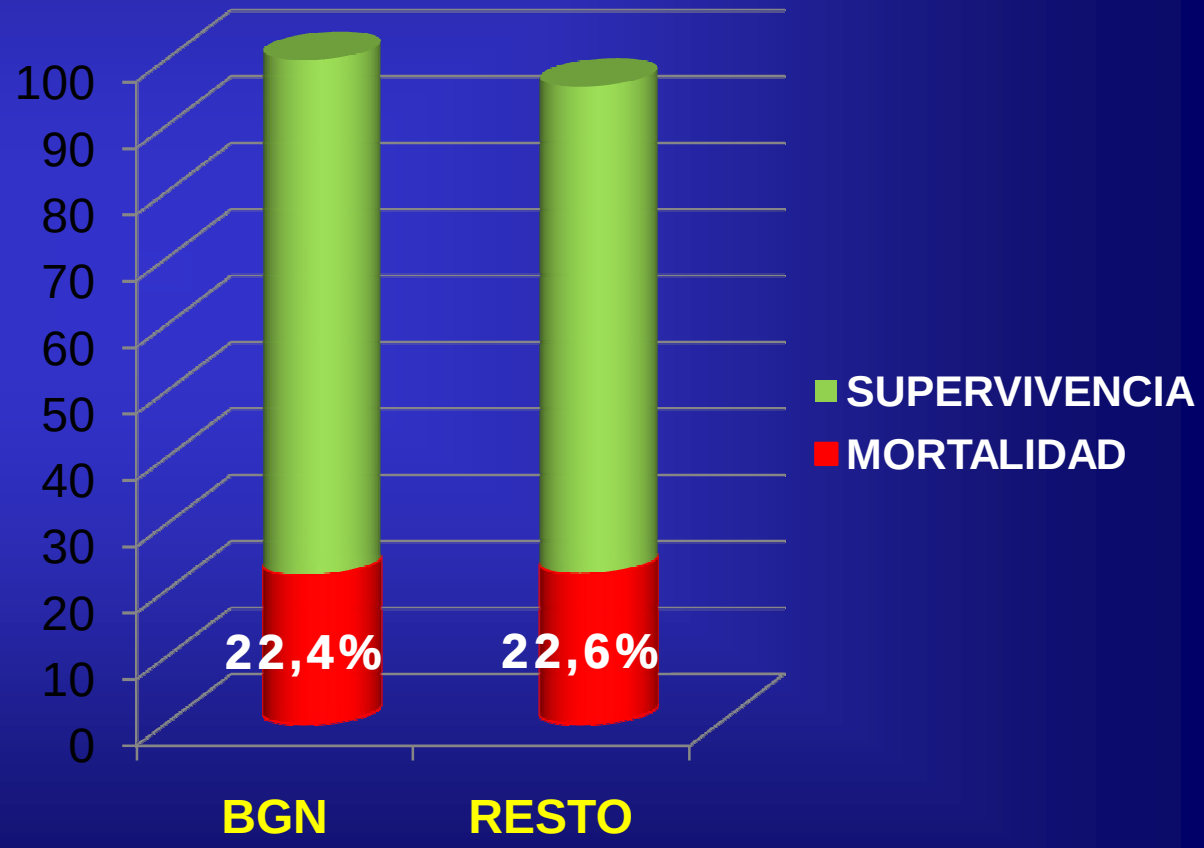
¿IMPORTA?

¿Y en GAME?

¿Y en GAME?

[redacted]





3 *E. coli* (2 BLEE)
7 *Klepsiella* sp. (1 BLEE; 1 MBL)
22 *Pseudomonas* sp. (2 carbap. R)

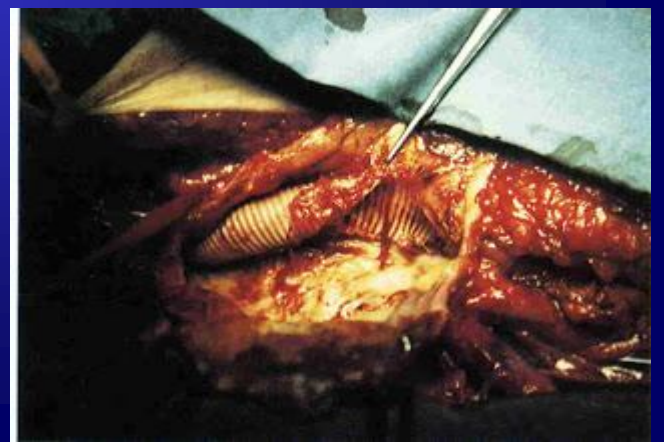
¿Y en infecciones de prótesis vasculares?

- Abdominal: 1-2%
- Femoropoplíteo: 6%

MICROBIOLOGÍA

- *Staphylococcus* (*aureus* y CNE)
- BGN: *E. coli*, *Salmonella* sp., *Pseudomonas* sp.

MORTALIDAD: >25%



CONCLUSIÓN:

- NO MUY FRECUENTE
- GRAVE
  - DIFICULTAD TERAPÉUTICA
  - COMORBILIDADES DEL PACIENTE

¿QUÉ TENEMOS?

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- **CEFTAZIDIMA-AVIBACTAM**

Dosis: 2 g/8h

Precio: 160 € vial

- **CEFTOLOZANO-TAZOBACTAM**

Dosis: 1-2 g/8h

Precio: 100 € vial

ACTIVIDAD *in vitro* Y RESISTENCIAS

- BGN (BLEE)
  - ✓ *E. coli*
  - ✓ *Klebsiella* sp.
  - ✓ *Proteus* sp.
  - ✓ *Serratia* sp.
  - ✓ *Enterobacter* sp (Amp-c?)
  - ✓ *P. aeruginosa* (PBP1b, 1c, 2 y 3, AmpC, OprD, bombas exp)

TEM, SHV, CTX-M

CARB, KP-A, MBL, BLEE-D (OXA-48)

- Anaerobios: *Fusobacterium, Prevotella, Bacteroides*

NO OTROS BACTEROIDES, *Acineto, Stenotrop, S. aureus*

Actividad *in vitro* frente a BLEE*

ENZIMA	CLASE	TAZOBACTAM	AVIBACTAM
TEM-1, TEM-2, SHV-1	A	SI	SI
TEM-3, SHV-2, CTX-M-14	A	SI	SI
KPC-2, KPC-3	A	NO	SI
IMP-1, NDM-1, VIM-1	B	NO	NO
AmpC	C	NO	SI
OXA-48	D	NO	SI

***van Duin *et al*. CID 2016; doi: 10.1093/cid/ciw243**

Table 1 In vitro activities of ceftolozane/tazobactam[a] and comparators against Gram-negative and Gram-positive aerobes

Organism	Ceftolozane			Ceftolozane/tazobactam[a]			Ceftazidime		Cefepime		Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Gram-negative aerobes												
Acinetobacter baumannii	–[b]	–	–	0.5	2	≤0.12 to 16	8	16	–	–	–	–
Acinetobacter spp.	8	>32	≤0.12 to ≥32	8	>32	≤0.12 to ≥32	32	>32	16	16	–	–
Burkholderia cepacia	4	32	≤0.25 to >256	–	–	–	4	32	32	>32	–	–
Citrobacter spp. (all)	0.5	16	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32	0.25	64	≤0.5	1	0.12	>8
Ceftazidime-resistant[c]	32	>32	1 to >32	16	>16	0.25 to >16	>64	>64	1	16	32	>32
Enterobacter cloacae	0.25	32	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32	0.25	≥32	0.06	4	–	–
Enterobacter spp.	0.5	16	–	0.25	8	≤0.03 to ≥32	0.25	>32	≤0.5	4	0.25	>8
Ceftazidime-resistant[c]/non-susceptible	>32	>32	4 to >32	8	32	0.25 to >32	>32	>32	2	>16	>32	>32
Escherichia coli (all)	0.12	0.5	0.12 to >64	0.12	0.5	≤0.12 to >32	0.25	8	≤0.5	4	≤0.06	>8
Ceftazidime resistant[c]	>32	>32	1 to >32	1	16	≤0.12 to >16	64	>64	>16	>16	>32	>32
ESBL producers	64	>64	0.25 to >64	0.5	4	≤0.12 to >32	16	>32	>16	>16	>8	>8
Haemophilus influenzae	0.12	0.25	≤0.12 to 1	≤0.12	0.25	≤0.12 to 1	≤0.06	0.12	0.06	0.25	–	–
Klebsiella oxytoca	–	–	–	≤0.12	0.5	≤0.12 to 2	≤0.25	0.5	–	–	–	–
Klebsiella pneumoniae (all)	0.25	16	≤0.12 to >64	0.25	8	≤0.12 to ≥32	0.25	64	≤0.06	8	–	–
Ceftazidime-resistant[c]	>32	>32	4 to >32	4	>16	≤0.12 to >16	>64	>64	8	>16	>32	>32
ESBL producers	32	>64	2 to >64	0.5	64	≤0.12 to >64	32	–	–	–	–	–
KPC producers	>32	>32	32 to >32	>16	>16	16 to >16	>64	>64	>16	>16	>32	>32
Klebsiella spp. (all)	0.25	>32	–	0.25	4	0.12 to >32	0.12	32	≤0.5	>16	≤0.06	>8
ESBL producers	>32	>32	–	2	>32	0.12 to >32	32	>32	>16	>16	>8	>8
Moraxella catarrhalis	≤0.12	0.5	–	–	–	–	≤0.06	0.12	0.25	1	–	–
Proteus mirabilis (all)	0.25	0.5	≤0.12 to 16	0.25	0.5	≤0.12 to 16	0.06	0.25	≤0.06	0.12	≤0.06	2
ESBL producers	8	>32	≤0.25 to >32	1	8	0.25 to >16	≤4	>64	4	>16	8	>32
Proteus spp., indole-positive	–	–	–	0.25	1	0.12 to ≥32	0.12	16	≤0.5	≤0.5	≤0.06	4
Ceftazidime-resistant[c]	>32	>32	4 to >32	2	>16	0.25 to >16	64	>64	0.5	16	8	>32
Pseudomonas aeruginosa (all)	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128	2	32	4	32	–	–
Serratia marcescens	0.5	1	0.25 to ≥32	0.5	1	≤0.12 to ≥32	0.25	0.5	0.06	0.25	–	–
Serratia spp.	0.5	1	–	0.5	1	0.12 to ≥32	0.12	0.5	≤0.5	≤0.5	0.25	1
Stenotrophomonas maltophilia	–	–	–	16	>64	0.5 to >64	32	>32	>16	>16	–	–
Gram-positive aerobes												
Enterococcus faecalis	64	>64	–	–	–	–	>64	>64	>32	>32	–	–
Enterococcus faecium	64	>64	–	–	–	–	>64	>64	>32	>32	–	–
Staphylococcus aureus	32	32	16 to 64	32	64	4 to 128	8	32	2	16	–	–
Streptococcus agalactiae	0.5	0.5	≤0.12 to 0.25	0.5	0.5	≤0.12 to 0.5	0.5	0.5	0.12	0.12	–	–

Table 3 In vitro activities of ceftolozane/tazobactam[a] and comparators against *Pseudomonas aeruginosa* and its various resistant phenotypes

P. aeruginosa phenotypes	Ceftolozane			Ceftolozane/tazobactam[a]			Ceftazidime		Cefepime	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
All	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128	2	32	4	32
Amikacin-resistant	1	32	≤0.5 to >32	2	–[b]	≤0.25 to >16	–	–	–	–
Aztreonam-resistant/non-susceptible	1	4	≤0.12 to >32	–	–	–	–	–	–	–
Cefepime-resistant/non-susceptible	1	4	≤0.12 to ≥128	4	–	2 to ≥16	–	–	–	–
Ceftazidime-resistant/non-susceptible	2	16	≤0.12 to ≥128	4	16	0.25 to >64	32	256	16	64
Ciprofloxacin-resistant	1	4	0.12 to ≥128	1	4	≤0.25 to >16	4	16	–	–
Doripenem non-susceptible	1	4	0.5 to >32	–	–	–	–	–	–	–
Gentamicin-resistant	1	4	<0.12 to >128	1	4	<0.25 to >16	–	–	–	–
Imipenem-resistant/non-susceptible	1	4	≤0.12 to ≥128	1	8	0.25 to >64	8	16	8	32
Levofloxacin-resistant/non-susceptible	1	4	0.25 to >32	–	–	–	–	–	–	–
Meropenem-resistant/non-susceptible	1	8	≤0.12 to ≥128	1	8	0.25 to >32	8	>32	8	>16
Piperacillin–tazobactam resistant/non-susceptible	2	4	≤0.12 to ≥128	2	4	0.5 to >64	32	128	16	32
Tobramycin-resistant	2	64	≤0.12 to ≥128	2	64	0.5 to >64	32	128	16	64
Ceftazidime- and imipenem non-susceptible	4	16	0.5 to >128	2	16	0.5 to >128	64	>128	16	>16
Ceftazidime- and meropenem non-susceptible	–	–	–	4	≥32	1 to ≥32	–	–	–	–
Multidrug-resistant[c]	2	16	0.12 to ≥128	1	2	0.5 to >64	64	256	16	64
Pan-β-lactam resistant[d]	–	–	1 to 4	–	–	–	–	–	–	–

Adapted from references [10, 11, 13, 15, 16, 31, 33, 34, 36, 38–40, 42, 46–48, 52, 54]

MIC_{50} minimum concentration (mg/L) to inhibit growth of 50 % of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90 % of isolates

[a] Fixed tazobactam concentration of 4 mg/L

[b] No data available. MIC_{90} not calculated when there were less than ten isolates

[c] Resistant to ≥3 antimicrobials of different classes (ceftazidime, imipenem, piperacillin/tazobactam, ciprofloxacin/levofloxacin, tobramycin)

[d] Resistant to all of ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem

ACTIVIDAD *in vitro* Y RESISTENCIAS

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"LOS MECANISMOS DE RESISTENCIA DE *P. aeruginosa* FRENTE A β-LACTÁMICOS NO AFECTAN A CEFTOLOZANO-TAZOB."

***Zhanel *et al*. Drugs 2014;74:31-51**

In vivo

Adis

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Table 6 Clinical trials of ceftolozane alone and ceftolozane/tazobactam

Trial description	Number of patients	Treatment regimens
Phase II treatment of cUTI, including pyelonephritis [78]	129	Ceftolozane 1,000 mg IV, q8h × 7–10 days Ceftazidime 1,000 mg IV, q8h × 7–10 days
Phase II treatment of cIAI [79]	122	Ceftolozane/tazobactam 1.5 g + metronidazole 500 mg IV, q8h × 7–14 days Meropenem 1,000 mg IV, q8h × 7–14 days
Phase III treatment of cUTI, including pyelonephritis	525	Ceftolozane/tazobactam 1.5 g IV, q8h × 7 days Levofloxacin 750 mg IV, once daily × 7 days
Phase III treatment of cIAI	~500	Ceftolozane/tazobactam 1.5 g + metronidazole 500 mg IV, q8h × 4–14 days Meropenem 1,000 mg IV, q8h × 4–14 days
Phase III treatment of ventilator-associated pneumonia	~300	Ceftolozane/tazobactam 3 g IV, q8h Piperacillin–tazobactam 4.5 g IV, q6h

CEFTOLOZANO/TAZOB.- ITU

	Ceftol-tazo 1+0,5q8h	Levofloxacino 0,75 q24h
Curación clínica	96%	93%
Erradicación microbiol.	85%	75%
EM Enterobact.	278/313=88,8%	253/325=78%
EM *P. aeruginosa*	6/7= 86%	7/12=58%

CEFTOLOZANO/TAZOB.- IIAc n=993

	Ceftol-tazo 1+0,5q8h + metronidazol	Meropenem 1 g q8h
Curación clínica	94%	94%
Erradicación microbiol.	94,2%	94,7%

CEFTOLOZANO/TAZOB.
IIAc +ITUc con BLEE
N =153 (11%) 103 ITUc, 50 IIAc

	Ceftol-tazo	Comparador
Curación clínica	98%	83%
Curación clínica IIAc	96%	88%
Erradicación microbiol. IIAc	96%	88%

Pacientes con bacteriemia, > mortalidad que carbapenem

CONCLUSIONES ESTUDIOS PIVOTALES

- COMPARADOR POCO ADECUADO
- >80% PNA (60 ITUc); edad media 48 años
- Muy pocos productores BLEE
- 24 bacteriemias
- 50% apendicitis (comunidad)
- Algo inferior en enf. + graves
- BACTERIEMIA 25% FALLOS CLINICOS VS 7,7% (n= 8 *vs* 13)

Pseudomonas spp. con resistencia mediada por KPC o MBL

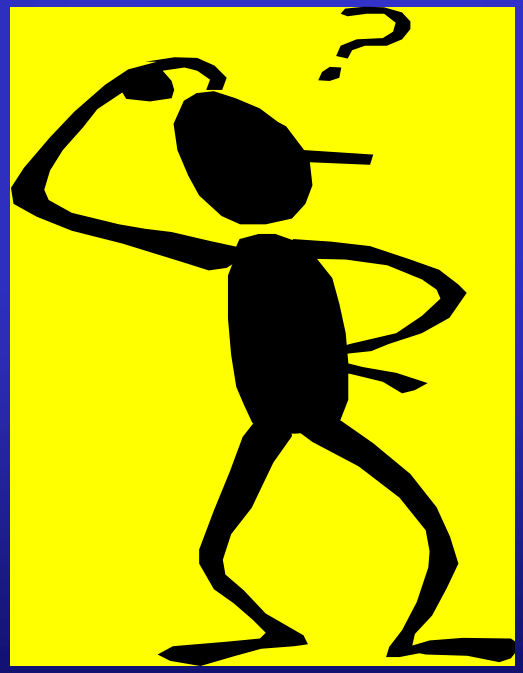
IMIPENEM / MEROPENEM SON GENÉRICOS (€)

Ensayos clinicos en ITUc e IIAc???

- ¿QUÉ APORTA EN ENDOCARDITIS E INFECCIONES ENDOVASCULARES?

- *Pseudomonas aeruginosa* (R, MDR)
- BGN-BLEE? (limitaciones)

  - Prótesis valvulares (postCCV)
  - Endovascular (aorta, grandes vasos)



NO IMPORTA CUANTOS RECURSOS TENGAS

SI NO SABES COMO UTILIZARLOS.
NUNCA SERÁ SUFICIENTE.

SEICAV
Sociedad Española de Infecciones Cardiovasculares