Convegno

Antimicrobico-resistenza: cure e ambiente

Firenze, 6 giugno 2018

SALONE DELLE ROBBIANE - Villa la Quiete - FORMAS (*via di Boldrone 2*)

Dr Bruno Viaggi
Dipartimento di Anestesia
SOD NeuroAnestesia e
Rianimazione CTO AOUC

Antibiotico resistenza in clinica

Dichiarazione su potenziali conflitti di interesse

Consulenze, partecipazione advisory boards, speaker's bureau, contratti/ contributi di ricerca e di eventi studio: **Abbott**, **Accelerate Diagnostics, Ada, Alifax, Angelini, Becton Dickinson, Bellco, Merck Sharp & Dohme, Pfizer, Thermofischer Scientific**

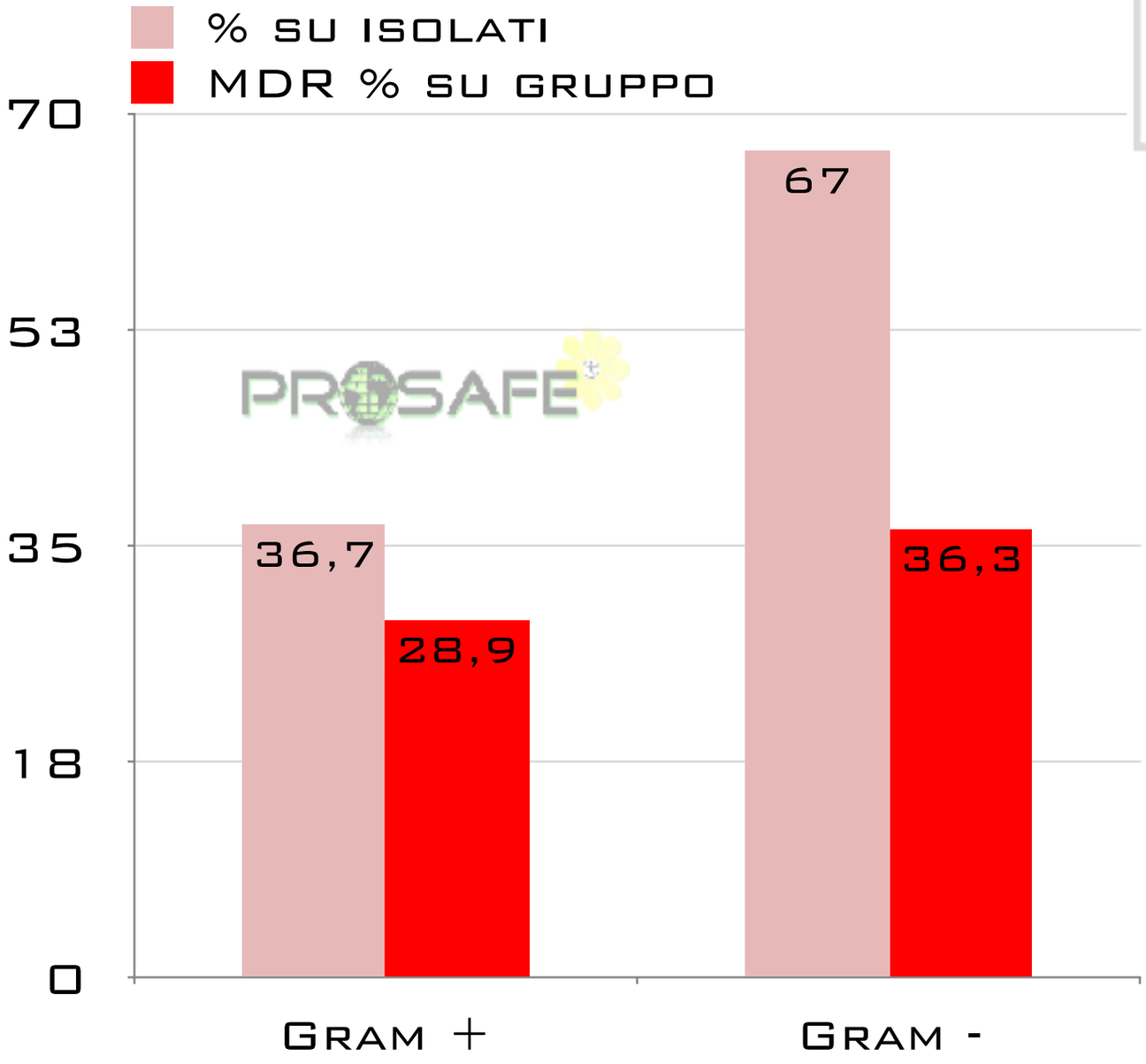
Infections in ICU: the new challenges

- **INCREASING COMPLEXITY OF PATIENTS** (aging, co-morbidities, new treatments increasing at risk-population, devices)
- **INCREASING COMPLEXITY OF BACTERIAL PATHOGENS:** new multi drug resistant (MDR) and extremely drug resistant (XDR) pathogens
- **INCREASING COMPLEXITY OF ANTIMICROBIAL CHEMOTHERAPY** (revival of old antibiotics, new antibiotics, antimicrobial combinations, new PK/PD concepts)
- **NOVEL DIAGNOSTIC TECHNOLOGIES IN CLINICAL MICROBIOLOGY** (more rapid, more sensitive, more expensive, different informational content)

ICU

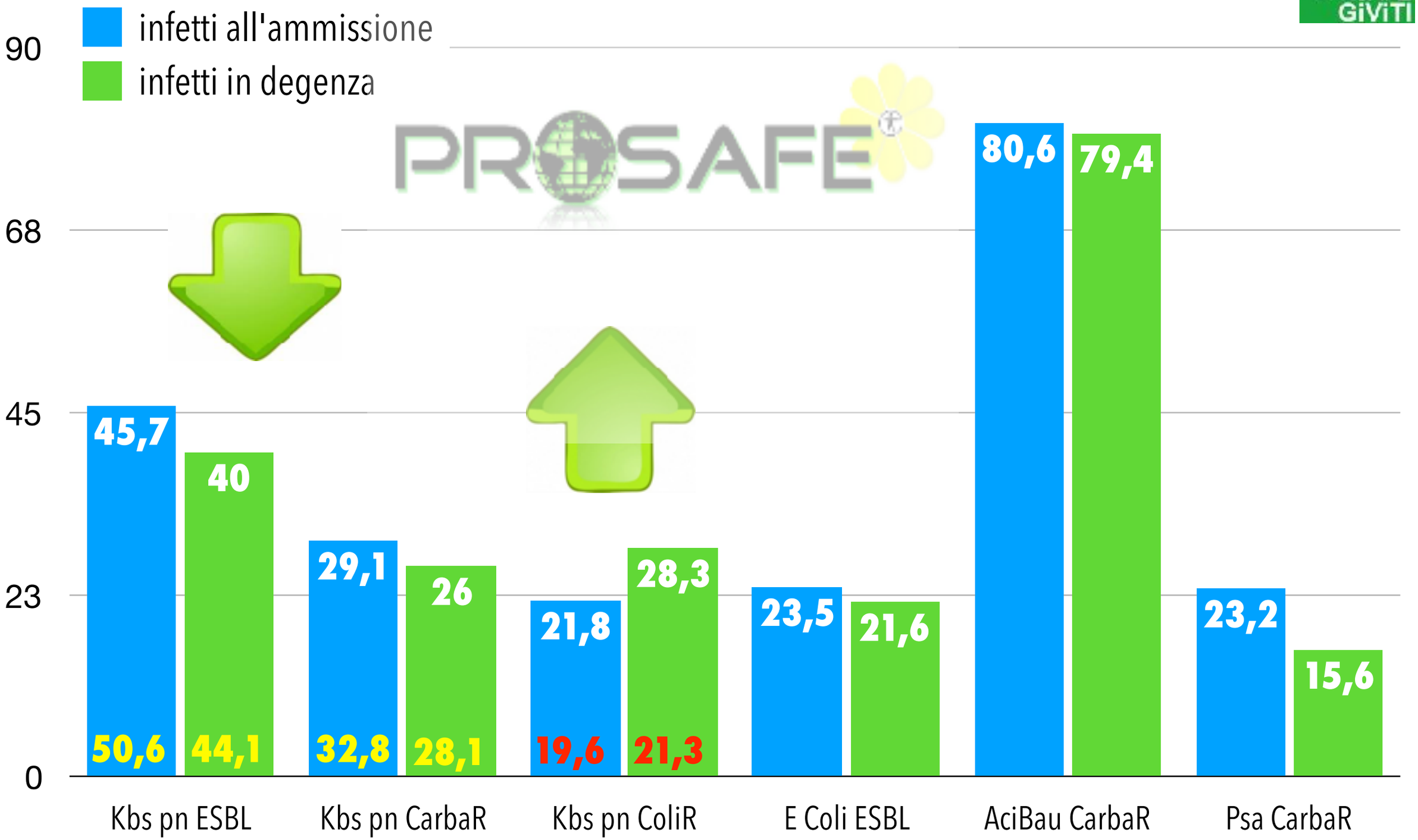
Petalo Infezioni anno 2017 TI Polivalenti nr pazienti 40154

Pazienti infetti SOLO in degenza (N=2428)		
Gravità massima dell'infezione	**N**	%
-	0	0.0
INFEZIONE SENZA SEPSI/SEPSI	1973	86.7
SHOCK SETTICO	302	13.3
Missing	153	
Mortalità per gravità dell'inf. (%)	**In TI**	**In H**
-	0.0	0.0
INFEZIONE SENZA SEPSI/SEPSI	18.0	23.9
SHOCK SETTICO	57.9	61.8

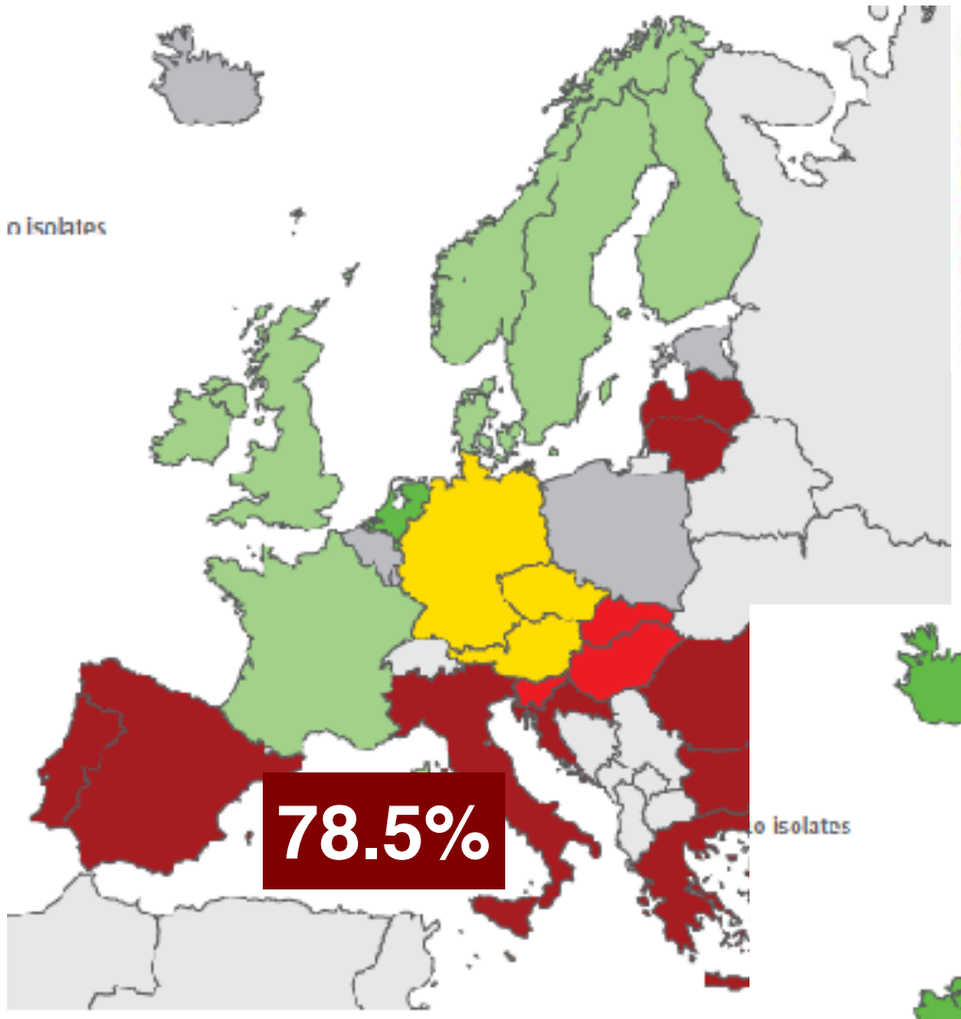


Infezioni all'ammissione e in degenza in ICU

Anno 2017

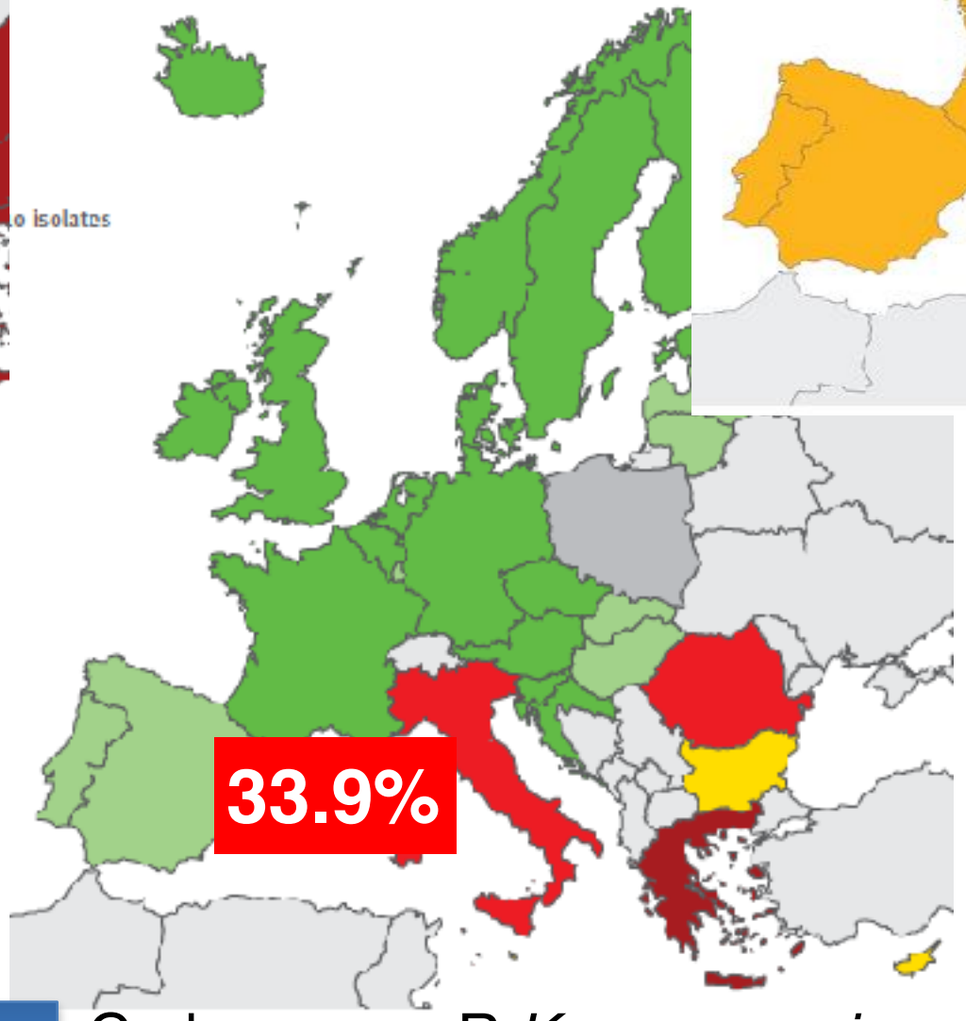


PATOGENI XDR incontrati con frequenza crescente nella pratica clinica



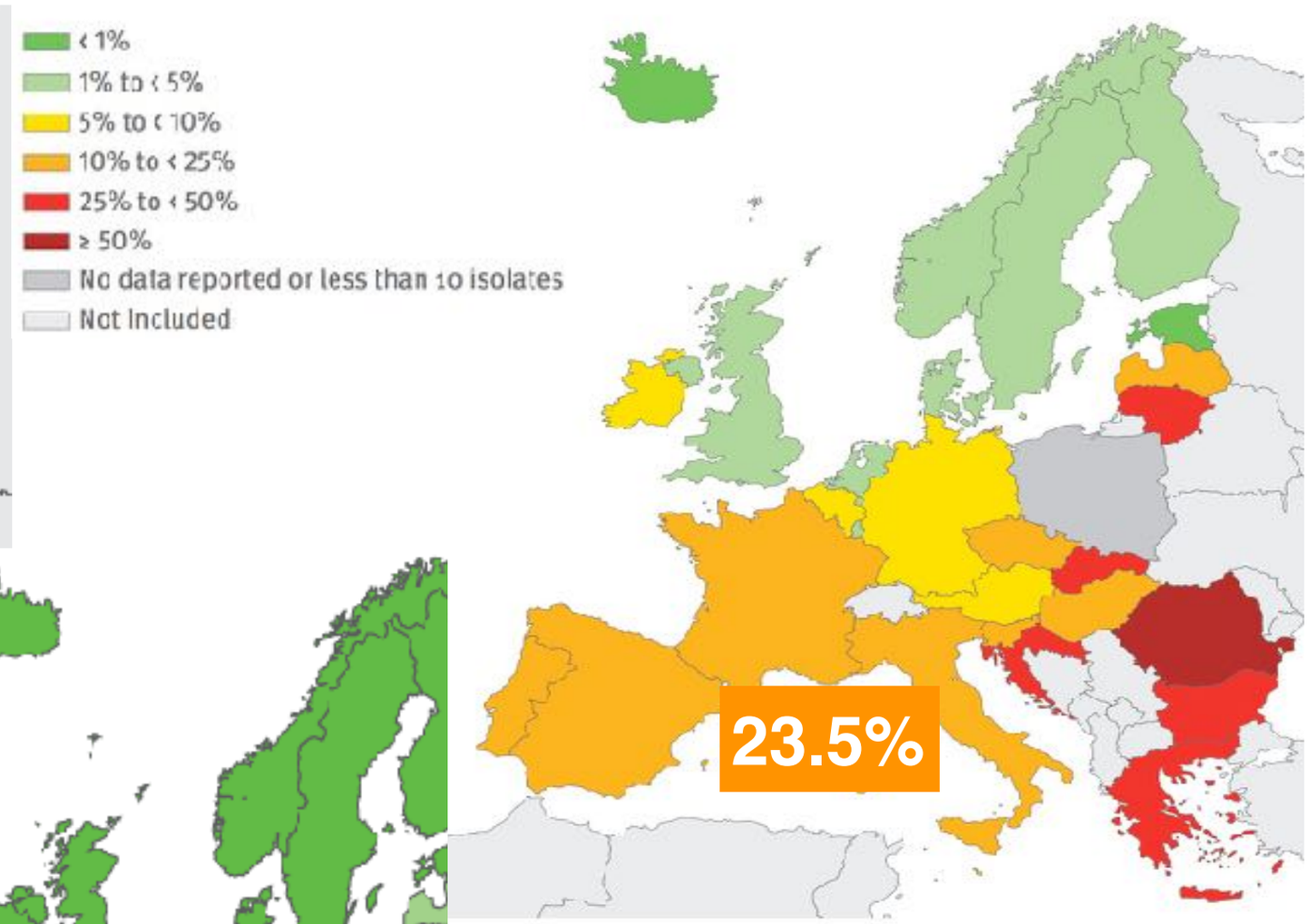
CRAb (carbapenem resistant *A. baumannii*)

Colistina



Colistina Fosfomicina

Carbapenem-R *K. pneumoniae*



XDR- *P. aeruginosa*

Colistina

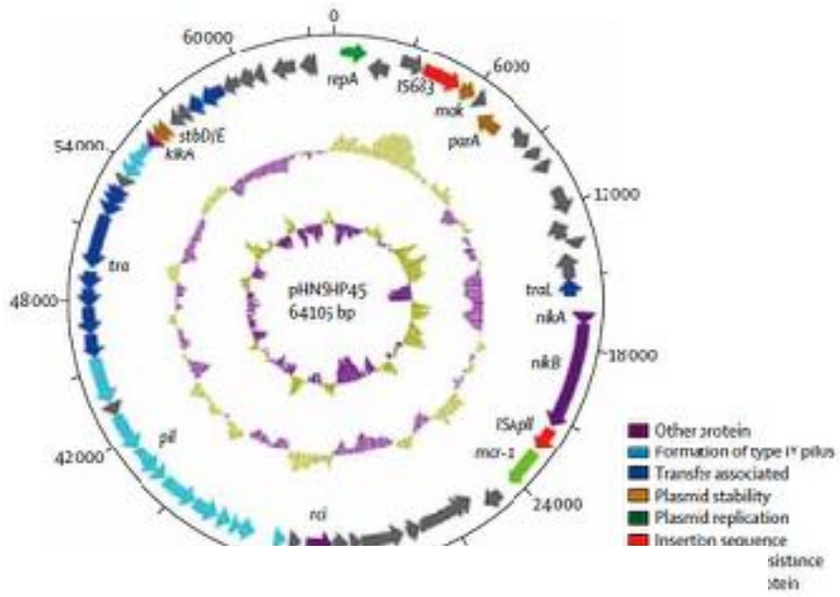
2016 EARS-NET

Articles

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

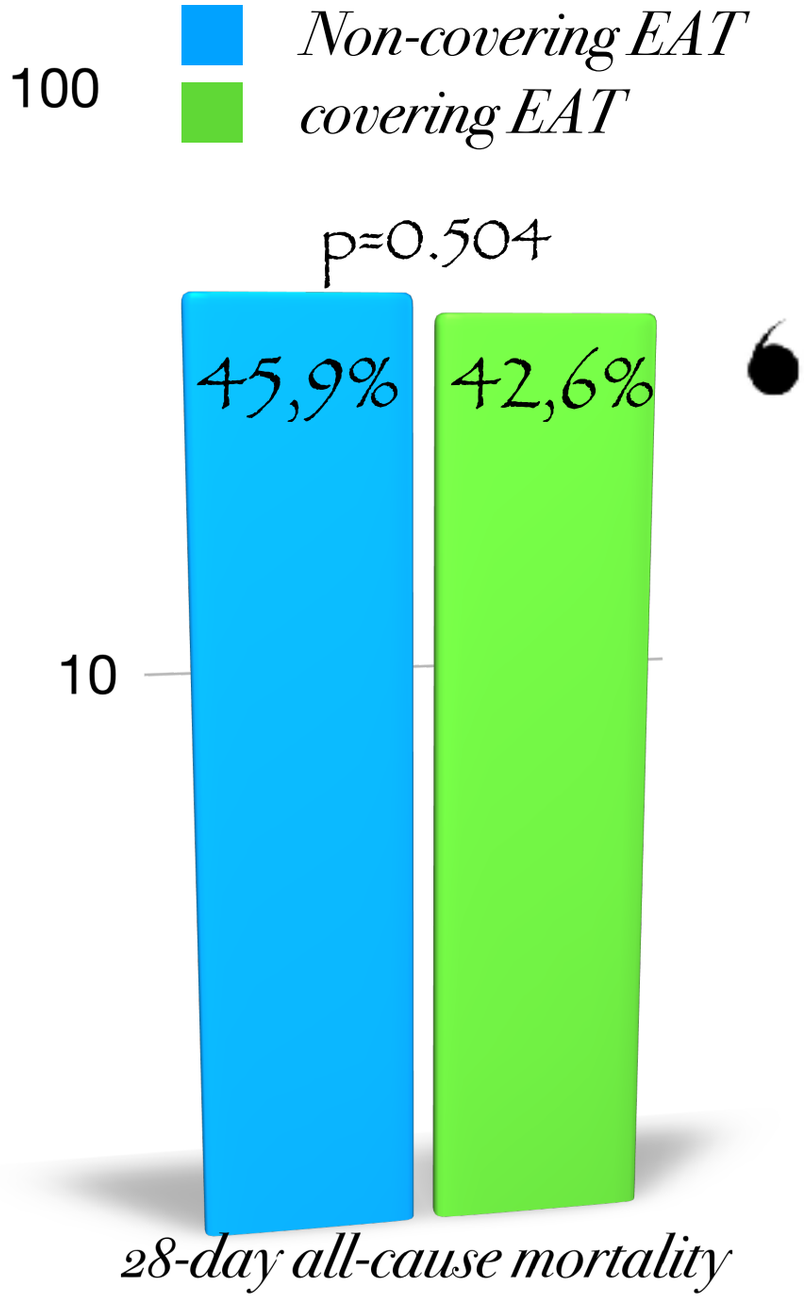
Antimicrob Agents Chemother 2016; 60(9):5612-5615

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]

The Association between Empirical ATB and Mortality in Severe Infections Caused by Carba-R GN Bacteria: A Prospective Study

Doron YZ et al. Clin Infect Dis apr 2018

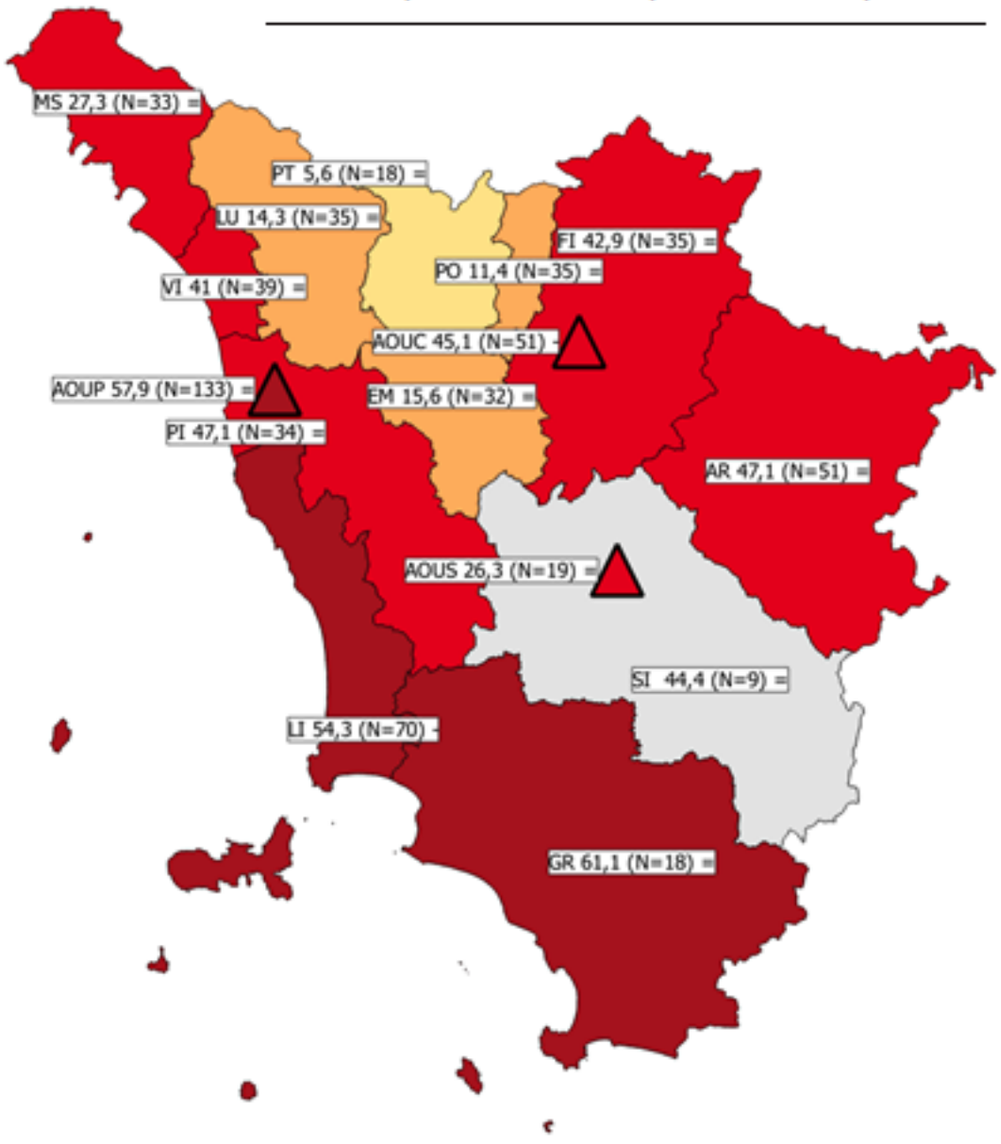
The study included 406 inpatients with severe CRGNB infections, mostly A. baumannii (312/406, 77%)

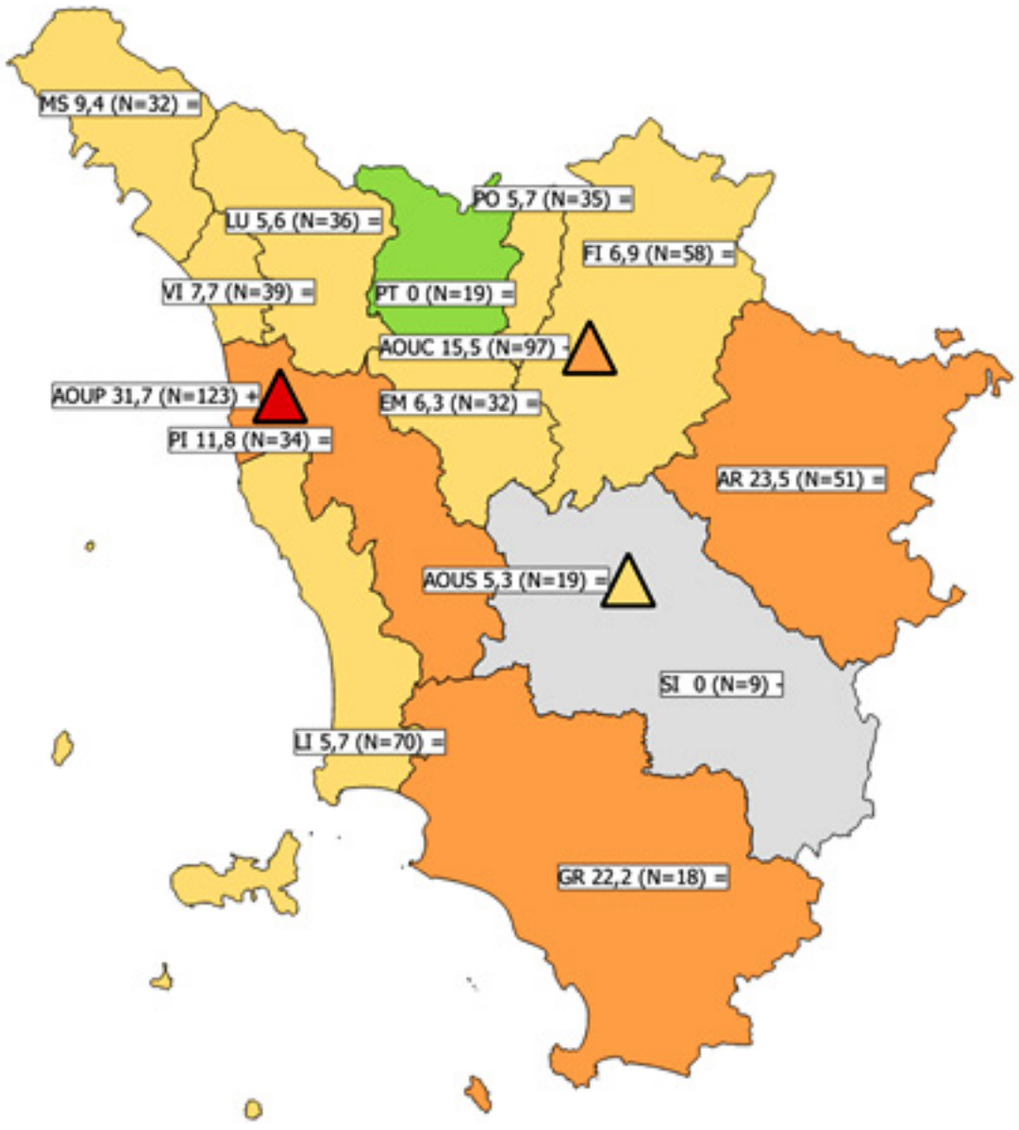


"Empirical use of colistin before pathogen identification, with or without a carbapenem, was not associated with survival following severe infections caused by CRGNBs, mainly A. baumannii"

ROLE OF ECOLOGICAL DATA of your hospital and your ward

TOSCANA 2015	ITALIA 2015	EU 2015
37,2	33,5	8,1





TOSCANA 2015	ITALIA 2015	EU 2015
14,1	-	-

REVIEW Open Access

Antibiotic strategies in the era of multidrug resistance

George Karam[1], Jean Chastre[2], Mark H. Wilcox[3] and Jean-Louis Vincent[4*]

....Three important categories can influence antimicrobial choices: patient characteristics; risk factors for infection with specific pathogens; and severity of illness...

Critical Care 2016: 20:136

....We have to adapt to this threat by **REDUCING** unnecessary antibiotic prescribing, both qualitatively and quantitatively. We need to **OPTIMIZE** control measures to minimize the risk of spread of resistant bacteria, and we have to find **NOVEL WAYS** to detect pathogens early. These approaches will help prevent the spread of MDR pathogens and could enable us to direct last-line (and in some cases, narrow-spectrum) antibiotics more effectively to those patients who need them most, rather than the current **"BROAD-SPECTRUM IS BEST"** approaches. ..

K. pneumoniae ST512 *KPC-3+ COL-R*

Antibiotico	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	>32 R
Fosfomicina	>128 R
Amikacina	>64 R
Gentamicina	>4 R
TMP/SXT	>320 R
Ciprofloxacina	>4 R
Tigeciclina	2 I
Colistina	>8 R

Ceppo PDR

Stesso ceppo

Saggiato con sistema automatico

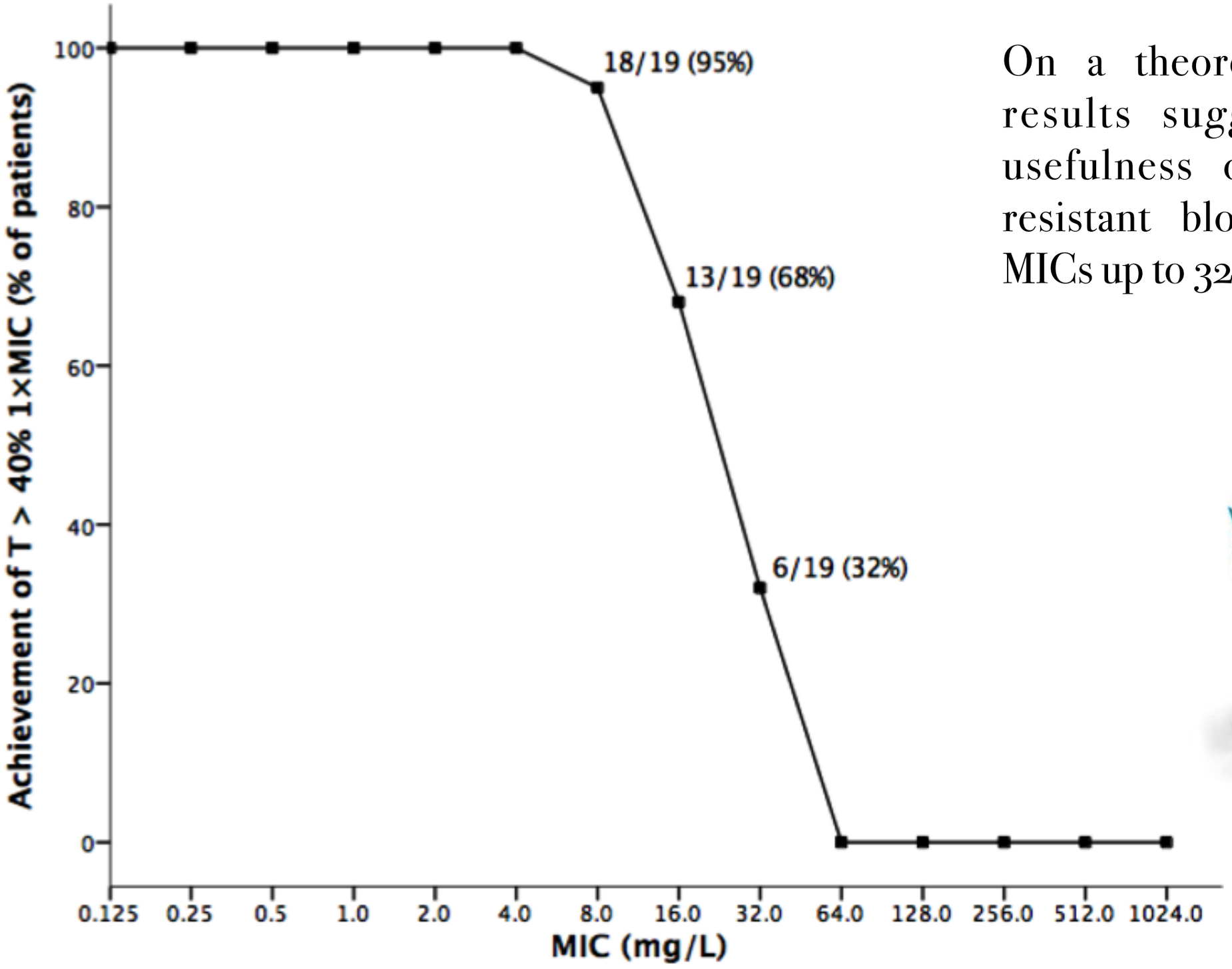
Saggiato con metodiche di riferimento: microdiluzione in brodo (AD per fosfomicina)

Antibiotico	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	64 R
Fosfomicina	32 S
Amikacina	>64 R
Gentamicina	2 S
TMP/SXT	>320 R
Ciprofloxacina	>4 R
Tigeciclina	1 S
Colistina	>8 R

Ceppo MDR

Meropenem for treating KPC-producing Klebsiella pneumoniae BSIs: should we get to the PK/PD root of the paradox?

Del Bono V et al Virulence 2016



On a theoretical basis, our results suggest a possible usefulness of MEM against resistant blood isolates with MICs up to 32 mg/L

Meropenem for treating KPC-producing Klebsiella pneumoniae BSIs: should we get to the PK/PD root of the paradox?

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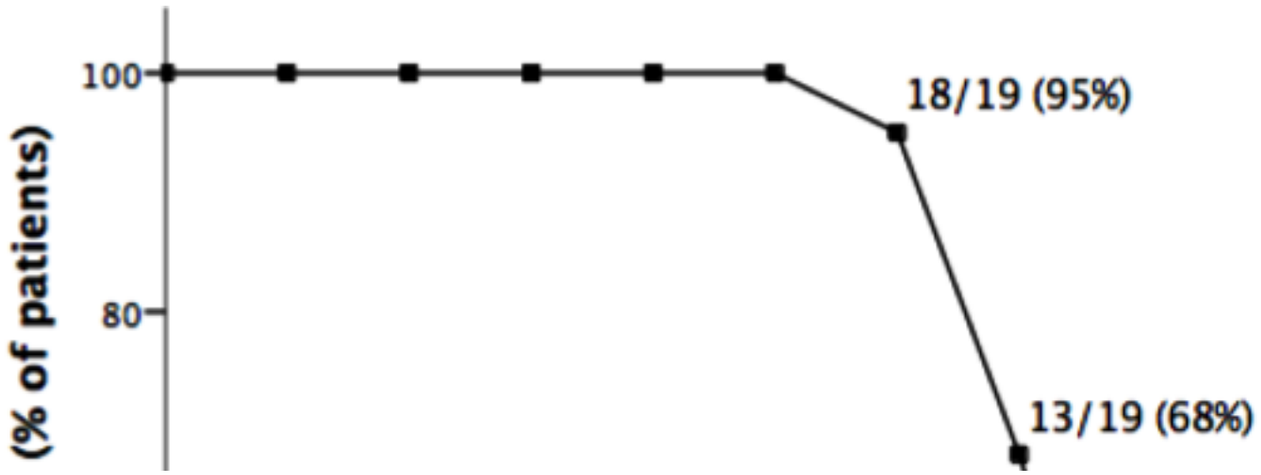

On a theoretical basis, our results suggest a possible usefulness of MEM against resistant blood isolates with MICs up to 32 mg/L

Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing *Klebsiella pneumoniae*?

Pea F et al Int J Antimicrob Agents 2017; 49(2):

TDM-guided meropenem dosing may help in treating KPC-Kp with an MIC ≤ 64 mg/L.

Treatment Options for Carbapenem-Resistant *Enterobacteriaceae* Infections

Morrill HJ et al Open Forum Infect Dis 2015

Table 2. Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing *Klebsiella pneumoniae**

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 µg/mL continue high-dose meropenem/ doripenem • MIC >16 µg/mL consider alternative in vitro active antimicrobial[a]
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	Polymyxin B/colistin: • MIC ≤ 2 µg/mL continue polymyxin B/colistin[b,c] • MIC >2 µg/mL consider alternative in vitro active antimicrobial
Gastrointestinal/ biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	If both meropenem/doripenem MIC (>16 µg/mL) and polymyxin B/colistin MIC (>2 µg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e]
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	Tigecycline: • MIC ≤1 µg/mL consider tigecycline[d] • MIC >1 µg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 µg/mL consider fosfomycin • MIC >32 µg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 µg/mL (Gentamicin/ Tobramycin) or ≤4 µg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 µg/mL (Amikacin) consider alternative in vitro active antimicrobial

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Lung	• High-dose	• Tigecycline	
Gastrointe biliary t			
Urine			

Therapeutic options for carbapenem-resistant Enterobacteriaceae infections

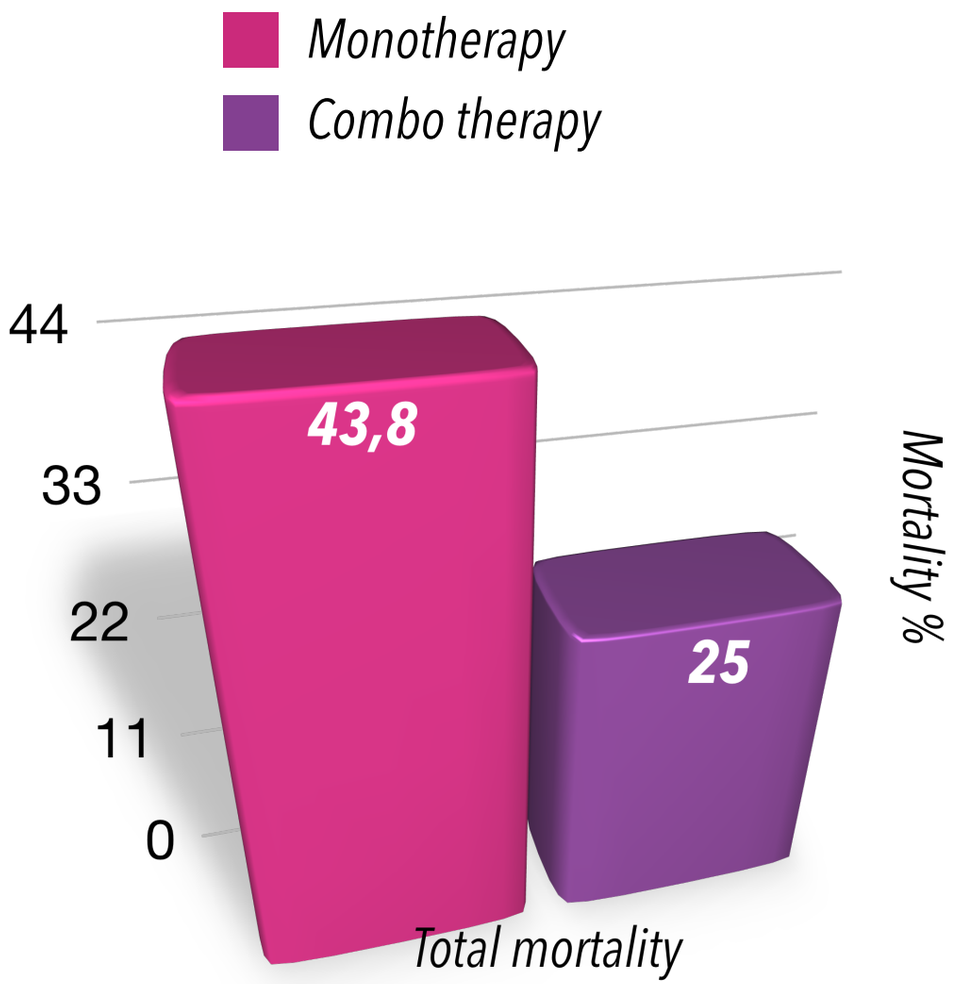
Enrico Maria Trecarichi & Mario Tumbarello

2017

The use of carbapenems in association with other active drugs is likely ineffective for CRE isolates with carbapenem Minimum Inhibitory Concentrations (MICs) >8 mg/l. The effectiveness of further therapeutic options for the treatment of extensively or pan-drug-resistant Enterobacteriaceae infections has been reported in vivo and in vitro, although few cases/case series have been reported. Novel antimicrobials that are effective against CRE are urgently needed.

Mortality Associated with BSI due to KPC Coli R with High-Level Meropenem Resistance: Importance of Combination Therapy without Colistin and Carbapenems

Marschal M et al. J Clin Microbiol 2017;55(7):2116



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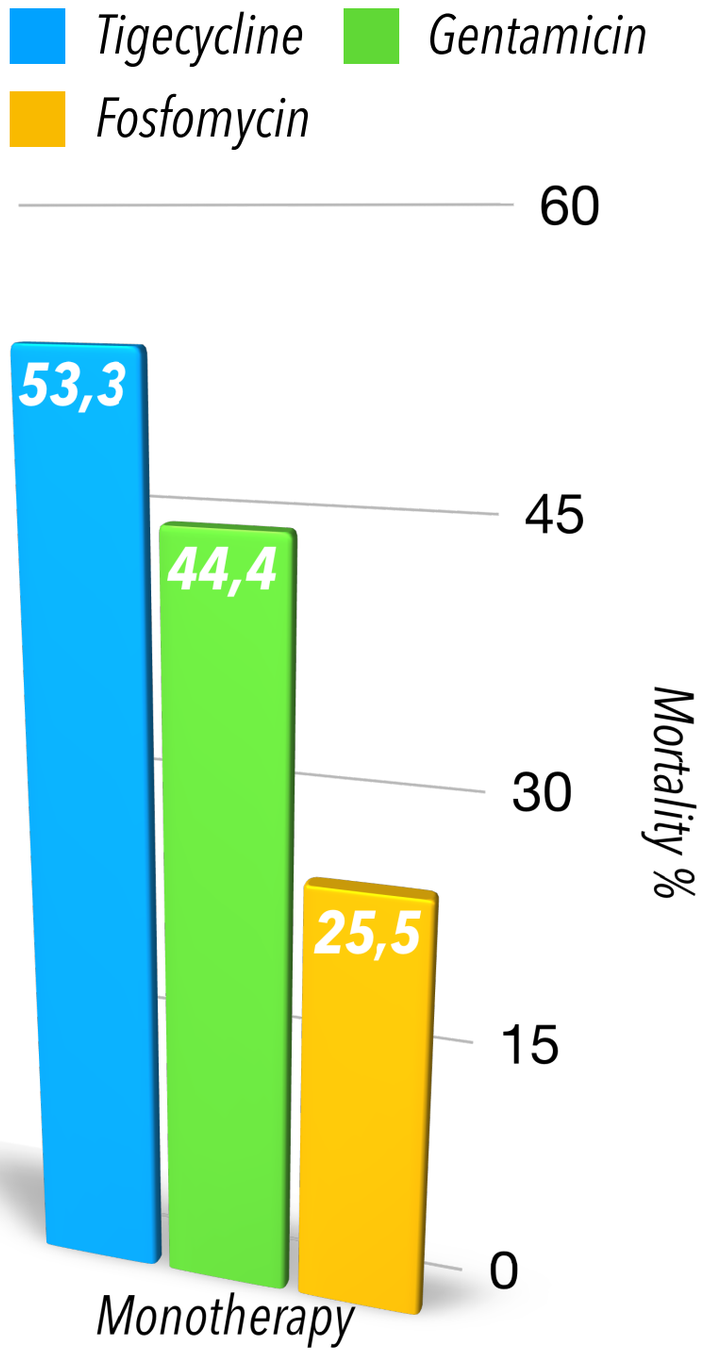
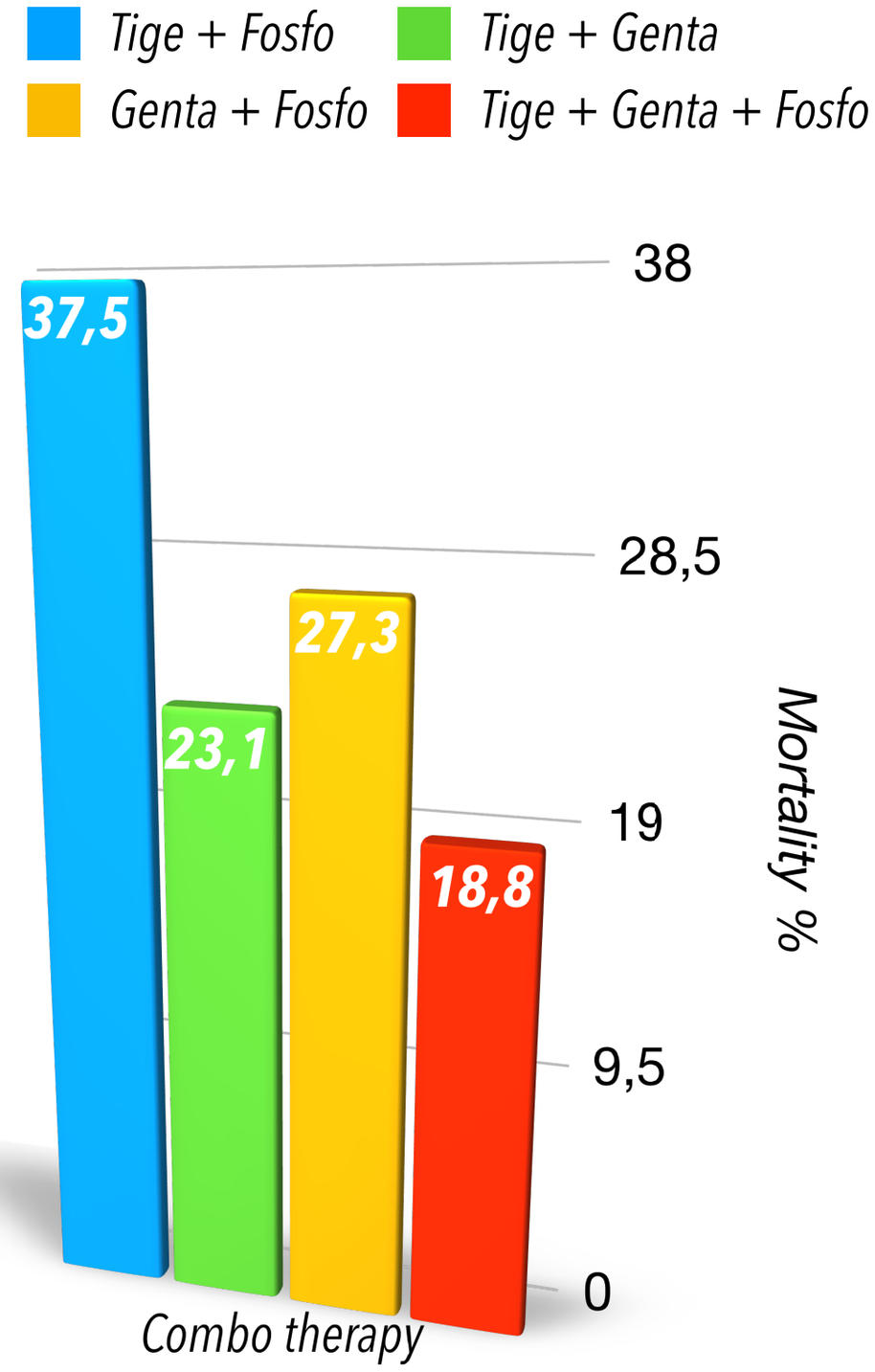
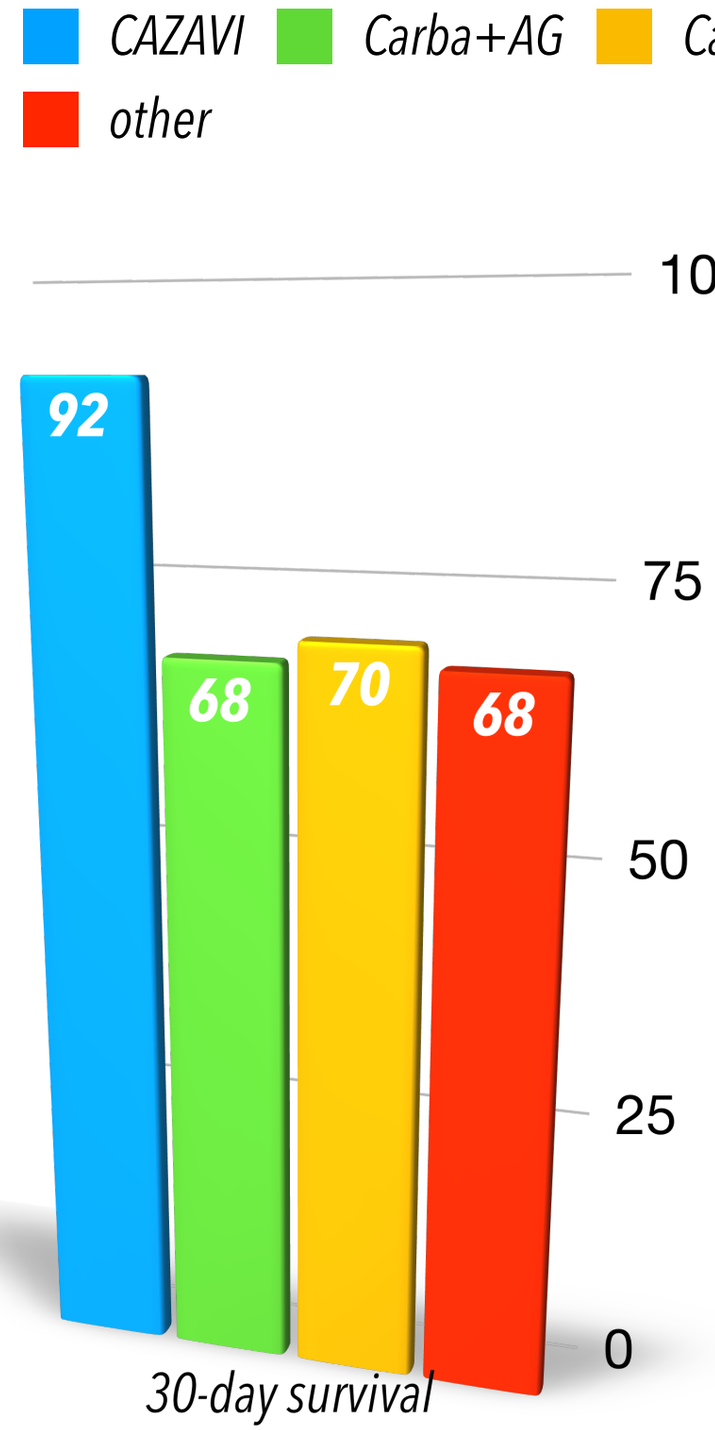
Marschal M et al. J Clin Microbiol 2017;55(7):2116

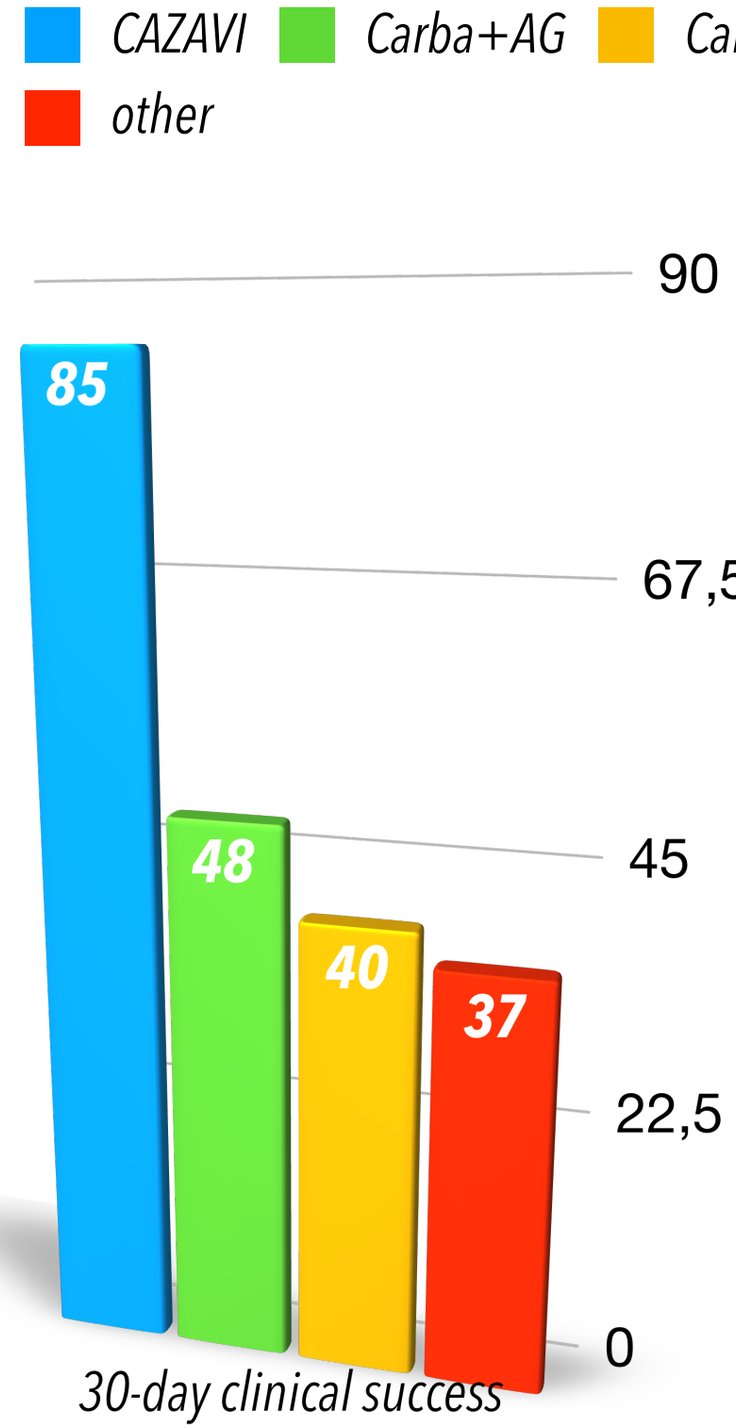




Ceftazidime-Avibactam is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia

Shields RK et al. Antimicrob Agents Chemother 2017;61(8):e00883-17





a retrospective study

CAZ-AVI: meccanismi di resistenza acquisita

- **Mutazioni KPC**
  - D179Y (perdita di attività su carbapenemi, pip/taz e aztreonam)
  - T243M (perdita di attività su carbapenemi e pip/taz)
  - 165EL166 (perdita di attività su carbapenemi, pip/taz e aztreonam)
  - V240G (ridotta attività su meropenem)

- **Mutazioni in OmpK36**
  - T333N
  - Inattivazione inserzionale (IS*5*)

- **Aumentata espressione di KPC**
  - aumento del numero di copie plasmidiche

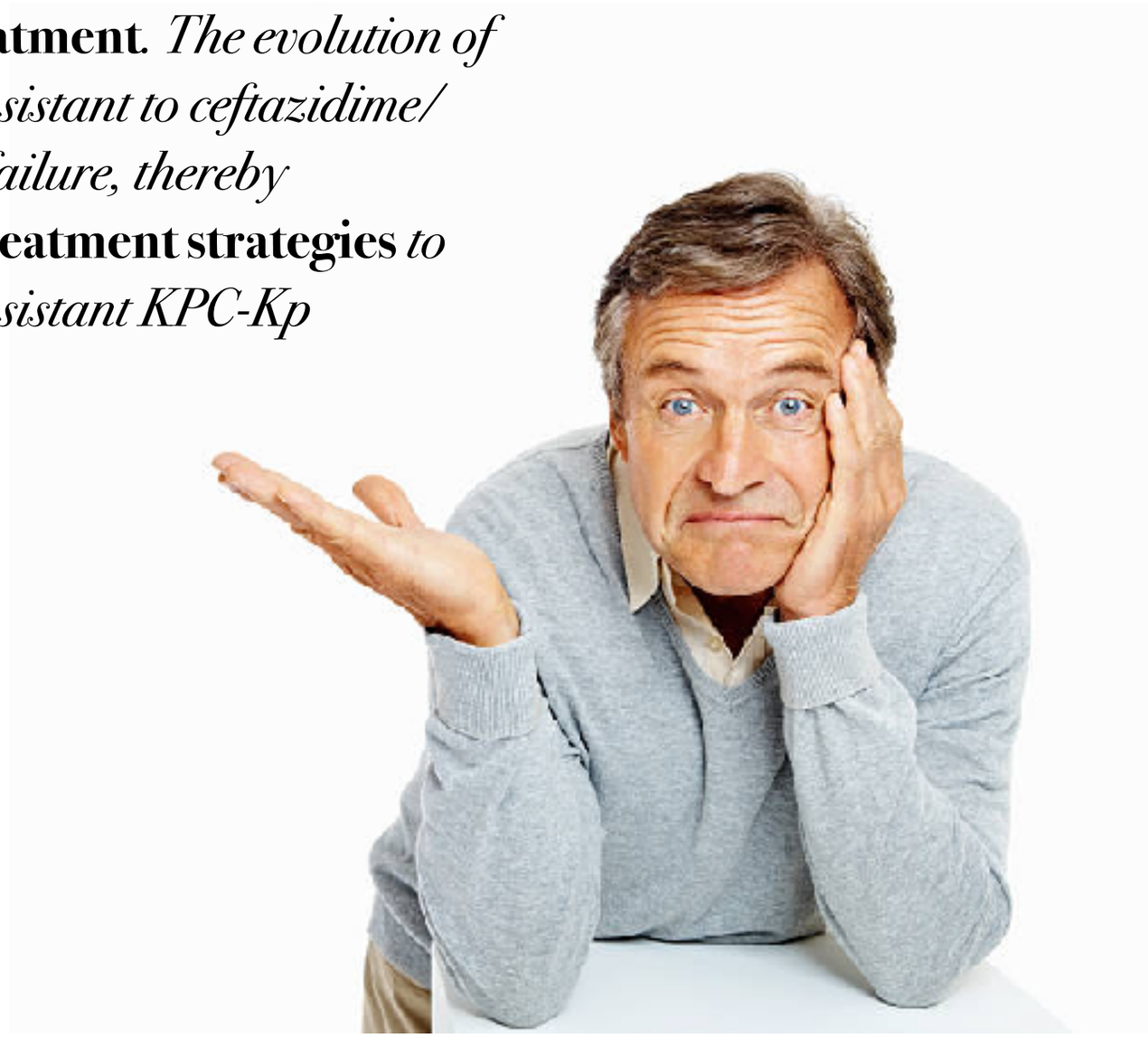
Haidar et al AAC 2017
Compain & Arthur AAC 2017
Shields et al AAC 2017
Humphries & Hamarajata AAC 2017
Shields et al OFID 2017

Cortesia Dr Giani

In vivo evolution of resistant subpopulations of KPC-producing Klebsiella pneumoniae during **ceftazidime/avibactam** treatment

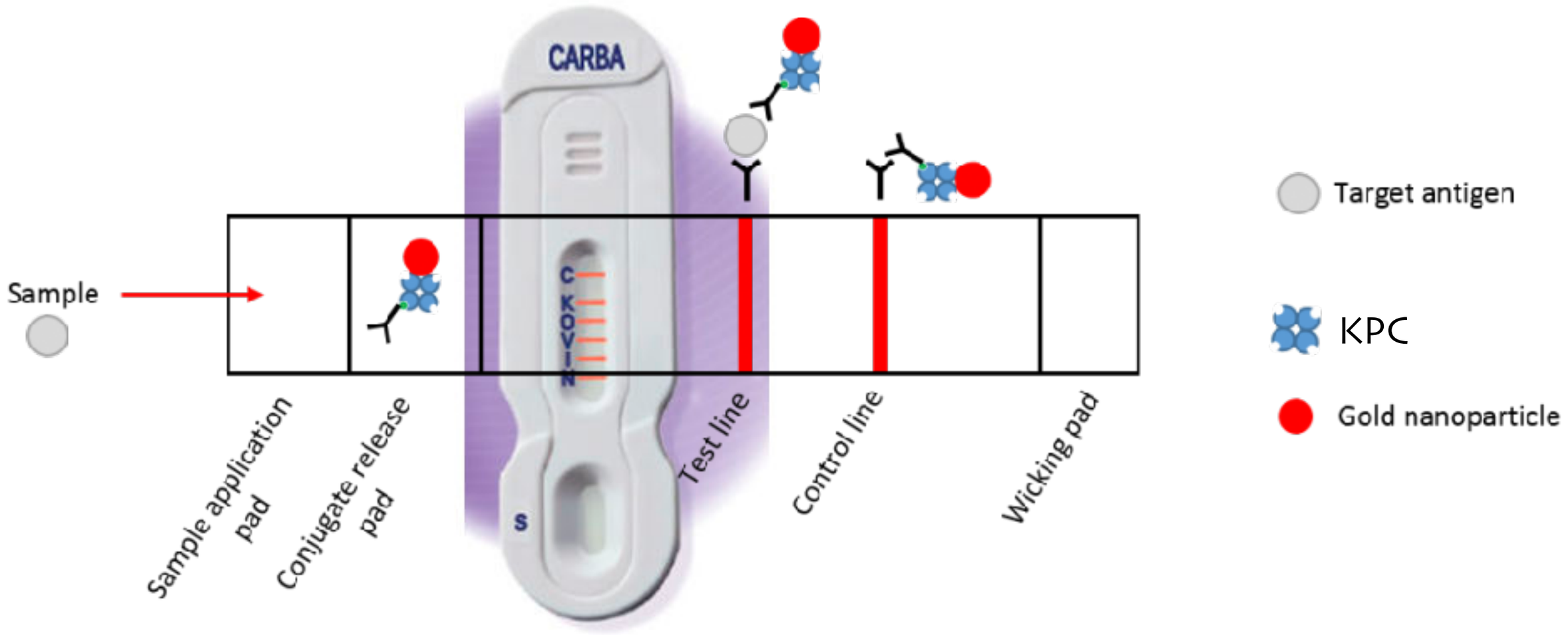
Gaibani P et al. J Antimicrob Chemother giu 2018

CONCLUSIONS: *Our analysis indicates that mixed subpopulations of ceftazidime/avibactam-resistant KPC-Kp emerge* **after ceftazidime/avibactam treatment**. *The evolution of different subpopulations that are highly resistant to ceftazidime/avibactam likely contributes to treatment failure, thereby highlighting* **the need for combination treatment strategies** *to limit selection of ceftazidime/avibactam-resistant KPC-Kp subpopulations.*



Lateral flow immunochromatography assay (lFIA)

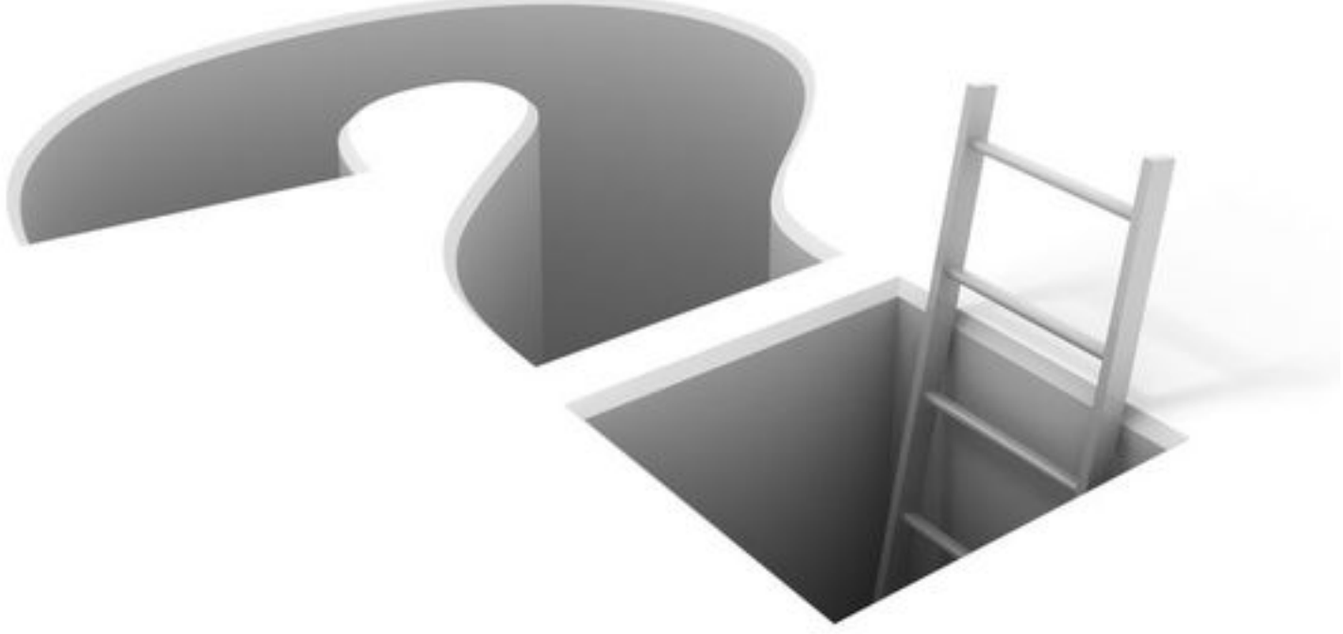
NG-TEST CARBA 5



CARBA5 *a multiplex lateral flow immunoassay for the rapid identification of NDM-, KPC-, IMP- and VIM-type and OXA-48-like carbapenemases-producing Enterobacteriaceae*

Boutal H t al J Antimicrob Chemother 2018;73:909-915

Overall, this assay reached 100% SENSITIVITY and 95.3% (retrospectively) to 100% (prospectively) SPECIFICITY.



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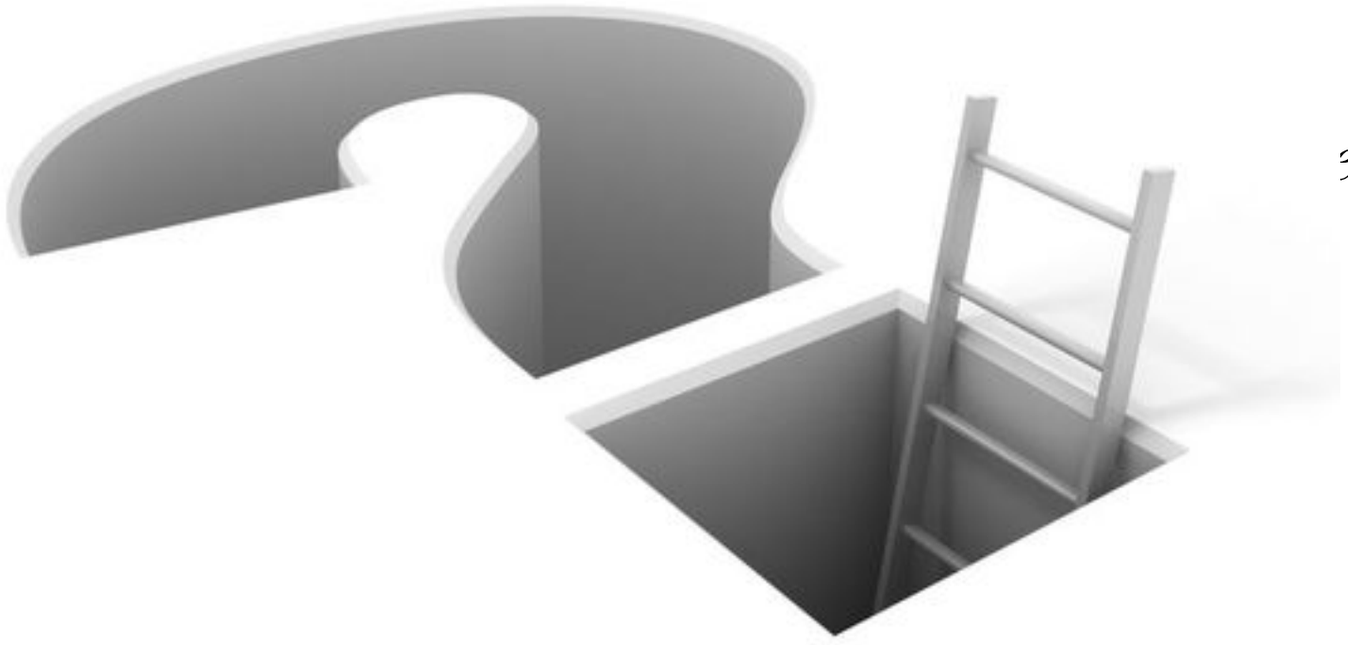
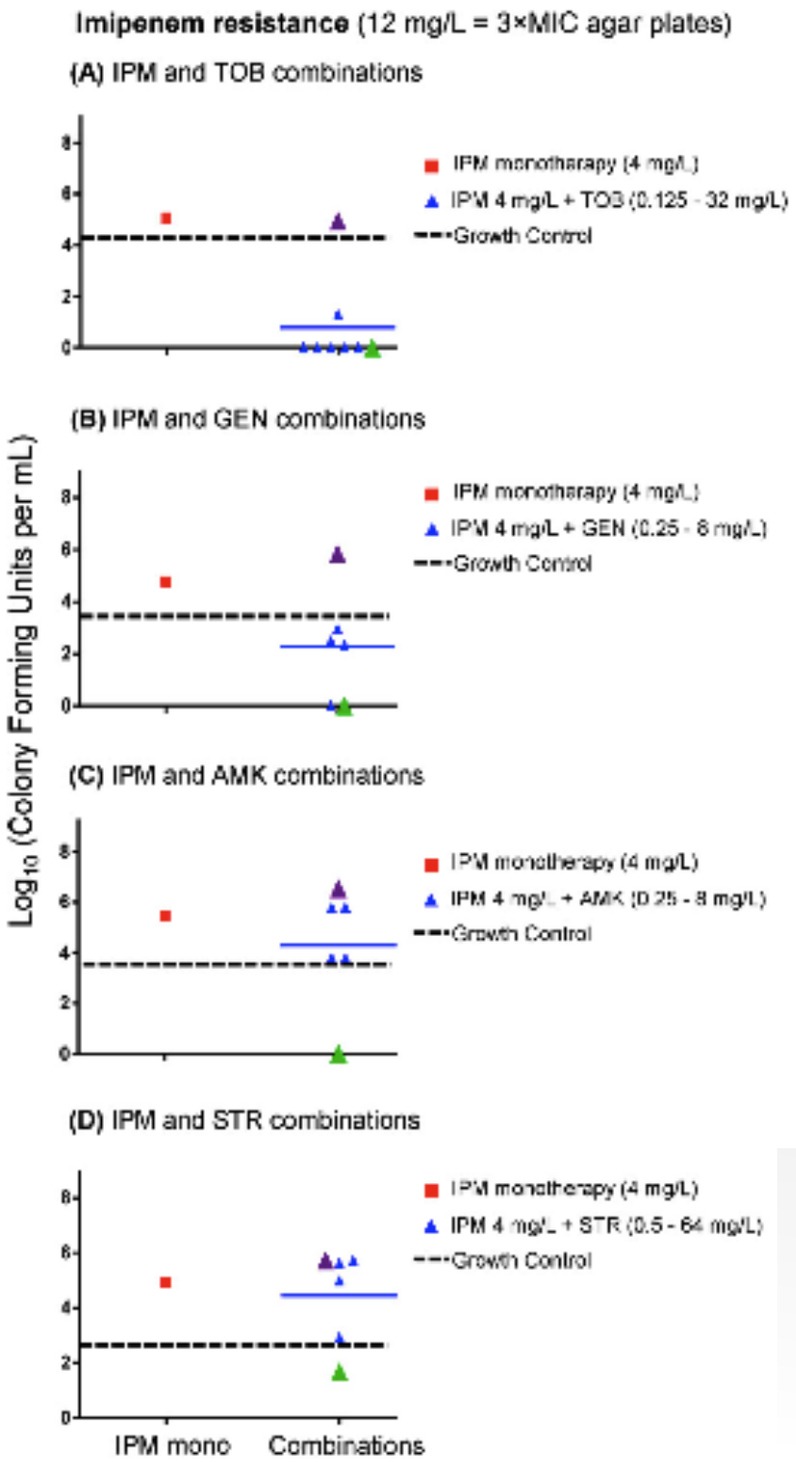
Boutal H t al J Antimicrob Chemother 2018;73:909-915



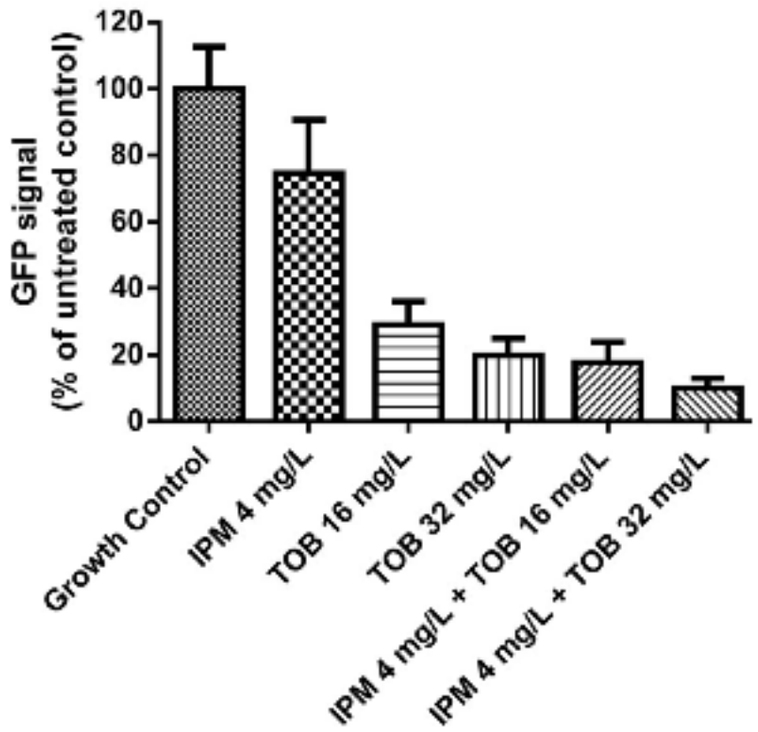
CONCLUSIONS: *Carba5 is efficient, rapid and easy to implement in the routine workflow of a clinical microbiology laboratory for confirmation of the five main carbapenemases encountered in Enterobacteriaceae.*

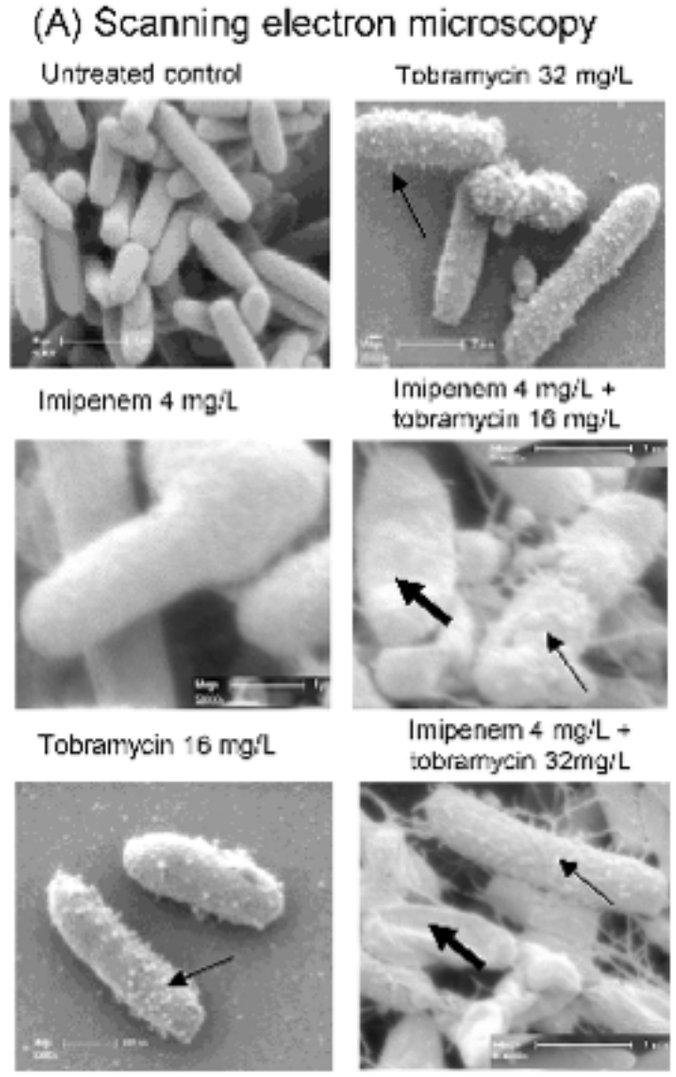
Aminoglycoside Concentrations Required for Synergy with Carbapenems against **Pseudomonas aeruginosa**

Yadav R et al Antimicrob Agents Chemother dec 2017



The MBM indicated that aminoglycosides enhanced the imipenem target site concentration up to 4.27-fold

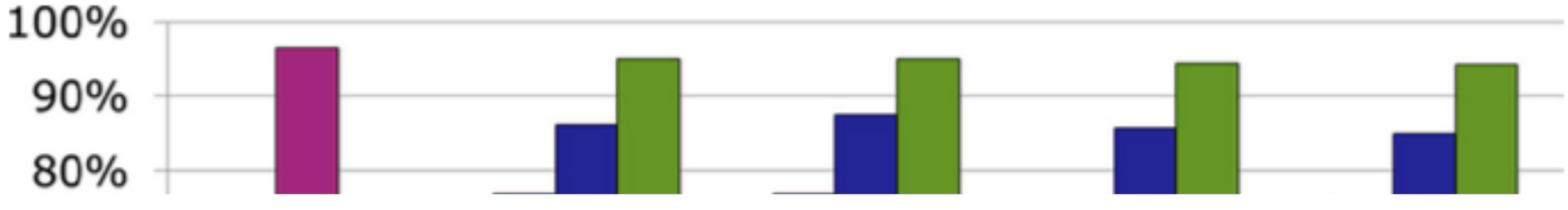




tobramycin was highly synergistic and displayed the maximum outer membrane disruption potential among the tested aminoglycosides. These findings support the optimization of highly promising antibiotic combination dosage regimens for critically ill patients.

In Vitro Comparison of **Ceftolozane-Tazobactam** to traditional Beta-Lactams and Ceftolozane-Tazobactam as an Alternative to Combination Antimicrobial Therapy for **Pseudomonas aeruginosa**

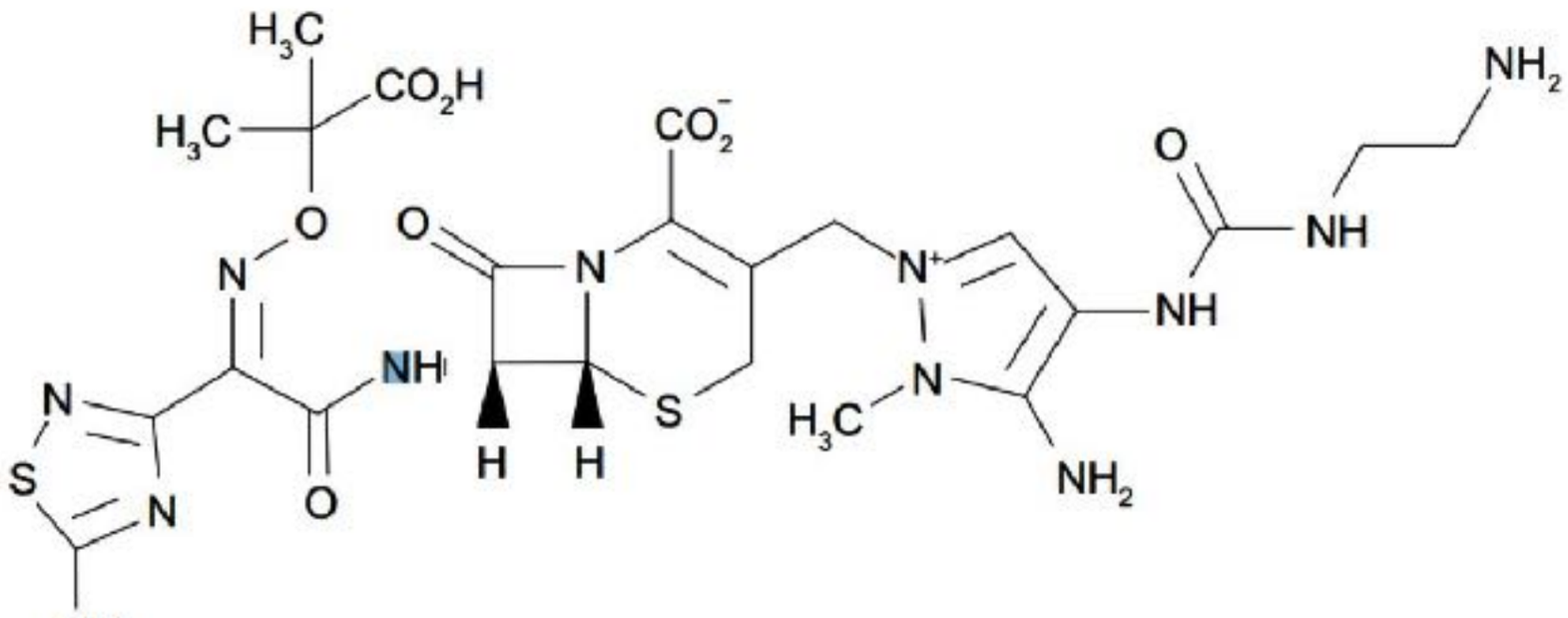
Goodlet KJ et al Antimicrob Agents Chemother dec 2017



Ceftolozane-tazobactam should be considered for use in patients at high risk for resistant *P. aeruginosa* infection and as an alternative to empirical combination therapy, especially for patients unable to tolerate aminoglycosides

Percent susceptibility of all *P. aeruginosa* isolates (**n 1,257**) to ceftolozane-tazobactam (pink bar) compared to that to B-lactams alone (light-blue bars) or in combination with ciprofloxacin (dark-blue bars) or tobramycin (green bars). Definitions: CAZ, ceftazidime; C/T, ceftolozane-tazobactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam.

Changing 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*

Considerations for effect site PK to estimate drug exposure: C of ATBs in the LUNG

Rodvold KA et al Curr Opin in Pharmacology 2018

Antibiotic	Dose	Penetration ratio (ELF-to-total plasma)	Penetration ratio (ELF-to-unbound plasma)
ceftazidime/ avibactam	2 g q8h	31,3%	NR
	0.5 g q8h	34,9%	NR
	3 g q8h	32,4%	NR
	1 g q8h	32%	NR
ceftolozane/ tazobactam	1 g 8h	**48%**	59%
	0.5 g 8h	**44**%	NR

ACS Infectious Diseases

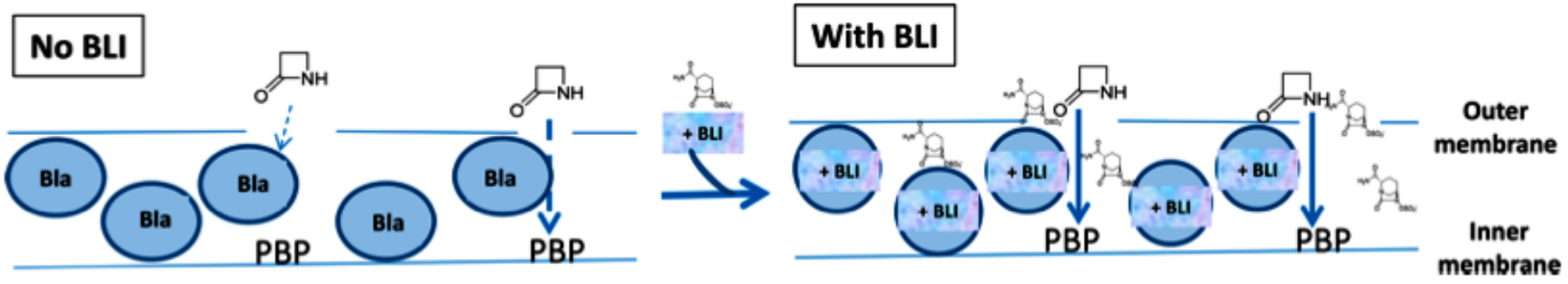
Viewpoint

Cite This: *ACS Infect. Dis.* XXXX, XXX, XXX−XXX

pubs.acs.org/journal/aidcbc

Game Changers: New β-Lactamase Inhibitor Combinations Targeting Antibiotic Resistance in Gram-Negative Bacteria

Karen Bush*

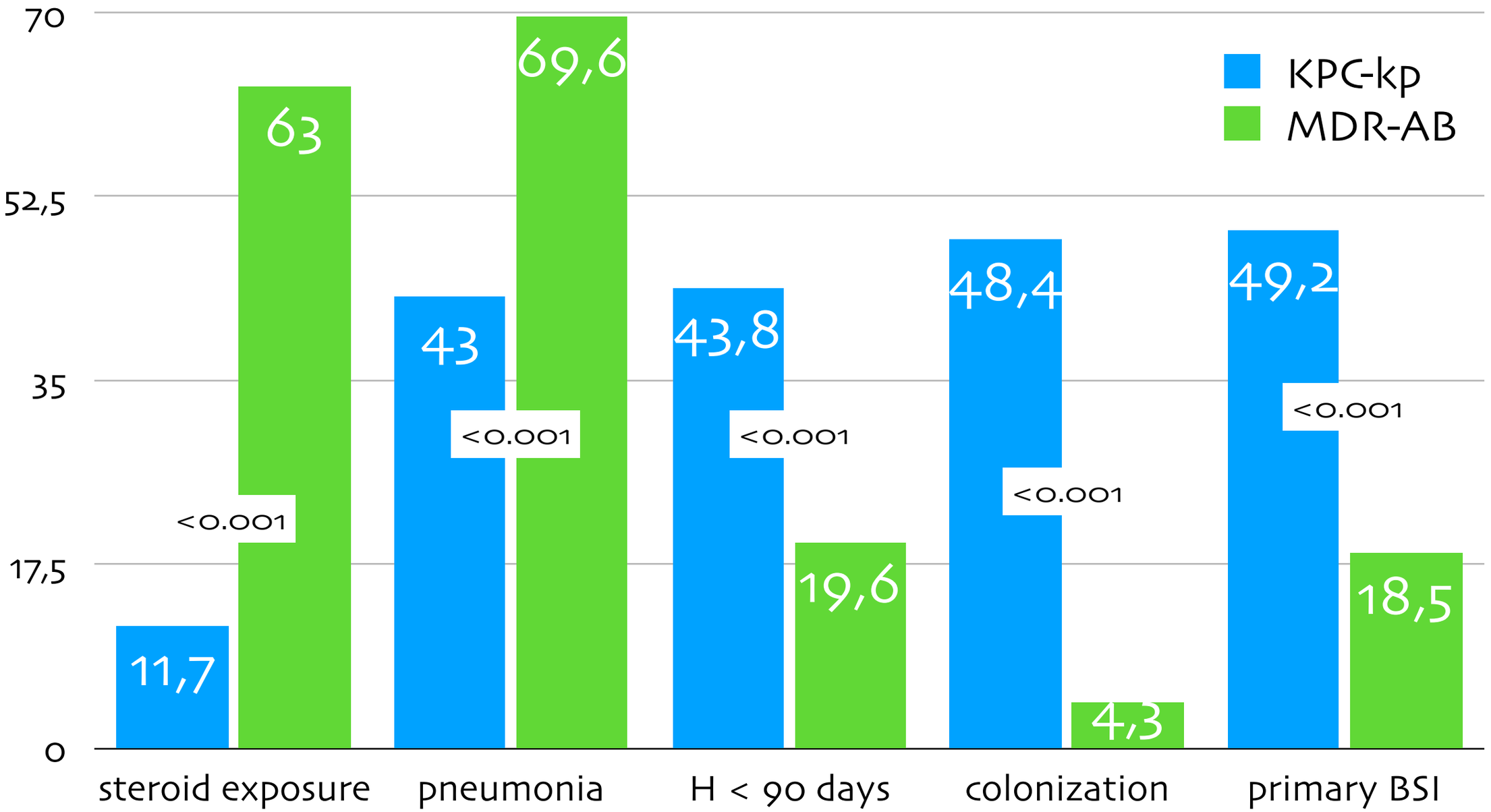


Gaps still exist for the treatment of infections caused by multidrug-resistant Acinetobacter spp, and metallo-β-lactamase-producing pathogens.

Comparison of **Septic Shock** due to MDR-AB or KPC-kp in ICU

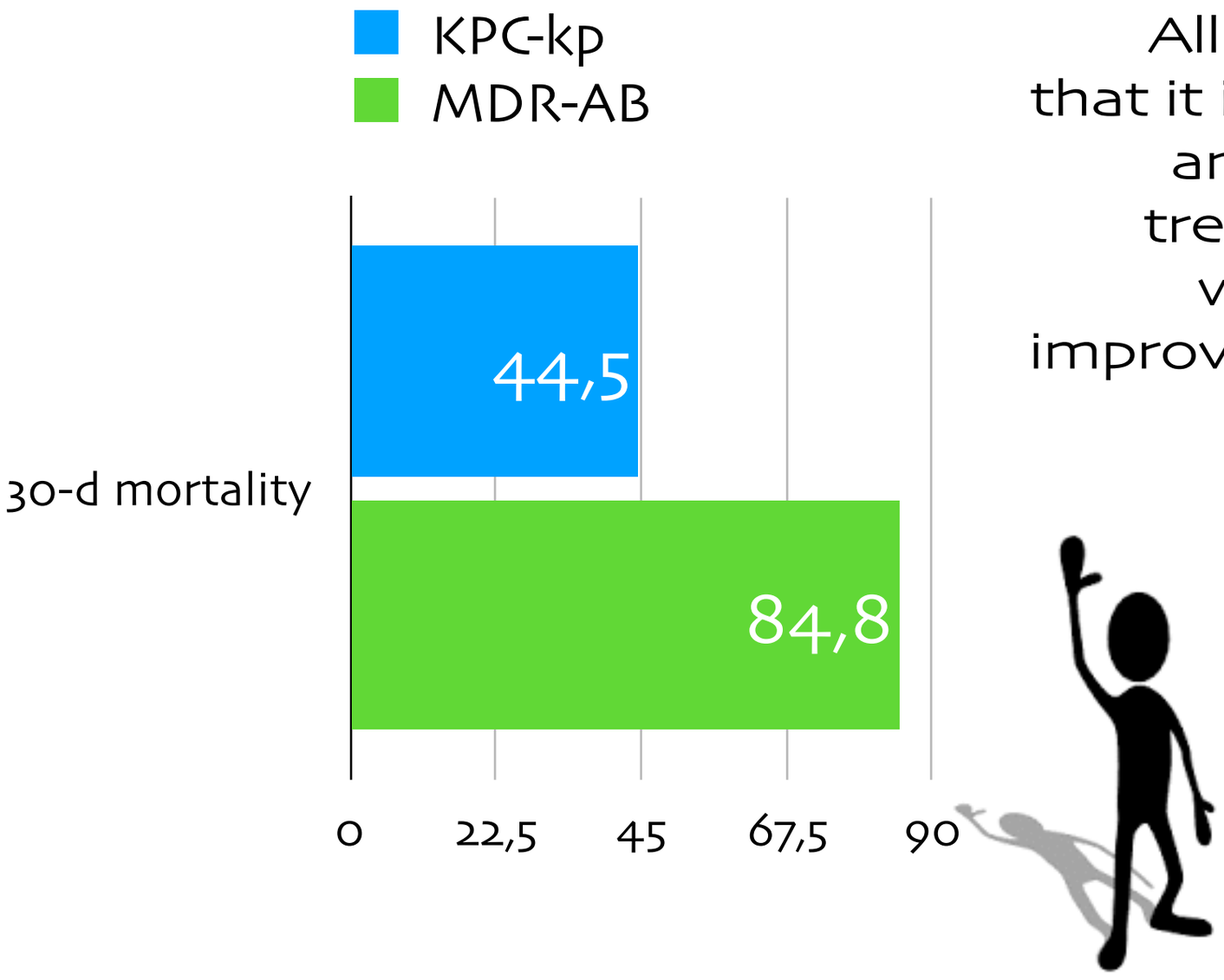
Russo A et al. AAC giu 2018

We retrospectively analyzed 220 patients admitted to the ICU of a teaching hospital from November 2010 to December 2015 who developed septic shock due to MDR-AB or KPC-Kp infection



Comparison of **Septic Shock** due to MDR-AB or KPC-kp in ICU

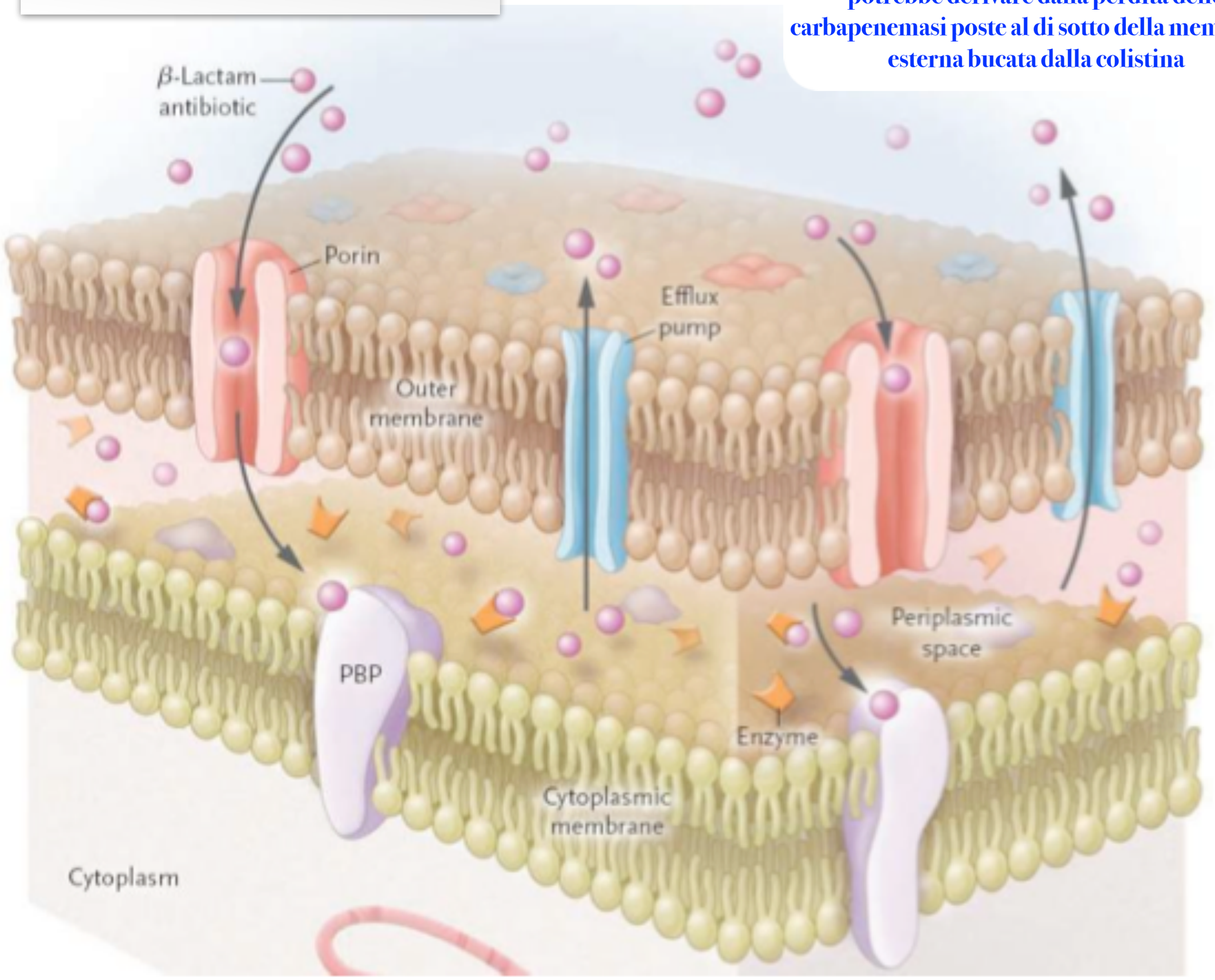
Russo A et al. AAC giu 2018



All these findings suggest that it is crucial to obtain new antibiotic options for the treatment of ICU patients with MDR-AB infection, improve treatment strategies, and reduce mortality.

Acinetobacter baumannii

Il sinergismo colistina+carbapenemico potrebbe derivare dalla perdita delle carbapenemasi poste al di sotto della membrana esterna bucata dalla colistina

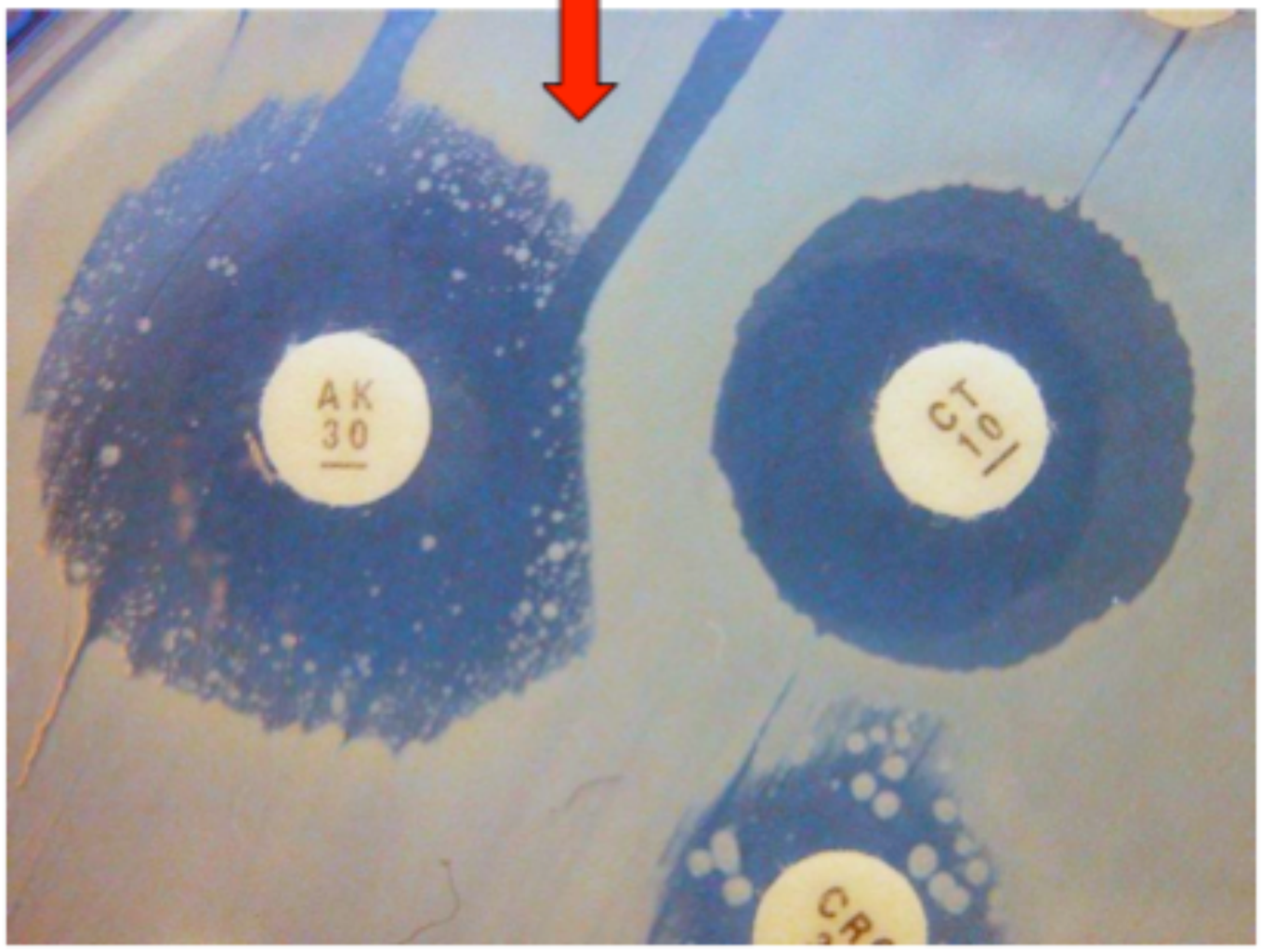


Acinetobacter baumannii

Il sinergismo colistina+carbapenemico potrebbe derivare dalla perdita delle carbapenemasi poste al di sotto della membrana esterna bucata dalla colistina

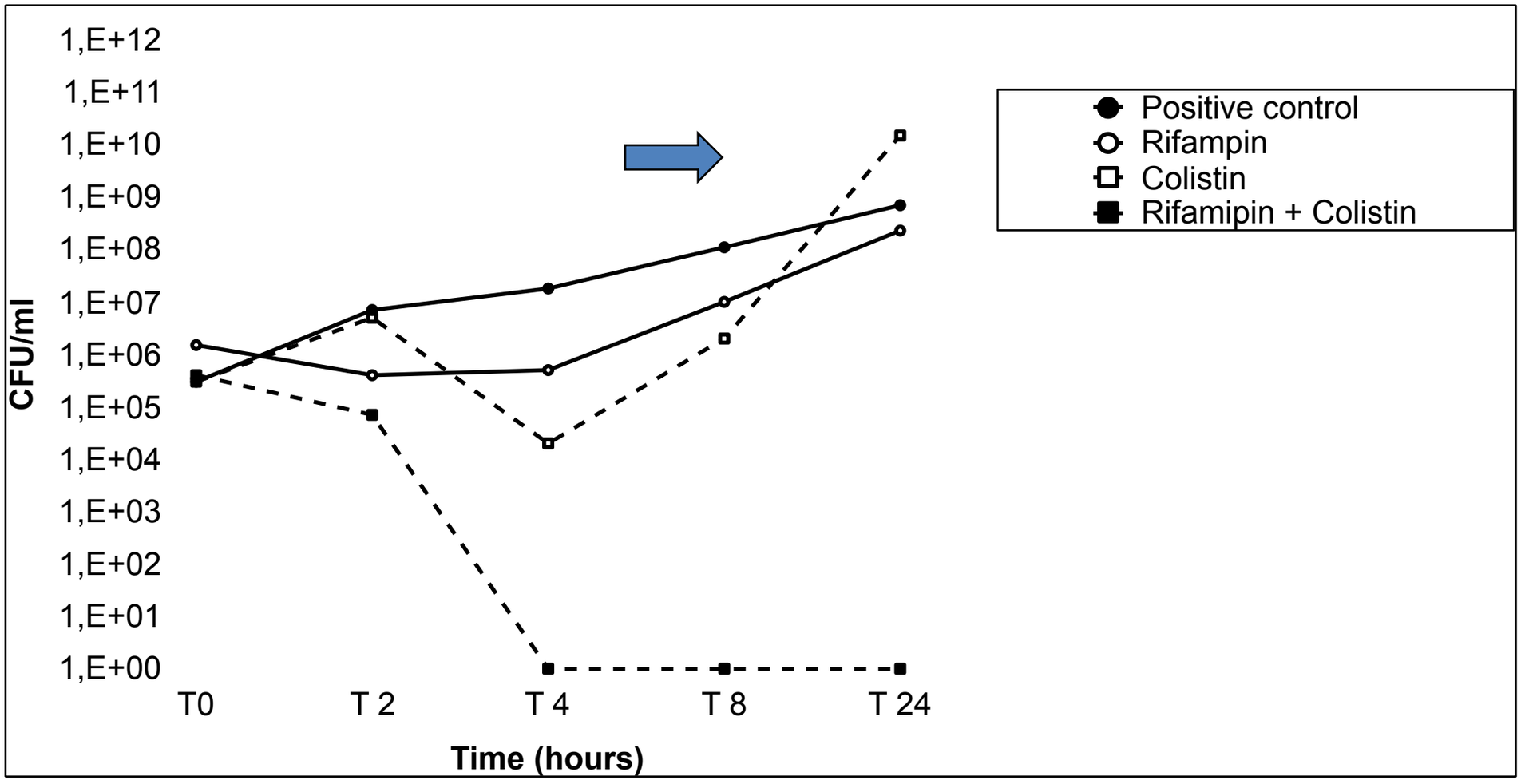
β-Lactam antibiotic

Antagonismo colistina-amikacina



Rifampin plus Colistin time-kill curve vs. MDR Ps. aeruginosa

Tascini et al. J Chemother 2004;16:282-7



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

Penwell WF et al Antimicrob Agents Chemother 2015;59(3):1680-1689

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

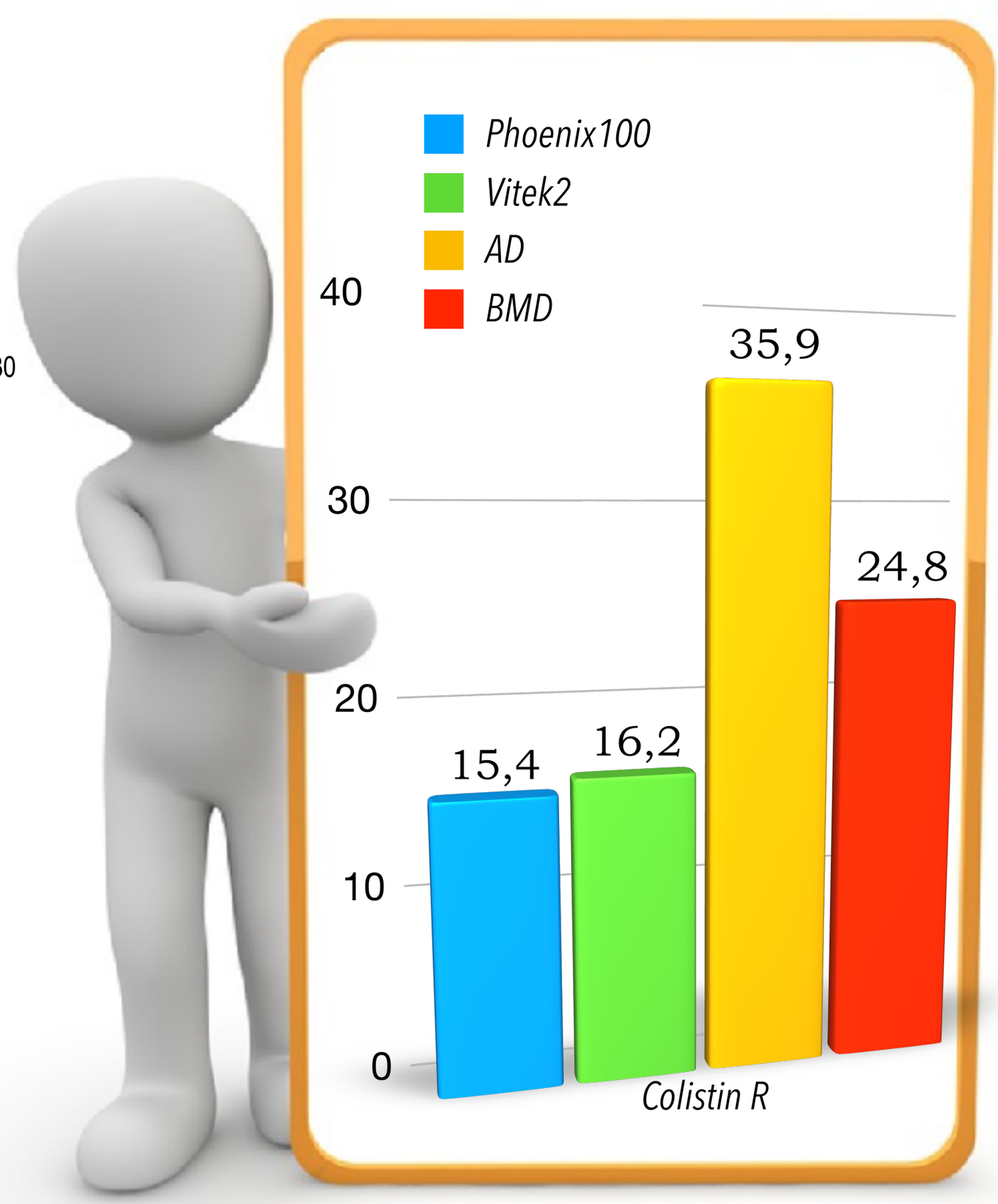
TABLE 1 Acylation rate constants for acylation of *A. baumannii* and *P. aeruginosa* PBP1a, PBP2, and PBP3 by various inhibitors

	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

Evaluation of two automated systems for **colistin** susceptibility testing of carbapenem-resistant **Acinetobacter baumannii** clinical isolates

Vourli S et al. J Antimicrob Chemother 2017; 72: 2528–2530

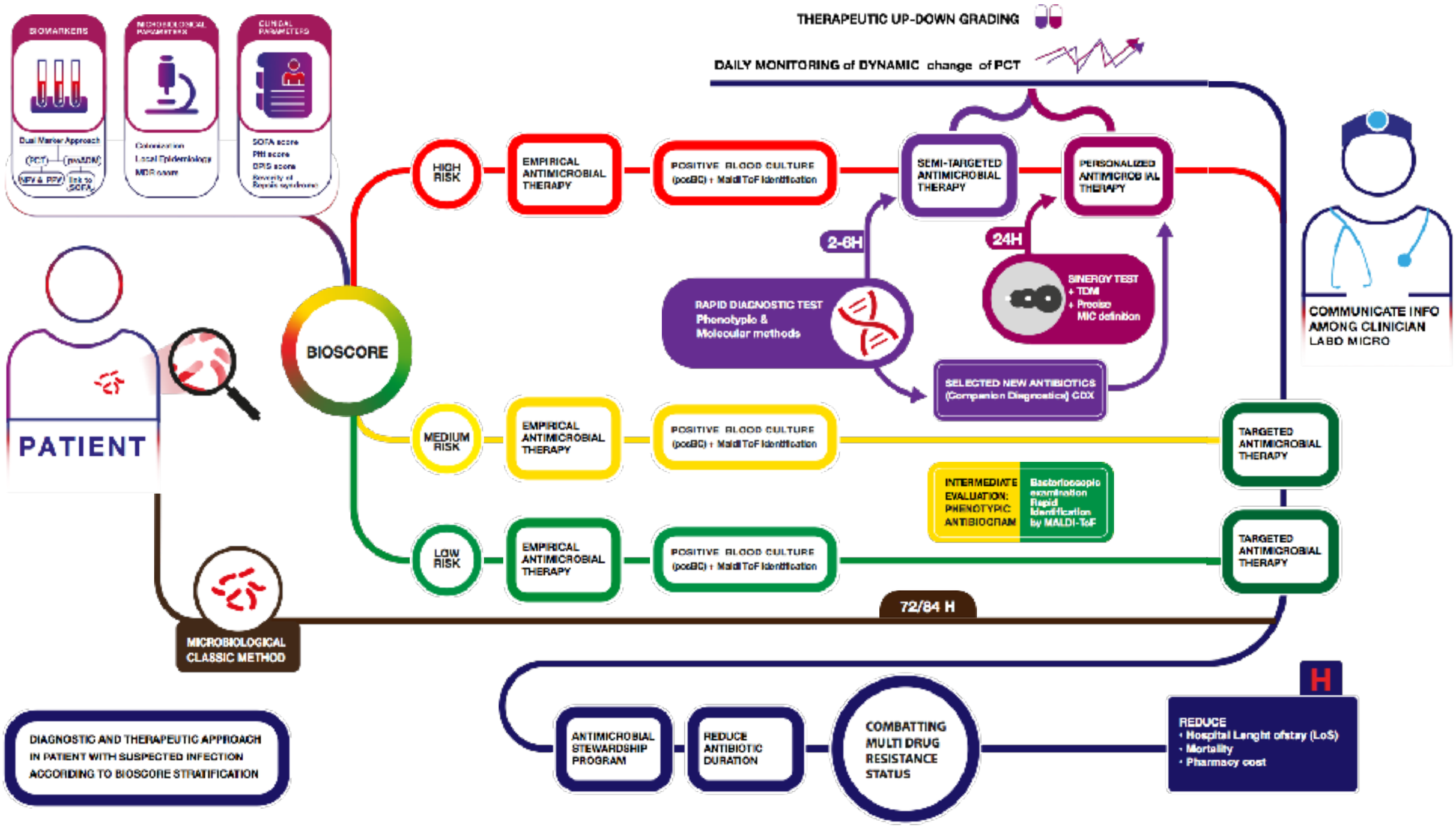


Unavailability of old antibiotics threatens effective treatment for common bacterial infections

Tangden T et al Lancet march 2018

In addition to the insufficient pipeline of new antibiotics, the unsustainable production and supply of old antibiotics is becoming a serious global problem that limits the treatment options for common bacterial infections.

THE LANCET


BIOMARKERS
Dual Marker Approach
(PCT)
(pro/MR)
NPV & PPV
link to SOFA
MICROBIOLOGICAL PARAMETERS
Colonization
Local Epidemiology
MDR cases
CLINICAL PARAMETERS
SOFA score
PIII score
DPIS score
Severity of Sepsis syndrome
PATIENT
BIOSCORE
THERAPEUTIC UP-DOWN GRADING
DAILY MONITORING of DYNAMIC change of PCT
HIGH RISK
EMPIRICAL ANTIMICROBIAL THERAPY
POSITIVE BLOOD CULTURE (pcoBC) + MaldiToF Identification
SEMI-TARGETED ANTIMICROBIAL THERAPY
PERSONALIZED ANTIMICROBIAL THERAPY
2-6H
24H
RAPID DIAGNOSTIC TEST Phenotypic & Molecular methods
SINERGY TEST + TDM + Precise MIC definition
SELECTED NEW ANTIBIOTICS (Companion Diagnostics) CDX
COMMUNICATE INFO AMONG CLINICIAN LABD MICRO
MEDIUM RISK
EMPIRICAL ANTIMICROBIAL THERAPY
POSITIVE BLOOD CULTURE (pcoBC) + MaldiToF Identification
TARGETED ANTIMICROBIAL THERAPY
INTERMEDIATE EVALUATION: PHENOTYPIC ANTIBIOGRAM
Bacterioscopic examination Rapid identification by MALDI-ToF
LOW RISK
EMPIRICAL ANTIMICROBIAL THERAPY
POSITIVE BLOOD CULTURE (pcoBC) + MaldiToF Identification
TARGETED ANTIMICROBIAL THERAPY
72/84 H
MICROBIOLOGICAL CLASSIC METHOD
DIAGNOSTIC AND THERAPEUTIC APPROACH IN PATIENT WITH SUSPECTED INFECTION ACCORDING TO BIOSCORE STRATIFICATION
ANTIMICROBIAL STEWARDSHIP PROGRAM
REDUCE ANTIBIOTIC DURATION
COMBATTING MULTI DRUG RESISTANCE STATUS
H
REDUCE
• Hospital Lenght ofstay (LoS)
• Mortality
• Pharmacy cost

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