Pseudomonas ed Acinetobacter MDR

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ASO Santa Croce e Carle
Cuneo

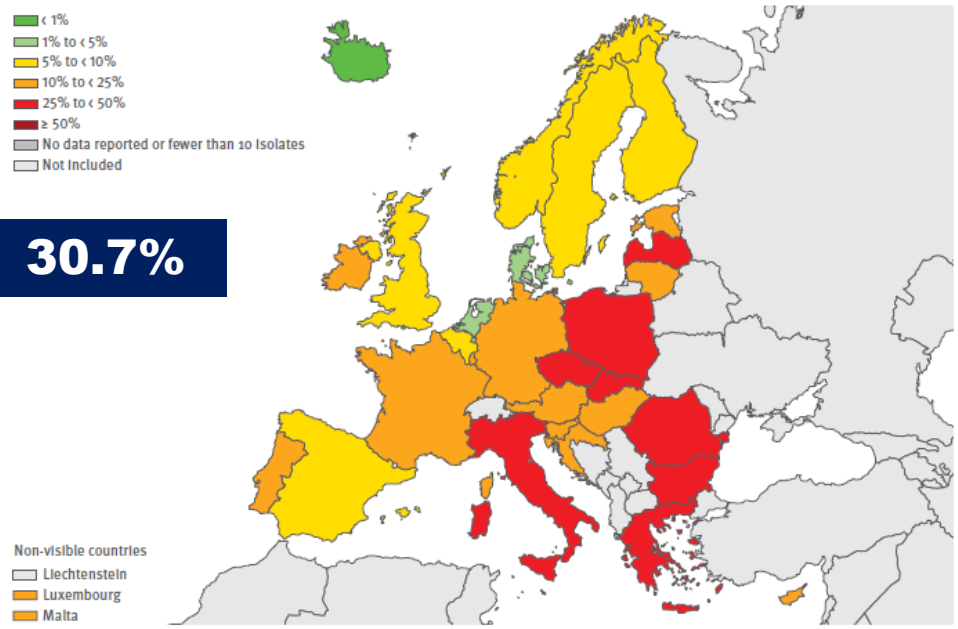
Convegno Nazionale
Terapia Antibiotica dei patogeni multiresistenti (MDRO): una sfida aperta

Cona (Fe) 15 giugno 2018
Nuovo "Arcispedale S. Anna"
Aula Congressi

"……The treatment of metallo-β-lactamase producers or non-fermenters such as Acinetobacter spp. remains more problematic……"

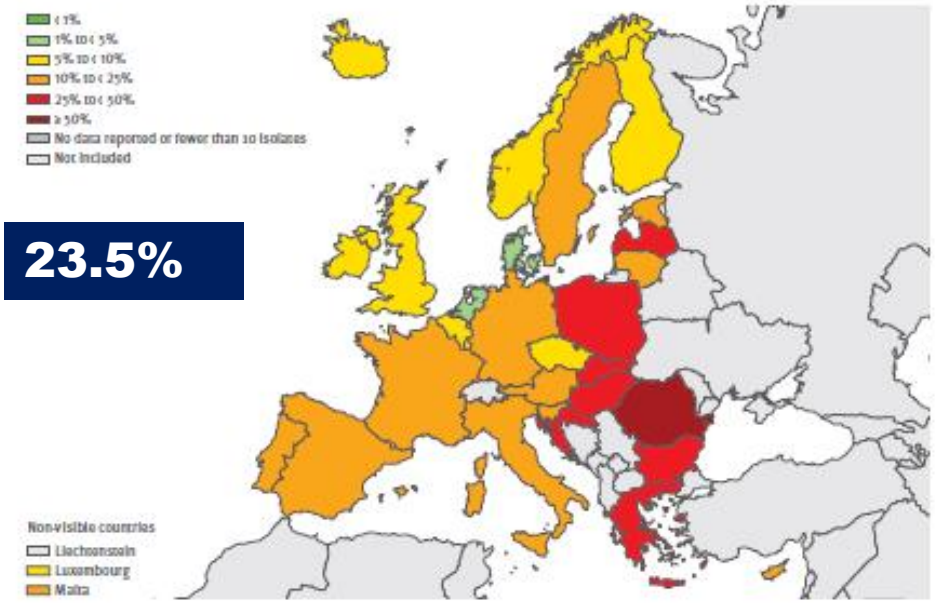
H. Wright, R.A. Bonomo, D.L. Paterson. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? Clinical Microbiology and Infection 23 (2017) 704e712

Figure 3.13. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to piperacillin ± tazobactam, by country, EU/EEA countries, 2016



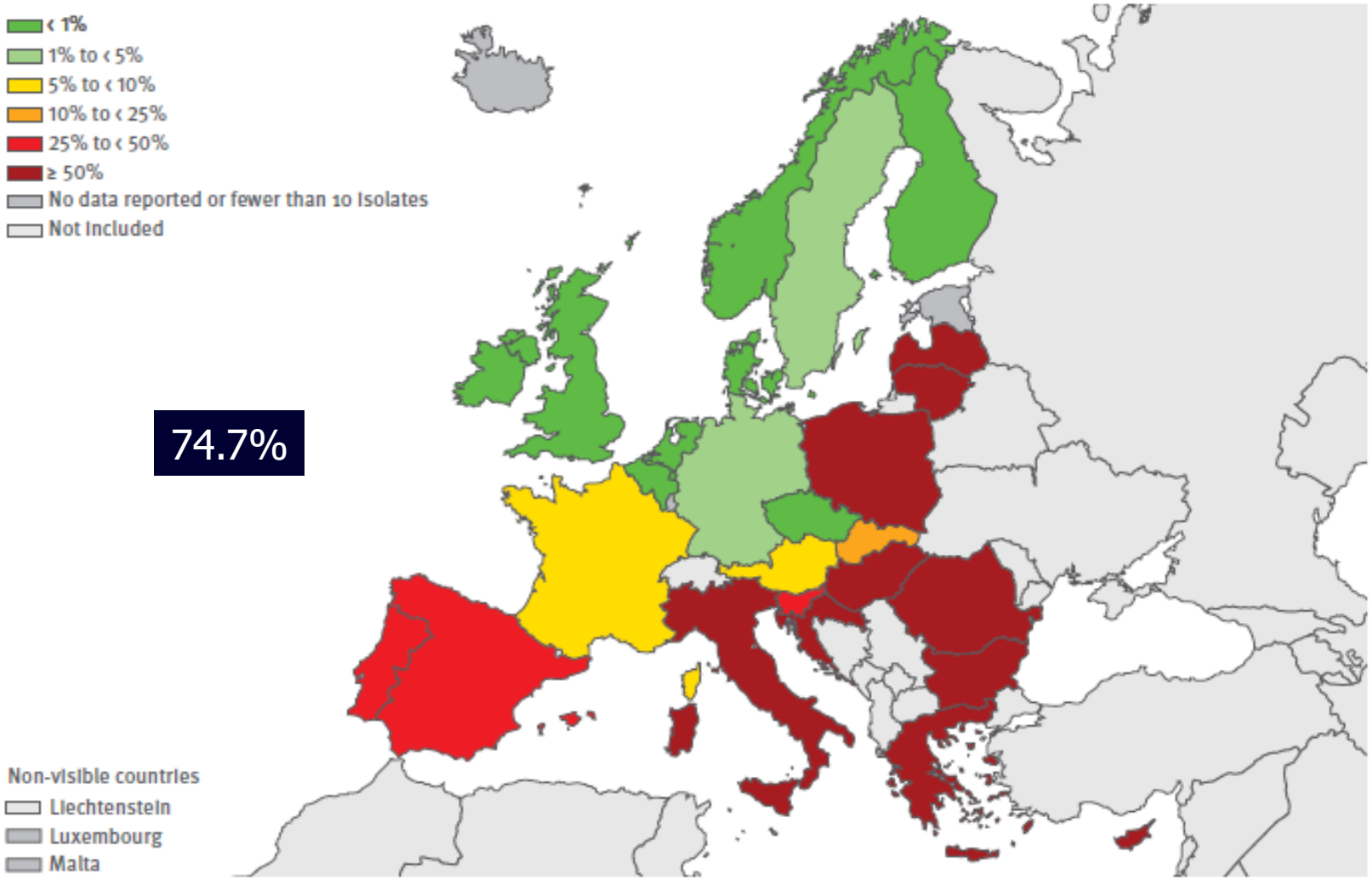
30.7%

Figure 3.17. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2016



23.5%

Figure 3.23. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems, by country, EU/EEA countries, 2016



74.7%

Prevalence of Carbapenem-Resistant Gram-Negative Infections in the United States Predominated by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

Bin Cai,[1] Roger Echols,[2] Glenn Magee,[3] Juan Camilo Arjona Ferreira,[1,*] Gareth Morgan,[1] Mari Ariyasu,[4] Takuko Sawada,[4] and Tsutae "Den" Nagata[4]

Open Forum Infectious Diseases, 2017

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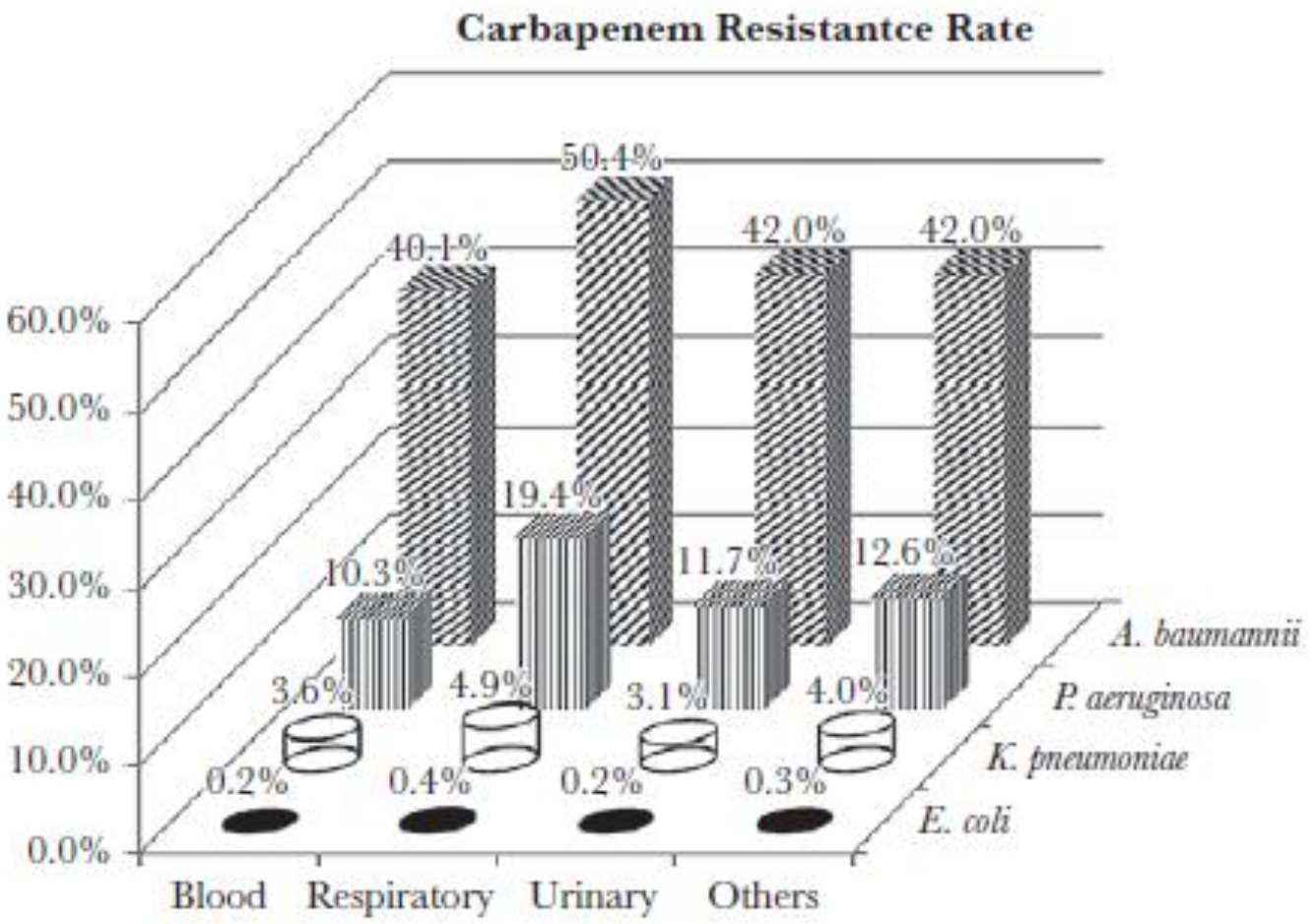


- ASO Santa Croce e Carle
- 700 letti
- 35.000 ricoveri/anno
- Ospedale di alta specializzazione

Isolamenti 2017 Pseudomonas

19 da emocoltura
62 da urinocoltura

molecola	n. resistenti	%
chinoloni	4/19	21
carbapenemi	3/18	16.7
Pipera/tazo	1/19	5.2

Epidemiology and carbapenem resistance mechanisms of carbapenem-non-susceptible *Pseudomonas aeruginosa* collected during 2009–11 in 14 European and Mediterranean countries

Mariana Castanheira[1]*, Lalitagauri M. Deshpande[1], Andrew Costello[1], Todd A. Davies[2] and Ronald N. Jones[1]

J Antimicrob Chemother 2014; **69**: 1804–1814

Country	No. of *P. aeruginosa* isolates (% from surveyed strains)			
	2009, 164 (26.2)	2010, 146 (23.0)	2011, 219 (24.0)	overall, 529 (25.5)
Belgium				.1)
France				.2)
German				.4)
Greece[a]				.7)
Ireland				.8)
Israel				.7)
Italy				.9)
Poland				.5)
Portugal				.6)
Spain				.0)
Sweden				.9)
Switzerland[b]	5 (21.7)	—	—	5 (21.7)
Turkey	37 (59.7)	27 (50.9)	32 (40.0)	96 (49.2)
UK	8 (25.0)	3 (9.7)	5 (14.3)	16 (16.3)

2070 ceppi, 529 R a doripenem, 106 (5%) classe molecolare B (IMP o VIM)

A Systematic Review and Meta-Analyses Show that Carbapenem Use and Medical Devices Are the Leading Risk Factors for Carbapenem-Resistant *Pseudomonas aeruginosa*

Anne F. Voor in 't holt,[a] Juliëtte A. Severin,[a] Emmanuel M. E. H. Lesaffre,[b,c] Margreet C. Vos[a]

Antimicrobial Agents and Chemotherapy p. 2626–2637 May 2014 Volume 58 Number 5

TABLE 5 Conventional meta-analyses of the different risk factors for acquisition and transmission of carbapenem-resistant *P. aeruginosa*[a]

Risk factor	No. of factors	Pooled OR (random effects)	95% CI	Range of OR in individual studies	Risk of publication bias			
					Egger	*P* value	Kendall's tau	*P* value
Carbapenem use	16	7.09	5.43–9.25	3.6–76.0	1.39	0.02	0.47	0.01
Medical devices	19	5.11	3.55–7.37	2.1–64.3	2.30	<0.001	0.49	0.003
Other antibiotic use	19	3.56	2.52–5.03	0.3–43.7	1.49	0.06	0.38	0.02
ICU admission	8	3.02	1.62–5.61	1.1–13.3	2.96	0.002	0.07	0.90
Quinolone use	11	2.73	1.27–5.87	0.1–48.4	0.89	0.56	0.45	0.06
Underlying disease	13	2.44	1.23–4.84	0.1–25.0	1.34	0.06	−0.05	0.77
Vancomycin use	3	2.10	1.42–3.09	1.8–2.9	NC	NC	NC	NC
Patient characteristics	13	1.46	1.22–1.75	1.0–13.9	2.02	<0.001	0.56	0.007
Length of hospital stay	9	1.06	1.02–1.09	1.0–6.7	3.05	0.0003	0.56	0.04

Pseudomonas aeruginosa

• Fibrosi Cistica	75%
• Bronchiectasie non FC	43%
• IPF	4-12%
• BPCO (FR: ospedalizzazione nei 3 mm prec, steroide, ATB, FEV-1 <30%)	5-10%

Report Registro CFF 2015
Yamazaki R et al. PLoS ONE, 2016, 11(12)
Sethi S, et al. N Engl J Med 2008;359:2355-65
Dimakou K, et al. Respiratory Medicine 116, 2016; 1-7
Woodhead M, et al. Clin Microbiol Infect. 2011; suppl 6: E1-59

Antimicrobial Susceptibility of *Pseudomonas aeruginosa* Isolated from Cystic Fibrosis Patients in Northern Europe

Muhammad-Hariri Mustafa,[a,b] Hussein Chalhoub,[a] Olivier Denis,[c] Ariane Deplano,[c] Anne Vergison,[c*] Hector Rodriguez-Villalobos,[d] Michael M. Tunney,[e] J. Stuart Elborn,[e] Barbara C. Kahl,[f] Hamidou Traore,[b] Francis Vanderbist,[b] Paul M. Tulkens,[a] Françoise Van Bambeke[a]

TABLE 2 MIC distributions for antipseudomonal antibiotics and corresponding percent susceptibility according to EUCAST or CLSI breakpoints[a]

	MIC (mg/liter)				Susceptibility according to: EUCAST[b]			CLSI[c]		
Antibiotic	Min	Max	50%	90%	% S	% I	% R	% S	% I	% R
TIC	1	>512	128	>512	16	NA	84	16	23	61
PIP	0.5	>512	256	>512	24	NA	76	24	15	61
TZP	0.5	>512	128	512	29	NA	71	29	17	54
CAZ	1	>512	64	512	31	NA	69	31	10	59
IPM	0.25	128	4	32	48	19	33	48	19	33
MEM	0.032	256	2	16	44	36	20	63	17	20
AMK	1	>512	32	128	22	17	61	39	15	46
TOB	0.064	>512	2	16	72	NA	28	72	12	16
CIP	0.064	64	1	8	24	20	56	44	29	27
CST	0.25	>512	1	4	92	NA	8	78	14	8

[a] Min, minimum; max, maximum; S, susceptible; I, intermediate; R, resistant; NA, not applicable (no I category); TIC, ticarcillin; PIP, piperacillin; TZP, piperacillin-tazobactam; CAZ, ceftazidime; IPM, imipenem; MEM, meropenem; AMK, amikacin; TOB, tobramycin; CIP, ciprofloxacin; CST, colistin.

[b] EUCAST breakpoints (in milligrams per liter): for TIC, S ≤ 16 and R > 16; for PIP, S ≤ 16 and R > 16; for TZP, S ≤ 16 and R > 16; for CAZ, S ≤ 8 and R > 8; for IPM, S ≤ 4 and R > 8; for MEM, S ≤ 2 and R > 8; for AMK, S ≤ 8 and R > 16; for TOB, S ≤ 4 and R > 4; for CIP, S ≤ 0.5 and R > 1; and for CST, S ≤ 4 and R > 4.

[c] CLSI breakpoints (in milligrams per liter): for TIC, S ≤ 16, I = 32 to 64, and R ≥ 128; for PIP, S ≤ 16, I = 32 to 64, and R ≥ 128; for TZP, S ≤ 16, I = 32 to 64, and R ≥ 128; for CAZ, S ≤ 8, I = 16, and R ≥ 32; for IPM, S ≤ 4, I = 8, and R ≥ 16; for MEM, S ≤ 4, I = 8, and R ≥ 16; for CIP, S ≤ 1, I = 2, and R ≥ 4; for AMK, S ≤ 16, I = 32, and R ≥ 64; for TOB, S ≤ 4, I = 8, and R ≥ 16; and for CST, S ≤ 2, I = 4, and R ≥ 8.

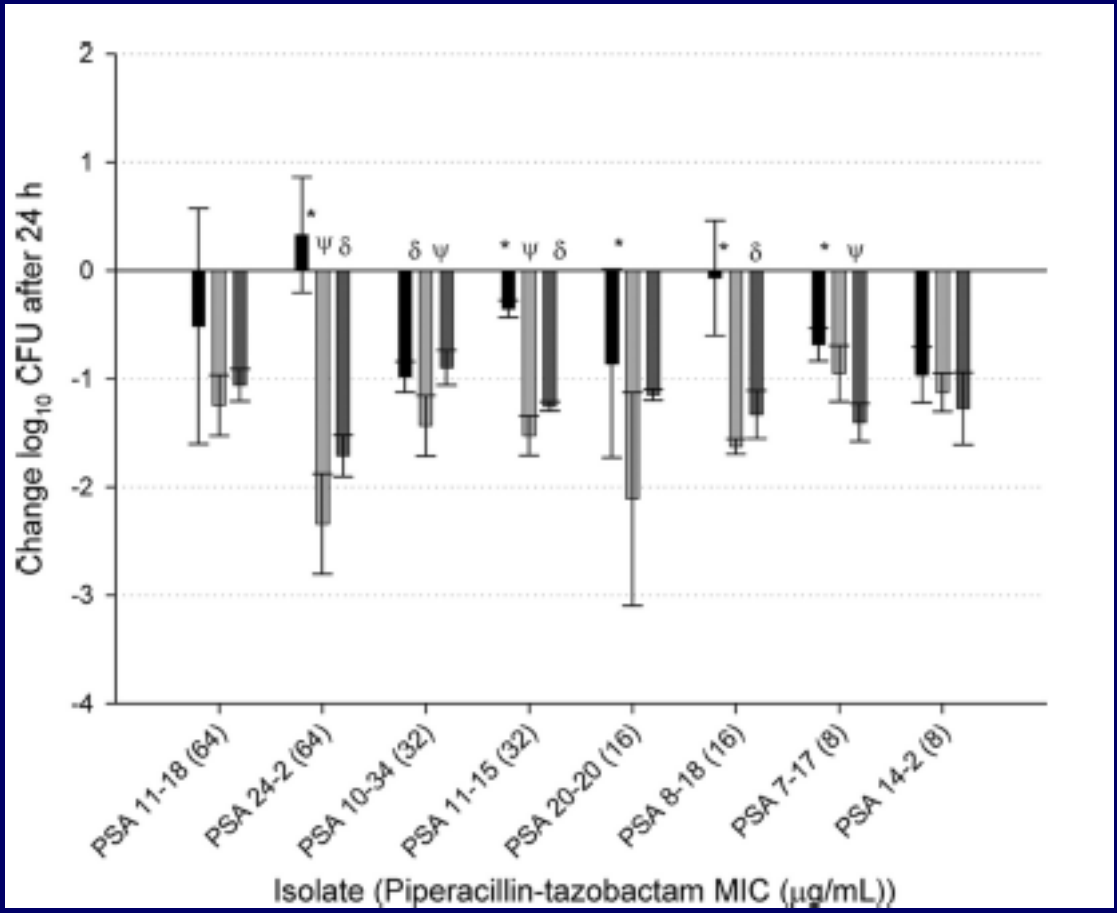
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Cosa abbiamo a disposizione: ceftolozano-tazobactam ceftazidime-avibactam

In Vivo Comparison of CXA-101 (FR264205) with and without Tazobactam versus Piperacillin-Tazobactam Using Human Simulated Exposures against Phenotypically Diverse Gram-Negative Organisms

Catharine C. Bulik,[a] Pamela R. Tessier,[a] Rebecca A. Keel,[a] Christina A. Sutherland,[a] and David P. Nicolau[a,b]

AAC, 2012; 56: 544-49



Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and Enterobacteriaceae with various

Table 1. Cumulative MIC distributions of ceftolozane/tazobactam tested against *P. aeruginosa* and Enterobacteriaceae, including various resistance subsets

Organism/resistance subset (no. tested)	Number of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC (mg/L) of										MIC_{50} (mg/L)	MIC_{90} (mg/L)
	≤0.12	0.25	0.5	1	2	4	8	16	32	>32		
P. aeruginosa (2191)	3 (0.1)	73 (3.5)	938 (46.3)	508 (69.5)	198 (78.5)	132 (84.5)	38 (86.3)	15 (86.9)	32 (88.4)	254 (100.0)	1	>32
MDR (698)		1 (0.1)	15 (2.3)	109 (17.9)	144 (38.5)	102 (53.2)	30 (57.4)	13 (59.3)	30 (63.6)	254 (100.0)	4	>32
XDR (538)			1 (0.2)	49 (9.3)	103 (28.4)	77 (42.8)	19 (46.3)	13 (48.7)	30 (54.3)	246 (100.0)	32	>32
CAZ-NS (371)		1 (0.3)	4 (1.3)	48 (14.3)	110 (43.9)	65 (61.5)	17 (66.0)	7 (67.9)	16 (72.2)	103 (100.0)	4	>32
MEM-NS (720)		2 (0.3)	88 (12.5)	136 (31.4)	113 (47.1)	81 (58.3)	22 (61.4)	13 (63.2)	26 (66.8)	239 (100.0)	4	>32
TZP-NS (810)		2 (0.3)	34 (4.4)	153 (23.3)	173 (44.7)	127 (60.4)	38 (65.1)	15 (66.9)	27 (70.3)	241 (100.0)	4	>32
CAZ-, MEM- and TZP-NS (476)				25 (5.3)	94 (25.0)	77 (41.2)	18 (45.0)	13 (47.7)	22 (52.3)	227 (100.0)	32	>32
Enterobacteriaceae (8341)	1652 (19.8)	3416 (60.8)	1740 (81.6)	583 (88.6)	243 (91.5)	180 (93.7)	125 (95.2)	90 (96.3)	74 (97.1)	238 (100.0)	0.25	2
MDR (1387)	8 (0.6)	146 (11.1)	331 (35.0)	204 (49.7)	158 (61.1)	123 (69.9)	77 (75.5)	55 (79.5)	62 (83.9)	223 (100.0)	2	>32
XDR (187)		2 (1.1)	13 (8.0)	11 (13.9)	17 (23.0)	13 (29.9)	13 (36.9)	11 (42.8)	15 (50.8)	92 (100.0)	32	>32
E. coli (3843)	1207 (31.4)	1921 (81.4)	452 (93.2)	144 (96.9)	47 (98.1)	23 (98.7)	18 (99.2)	13 (99.5)	9 (99.8)	9 (100.0)	0.25	0.5
ESBL screen positive (715)	19 (2.7)	177 (27.4)	271 (65.3)	132 (83.8)	44 (89.9)	23 (93.1)	18 (95.7)	13 (97.5)	9 (98.7)	9 (100.0)	0.5	4
K. pneumoniae (1408)	181 (12.9)	448 (44.7)	239 (61.6)	134 (71.2)	73 (76.3)	65 (81.0)	25 (82.7)	25 (84.5)	42 (87.5)	176 (100.0)	0.5	>32
MEM-S, ESBL screen positive (493)	5 (1.0)	41 (9.3)	93 (28.2)	92 (46.9)	67 (60.4)	65 (73.6)	25 (78.7)	19 (82.6)	26 (87.8)	60 (100.0)	2	>32
MEM-NS (140)				1 (0.7)	1 (1.4)	0 (1.4)	0 (1.4)	6 (5.7)	16 (17.1)	116 (100.0)	>32	>32
K. oxytoca (304)	94 (30.9)	123 (71.4)	39 (84.2)	15 (89.1)	13 (93.4)	6 (95.4)	3 (96.4)	2 (97.0)	1 (97.4)	8 (100.0)	0.25	2
Enterobacter spp. (899)	65 (7.2)	370 (48.4)	186 (69.1)	55 (75.2)	57 (81.5)	52 (87.3)	50 (92.9)	21 (95.2)	17 (97.1)	26 (100.0)	0.5	8
CAZ-NS (304)		12 (3.9)	41 (17.4)	38 (29.9)	50 (46.4)	50 (62.8)	49 (78.9)	21 (85.9)	17 (91.4)	26 (100.0)	4	32
Citrobacter spp. (389)	48 (12.3)	218 (68.4)	38 (78.1)	20 (83.3)	6 (84.8)	13 (88.2)	15 (92.0)	20 (97.2)	2 (97.7)	9 (100.0)	0.25	8
P. mirabilis (476)	3 (0.6)	87 (18.9)	327 (87.6)	30 (93.9)	12 (96.4)	4 (97.3)	6 (98.5)	6 (99.8)	1 (100.0)		0.5	1
Indole-positive *Proteae* (449)	39 (8.7)	196 (52.3)	158 (87.5)	35 (95.3)	8 (97.1)	3 (97.8)	2 (98.2)	2 (98.7)	1 (98.9)	5 (100.0)	0.25	1
Serratia spp. (485)	3 (0.6)	21 (4.9)	278 (62.3)	140 (91.1)	25 (96.3)	8 (97.9)	4 (98.8)	1 (99.0)	0 (99.0)	5 (100.0)	0.5	1

CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin/tazobactam; NS, non-susceptible.

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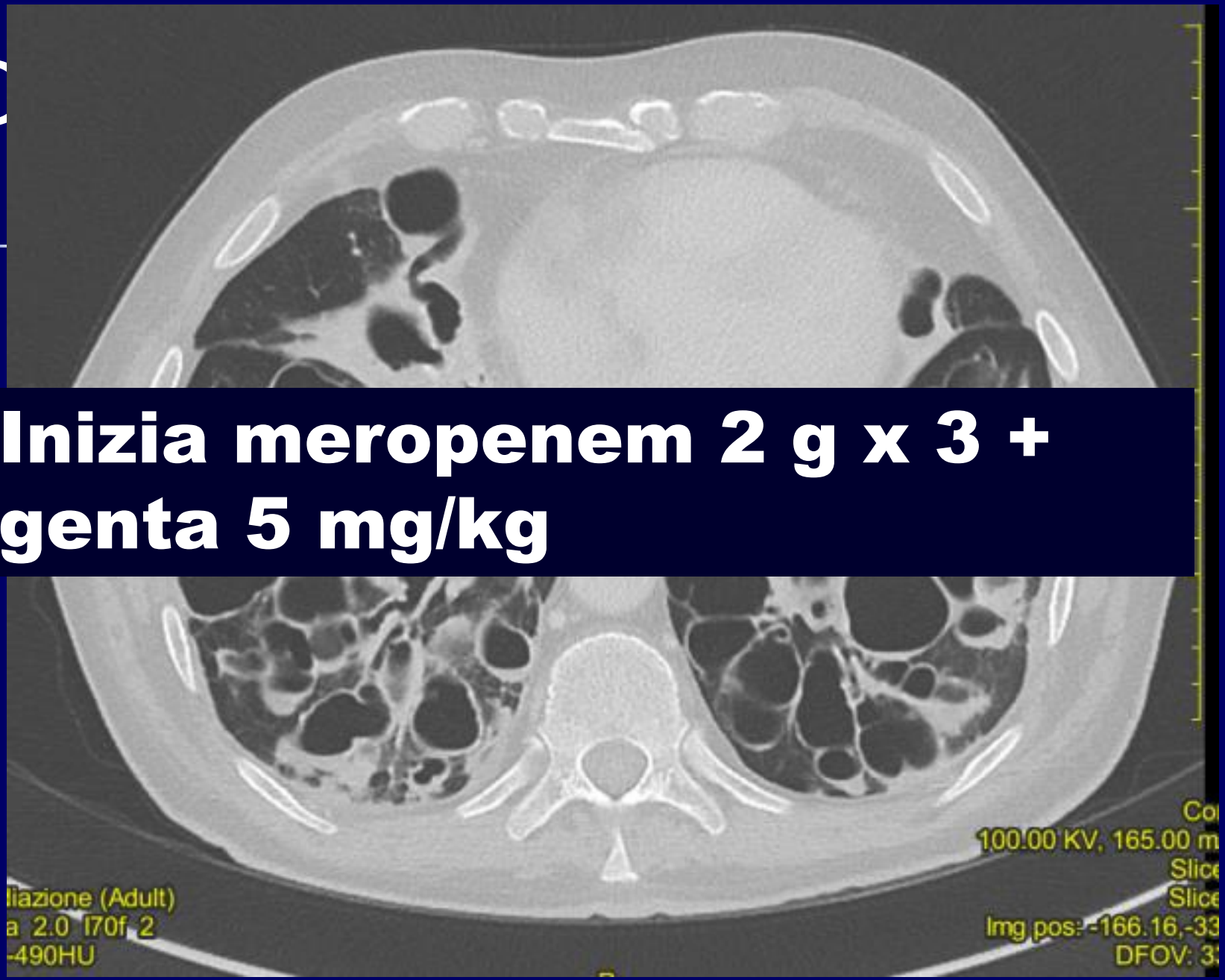
Inizia meropenem 2 g x 3 +
genta 5 mg/kg
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	Pseudomonas aeruginosa
Amikacina	**S**
Ciprofloxacina	**R**
Cefepime	**R**
Piperacillina/tazobactam	**R**
Ceftolozane/tazobactam	**S (1 mg/L)**
Ceppo mucoide 10.000 CFU	

Fallimento terapia con mem + genta → ceftolozane/tazobactam 3g x 3/die + amicacina, risposta clinica completa

E in prospettiva?

In vitro activity of cefiderocol (S-649266), a siderophore cephalosporin, against carbapenem-susceptible and resistant non-fermenting Gram-negative bacteria

P0187 Bonomo et al. ECCMID 2018

Species	Cefiderocol MICs (mg/L)							
	Meropenem susceptible				Meropenem resistant			
	N	Range	MIC_{50}	MIC_{90}	N	Range	MIC_{50}	MIC_{90}
A. baumannii and spp.	56	≤0.03-4	0.12	0.25	19	≤0.03-0.25	0.12	0.3
S. maltophilia	NA	-	-	-	25	≤0.03-0.25	0.06	0.3
P. aeruginosa	NA	-	-	-	19	≤0.03-1	0.25	1

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-Nonsusceptible Isolates (SIDERO-WT-2014 Study)

Meredith A. Hackel,[a] Masakatsu Tsuji,[b] Yoshinori Yamano,[c] Roger Echols,[d] James A. Karlowsky,[e] Daniel F. Sahm[a]

AAC, 2017

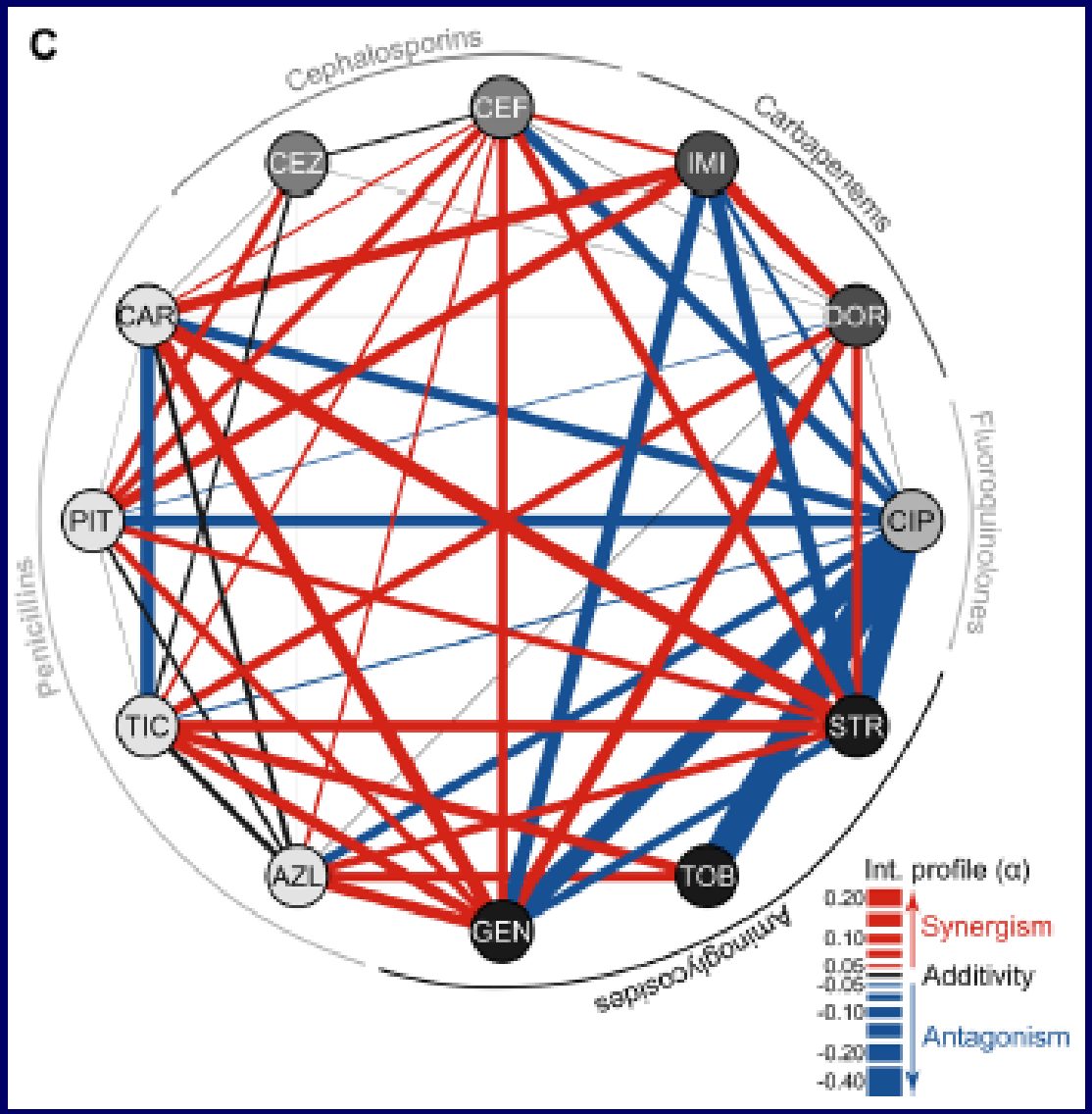
Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]			MIC interpretation[b]		
		Range	MIC_{50}	MIC_{90}	% susceptible	% intermediate	% resistant
Meropenem-nonsusceptible *Pseudomonas aeruginosa* (151)	Cefiderocol	≤0.002–4	0.06	0.5			
	Cefepime	1 to >64	8	32	53.6	21.9	24.5
	Ceftazidime-avibactam	0.5 to >64	4	8	90.7	0	9.3
	Ceftolozane-tazobactam	0.25 to >64	1	4	90.1	4.6	5.3
	Ciprofloxacin	≤0.12 to >8	2	>8	43.7	12.6	43.7
	Colistin	≤0.25–4	1	1	99.3	0.7	0
	Meropenem	4 to >64	8	16	0	30.5	69.5
Meropenem-nonsusceptible *Acinetobacter baumannii* (173)	Cefiderocol	≤0.002–8	0.25	1			
	Cefepime	4 to >64	32	>64	16.8	31.8	51.5
	Ceftazidime-avibactam	4 to >64	32	>64			
	Ceftolozane-tazobactam	0.5 to >64	16	>64			
	Ciprofloxacin	0.25 to >8	>8	>8	1.7	0	98.3
	Colistin	≤0.25 to >8	0.5	2	91.3	0	8.7
	Meropenem	4 to >64	64	>64	0	2.9	97.1

RESEARCH ARTICLE

Antibiotic combination efficacy (ACE) networks for a *Pseudomonas aeruginosa* model

Camilo Barbosa[1], Robert Beardmore[2], Hinrich Schulenburg[1]*, Gunther Jansen[1]*

PLOS Biology | https://doi.org/10.1371/journal.pbio.2004356 April 30, 2018



«Acinetobacter is a gram-negative coccobacillus that during the past three decades has emerged from an organism of questionable pathogenicity to an infectious agent of importance to hospitals worldwide»

NEJM, 2008

VAP-BSI

>lenght of hospital stay

A.baumannii

Emergent: A.pittii, A.ursingii

Isolamenti 2017 Acinetobacter

19 (vs 58 nel 2016)
4 da emo

molecola	n. resistenti	%
carbapenemi	**11/18**	**61.1**

Surveillance Cultures and Duration of Carriage of Multidrug-Resistant *Acinetobacter baumannii*[▽]

Dror Marchaim,[1]* Shiri Navon-Venezia,[1] David Schwartz,[2] Jalal Tarabeia,[1] Iris Fefer,[1] Mitchell J. Schwaber,[1] and Yehuda Carmeli[1]

JOURNAL OF CLINICAL MICROBIOLOGY, May 2007, p. 1551–1555

30 pazienti con precedente, remoto (≥ 6 mesi prima) isolato clinico di *A. baumannii* e nuovamente ricoverati nello stesso ospedale (TASMC)
5 pazienti positivi
Intervallo medio da isolato clinico 20 mm (range 8-42)

Evaluation of carriage and environmental contamination by carbapenem-resistant *Acinetobacter baumannii*

A. Nutman [1,2,*], A. Lerner [1], D. Schwartz [1], Y. Carmeli [1,2]

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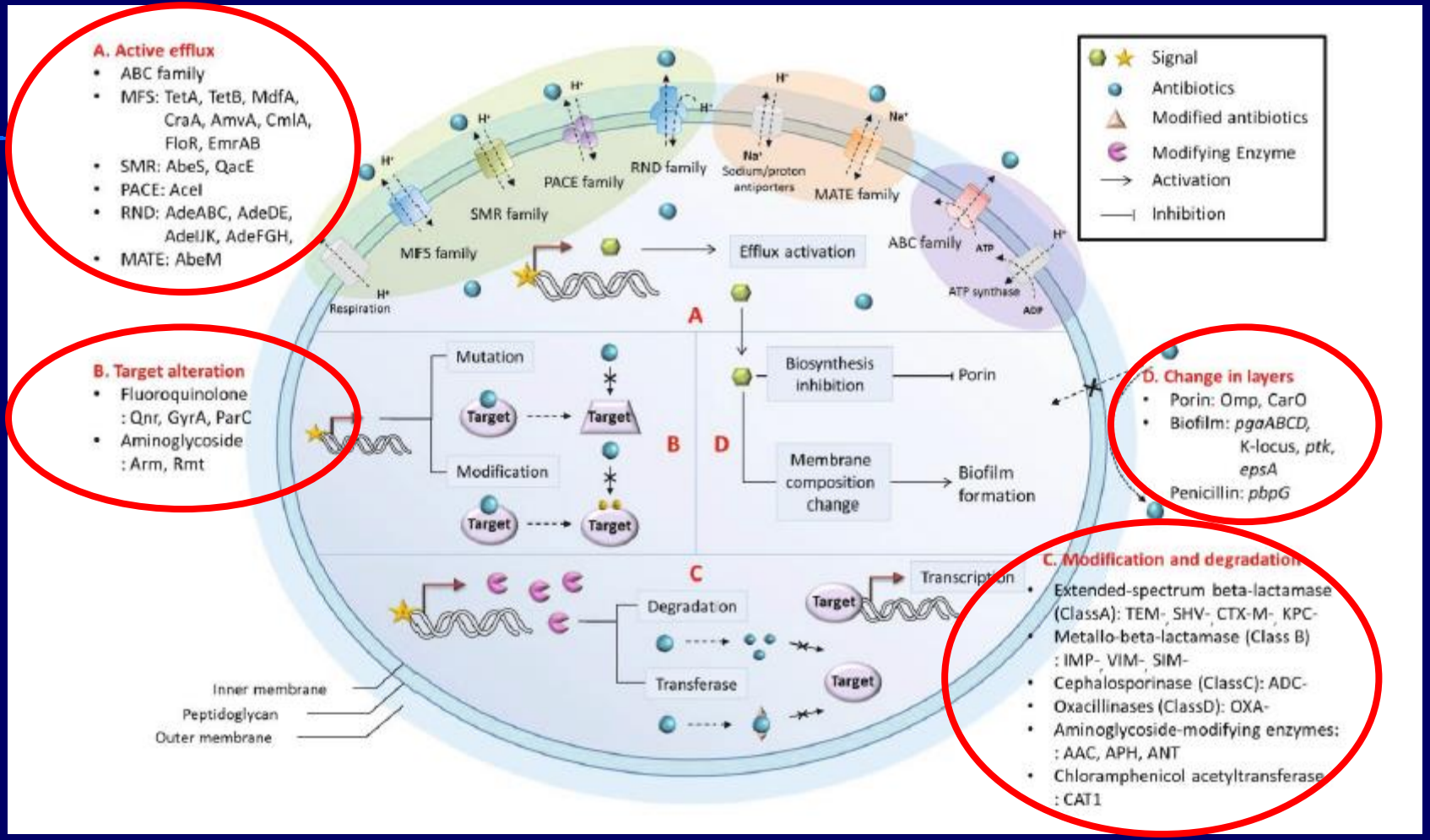
Table 2
Proportion of patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection who had CRAB detected in their immediate environment, by site

Surveillance site	Positive by direct inoculation or after enrichment	Positive by direct inoculation
	Positive sites/total sites tested, % (95% CI)	Positive sites/total sites tested, % (95% CI)
Sheet	31/34, 91.2 (76.3–98.1)	17/28, 60.7 (40.6–78.5)
Bedrail	30/34, 88.2 (72.5–96.7)	20/28, 71.4 (51.3–86.8)
Cabinet	14/24, 58.3 (36.6–77.9)	6/18, 33.3 (13.3–59)
Monitor	12/23, 52.2 (30.6–73.2)	4/21, 19 (5.4–41.9)
Ventilator	11/19, 57.9 (33.5–79.7)	5/17, 29.4 (10.3–56)
Feeding pump	18/24, 75 (53.3–90.2)	10/23, 43.5 (23.2–65.5)
Infusion pump	16/22, 72.7 (49.8–89.3)	9/21, 42.9 (21.8–66)
Any site	34/34, 100 (89.7–100)*	25/28, 89.3 (71.8–97.7)

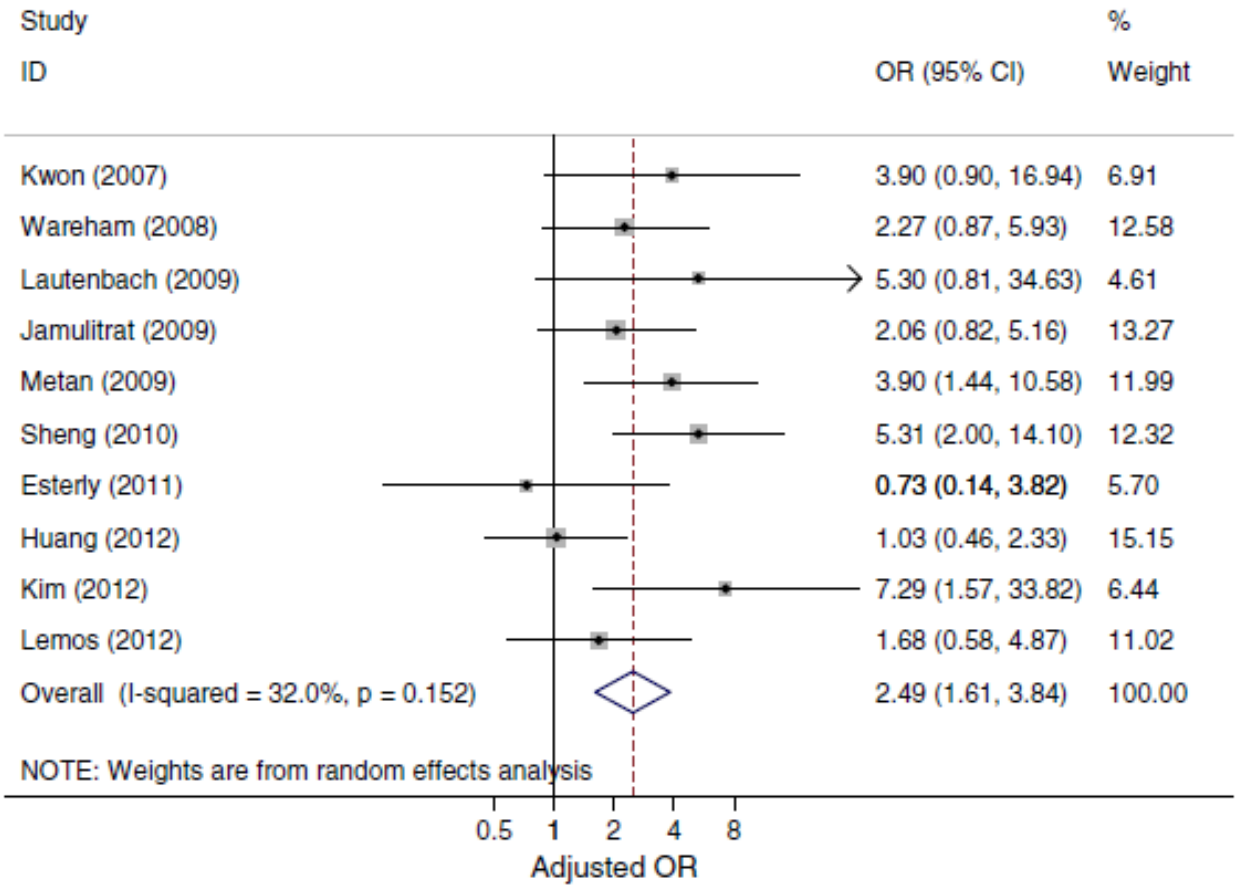
* One-sided 97.5% confidence interval.


A. Active efflux
• ABC family
• MFS: TetA, TetB, MdfA, CraA, AmvA, CmlA, FloR, EmrAB
• SMR: AbeS, QacE
• PACE: AceI
• RND: AdeABC, AdeDE, AdeIJK, AdeFGH,
• MATE: AbeM
B. Target alteration
• Fluoroquinolone : Qnr, GyrA, ParC
• Aminoglycoside : Arm, Rmt
C. Modification and degradation
• Extended-spectrum beta-lactamase (ClassA): TEM-, SHV-, CTX-M-, KPC-
• Metallo-beta-lactamase (Class B) : IMP-, VIM-, SIM-
• Cephalosporinase (ClassC): ADC-
• Oxacillinases (ClassD): OXA-
• Aminoglycoside-modifying enzymes: : AAC, APH, ANT
• Chloramphenicol acetyltransferase : CAT1
D. Change in layers
• Porin: Omp, CarO
• Biofilm: pgaABCD, K-locus, ptk, epsA
Penicillin: pbpG
Signal
Antibiotics
Modified antibiotics
Modifying Enzyme
Activation
Inhibition
PACE family
RND family
Sodium/proton antiporters
MATE family
SMR family
MFS family
ABC family
ATP
ATP synthase
ADP
Respiration
Efflux activation
A
Mutation
Target
Modification
B
D
Biosynthesis inhibition
Porin
Membrane composition change
Biofilm formation
C
Degradation
Transferase
Transcription
Inner membrane
Peptidoglycan
Outer membrane

Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis

E. V. Lemos[1,3], F. P. de la Hoz[2], T. R. Einarson[4], W. F. McGhan[1], E. Quevedo[3], C. Castañeda[2,3] and K. Kawai[5]

Clin Microbiol Infect 2014; **20:** 416–423



Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

Emanuele Durante-Mangoni,[1] Giuseppe Signoriello,[2] Roberto Andini,[1] Annunziata Mattei,[3] Maria De Cristoforo,[4] Patrizia Murino,[3] Matteo Bassetti,[5,a] Paolo Malacarne,[6] Nicola Petrosillo,[7] Nicola Galdieri,[3] Paola Mocavero,[3] Antonio Corcione,[3] Claudio Viscoli,[5] Raffaele Zarrilli,[8] Ciro Gallo,[2] and Riccardo Utili[1]

Clinical Infectious Diseases 2013;57(3):349–58

Table 2. Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .

Table 4. Comparisons of treatment failure among different anti-CRAB strategies in patients with CRAB pneumonia

Treatment	Failure [a] (N = 154)	Success [a] (N = 84)	*P* value	Adjusted OR (95% CI) [b]	*P* value
Tigecycline-based vs non-tigecycline					
Non-tigecycline therapy (ref)	40 (50.6)	39 (49.4)		(ref)	
Tigecycline-based therapy	114 (71.7)	45 (28.3)	**0.002**	2.51 (1.39-4.54)	**0.002**
Tigecycline monotherapy vs tigecycline combination					
Tigecycline combination [c] (ref)	50 (66.7)	25 (33.3)		(ref)	
Tigecycline monotherapy	64 (76.2)	20 (23.8)	0.218	1.51 (0.73-3.13)	0.268
Colistin-based vs non-colistin					
Non-colistin therapy (ref)	92 (71.9)	36 (28.1)		(ref)	
Colistin-based therapy	62 (56.4)	48 (43.6)	**0.015**	0.48 (0.27-0.86)	**0.013**
Colistin monotherapy vs colistin combination					
Colistin combination [c] (ref)	44 (57.9)	32 (42.1)		(ref)	
Colistin monotherapy	18 (52.9)	16 (47.1)	0.680	1.07 (0.42-2.73)	0.890
Anti-CRAB strategies vs tigecycline monotherapy					
Tigecycline monotherapy (ref)	64 (76.2)	20 (23.8)	**0.009**	(ref)	
Tigecycline combination [d]	24 (75.0)	8 (25.0)		1.06 (0.39-2.88)	0.912
Tigecycline with colistin	26 (60.5)	17 (39.5)		0.44 (0.19-1.04)	0.060
Colistin combination [e]	18 (54.5)	15 (45.5)		0.34 (0.14-0.85)	**0.020**
Colistin monotherapy	18 (52.9)	16 (47.1)		0.39 (0.16-0.95)	**0.038**
Sulbactam-based therapy [f]	4 (33.3)	8 (66.7)		0.14 (0.04-0.55)	**0.005**

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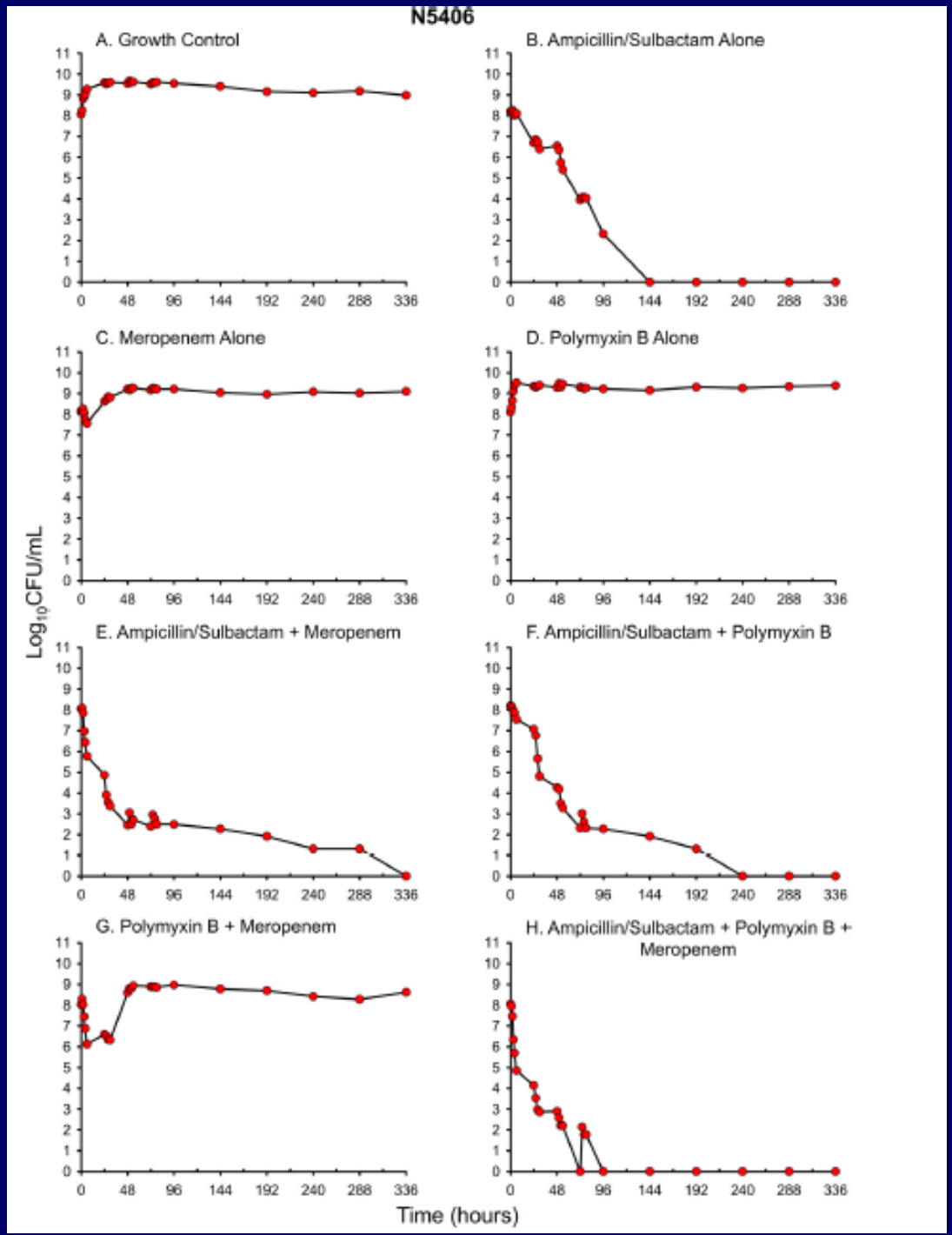
- A

The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii*

T. Amat [1,*], A. Gutiérrez-Pizarraya [2], I. Machuca [1], I. Gracia-Ahufinger [1], E. Pérez-Nadales [1], Á. Torre-Giménez [4], J. Garnacho-Montero [3], J.M. Cisneros [2], J. Torre-Cisneros [1]

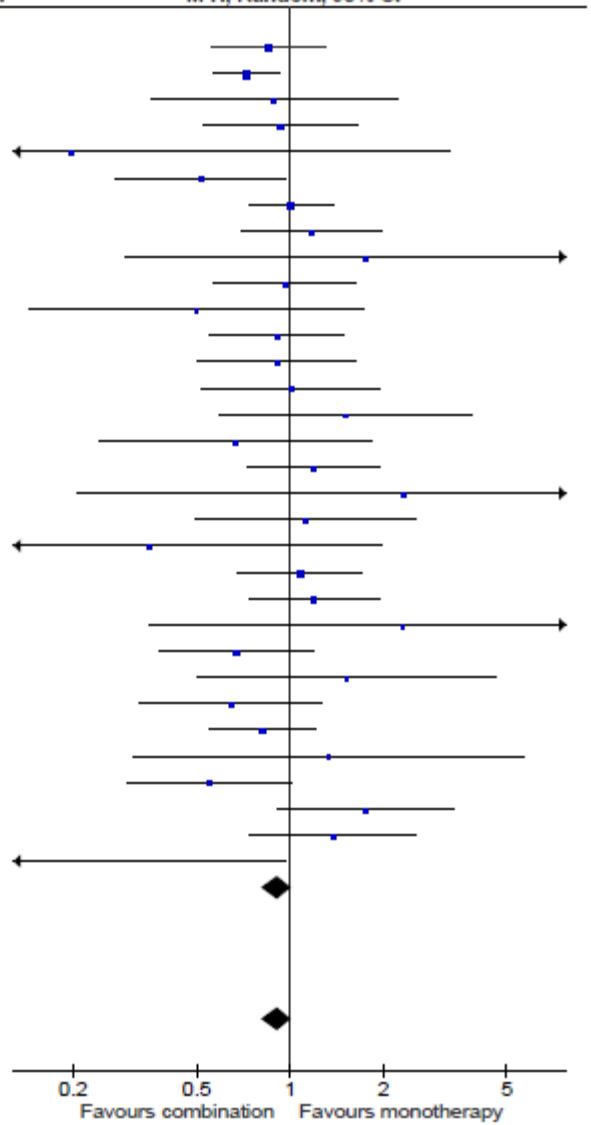
Table 2
Univariate and multivariate Cox regression analysis of the association between different variables and 30-day mortality

Variables	Death ($n = 71$)	Survivors ($n = 47$)	*Univariate analysis*		*Multivariable model*	
			p	HR (95% CI)	p	HR (95% CI)
Demographic variables						
Age (years), mean ± SD	59 ± 14	54 ± 16	0.059	1.02 (0.99–1.03)		
Sex (male)	46 (65%)	28 (60%)	0.632	0.89 (0.55–1.46)		
Patient origin at ICU admission:						
From community	18 (25%)	19 (40%)		Baseline		
From hospital	53 (74%)	28 (60%)	0.302	1.33 (0.78–2.27)		
Previous admission to ICU	6 (8%)	6 (13%)	0.404	0.71 (0.30–1.62)		
Surgery before bacteraemia	12 (16%)	14 (27%)	0.869	0.95 (0.51–1.77)		
APACHE II score, mean ± SD	25 ± 6	22 ± 9	0.088	1.03 (0.99–1.06)		
Charlson Index, mean ± SD	3 ± 2	2 ± 1.6	0.002	1.20 (1.07–1.35)	0.028	1.16 (1.02–1.32)
Source of bacteraemia:						
Primary	13 (18%)	8 (17%)	0.212	0.68 (0.37–1.25)		
Secondary:	58 (82%)	39 (83%)				
+Ventilator-associated pneumonia	49 (69%)	27 (57%)	0.640	1.13 (0.68–0.87)		
+Other foci[a]	8 (11%)	8 (17%)	0.170	0.59 (0.29–1.25)		
Septic shock	47 (66%)	32 (68%)	0.198	1.38 (0.84–2.26)		
Previous use of carbapenems	60 (85%)	41 (87%)	0.878	1.05 (0.55–2.00)		
Empirical therapy with colistin	37 (52%)	11 (23%)	0.003	2.05 (1.28–3.27)	0.003	2.25 (1.33–3.80)
Targeted therapy:						
Monotherapy (colistin)	47 (66%)	29 (62%)		Reference		
Combined therapy (colistin + tigecycline)	24 (34%)	18 (38%)	0.832	1.06 (0.64–1.73)	0.494	1.29 (0.64–2.58)
Renal dysfunction before treatment	24 (34%)	13 (28%)	0.045	1.66 (1.01–2.74)	0.045	1.91 (1.01–3.61)
Propensity score for combined therapy			0.983	0.99 (0.46–2.14)	0.494	0.65 (0.19–2.25)


N5406
A. Growth Control
B. Ampicillin/Sulbactam Alone
C. Meropenem Alone
D. Polymyxin B Alone
E. Ampicillin/Sulbactam + Meropenem
F. Ampicillin/Sulbactam + Polymyxin B
G. Polymyxin B + Meropenem
H. Ampicillin/Sulbactam + Polymyxin B + Meropenem
Log10CFU/mL
Time (hours)
0 48 96 144 192 240 288 336
0 1 2 3 4 5 6 7 8 9 10 11

Intravenous colistin combination antimicrobial tre… rev…

Study or Subgroup	Combination Events	Total	Monotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Retrospective						
Aydemir et al. 2013	13	21	16	22	5.9%	0.85 [0.56, 1.30]
Batirel et al 2014	112	214	26	36	14.1%	0.72 [0.57, 0.92]
Capone et al 2013	12	37	4	11	1.4%	0.89 [0.36, 2.21]
Chuang et al 2014	7	15	52	104	3.4%	0.93 [0.53, 1.66]
Daikos et al. 2009	0	8	4	15	0.2%	0.20 [0.01, 3.27]
Daikos et al. 2014	11	39	12	22	2.9%	0.52 [0.28, 0.97]
Durante-Mangoni et al 2013	45	104	45	105	9.7%	1.01 [0.74, 1.38]
Falagas et al 2009	78	218	11	36	4.1%	1.17 [0.69, 1.98]
Falagas et al. 2008	7	16	1	4	0.4%	1.75 [0.29, 10.44]
Garnacho-Montero et al 2013	14	29	14	28	4.0%	0.97 [0.57, 1.64]
Hernadez-Torres et al. 2011	5	20	2	4	0.8%	0.50 [0.14, 1.73]
Jang et al 2009	11	19	14	22	4.5%	0.91 [0.55, 1.50]
Kontopidou et al. 2013	13	31	12	26	3.3%	0.91 [0.51, 1.63]
Ku et al.2012	7	19	26	71	2.6%	1.01 [0.52, 1.95]
Lim et al 2011	5	11	6	20	1.4%	1.52 [0.60, 3.84]
Lopez-Cortes et al 2014	4	23	12	46	1.2%	0.67 [0.24, 1.84]
Mouloudi et al. 2010	11	18	18	35	4.6%	1.19 [0.73, 1.94]
Navarro et al. 2012	10	17	0	1	0.2%	2.33 [0.21, 26.56]
Ozvatan et al. 2015	50	89	3	6	1.8%	1.12 [0.49, 2.55]
Papadimitriou et al. 2014	3	17	1	2	0.4%	0.35 [0.06, 1.98]
Parchem et al. 2016	19	41	21	49	5.1%	1.08 [0.68, 1.72]
Petrosillo et al 2014	35	105	17	61	4.6%	1.20 [0.74, 1.94]
Pintado et al 2008	15	52	1	8	0.3%	2.31 [0.35, 15.16]
Porwal et al 2014	13	29	8	12	3.5%	0.67 [0.38, 1.19]
Samonis et al. 2014	4	7	3	8	1.0%	1.52 [0.51, 4.58]
Simsek et al 2012	10	31	10	20	2.6%	0.65 [0.33, 1.26]
Sirijatuphat et al 2014	22	47	27	47	6.7%	0.81 [0.55, 1.21]
Souli et al 2008	8	12	1	2	0.6%	1.33 [0.32, 5.64]
Tumbarello et al 2012	14	51	11	22	3.1%	0.55 [0.30, 1.01]
Vardakas et al. 2014	26	37	6	15	2.7%	1.76 [0.91, 3.38]
Yilmaz et al 2015	30	53	7	17	3.0%	1.37 [0.74, 2.54]
Zarkotou et al. 2011	0	14	4	7	0.2%	0.06 [0.00, 0.97]
Subtotal (95% CI)		1444		884	100.0%	0.91 [0.82, 1.02]
Total events	614		395			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 33.68$, df = 31 (P = 0.34); $I^2 = 8\%$						
Test for overall effect: Z = 1.63 (P = 0.10)						
Total (95% CI)		1444		884	100.0%	0.91 [0.82, 1.02]
Total events	614		395			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 33.68$, df = 31 (P = 0.34); $I^2 = 8\%$						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Not applicable						



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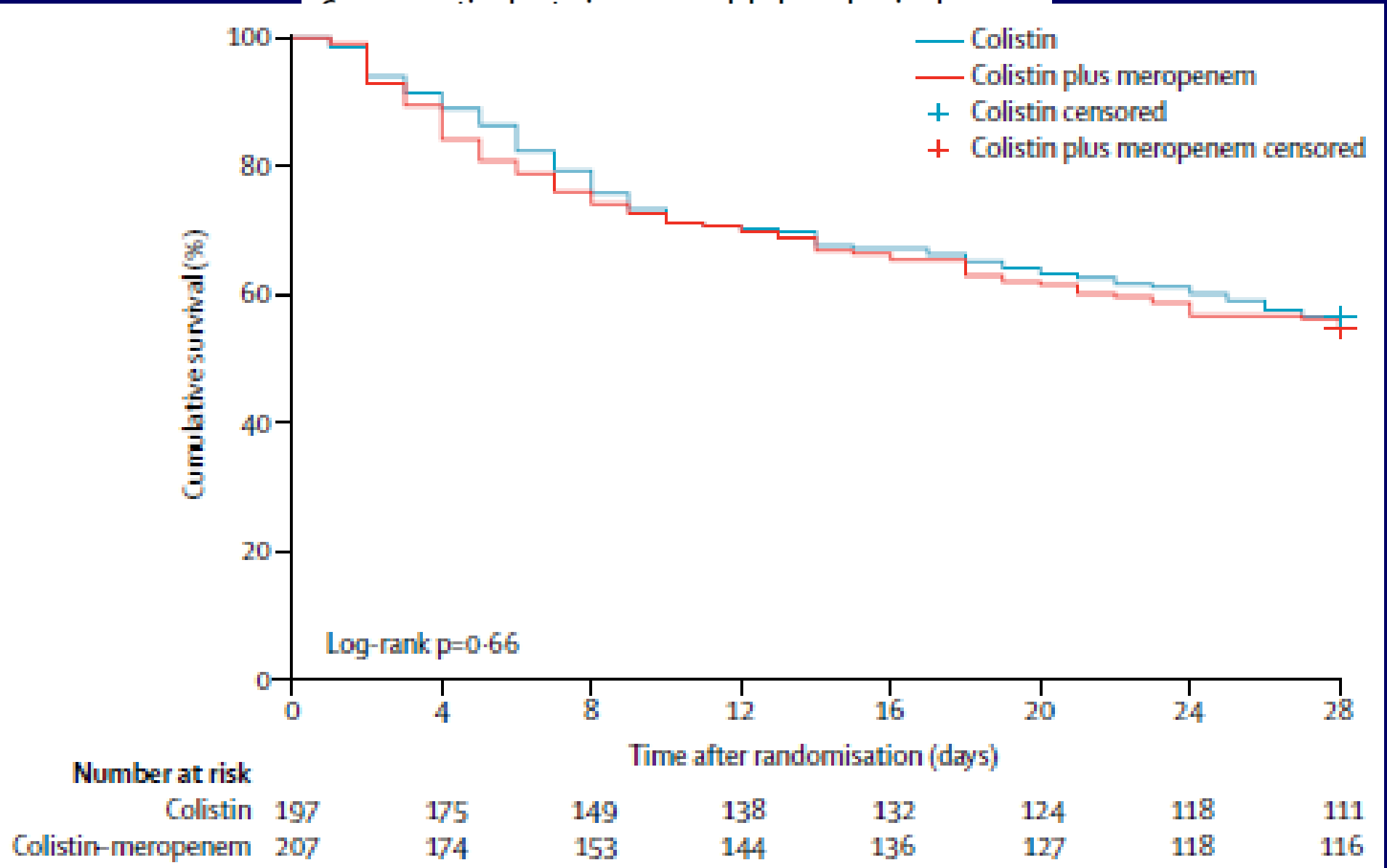
Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant



Number at risk								
Colistin	197	175	149	138	132	124	118	111
Colistin–meropenem	207	174	153	144	136	127	118	116

Accepted Manuscript

Title: *In-vitro* activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*

Author: Harald Seifert, Danuta Stefanik, Joyce A. Sutcliffe, Paul G. Higgins

PII: S0924-8579(17)30271-6
DOI: http://dx.doi.org/doi: 10.1016/j.ijantimicag.2017.06.022

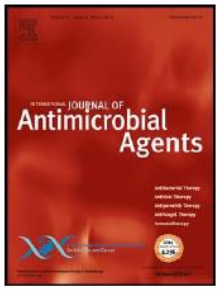


Table 1: MIC distributions, MIC_{50} and MIC_{90} values and antimicrobial susceptibilities of 286 carbapenem-resistant *A. baumannii* isolates

Antimicrobial Agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128	MIC_{50}	MIC_{90}	MIC Range	%S	%I	%R
Amikacin				4	11	11	11	3	**15**[a]	11	32	188	≥128	≥128	0.5 - ≥128	19.2	3.9	76.9
Sulbactam[b]						3	12	39	79	114	35	4	32	64	2 - ≥128	-	-	-
Colistin				1	51	149	**47**[a]	12	11	2	1	2	10	1	4	0.125 - ≥128	86.7	-	13.3
Doxycycline	3	7	7	13	33	21	**5**[a]	4	10	61	122[c]		32	≥64	≤0.06 - ≥64	67.5	1.4	31.1
Eravacycline[b]	11	20	45	147	53	9		1					0.5	1	≤0.06 - 8	-	-	-
Imipenem						**0**[a]	2	9	66	161	43	5	32	64	4 - 128	0.0	0.7	99.3
Levofloxacin				1		1	**5**[a]	32	87	127	15	13	5	16	32	0.25 - ≥128	2.4	11.2	86.4
Meropenem						**1**[a]	2	18	36	88	106	35	32	128	2 - ≥128	0.3	0.7	99.0
Minocycline	10	5	12	37	33	21	**66**[a]	74	28				4	8	≤0.06 - 16	64.3	25.9	9.8
Tigecycline[b]		3	23	42	140	59	18	1					1	2	0.125 - 8	-	-	-
Tobramycin		2	23	38	15	5	**4**[a]	11	18	26	6	138	64	≥128	0.125 - ≥128	30.4	3.8	65.8

[a] susceptible breakpoint values are indicated in boldface; [b] no CLSI breakpoint available; [c] ≥ 64 mg/L;

Considerazioni conclusive

- Mancanza di RCTs
- Pseudo: ceppi MDR ceftolozano/tzb o ceftazidime/AVB, in prospettiva cefiderocol
- MBL colistina HD, in prospettiva aztreonam/AVB
- Acineto MDR: colistina HD, non necessaria Tige, meglio AMP/SULB
- In prospettica cefiderocol, eravaciclina
- Prevenire colonizzazioni: sorveglianza!

Grazie per l'attenzione!