25° Meeting GiViTI

19-20-21 Ottobre 2016

Baia Flaminia Resort, Pesaro

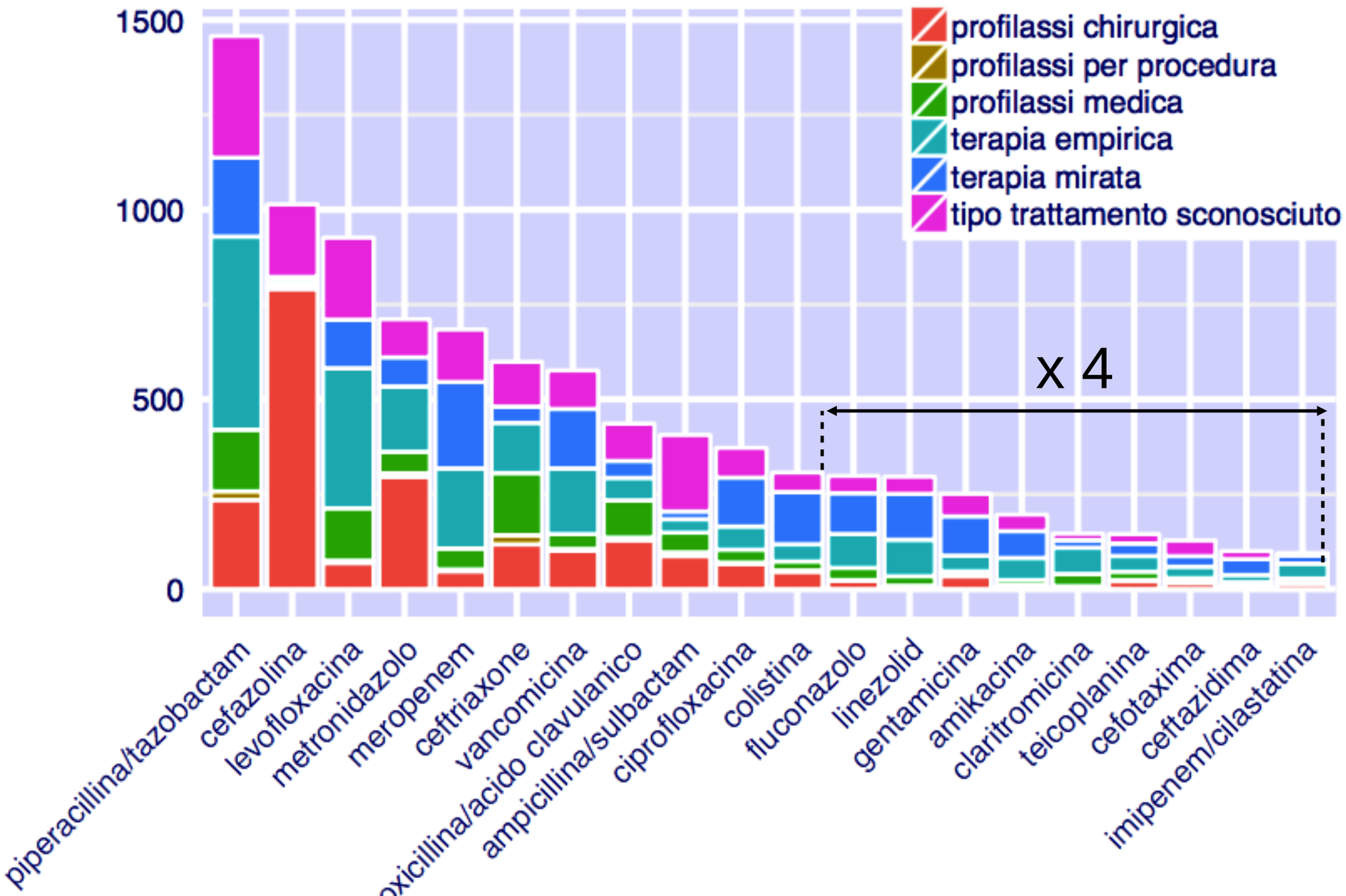
La scelta dell'antibiotico-terapia empirica e mirata guardando ai dati di MargheritaTre: dalla pratica alla teoria e ritorno, passando per nuovi farmaci e nuove tecnologie di diagnostica rapida

Bruno Viaggi
Dipartimento di Anestesia
NeuroAnestesia e Rianimazione
CTO AOU Careggi, Firenze

Stefano Finazzi
Laboratorio di Epidemiologia Clinica
IRCCS-IRFMN

Gian Maria Rossolini
Dip. Medicina Sperimentale e Clinica
Università di Firenze
Dip. Biotecnologie Mediche
Università di Siena
SODc Microbiologia e Virologia
A.O.U. Careggi, Firenze

Martin Langer
Dip. di Anestesia Rianimazione e Cure Palliative
SC Anestesia e Rianimazione
IRCCS Istituto Nazionale dei Tumori
Scuola Specializzazione Anestesia Rianimazione
Università di Milano


1500
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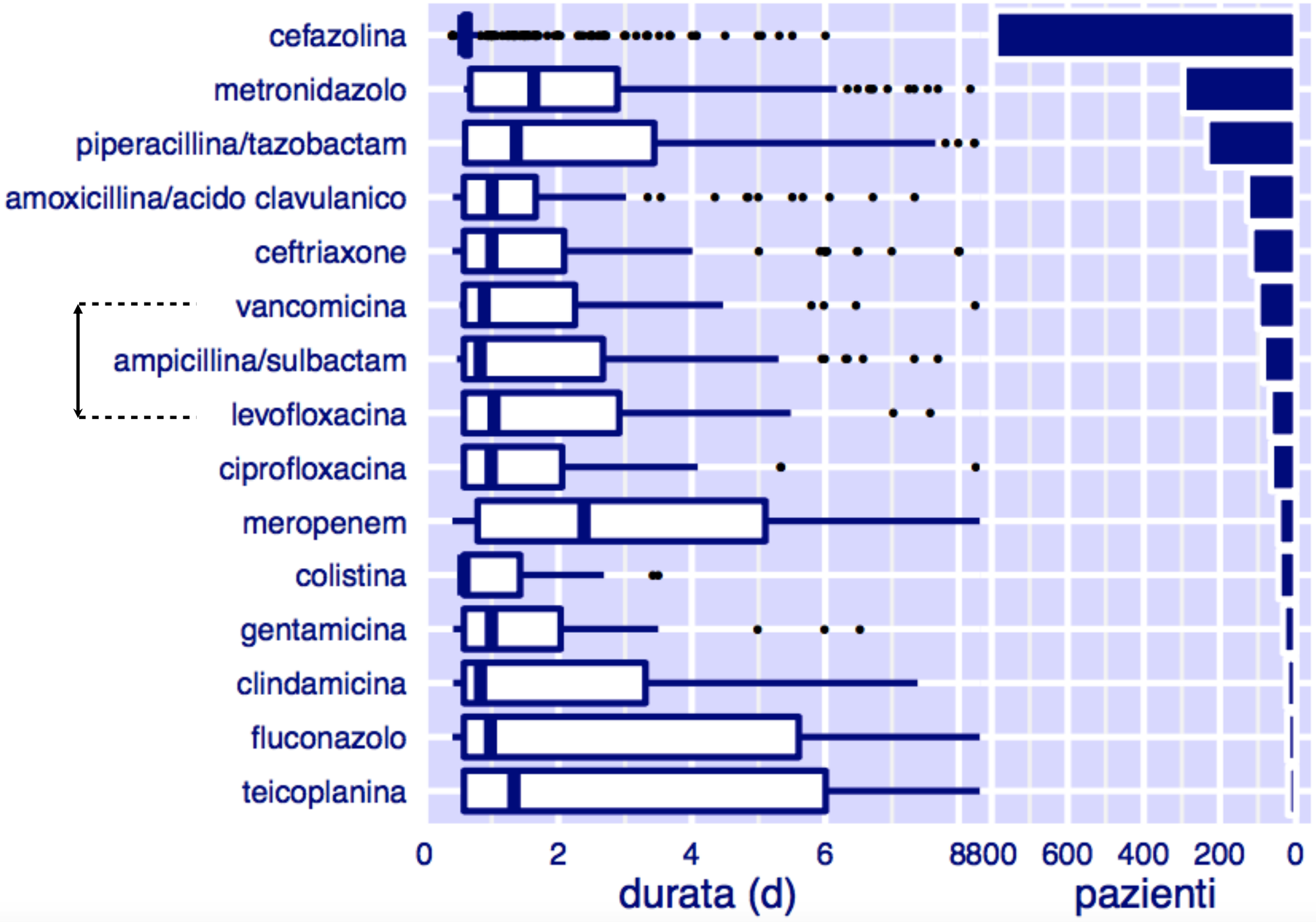
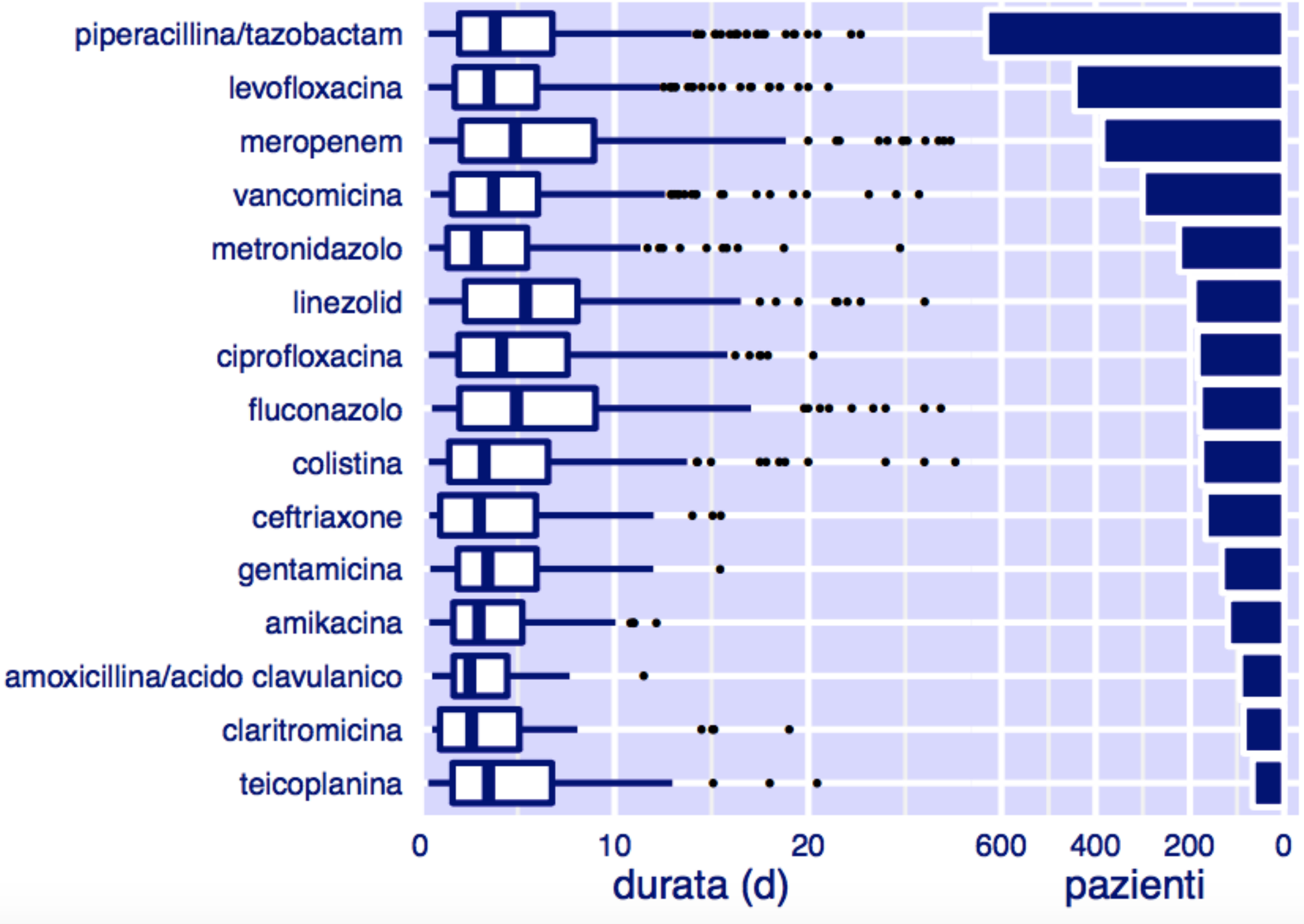
profilassi chirurgica
profilassi per procedura
profilassi medica
terapia empirica
terapia mirata
tipo trattamento sconosciuto
x 4
piperacillina/tazobactam
cefazolina
levofloxacina
metronidazolo
meropenem
ceftriaxone
vancomicina
amoxicillina/acido clavulanico
ampicillina/sulbactam
ciprofloxacina
colistina
fluconazolo
linezolid
gentamicina
amikacina
claritromicina
teicoplanina
cefotaxima
ceftazidima
imipenem/cilastatina

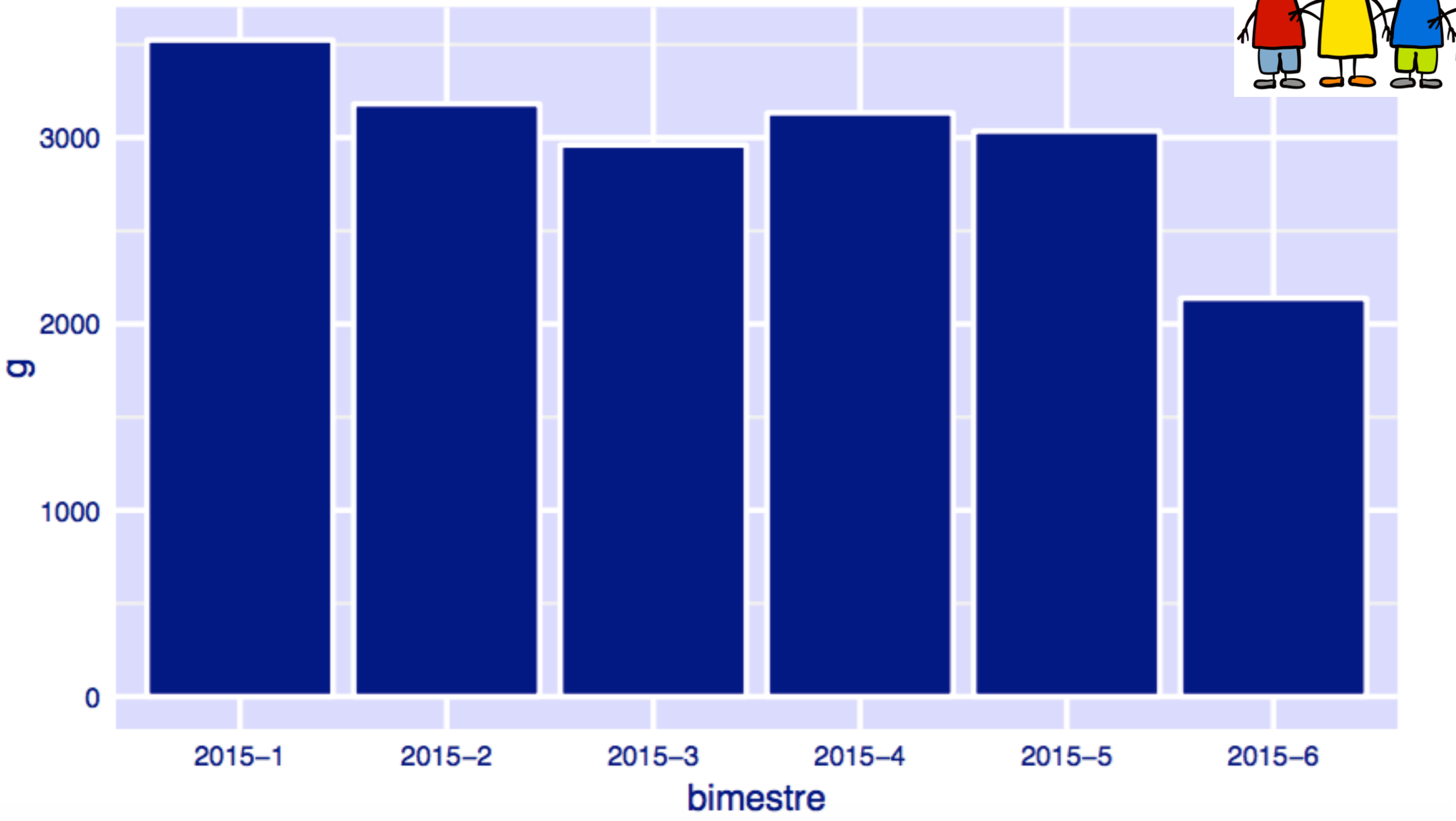
Profilassi chirurgiche



Frequenza durata terapia



Consumo Meropenem



- Global dissemination
- Hospital-, but also community-acquired infections
- Dissemination in long-term care facilities and nursing homes

Doi et al - Clin Infect Dis 2013
Rooney et al - J Antimicrob Chemother 2009
Dhanji et al -J Antimicrob Chemother 2011

The domino effect of the ESBL epidemic

Dissemination of Enterics producing ESBLs

Carbapenem overuse

Dissemination of CRAb and CRE

Dissemination of CPE

Further Carbapenem overuse

Colistin overuse

Dissemination of Colistin-R strains

SURVEILLANCE AND OUTBREAK REPORTS

Epidemic diffusion of KPC carbapenemase-producing *Klebsiella pneumoniae* in Italy: results of the first countrywide survey, 15 May to 30 June 2011

22.4%

RAPID COMMUNICATIONS

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

43%

Figura 3.16 - *K. pneumoniae*: percentuale (%) di isolati resistenti alla Colistina nei territori delle Aziende sanitarie toscane (Toscana, 2014 - valore medio regionale: 16%).

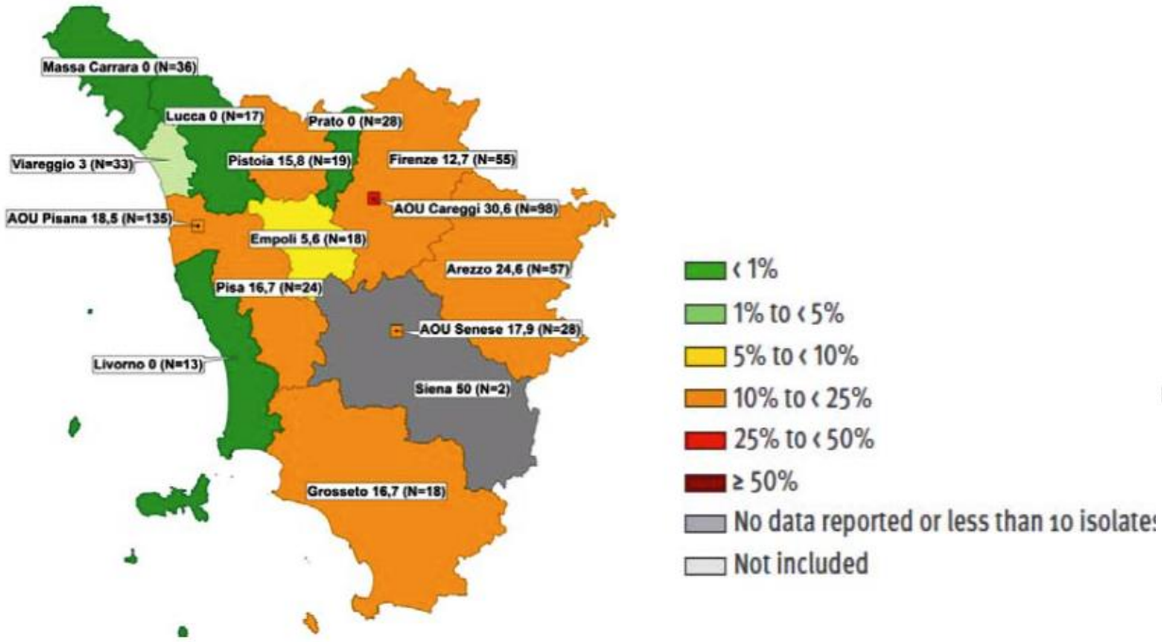
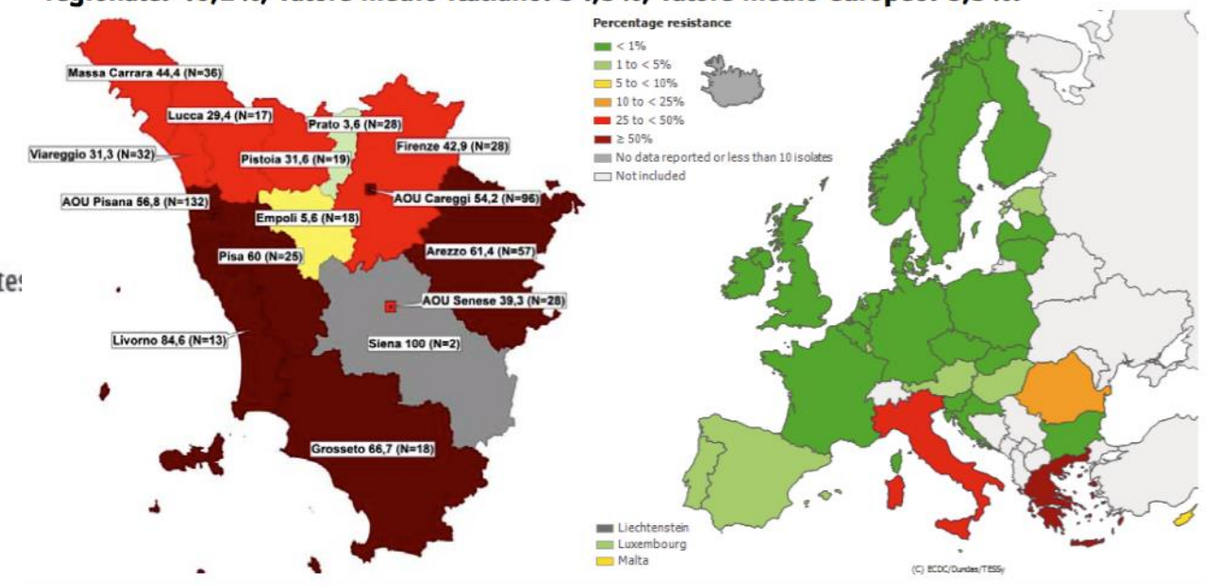


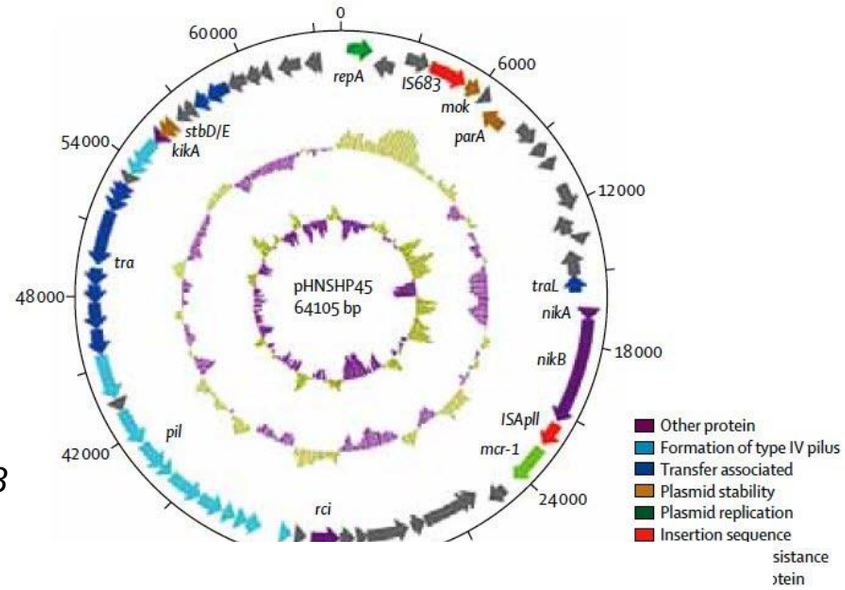
Figura 3.14 - *K. pneumoniae*: percentuale (%) di isolati resistenti ai carbapenemi nei territori delle Aziende sanitarie toscane (Toscana, 2014) e nei paesi europei (2013) - valore medio regionale: 46,2%; valore medio italiano: 34,3%; valore medio europeo: 8,3%.



Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS†, Yang Wang, PhD†, Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren, BS, Xiaojie Chen, MS, Luchao Lv, MS, Dandan He, MS, Hongwei Zhou, PhD, Prof Zisen Liang, MS, Prof Jian-Hua Liu, PhD, Prof Jianzhong Shen, PhD

Lancet 2016;2:161-168



Correspondence

Dissemination of the *mcr-1* colistin resistance gene

Maris S Arcilla†, Jarne M van Hattem†, Sebastien Matamoros, Damian C Melles, John Penders, Menno D de Jong, Constance Schultsz for the COMBAT consortium‡

Lancet Infect Dis 2016;16(2):147-149

mcr-1.2, a New *mcr* Variant Carried on a Transferable Plasmid from a Colistin-Resistant KPC Carbapenemase-Producing *Klebsiella pneumoniae* Strain of Sequence Type 512

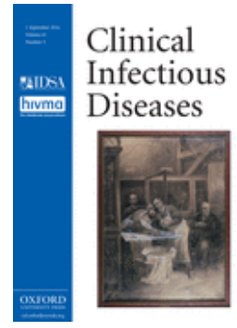
Antimicrob Agents Chemother 2016; 60(9):5612-561

Vincenzo Di Pilato,[a] Fabio Arena,[b] Carlo Tascini,[c] Antonio Cannatelli,[b] Lucia Henrici De Angelis,[b] Simona Fortunato,[c] Tommaso Giani,[b] Francesco Menichetti,[c] Gian Maria Rossolini[b,d,e,f]

Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Maria Josephine Mura Ondok,[1] Adriana Mosca,[2] Rosa Monno,[3] Sara Coppolecchia,[1] Maria Luigia Spada,[1] Francesco Bruno,[1] and Nicola Brienza[1]

Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]



Clin Infect Dis 2015;61:1771-7

Conclusions: Our study shows that in severely ill patients receiving colistin according to CrCl-driven dosing approach, the high-dose, extended-interval CMS regimen may predict efficacy, without significant renal toxicity

negative bacteria, the high-dose, extended-interval CMS regimen may predict efficacy, without significant renal toxicity administration of ascorbic acid markedly reduces AKI risk, allowing safer use of colistin

Clin Infect Dis 2012;54:1720-6

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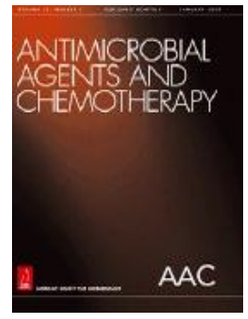
Influence of Colistin Dose on Global Cure in Patients with Bacteremia Due to Carbapenem-Resistant Gram-Negative Bacilli

Gabrielle A. Gibson,* Seth R. Bauer, Elizabeth A. Neuner, Stephanie N. Bass, Simon W. Lam

Department of Pharmacy, Cleveland Clinic, Cleveland, Ohio, USA



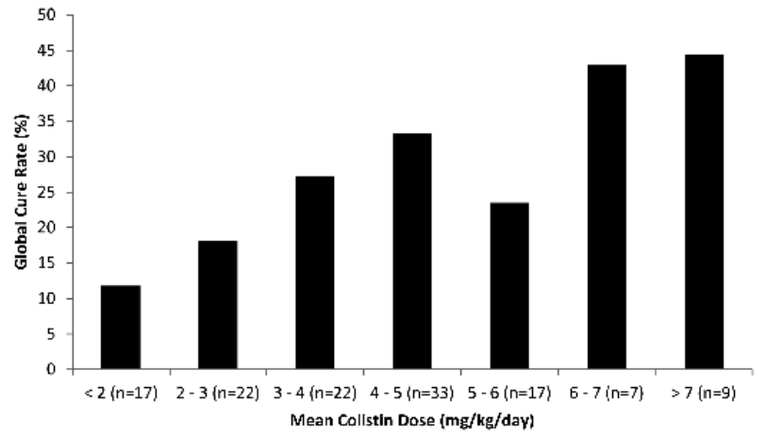
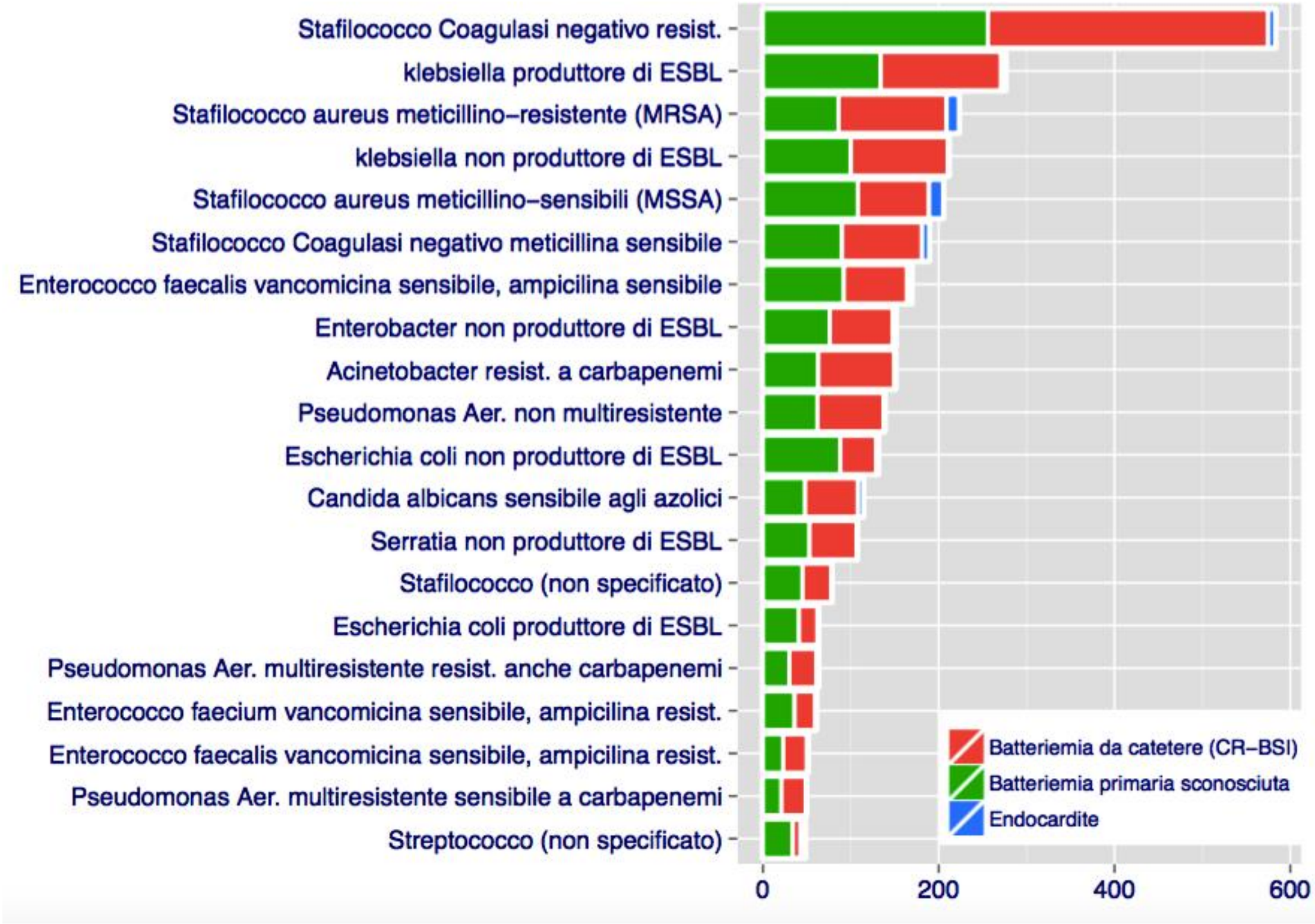


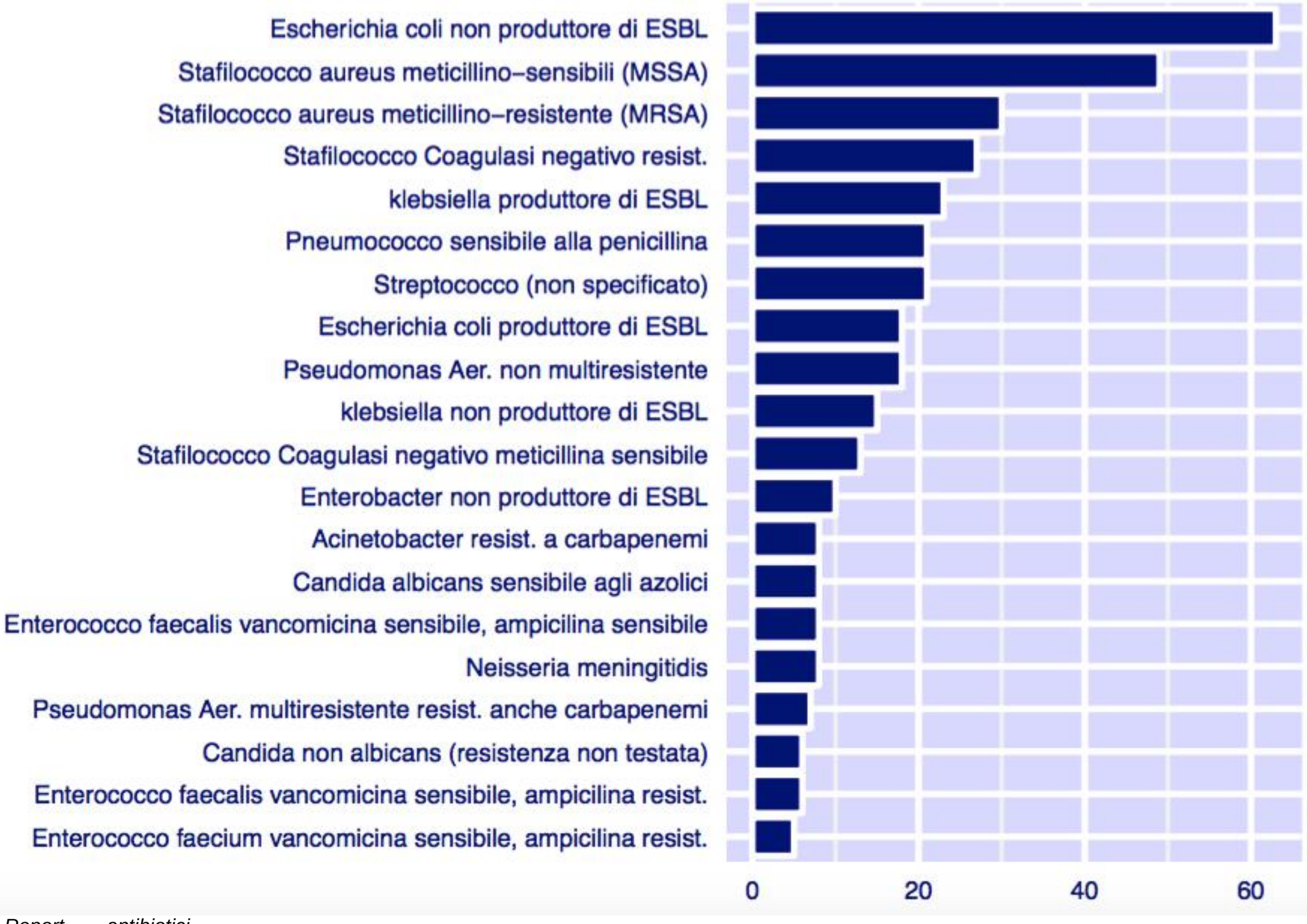
FIG 1 Day 7 global cure rates versus average daily colistin doses ($P = 0.035$; Mantel-Haenszel chi-square test).

Antimicrob Agents Chemother 2016;60(1):431-436

Germi BSI/Endocarditi degenza



Germi BSI/Endocarditi degenza



Nei CoNS la MR non sempre si correlata al gene mecA ed è specie dipendente

TABLE 1. Correlation between the oxacillin MIC and the presence of the *mecA* gene

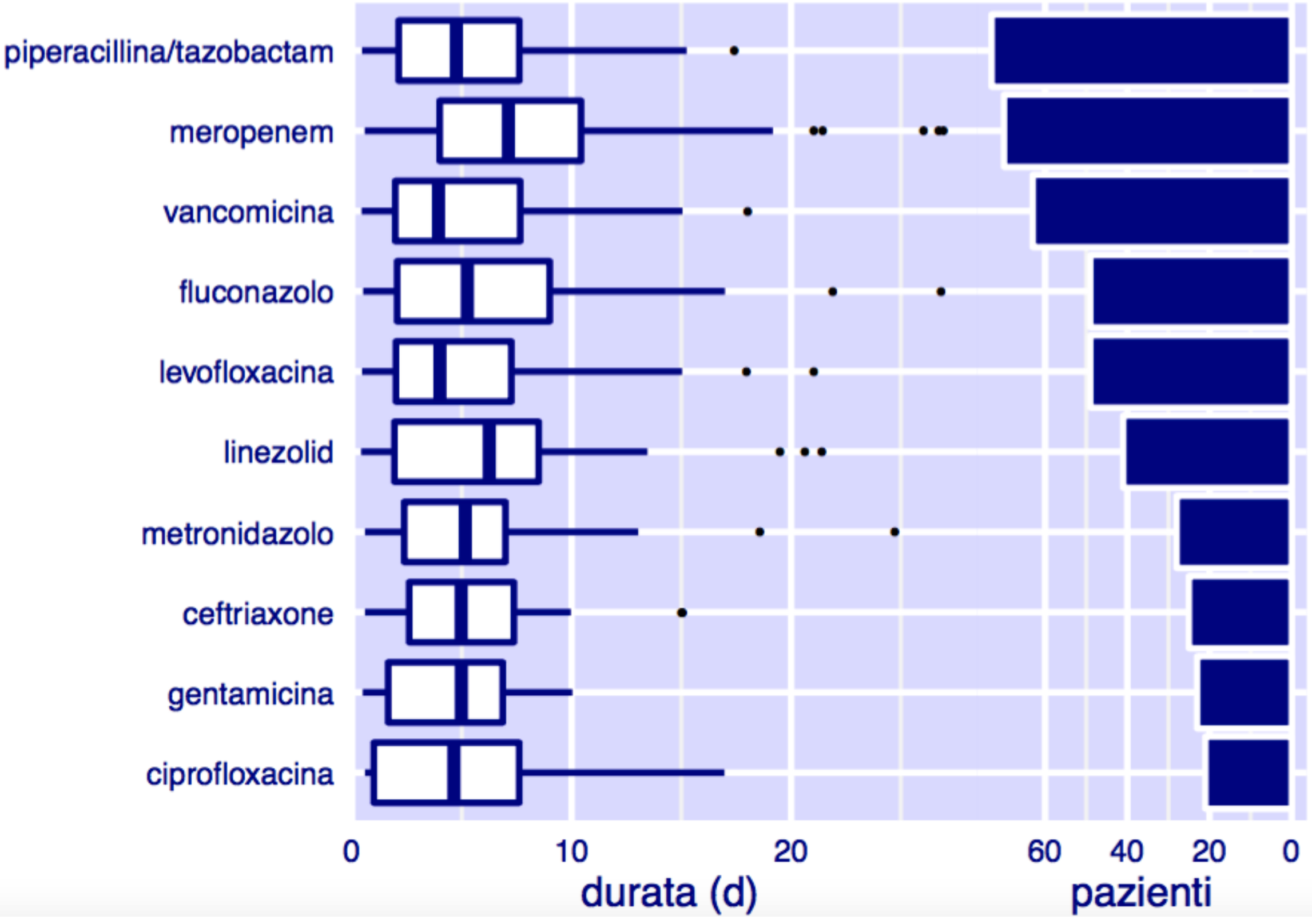
Category and species	Presence (+) or absence (−) of *mecA*	Total no. of strains tested	No. of strains for which the MIC was:						
			0.125	0.25	0.5	1	2	4.0	>4.0
I									
S. epidermidis	−	101	101	0	0	0	0	0	0
	+	164	0	0	5	6	6	19	128
S. hominis	−	41	41	0	0	0	0	0	0
	+	44	0	0	2	3	3	6	30
S. haemolyticus	−	5	5	0	0	0	0	0	0
	+	25	0	0	0	0	0	0	25

il gene mecA correla con MIC ≥ 0,5 mg/L

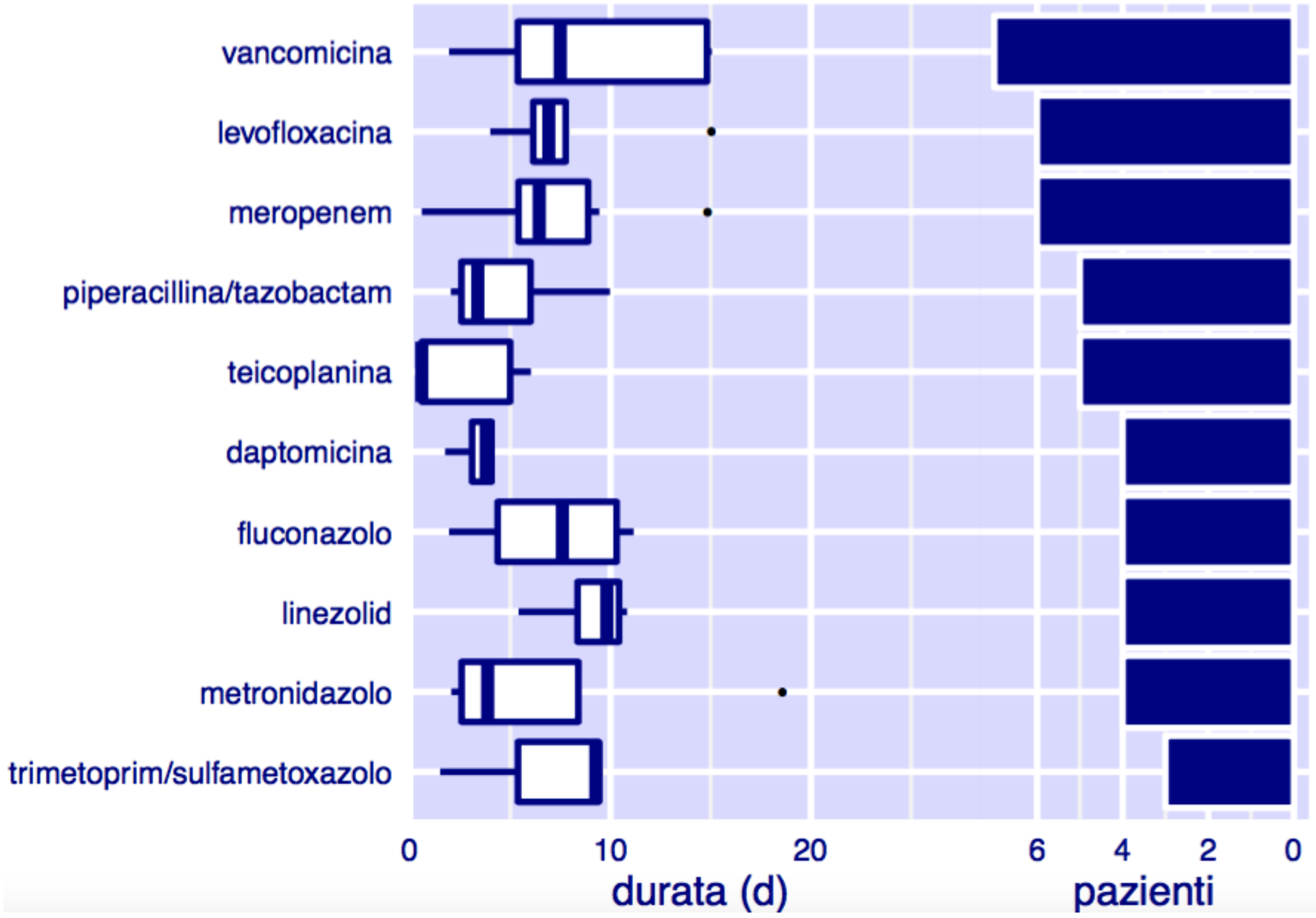
2015 - Anno

Antibiotico	N.sagg.	%R	%I	%S	N.sagg.	%R	%I	%S	N.sagg.	%R	%I	%S	N.sagg.	%R	%I	%S
Microrganismo:	**Staphylococcus capitis**															
Acido Fusidico	65	13.8		86.2	0				0				0			
Clindamicina	68	45.6	1.5	52.9	0				0				0			
Cotrimoxazolo	68	2.9	1.5	95.6	0				0				0			
Daptomicina	65	18.5		81.5	0				0				0			
Eritromicina	67	47.8		52.2	0				0				0			
Gentamicina	68	38.2		61.8	0				0				0			
Levofloxacina	67	35.8		64.2	0				0				0			
Linezolide	68			100.0	0				0				0			
Oxacillina	68	54.4		45.6	0				0				0			
Rifampicina	67	6.0		94.0	0				0				0			
Teicoplanina	68	8.8		91.2	0				0				0			
Tetraciclina	67	13.4	16.4	70.1	0				0				0			
Tigeciclina	65	1.5		98.5	0				0				0			
Vancomicina	68			100.0	0				0				0			

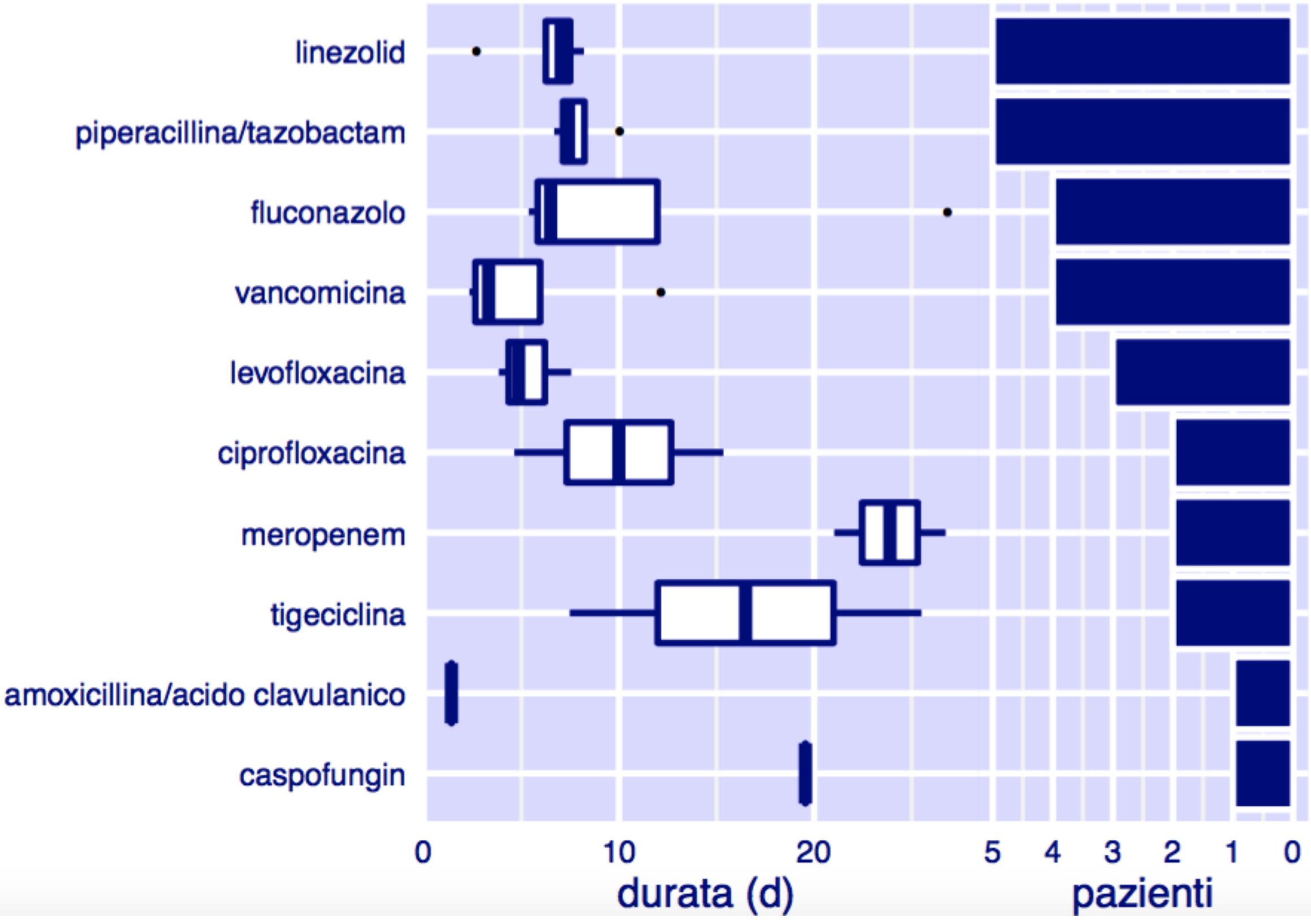
Mirata BSI/Endocarditi



Mirata BSI/Endocarditi MRSA



Mirata BSI/Endocarditi CoNS OXA R



Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Alex Soriano,[1] Francesc Marco,[2] José A. Martínez,[1] Elena Pisos,[1] Manel Almela,[2] Veselka P. Dimova,[2] Dolores Alamo,[2] Mar Ortega,[1] Josefina Lopez,[1] and Josep Mensa[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain

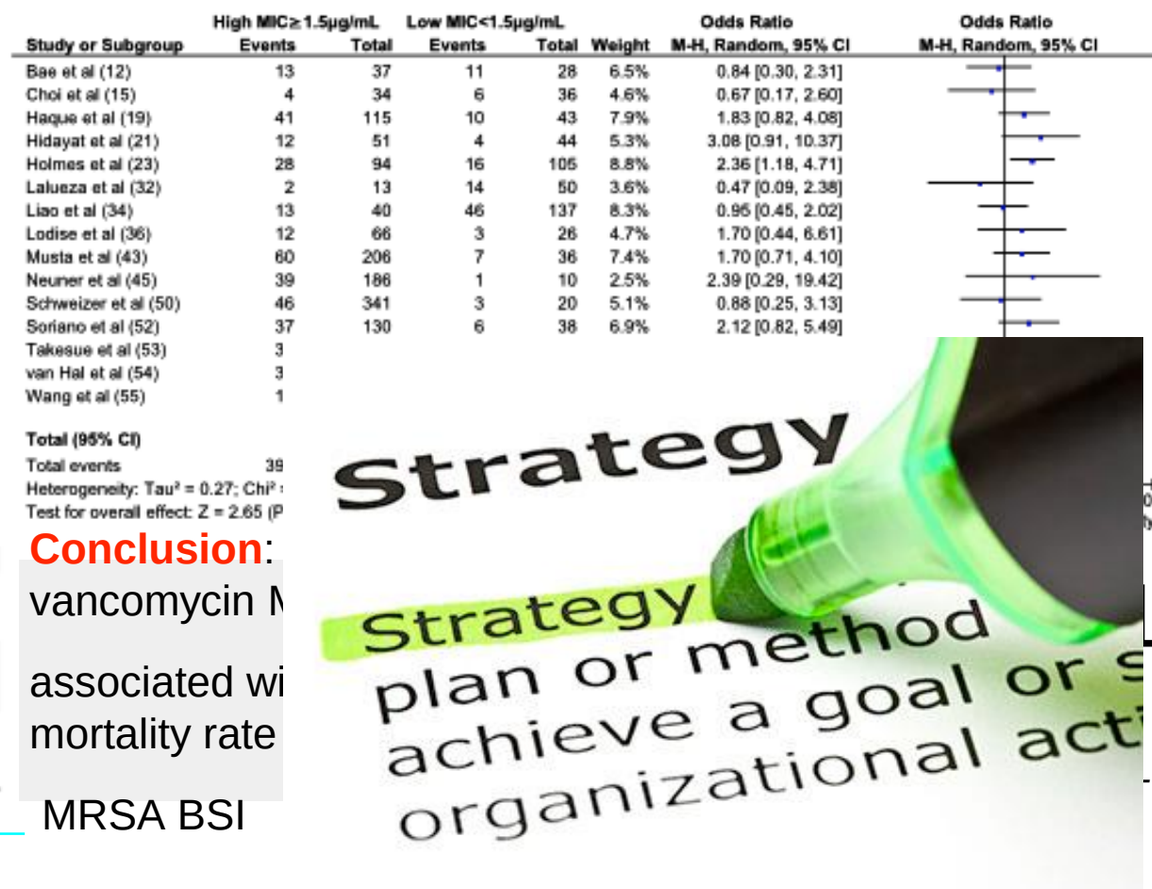
Table 4. Overall Probability of Achieving an AUC/MIC Ratio of 400, by MIC Value, versus the Probability of a Nephrotoxic Event

	AUC/MIC ratio ≥400			Nephrotoxic event	
MIC value	0.5mg/L (%)	1.0mg/L (%)	2.0mg/L (%)	Non-ICU (%)	ICU (%)
500 mg IV Q12H	57	15	0.7	3	10
1000 mg IV Q12H	90	57	15	6	16
1500 mg IV Q12H	97	79	38	9	25
2000 mg IV Q12H	98	90	57	14	34

Clin Infect Dis 2008;46(2):193-200

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

S. J. van Hal,[1,2] T. P. Lodise,[3] and D. L. Paterson[4]



Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	3					
van Hal et al (54)	3					
Wang et al (55)	1					
Total (95% CI)						
Total events	39					
Heterogeneity: Tau² = 0.27; Chi² =						
Test for overall effect: Z = 2.65 (P						

Conclusion:
vancomycin M
associated wi
mortality rate

MRSA BSI

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Optimizing the Clinical Use of Vancomycin

Rocío Álvarez, Luis E. López Cortés, José Molina, José M. Cisneros, Jerónimo Pachón

Antimicrobial Agents Chemother 2016;60(5):2601-2609

serum trough levels of 15 to 20 mg/liter are considered a surrogate marker of an **AUC/MIC ratio of >400** *for a* **MIC of <1 mg/liter**. *For Staphylococcus aureus strains presenting with a MIC >1 mg/liter, an alternative agent should be considered*

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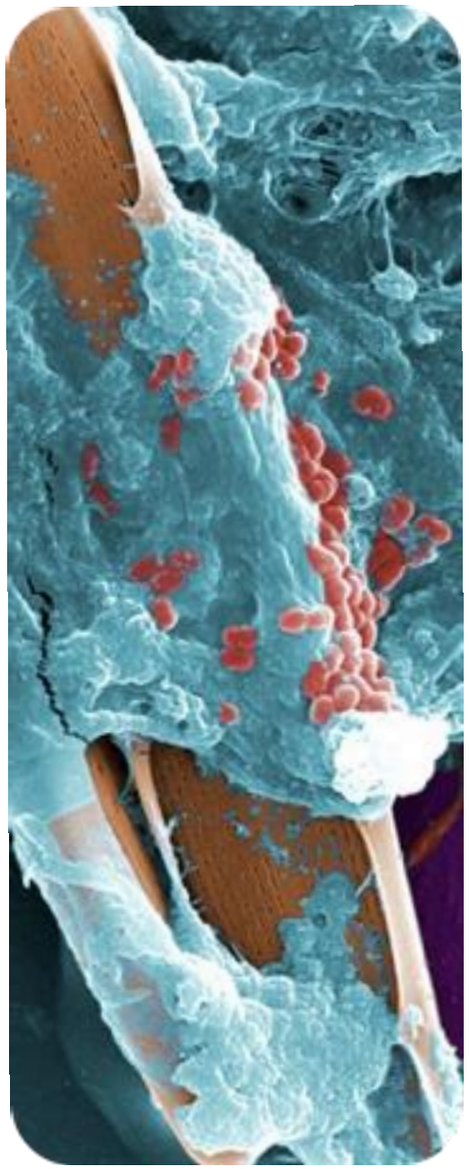
Impact of biofilm on the *in vitro* activity of vancomycin alone and in combination with tigecycline and rifampicin against *Staphylococcus aureus*

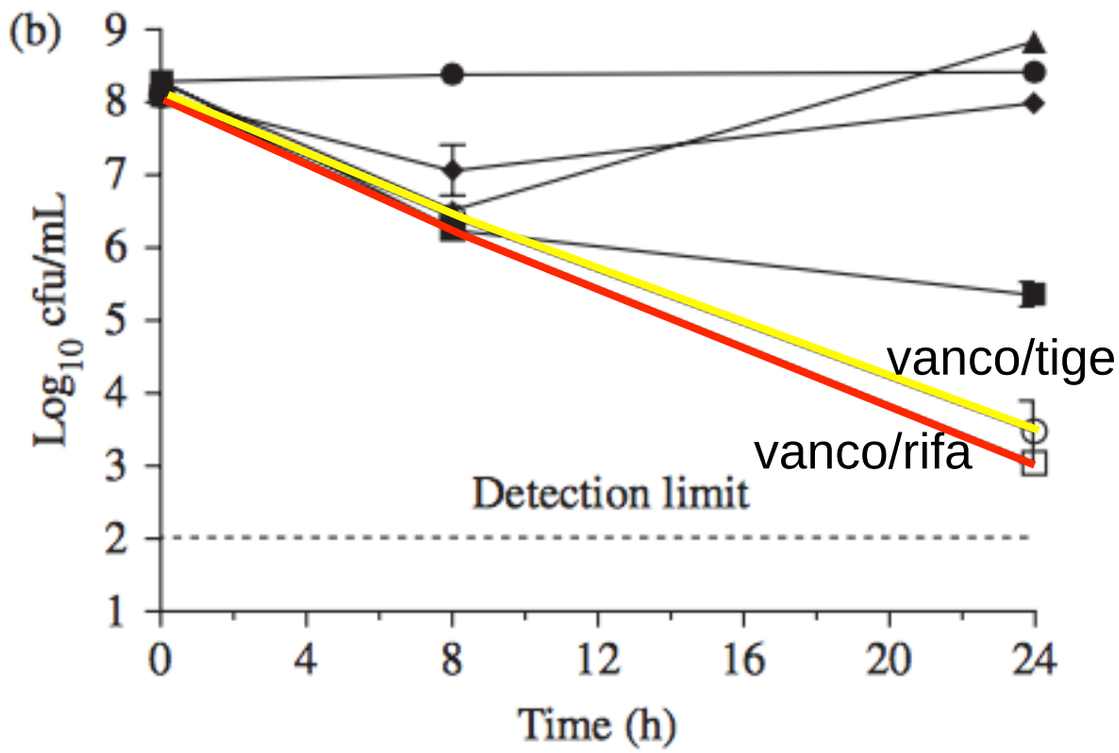
Rose WE



Results: Vancomycin susceptibility displayed a 4-fold and an 8-fold increase in the MIC_{50} and MIC_{90}, respectively, in the presence of biofilm. Rifampicin and tigecycline susceptibilities also increased in biofilms, but still remained within the susceptibility breakpoints except for a tigecycline MIC_{90} of 1 mg/L. High biofilm production was detected in 60% of the isolates. In time–kill analysis, 15 mg/L vancomycin achieved bactericidal activity against only low-biofilm-producing strains with a 1.8 $\log_{10}$ cfu/mL difference in bacterial kill compared with high-biofilm-producing strains ($P < 0.001$). Rifampicin alone had minimal activity, resulting in resistance. Tigecycline was minimally effective and was not bactericidal, but no difference was observed in the comparison of biofilm-producing strains. Vancomycin in combination with rifampicin or tigecycline was bactericidal against all strains (mean kill 4.5 ± 0.5 $\log_{10}$ cfu/mL), regardless of biofilm production.

Conclusions: Vancomycin exposures at 15 mg/L may not be adequate in eradicating biofilm-producing *S. aureus*. Alternative treatments or combination therapy should be explored to optimize outcomes in biofilm-associated infections.

Growth mode	Vancomycin	Rifampicin	Tigecycline
Planktonic			
MIC_{50}	1	<0.03	<0.06
MIC_{90}	1	<0.03	0.25
MBC range	0.5–4	<0.06–16	0.13–32
Biofilm			
MIC_{50}	4	0.03	0.5
MIC_{90}	8	0.13	1
MBEC range	1–64	0.13–32	2–32



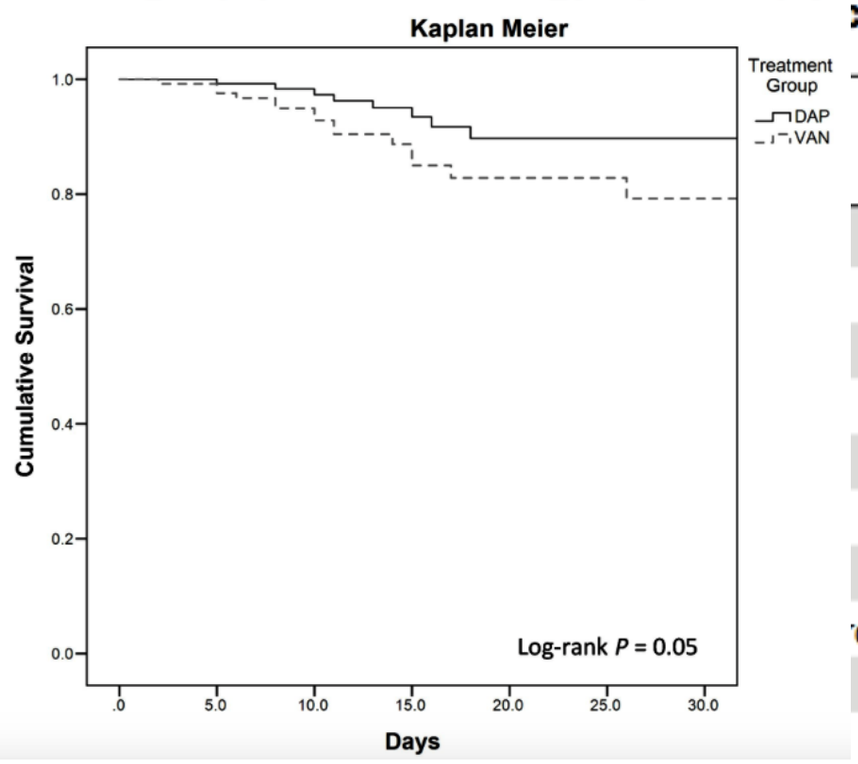
J Antimicrob Chemother 2009;63:485-488

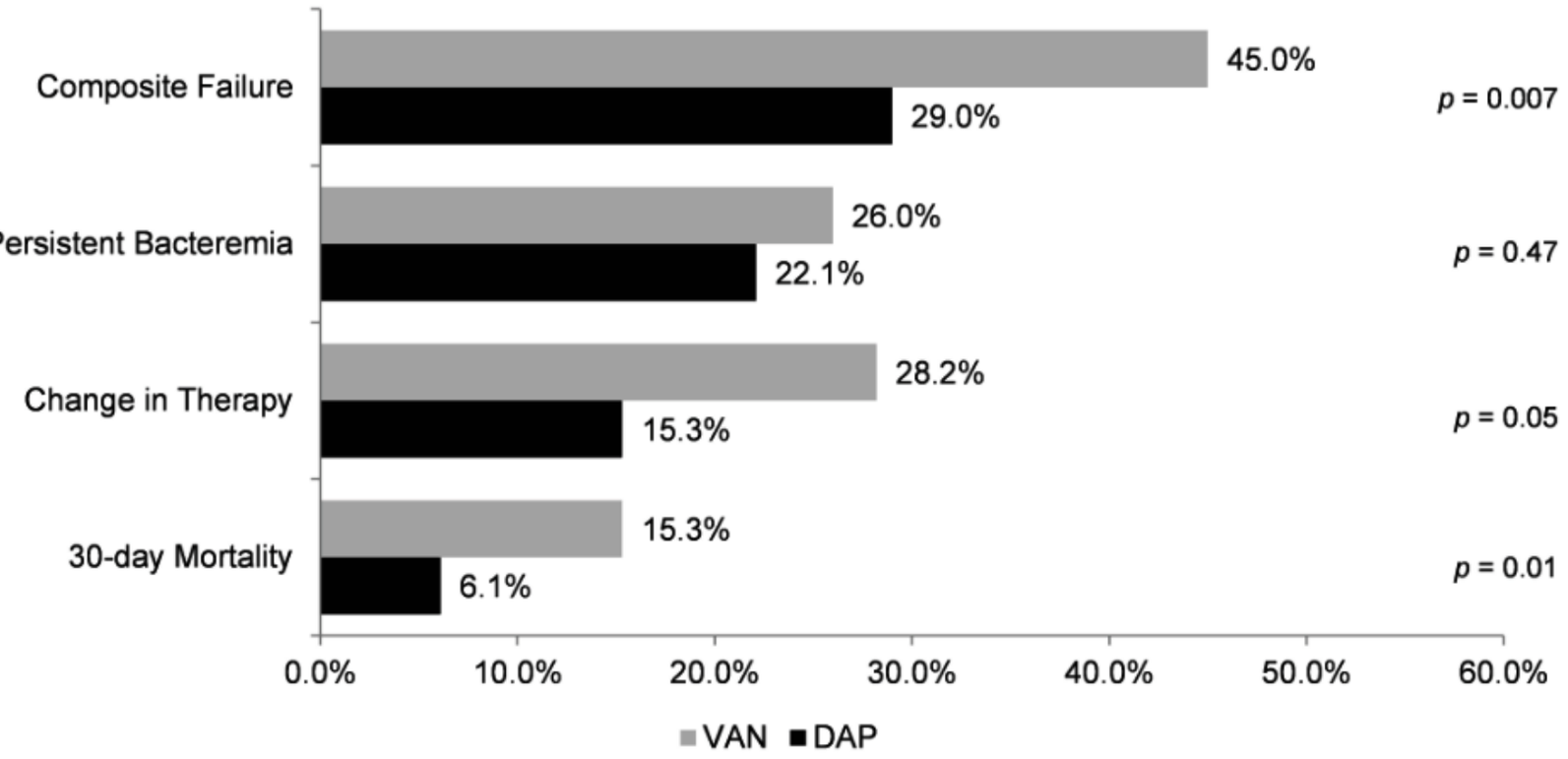
Propensity Matched Analysis of Early Daptomycin versus Vancomycin for Methicillin-Resistant *S. aureus* Bloodstream Infections: Daptomycin Improves Outcomes Regardless of Vancomycin MIC

Claeys KC

Vancomycin Minimum I
Concentration: A Case-C

Table 2. Comparative Outcomes of Van





CONCLUSIONS: Treatment of MRSA BSI with daptomycin was associated with reduced clinical failure and 30-day mortality; this finding was independent of vancomycin BMD MIC

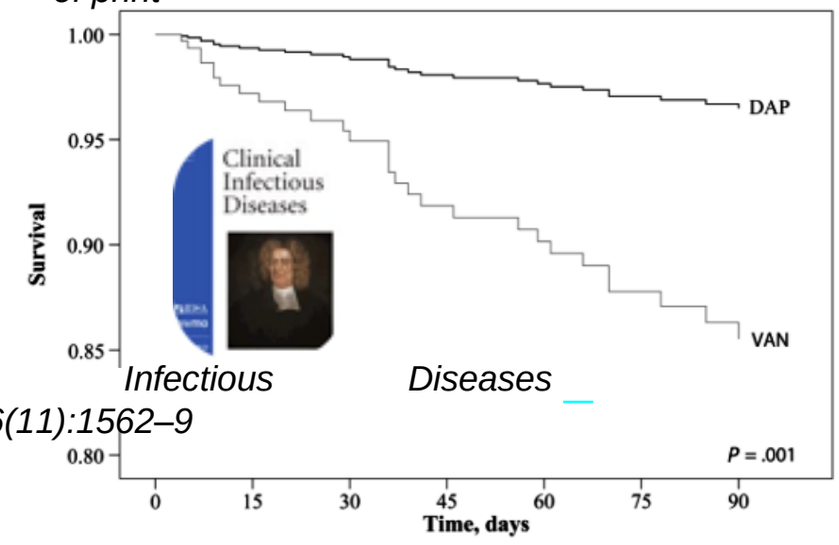
Antimicrobial Agents Chemother 2016;Jul 18:Epub ahead of print

		7 (27)	2 (15)
		11 (29)	2 (11)
High risk		19 (35)	

.166

Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: A Matched Cohort Study

Kyle P. Murray,[1] Jing J. Zhao,[1] Susan L. Davis,[3] Ravina Kullar,[3] Keith S. Kaye,[2] Paul Lephart,[4] and Michael J. Rybak[1,2,3]



Clinical Infectious Diseases 2013;56(11):1562–9

Daptomycin-Oxacillin Combinations in Treatment of Experimental Endocarditis Caused by Daptomycin-Nonsusceptible Strains of Methicillin-Resistant *Staphylococcus aureus* with Evolving Oxacillin Susceptibility (the "Seesaw Effect")[▽]

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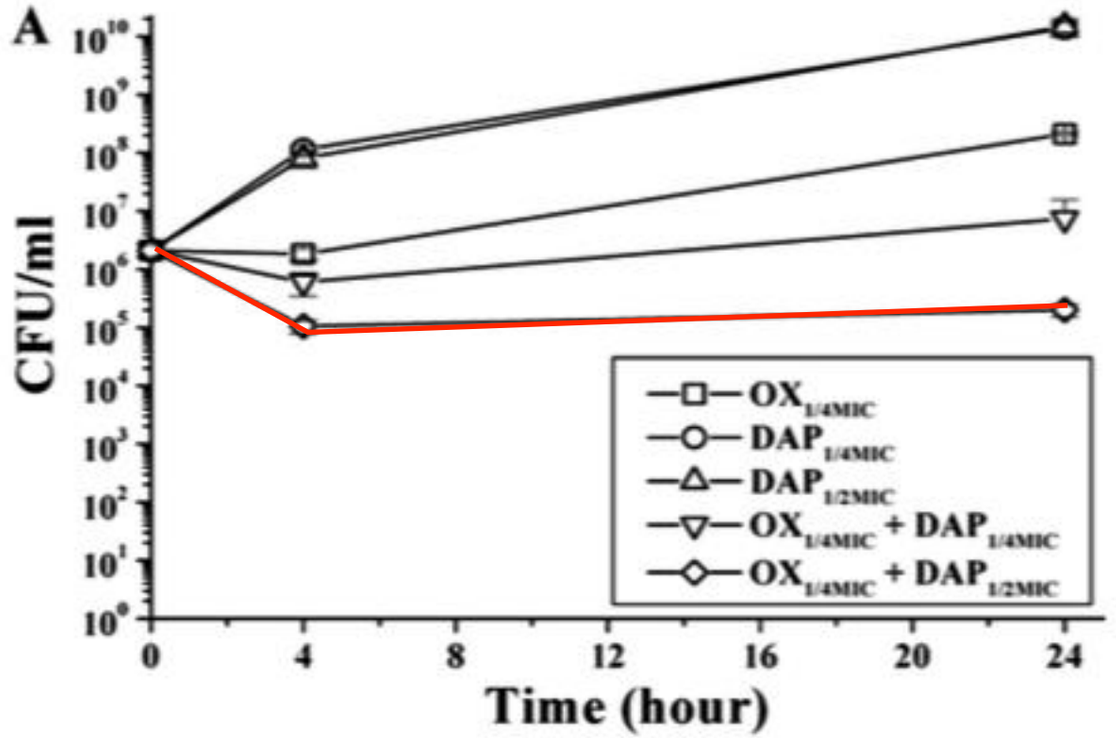
Antimicrobial Agents Chemother 2010;54(8):3161-3169



Il principale meccanismo di azione di questo sinergismo è dovuto al fatto che l'esposizione ai beta-lattamici incrementa la carica negativa sulla parete batterica dei batteri gram positivi, il che a sua volta incrementa il legame con la daptomicina complessata al calcio2+(molecola carica positivamente)

In vitro prevention of the emergence of daptomycin resistance in *Staphylococcus aureus* and enterococci following combination with amoxicillin/clavulanic acid or ampicillin

Addition of amoxicillin/clavulanic acid or ampicillin to daptomycin prevents, or greatly delays, daptomycin resistance in vitro. Future studies in animal models are needed to predict the utility of these combinations in humans

Int J Antimicrobial Agents 2010;35:451-456

Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Falcone M

Clinical Infectious Diseases

Table 2. Comparison of Clinical Characteristics and Outcomes of Patients With Augmented Daptomycin Clearance Compared to Those With Normal Clearance

Variable	Augmented CL (n = 13)	Normal CL (n = 37)	*P* Value
Type of infection			
Bacteremia—endocarditis	13 (100%)	8 (21.6%)	<.001
Skin and soft tissue infection	0	20 (54.1%)	<.001
Prosthetic joint infection	0	6 (16.2%)	<.001
Osteomyelitis	0	4 (10.8%)	<.001
Causative pathogen			
MRSA	11 (84.6%)	2 (5.2%)	<.001
MRSE	0	8 (21%)	<.001
MRSH	0	7 (18.4%)	<.001
Other	2 (15.4%)	14 (36.8%)	<.001
Comorbidities and outcomes			
COPD	8 (61.5%)	21 (55.2%)	.71
Heart failure	7 (53.8%)	19 (50%)	.29
Diabetes mellitus	7 (53.8%)	18 (47.3%)	.18
Neoplasm	2 (15.3%)	4 (10.5%)	.68
Chronic liver disease	3 (23%)	7 (18.4%)	.08
Presence of at least 2 comorbidities	9 (69.2%)	22 (57.8%)	.09
Recent surgery, previous 30 d	6 (46.1%)	9 (24.3%)	.07
ICU acquisition of infection	8 (61.5%)	12 (31.5%)	.04
Severe sepsis or septic shock[a]	13 (100%)	9 (24.3%)	.01
SOFA score, mean (SD)	3.31 (1.03)	2.11 (0.84)	<.001
Mean length of hospital stay, days	36.8	22.5	<.001
In-hospital mortality	4 (30.7%)	4 (10.8%)	<.001

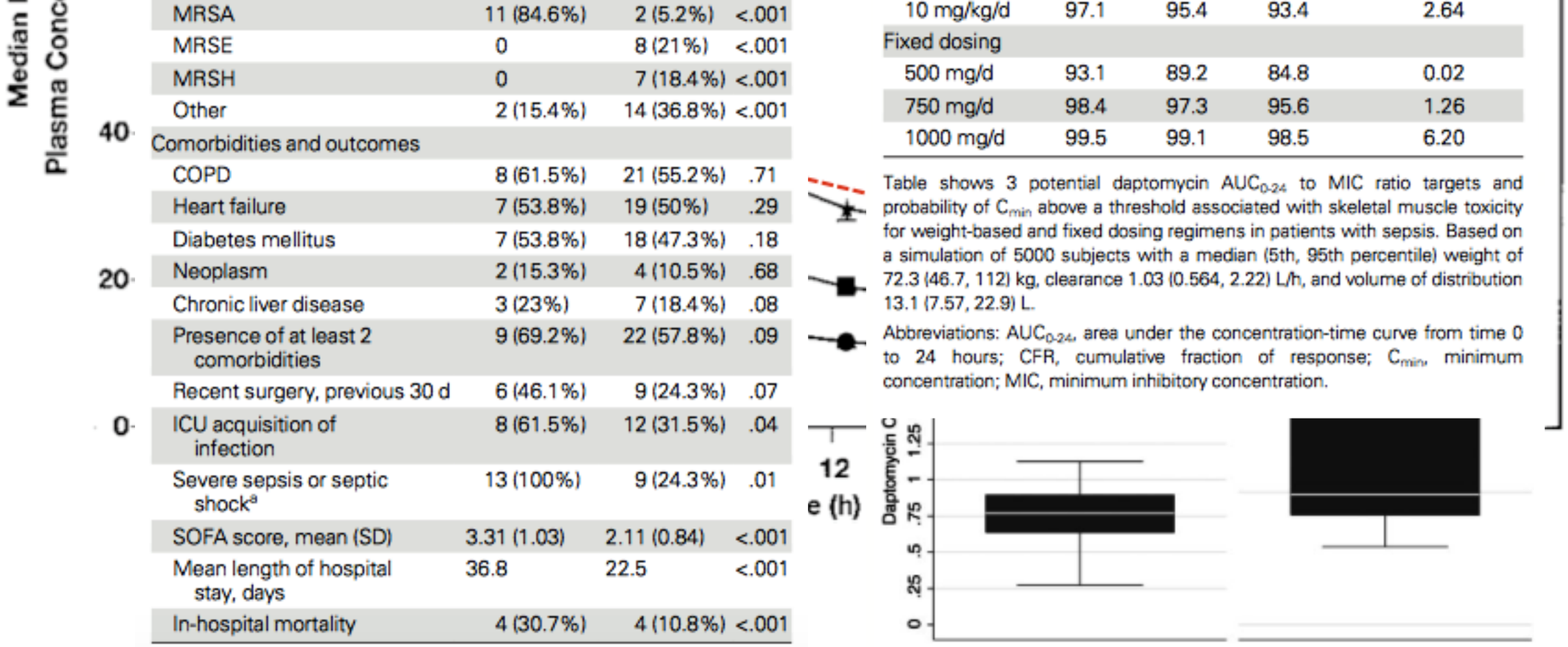
Day 1: 6 mg/kg

Table 5. Cumulative Fraction of Response in Patients With Sepsis

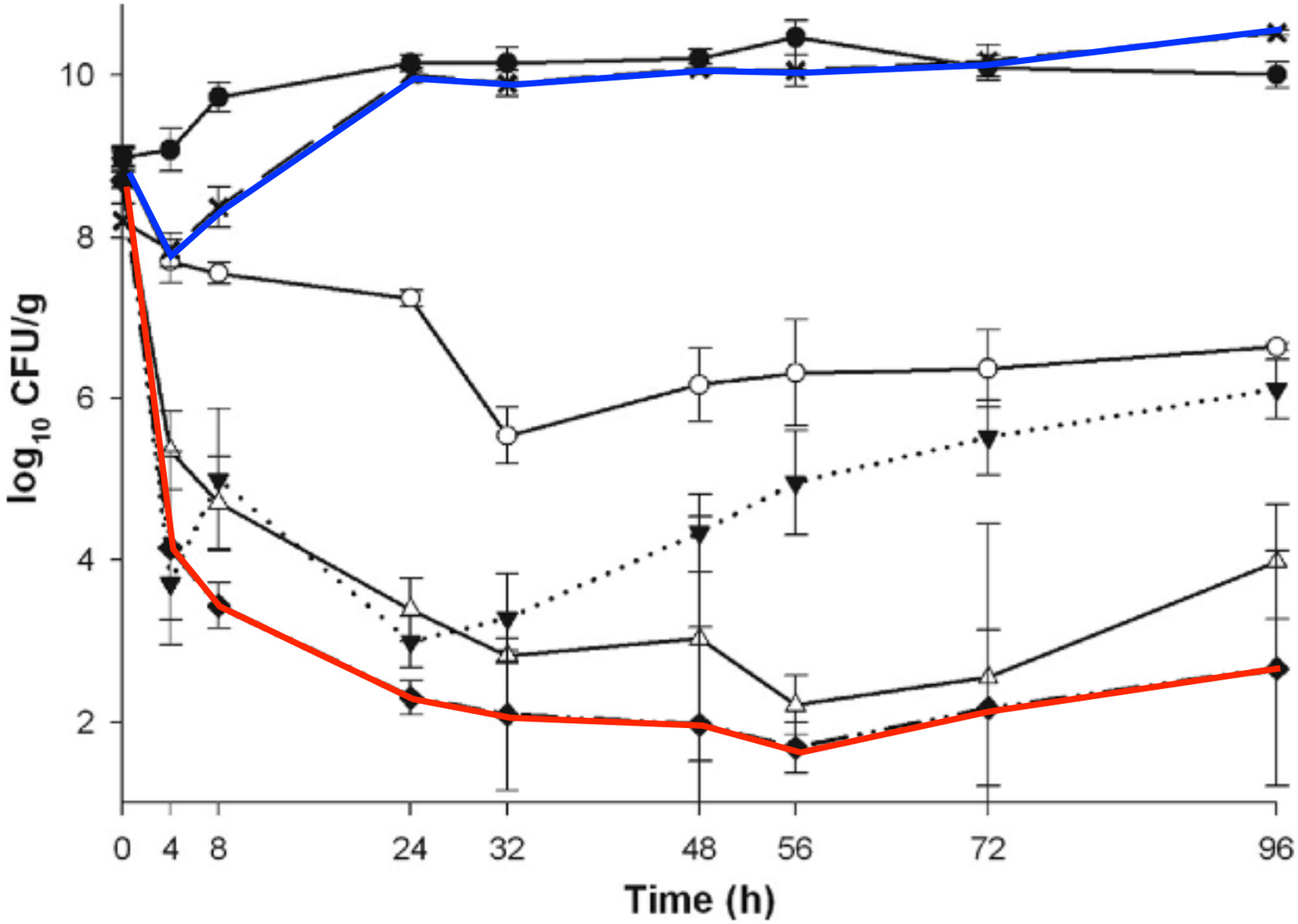
Daily Dose	% CFR Based on AUC_{0-24}/MIC ≥579	≥666	≥753	% Probability C_{min} ≥ 24.3 mg/L
Weight-based dosing				
6 mg/kg/d	87.3	82.1	77.2	0.08
8 mg/kg/d	94.1	91.3	88.0	0.78
10 mg/kg/d	97.1	95.4	93.4	2.64
Fixed dosing				
500 mg/d	93.1	89.2	84.8	0.02
750 mg/d	98.4	97.3	95.6	1.26
1000 mg/d	99.5	99.1	98.5	6.20

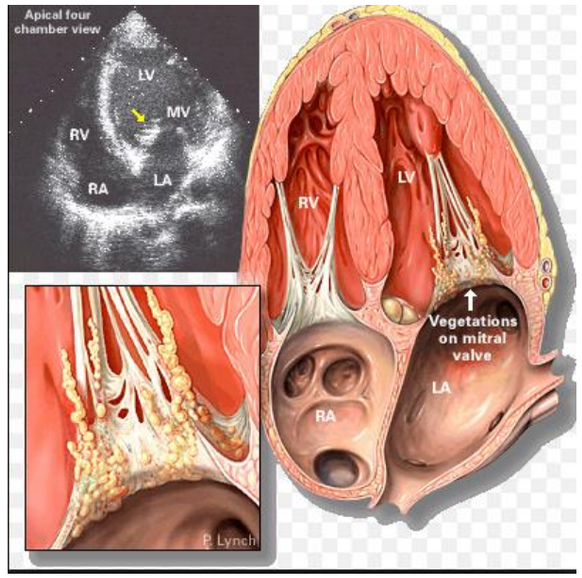
Table shows 3 potential daptomycin AUC_{0-24} to MIC ratio targets and probability of C_{min} above a threshold associated with skeletal muscle toxicity for weight-based and fixed dosing regimens in patients with sepsis. Based on a simulation of 5000 subjects with a median (5th, 95th percentile) weight of 72.3 (46.7, 112) kg, clearance 1.03 (0.564, 2.22) L/h, and volume of distribution 13.1 (7.57, 22.9) L.

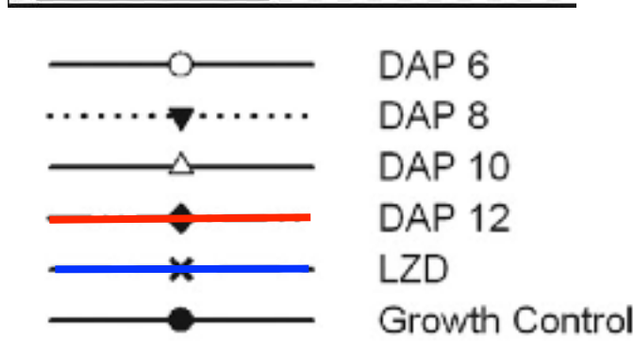
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; CFR, cumulative fraction of response; C_{min}, minimum concentration; MIC, minimum inhibitory concentration.



High-dose daptomycin vs linezolid against VRE

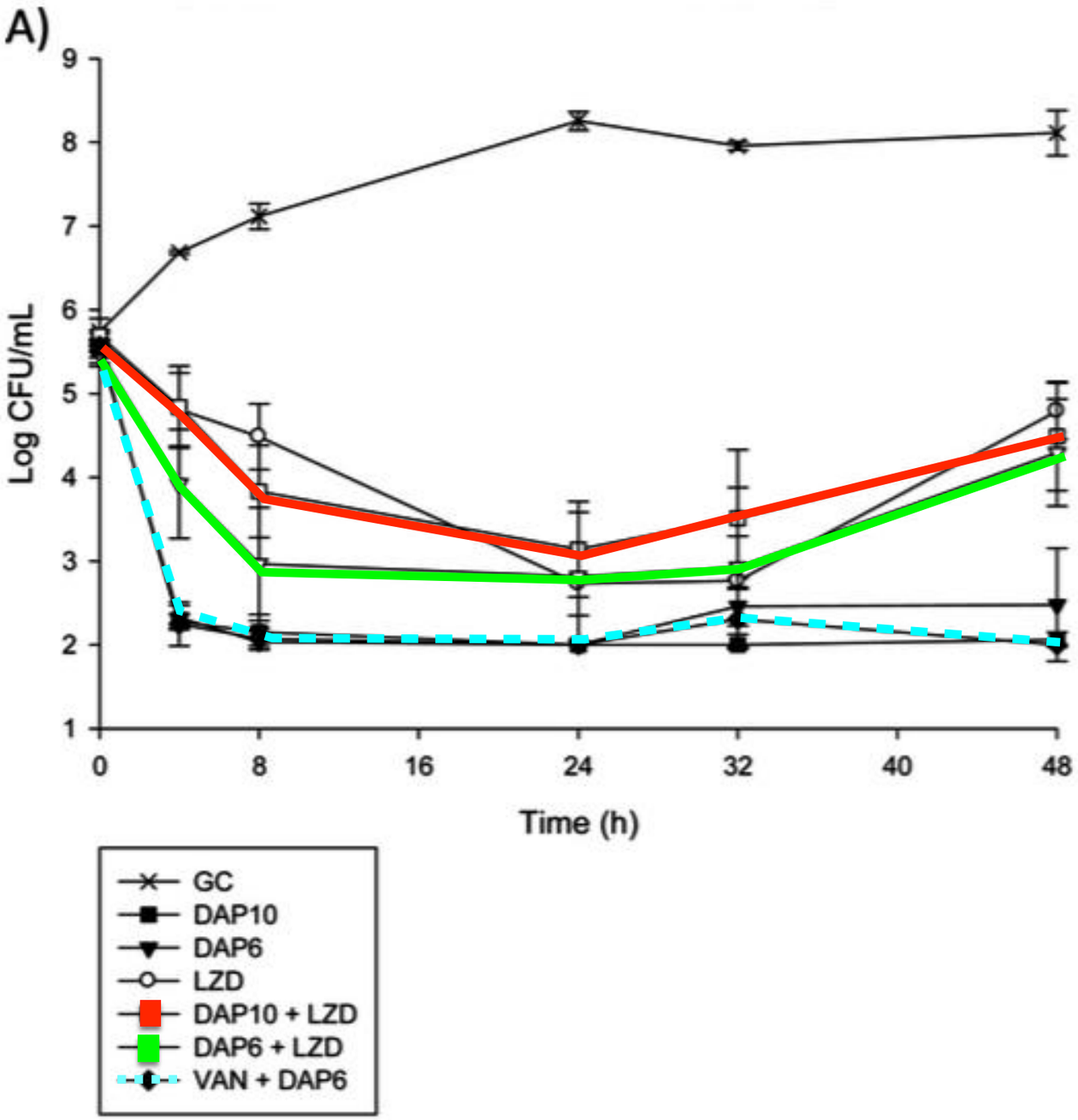


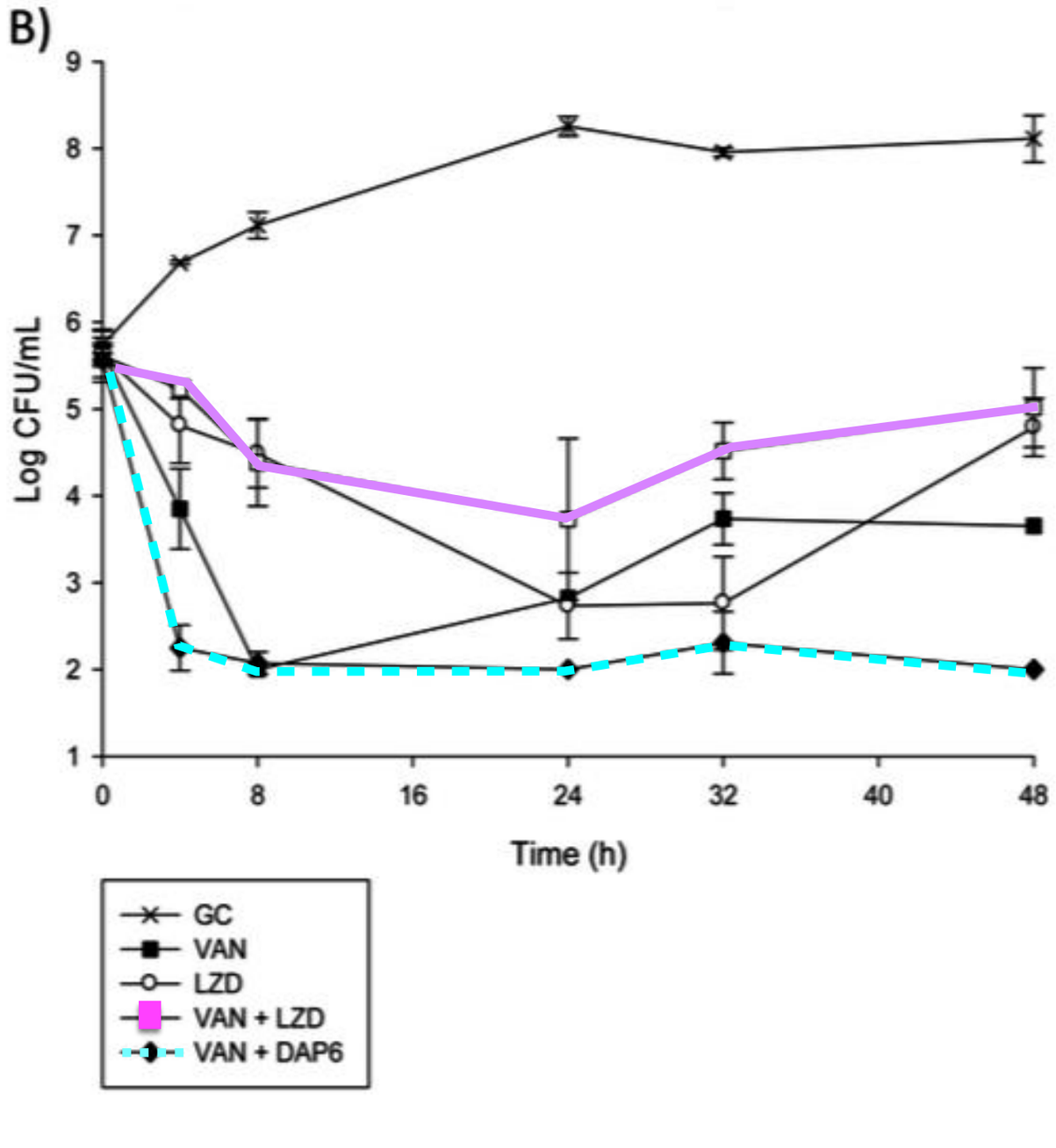




Daptomycin displayed a dose-dependent response ... high-dose producing sustained bactericidal activity

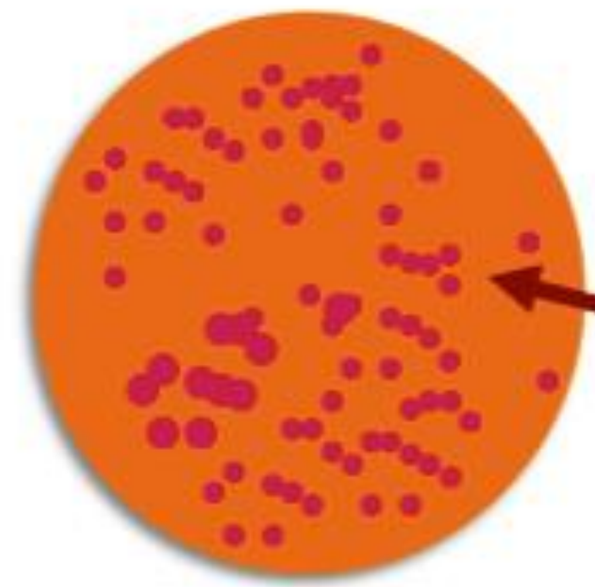
Observed Antagonistic Effect of Linezolid on Daptomycin or Vancomycin Activity against Biofilm-Forming Methicillin-Resistant *Staphylococcus aureus* in an *In Vitro* Pharmacodynamic Model





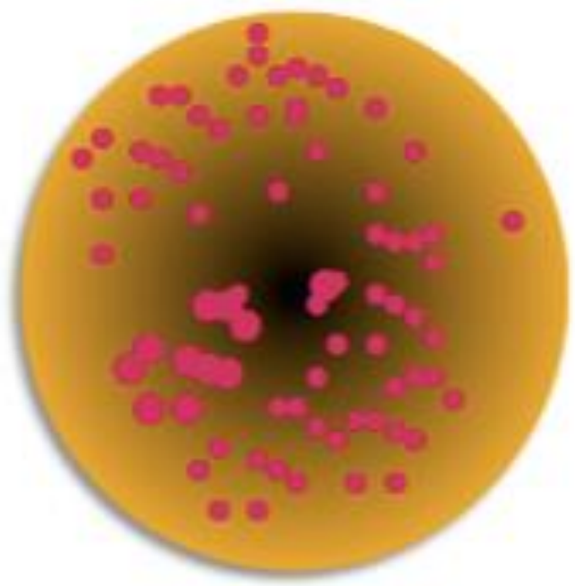
Linezolid antagonized the activity of vancomycin and daptomycin 6 mg/kg and 10 mg/kg at 24 and 48 h.

Diffusione degli antibiotici nelle vegetazioni



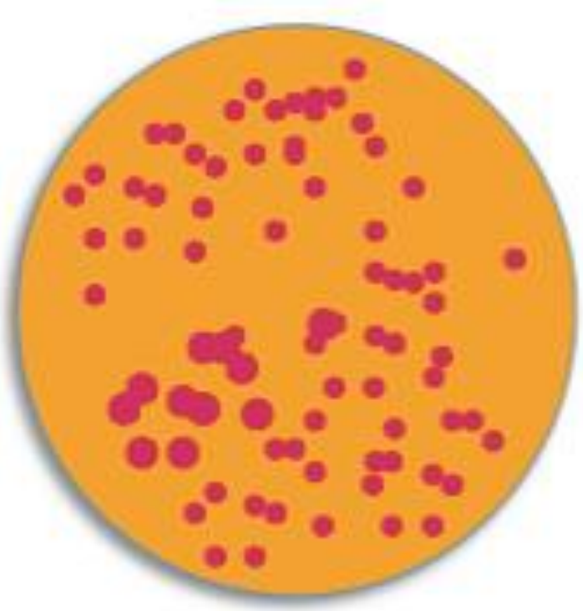
Vegetazione settica

Colonie batteriche



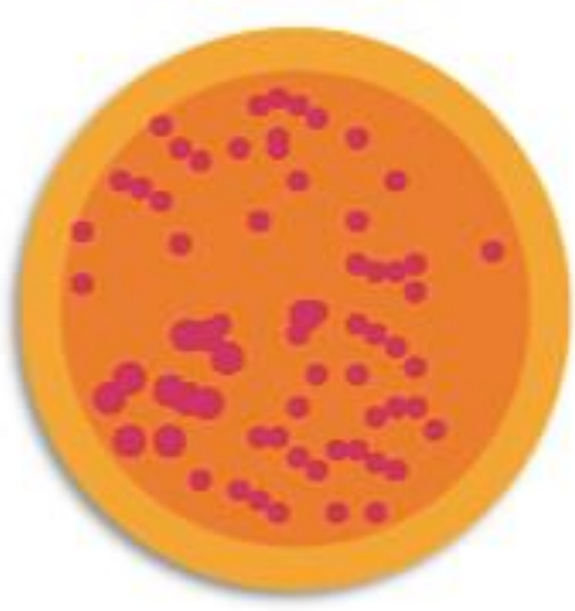
Diffusione a gradiente

- β-Lattamici



Diffusione omogenea

- Aminoglicosidi
- Chinoloni
- Rifampicina
- Daptomicina



Diffusione periferica

- Vancomicina
- Teicoplanina

Antimicrob Agents Chemother 1989;36:2611-2616
J Infect Dis 1989;159:938-944

Anti-MRSA agents: a relatively broad repertoire

Older agents

- Vancomycin
- Teicoplanin

Recent agents

- Linezolid
- Daptomycin
- Tigecycline
- Telavancin
- Ceftaroline

New agents

- Dalbavancin
- Oritavancin
- Tedizolid
- Ceftobiprole

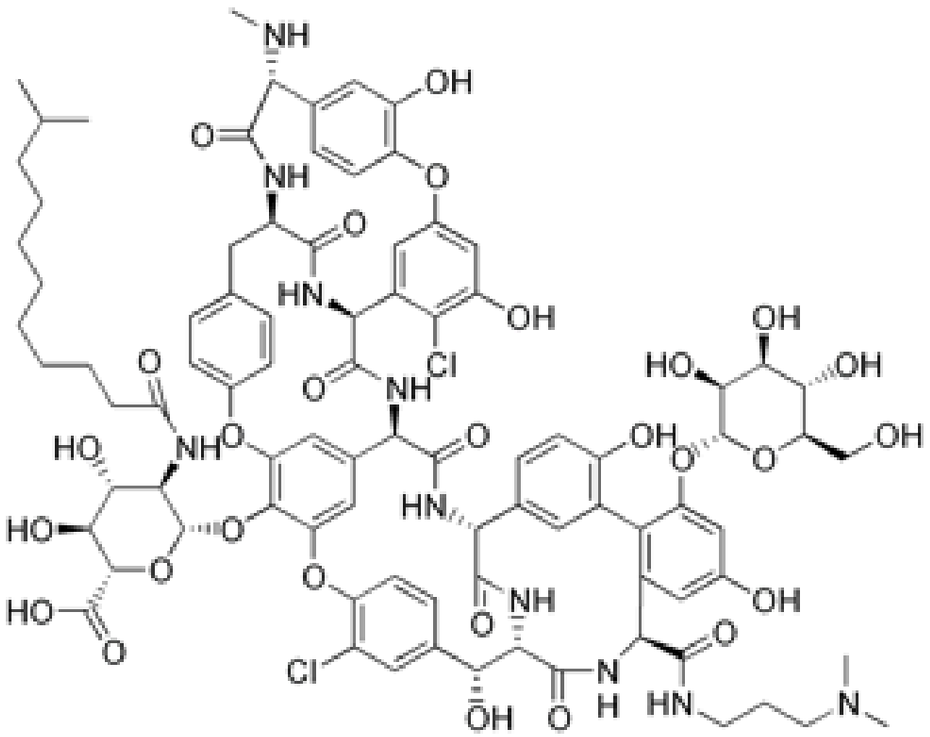
New long-acting glycopeptides

New once-a-day oxazolidinone

New anti-MRSA beta-lactams
(5th generation cephalosporins)

Resistance with these drugs is reported but overall remains uncommon

Dalbavancin



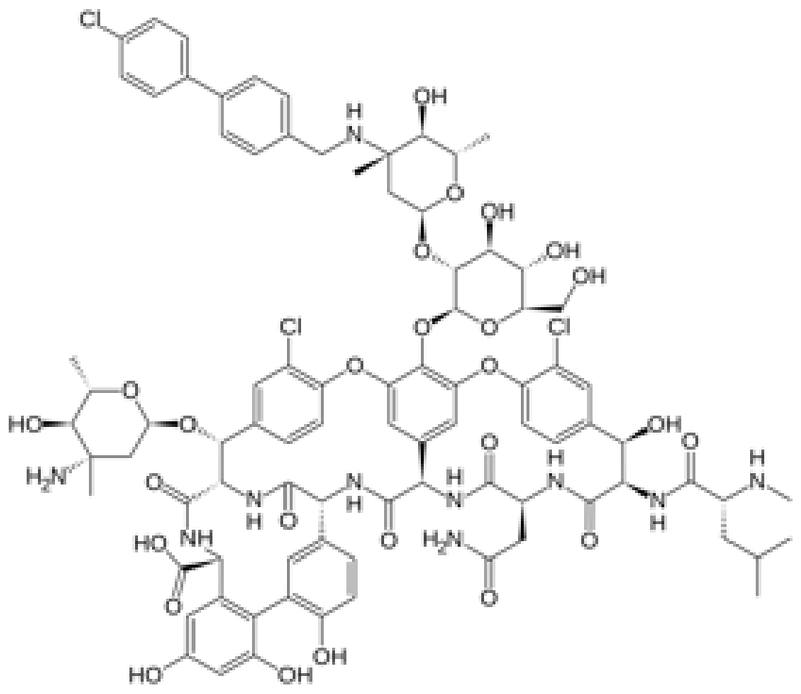
Dalbavancin

Label: ABSSSI

- ✧ New lipoglycopeptide long-acting (1.5 g single shot)
- ✧ Spectrum: anti-Gram+ (including MRSA, no VRE)
- ✧ More potent than vancomycin/teicoplanin
- ✧ Excellent safety profile

Bouchner et al NEJM 2014
Dunne et al Clin Infect Dis 2016
Dunne et al Drug Saf 2016

Oritavancin



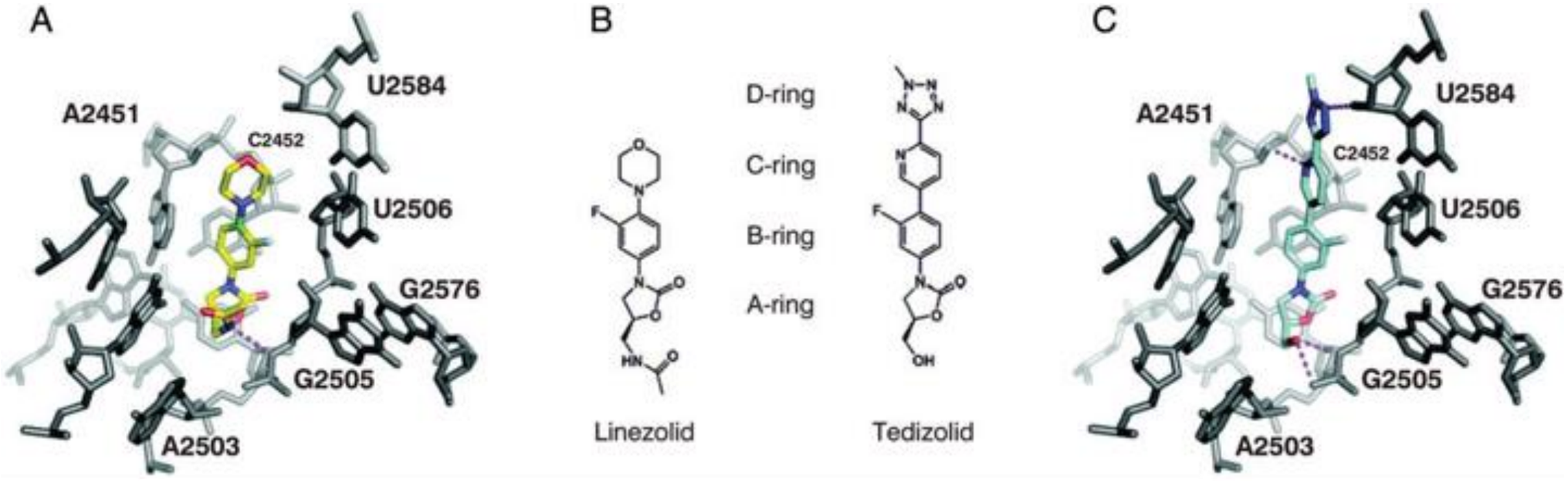
Oritavancin

Label: ABSSSI

- ✧ New lipoglycopeptide long-acting (1.2 g single shot)
- ✧ Additional MoA: membrane damage, which confers rapid bactericidal activity
- ✧ Spectrum: anti-Gram+ (including MRSA, VRE)
- ✧ Safety profile: similar to vancomycin (*osteomyelitis warning*)

Zhanel et al Clin Infect Dis 2012
Brade et al Inf Dis Ther 2016

Tedizolid



- ✧ New oxazolidinone once-a-day (OS/IV)
- ✧ Spectrum: anti-Gram+ (including MRSA, VRE)
- ✧ More potent than LZD; activity *vs*. some LZD-R strains; lower propensity for selection of R mutants
- ✧ Less toxic that LZD (GI AEs)

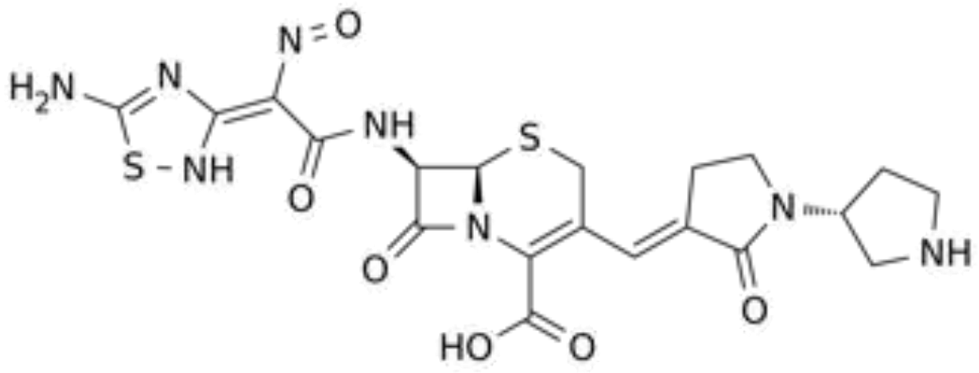
Tedizolid

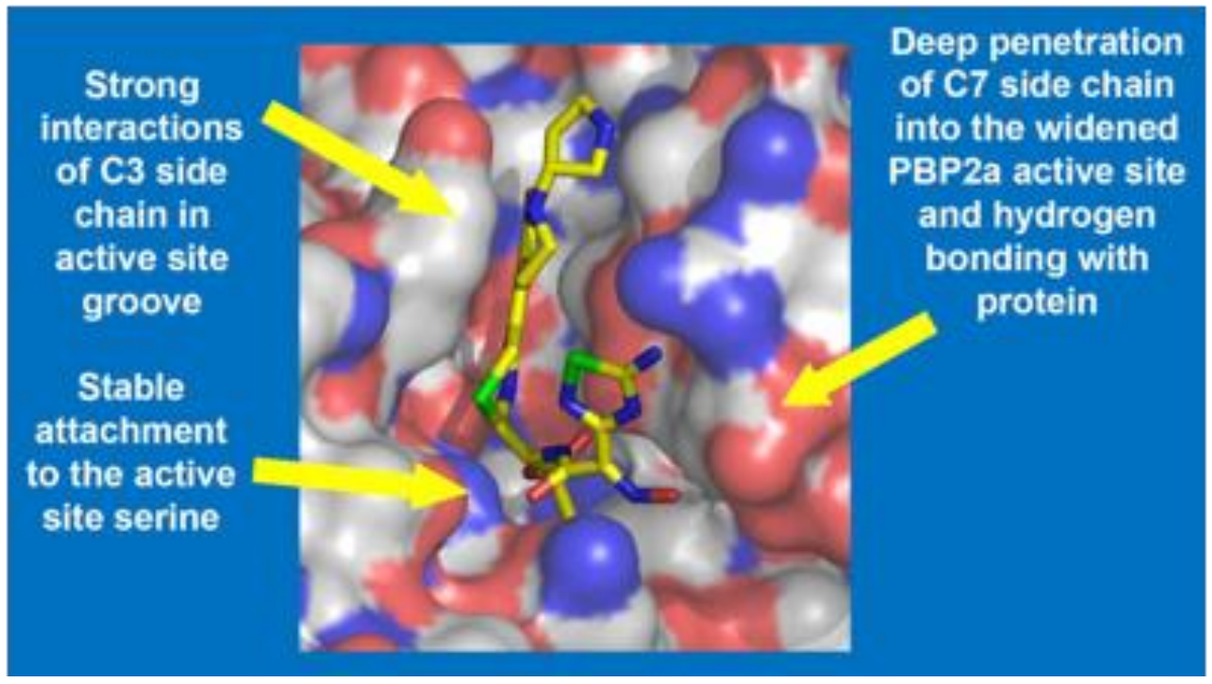
Label: ABSSSI

Locke et al Clin Infect Dis 2014
Burdette & Trotman Clin Infect Dis 2015

Ceftobiprole

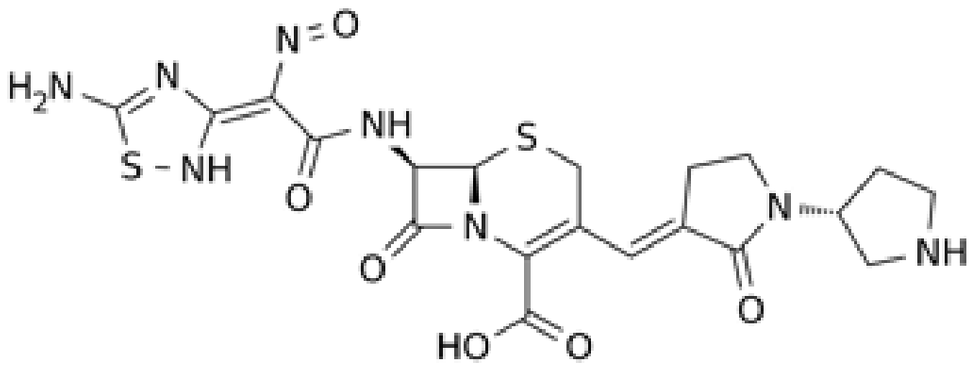
Ceftobiprole is a cephalosporin able to inhibit PBP2a of MRSA and MRCoNS (5th generation cephalosporin)





Lovering et al J Biol Chem 2014

Ceftobiprole

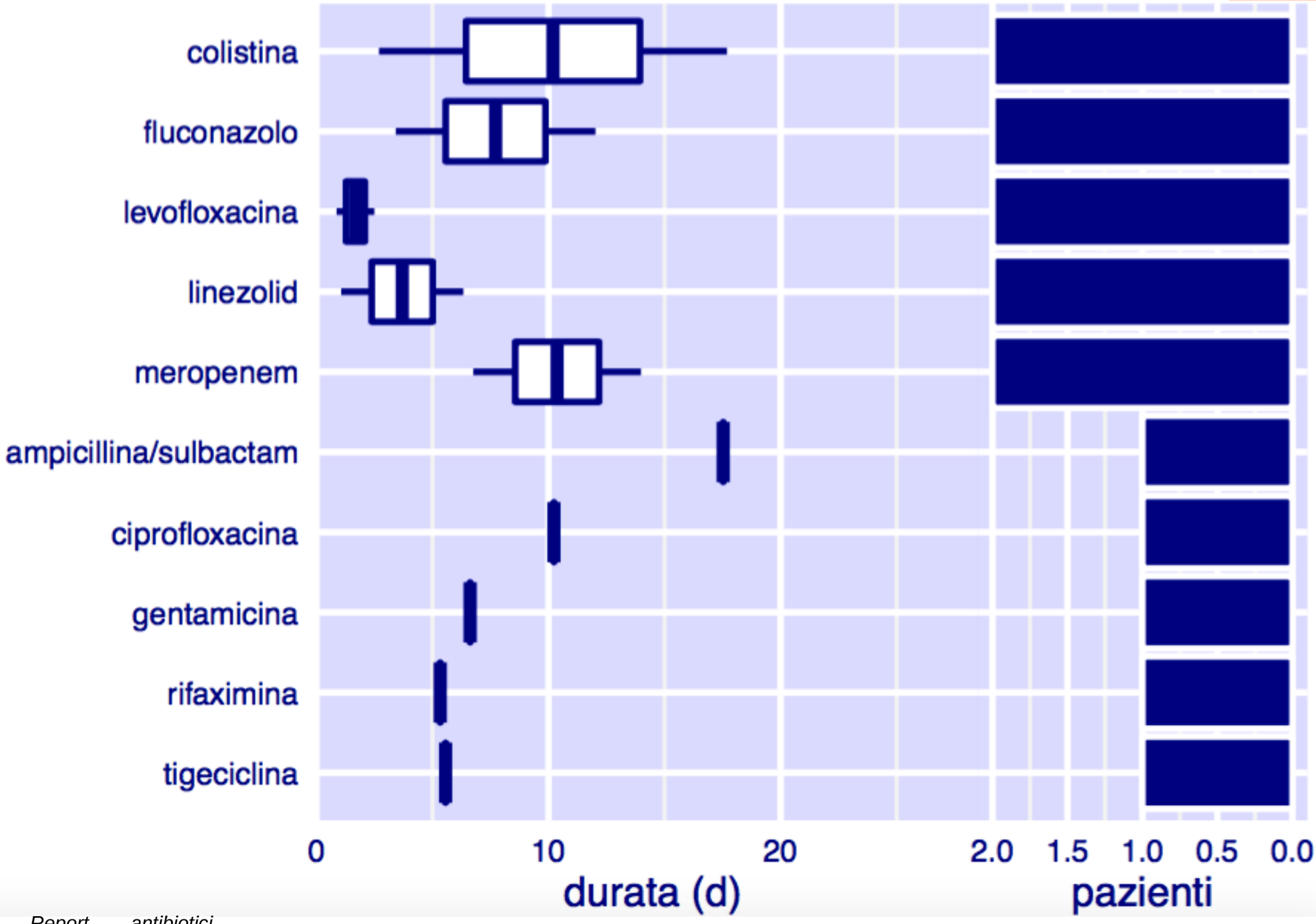


Ceftobiprole

Label: CAP & HAP (no VAP)

- Activity *vs*. several Gram+ (incl. MRSA, MRCoNS)
- Activity *vs*. Gram- (Enterics and *Pseudomonas*)
- Not active against ESBL and carbapenemase producers

Mirata BSI/Endocarditi AciBau Carba R



GiViTI

el combinations are the only remaining therapeutic optio

Novel Antibiotic Combinations against Infections with Almost Completely Resistant *Pseudomonas aeruginosa* and *Acinetobacter* Species

James J. Rahal

Infectious Disease Section and Lang Research Center, New York Hospital Queens, and Department of Medicine, Weill College of Medicine, Cornell University, New York, New York

Clin Infect Dis 2006;43:S95-

studies have suggested tha
preferable for patients wit
r *Acinetobacter baumann*
tibiotic combinations dem-
er these combinations yield
remains to be determined.
nyxins, novel combinations

Bull Johns Hopkins Hosp. 1947 Jul;81(1):43-54.

Polymyxin: a new chemotherapeutic agent.

STANSLY PG, SHEPHERD RG, WHITE HJ.

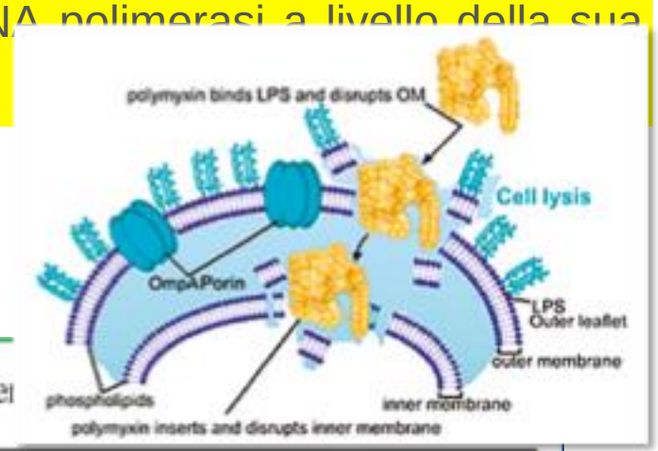
PMID: 20259524 [PubMed - indexed for MEDLINE]

Trattamento infezioni da MDROs

RAZIONALE

meccanismo sequenziale di azione

- la **colistina** disorganizzando la membrana permette alla rifampicina di entrare nel batterio
- la **rifampicina** inibisce la RNA polimerasi a livello della sua subunità ß



Organism (no. of isolates)	Polymyxin studied	Combined-drug synergy (% of isolates with syner	
A. baumannii (13)	Colistin	Rifampin (85)	74
A. baumannii (5)	Polymyxin B	Rifampin (60); ampicillin-sulbactam (0)	172
A. baumannii (55)	Polymyxin B	Rifampin (76); imipenem (58)	26

frontiers in MICROBIOLOGY

REVIEW ARTICLE
published: 20 October 2014
doi: 10.3389/fmicb.2014.00551

A new strategy to fight antimicrobial resistance: the revival of old antibiotics

Nadim Cassir[1,2]*, Jean-Marc Rolain[1] and Philippe Brouqui[1,2]

[1] *Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UM63 CNRS 7278 IRD 198 INSERM U1095, Facultés de Médecine et de Pharmacie, Aix-Marseille Université, Marseille, France*

[2] *Institut Hospitalo-Universitaire en Maladies Infectieuses et Tropicales, Hôpital Nord, Assistance Publique - Hôpitaux de Marseille, Marseille, France*

In Vitro Activities of Combinations of Rifampin with Other Antimicrobials against Multidrug-Resistant *Acinetobacter baumannii*

Bai Y

73 MDR Acinetobacter bauma

TABLE 1 MICs of rifampin, biapenem, colistin, and tigecycline used alone and in combination against multidrug-resistant *Acinetobacter baumannii*[a]

	Data for the indicated antibiotic used alone					Data for the indicated antibiotic used in combination[e]				
Antimicrobial	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC_{range}[b] (μg/ml)	%S[c]	% < C_{max}[d]	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	%S	% < C_{max}
Rifampin	4	8	1–16	30	83.1	1	2	0.25–4	95.9/90.4/97.3	100
Biapenem	32	64	1–64	5.5	30.1–76.7	8	16	0.0625–32	26	90.4–100
Colistin	0.5	1	0.125–1	100	100	0.125	0.25	0.0625–0.5	100	100
Tigecycline	1	2	0.25–2	82.2/98.6	24.7–82.2	0.25	0.5	0.125–1	100	91.8–100

TABLE 2 FICIs of rifampin combined with each of the three other antimicrobials against multidrug-resistant *Acinetobacter baumannii*[a]

		FICI of rifampin combined with:					
		Biapenem		Colistin		Tigecycline	
Standard of result judgment	Interaction	No. (%)[b]	No. < 1/3C_{max}[c]	No. (%)	% < 1/16C_{max}[d]	No. (%)	% < 1/3C_{max}
FICI ≤ 0.5	Synergistic	23 (31.51)	56.6	25 (34.25)	92	23 (31.51)	91.3
0.5 < FICI < 1	Partially synergistic	36 (49.31)	47.2	32 (43.83)	68.7	35 (47.94)	45.7
FICI = 1	Additive	14 (19.18)	28.5	16 (21.92)	15.4	15 (20.55)	66.7
1 < FICI < 4	Indifferent	0 (0.00)	NA[e]	0 (0.00)	NA	0 (0.00)	NA
FICI ≥ 4	Antagonistic	0 (0.00)	NA	0 (0.00)	NA	0 (0.00)	NA

Molecular Mechanisms of Sulbactam Antibacterial Activity and Resistance Determinants in *Acinetobacter baumannii*

Penwell WF

AAC Journals.ASM.org

Sulbactam inhibits PBP1 and PBP3 but not PBP2 in A. baumannii

TABLE 1 Acylation rate constants for acylation of *A. baumannii* and *P. aeruginosa* PBP1a, PBP2, and PBP3 by various inhibitors

	k_{on}/K_i (M^{-1} s^{-1})					
	A. baumannii			*P. aeruginosa*		
Compound	PBP1a	PBP2	PBP3	PBP1a	PBP2	PBP3 .
Bocillin FL	5,500	13,000	32,000	9,270	1,030	18,600
Aztreonam	1,200	0.12	520	85	<5	296,000
Ceftazidime	5,000	1.2	780	3,760	<5	69,000
Mecillinam	1.6	6,200	<15	<7	1,500	NT[a]
Meropenem	28,000	25,000	1,600	5,040	1,200	49,000
Sulbactam	8.8	0.34	17	5.9	0.12	1.7

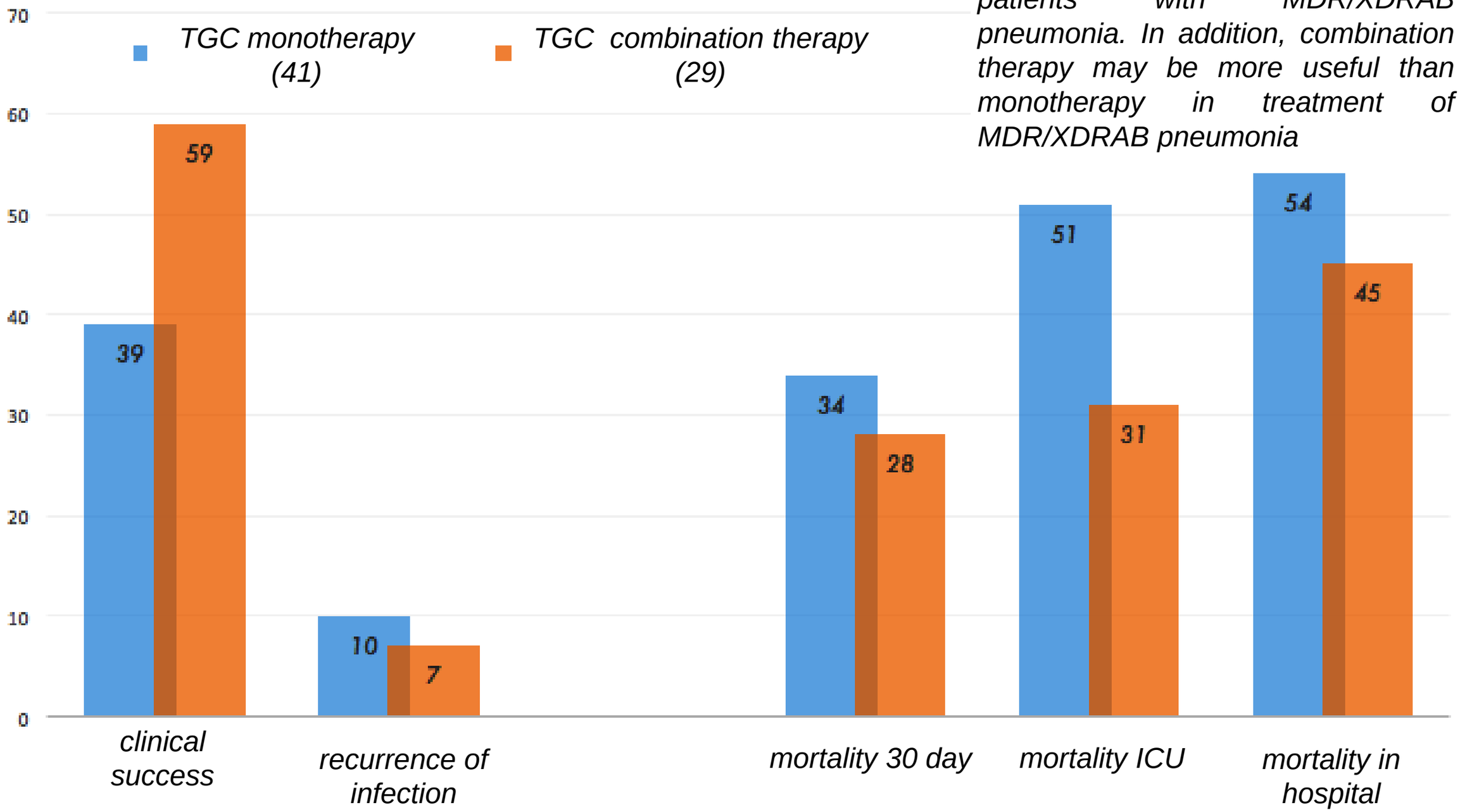
Sulbactam *preferentially inhibited* PBP1a *and* PBP3 *over* PBP2*, as did* aztreonam *and* ceftazidime*, although the latter two compounds were notably more reactive.* Mecillinam *reacted predominantly with PBP2, whereas* meropenem *was quite reactive with all three PBPs tested but with lower potency against PBP3 than against PBP1a or PBP2, as described previously*

Antimicrob Agents Chemother 2015;59(3):1680-1689

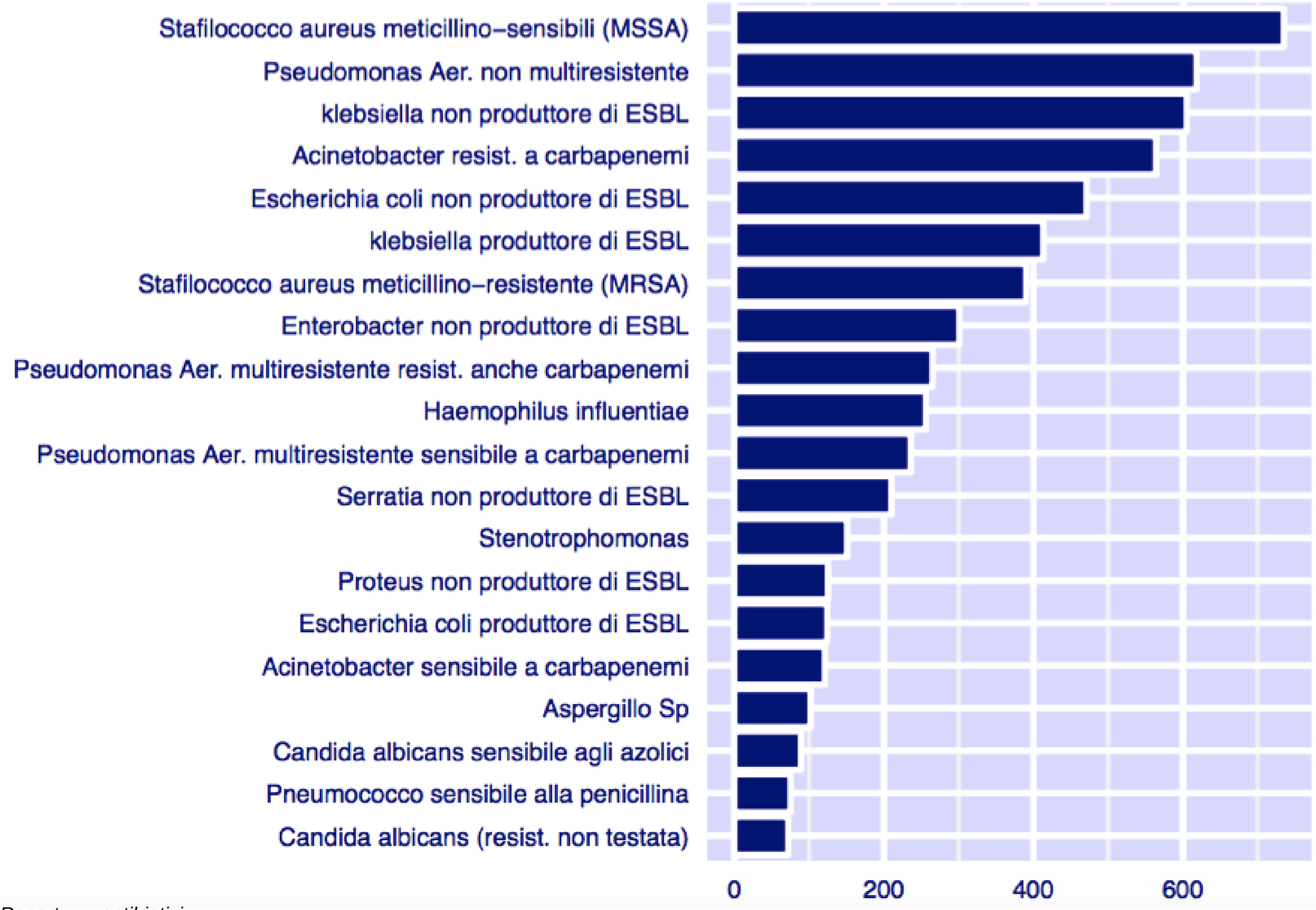
RESEARCH ARTICLE

Comparable Efficacy of Tigecycline versus Colistin Therapy for Multidrug-Resistant and Extensively Drug-Resistant *Acinetobacter baumannii* Pneumonia in Critically Ill Patients

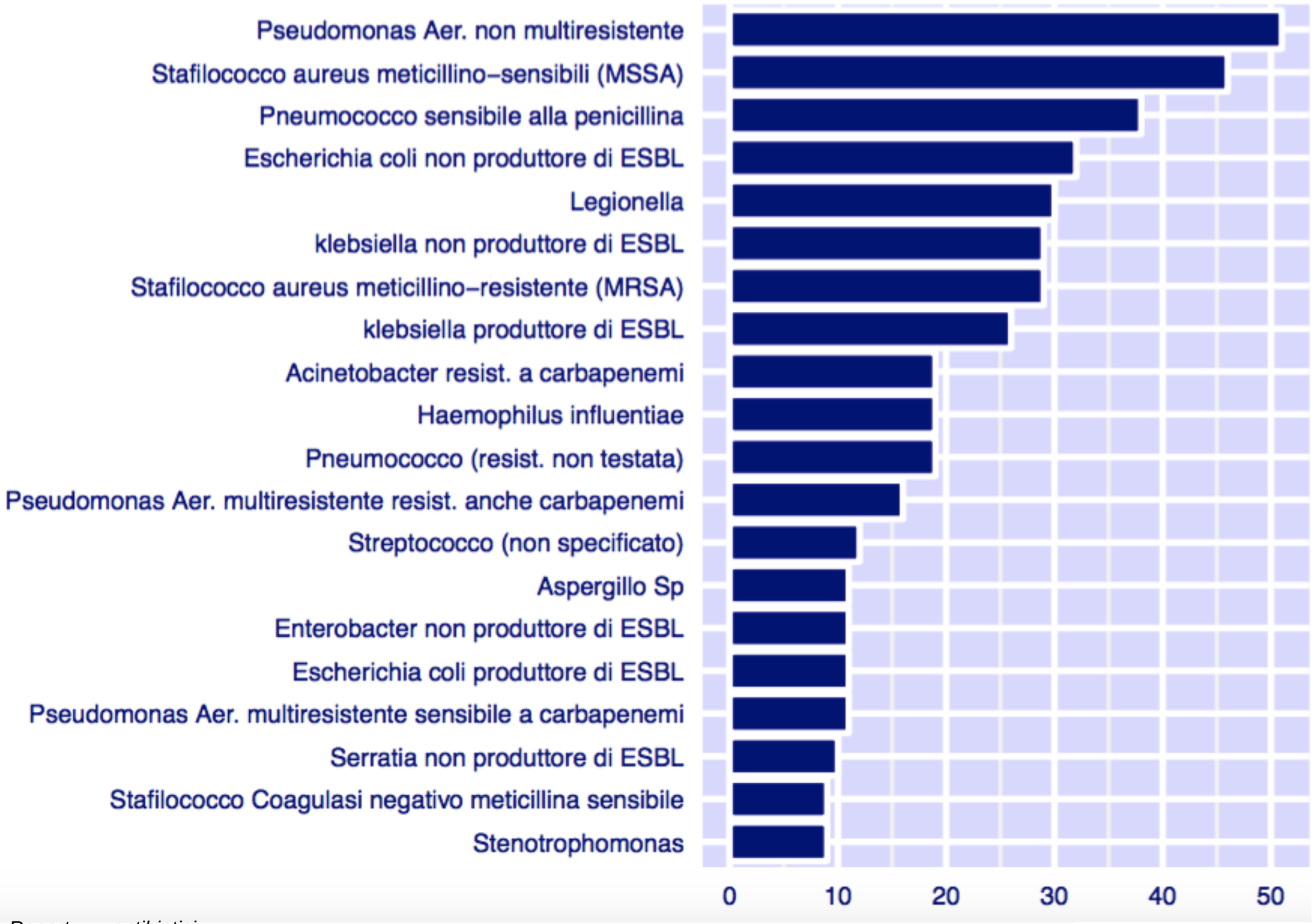
Our results suggest that tigecycline-based therapy was tolerable and the clinical outcome was comparable to that of colistin-based therapy for patients with MDR/XDRAB pneumonia. In addition, combination therapy may be more useful than monotherapy in treatment of MDR/XDRAB pneumonia



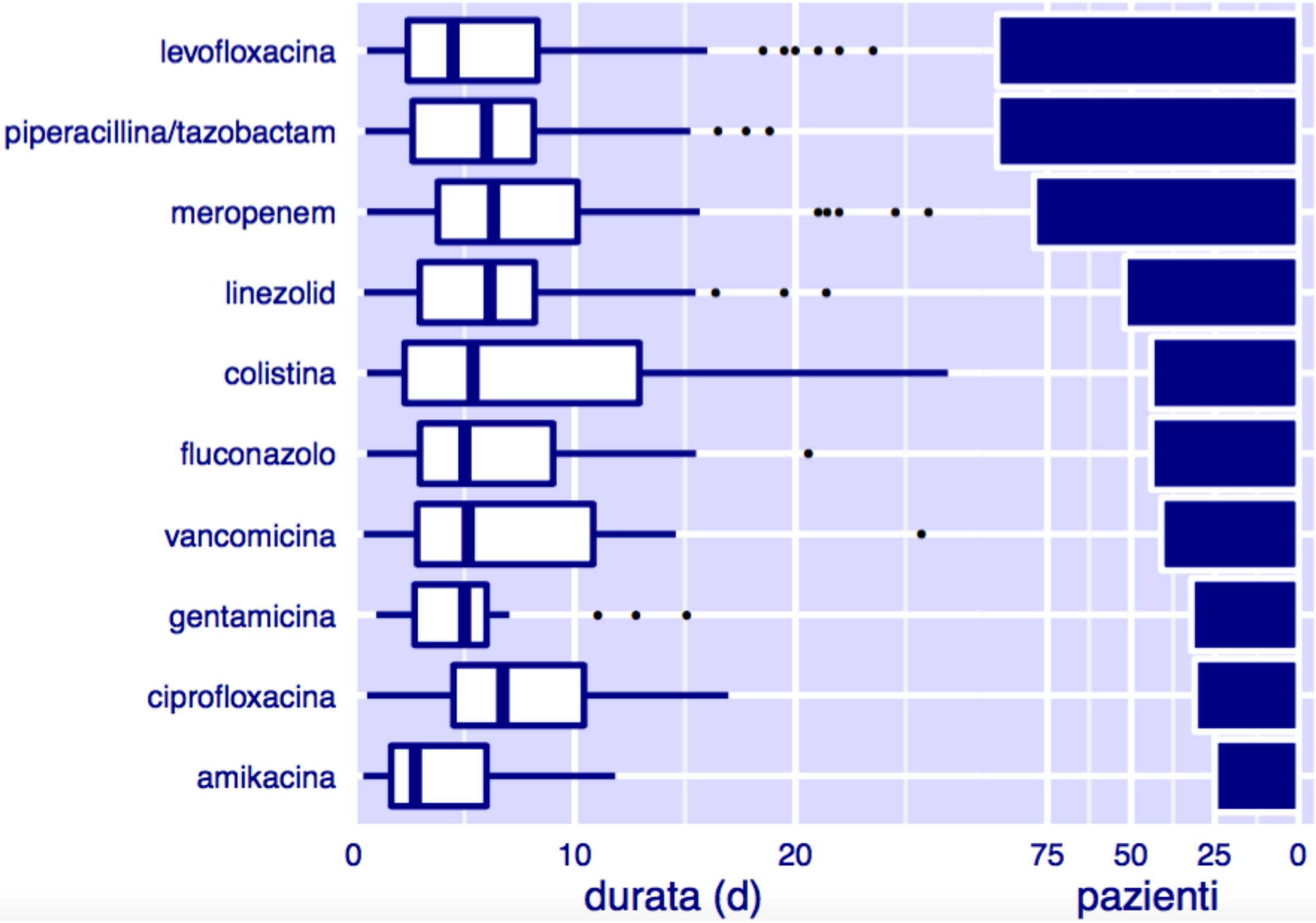
Germi Polmoniti degenza



Germi Polmoniti degenza



Mirata polmoniti



In vivo evolution of resistance of *Pseudomonas aeruginosa* strains isolated from patients admitted to an intensive care unit: mechanisms of resistance and antimicrobial exposure

Strain	Date of isolation	MIC (mg/L)[a] CAZ	FEP	TZP	CIP	IPM	MEM	Group	Resistance mechanism[b] *mexB*	*mexD*	*mexF*	*mexY*	*ampC*	OprD	Days of
16A	18/11/06	8	2	16	0.125	4	0.25	I							
16B	27/11/06	4	4	8	**2**	4	0.25	I		+ (NfxB E146K)					
144A	28/07/08	4	2	2	0.125	4	0.125	I							
144B	04/08/08	2	1	2	**2**	4	0.25	I			+ (MexS				
87A															
87B															
125															
125															
155															
155															
72A															
72B															
30A															
30B															
66A															
66B															
41A															
41B															
154															
154															
162A	17/09/08	8	8	32	0.25	2	0.25	II	+ (MexR T69P)						2 CAZ[2]
162B	29/09/08	8	8	32	**1**	**32**	**8**	II	+ (MexR T69P)		+ (unk)	–			8 MEM[2]*, 10 CIP[2], 2 TZP[1]
13A	22/01/07	4	1	4	0.125	1	0.25	II							
13B	19/02/07	**32**	**16**	**16**	0.25	**16**	**8**	II	+ (unk)			–			13 MEM[1], 12 CIP[2], 17 CAZ[2]

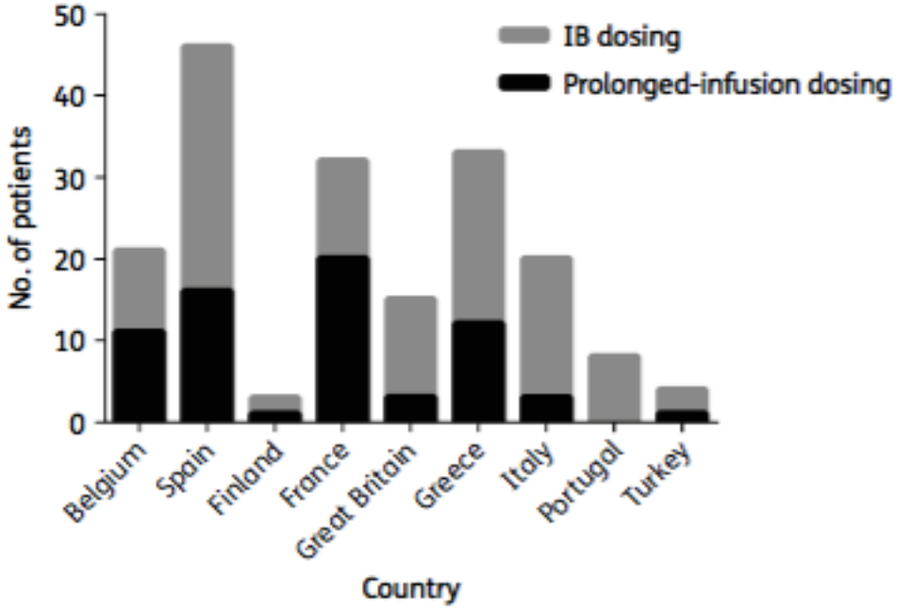
piperacillin/tazobactam combination has the lowest potenti
overproducing efflux pump and AmpC derepressed mutan

The lower ability of piperacillin/ tazobactam to select for AmpC hyperproduction may be due to the sli
tazobactam against this b-lactamase class and the higher activity of this combination against derepressed mutants

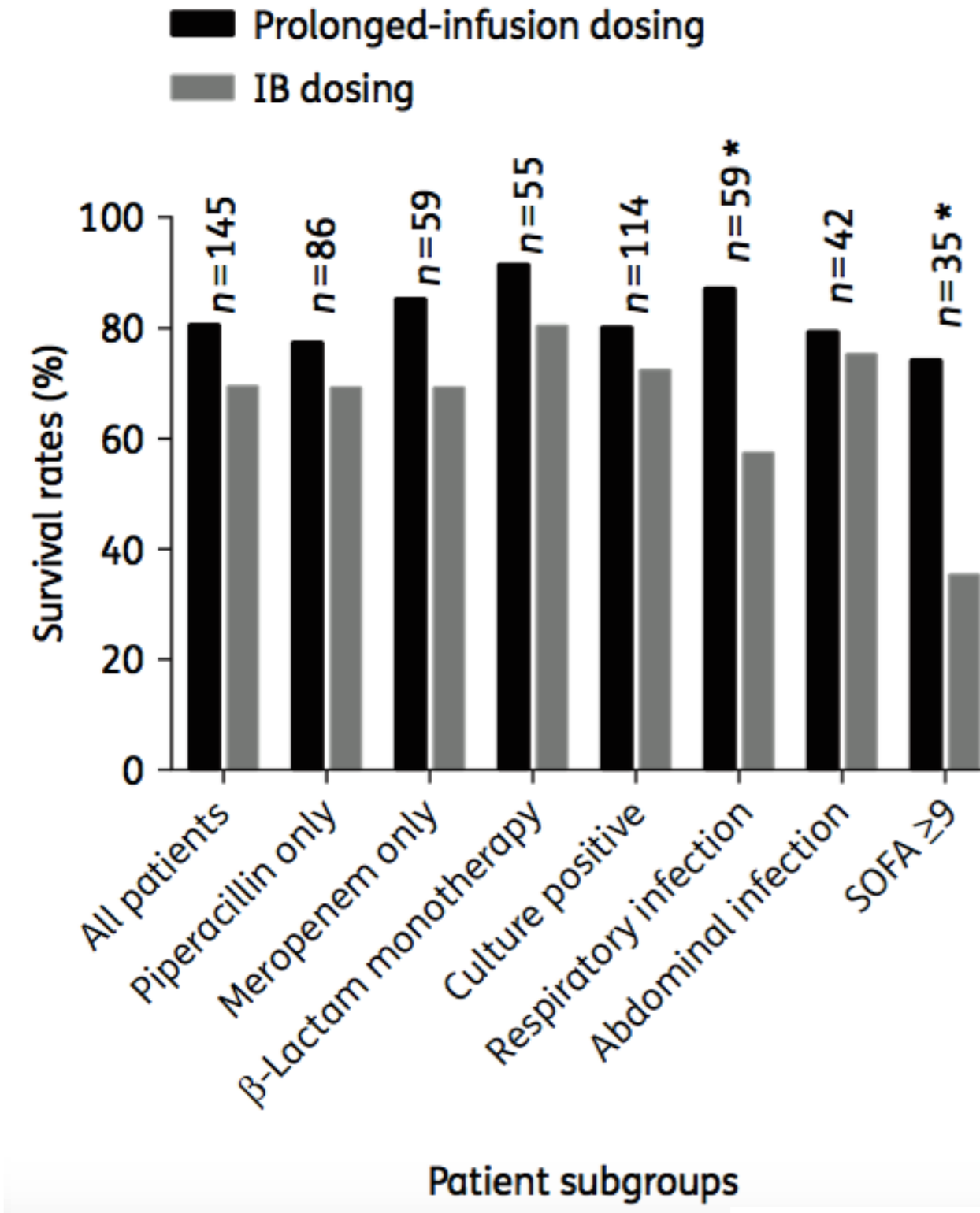
Taking into account that no strain was resistant to **amikacin**, the use of piperacillin/ tazobactam and/or amikacin seems to be appropriate for treating these complicated infections in this particular patient population.

Se **TOBRAMICINA** *R*
deve essere refertata R
anche **l'AMIKACINA**
anche se è data come S
per la presenza dell'enzima
AAC(6') che modifica
l'amikacina anche senza
dare espressione fenotipica

Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/ pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort



This study provides additional PK/PD and clinical outcome data to support the practice of administration of piperacillin/tazobactam and meropenem by prolonged infusion in critically ill patients, particularly for patients with respiratory infections



J Antimicrob Chemother 2016;71:196-207

Impact of the MIC of piperacillin/tazobactam on the outcome for patients with bacteraemia due to Enterobacteriaceae: the Bacteraemia-MIC project

GiViTI

prospective cohort study

Variable	All patients, $n=287$	Low MIC (≤4 mg/L), $n=248$	Borderline MIC (8–16 mg/L), $n=27$	P^a	High MIC (≥32 mg/L), $n=12$
Outcome at day 21					
clinical cure	227 (79.1)	200 (80.6)	19 (70.4)	0.21	8 (66.7)
improvement	34 (11.8)	26 (10.5)	6 (22.2)	0.11	2 (16.7)
failure	26 (9.1)	22 (8.9)	2 (7.4)	1	2 (16.7)
Outcome at the end of treatment with piperacillin/tazobactam					
clinical cure	57 (19.9)	47 (19.0)	7 (25.9)	0.39	3 (25.0)
improvement	185 (64.5)	162 (65.3)	18 (66.7)	0.89	5 (41.7)
failure	45 (15.7)	39 (15.7)	2 (7.4)	0.39	4 (3.3)
Mortality at day 30	31 (10.8)	26 (10.5)	3 (11.1)	1	2 (16.7)

Table 3. Estimated $fT_{>MIC}$ reached by piperacillin/tazobactam among patients with bacteraemia due to Enterobacteriaceae; only patients for whom creatinine clearance could be calculated are included ($n=251$, 87.4% of the whole series)

MIC (mg/L)	$fT_{>MIC}$ (mean ± SD)	40% $fT_{>MIC}$, n (%)	50% $fT_{>MIC}$, n (%)	100% $fT_{>MIC}$, n (%)
≤1 ($n=86$)	98.53 ± 7.39	86 (100)	85 (98.8)	80 (93.0)
2 ($n=87$)	97.31 ± 7.19	87 (100)	87 (100)	75 (86.2)
4 ($n=47$)	96.66 ± 7.46	47 (100)	47 (100)	34 (72.3)
8 ($n=13$)	82.80 ± 22.34	13 (100)	11 (84.6)	5 (38.5)
16 ($n=8$)	73.77 ± 20.74	8 (100)	7 (87.5)	2 (25.0)
≥32 ($n=10$)	43.45 ± 37.92	6 (60)	5 (50.0)	0 (0)

*EUCAST recommends considering Enterobacteriaceae with **MICs** of ≤8 mg/L as susceptible, MICs of 16 mg/L are intermediate and those with >16 mg/L as resistant; intermediate MIC can be higher doses*

Optimizing the Initial Amikacin Dosage in Adults

White BP

We clearly show that the regulatory approved dose of 15 mg/kg/day is expected to be suboptimal based on PK-PD targets. Recent clinical studies corroborate this approach by suggesting that an initial amikacin dose ≥ 25 mg/kg is likely needed as empirical therapy of certain Gram- negative infections

Crit

Intensive Care Med 2014;40:998-

Cmax/MIC≥10
AUC/MIC≥75

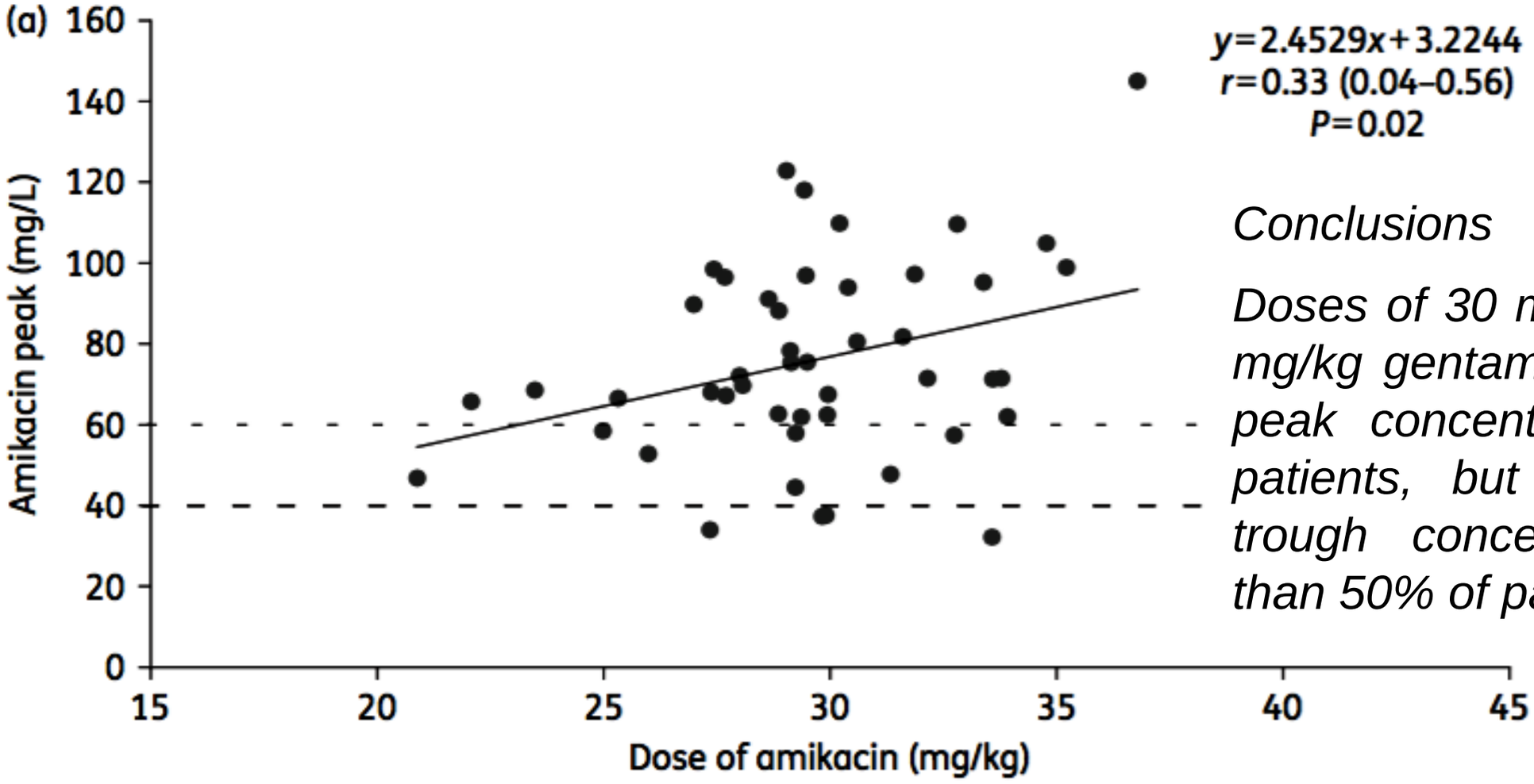
A 2,400

Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis

harmacol 2015;71:75-

ment and

Recent recommendations suggest target peak concentrations of 30–40 mg/L for gentamicin and 60 – 80 mg/L for amikacin (EUCAST)

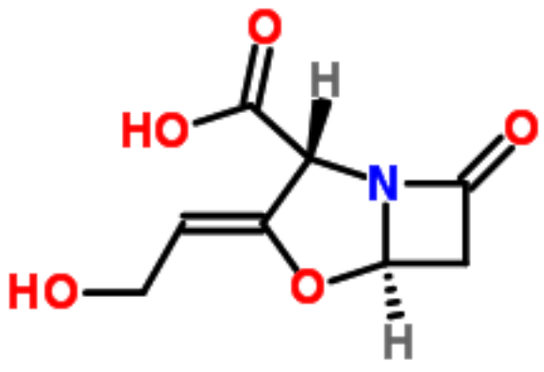


Conclusions

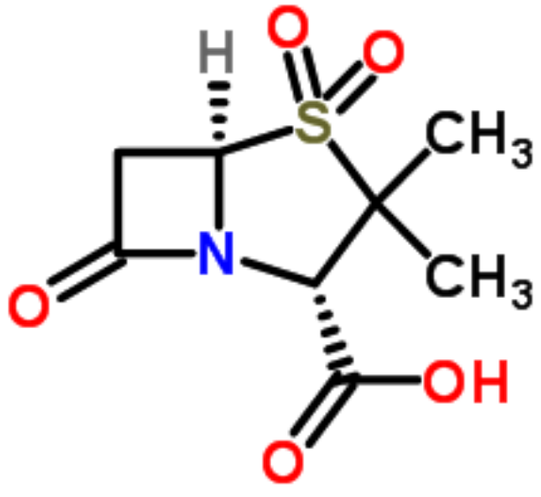
Doses of 30 mg/kg amikacin or 8 mg/kg gentamicin led to targeted peak concentrations in 59% of patients, but they led to high trough concentrations in more than 50% of patients

J Antimicrob Chemother 2016;71:208-212

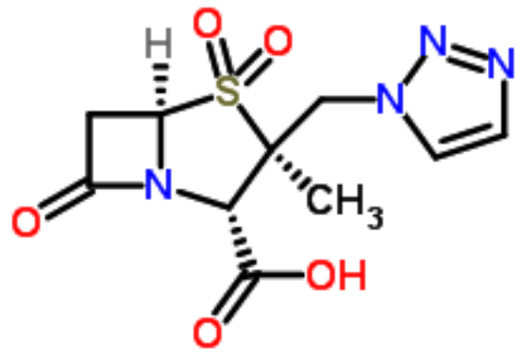
Old β-lactamase inhibitors



Clavulanic acid



Sulbactam



Tazobactam

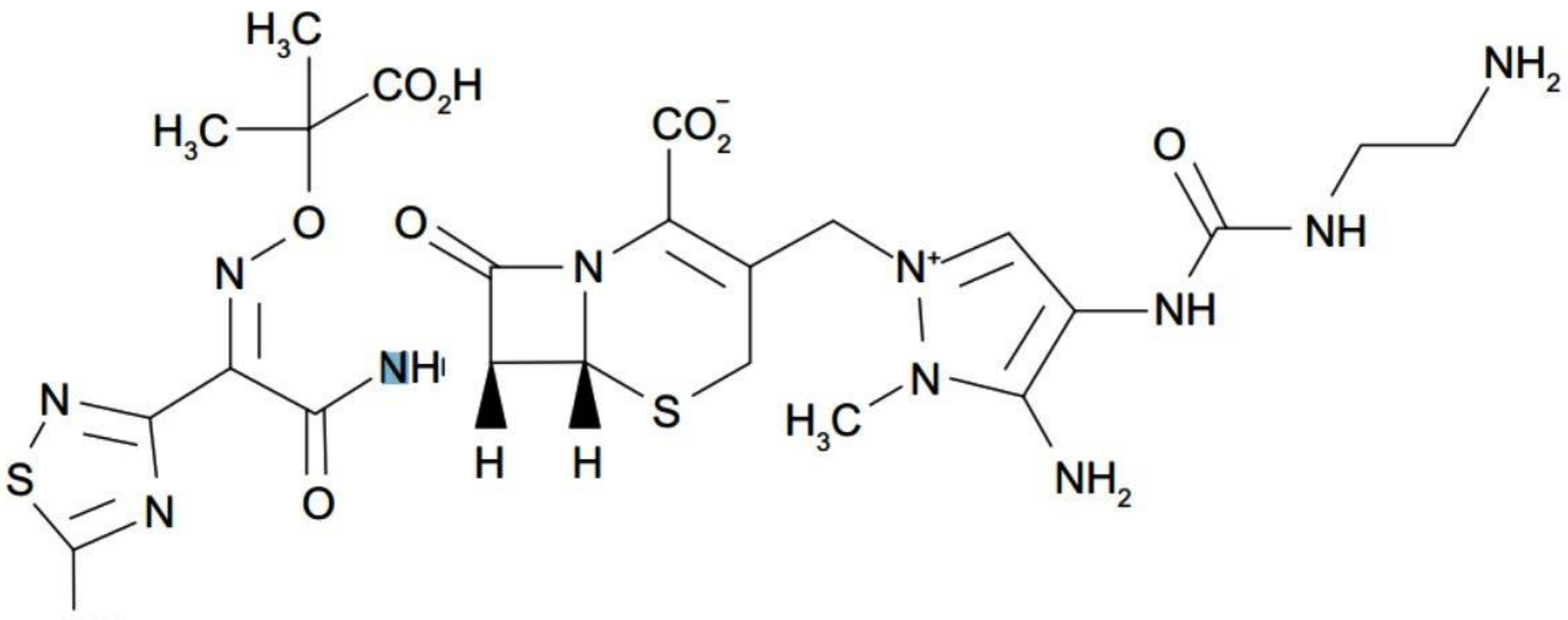
Activity vs:

- *Broad-spectrum β-lactamases and ESBLs of class A (TEM, SHV, CTX-M)*

No/poor activity vs:

- *Carbapenemases (MBLs, KPC, OXA)*
- *AmpC-type β-lactamases*
- *OXA-type β-lactamases*
- *Inhibitor-R TEM (IRTs)*

nging the b-lactam partner: Ceftolozane-Tazobactam



Activity vs:

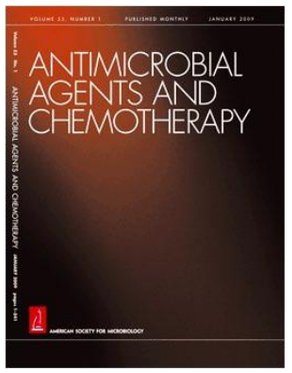
- *Broad-spectrum β-lactamases and ESBLs of class A (TEM, SHV, CTX-M)*
- *AmpC-type B-lactamases*
- *Some class D oxacillinases (OXA-1)*

No/poor activity vs:

- *Carbapenemases (MBLs, KPC, OXA)*
- *OXA-type β-lactamases*

Ceftolozane: basis for potent anti-Pseudomonas activity

- Stable *vs*. *Pseudomonas* AmpC beta-lactamase
- Entry independent of OprD porin
- Not affected by efflux systems (MexAB, MexXY)



Resistance Mechanisms	Outer Membrane Porin Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane				
Ceftazidime				
Cefepime	●	◐	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

The 6th generation of cephalosporins?

● Not affected ◐ Partially affected ○ Affected

Castanheira et al – AAC 2014

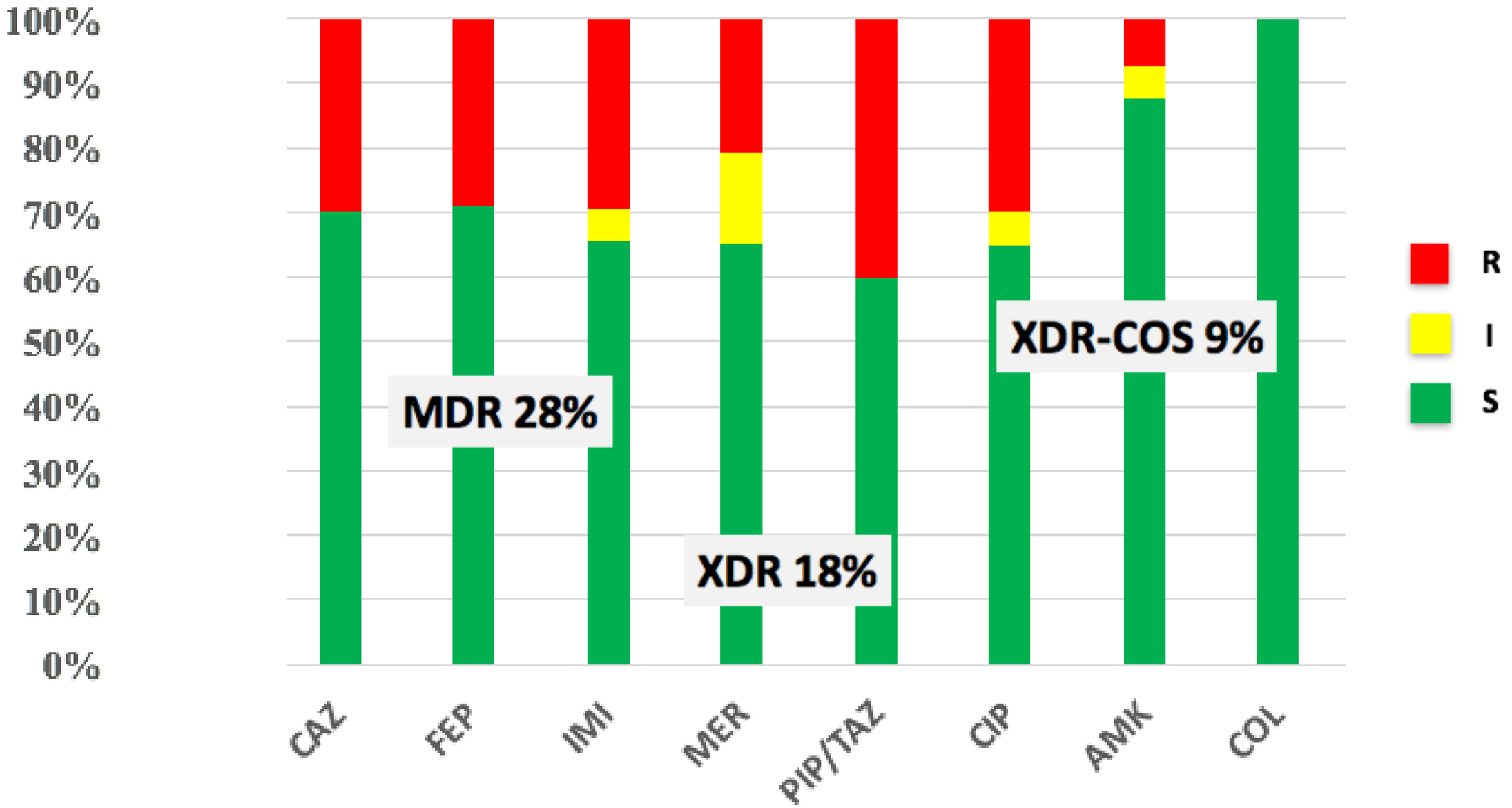
Pseudomonas aeruginosa
(Italian countrywide surveillance 2013-14)

Centers involved: 20

Study period : Sep. 2013- Nov. 2014

939 *P. aeruginosa* from HAP/VAP or BSI

domonas aeruginosa Italian countrywide surveillance

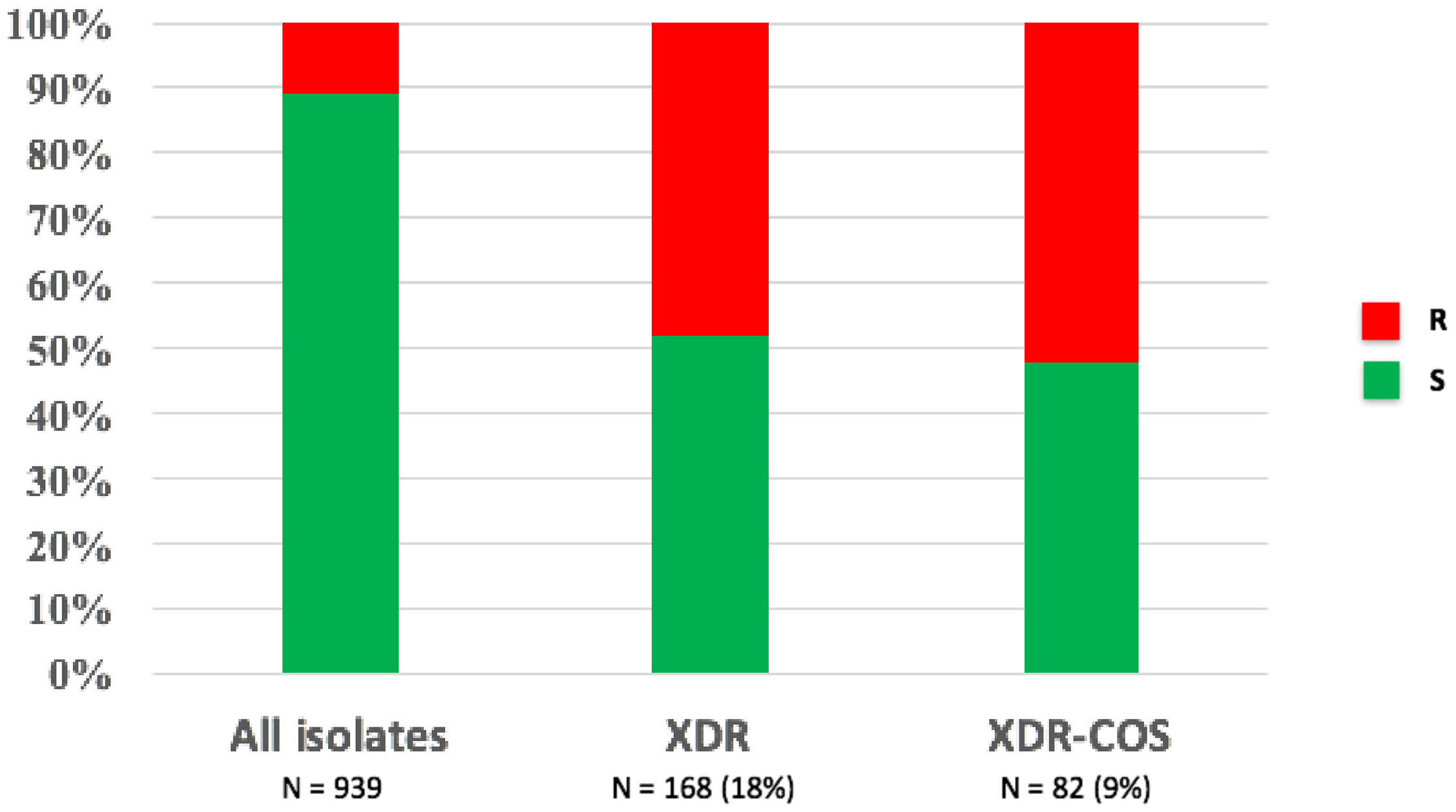


N = 939 nonreplicate isolates from BSI or HAP/VAP

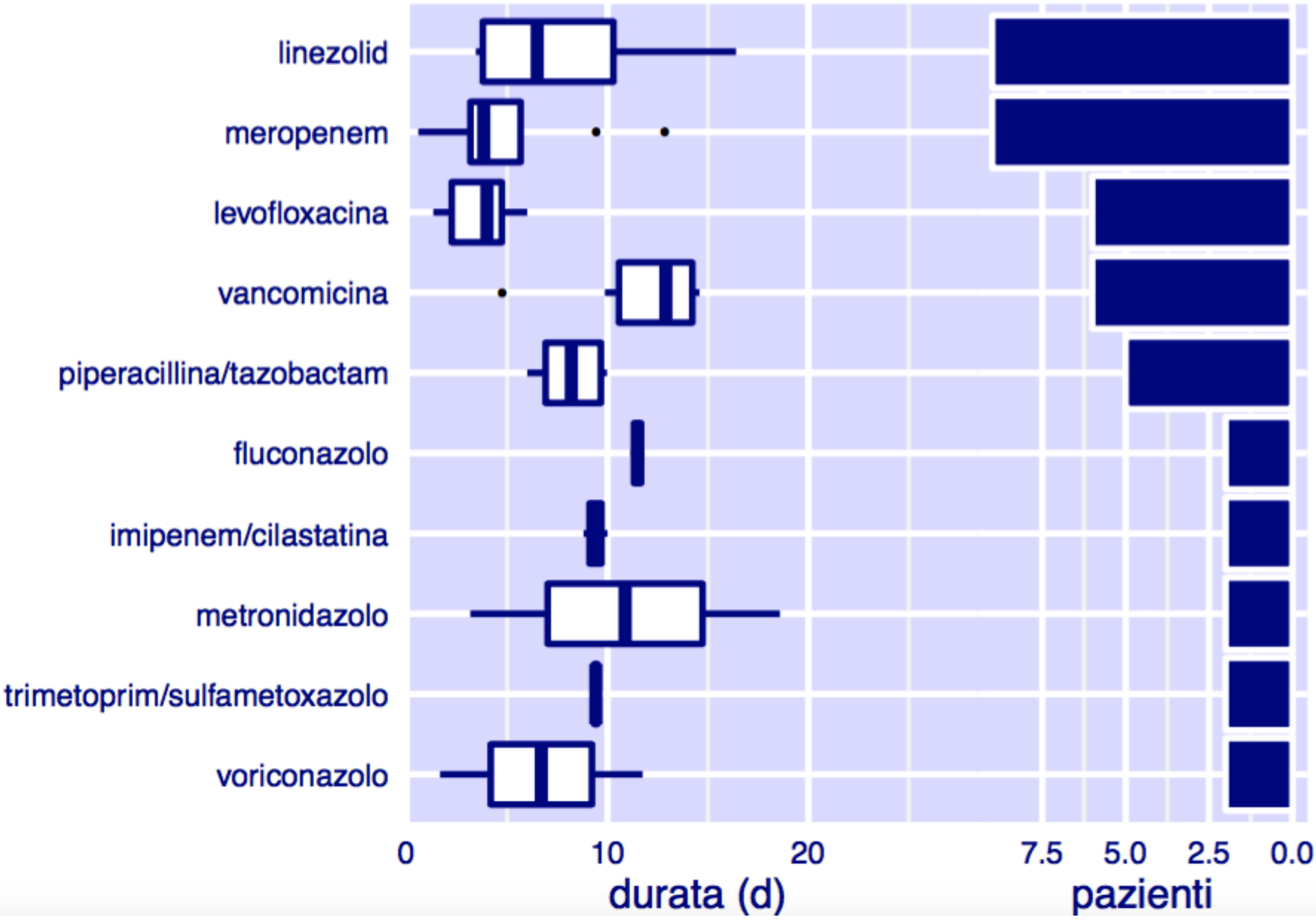
Interpretation according to EUCAST breakpoints (6.0)

ozane/Tazobactam vs XDR Pseudomonas aeruginosa

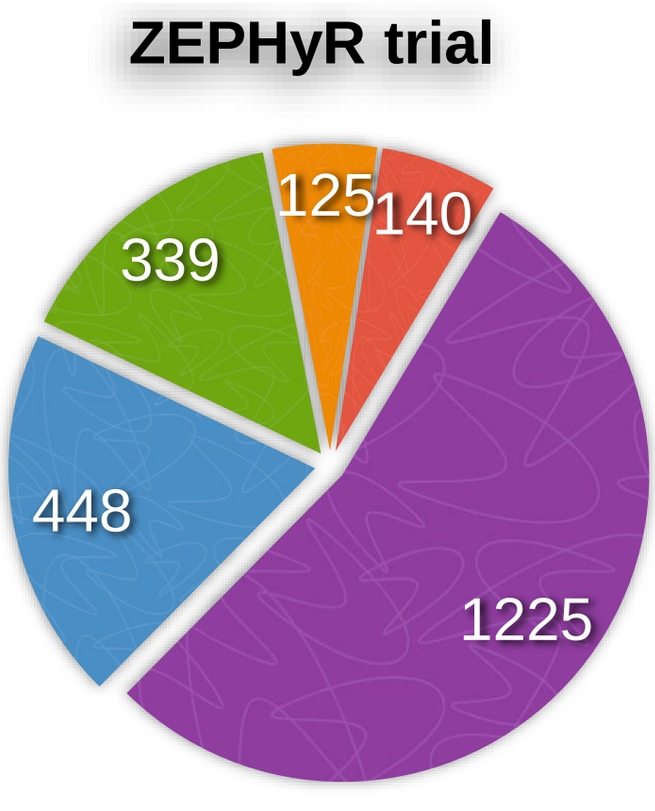
(Italian countrywide surveillance 2013-14)



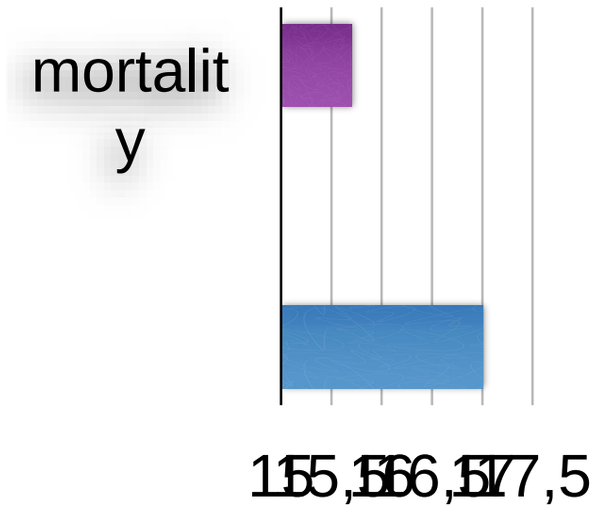
Mirata Polmoniti MRSA

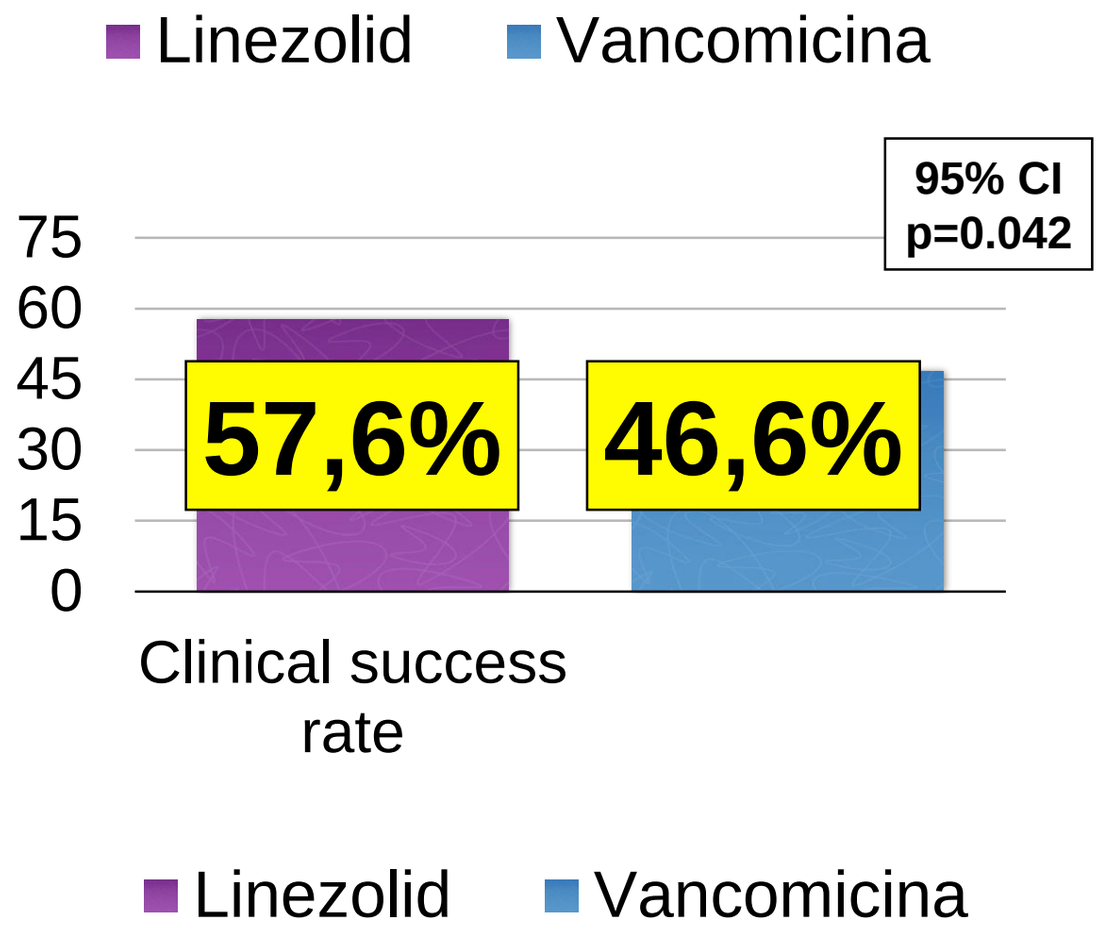


ZEPHyR trial

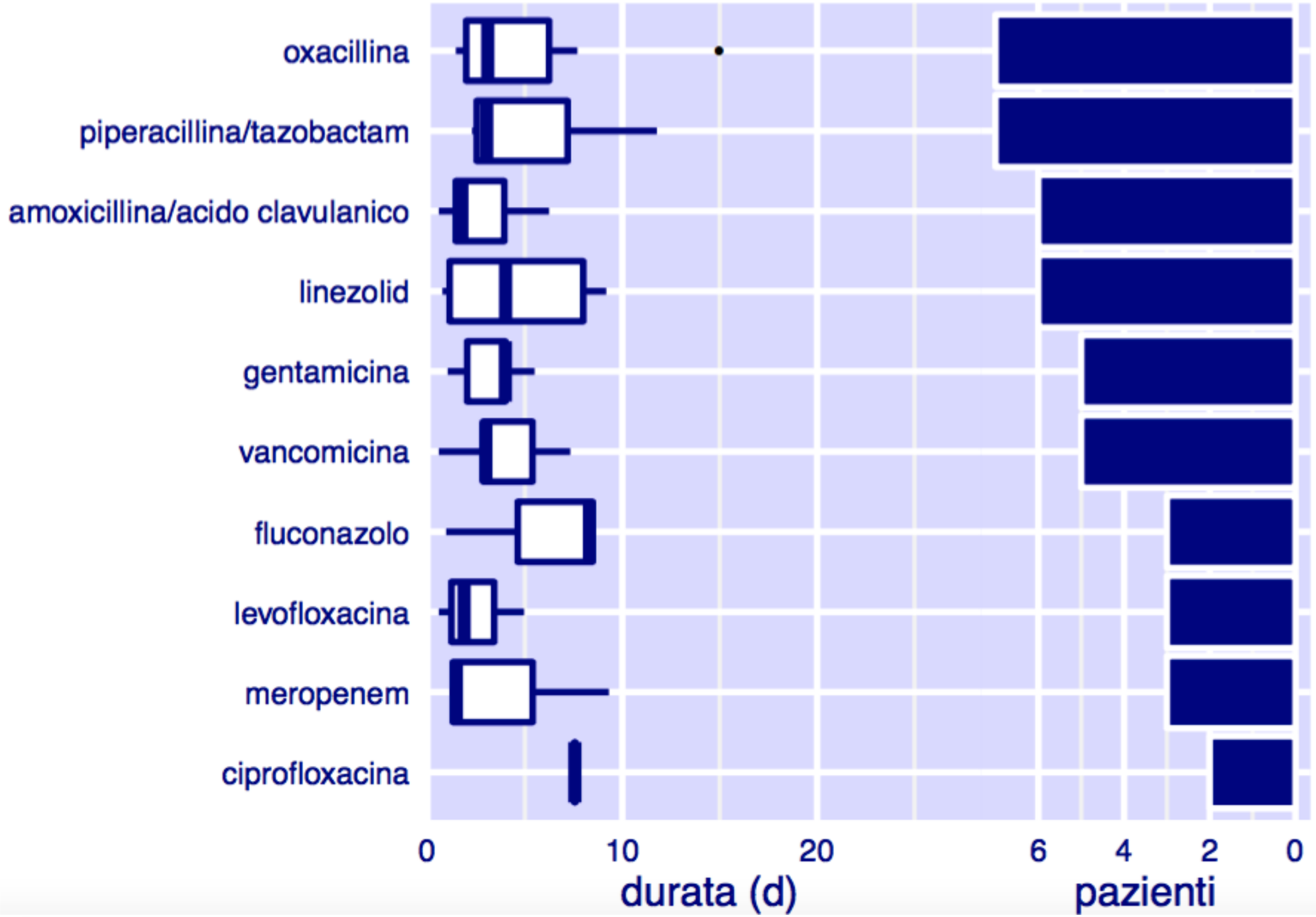


- pazienti randomizzati
- polmoniti da MRSA
- inclusi nello studio
- gruppo LZD (68.3%)
- gruppo Vanco (74,5%)





Mirata MSSA


oxacillina
piperacillina/tazobactam
amoxicillina/acido clavulanico
linezolid
gentamicina
vancomicina
fluconazolo
levofloxacina
meropenem
ciprofloxacina
0
10
20
durata (d)
6
4
2
0
pazienti

Schweizer *et al. BMC Infectious Diseases* 2011, 11:279
http://www.biomedcentral.com/1471-2334/11/279

BMC Infectious Diseases

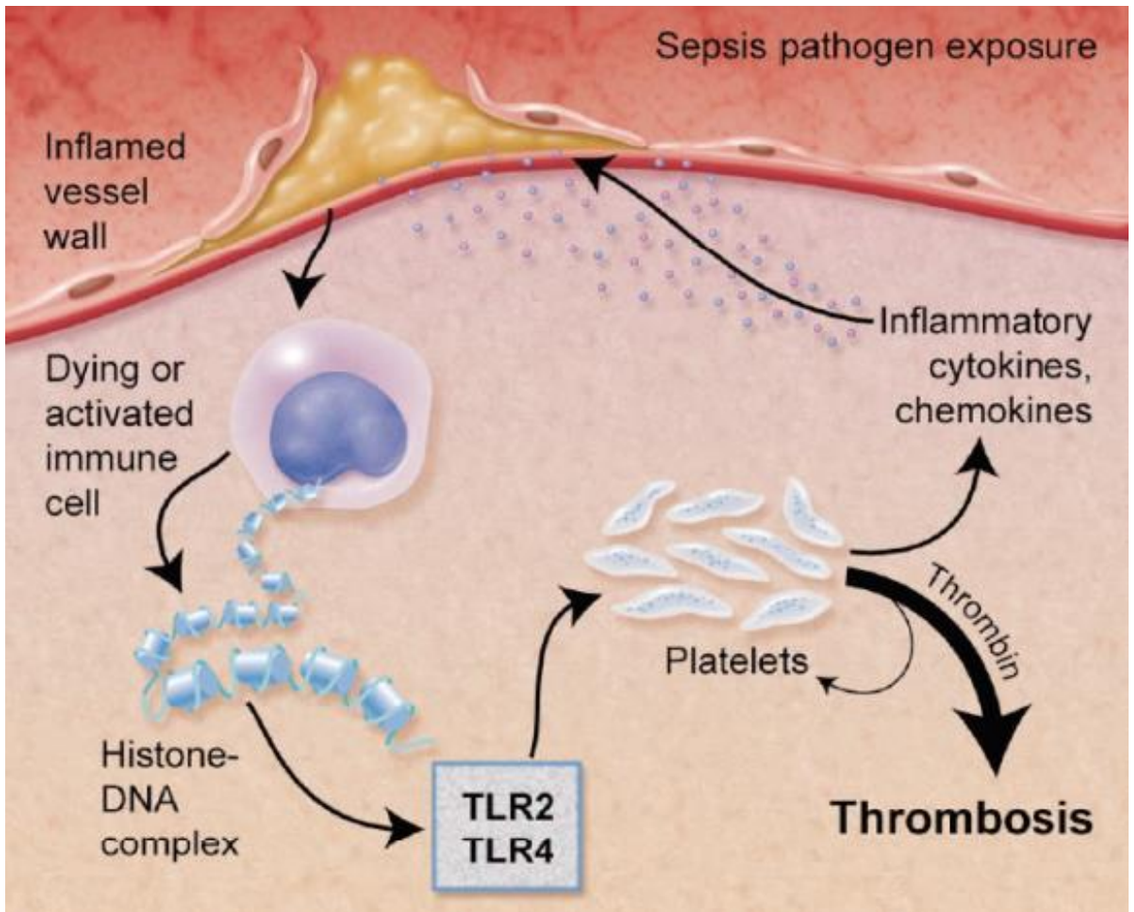
GiViTI

RESEARCH ARTICLE Open Access

Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia

Marin L Schweizer[1,2,3*], Jon P Furuno[1], Anthony D Harris[1], J Kristie Johnson[4], Michelle D Shardell[1], Jessina C McGregor[5], Kerri A Thom[1], Sara E Cosgrove[6], George Sakoulas[7,8] and Eli N Perencevich[1,2,3]

Among the 122 ptz who initially received vancomycin empirically, those who were switched to naftcillin or cefazolin (66/122) had **69% lower mortality** hazards compared to those who remained on vancomycin



I Glicopeptidi intrinsecamente sono meno efficaci contro gli stafilococchi rispetto ai beta-lattamici con potere anti stafilococcico

le penicilline semi-sintetiche come l'oxacillina presentano un potente effetto battericida in vitro se comparato con i glicopeptidi.

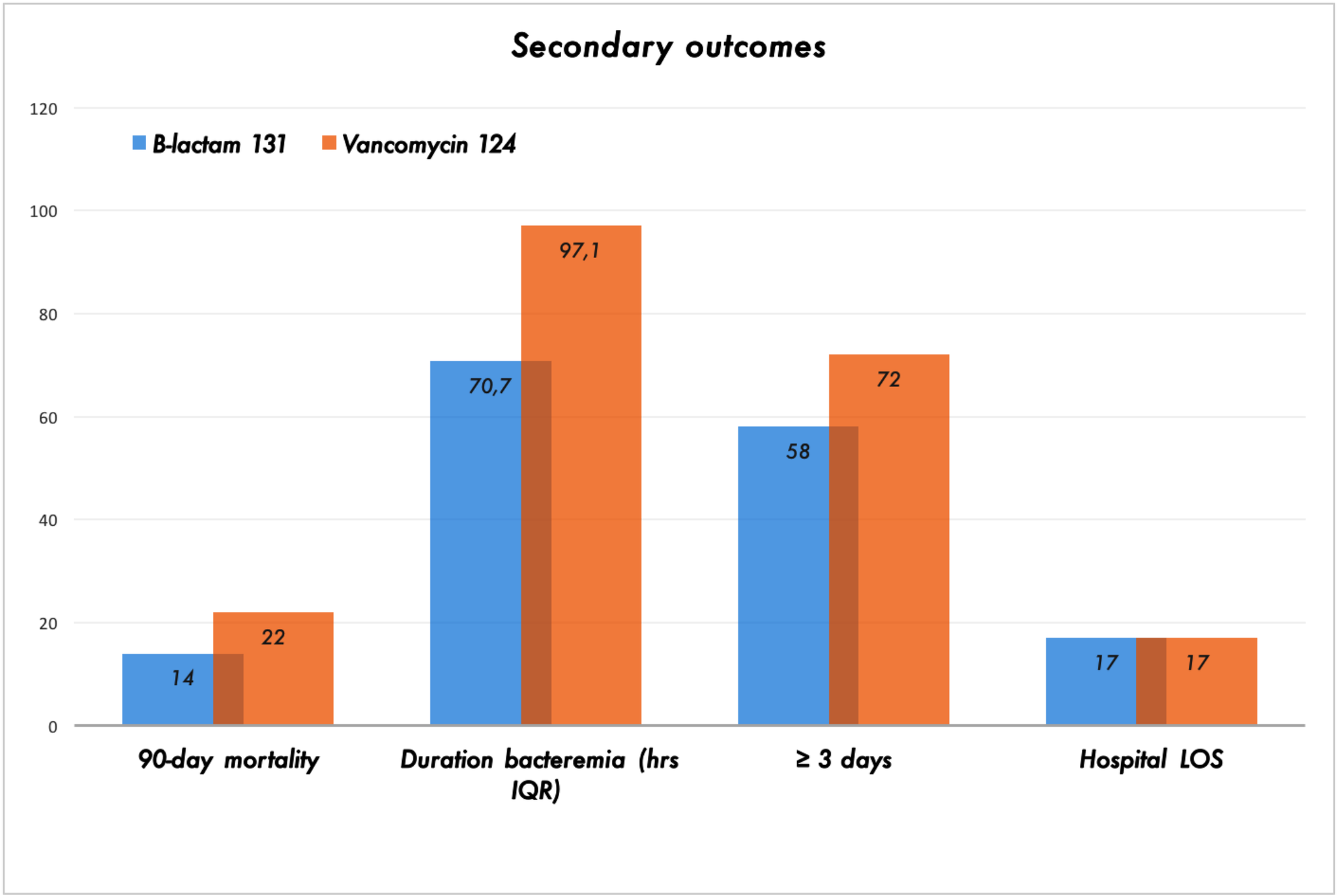
l'oxacillina interagisce sinergicamente con peptidi antimicrobici cationici chiamati tPMP-1 (thrombin-induced platelet microbicidal protein) che posseggono potente attività battericida

Blood 201;118:1714-1715

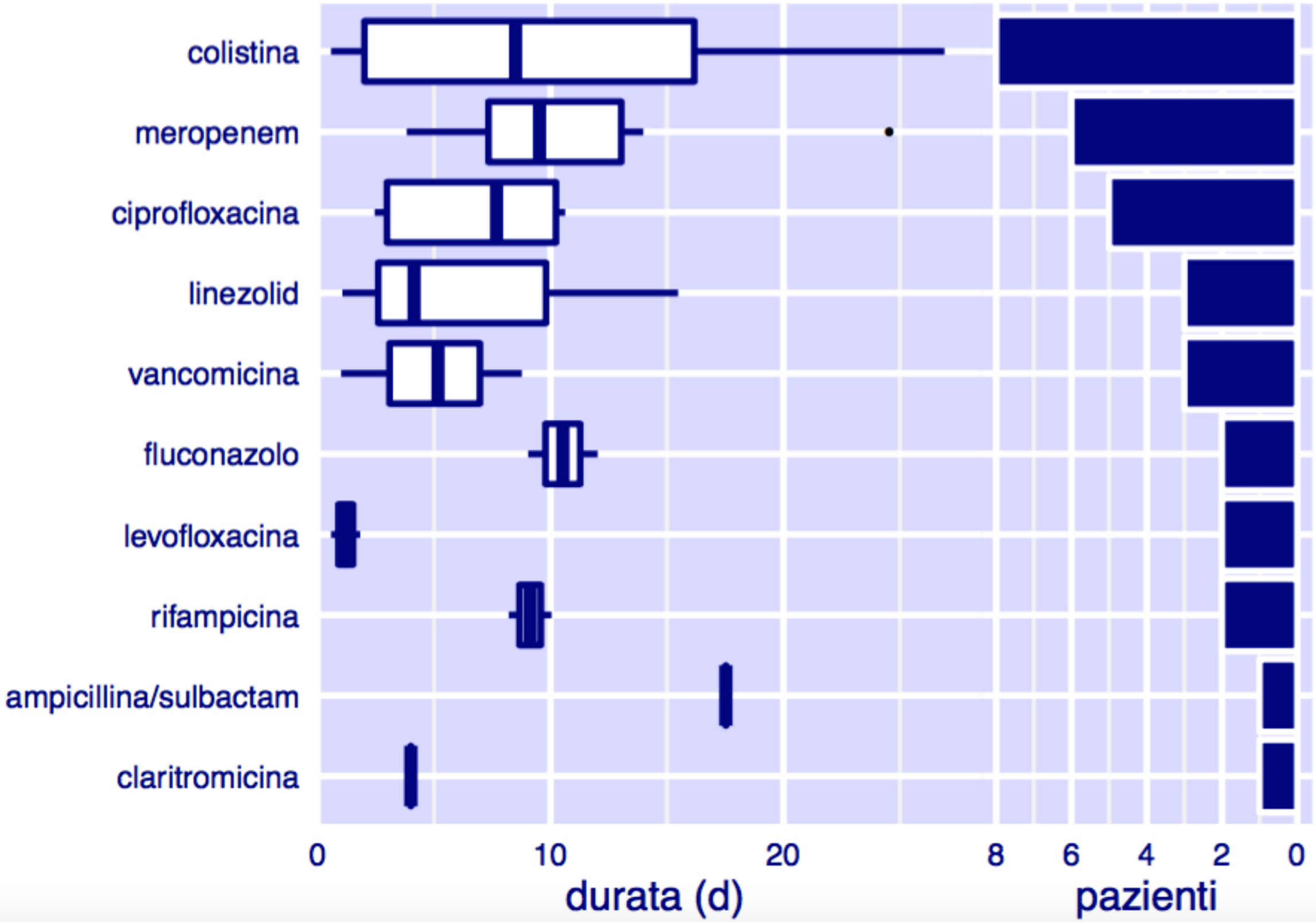
RESEARCH Open Access

Annals of Clinical Microbiology and Antimicrobials

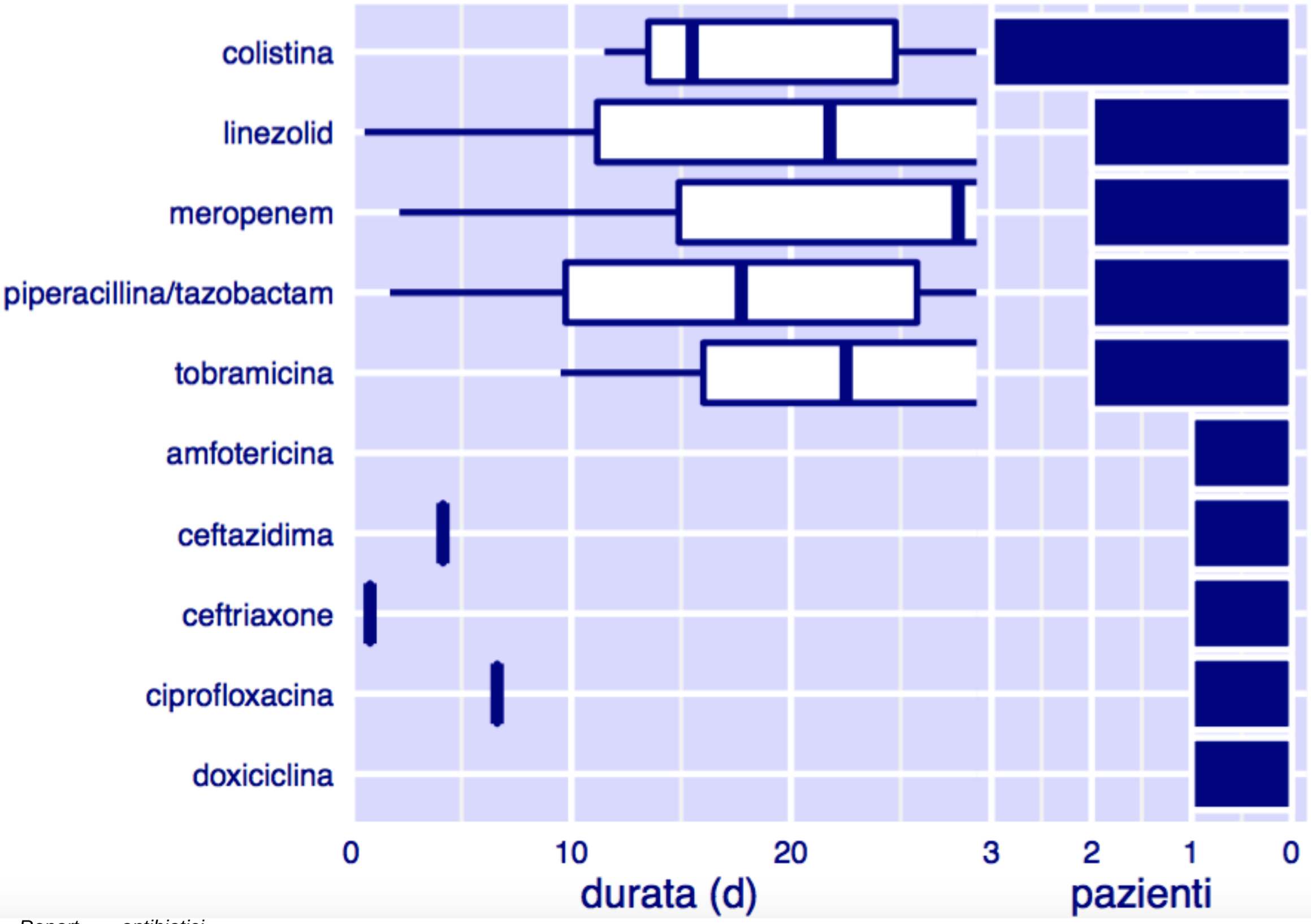
Comparative effectiveness of β-lactam versus vancomycin empiric therapy in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia



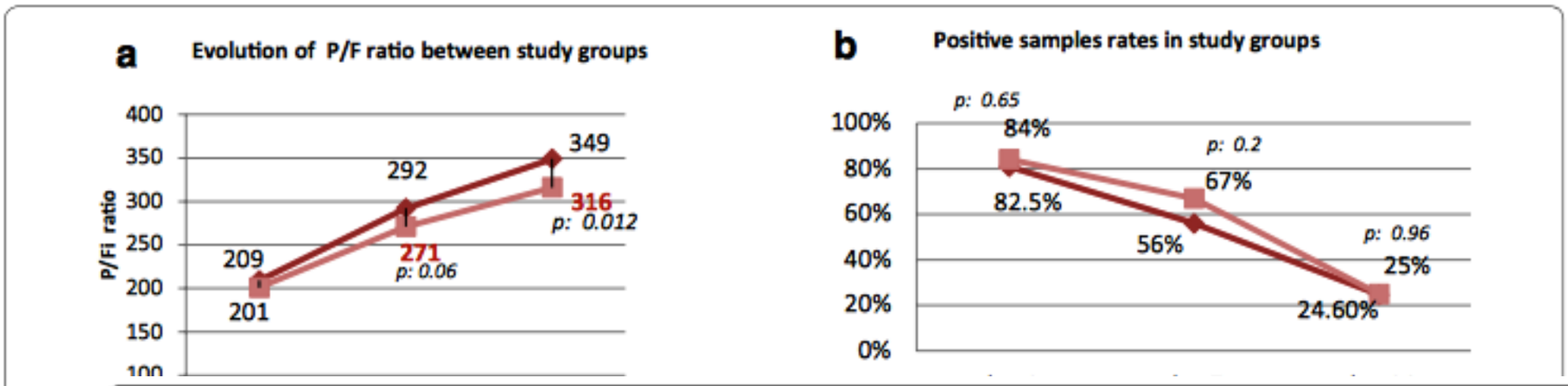
Mirata Polmoniti AciBau Carba R



Mirata Polmoniti
Pseudomonas Carba R



Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial



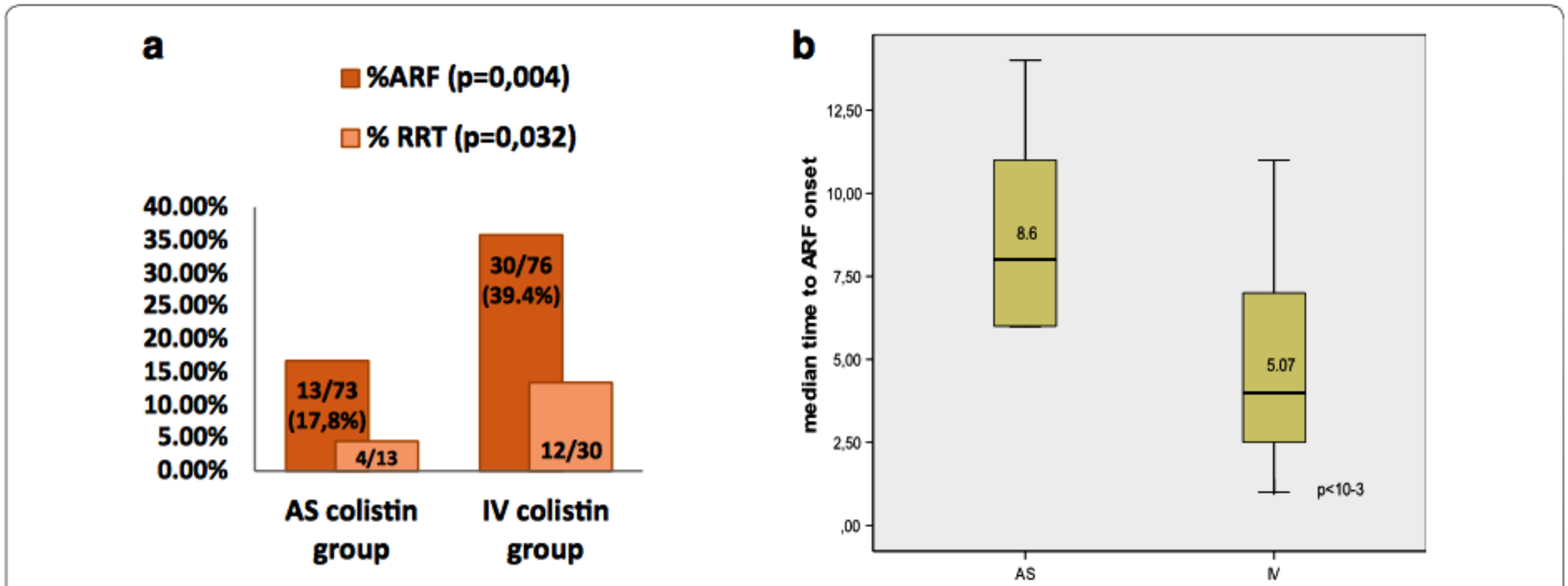


Fig. 4 (TBE) b

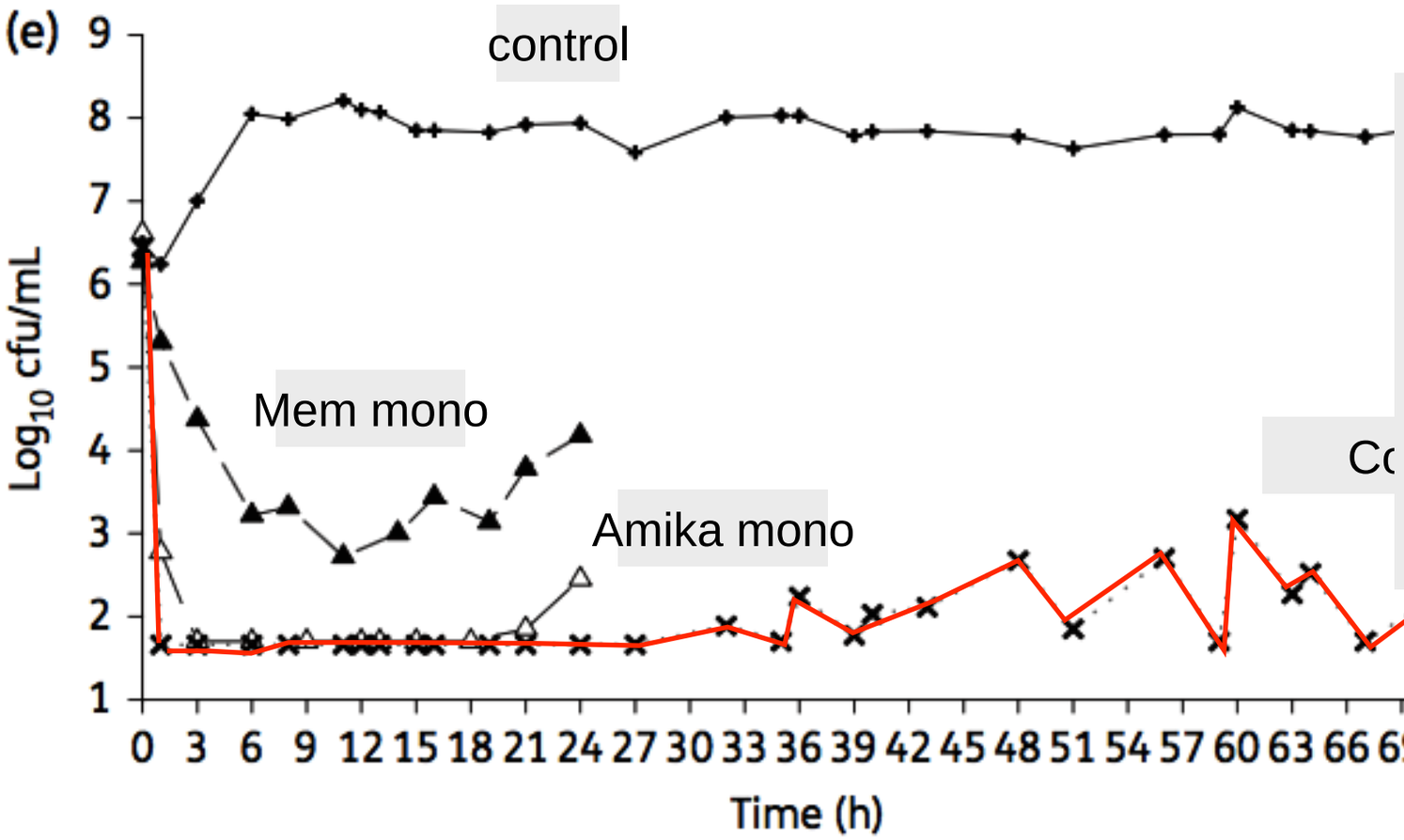
Fig. 5 **a** Incidence of acute renal failure (ARF) and necessity of replacement renal therapy (RRT) in both groups. **b** Mean time to ARF onset in both groups

Antibacterial activity of achievable epithelial lining fluid exposures of Amikacin Inhale with or without meropenem

inhaled amikacin 400 mg every 12h
ELF

iv meropenem 2gr every 8h

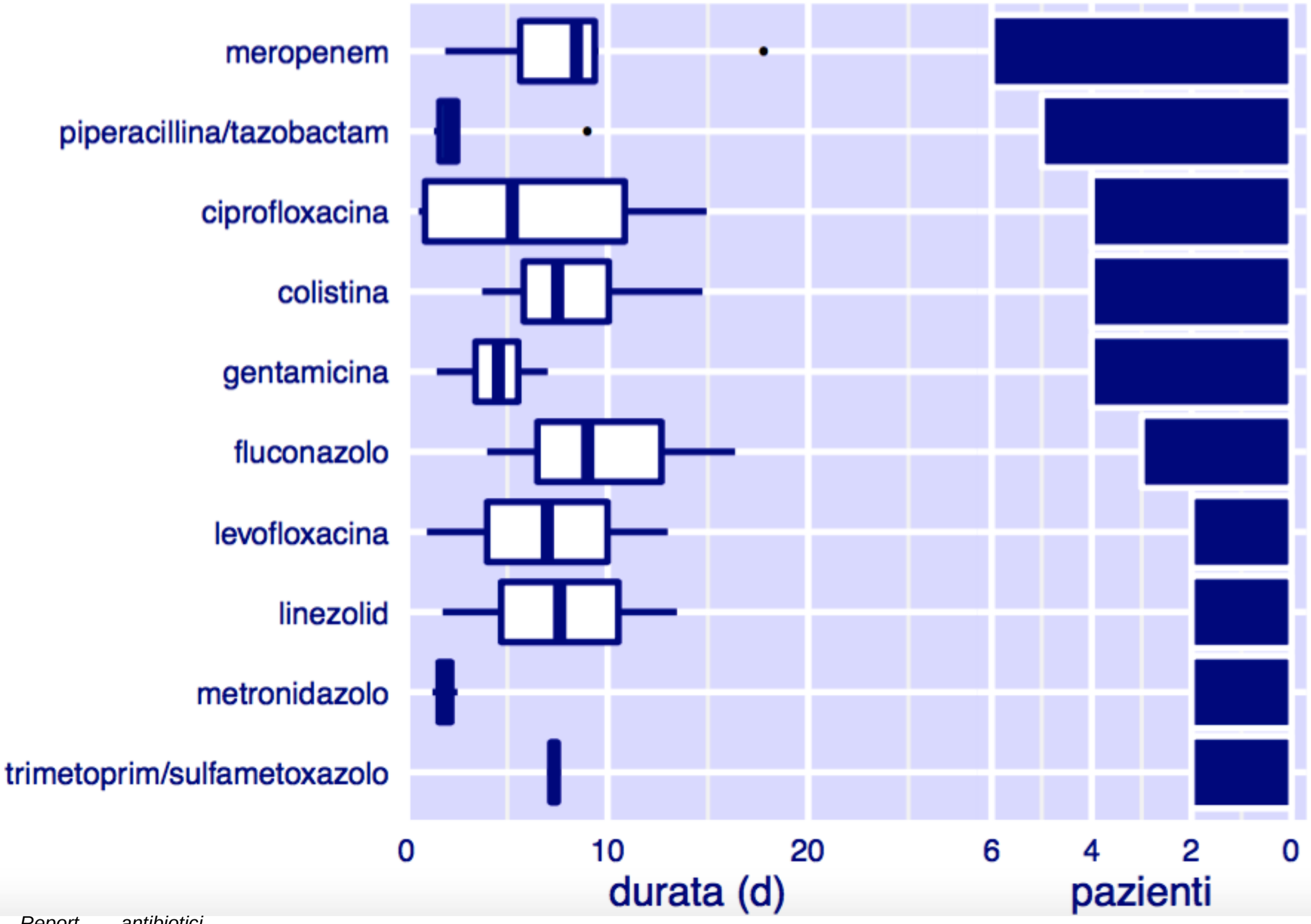
combo



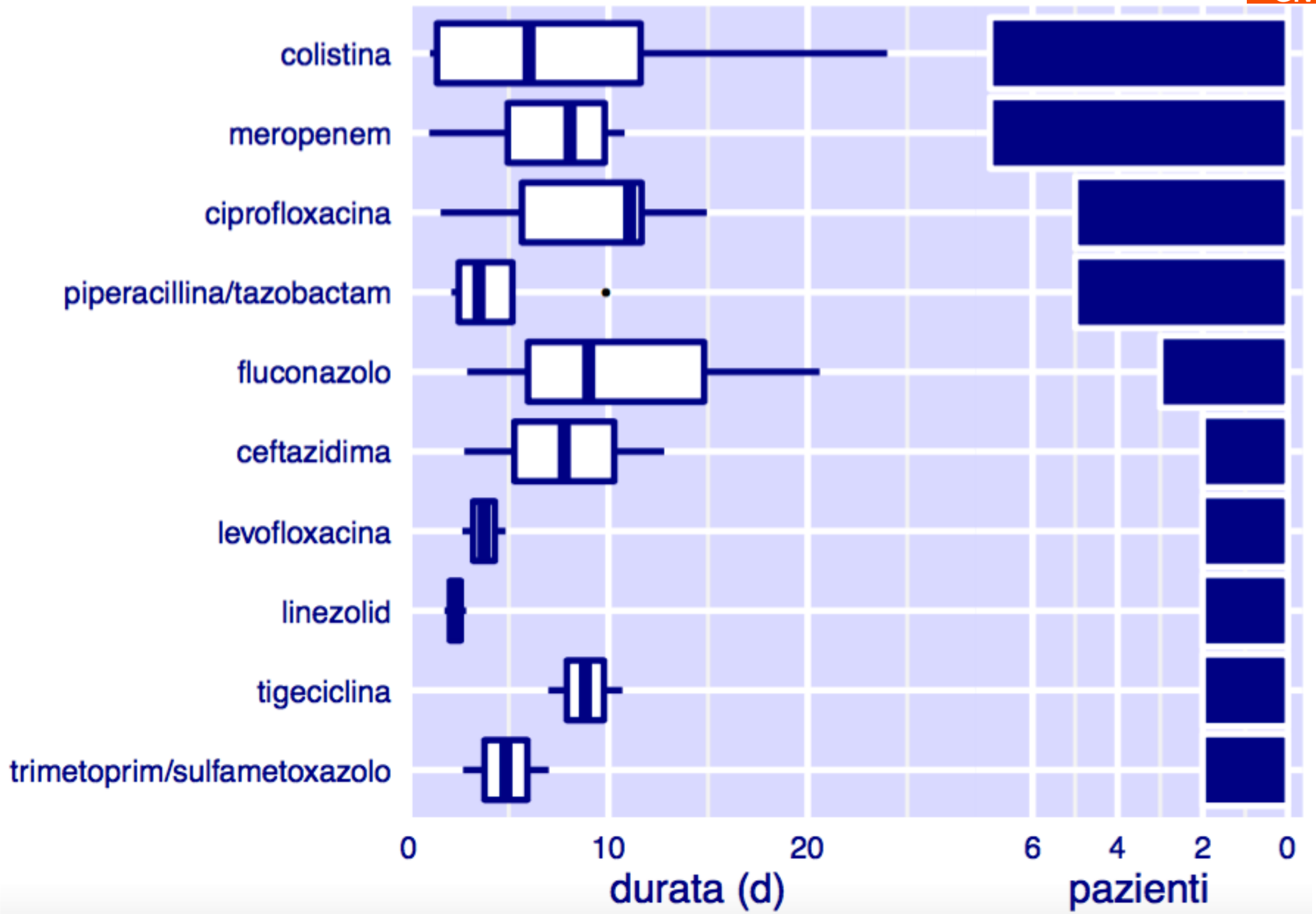
Inhaled **AMIKACIN** monotherapy showed bactericidal activity against most isolates tested with amikacin MICs ≤256 mg/L. ADJUNCT INHALED **AMIKACIN PLUS MEROPENEM** sustained this activity for 72 h for the tested isolates with amikacin/meropenem MIC ≤64/32 mg/L.

Isolate number[b]	MLST[c]	Genotype	Amikacin MIC (mg/L)	Meropenem MIC (mg/L)
PSA 1504[d,e]	254	*aph(3′)-IIb*, bla_{OXA-50}, *catB4*, *fosA1*, probable MexXY-OprM mutation(s)	64	2

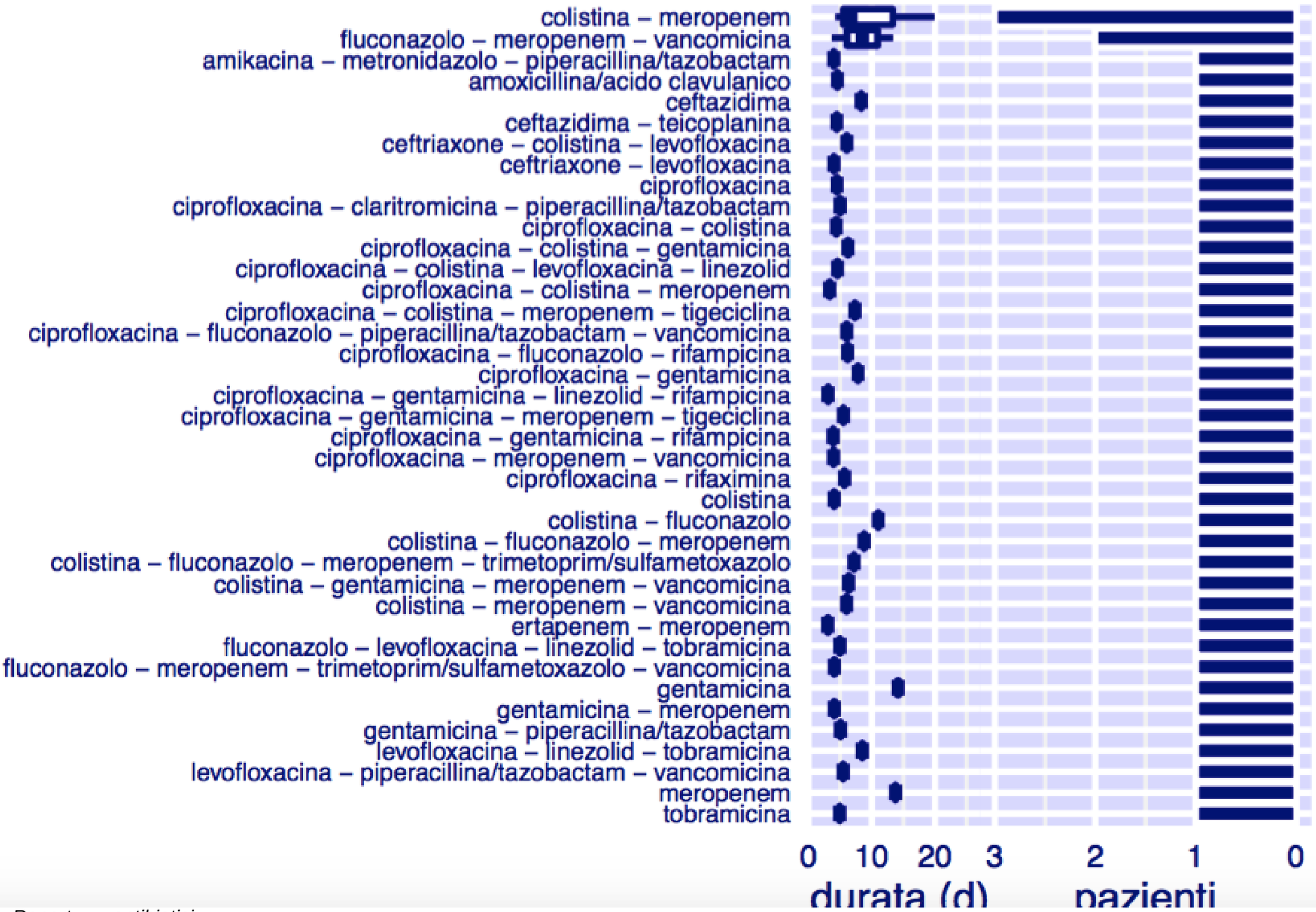
Mirata BSI/Endocarditi Klebsiella KPC



Mirata Polmoniti
Klebsiella KPC



Mirata KPC durata > 72 ore



Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Tumbarello M

Mortality rates: *30.4% tigecycline plus colistin; 50% tigecycline plus gentamicin; 57% colistin plus gentamicin; 12.5% tigecycline, colistin, and meropenem; and 16.6% tigecycline, gentamicin, and meropenem*

GiViTI

Variable	No. (%) of Patients: Nonsurvivors (n = 52)	Survivors (n = 73)	*P* Value	OR (95% CI)
Univariate analysis				
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	.54	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.36 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	.002	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	<.001	…

Clin Infect Dis 2012;67(11):2560-2569

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

Tumbarello M

Table 3. Impact of combination therapy versus monotherapy on 14 day mortality in patients with infections caused by KPC-Kp

	Numbers (%) of non-survivors: all	those who received combination therapy	those who received monotherapy	OR (95% CI)	*P*
Infection characteristics					
BSI	173/447 (38.7)	93/291 (32.0)	80/156 (51.3)	0.45 (0.29–0.68)	<0.001
low-risk BSI	32/103 (31.1)	19/74 (25.7)	13/29 (44.8)	0.42 (0.16–1.16)	0.06
high-risk BSI	141/344 (41.0)	74/217 (34.1)	67/127 (52.8)	0.46 (0.29–0.74)	<0.001
non-bacteraemic infections (all)	52/214 (24.3)	14/63 (22.2)	38/151 (25.2)	0.85 (0.39–1.78)	0.65
lower respiratory tract	34/85 (40.0)	8/32 (25.0)			
intra-abdominal	12/42 (28.6)	4/17 (23.5)			
urinary tract	4/82 (4.9)	1/11 (9.1)			
other	2/5 (40.0)	1/3 (33.3)			
clinical presentation					
septic shock	57/100 (57.0)	30/67 (44.8)	27/33 (81.8)	0.18 (0.05–0.53)	<0.001
APACHE III score ≥15	208/481 (43.2)	98/267 (36.7)	110/214 (51.4)	0.55 (0.37–0.80)	0.001
KPC-Kp isolate characteristics					
colistin resistant	62/132 (47.0)	23/54 (42.6)	39/78 (50.0)	0.74 (0.35–1.58)	0.40
tigecycline resistant	51/152 (33.5)	29/91 (31.9)	22/61 (36.1)	0.83 (0.40–1.74)	0.59
gentamicin resistant	47/118 (39.8)	25/69 (36.2)	22/49 (44.9)	0.70 (0.31–1.57)	0.34
meropenem MIC ≤8 mg/L	79/243 (32.5)	43/154 (27.9)	36/89 (40.4)	0.57 (0.32–1.03)	0.04
meropenem MIC ≥16 mg/L	146/418 (34.9)	64/200 (32.0)	82/218 (37.6)	0.78 (0.51–1.19)	0.22
Inadequate empirical antibiotic therapy	144/365 (39.4)	71/212 (33.5)	73/153 (47.7)	0.55 (0.35–0.86)	0.006

J Antimicrob Chemother 2015;70:2133-2143

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

C. Tascini[1], B. Viaggi[2]* and F. Menichetti[1]

J Antimicrob Chemother 2015;17:1135-1141

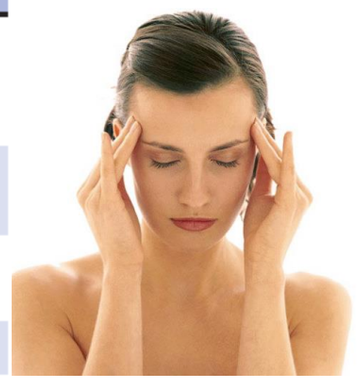
Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Gonzales-Padilla M

J Antimicrob Chemother 2015;70:905-913

Table 5. Expert opinion treatment options for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Dose adjustment is recommended depending on renal function and antimicrobial susceptibility tests[a]

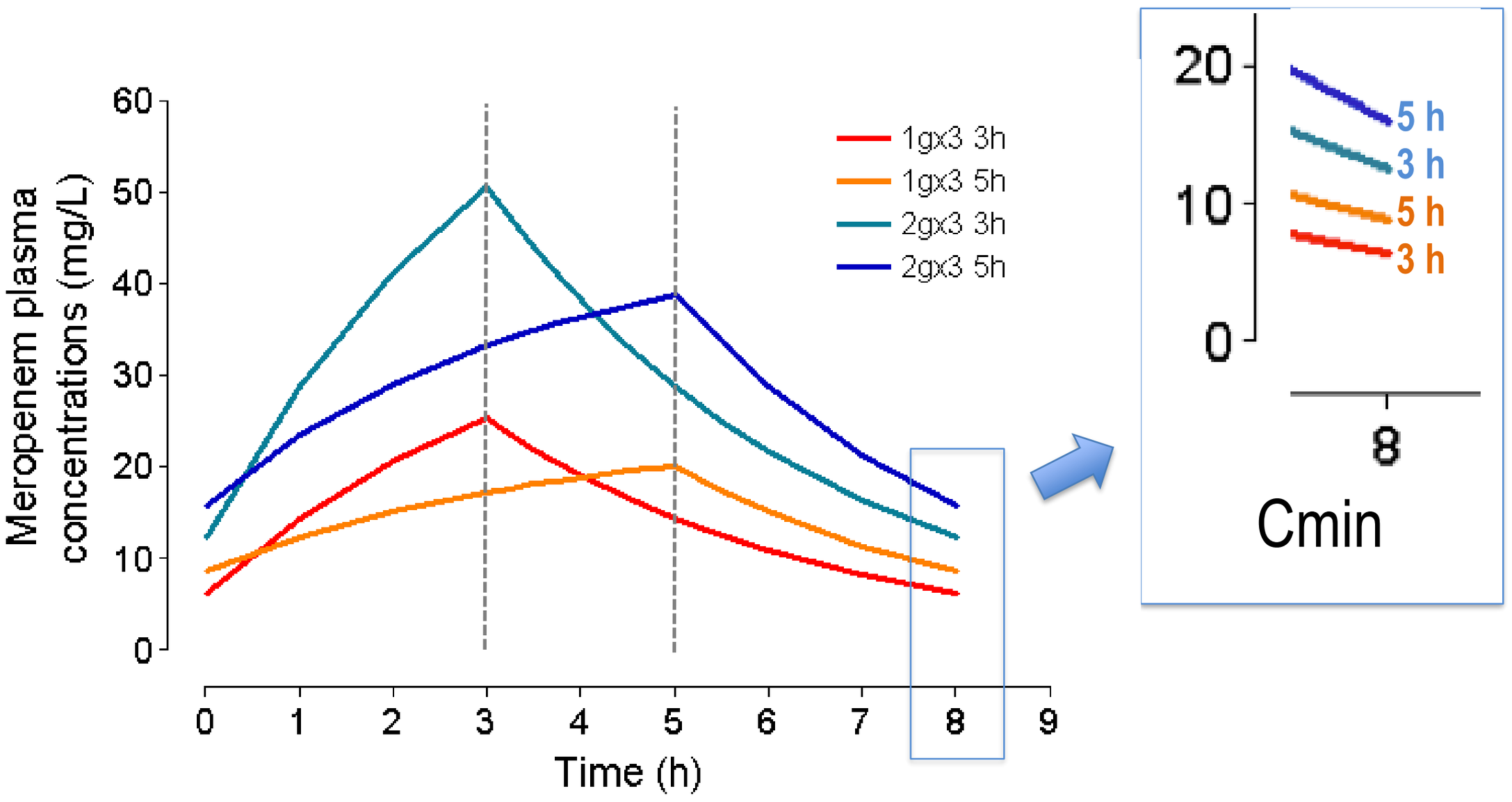
KPC-Kp treatment options			
KPC-Kp meropenem MIC ≤ 8–16 mg/l			
Primary bloodstream infections	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Meropenem 2 g every 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Inhaled antibiotics[b] + meropenem 2 g every 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycine 4 g every 4 h i.v.	Meropenem 2 g every 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Meropenem 2 g every 8 h i.v. (f) + fosfomycin 4 g every 4 h i.v. + gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or colistin 4.5 MU every 12 h i.v. (h)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.
KPC-Kp meropenem MIC > 8–16 mg/l			
Primary bloodstream infections	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h .i.v (g) + colistin 4.5 MU every 12 h i.v. (h) + fosfomycin 4 g every 4 h i.v. or gentamicin 3–5 mg/kg/day every 24 h i.v. (i)	Inhaled antibiotics[b] + colistin 4.5 MU every 12 h i.v. (h) + tigecycline 100 mg every 12 h i.v. (g) or gentamicin 3 mg/kg/day every 24 h i.v. (i) +/− rifampin 600–900 mg every 24 h i.v.	Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + gentamicin 3–5 mg/kg/day every 24 (i)	Colistin 4.5 MU every 12 h i.v. (i) + fosfomycin 4 g every 6 h i.v. +/− trimethoprim–sulfamethoxazole 20 mg/kg/day (m)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.
KPC-Kp meropenem MIC > 8–16 mg/l 16 Colistin-R			
Primary bloodstream infections	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + rifampin 600–900 mg every 24 h i.v.	As for bloodstream infections + inhaled antibiotics[b]	As for bloodstream infections	As for bloodstream infections
Ertapenem 500 mg every 6 h i.v. (c) + meropenem 2 g every 8 h i.v. (f)			
Ertapenem 500 mg every 6 h i.v. (c) + doripenem 500 mg every 8 h (l)			
Ceftazidime-avibactam 2.5 g every 8 h i.v.			



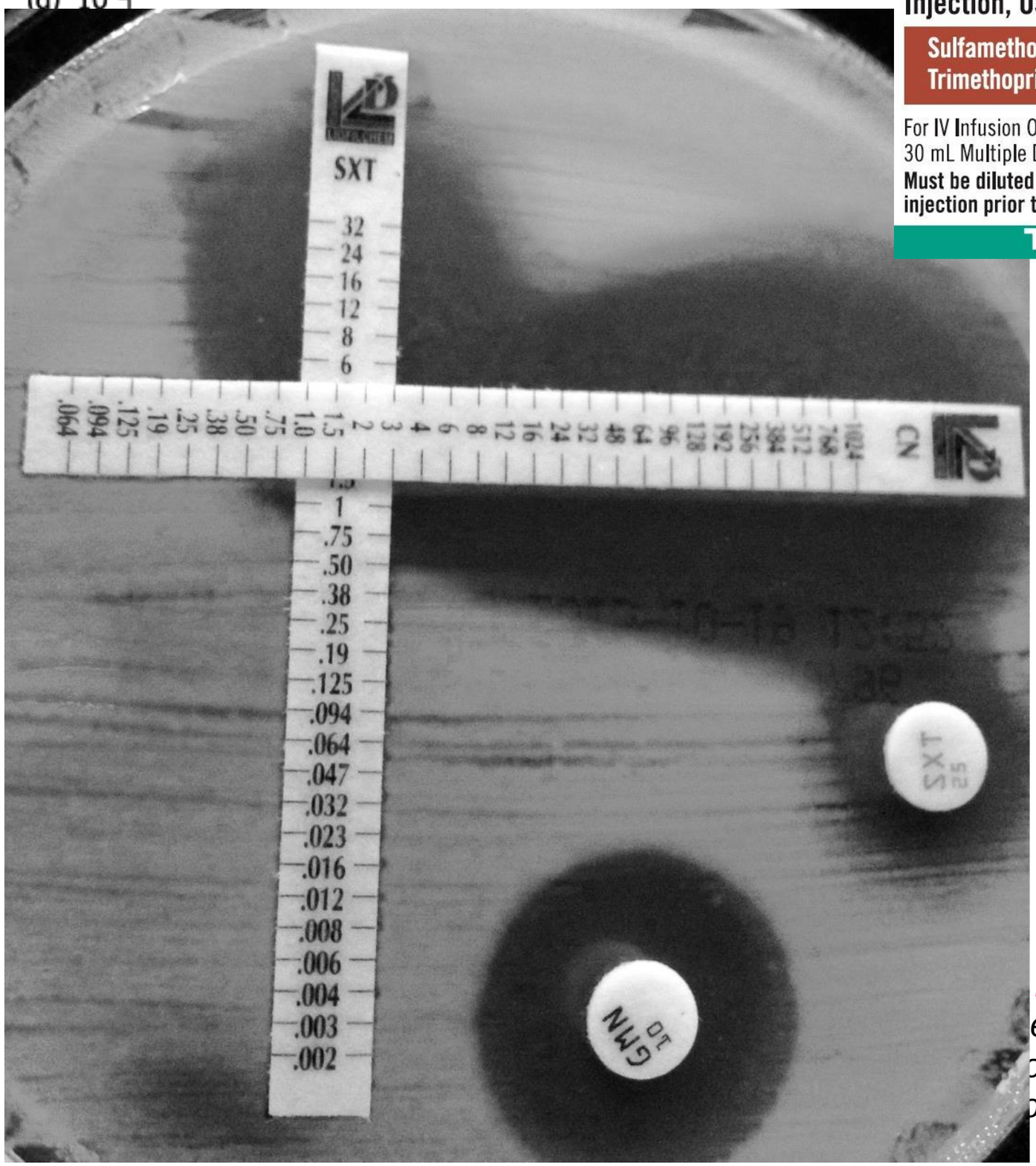
Meropenem, CRRT e infusioni prolungate

1000 individui

Meropenem 1-2 g in infusione i.v. di 3-5 ore x3/die



Synergisti two Old Drug



NDC 0703-9526-01 Rx only

Sulfamethoxazole and Trimethoprim Injection, USP

Sulfamethoxazole	80 mg/mL
Trimethoprim	16 mg/mL

For IV Infusion Only
30 mL Multiple Dose Vial
Must be diluted with 5% dextrose injection prior to administration.

Each mL contains: sulfamethoxazole 80 mg; trimethoprim 16 mg; propylene glycol 400 mg; alcohol 12.3% (v/v); diethanolamine 3 mg; benzyl alcohol 10 mg as preservative; sodium metabisulfite 1 mg as an antioxidant; water for injection q.s.; air replaced with nitrogen; pH adjusted with sodium hydroxide and/or hydrochloric acid if necessary. pH 9.5–10.5.

After initial entry into the vial, the remaining contents must be used within 48 hours.

Store at 20° to 25°C (68° to 77°F)
[See USP Controlled Room Temperature].

Usual Dosage: See Package Insert.

DO NOT REFRIGERATE DILUTED SOLUTION.

NOT FOR ADMIXTURE WITH OTHER DRUGS.

Teva Parenteral Medicines, Inc.
Irvine, CA 92618 Rev. A 10/2011

TEVA

5
4

KPC+ ST 258/512

Antibiotic	MIC mg/L(S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>8 R
Imipenem	>16 R
Meropenem	>16 R
Amikacin	>64 R
Gentamicin	1 S
Ciprofloxacin	>4 R
Tigecycline	1 S
Colistin	0.5 S
SXT	>4

KPC+ ST 101 with *armA*

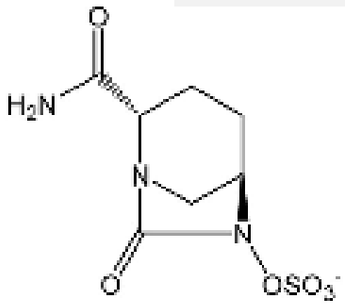
Antibiotic	MIC mg/L(S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>8 R
Imipenem	>16 R
Meropenem	>16 R
Amikacin	>64 R
Gentamicin	>8 R
Ciprofloxacin	>4 R
Tigecycline	1 S
Colistin	0.5 S
SXT	2

J Antimicrob Chemother 2015;70(9):2589-97

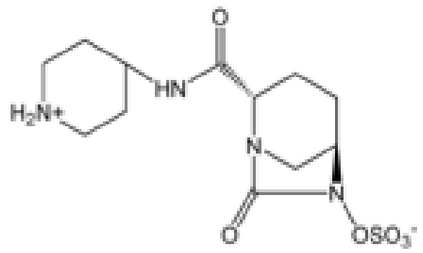
eta-lactamase inhibitors: a breakthrough against CRE

Diaza Bicyclo Octanes (DBOs)

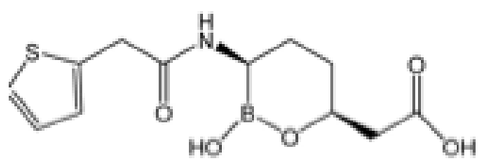
Avibactam



Relebactam



Boronate derivatives



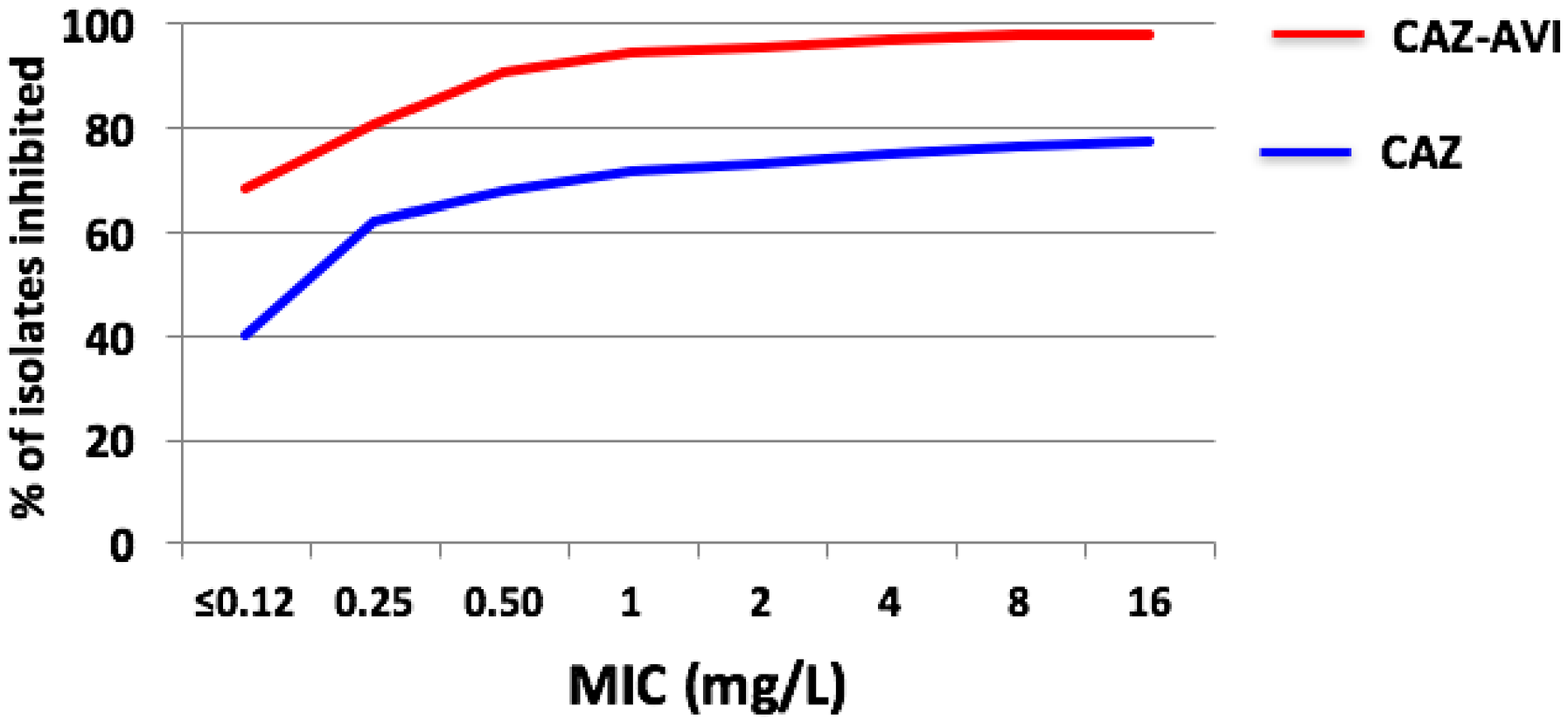
Vaborbactam

- **Active against ESBL, KPC, AmpC**
- **Variable activity *vs.* OXA**
- **No activity *vs.* MBLs**

Drawz et al Antimicrob Agents Chemother 2014
Lahiri et al IACS Chem Biol 2014

ctivity of Ceftazidime +/- Avibactam vs Enterics

N=183 recent clinical isolates (*E. coli*, *Klebsiella* spp., *Enterobacter* spp. *C. freundii*) from France, Germany, Italy and Spain



mmary of susceptibility data from 11 in vitro studies

Organism	Ceftazidime–avibactam			Ceftazidime		
	$MIC_{50/90}$	MIC range	%S	$MIC_{50/90}$	MIC range	%S
Citrobacter freundii	0.125/0.5	≤0.06–2	100	0.5/>32	≤0.25–>32	78.2
Enterobacter aerogenes	0.25/0.5	≤0.06–16	98.5	0.5/>32	≤0.25–>32	76.9
Enterobacter cloacae	0.25/1	≤0.06–16	99.5	0.5/>32	≤0.25–>32	78.7
Escherichia coli	0.12/0.25	≤0.06–4	100	≤0.25/1	≤0.25–>32	94.9
ESBL-producing	0.12/0.25	≤0.06–1	100	16/>32	1–>32	34.8
AmpC-hyperproducing	0.12/0.5	≤0.06–2	100	16/>32	1–>32	41.4
Klebsiella oxytoca	0.12/2	≤0.06–2	100	≤0.25/0.5	≤0.25–>32	99.3
Klebsiella pneumoniae	0.12/0.5	≤0.06–8	99.9	≤0.25/1	≤0.25–>32	98.5
ESBL-producing	0.5/1	≤0.06–2	100	32/>32	4–64	66.7
OXA-48-producing	0.25/0.5	<0.008–1	100	256/512	≤0.12–512	N/A
KPC-producing	0.25/1	≤0.06–1	100	>256/>256	32–>256	0
Carbapenem-non-susceptible	0.5/2	≤0.03–32	N/A	>32/>32	N/A	N/A
Morganella morganii	≤0.06/0.12	≤0.06–0.5	100	≤0.25/8	≤0.25–16	89.7
Proteus mirabilis	≤0.06/0.12	≤0.06–0.25	100	≤0.25/≤0.25	≤0.25–32	99.6
Proteus vulgaris	0.06/0.25	≤0.03–2	100	0.12/8	N/A	N/A
Salmonella enterica	0.25/0.5	≤0.03–0.5	100	0.25/0.5	N/A	N/A
Serratia marcescens	0.25/0.5	≤0.06–2	100	≤0.25/1	≤0.25–16	99.6
Burkholderia cepacia	8/>128	≤1–>128	N/A	64/>128	8–>128	N/A
Pseudomonas aeruginosa	2/8	≤0.06–>16	94.7	4/32	≤0.25–>32	82.8
Multidrug-resistant	8/>16	4–>16	60.0	>16/>16	4–>16	4.
AmpC-derepressed	4/8	≤1–64	96.2	64/>126	8–>128	3.8
Acinetobacter baumannii	8/>16	0.5–>16	60.3	8/>32	N/A	78.2
Carbapenem-resistant	32/>32	0.25–>32	N/A	>32/>32	N/A	N/A
Haemophilus influenzae	≤0.06/≤0.06	≤0.06–0.1	100	N/A	N/A	N/A

Mortality attributable to Klebsiella pneumoniae resistant to carbapenems and colistin in patients admitted to ICU with infection on admission.
Analysis of 801 patients admitted to 137 Italian ICUs

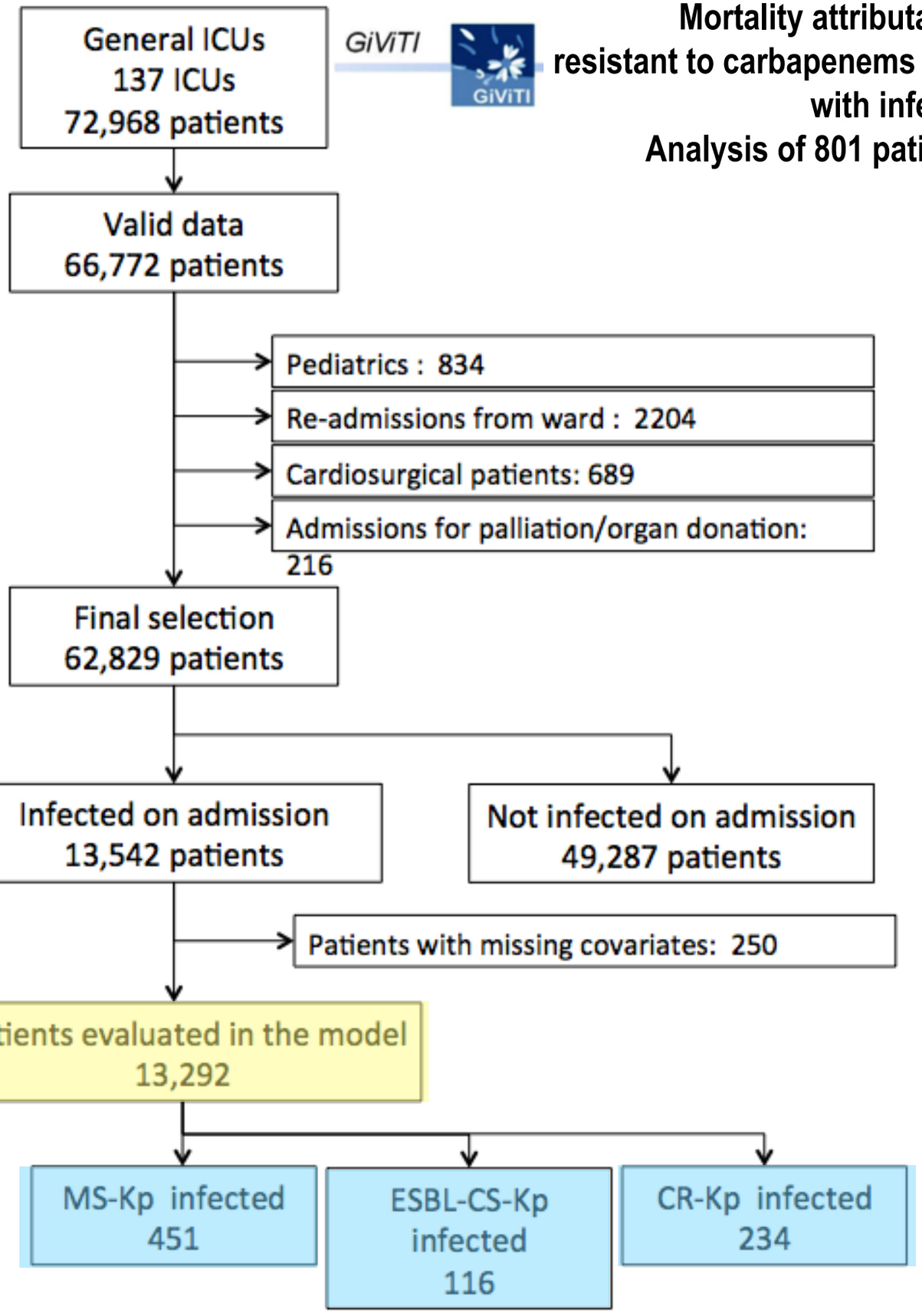
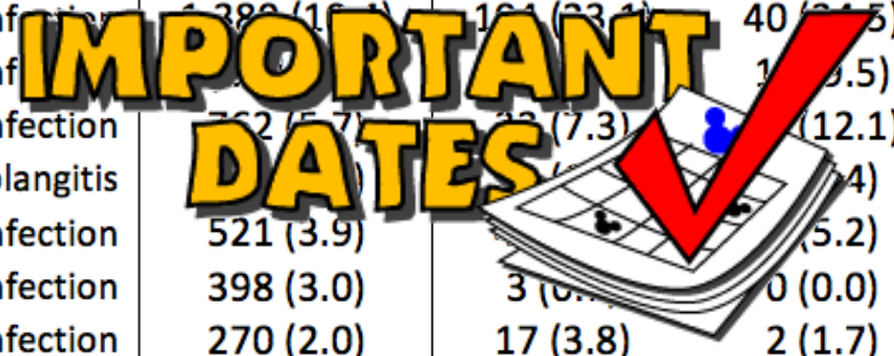
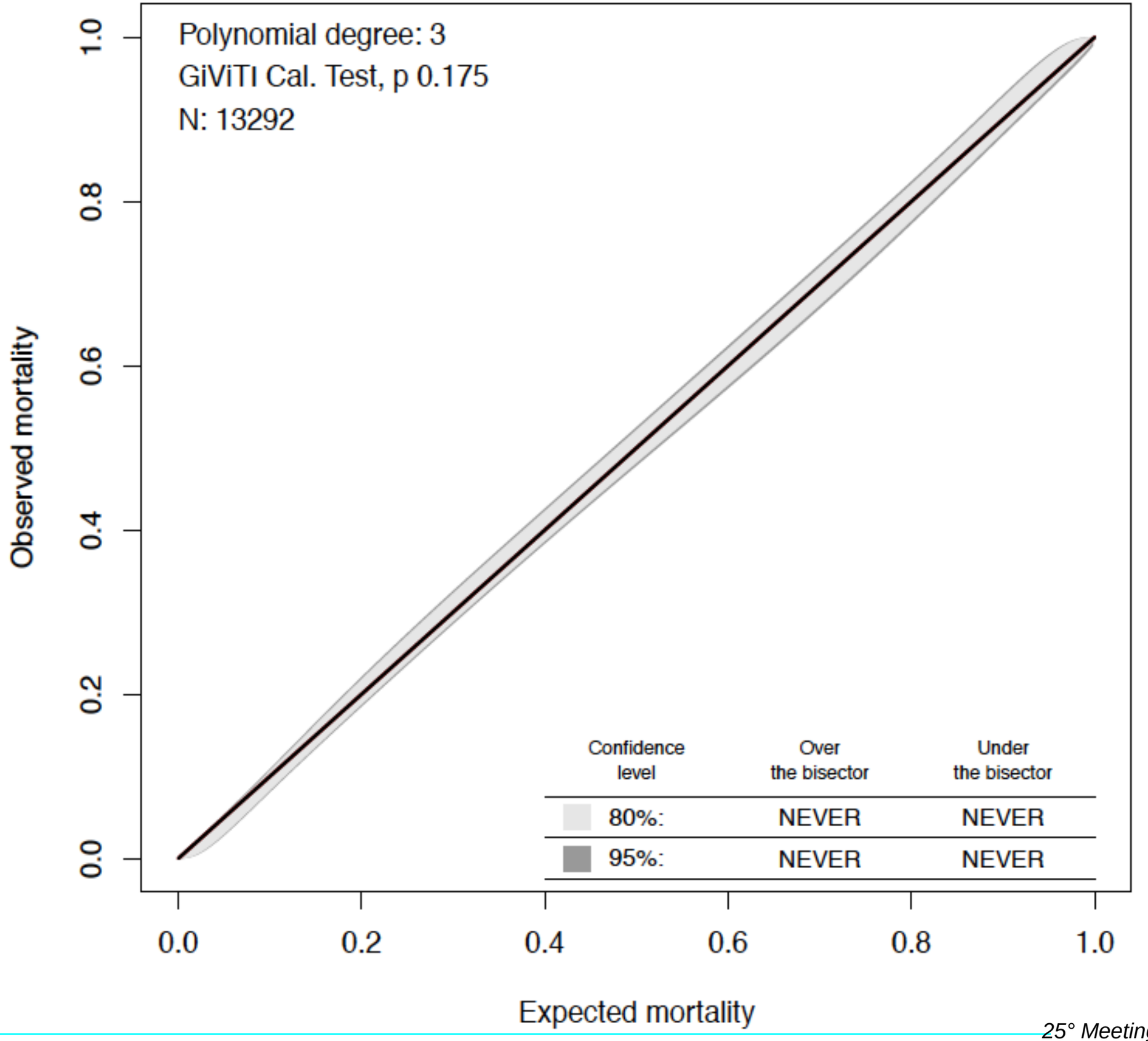


Table 2. Details of infections

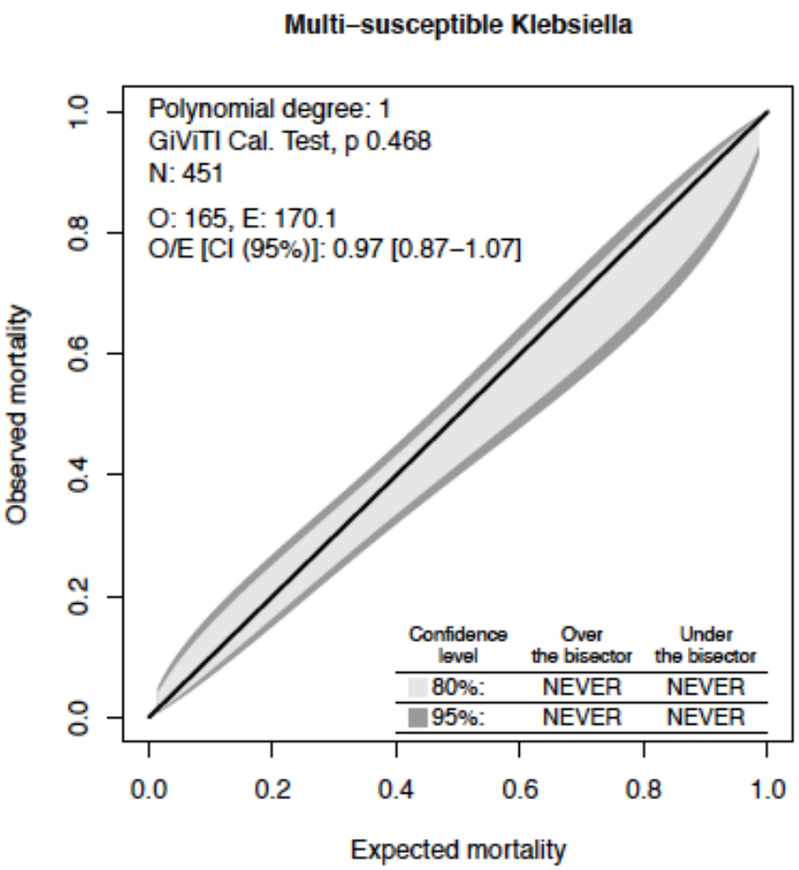
	Infected at admission	MS-Kp	ESBL-CS-Kp	CR-Kp	*p*-value[1]
N	13,292	451	116	234	-
Type of infection[2] **-** N (%)					
Extrahospital	8,213 (61.8)	223 (49.4)	38 (32.8)	48 (20.5)	
Hospital (not ICU) /long-term rehabilitation unit	4,310 (32.4)	158 (35.0)	56 (48.3)	137 (58.5)	<0.001
Other ICU	769 (5.8)	70 (15.5)	22 (19.0)	49 (20.9)	
Severity of infection on admission - N (%)					
Simple infection	4,946 (37.2)	154 (34.1)	42 (36.2)	81 (34.6)	
Severe sepsis	3,973 (29.9)	118 (26.2)	33 (28.4)	71 (30.3)	0.70
Septic Shock	4,373 (32.9)	179 (39.7)	41 (35.3)	82 (35.0)	
Max severity of infection during the stay - N (%)					
Simple infection	4,190 (31.5)	123 (27.3)	36 (31.0)	69 (29.5)	
Severe sepsis	4,070 (30.6)	117 (25.9)	37 (31.9)	67 (28.6)	0.38
Septic Shock	5,032 (37.9)	211 (46.8)	43 (37.1)	98 (41.9)	
Site of infection (top 10) - N (%)					
Pneumonia	5,595 (42.1)	170 (37.7)	47 (40.5)	96 (41.0)	0.66
Peritonitis	2,814 (21.2)	88 (19.5)	20 (17.2)	42 (17.9)	0.80
Urinary tract infection	[illegible]	[illegible]	40 ([illegible])	65 (27.8)	0.035
Lower respiratory tract infection	[illegible]	[illegible]	[illegible].5)	25 (10.7)	0.41
Skin and soft tissue infection	[illegible]	[illegible] (7.3)	[illegible] (12.1)	21 (9.0)	0.25
Cholecystitis/cholangitis	[illegible]	[illegible]	[illegible]4)	3 (1.3)	0.010
Primary bloodstream infection	521 (3.9)	[illegible]	[illegible].2)	13 (5.6)	0.51
CNS infection	398 (3.0)	3 ([illegible])	0 (0.0)	3 (1.3)	0.18
Upper respiratory tract infection	270 (2.0)	17 (3.8)	2 (1.7)	10 (4.3)	0.50
Gastroenteritis	261 (2.0)	8 (1.8)	0 (0.0)	9 (3.8)	0.048
Hospital mortality by severity on admission - N deaths (Mortality)					
Simple infection	1,248 (25.2)	56 (36.4)	9 (21.4)	30 (37.0)	0.16
Severe sepsis	1,329 (33.5)	35 (29.7)	13 (39.4)	32 (45.1)	0.093
Septic Shock	2,366 (54.1)	74 (41.3)	24 (58.5)	63 (76.8)	<0.001

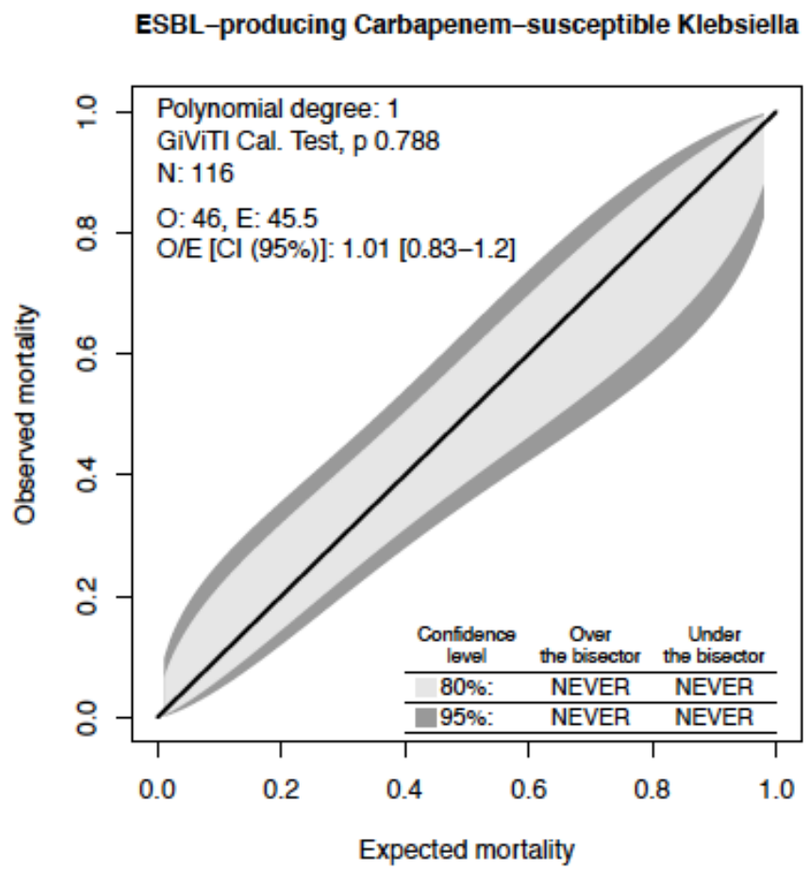


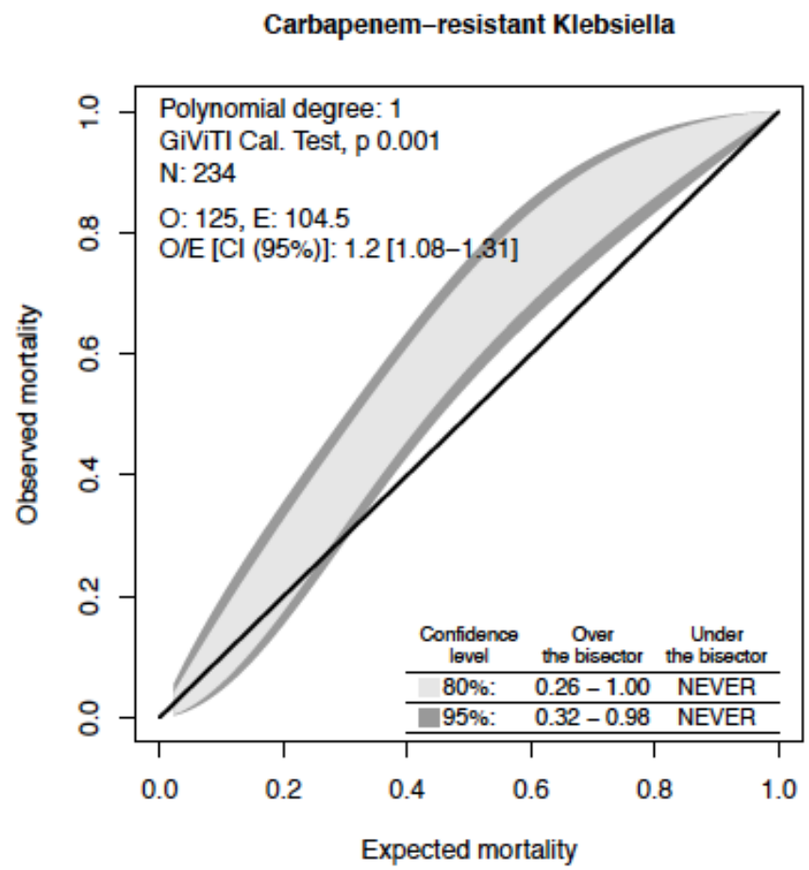
GiViTi Calibration Test and Belt



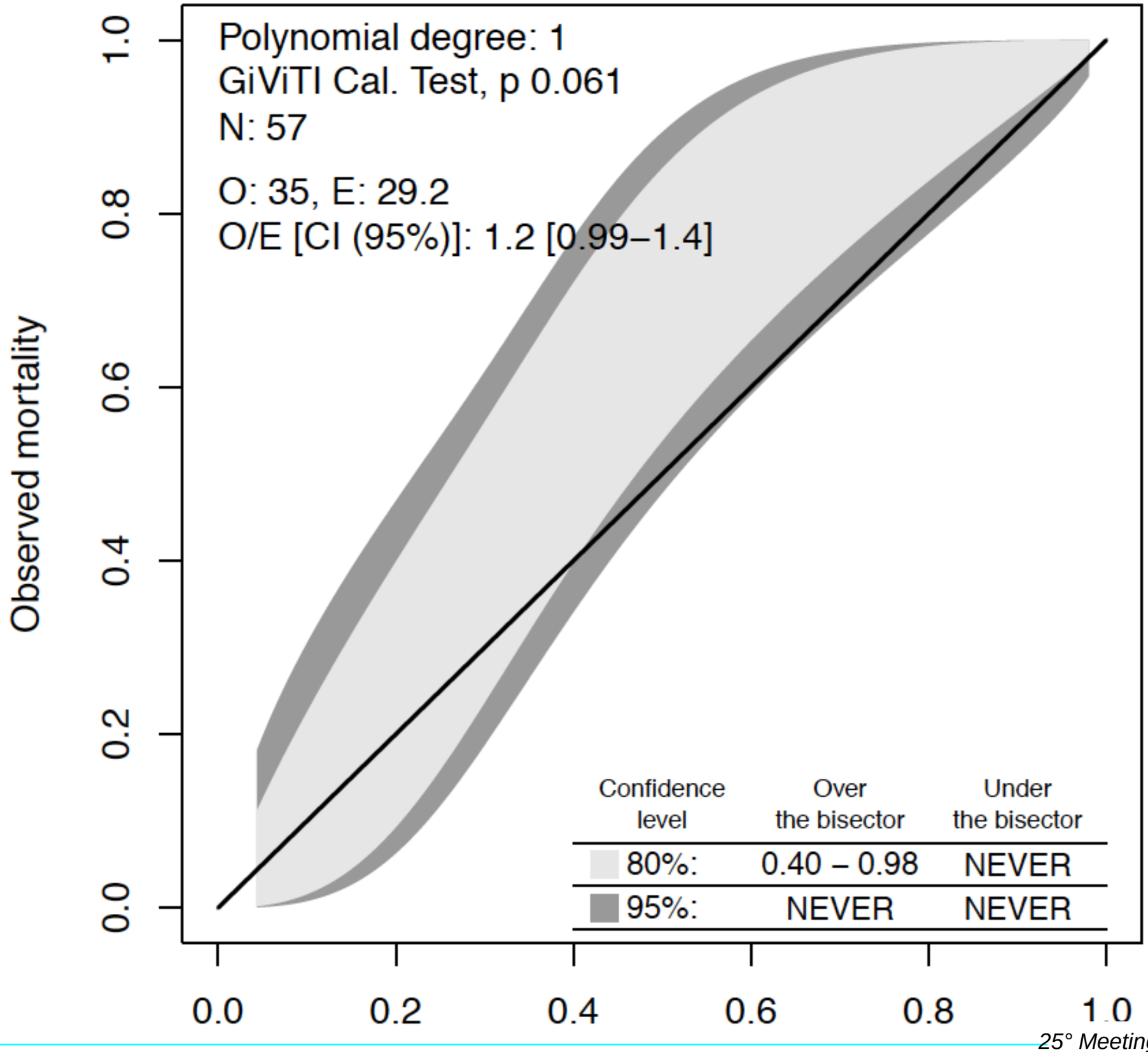
Mortality attributable to Klebsiella pneumoniae resistant to carbapenems and colistin in patients admitted to ICU with infection on admission. Analysis of 801 patients admitted to 137 Italian ICUs







Carbapenem and Colistin–resistant Klebsiella



A Microbiology Lab of early 2000s

Nuove tecnologie in diagnostica microbiologica

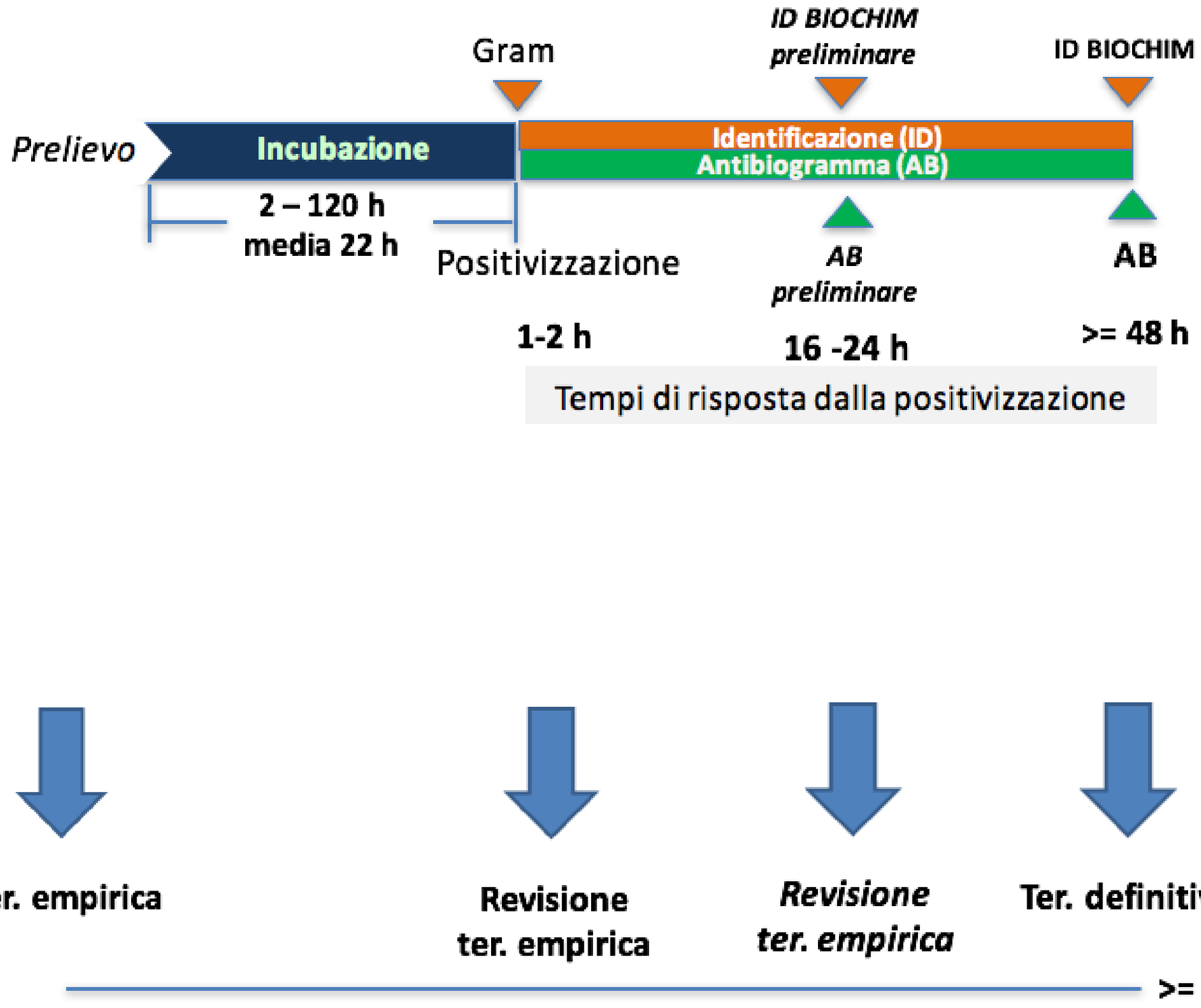
- **Spettrometria di massa con tecnologia MALDI-TOF per l'identificazione rapida di batteri e funghi**

- **AB rapido fenotipico con tecnologia *light-scattering* (LST)**

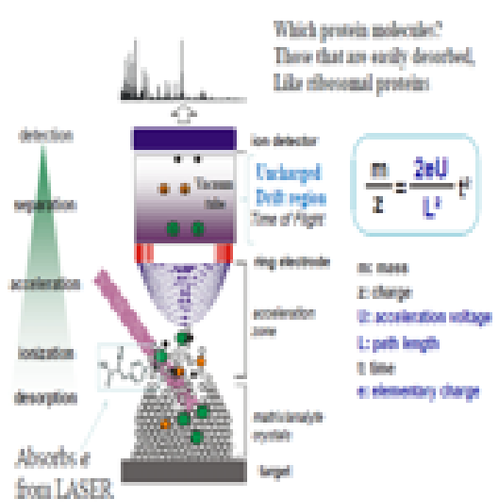
- **Single cell automated time-lapse microscopy (SC-ATLM) per identificazione ed antibiogramma rapido**

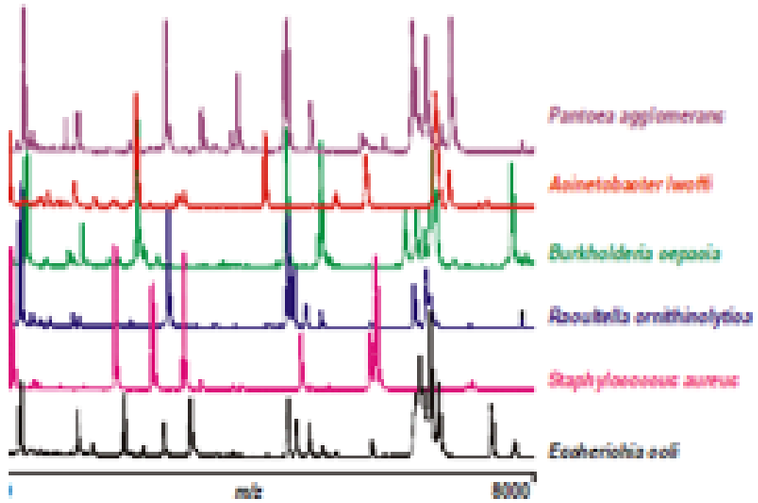
- **Biologia molecolare per identificazione ed antibiogramma molecolare**

I tempi delle analisi batteriologiche (emocoltura)



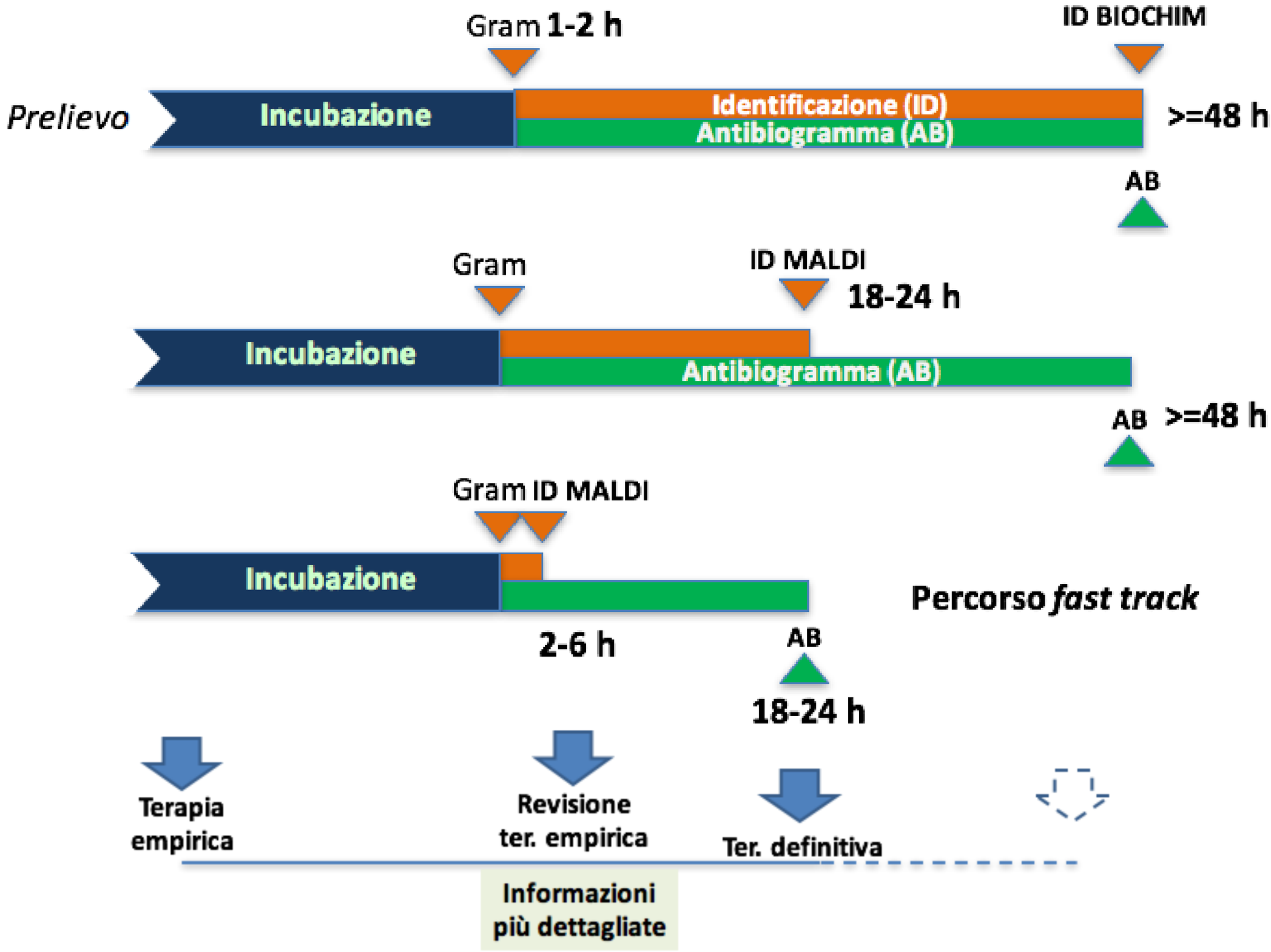
pettrometria di massa con tecnologia MALDI-TOF





- ✚ **ID rapida di batteri e miceti (minuti *vs.* ore) da colonia o emocoltura positiva monomicrobica**
- – **Non fornisce dati di sensibilità**

Workflow delle emocolture con MALDI-TOF



Impact of Rapid Organism Identification via Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Combined With Antimicrobial Stewardship Team Intervention in Adult Patients With Bacteremia and Candidemia

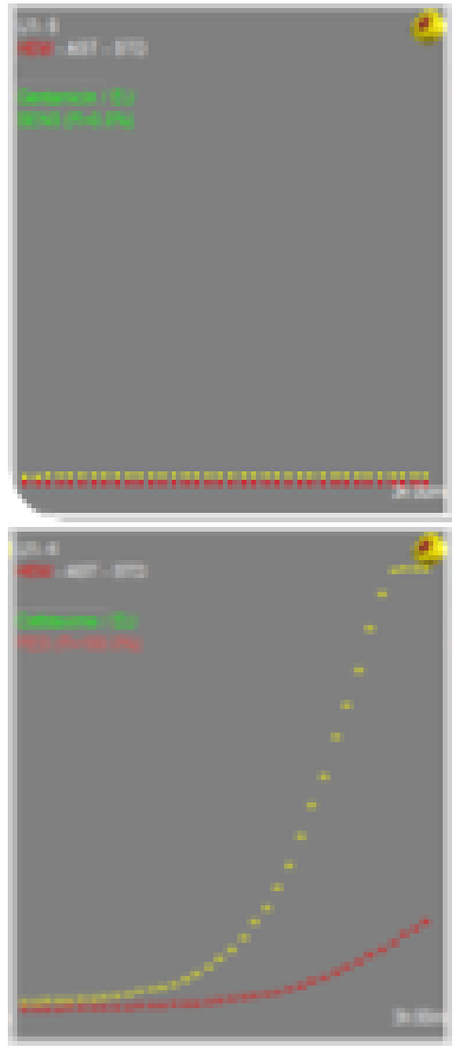
Angela M. Huang,[1,2] Duane Newton,[5,6] Anjly Kunapuli,[1,2] Tejal N. Gandhi,[3] Laraine L. Washer,[3,4] Jacqueline Isip,[1,2] Curtis D. Collins,[1,2] and Jerod L. Nagel[1,2]

N=501 patients

MALDI-TOF + antimicrobial stewardship team

- **Time to ID: 84 h → 56 h**
- **Time to optimal therapy: 90 h → 47 h (p < .001)**
- **Mortality (30d, all cause): 20% → 13% (p = .021)**
- **Length of stay in ICU: 15 → 8 days (p = .014)**

ogramma rapido con tecnologia light scattering (LST)



- ✚ **Risultati rapidi (4 – 6 h)**
- ✚ **Costi contenuti (2 – 4 x)**

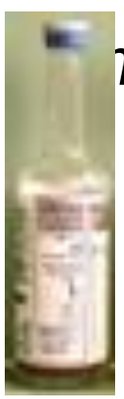
- – **Saggia solo alcuni antibiotici**
- – **Non funziona con campioni polimicrobici**
- – **Risultati sensibilità solo qualitativi (S/R)**

- ○ **Non sostituisce coltura e antibiogramma convenzionale**
- ○ **Uso come test aggiuntivo in casi selezionati**

ramma rapido in LST come strumento utile per la stewardship antibiotica

epsi in un paziente post-intervento cardiochirurgico

Terapia empirica: PIP/TAZ + VANCO



mocoltura positiva dopo 5 h (bacillo Gram-negativo)

- ID (MALDI da brodo eugonico): *Klebsiella pneumoniae* 3 h

- AB rapido fenotipico con tecnologia LST 6 h

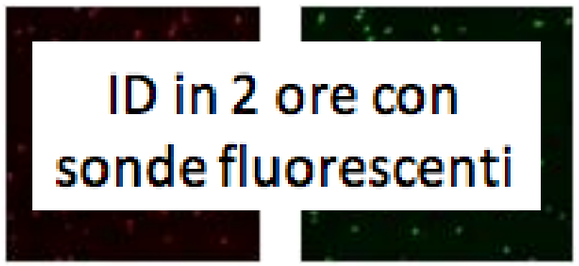
Cefotaxime R
Pip/Tazo R
Meropenem R
Gentamicina S
Colistina S

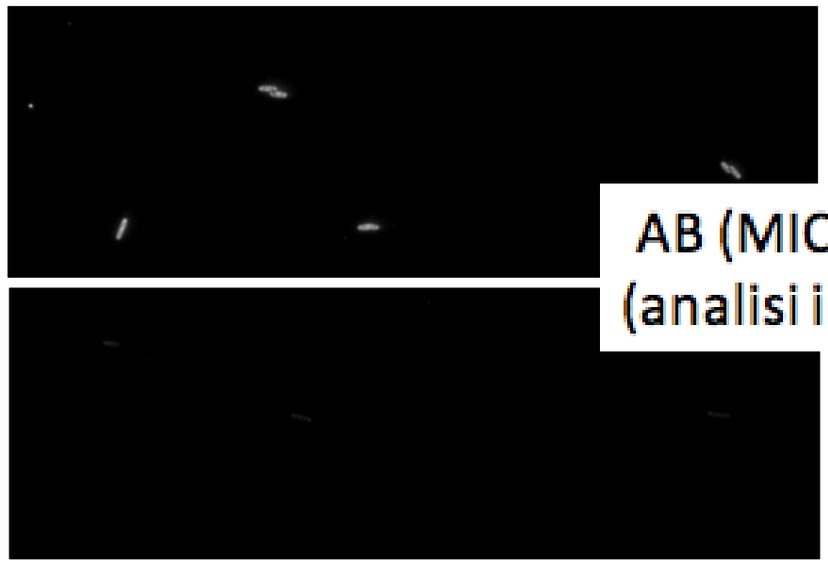
Antibiogramma definitivo, dopo 42 ore
ha confermato il profilo di sensibilità

***Revisione**: Colistina + Gentamicina + Meropenem^{HD}*

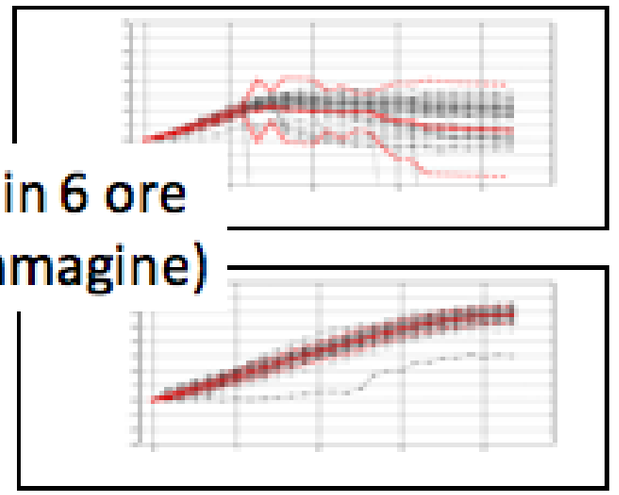
Revisione con anticipo di 2 giorni

Single Cell Automated Time-lapse Microscopy





AB (MIC) in 6 ore
(analisi immagine)



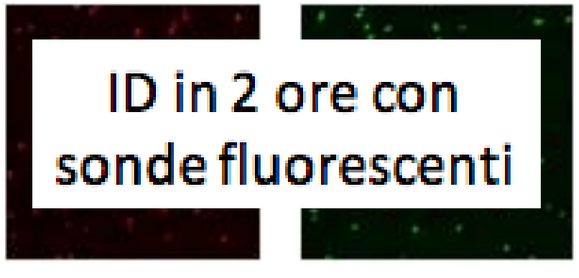
- ✚ **Risultati rapidi**
- ✚ **Funziona anche con campioni polimicrobici**
- ✚ **Riporta i valori di MIC**

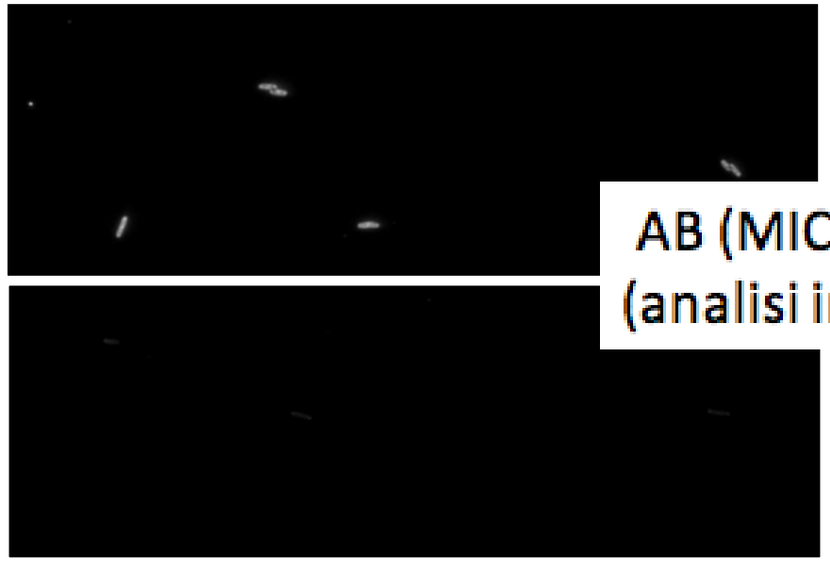
- – **Non identifica tutte le specie batteriche**

- – **Costo elevato (20 – 30 x)**

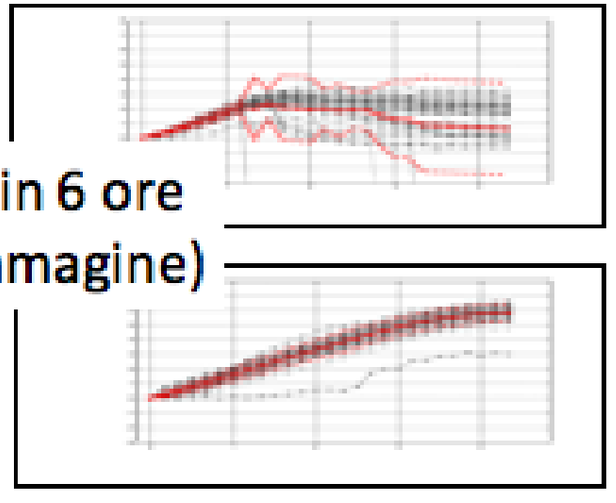
  - ○ **Può sostituire nella maggior parte dei casi coltura e antibiogramma convenzionale**

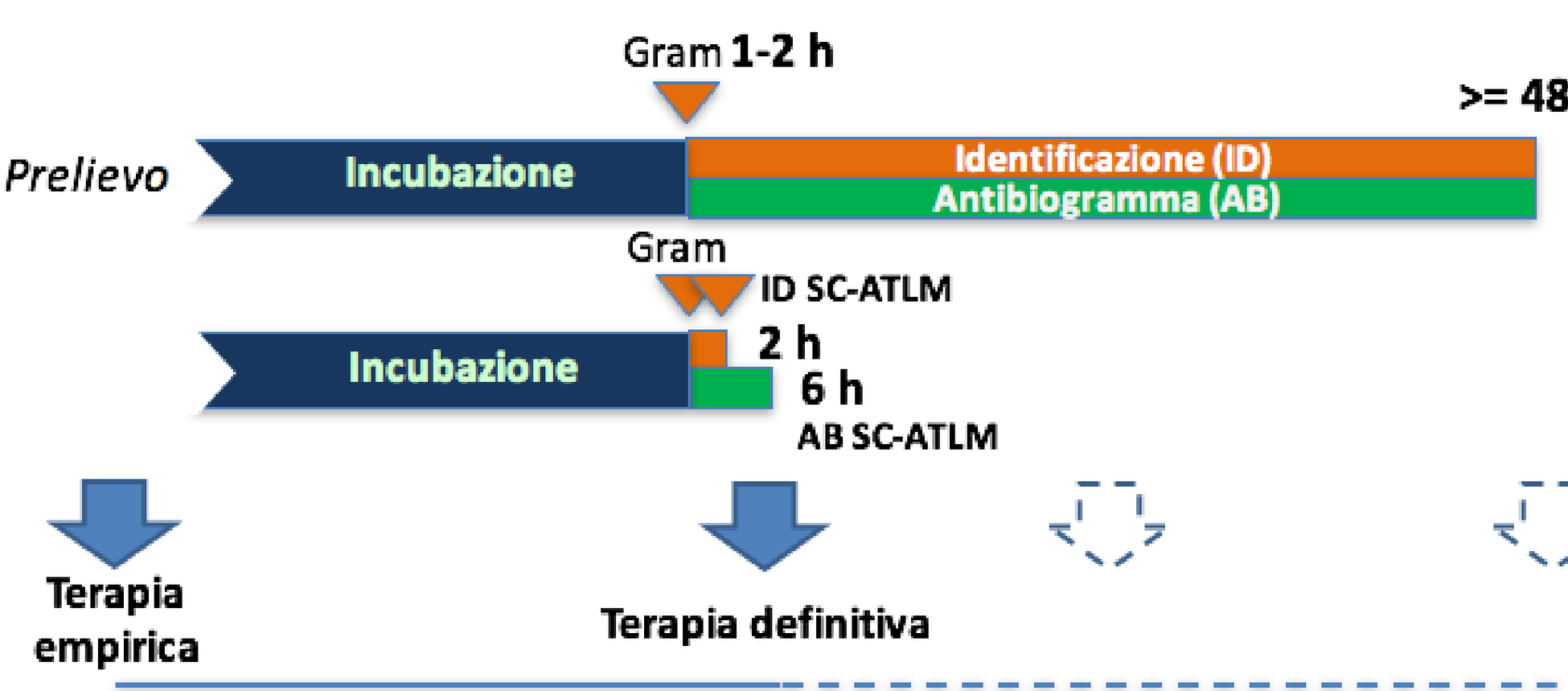
Single Cell Automated Time-lapse Microscopy





AB (MIC) in 6 ore
(analisi immagine)

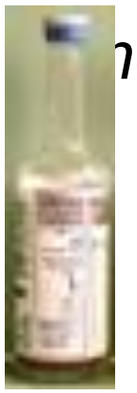




amma rapido con SC-ATLM come strumento utile per la stewardship antib

sepsi in ptz diabetico con ipertrofia prostatica e storia pregressa di IVU (trasferito da E

Terapia empirica: Meropenem



hocoltura positiva dopo 11 h (bacillo Gram-negativo)

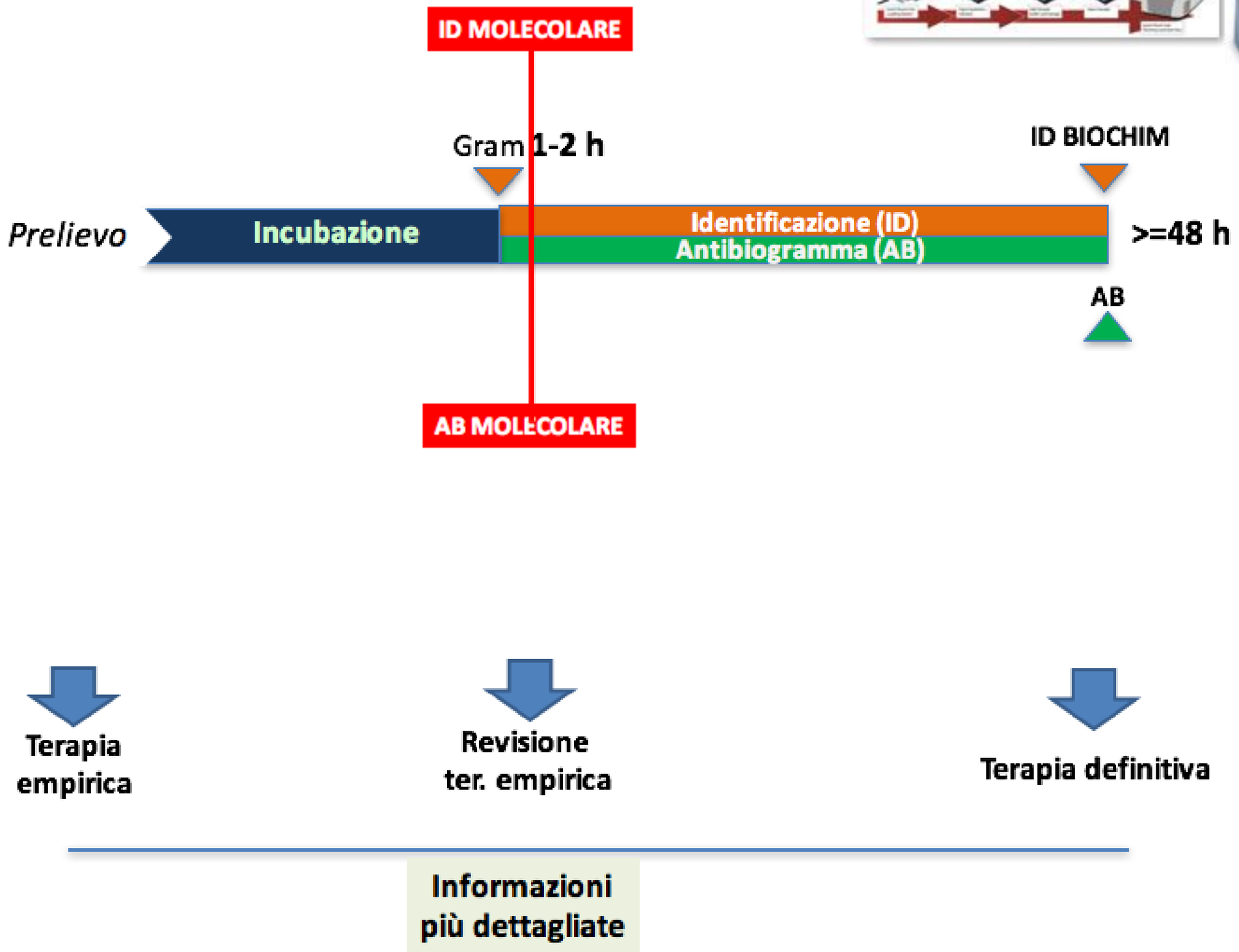
Antibiotic	MIC (mg/L)
Amikacin	16
Gentamicin	≤1
Ciprofloxacin	≥8
Cefepime	≥32
Ceftazidime	≥32
Ceftriaxone	≥8
Ertapenem	0.25
Meropenem	≤0.25
Pip-Tazo	≤4
Colistin	≤0.5

- ID: ***E. coli*** — 2 h
- **AB rapido** — 7 h

***Revisione suggerita**: Piperacillina/tazobactam*

Revisione con anticipo di 2 giorni

Identificazione e antibiogramma molecolare



Identificazione e antibiogramma molecolare

Rilevazione di determinanti genetici di resistenza

Vantaggi

- Rapidità

Proxy per il fenotipo di resistenza

Limiti

- Cerca solo alcune resistenze
- Non informa sulle MIC
- Può sovrastimare le resistenze

Decisione terapeutica

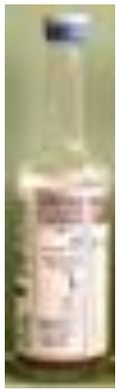
Al momento non sostituisce AB fenotipico (uso aggiuntivo)

biogramma molecolare come strumento utile per la stewardship antibiotica

e neutropenico febbrile colonizzato da Klebsiella pneumoniae Carba-R (COL-S, TIG-S,

erapia empirica: Meropenem^{HD}+COL+TIG^{HD}

Revisione con anticipo di 2 giorni



Emocoltura positiva (bacillo Gram-negativ

ID e rilevamento geni per ESBL/carbapenemasi

1.5 h

E. coli
ESBL+
KPC-, OXA-
NDM-, VIM-

Downgrade

K. pneumoniae
ESBL-
KPC+, OXA-
NDM-, VIM-

Conferma

CAZ-AVI

Importanza di utilizzare sistemi che cercano i principali geni di resistenza clinicamente rilevanti

K. pneumoniae

Importanza di trasmettere l'informazione dell'antibiogramma molecolare in modo comprensibile al clinico

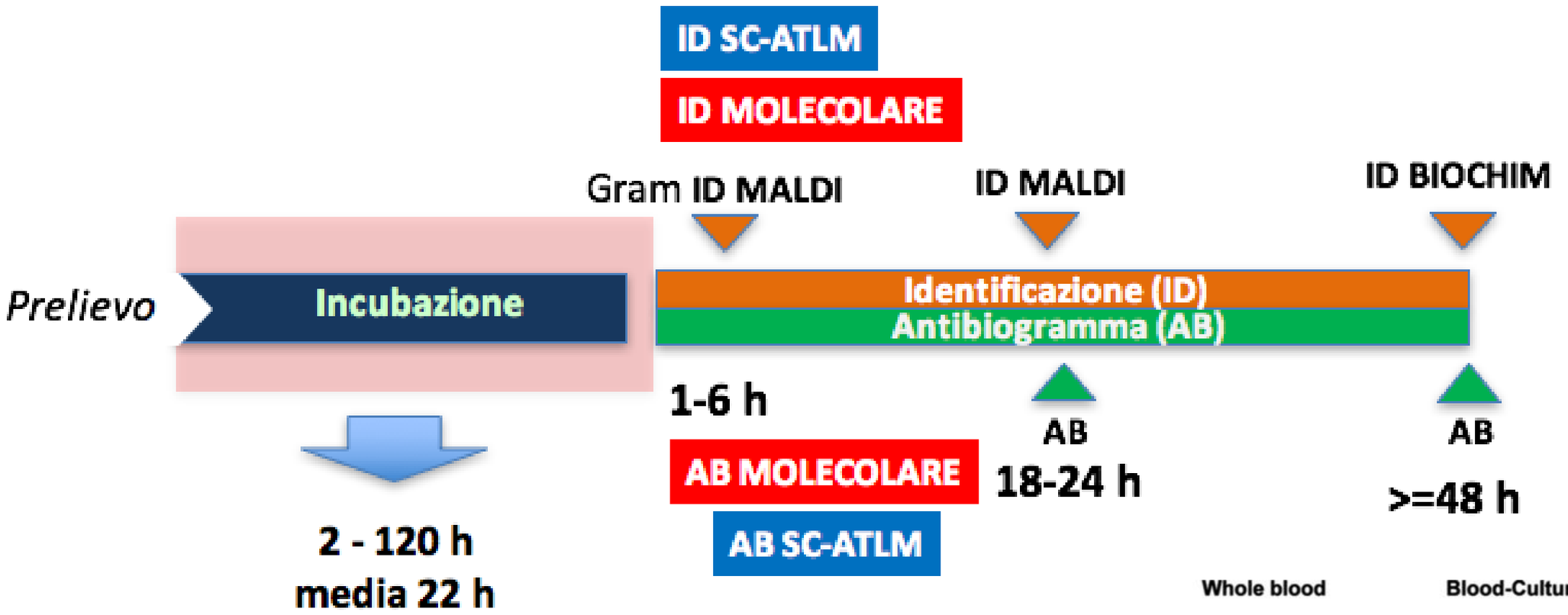
Conferma

New beta-lactamase inhibitor combinations (BLICs)

	Targeted resistance mechanisms			
Ceftazidime Avibactam	KPC	OXA-48		
Imipenem Relebactam	KPC			
Meropenem Vaborbactam	KPC			
Aztreonam Avibactam	KPC	OXA-48	VIM	NDM

Rapid ID of the resistance mechanism is essential for appropriate selection

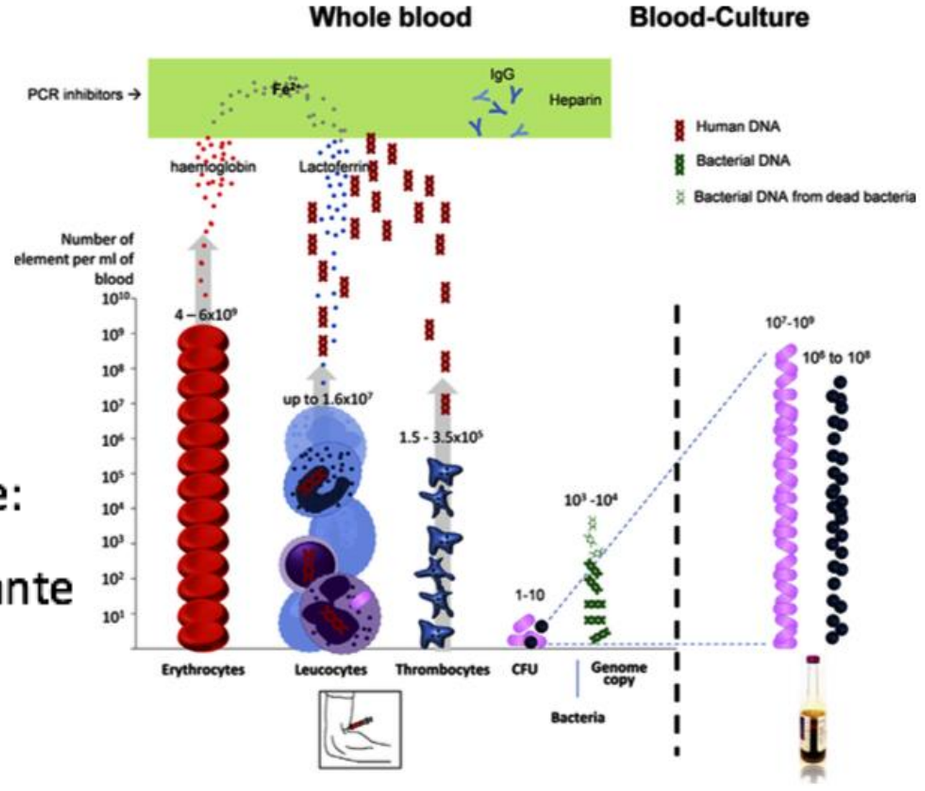
Workflow delle emocolture



Ricerca diretta del patogeno da sangue

Tecnicamente più difficile:

- target meno abbondante
- presenza di inibitori e sostanze interferenti



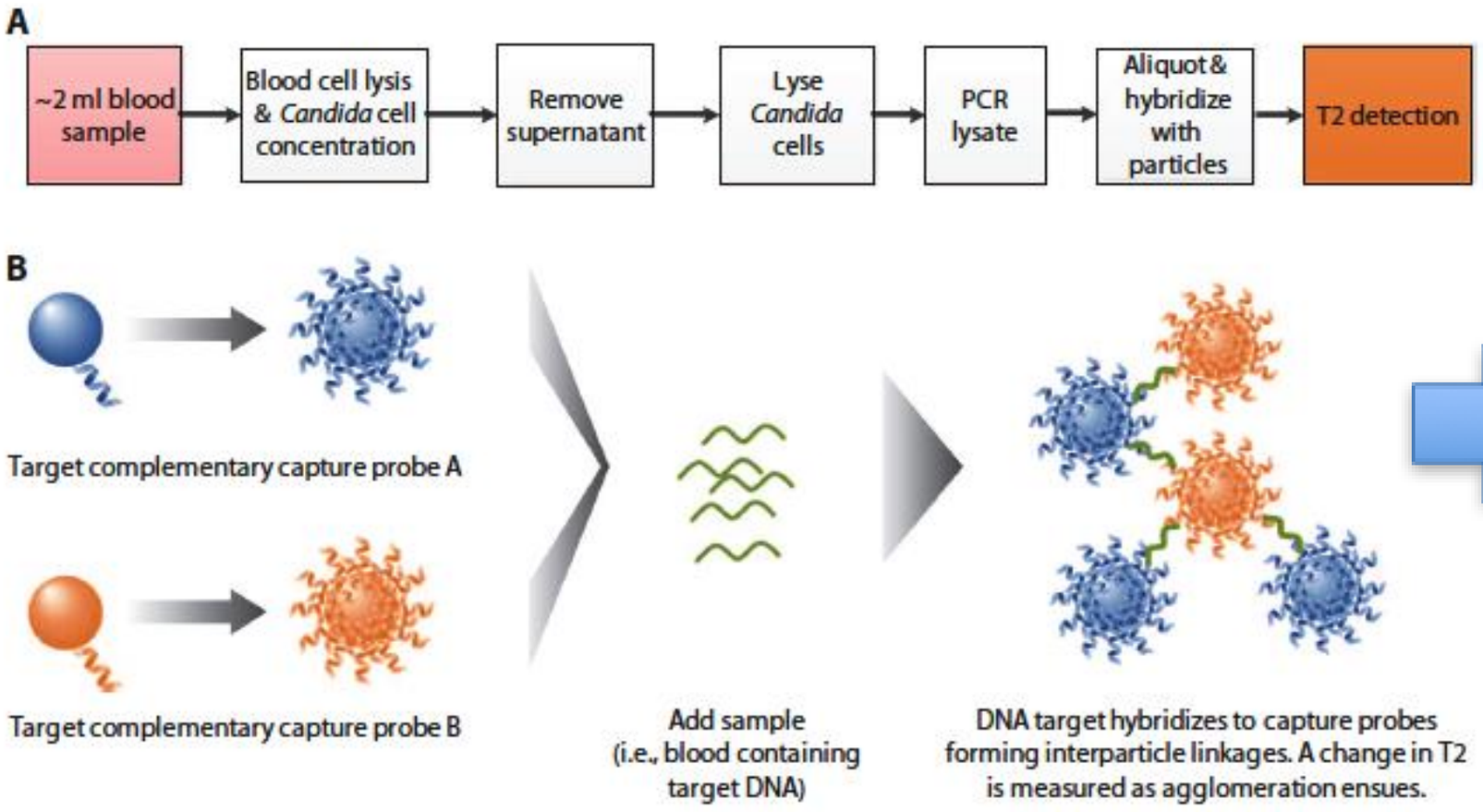
Ricerca di patogeni direttamente da sang

DIAGNOSTICS

T2 Magnetic Resonance Enables Nanoparticle-Mediated Rapid Detection of Candidemia in Whole Blood

Lori A. Neely,[1] Mark Audeh,[1] Nu Ai Phung,[1] Michael Min,[1] Adam Suchocki,[1] Daniella Plourde,[1] Matthew Blanco,[1] Vasiliki Demas,[1] Lynell R. Skewis,[1] Theodora Anagnostou,[2] Jeffrey J. Coleman,[2,3] Parris Wellman,[1] Eleftherios Mylonakis,[2,3] Thomas J. Lowery[1]*

- Time to results: 4-5 h
- Limit of detection 1 CFU/mL

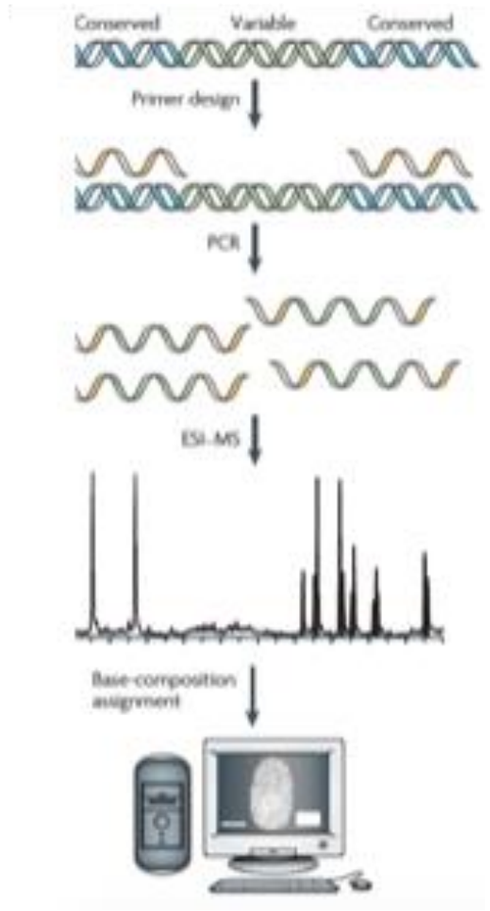


THE T2CANDIDA PANEL DETECTS THESE FIVE SPECIES OF CANDIDA:

- Candida albicans
- Candida tropicalis
- Candida parapsilosis
- Candida krusei
- Candida glabrata

Ricerca diretta di patogeni da sangue o altri campioni clinici

PCR / ESI-MS



ASSAY	COVERAGE	SAMPLE TYPE
BAC BSI	**750+ Bacteria**, Candida and 4 Antibiotic Resistance Markers: mecA, vanA, vanB and kpc	5ml EDTA whole blood
BAC SFT		Sterile fluids and tissues
BAC LRT	Identical coverage as BAC BSI and BAC SFT with additional **semi-quantitative threshold**	BAL and ETA
Fungal	**200+** fungi	BAL and Isolates
Viral IC	**130+** viruses in 13 reporting groups	Plasma

- **Limit of detection: 16 CFU/mL**
- **Costo elevato**
- **Esperienza limitata in clinica, risultati controversi**

Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Broad-Range PCR Coupled with Electrospray Ionization Time of Flight Mass Spectrometry for Detection of Bacteremia and Fungemia in Patients with Neutropenic Fever

S. Desmet,[a,b] J. Maertens,[b,c] K. Bueselinck,[a] K. Lagrou[a,b]

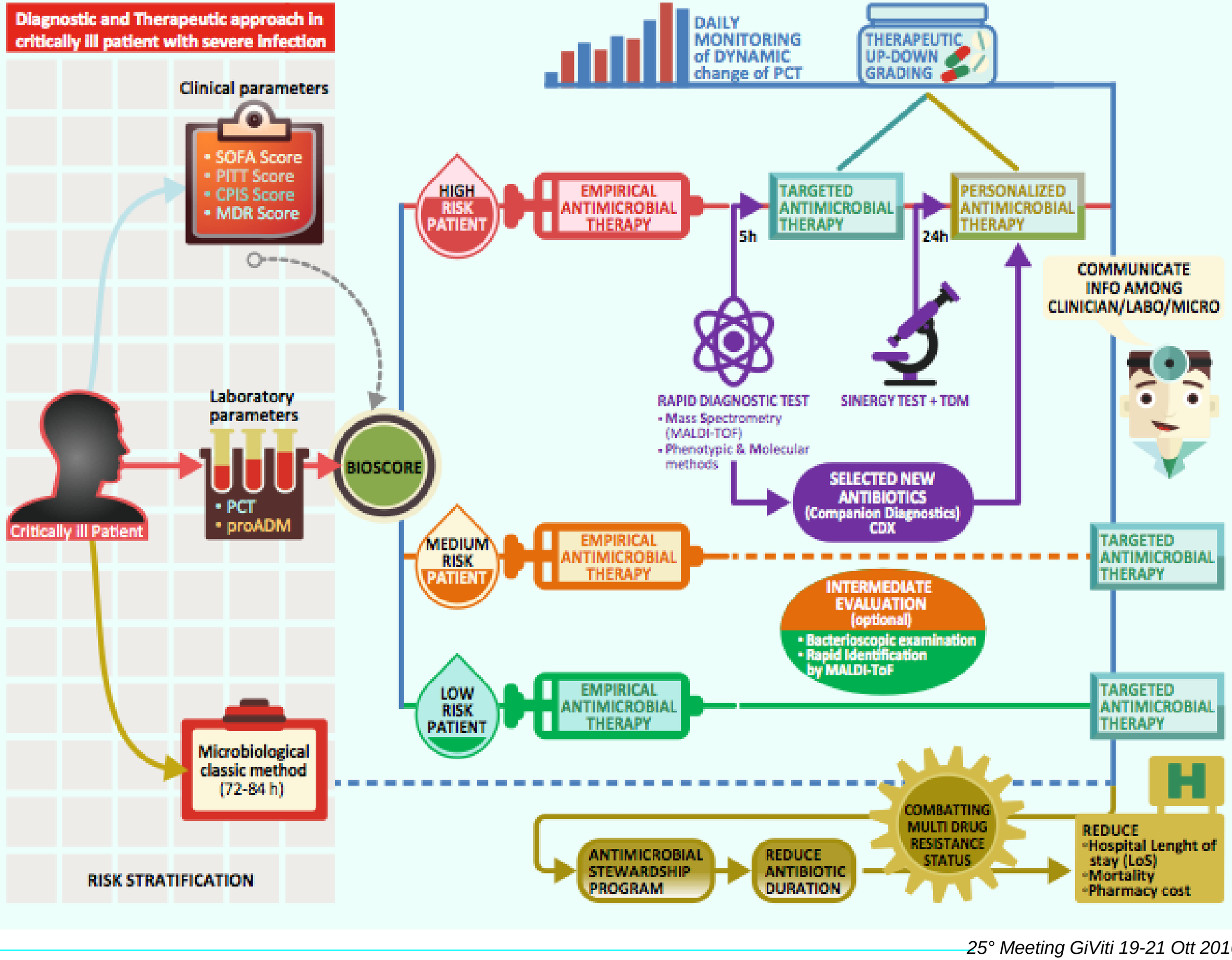
University Hospitals Leuven, Department of Laboratory Medicine, Leuven, Belgium[a]; KU Leuven, University of Leuven, Department of Microbiology and Immunology, Leuven, Belgium[b]; University Hospitals Leuven, Department of Hematology, Leuven, Belgium[c]

105 campioni di sangue da 74 ptz con neutropenia febbrile, esaminati con PCR-ESI/MS ed emocoltura

- Positivo concordante: 14 casi
- Positivo solo ESI/MS: 5 casi
- Positivo solo emocoltura: 17 casi

- Specificità ESI/MS: 93%
- Sensibilità ESI/MS: 45%

Diagnostic and Therapeutic approach in critically ill patient with severe infection




Thank for your attention