



GiViTI  Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva

Mercoledì 4 Ottobre

- 13:30 – 14:15 Registrazione
- 14:15 – 14:30 Benvenuto S. Finazzi, M. Tavola

Comunicazione

- 14:30 – 15:00 Il nuovo sito GiViTI e social A. Lavetti (20 min)

Infezioni: aggiornamenti

Moderatore: L. Dalfino

- 15:00 – 15:30 Il progetto ASAP: risultati V. Barbetta, D. Magatti (20 min)
- 15:30 – 16:30 Come cambiano le KPC in Italia: il problema della discrepanza isogenetica B. Viaggi (40 min)

Come cambiano le KPC in Italia: il problema della discrepanza isogenetica



Bruno Viaggi
Dipartimento di Anestesia
NeuroAnestesia e
Rianimazione AOU Careggi
Gruppo Tecnico Programma Lotta alla Sepsi
Coordinamento e Gruppo Tecnico AID
REGIONE TOSCANA

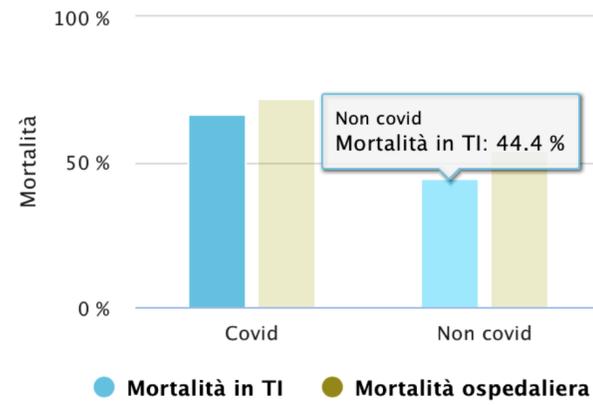


Dichiarazione su potenziali conflitti di interesse

Consulenze, partecipazione advisory boards, speaker's bureau, contratti/ contributi di ricerca e di eventi studio:

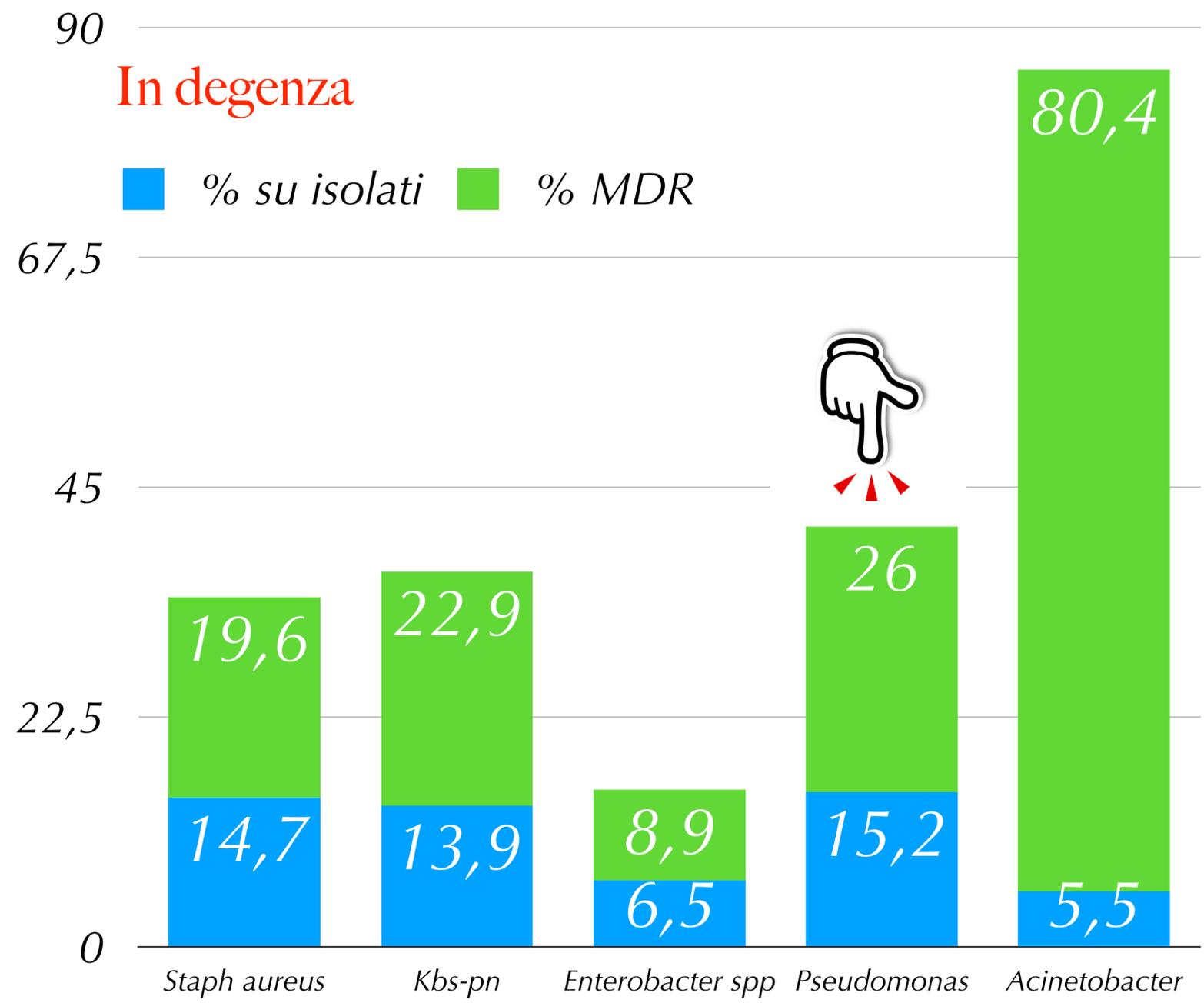
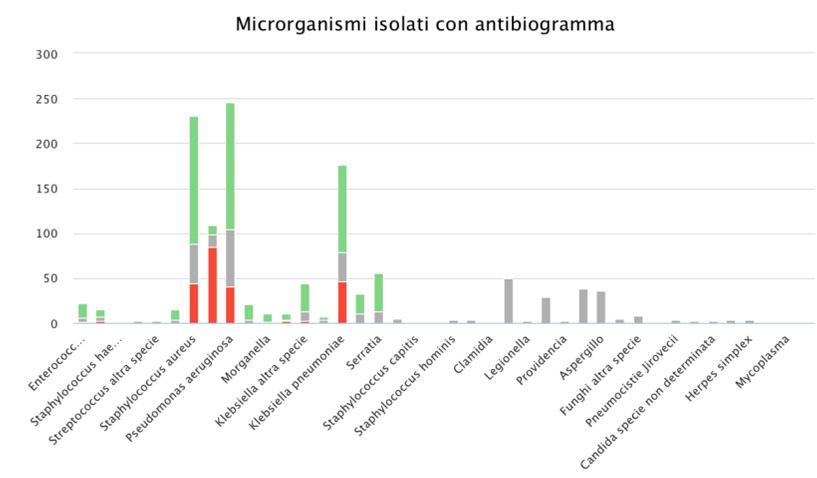
Abbott, Accelerate Diagnostics, Ada, Advanz Pharma, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Diasorin, Emmegi Diagnostica, Gilead, Menarini, MSD Italia, Nordic Pharma, Pfizer, Shionogi, Thermofischer Scientific, Viatris

Mortalità - Pazienti infetti all'ammissione con shock settico - COVID VS NON COVID



Mortalità						
Pazienti	N pazienti	N morti TI	TI	N pazienti (escluso riamm.)	N morti H	H
Covid	453	300	66.4	449	319	71.7
Non covid	3122	1384	44.4	2974	1583	53.7

Microrganismi isolati nei pazienti infetti in degenza con VAP



Difficult-to-Treat Resistance in Gram-negative

Kadri SS. et al *Clin Infect Dis* 2018



Antibiotico	MIC mg/l
Piperacillina/tazobactam	≥128 R
Ceftazidime	64 R
Cefepime	64 R
Aztreonam	≥64 R
Imipenem	32 R
Meropenem	16 R
Amikacina	≥64 R
Gentamicina	>32 R
Ciprofloxacina	>32 R
Ceftolozane/tazobactam	≥8 R
Fosfomicina	128 IE
Colistina	1 S
Cefiderocol	1 S

Pseudomonas aeruginosa

VIM-1

Antibiotico	MIC mg/l
Imipenem	>32 R
Meropenem	64 R
Amikacina	32 R
Gentamicina	>16 R
Ciprofloxacina	>32 R
TMP/SMT	>320 R
Colistina	1 S
Cefiderocol	2 S IE

Acinetobacter baumannii

OXA-23

Antibiotico	MIC mg/l
Piperacillina/tazobactam	≥128 R
Ceftriaxone	≥4 R
Ceftazidime	>128 R
Cefepime	>32 R
Imipenem	16 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	≥16 R
Gentamicina	2 S
Ciprofloxacina	>4 R
Tigeciclina	0.5 IE
Colistina	8 R
CAZ/AVI	2 S
MEM/VAB	0.5 S
Cefiderocol	2 S

Klebsiella pneumoniae

KPC-3

Antibiotico	MIC mg/l
Piperacillina/tazobactam	≥128 R
Ceftriaxone	≥4 R
Ceftazidime	>128 R
Cefepime	>32 R
Imipenem	>16 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Tigeciclina	1 IE
Colistina	0.5 S
CAZ/AVI	>16 R
MEM/VAB	>16 R
Cefiderocol	1 S

Klebsiella pneumoniae

NDM-1

Difficult-to-Treat Resistance in Gram-negative

Kadri SS. et al *Clin Infect Dis* 2018

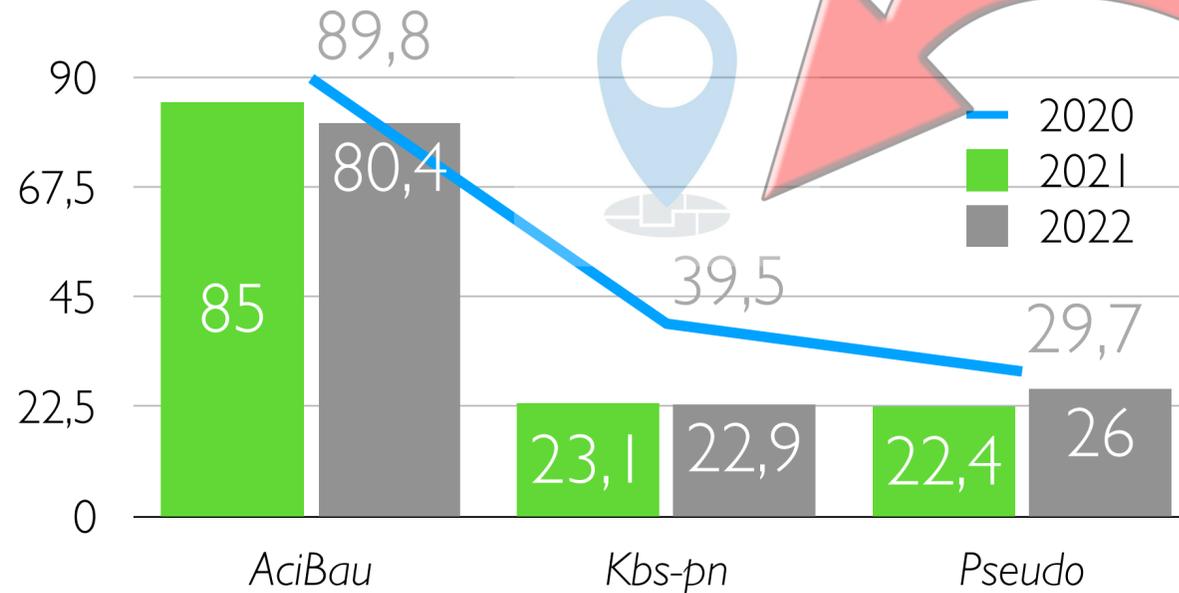


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Fosfomicina	128 IE
Colistina	1 S
Cefiderocol	1 S

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Acinetobacter baumannii

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Klebsiella pneumoniae

KPC-3

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CAZ/AVI	>16 R
MEM/VAB	>16 R
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Klebsiella pneumoniae

NDM-1

Impact of Difficult-to-Treat Resistance in Gram-negative Bacteremia on Mortality: Retrospective Analysis of Nationwide Surveillance Data

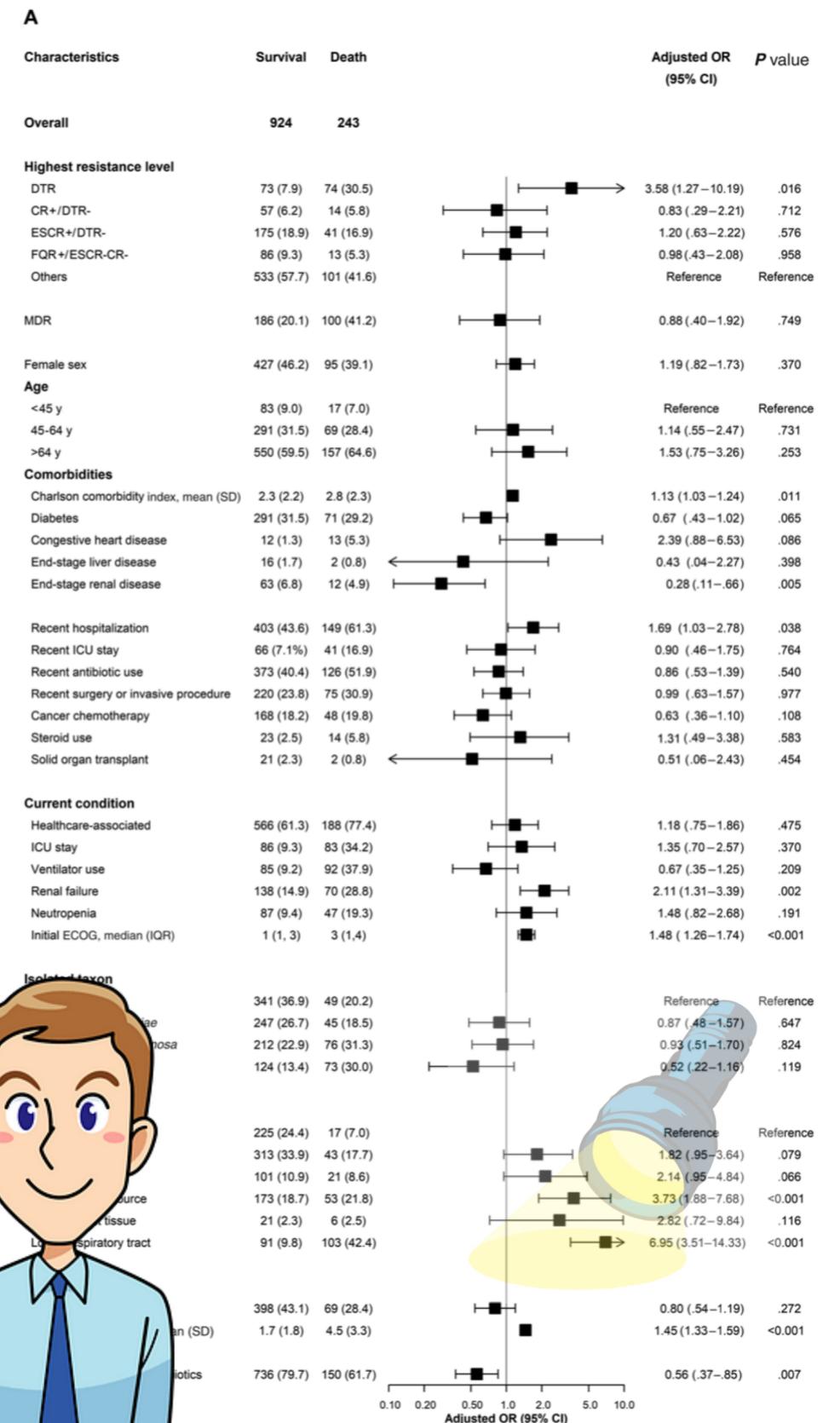
Huh K. et al *Clin Infect Dis* 2020; 71:e487

Resistance	Survival	Death	Adjusted OR for mortality	Odds ratio (95% CI)	P value
Total cohort					
DTR	73 (7.9)	74 (30.5)		3.58 (1.27-10.19)	.016
CR+/DTR-	57 (6.2)	14 (5.8)		0.83 (.29-2.21)	.712
ESCR+/DTR-	175 (18.9)	41 (16.9)		1.20 (.63-2.22)	.576
FQR+/ESCR-CR-	86 (9.3)	13 (5.3)		0.98 (.43-2.08)	.958
Others	533 (57.7)	101 (41.6)		Reference	Reference

Propensity score	Survival	Death
DTR		
Non-DTR		

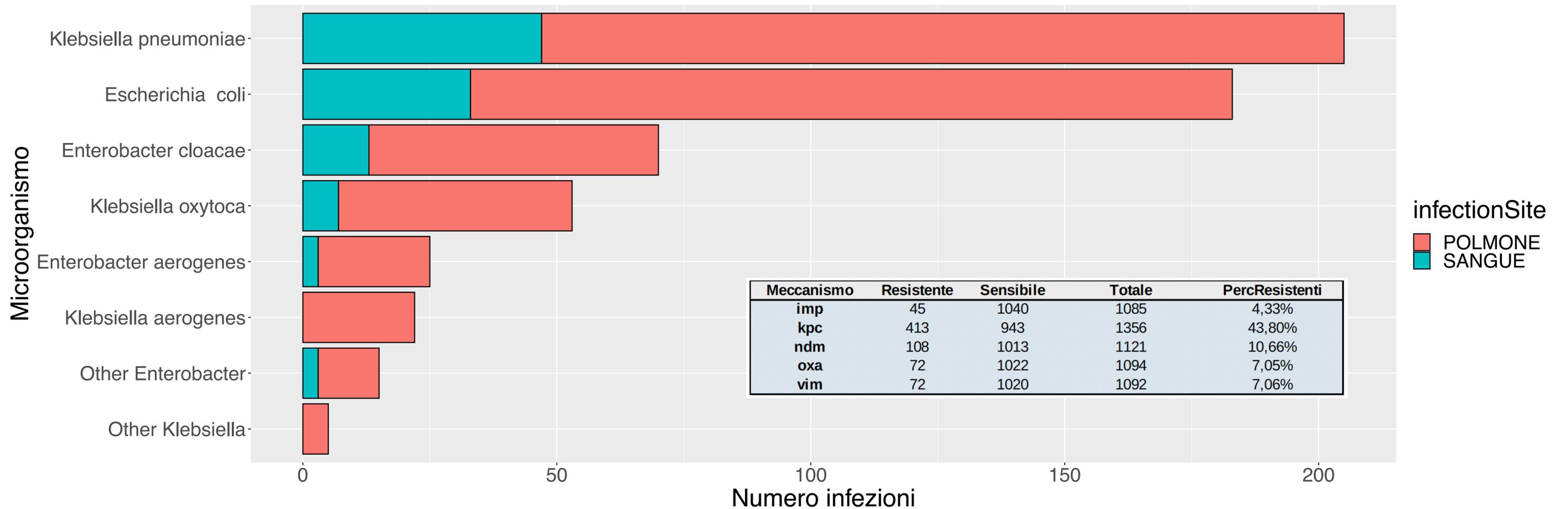
CONCLUSION

Crude mortality for GNBSI caused by DTR was 50.3%. A multivariable model showed that only DTR, but not other categories, was significantly associated with mortality (adjusted odds ratio [aOR], **3.58** [95% confidence interval {CI}, 1.27–10.19]). DTR was also a significant predictor for mortality in the analysis of propensity score–matched cohorts (aOR, 3.48 [95% CI, 1.82–6.79]). In patients with GNBSI, **DTR was associated with higher mortality** than those in other resistance categories



Numero di Infezioni con sede (POLMONE, SANGUE) con prescrizione antibiotica associata

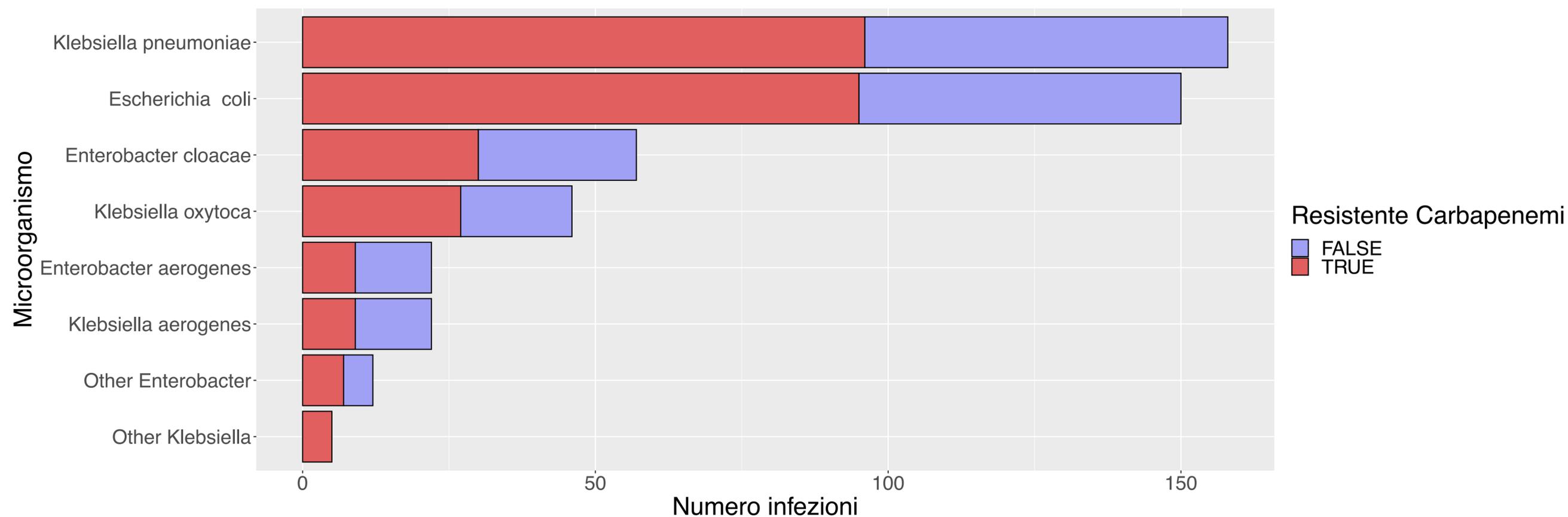
Microorganismo	PercProsafte20212022	NumtM320192023	PercM320192023	NumM320192023	PercM320192023
KLEBSIELLA PNEUMONIAE	31,45%	357	28,53%	205	32,88%
KLEBSIELLA ALTRA SPECIE	9,37%	154	11,66%	80	11,94%
ENTEROBACTER SPP	12,63%	273	21,12%	110	21,14%
ESCHIRICHIA COLI	43,71%	487	38,68%	183	34,05%
ALTRO ENTEROBACTERALES	2,84%				
KLEBSIELLA	40,82%	293	40,19%	229	44,81%
	*non filtrato su sede infezione	*non filtrato su sede infezione		*sede = (sangue, polmone)	



Numero Infezioni con sede (POLMONE)

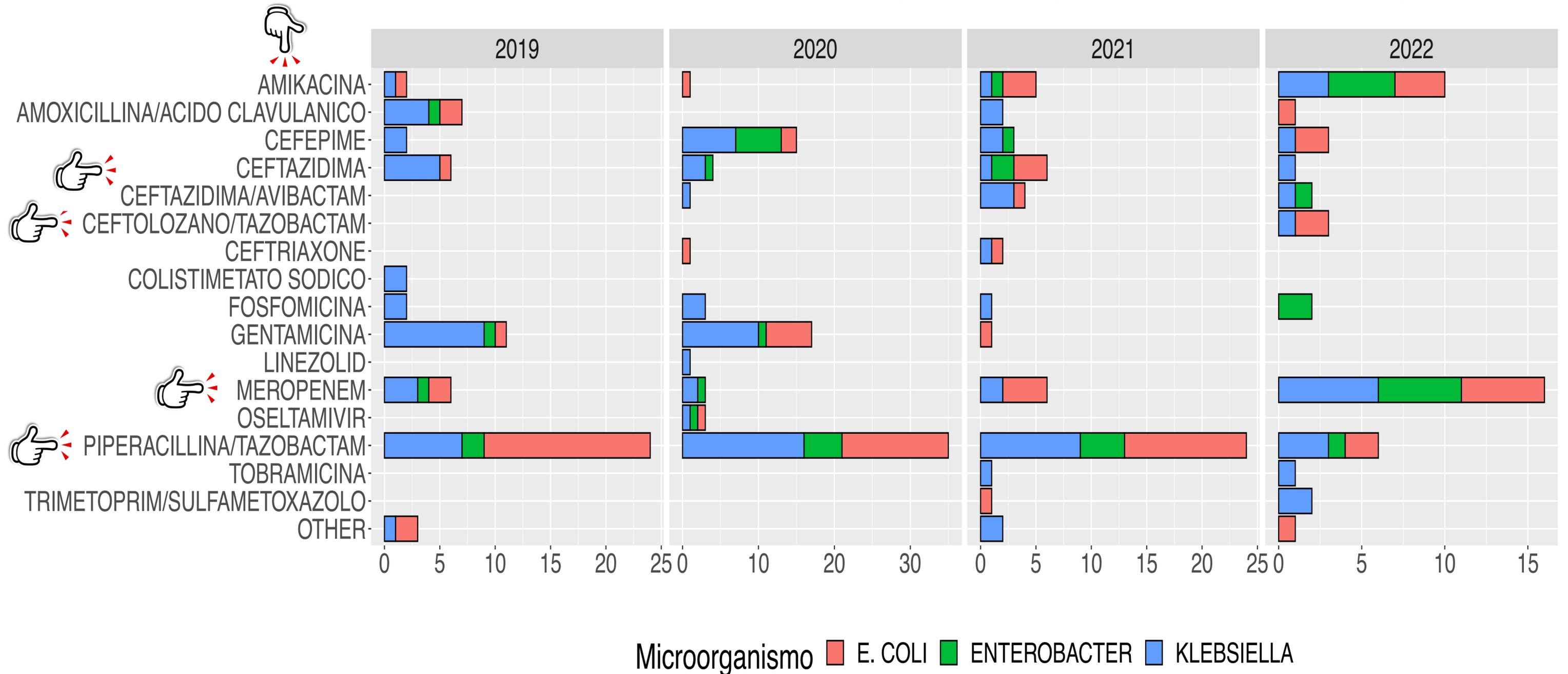
Considerati solo microorganismi per i quali è presente un antibiogramma

Anno	2018	2019	2020	2021	2022	2023
Numero Prescrizioni	5	145	174	124	98	32



Prescrizioni antibiotico per infezione localizzata nel polmone – germi resistenti ai carbapenemi

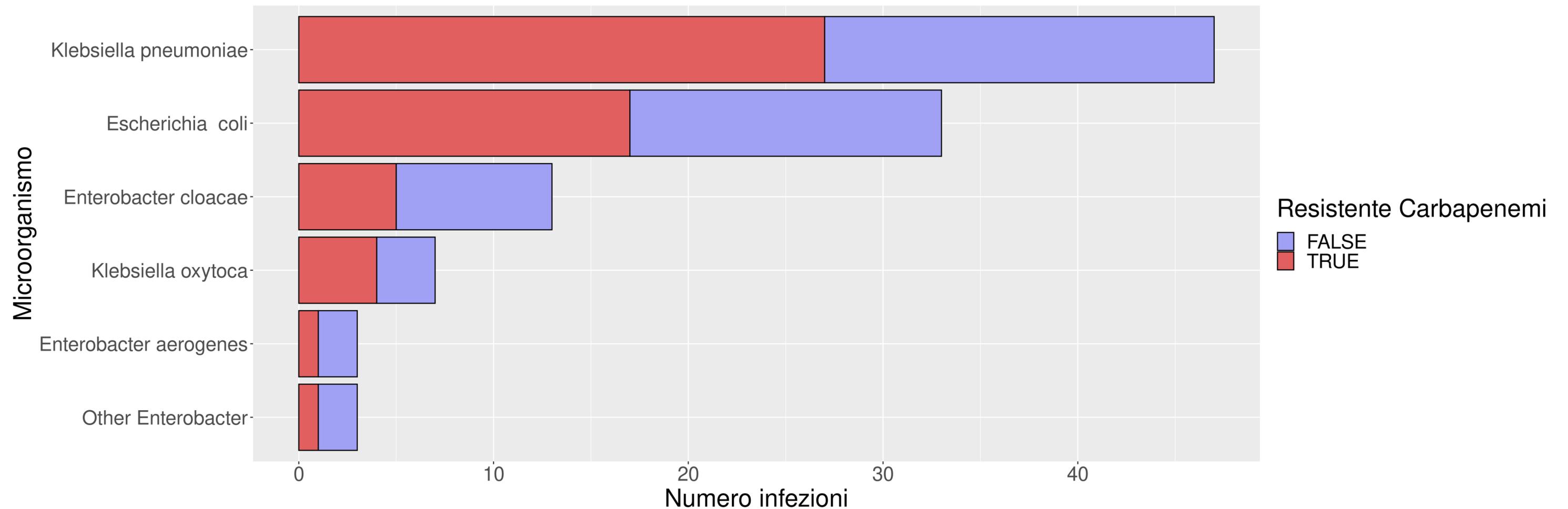
Prescrizioni antibiotico – Infezione polmone – germe resistente ai Carbapenemi



Numero Infezioni con sede (SANGUE)

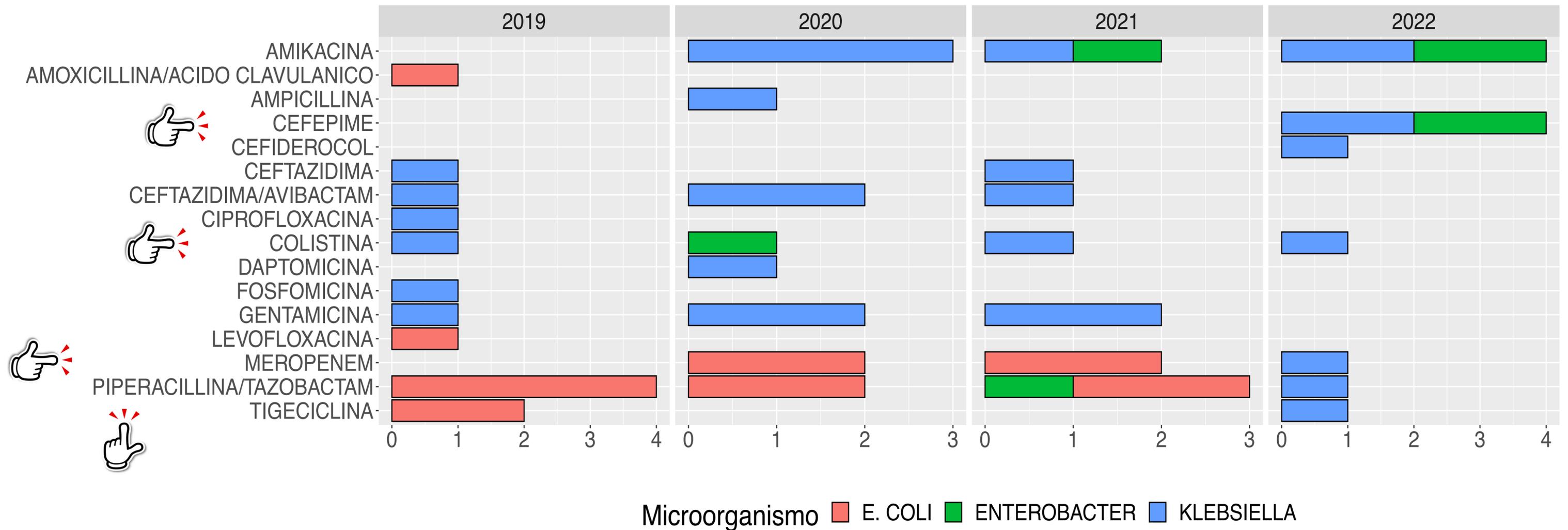
Un microorganismo è considerato resistente ai carbapenemi se è resistente ad almeno un antibiotico appartenente a tale categoria.
Considerati solo microorganismi per i quali è presente un antibiogramma

Anno	2018	2019	2020	2021	2022	2023
Numero Prescrizioni	2	30	27	21	24	2

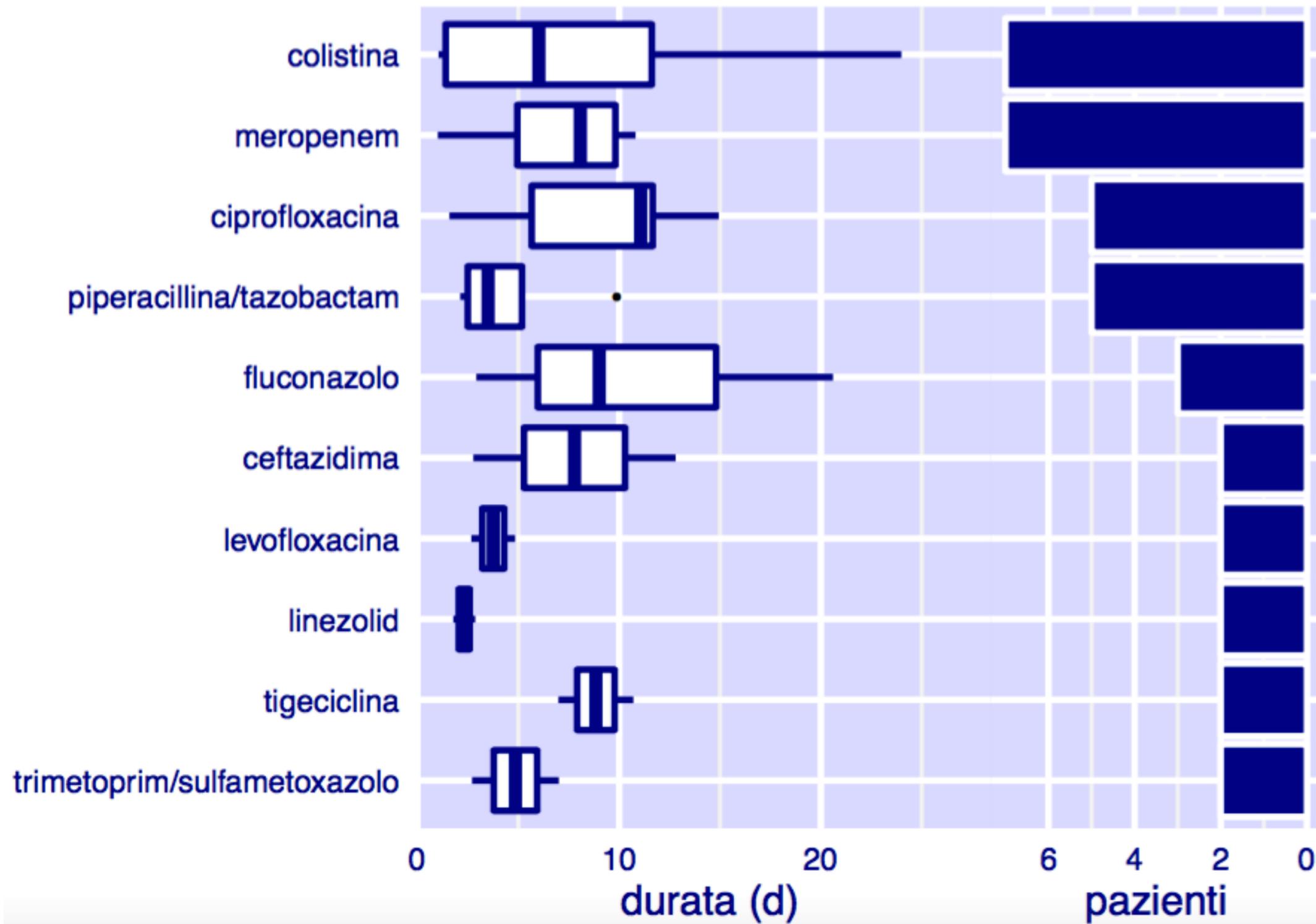


Prescrizioni antibiotico per infezione localizzata nel sangue – germi resistenti ai carbapenemi

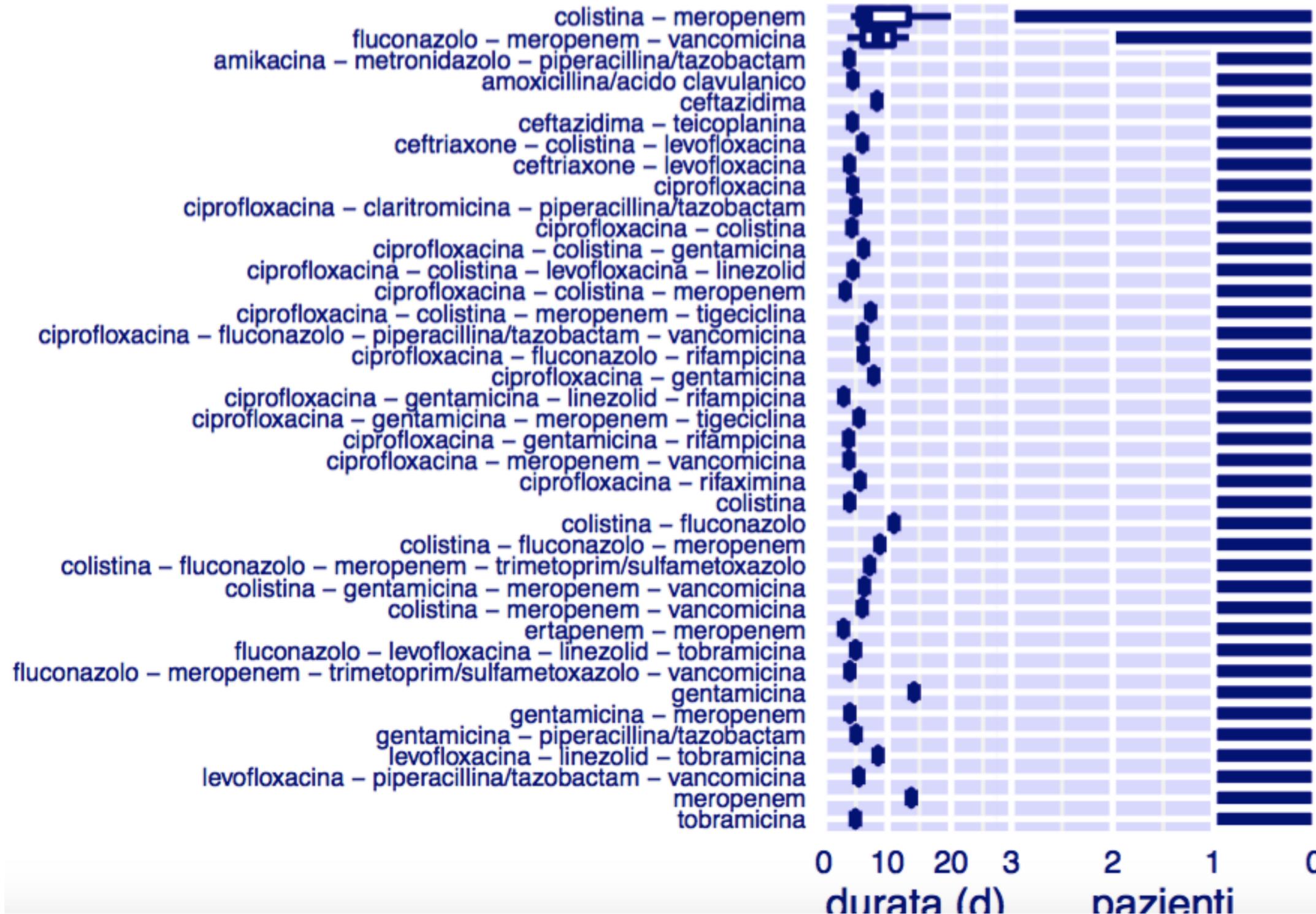
Prescrizioni antibiotico – Infezione sangue – germe resistente ai Carbapenemi

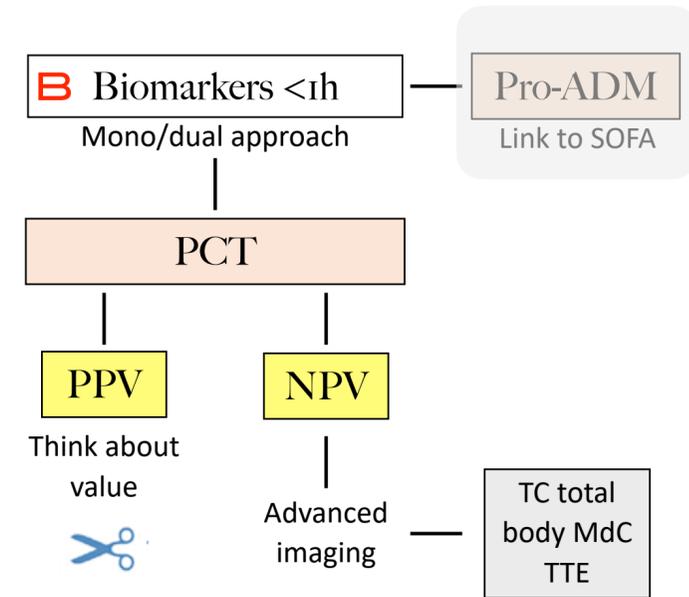


Mirata Polmoniti *Klebsiella pneumoniae* KPC - Report antibiotici anno 2015



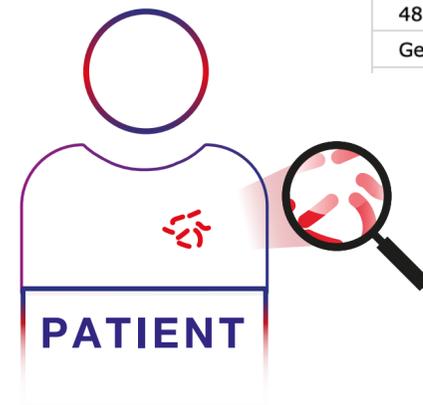
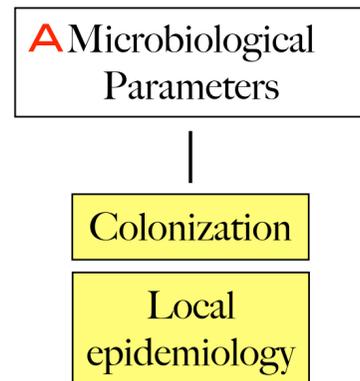
Mirata KPC durata > 72 ore - Report antibiotici anno 2015





“The role of stratification of the risk of infection”

Tampone rettale PCR Arrow	Tampone rettale
Gene per Carbapenemasi KPC	Non rilevato
Gene per Carbapenemasi NDM	Non rilevato
Gene per Carbapenemasi IMP	Non rilevato
Gene per Carbapenemasi VIM	Non rilevato
Gene per Carbapenemasi OXA 48	Non rilevato
Gene per VanA	Non rilevato



What's Next

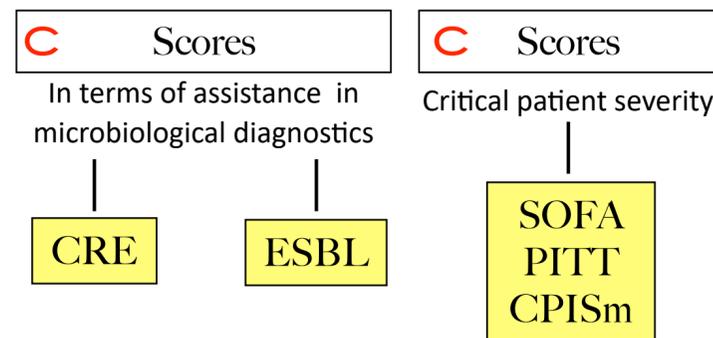
Multivariate analysis
OR (95% CI) P-value
3.39 (1.41,8.16) 0.007

“the impact of initial antibiotic treatment failure: role of AMR”

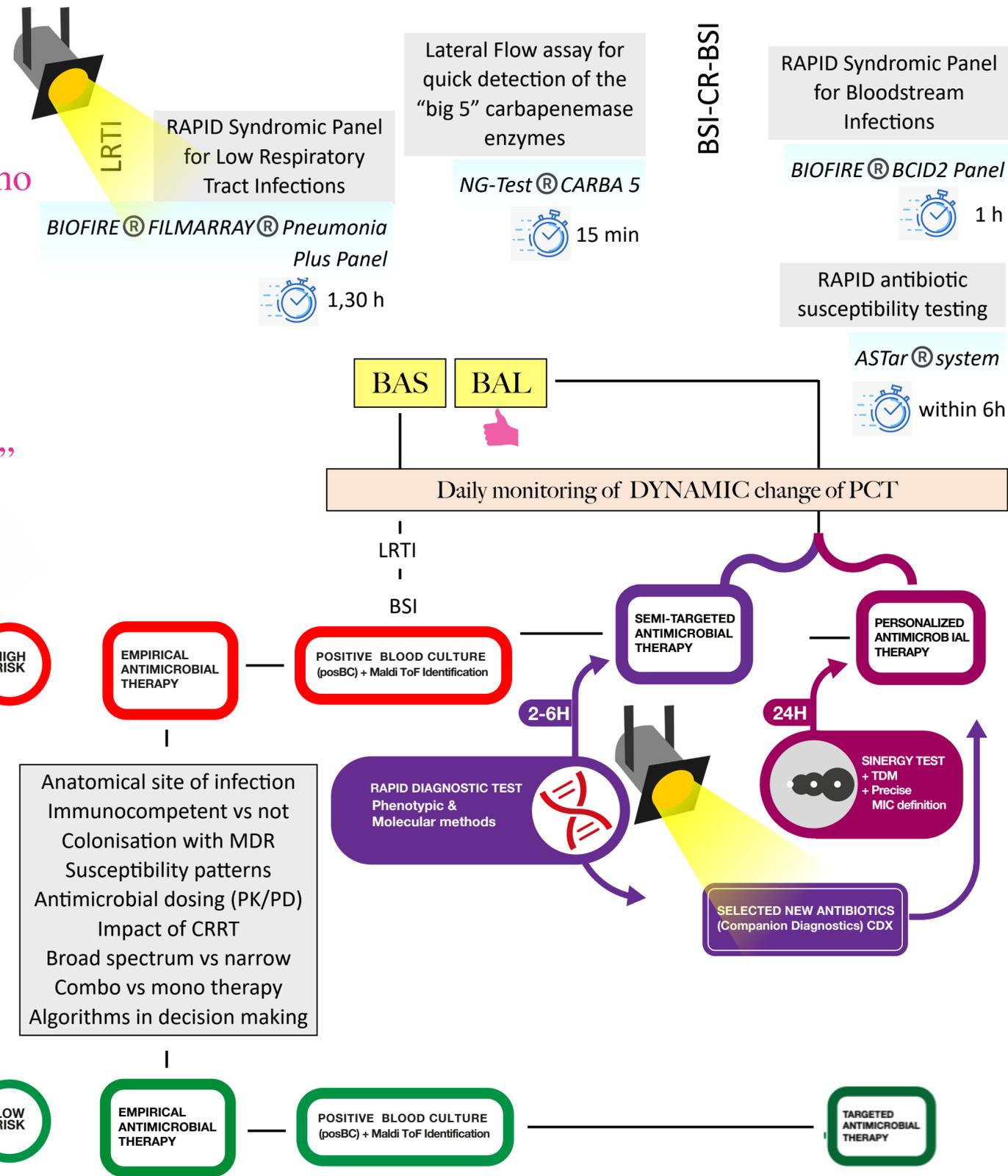
The **impact of initial antibiotic treatment failure**: real-world insights in healthcare-associated or nosocomial pneumonia

Ryan K. J Infection 2018; 77(1):9-17

Potential risk factor	Univariate analysis	
	OR (95% CI)	P-value
ICU admission	1.59 (1.05,2.21)	0.028
Resistance to carbapenems	0.99 (0.98,1.00)	0.059
R to 3 rd gen cephalosporins and carbapenem	0.98 (0.97,1.00)	0.015
Presence of MDR pathogen	1.88 (1.08,3.27)	0.015
Mechanical Ventilation	3.77 (2.44,5.82)	<0.001



“Who goes into rapid diagnostics? Or rather, who is the right patient who can best benefit by rapid diagnostics?”



		A. baumannii	C. freundii	C. koseri	Enterobacter cloacae	Esch. coli	K. aerogenes	K. oxytoca	K. pneumoniae	Proteus mirabilis	Ps. aeruginosa	
Amikacin	4 - 16	●	●	●	●	●	●	●	●	●	●	10
Amoxicillin / Clavulanate	4/2 - 16/2			●	●	●	●	●	●	●		5
Ampicillin	4 - 8				●	●	●	●	●	●		2
Aztreonam	1 - 16		●	●	●	●	●	●	●	●	●	8
Cefepime	0.125 - 64		●	●	●	●	●	●	●	●	●	8
Cefotaxime	0.125 - 4		●	●	●	●	●	●	●	●	●	8
Cefoxitin	8 - 16			●	●	●	●	●	●	●		5
Ceftazidime	0.125 - 64		●	●	●	●	●	●	●	●	●	9
Ceftazidime/avibactam	0.25/4, 1/4 - 16/4		●	●	●	●	●	●	●	●	●	9
Ceftazidime/Clavulanate	0.25/4 - 8/4				●	●	●	●	●	●		3
Ceftolozane_Tazobactam	1/4 - 4/4				●	●	●	●	●	●		6
Ciprofloxacin	0.06, 0.25 - 1	●	●	●	●	●	●	●	●	●	●	10
Ertapenem	0.125 - 1		●	●	●	●	●	●	●	●		8
Gentamicin	2 - 4	●	●	●	●	●	●	●	●	●		9
Imipenem	1 - 8		●	●	●	●	●	●	●	●		9
Levofloxacin	0.25 - 1		●	●	●	●	●	●	●	●		10
Meropenem	0.125 - 8		●	●	●	●	●	●	●	●		10
Meropenem_vaborbactam	2/8 - 8/8			●	●	●	●	●	●	●	●	9
Piperacillin	8 - 16		●	●	●	●	●	●	●	●		8
Piperacillin/tazobactam	4/4 - 16/4		●	●	●	●	●	●	●	●	●	9
Tigecycline	0.5 - 1			●	●	●	●	●	●	●		2
Tobramycin	2 - 4	●	●	●	●	●	●	●	●	●	●	10
Trimethoprim/Sulfamethoxazole	2/38 - 4/76	●	●	●	●	●	●	●	●	●	●	9
Total		8	17	19	18	23	17	21	21	18	14	176

Coverage of **SPECIFIC REVEAL® Gram negative PANEL**



IMPORTANT MESSAGE
 test results in an average of **5.5 hours** from availability of a positive blood culture

Guidance by Molecular Antibiogram (*Enterobacterales*)

Antibiogr. molecolare		Antibiogr. molecolare		Antibiogr. molecolare		Antibiogr. molecolare	
CTX-M	RIL / No ril	CTX-M	RIL / No ril	CTX-M	RIL / No ril	CTX-M	RILEVATO
KPC	RILEVATO	KPC	RIL / No ril	KPC	RIL / No ril	KPC	Non rilevato
OXA-48	Non rilevato	OXA-48	RIL / No ril	OXA-48	RILEVATO	OXA-48	Non rilevato
IMP	Non rilevato	IMP		IMP	Non rilevato	IMP	Non rilevato
VIM	Non rilevato	VIM	RILEVATO (qualsiasi)	VIM	Non rilevato	VIM	Non rilevato
NDM	Non rilevato	NDM		NDM	Non rilevato	NDM	Non rilevato

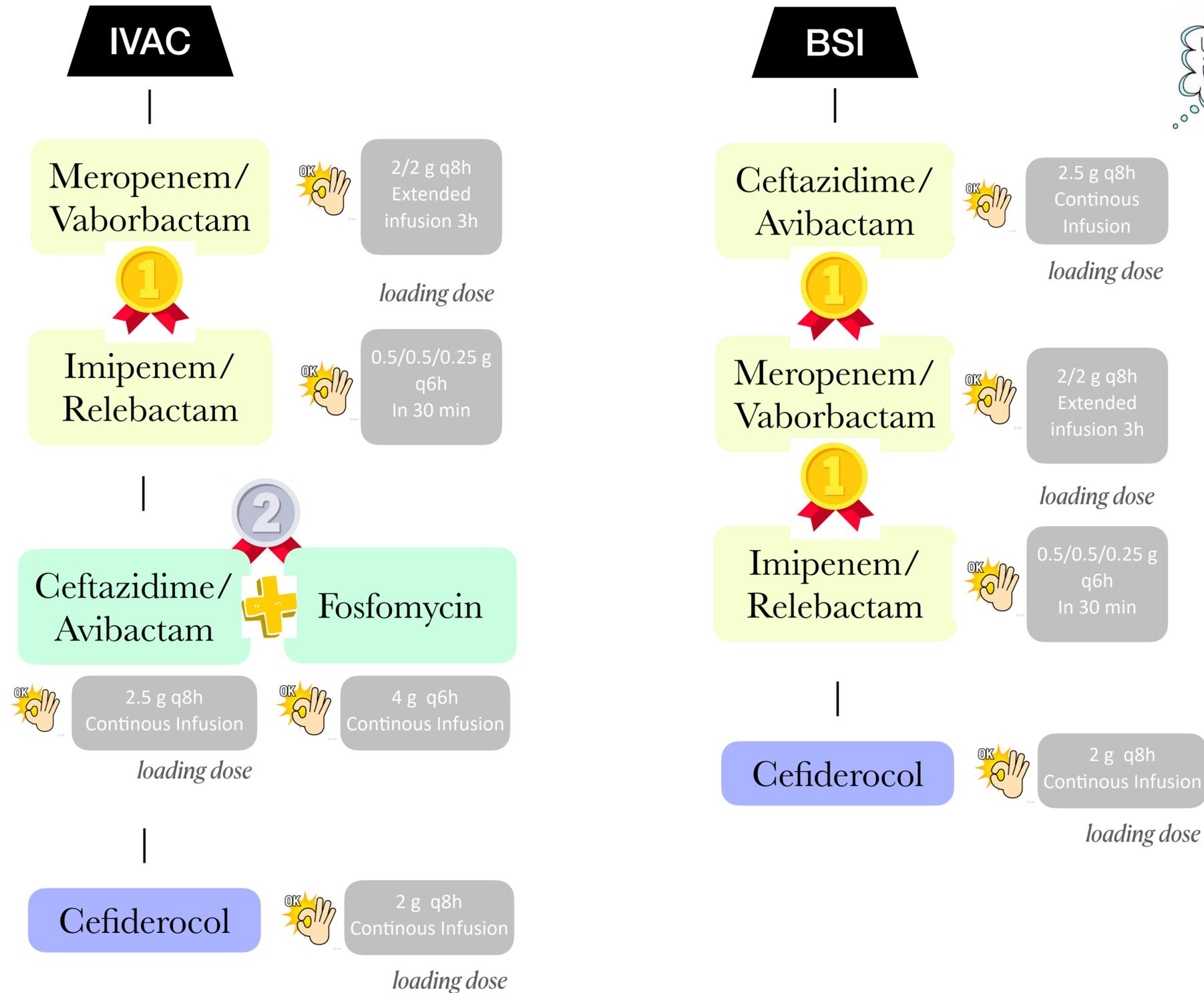


CAZ-AVI MER-VAB IMI-REL FDC	FDC ATM + CAZ-AVI	CAZ-AVI FDC	Carbapenems TOL-TAZ CAZ-AVI
Carbapenems TOL-TAZ	Carbapenems TOL-TAZ CAZ-AVI MER-VAB IMI-REL	Carbapenems MER-VAB IMI-REL	

CAZ-AVI, Ceftazidime-Avibactam
 MER-VAB, Meropenem-Vaborbactam
 IMI-REL, Imipenem-Cilastatin-Relebactam
 FDC, Cefiderocol
 TOL-TAZ, Ceftolozane-Tazobactam

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P
 Exp Rev Anti Infect Ther Sep 2021
 Infect Drug Resist Jun 2021

Algorithms for targeted therapy of IVACs/BSIs caused by *Enterobacterales* **KPC +** in critically ill adult patients

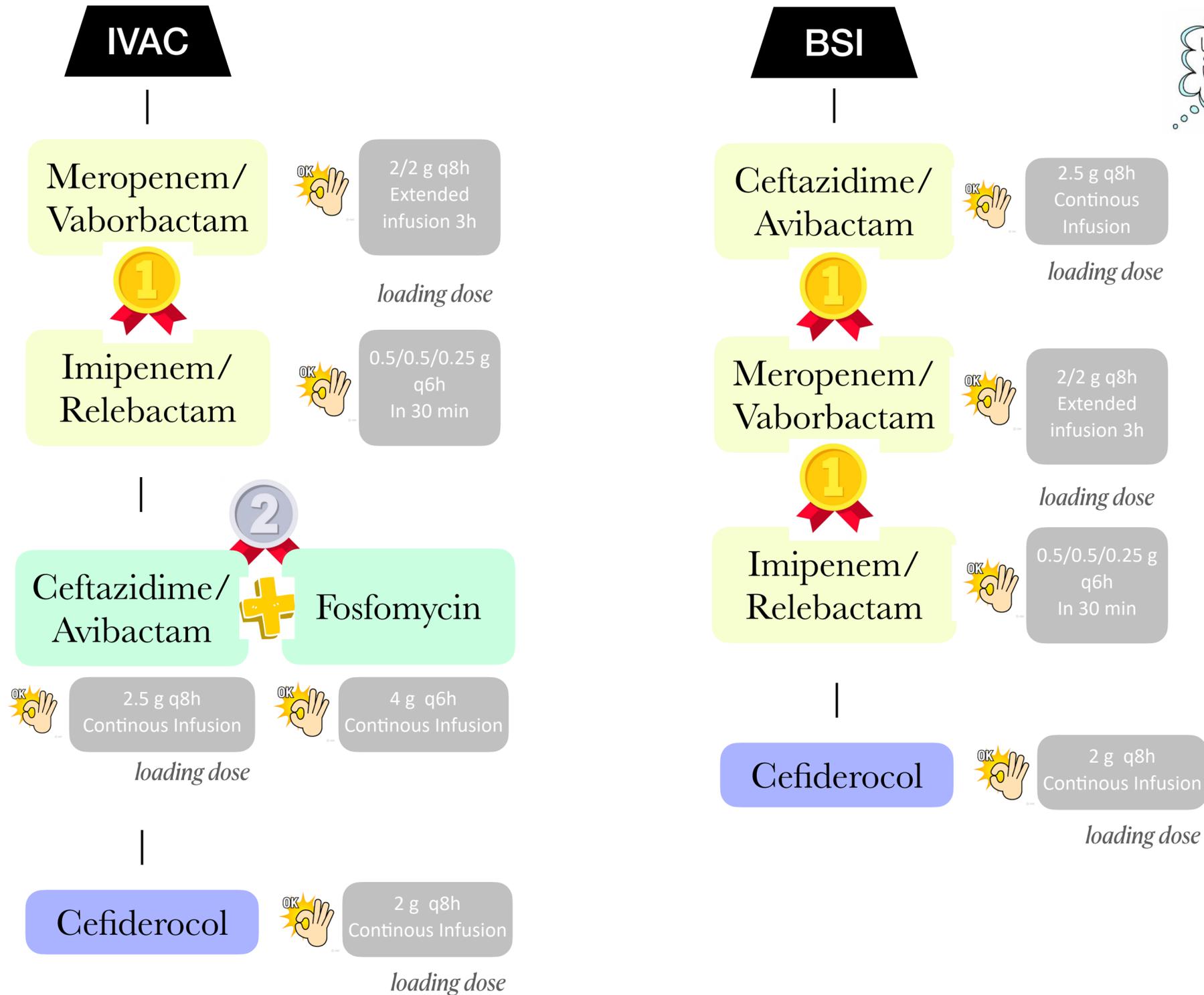


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Fosfomicina	>128 R
Amikacina	>16 R
Gentamicina	1 S
Ciprofloxacina	>4 R
Colistina	0,5 S
CZA	32 R
MVB	0,5 S
CFD	2 S

K. pneumoniae KPC-31

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P *Exp Rev Anti Infect Ther* Sep 2022 - *Infect Drug Resist* Jun 2021 - *Antibiotics* dec 2021

Algorithms for targeted therapy of IVACs/BSIs caused by *Enterobacterales* **KPC +** in critically ill adult patients



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Meropenem	>64 R
Fosfomicina	32 S
Amikacina	8 S
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>8 R
CZA	16 R
MVB	32 R
CFD	2 S

K. pneumoniae KPC-3
 IPERESPRESSA



Penetration of Antibacterial Agents

into Pulmonary Epithelial Lining Fluid: An Update

Drwiega EN et al. Clin Pharmacokinet 2021



Antibacterial agent	Dosage regimen	ELF to plasma ratio based on AUC
Ceftaroline	600 mg IV q12h x 7 doses	0.23
Cefiderocol	2000 mg IV x 1 dose	0.24
Piperacillin/tazobactam	Piperacillin 4 g IV q6h x 3 doses / Tazobactam 0.5 g IV q6h x 3 doses	0.26 0.54
Ceftolozane/tazobactam	Ceftolozane 1 g IV q8h x 3 doses / Tazobactam 0.5 g IV q8h 3 doses	0.48 0.44
Ceftazidime/avibactam	Ceftazidime 2000 mg IV q8h x 9 doses / Avibactam 500 mg IV q8h x 9 doses	0.31 0.35
Cefepime/zidebactam	Cefepime 2 g IV q8h x 7 doses / Zidebactam 1 g IV q8h x 7 doses	0.39 0.38
Cefepime/enmetazobactam	Cefepime 2 g IV over 2h q8h x 9 doses / Enmetazobactam 1 g IV over 2h q8h x 9 doses	0.61 0.53
Meropenem/vaborbactam	Meropenem 2 g IV q8h x 3 doses / Vaborbactam 2 g IV q8h x 3 doses	0.63/0.65 0.53/0.79
Imipenem/relebactam	Imipenem 500 mg IV q6h x 5 doses / Relebactam 250 mg IV q6h x 5 doses	0.44/0.55 0.43/0.54



Systematic Review

Tissue Penetration of Antimicrobials in Intensive Care Unit Patients: A Systematic Review – Part I

Stefano Finazzi ^{1,2,†}, Giacomo Luci ^{3,†}, Carlo Olivieri ^{2,4}, Martin Langer ², Giulia Mandelli ¹, Alberto Corona ⁵, Bruno Viaggi ^{2,6,†} and Antonello Di Paolo ^{3,*,†}



Systematic Review

Tissue Penetration of Antimicrobials in Intensive Care Unit Patients: A Systematic Review—Part II

Bruno Viaggi ^{1,2,†}, Alice Cangialosi ^{3,†}, Martin Langer ², Carlo Olivieri ⁴, Andrea Gori ⁵, Alberto Corona ^{6,†}, Stefano Finazzi ^{7,†,‡} and Antonello Di Paolo ^{3,*,†,‡}

2022 Aug 29;11(9):1164

2022 Sep 3;11(9):1193



Durlobactam/ sulbactam
Durlobactam 1 g IV q6h x 3 doses Sulbactam 1 g IV q6h x 3 doses
0.50/0.81 0.37/0.41

the knowledge of tissue penetration ratio values ***retains its importance***, especially in ICU settings, where the expected clinical benefit depends on prompt and adequate chemotherapy to treat infections. The choice of drug doses, the administration scheme, and the evaluation of plasma concentrations by TDM protocols ***are based on that knowledge***, which is still in need of further clinical studies

Ceftazidime-Avibactam for Carbapenem-Resistant Gram-Negative Bacteria Infections: A Real-World Experience in the ICU

Yu J. et al. *Infect Drug Res* 2023; 16:6209-6216

a single-center, retrospective and observational study

RESULTS: a total of **43** patients with CR-GNB infection were enrolled, including 14 (**32.6%**) patients received C-A monotherapy. C-A **monotherapy and combination with other agents did not affect** 14-day clinical response or 90-day survival. All-cause mortality at 90-days was **39.5%** (17/43). Multivariate Cox analysis showed that concomitant with bloodstream infection was independent risk factors for 90-day mortality and that **the time to initiation of C-A** and Acute Physiology and Chronic Health Evaluation (APACHE) score was independent predictors of 14-day clinical response. Five CRRT patients who received high-dose C-A then compared with 5 who received low-dose



CONCLUSION
C-A was **an effective therapy for severe CR-GNB infections** and **clinical response correlated with the time of C-A initiation**. A dosage >3.75g/d C-A was associated with prolonged survival of CRRT patients. Randomized controlled trials or multicenter studies are needed to confirm these findings

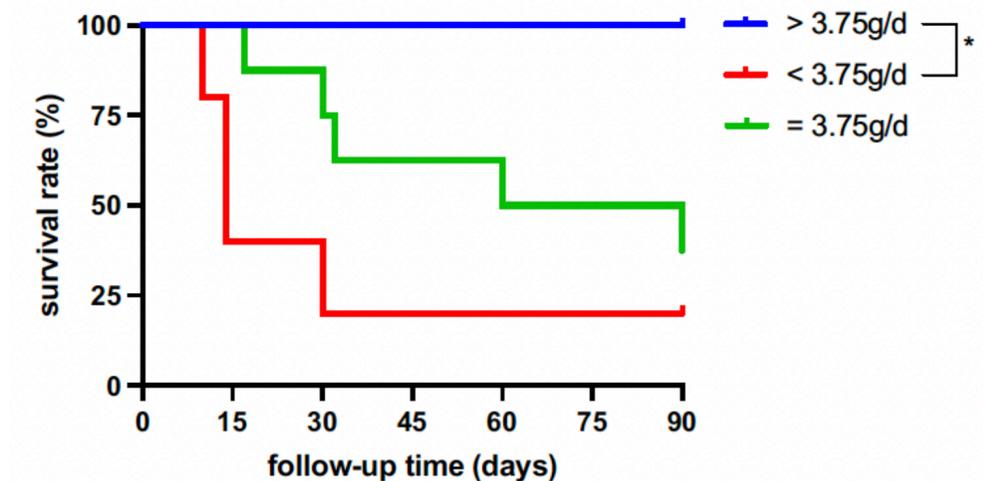
PURPOSE: Ceftazidime-avibactam (C-A) is a treatment option for carbapenem-resistant gram-negative bacterial (CR-GNB) infections, but little is known regarding its suitability for the intensive care unit (ICU). The current study aimed to analyze use of C-A for critically ill patients, determine independent predictors of clinical outcome and mortality and explore routine dosages for patients in continuous renal replacement therapy (CRRT)

Table 3 Multivariate Logistic Regression Analysis of Variables Associated with Unfavorable Clinical Response

	Univariate Analysis		Multivariate Analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Bloodstream infection	0.122	2.698 (0.766–9.506)	0.157	3.180 (0.640–15.789)
ICU duration (days)	0.834	0.999 (0.989–1.009)	–	–
APACHE II	0.019*	1.301 (1.044–1.620)	0.007*	1.485 (1.113–1.980)
CRRT	0.224	2.186 (0.620–7.700)	–	–
Duration of ventilator (hours)	0.880	1.000 (1.000–1.001)	0.596	1.000 (1.000–1.001)
ECMO	0.999	–	–	–
The time to initiation of C-A (days)	0.081	1.118 (0.986–1.267)	0.049*	1.174 (1.001–1.377)

Note: *P < 0.05, there was statistically significant difference.

Abbreviations: OR, odds ratios; CI, Confidence interval; C-A, Ceftazidime-avibactam; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, Continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.



Combination Therapy of Ceftazidime/Avibactam for the Treatment of Patients Infected with Carbapenem-Resistant *Klebsiella pneumoniae*: A Multicenter Retrospective Study

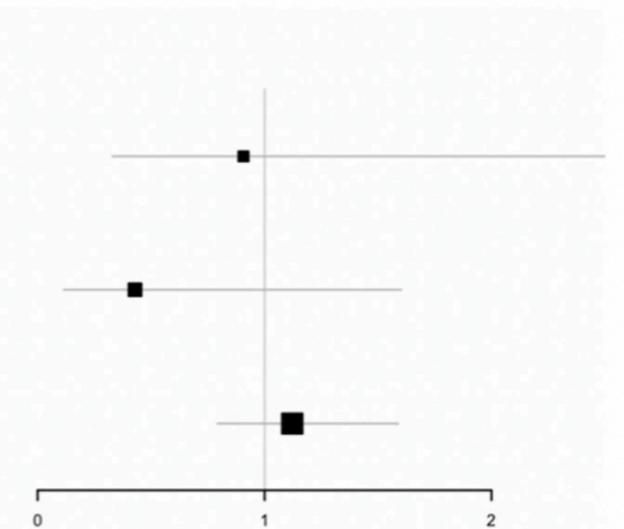
Lin J et al. *Infect Dis Ther* 2023; <https://doi.org/10.1007/s40121-023-00852-8>
published online 01 September

METHODS: we retrospectively analyzed observational multicenter data from 38 hospitals in China

RESULTS: a total of **132** eligible patients were divided into CAZ/AVI combination therapy (n = **43**) and monotherapy (n = **89**) groups. Multivariate logistic regression showed **was no statistically significant relationship** between combination therapy and a lower mortality [odds ratio (OR) 0.907, 95% confidence interval (CI) 0.329–2.498, p = 0.85].

CONCLUSION
Combination therapy (or CAZ/AVI combined with tigecycline) and monotherapy with CAZ/AVI **had similar prognoses in patients with only CRKP infection** (or CRKP-associated pneumonia), as well as in critically ill patients

OR (95%CI)	p
0.329-2.498	0.85
0.115-1.602	0.208
0.792-1.589	0.517



PSM propensity score matching,
IPTW inverse probability of treatment weight

In the subgroup of critical patients who were in the intensive care unit (ICU) (OR 0.943, 95% CI 0.221–4.033, p = 0.937) or with sequential organ failure assessment (SOFA) ≥ 3 (OR 0.733, 95% CI 0.191–2.808, p = 0.650), **CAZ/AVI combination therapy was not a lower risk factor for** in-hospital mortality



Jumping into the future: overcoming pharmacokinetic/pharmacodynamic hurdles to optimize the treatment of severe sepsis to treat-Gram-negative infection with novel beta-lactams

Gatti M. et al. *Expert Rev Anti Infect Ther* 2023; 21(2):149-166

Sepsis-associated transient acute kidney injury (AKI) is a common complication. The application of continuous renal replacement therapy (CRRT) and augmented renal clearance (ARC) are two of the three most challenging scenarios in critically ill renal patients in which the application of altered dosing strategies may be needed for maximizing PK/PD targets



Real-world evidence showed that when administering the CZA and MEV at the labeled dosing regimens aggressive PK/PD targets against pathogens with an MIC up to the clinical breakpoint **were not attainable**

Kline EG. et al. *Open Forum Infect Dis* 2020; 7:S663-4
Kufel WD. et al. *J Antimicrob Chemother* 2019; 74:2117

Novel beta-lactams – Renal function alterations in critically septic patients



CRRT

ARC

Assessment of CRRT setting, antibiotic physicochemical/PK features, site of infection, and pathophysiological conditions

Assessment of high-risk populations

No renal dose adjustment in higher intensity CRRT
Higher dosage or prolonged infusion if residual diuresis or non-susceptible MIC exists

Consider higher dosage coupled with prolonged infusion
Real-time TDM strongly suggested

Adaptive real-time TDM
Higher PK/PD target
100% $fT_{>4-8 \times MIC}$

REVIEW

Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors

Milo Gatti^{a,b} and Federico Pea^{a,b} *Exp Rev Clin Pharmacol* 2021



A proposal of algorithm for the management of critically ill patients requiring novel beta-lactams in challenging scenarios concerning variations in renal function. **In case of persistent AKI after 48 hours**, renal dose adjustment without adjustment of dosing interval would be recommended

Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors

Milo Gatti^{a,b} and Federico Pea^{a,b} Exp Rev Clin Pharmacol 2021

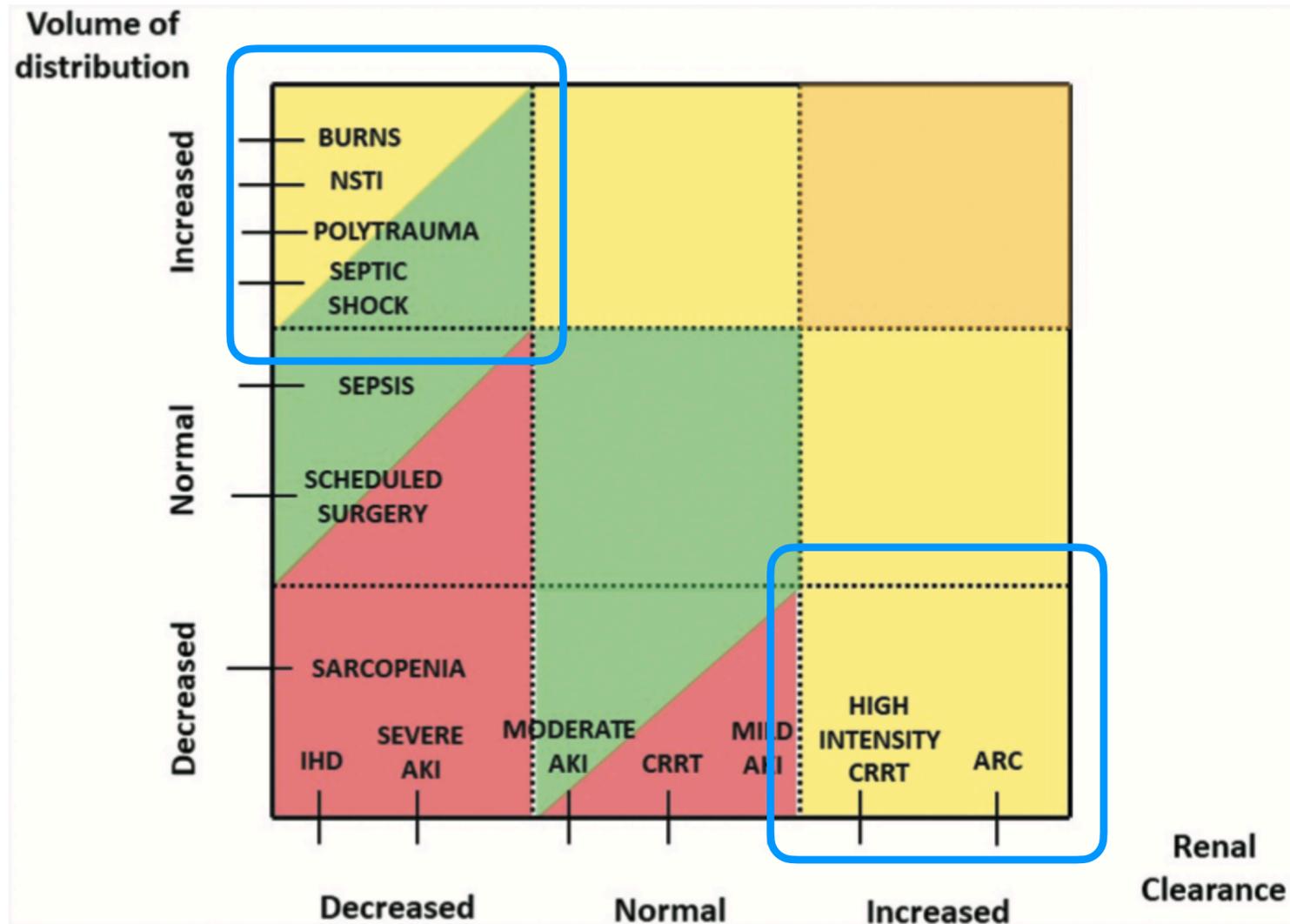


Table 3. Dosing adjustments of novel BL and/or BL/BLIs in renal patients retrieved from summary of product characteristics and pivotal trials.

BL and/or BL/BLIs	PK/PD target adopted in pivotal trials	Dosing adjustments in patients with various classes of renal function (CLCr in mL/min)	Preservation of more refracted dosing regimens in renal impairment	Scheduled prolonged infusion	Scheduled dose adjustment for IHD	Scheduled dose adjustment for CRRT	Scheduled dose adjustment for ARC
Cefiderocol	75% $fT_{>MIC}$	CLCr \geq 120: 2 g every 6 h CLCr 60–120: 2 g every 8 h CLCr 30–59: 1.5 g every 8 h CLCr 15–29: 1 g every 8 h CLCr < 15/IHD: 0.75 g every 12 h	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 h	✓	✓ 1 g every 12 h (CVVH) 1.5 g every 12 h (CVVHD/CVDDHF)**	✓ 2 g every 6 h
Ceftazidime-Avibactam	50% $fT_{>MIC}$	CLCr > 50: 2.5 g every 8 h CLCr 31–50: 1.25 g every 8 h CLCr 16–30: 0.9375 g every 12 h CLCr 6–15: 0.9375 g every 24 h CLCr \leq 5/IHD: 0.9375 g every 48 h	✗	✓ Extended infusion in 2 h	✓	✗	✗
Ceftolozane-Tazobactam	30% $fT_{>MIC}$	CLCr > 50: 3.0*/1.5 g every 8 h CLCr 30–50: 1.5*/0.75 g every 8 h CLCr 15–29: 0.75*/0.375 g every 8 h CLCr < 15/IHD: LD 1.5*/0.75 g \rightarrow MD 0.30*/0.15 g every 8 h	✓ Maintained frequency of administration every 8 h	✗ Intermittent infusion in 1 h	✓	✗	✗
Imipenem-Relebactam	40% $fT_{>MIC}$	CLCr 90–150: 1.25 g every 6 h CLCr 60–89: 1 g every 6 h CLCr 30–59: 750 mg every 6 h CLCr 15–29: 500 mg every 6 h IHD: 500 mg every 6 h CLCr < 15 and not IHD: should not be administered	✓ Maintained frequency of administration every 6 h	✗ Intermittent infusion in 0.5 h	✓	✗	✓ Scheduled dose may be inadequate for CLCr \geq 150 (consider higher dosage)
Meropenem-Vaborbactam	45% $fT_{>MIC}$	sCLCr \geq 40: 4 g every 8 h CLCr 20–39: 2 g every 8 h CLCr 10–19: 2 g every 12 h CLCr < 10: 1 g every 12 h	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 h	✓	✗	✗

* The doubled dose is indicated for nosocomial pneumonia including ventilator-associated pneumonia

** Dosing schedule predicted on the basis of the CL_{CRRT} of cefepime, according to the principle of similar PK features shared by cefepime and cefiderocol in terms of molecular weight and protein binding

ARC: augmented renal clearance; CVVH: continuous veno-venous haemofiltration; CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous haemodiafiltration; CRRT: continuous renal replacement therapy; IHD: intermittent hemodialysis LD: loading dose; MD: maintenance dose; PK/PD: pharmacokinetic/pharmacodynamic.

Loading dose plus continuous/extended infusion versus intermittent bolus of β -lactams for the treatment of Gram-negative bacteria bloodstream infections: a propensity score-adjusted retrospective cohort study

Bavaro DF. et al. J Antimicrob Chemother 2023

RESULTS: Overall, 224 patients were enrolled: 140 and 84 in the IB and EI/CI groups, respectively. β -Lactam regimens were chosen according to pathogen antibiogram, clinical judgement and current guidelines. Interestingly, the LD + EI/CI regimen was associated with a significant lower mortality rate (17% versus 32%, P = 0.011)

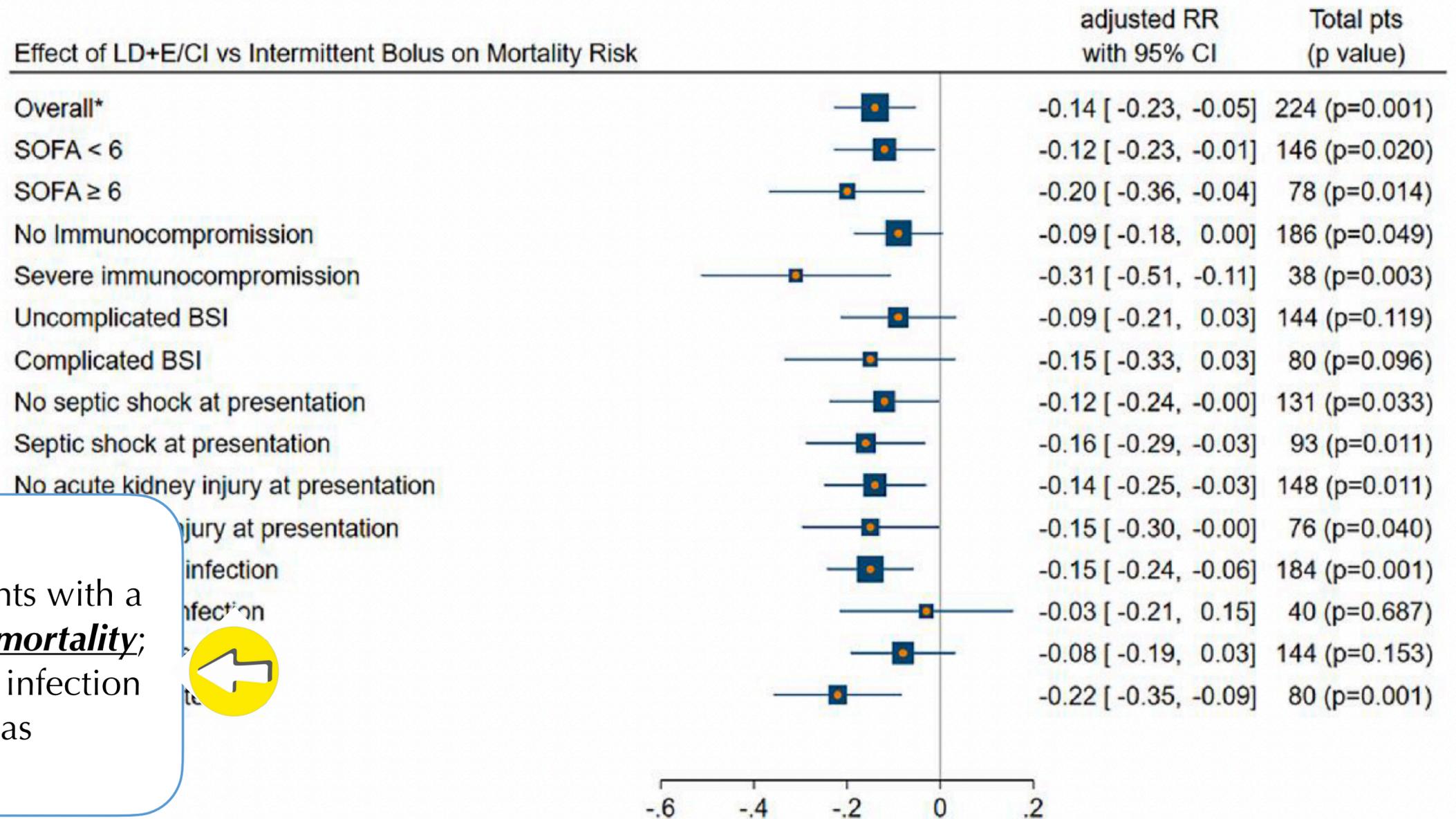
CONCLUSION

The use of LD + EI/CI of β -lactams in patients with a GNB-BSI **may be associated with reduced mortality**; also in patients with severe presentation of infection or with additional risk factors, such as immunodepression



BACKGROUND: Optimal β -lactam dosing for the treatment of Gram-negative bacteria bloodstream infections (GNB-BSIs) remains a debated issue. Herein, the efficacy and safety of a loading dose (LD) followed by extended/continuous infusion (EI/CI) versus intermittent bolus (IB) of these drugs for the treatment of GNBSIs was evaluated

Effect of LD+E/CI vs Intermittent Bolus on Mortality Risk



Clinical consequences of very major errors with semi-automated testing systems for antimicrobial susceptibility of carbapenem resistant *Enterobacterales*

Bartoletti M. et al. *Clin Microbiol Infect* 2022

Overall, VMEs and MEs led clinicians to inappropriate therapy

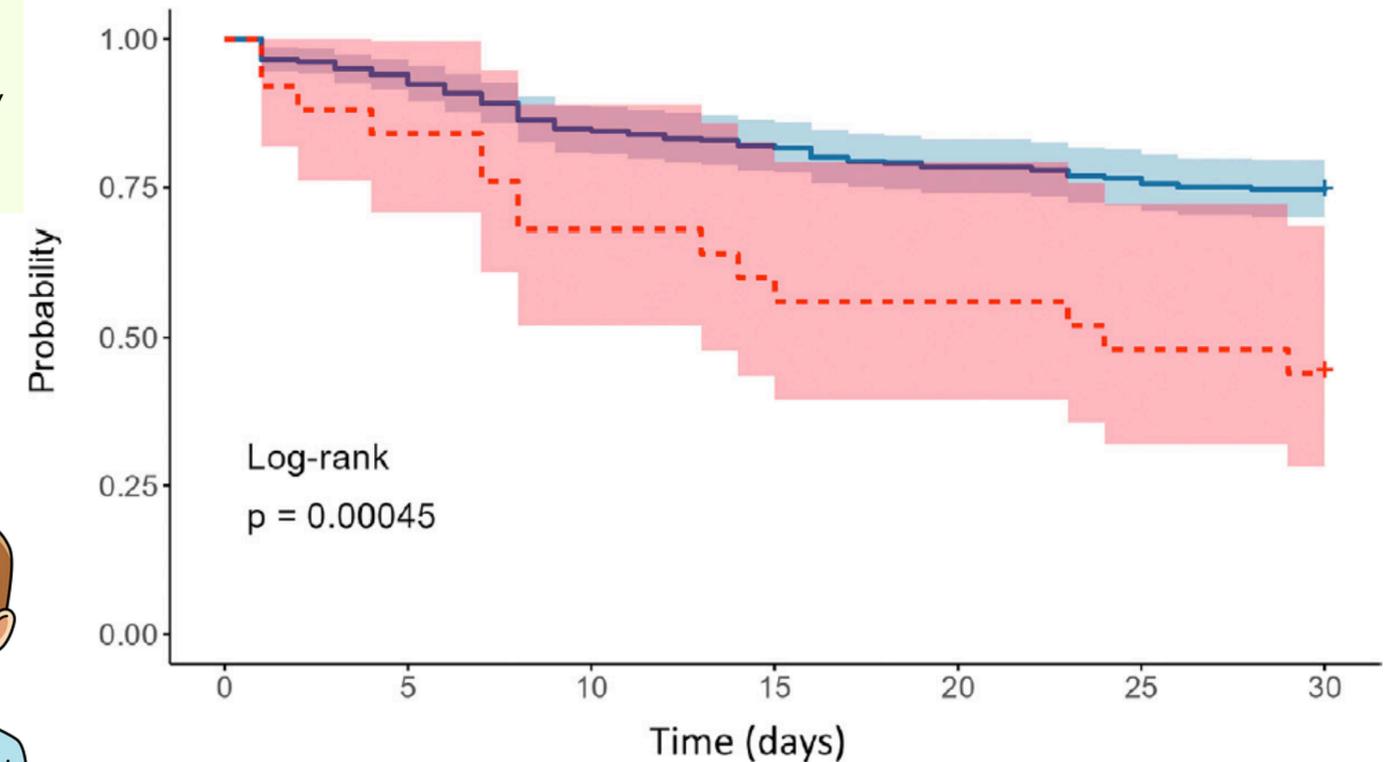
IN CONCLUSION
our results showed that MEs and VMEs of semiautomated AST systems are common and ***might be associated with poor outcome*** due to the more frequent inappropriate use of antibiotics

Results: We enrolled 300 compared with the results of those of the semi-automated systems. The rates of very major errors (VMEs; i.e. **false susceptibility**) and major errors (MEs; i.e. **false resistances**). The high rates of VMEs were observed with **fosfomycin (14%)** and **colistin (13.9%)**, and the highest rates of MEs were observed with **gentamicin (21%)**, **fosfomycin (7.7%)**, and **tigecycline (34%)**



Appropriate Targeted therapy
Inappropriate targeted therapy due to errors of semi-automated tests

a multicentre, retrospective study enrolling patients with monomicrobial BSI caused by CRE from January 2013 to December 2016



	0	5	10	15	20	25	30
Appropriate Targeted therapy	316	297	268	259	248	242	236
Inappropriate targeted therapy due to errors of semi-automated tests	25	21	17	15	14	12	11



RYAN K. SHIELDS,
PHARM.D, MS

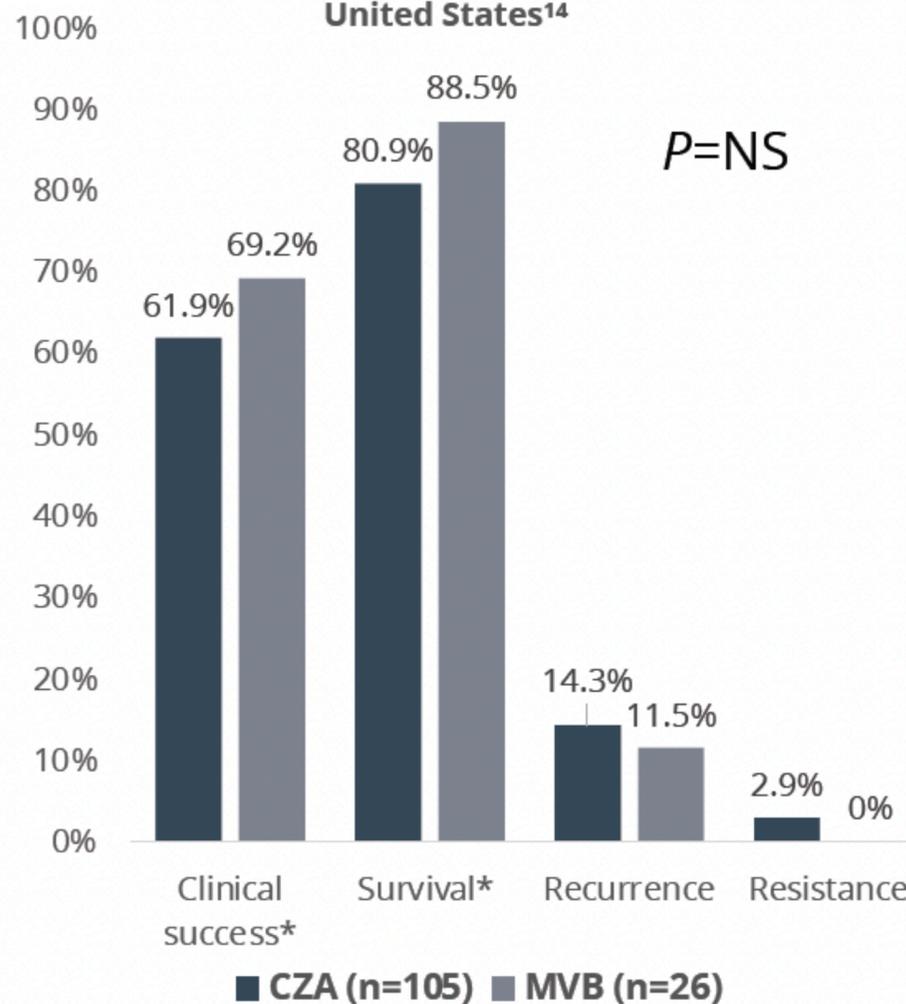
Is There a Preferred β -Lactam/ β -Lactamase Inhibitor Agent for treatment of KPC-Producing Enterobacterales Infection?

Carbapenem-resistant Enterobacterales present considerable treatment challenges. Recent cumulative evidence supports preference for therapies.

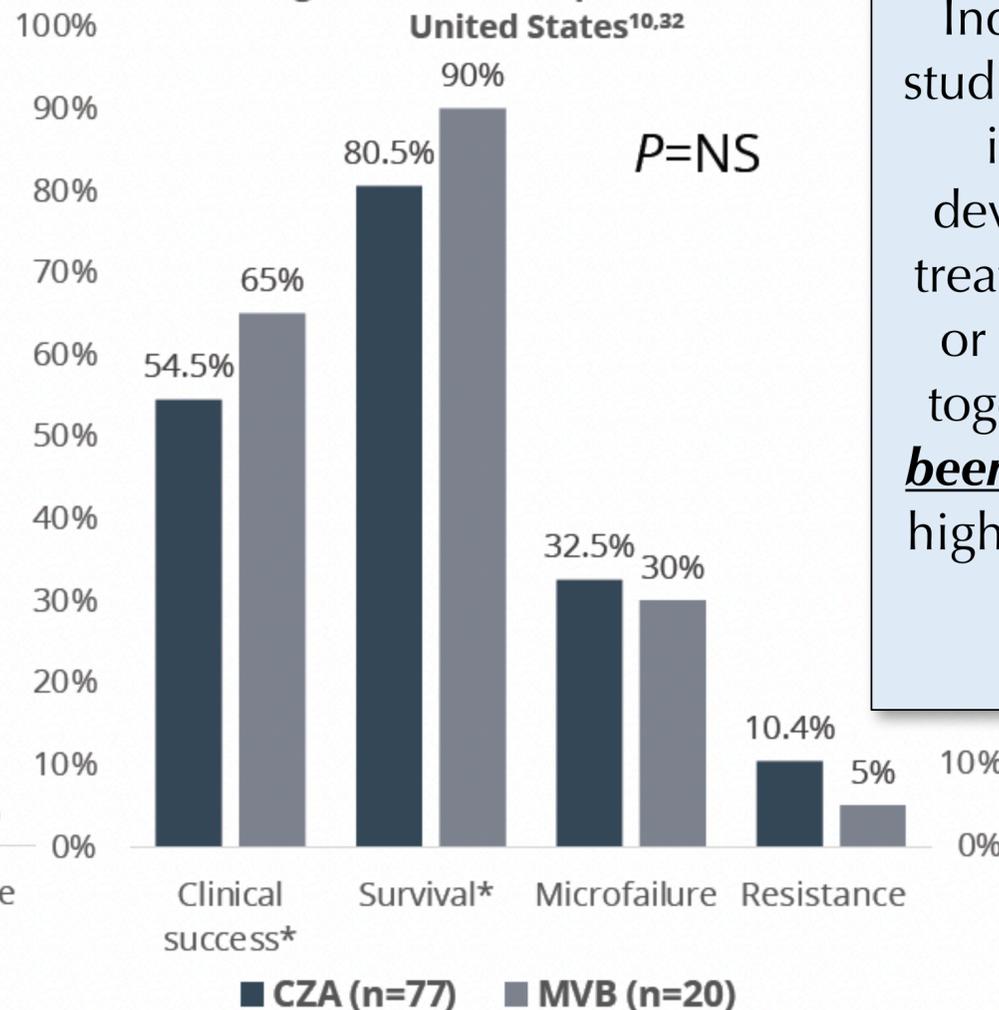
by RYAN K. SHIELDS, PHARM.D, MS

Treatment of KPC-Kp infections *has dramatically shifted in the past decade* away from less desirable aminoglycoside-, polymyxin-, or tetracycline-based combination therapy to newer β -lactam/ β -lactamase inhibitors such as ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam

Multicenter, retrospective study in the United States¹⁴



Two single-center, retrospective studies in United States^{10,32}



IN CONCLUSION ..

Individually, *no findings* from these studies have demonstrated a difference in clinical efficacy, mortality, or development of resistance following treatment with ceftazidime-avibactam or meropenem-vaborbactam. Taken together, however, *some trends have been consistently identified*, including higher rates of survival and lower rates of resistance associated with meropenem-vaborbactam



Tumbarello M. et al. *Clin Infect Dis* 2019;68(3):355-364 - Ackley R. et al. *Antimicrob Agents Chemother* 2020;64(5):e02313-19 - Shields RK. et al. *Antimicrob Agents Chemother* 2018;62(5):e02497-17

Antibiogramma molecolare vs convenzionale di *K. pneumoniae* **KPC+**

CTX	Non rilevato
KPC	Rilevato
VIM	Non rilevato
IMP	Non rilevato
NDM	Non rilevato
OXA-48	Non rilevato



Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	>128 R
Ceftiaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	>16 R
Gentamicina	1 S
Ciprofloxacina	>4 R
Colistina	1 S
CZA	4 S
MVB	1 S
CFD	1 S

K. pneumoniae KPC-3

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	32 R
Ceftiaxone	>4 R
Ceftazidime	>128 R
Cefepime	16 R
Meropenem	2 S
Fosfomicina	>128 R
Amikacina	>16 R
Gentamicina	1 S
Ciprofloxacina	>4 R
Colistina	0,5 S
CZA	32 R
MVB	0,5 S
CFD	2 S

K. pneumoniae KPC-31

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	>128 R
Ceftiaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	8 S
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>8 R
CZA	16 R
MVB	32 R
CFD	2 S

K. pneumoniae KPC-3
IPERESPRESSA

Courtesy Prof Rossolini

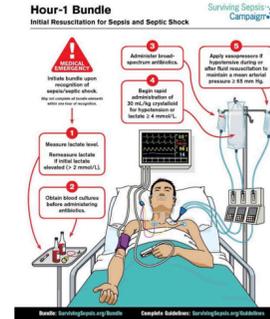
dati clinici paziente

- ❖ **NIHSS 8 occlusione passaggio M1-M2 di ACM sx** - uomo 68 AA
- ❖ Iperensione arteriosa
- ❖ Seminoma metastatico, orchietomia, in corso primo ciclo di CHT
- ❖ Trombolisi sistemica rTPA 76.5 mg e successiva procedura endovascolare - Stroke Unit
- ❖ **Neutropenia e piastrinopenia**
- ❖ Ricovero in Malattie Infettive: meropenem + vancomicina in empirica - dopo 5 gg deterioramento neurologico GCS 8 nuova TC e ricovero in TINCH



Notte

Gb 3.86 mila
Linfociti 340
pct 3.27 ng/ml



norAdr 0.8
Amiodarone
Lattati 3.4

Pf 140
Fibrillo/flutter
PAS 90/60

MEM 2g x 3
LNZ 600 x 2



11 lug
2023

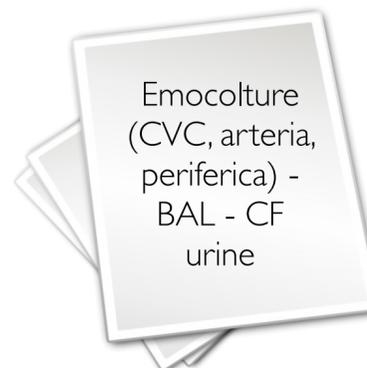
11 lug
2023

Tp
empirica

Tampone rettale PCR	Tampone rettale
Gene per Carbapenemasi KPC	Non Rilevato
Gene per Carbapenemasi NDM	Non Rilevato
Gene per Carbapenemasi IMP	Non Rilevato
Gene per Carbapenemasi VIM	Non Rilevato
Gene per Carbapenemasi OXA-48	Non Rilevato
Gene per Carbapenemasi VanA	Non Rilevato

09 lug
2023

What's
Next



Test con molecolare con pannello sindromico (TTR 75 min)

ID molecolare:

K. pneumoniae group

Antibiogr. molecolare

CTX-M	RILEVATO
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

Nuovo tampone rettale

Tampone rettale PCR	Tampone rettale
Gene per Carbapenemasi KPC	Non Rilevato
Gene per Carbapenemasi NDM	Non Rilevato
Gene per Carbapenemasi IMP	Non Rilevato
Gene per Carbapenemasi VIM	Non Rilevato
Gene per Carbapenemasi OXA-48	Non Rilevato
Gene per Carbapenemasi VanA	Rilevato

IMI/REL
q6 in 1.5h
LNZ 600 x 2

12 lug
2023

TAC TORACE
ENCEFALO

Addensamenti consolidativi
bibasali con broncogramma aereo
e versamento pleurico
consensuale di 2 cm
Maggiormente definita la nota
ipodensità cortico-sottocorticale
fronto-parieto insulare sx

IMI/REL
q6 in 1.5h
LNZ 600 x 2

13 lug
2023

Gb 6.67 mila
Linfociti 360
pct 1.92 ng/ml

Pf 212
PAS 138/75
norAdr 0.3
Lattati 1.3

IMI/REL
q6 in 1.5h
LNZ 600 x 2

14 lug
2023

DOPO 48H

Gb 5.69 mila
Linfociti 460
pct 1.10 ng/ml

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>16 R
Piperacillina/tazobactam	>128 R
Ceftriaxone	>4 R
Ceftazidime	>128 R
Meropenem	32 R
Fosfomicina	0.5 S
Amikacina	>16 R
Gentamicina	>4 R
Ciprofloxacina	>4 R
Colistina	1 S
Tigeciclina	0.5
CZA	4 S
MER/VBR	1 S
IMI/REL	0.5 S
Cefiderocol	0.5 S

IMI/REL
q6 in 1.5h

15 lug
2023

Pf 289
PAS 138/75
Lattati 0.9

20 lug
2023

STOP

The ***changing epidemiology*** of carbapenemase-producing *Klebsiella pneumoniae* in Italy: toward polyclonal evolution with emergence of high-risk lineages

Di Pilato V. et al. *J Antimicrob Chemother* 2021; 76:355-361

RESULTS: 24 laboratories provided ***157 CR-KP isolates***, of which 156 were confirmed as *K. pneumoniae* sensu stricto by WGS and found to carry at least one carbapenemase-encoding gene, corresponding in most cases (***96.1%***) to bla_{KPC}. MLST- and SNP-based phylogeny revealed that ***87.8%*** of the isolates clustered in four major lineages: ***CG258 (47.4%)***, with ***ST512*** as the most common clone, ***CG307 (19.9%)***, ***ST101 (15.4%)*** and ***ST395 (5.1%)***. A close association was identified between lineages and antibiotic resistance phenotypes and genotypes, virulence traits and capsular types. Colistin resistance, mainly associated with ***mgrB mutations***, was common in all major lineages except ST395

MLST: Multi Locus Sequence Typing - **SNP:** Single Nucleotide Polymorphism

Table 2. Antibiotic susceptibility profiles of 156 CR-KP isolates collected by hospital laboratories participating in the AR-ISS and of the four major lineages

	All isolates (%) (n=156)			CG258 (%) (n=74)			CG307 (%) (n=31)			ST101 (%) (n=24)			ST395 (%) (n=8)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Meropenem	0.0	8.3	91.7	0.0	0.0	100.0	0.0	19.4	80.6	0.0	4.2	95.8	0.0	25.0	75.0
Imipenem	1.9	1.9	96.2	0.0	0.0	100.0	0.0	3.3	96.7	0.0	4.2	95.8	12.5	12.5	75.0
Ertapenem	0.0	-	100.0 ^a	0.0	-	100.0	0.0	-	100.0	0.0	-	100.0 ^b	0.0	-	100.0
Ceftazidime/ avibactam	97.4	-	2.6	100.0	-	0.0	100.0	-	0.0	91.7	-	8.3	100.0	-	0.0
Gentamicin	59.6	-	40.4	85.1	-	14.9	41.9	-	58.1	20.8	-	79.2	12.5	-	87.5
Amikacin	44.9	-	55.1	21.6	-	78.4	93.5	-	6.5	16.7	-	83.3	87.5	-	12.5
Ciprofloxacin	1.9	0.6	97.5	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0
Trimethoprim/ sulfamethoxazole	24.4	3.8	71.8	16.2	1.4	82.4	6.5	3.2	90.3	58.3	12.5	29.2	50.0	12.5	37.5
Colistin	59.6	-	40.4	56.8	-	43.2	51.6	-	48.4	41.7	-	58.3	100.0	-	0.0
Chloramphenicol	16.0	-	84.0	1.4	-	98.6	45.2	-	54.8	8.3	-	91.7	0.0	-	100.0
Fosfomicin	82.7	-	17.3	74.3	-	25.7	93.5	-	6.5	87.5	-	12.5	87.5	-	12.5
Tigecycline	50.6	-	49.4	41.9	-	58.1	54.8	-	45.2	54.2	-	45.8	75.0	-	25.0

S, susceptible, standard dosing regimen; I, susceptible, increased exposure; R, resistant.

^aPercentage calculated on 153 isolates, as for 3 isolates susceptibility testing yielded an MIC ≤1 mg/L that did not allow categorization of these isolates as S or R.

^bPercentage calculated on 23 isolates, as for 1 isolate susceptibility testing yielded an MIC ≤1 mg/L.



The **changing epidemiology** of carbapenemase-producing *Klebsiella pneumoniae* in Italy: toward polyclonal evolution with emergence of high-risk lineages

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MLST: Multi Locus Sequence Typing - SNP: Single Nucleotide Polymorphism



CONCLUSION
 This WGS-based survey showed that, although CG258 remained the most common CR-KP lineage in Italy, **a polyclonal population has emerged** with the spread of the new high-risk lineages CG307, ST101 and ST395, while KPC remained the most common carbapenemase

laboratories participating in the AR-ISS and of the four major

	ST101 (%) (n=24)			ST395 (%) (n=8)		
	R	S	I	R	S	I
(n=31)	80.6	0.0	4.2	95.8	0.0	25.0
	96.7	0.0	4.2	95.8	12.5	12.5
	100.0	0.0	-	100.0 ^b	0.0	-
	0.0	91.7	-	8.3	100.0	0.0
	58.1	20.8	-	79.2	12.5	-
	6.5	16.7	-	83.3	87.5	-
	100.0	0.0	0.0	100.0	0.0	0.0
	90.3	58.3	12.5	29.2	50.0	12.5
	48.4	41.7	-	58.3	100.0	-
	54.8	8.3	-	91.7	0.0	-
	6.5	87.5	-	12.5	87.5	-
	45.2	54.2	-	45.8	75.0	-

Colistin												
Chloramphenicol	16.0	-	84.0	1.4	-	98.6	45.2	-	54.8	8.3	-	100.0
Fosfomicin	82.7	-	17.3	74.3	-	25.7	93.5	-	6.5	87.5	-	12.5
Tigecycline	50.6	-	49.1		-	58.1	54.8	-	45.2	54.2	-	25.0

S, susceptible, standard dosing regimen; I, susceptible after prolonged exposure; R, resistant.
^aPercentage calculated on 153 isolates, as for 3 isolates susceptibility testing yielded an MIC ≤1 mg/L that did not allow categorization of these isolates as S or R.
^bPercentage calculated on 23 isolates, as for 1 isolate susceptibility testing yielded an MIC ≤1 mg/L.

136 varianti KPC

[Nov/2022 - NCBI AMR database]

Non rilevate dai sistemi LFIA commerciali con mutazioni nell' Ω loop:

KPC-31, KPC-33, KPC-66, KPC-68, KPC-69, KPC-70

Rilevate con sistemi LFIA commerciali e mutazioni esterne all' Ω loop: **KPC-14, KPC-28, KPC-29***, **KPC-53, KPC-67***

***attività carbapenemasi mantenuta**

Haidar et al. AAC 2017

Compain & Arthur AAC 2017

Shields et al. AAC 2017

Humphries & Hamarajata AAC 2017

Shields et al. *OF Infect Dis* 2017

Barnes et al. *mBio* 2018

Wand et al. *JGAR* 2019

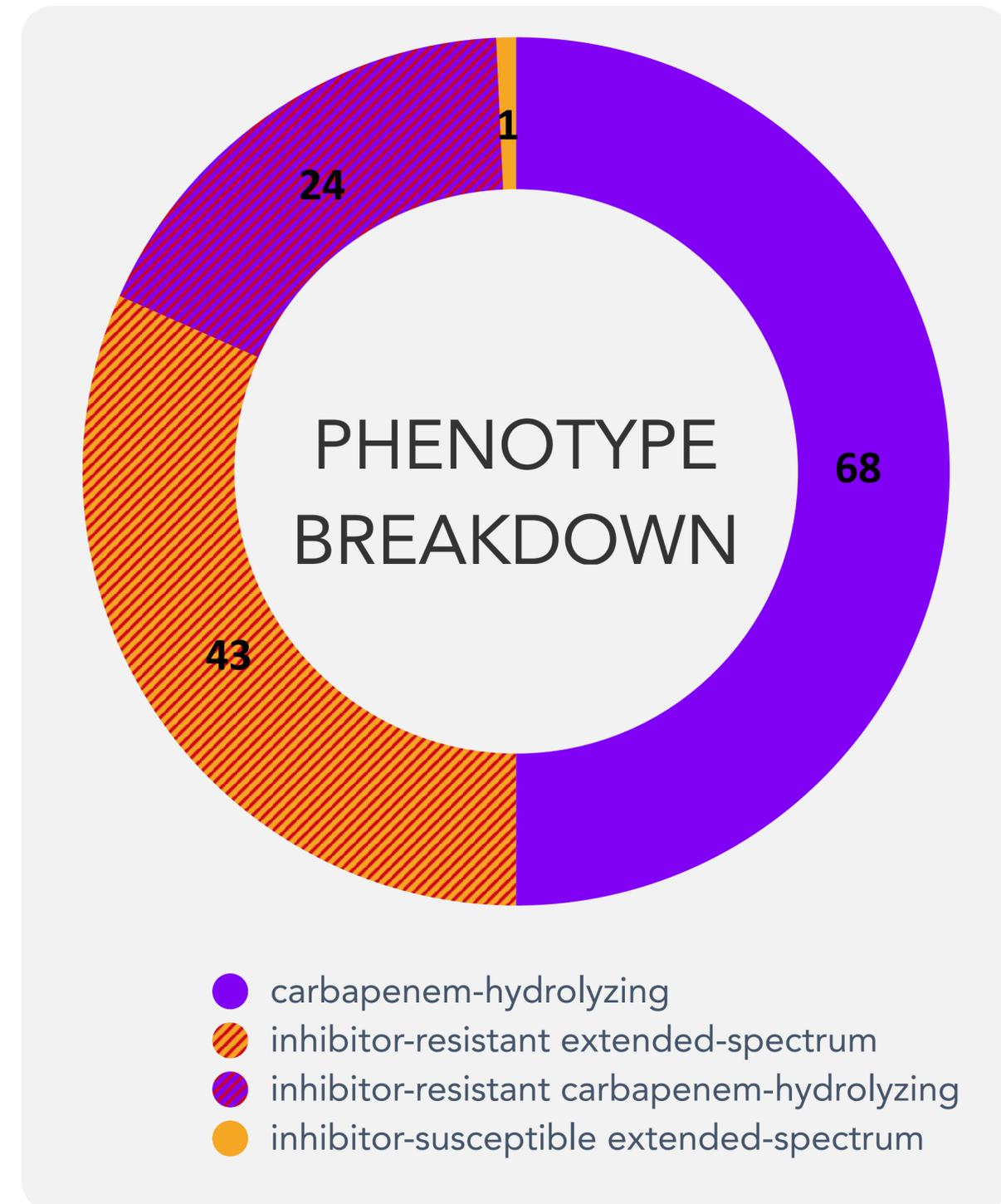
Antonelli et al. *JAC* 2019

Oueslati et al. *JAC* 2019

Carattoli et al. AAC 2021

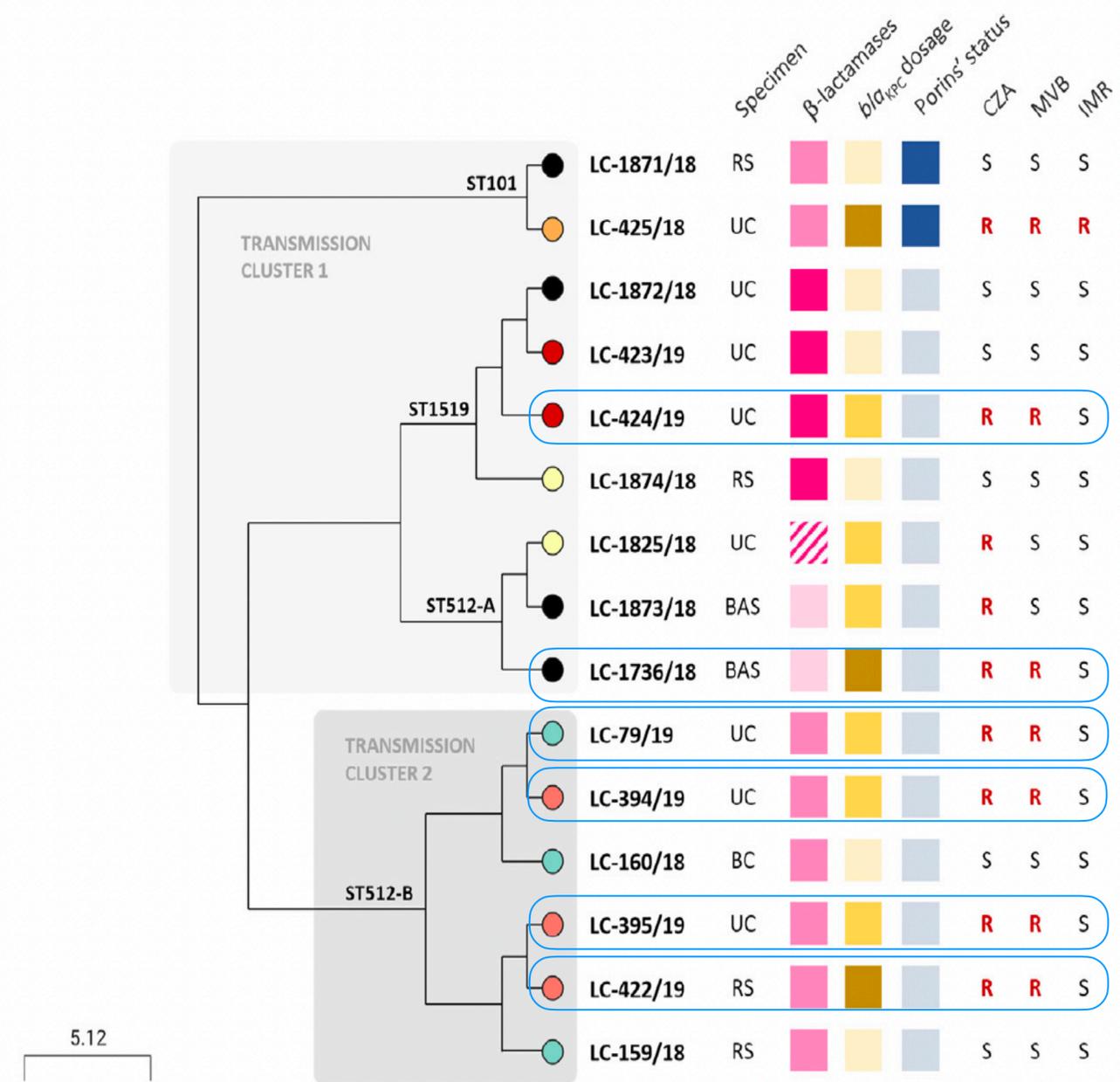
Bianco et al. *JGAR* 2021

Bianco et al. *JHI* 2022



Deciphering variable resistance to novel carbapenem-based β -lactamase inhibitor combinations in a multi-clonal outbreak caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam

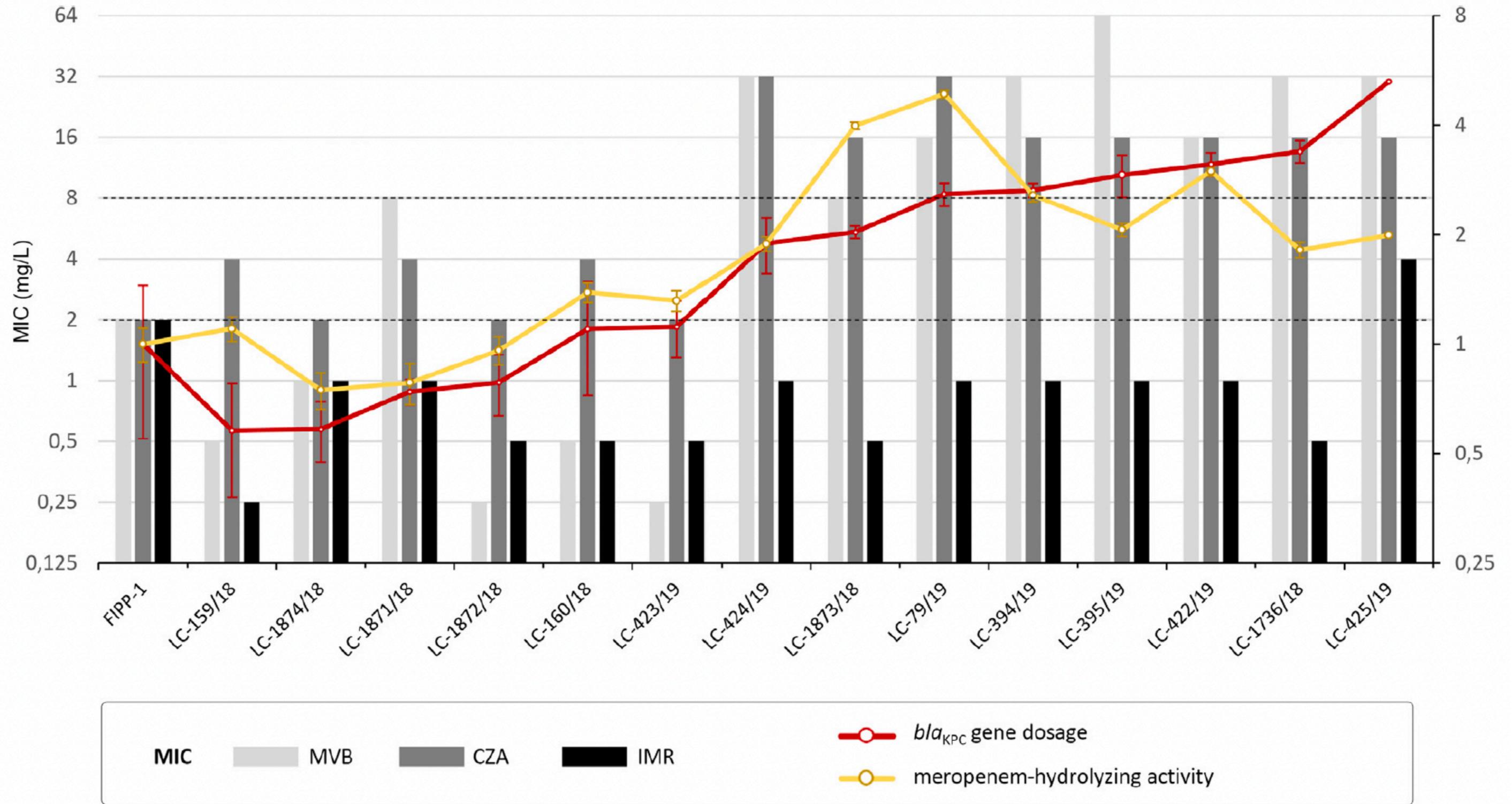
Di Pilato V. et al. *Clin Microbiol Infect* 2023



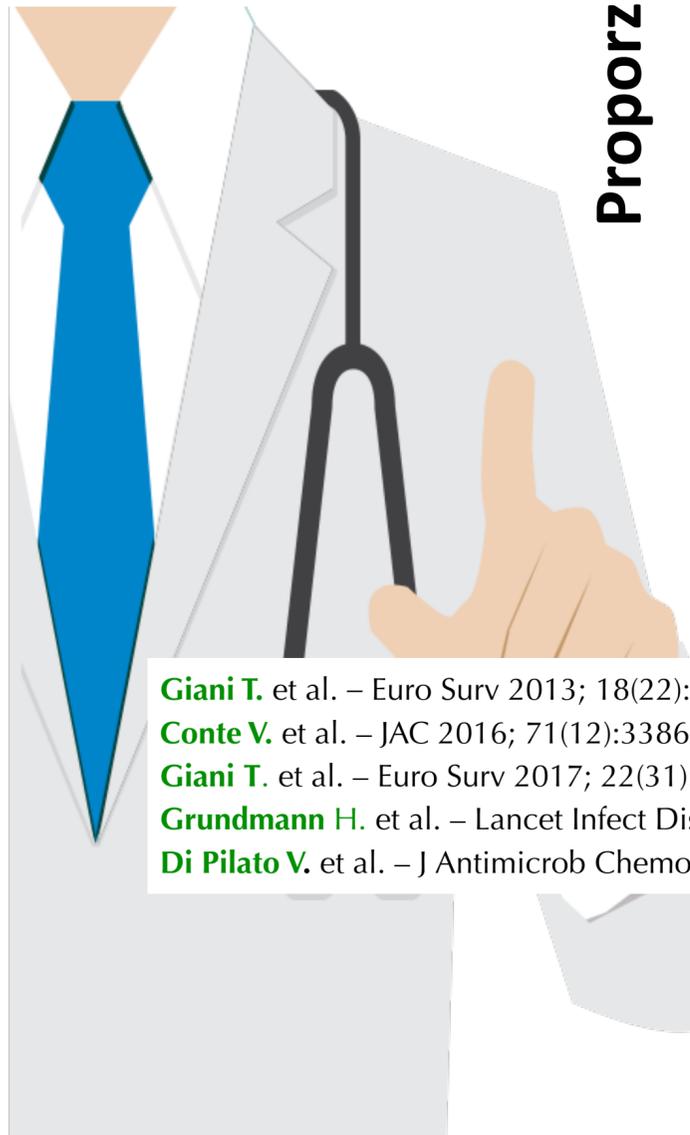
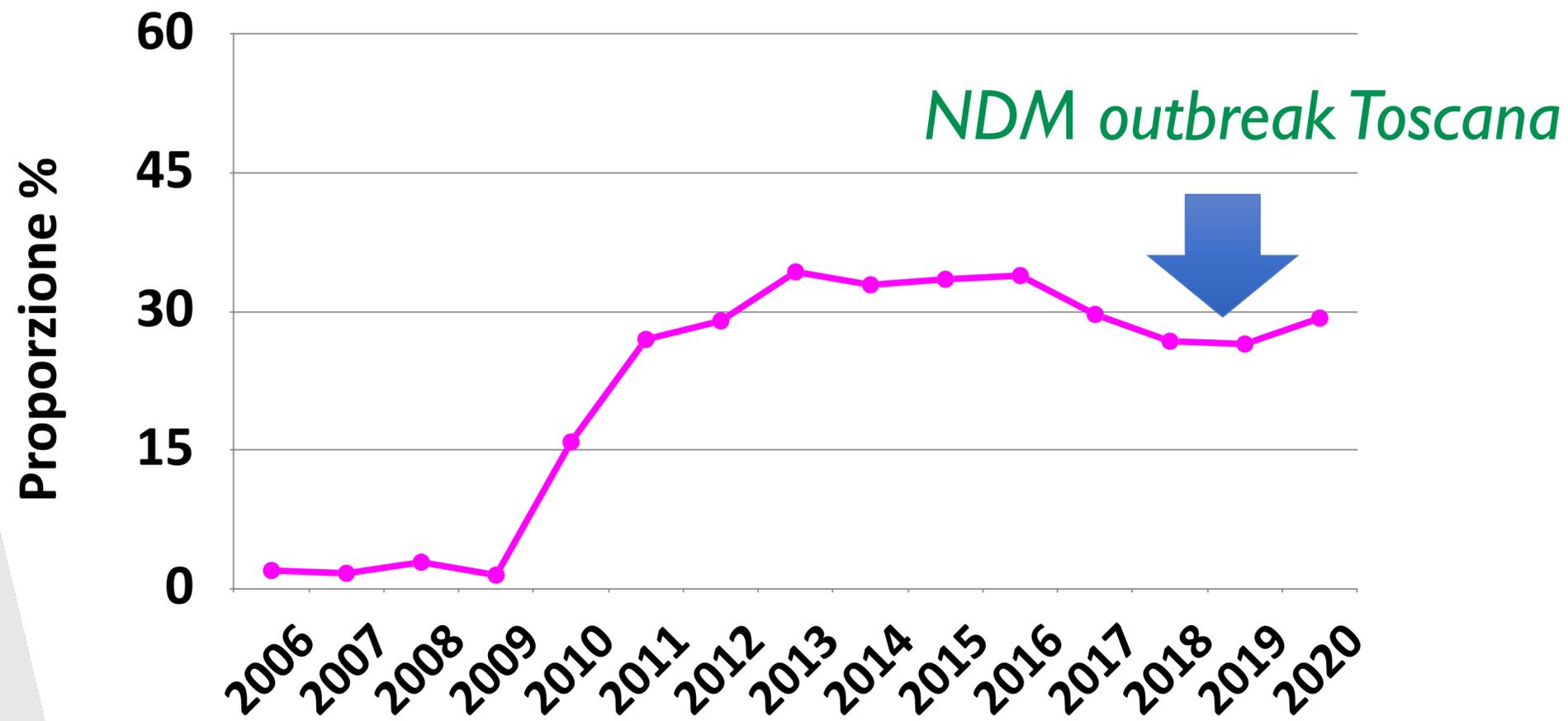
Patients' code		β -lactamases	bla_{KPC} dosage	Porins' status
● P1	● P4	■ KPC-3	■ 0.5 – 2	■ OmpK35 (AA89*) – OmpK36 (dup.GD)
● P2	● P5	■ KPC-3, TEM-1	■ 2 – 3	■ OmpK35 (AA63*) – OmpK36 (dup.TD)
● P3	● P6	■ KPC-3, CMY-16	■ >3	
		■ KPC-53		

CONCLUSIONS: in this multi-clonal outbreak of KPC-Kp, the overproduction of KPC-3 was the leading mechanism of cross-resistance to CZA and MVB, whereas resistance to IMR appeared less affected. The emergence and dissemination of similar resistance mechanisms may have relevant clinical and diagnostic implications, and their surveillance is warranted

Comparison of the MIC of different BLICs with bla_{KPC} gene dosage and meropenem-hydrolyzing activity in KPC-Kp included in this study

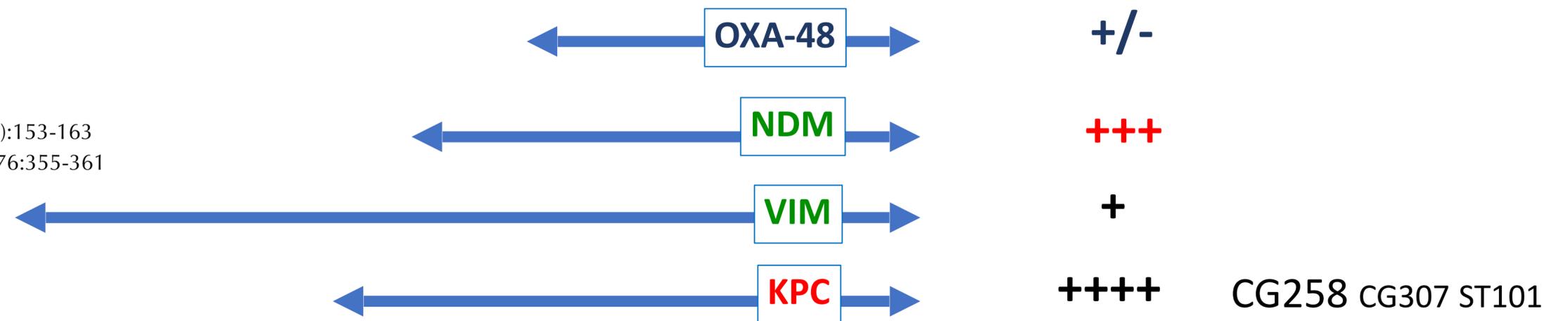


Carbapenem resistant *Klebsiella pneumoniae*- Italia



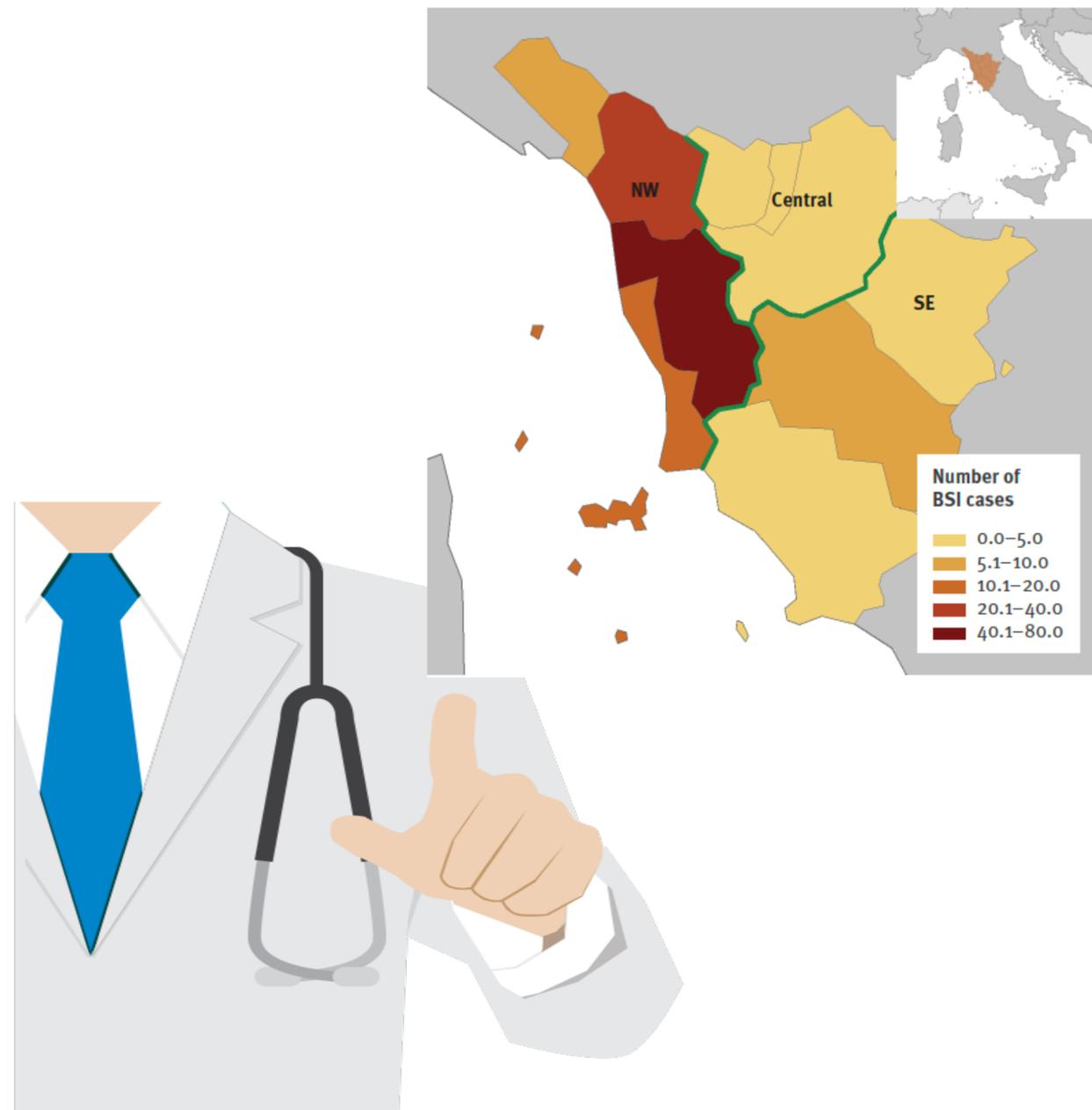
Giani T. et al. – Euro Surv 2013; 18(22):20489
 Conte V. et al. – JAC 2016; 71(12):3386-3391
 Giani T. et al. – Euro Surv 2017; 22(31):30583
 Grundmann H. et al. – Lancet Infect Dis 2017; 17(2):153-163
 Di Pilato V. et al. – J Antimicrob Chemother 2021; 76:355-361

Impatto Epidemiologico



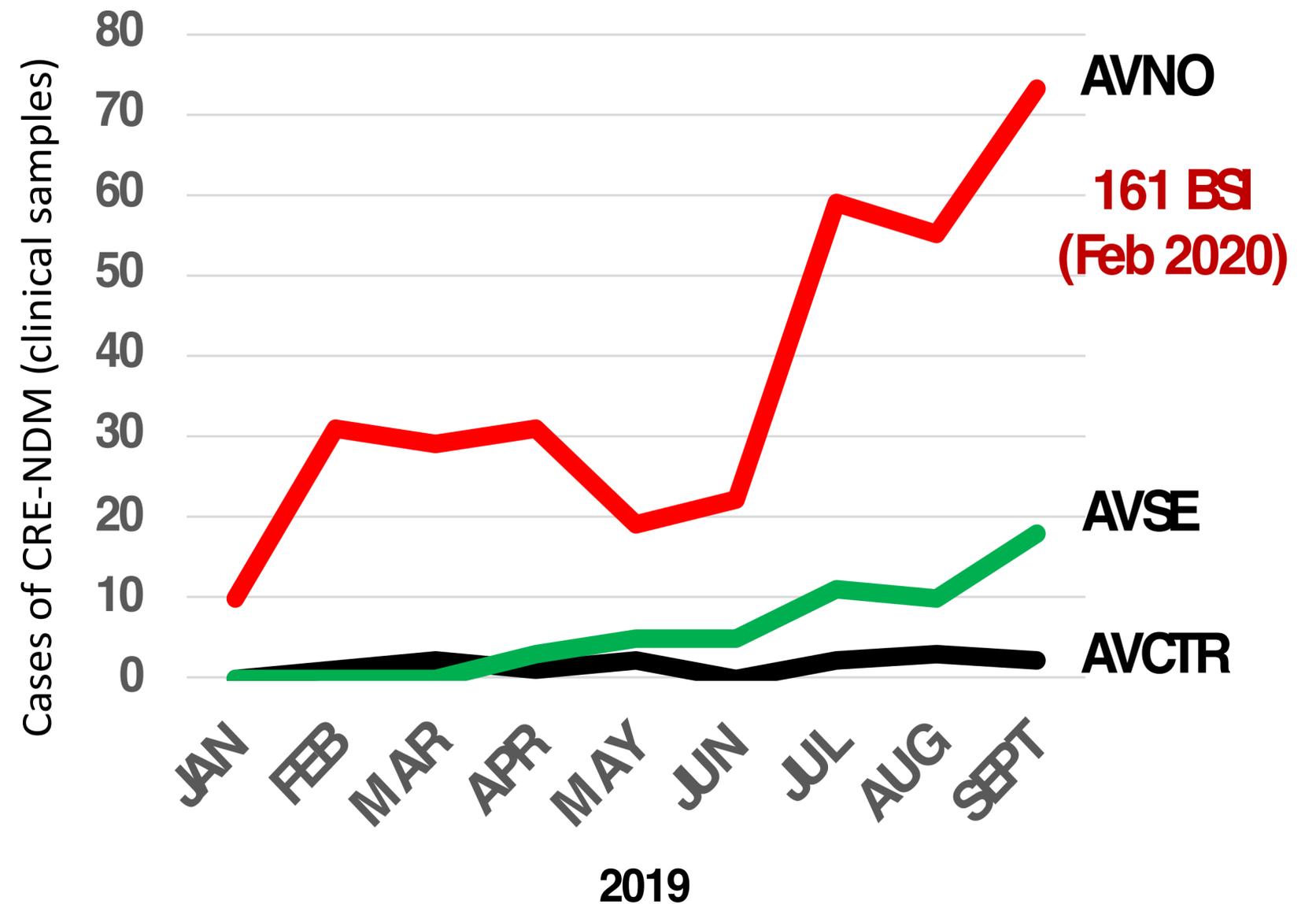
Prolonged ***outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE)***, Tuscany, Italy, 2018 to 2019

Tavoschi L. et al. *Euro Surveill* 2020; 25(6):2000085



Tra novembre 2018 e il 30 giugno 2022 i batteri NDM in Toscana sono stati isolati nel sangue di **503** pazienti

2021: 153 casi 2022: 88 casi



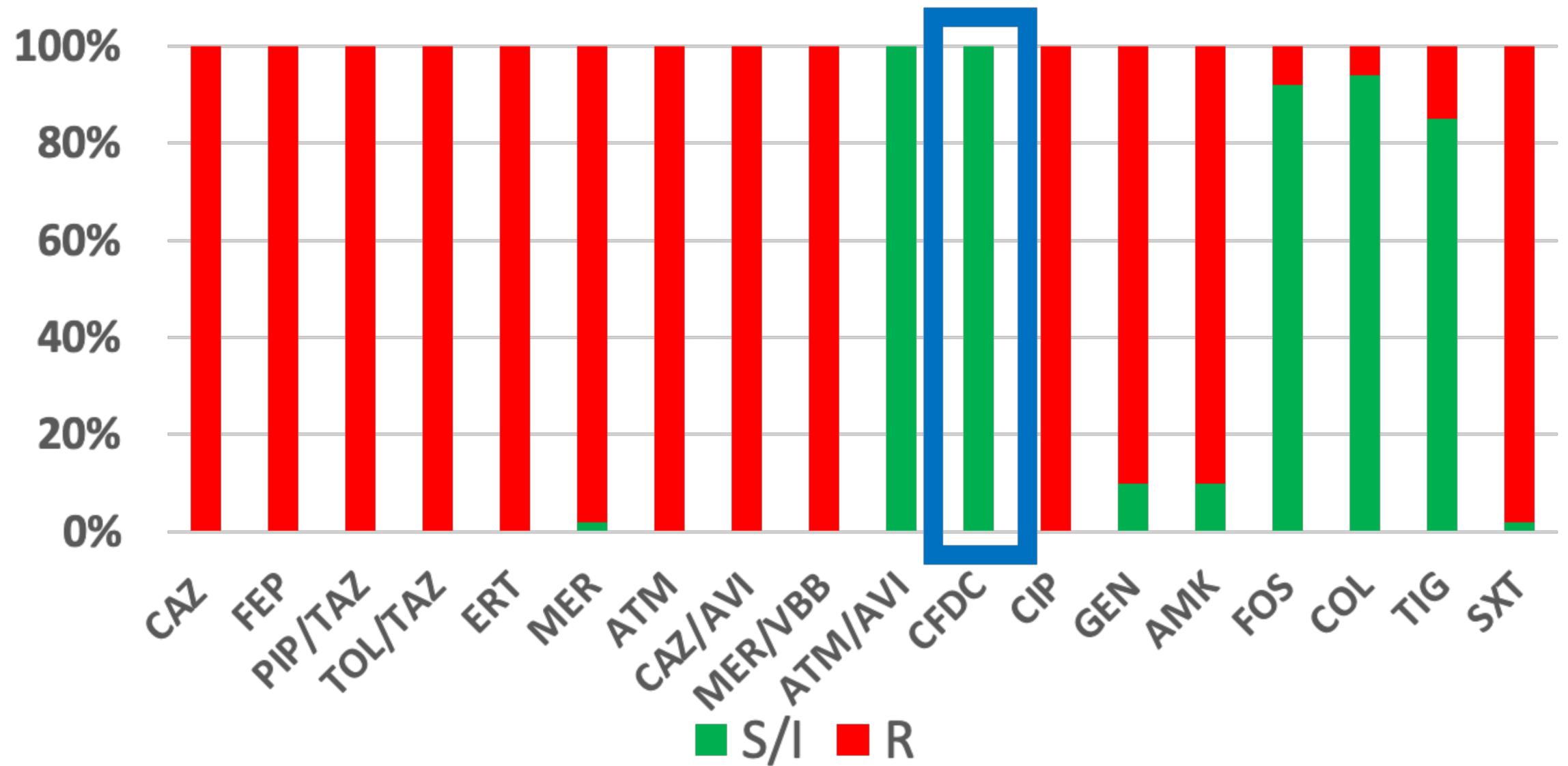
www.ars.toscana.it

CRE-NDM outbreak Toscana:
resistenza agli antibiotici



N = 48 isolati di *K. pneumoniae* ST147 NDM-1+ (BSI)

Di Pilato V. et al. *Lancet Microbe* 2022



Progressive Development of Cefiderocol Resistance in *Escherichia coli* During Therapy is Associated With an Increase in *bla*_{NDM-5} Copy Number and Gene Expression

Simner PJ. et al. *Clin Infect Dis* 2022; 75(1):47-54

Synergy testing with the combination of **ceftazidime-avibactam and aztreonam** demonstrated expansion of the zone of inhibition between the disks for all isolates. The patient was successfully treated with this combination and remained infection free 1 year later

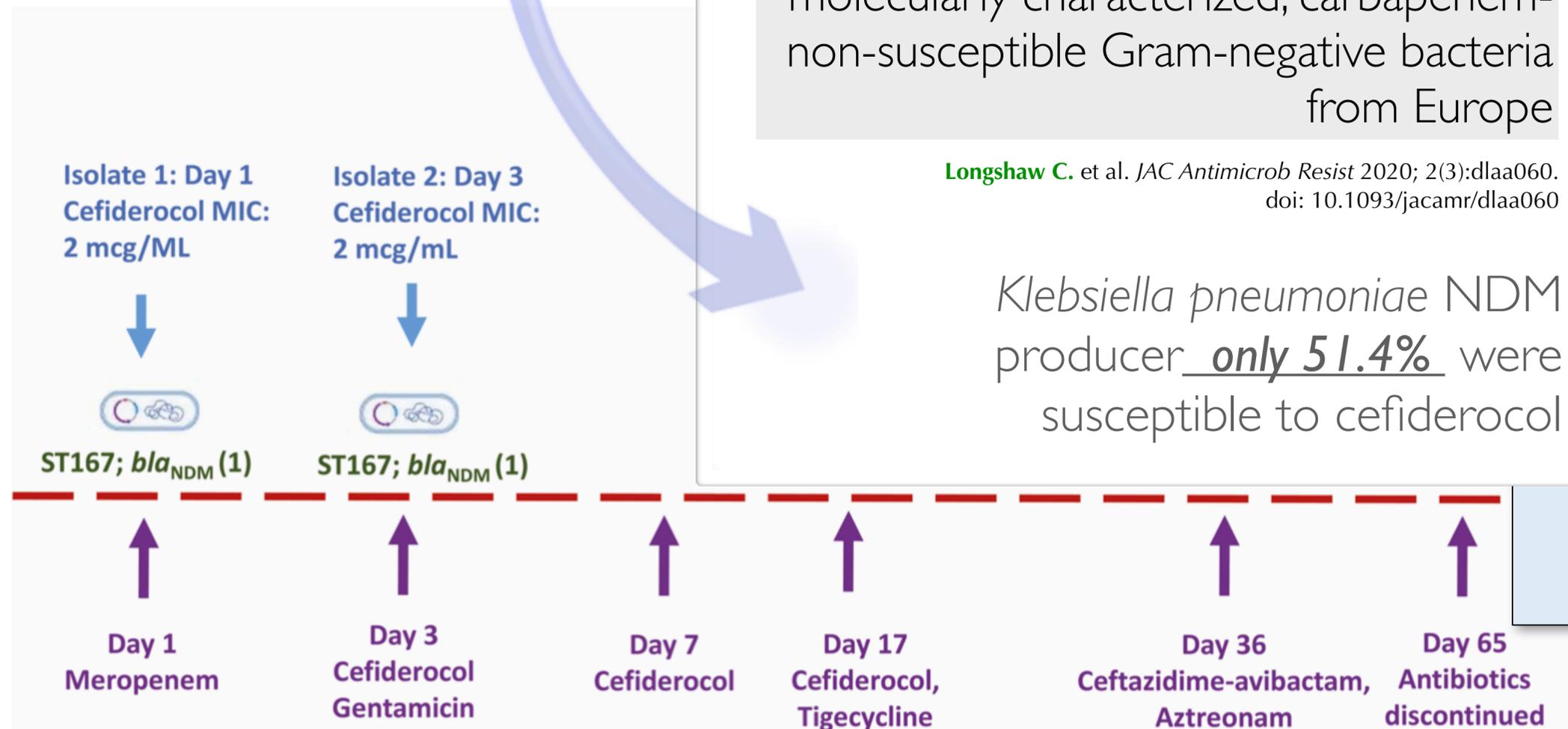
In vitro **activity of** the siderophore cephalosporin, **cefiderocol**, against molecularly characterized, carbapenem-non-susceptible Gram-negative bacteria from Europe

Longshaw C. et al. *JAC Antimicrob Resist* 2020; 2(3):dlaa060. doi: 10.1093/jacamr/dlaa060

Klebsiella pneumoniae NDM producer **only 51.4%** were susceptible to cefiderocol

CONCLUSION

The findings in our patient suggest that increased copy numbers of *bla*_{NDM} genes through slocation events are used by *Enterobacterales* to evade cefiderocol-mediated cell death. The frequency of increased *bla*_{NDM-5} expression in contributing to cefiderocol resistance needs investigation



CRE-NDM outbreak Toscana:
resistenza agli antibiotici

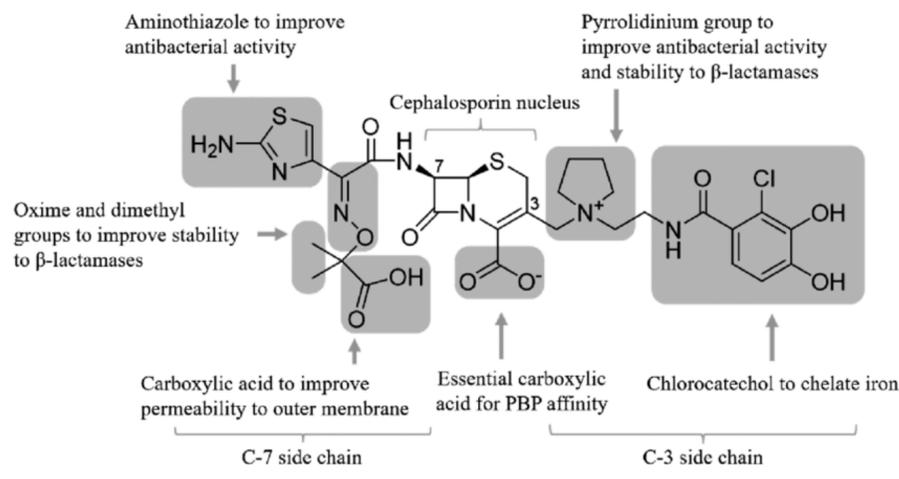
Pz. COVID+ ricoverato in TI
Cardiotoracica



Klebsiella pneumoniae

Antibiogr. molecolare	
CTX-M	RILEVATO
KPC	Non rilevato
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	RILEVATO

Emocoltura positiva



Sequenziamento Genoma

bla_{NDM-1} , $bla_{CTX-M-15}$, $\Delta cirA$

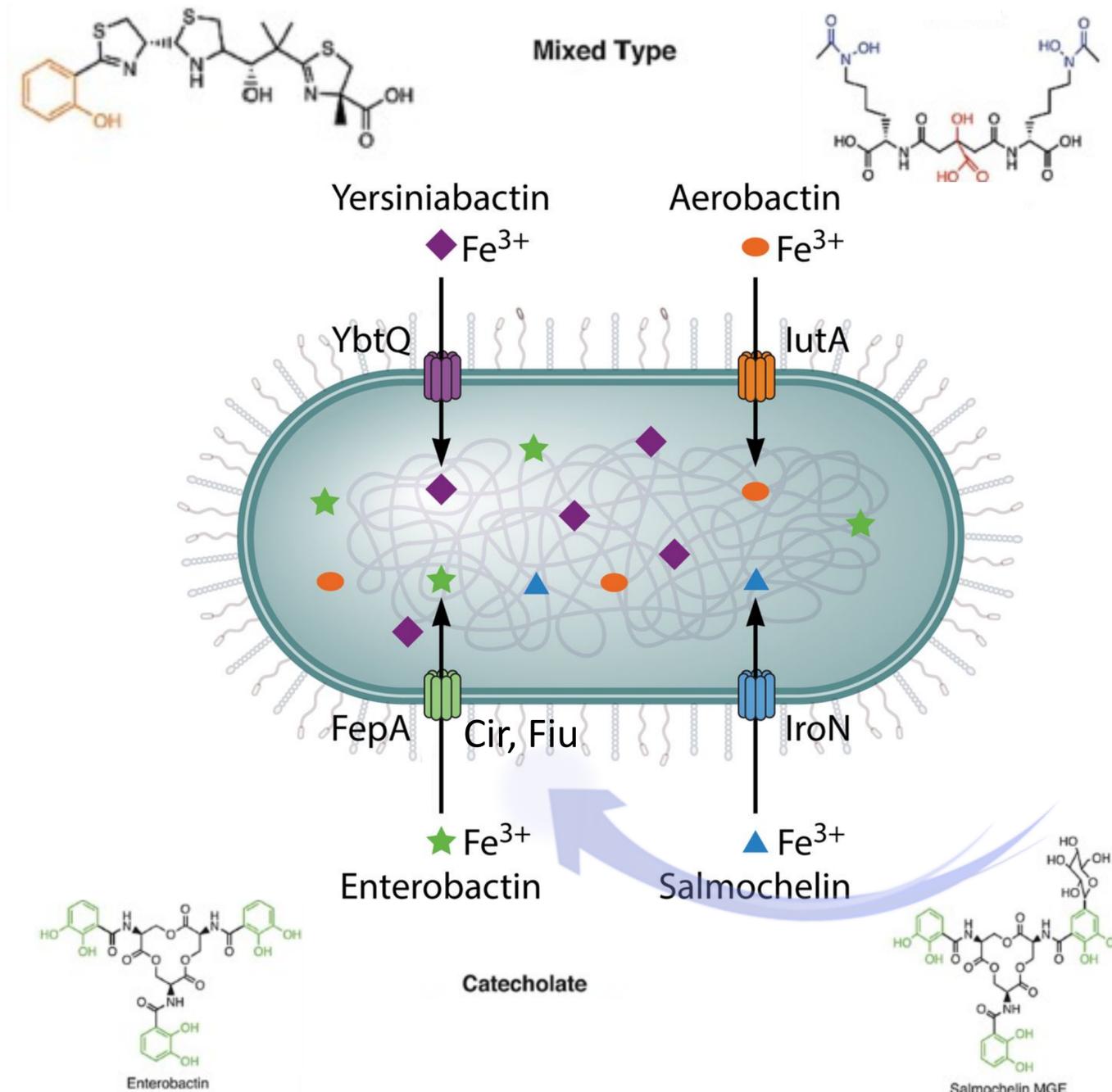
ATB fenotipico



Klebsiella pneumoniae NDM+

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	128 R
Ceftriaxone	>4 R
Ceftazidime	>64 R
Cefepime	>16 R
Meropenem	>16 R
Cefto/Tazob	>32 R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	0.5 S
CZA	>64 R
MER/VBR	>32 R
Cefiderocol	128 R

Siderofori in *Klebsiella pneumoniae*



❖ *K. pneumoniae* utilizza un'ampia varietà di gruppi chimici nei siderofori

❖ L' **enterobactina** (trasportata da FepA, Cir e Fiu) è il sistema di assorbimento del ferro primario utilizzato da *K. pneumoniae*

❖ Il **cefiderocol** presenta un gruppo catecolato simile all'enterobactina

Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022

Marco Coppi^{1,2}, Alberto Antonelli^{1,2}, Claudia Niccolai¹, Andrea Bartolini¹, Laura Bartolini², Maddalena Grazzini³, Elisabetta Mantengoli^{3,4}, Alberto Farese⁴, Filippo Pieralli⁵, Maria Teresa Mechi³, Vincenzo Di Pilato^{2,6}, Tommaso Gianì^{1,2}, Gian Maria Rossolini^{1,2}

Euro Surveill 2022

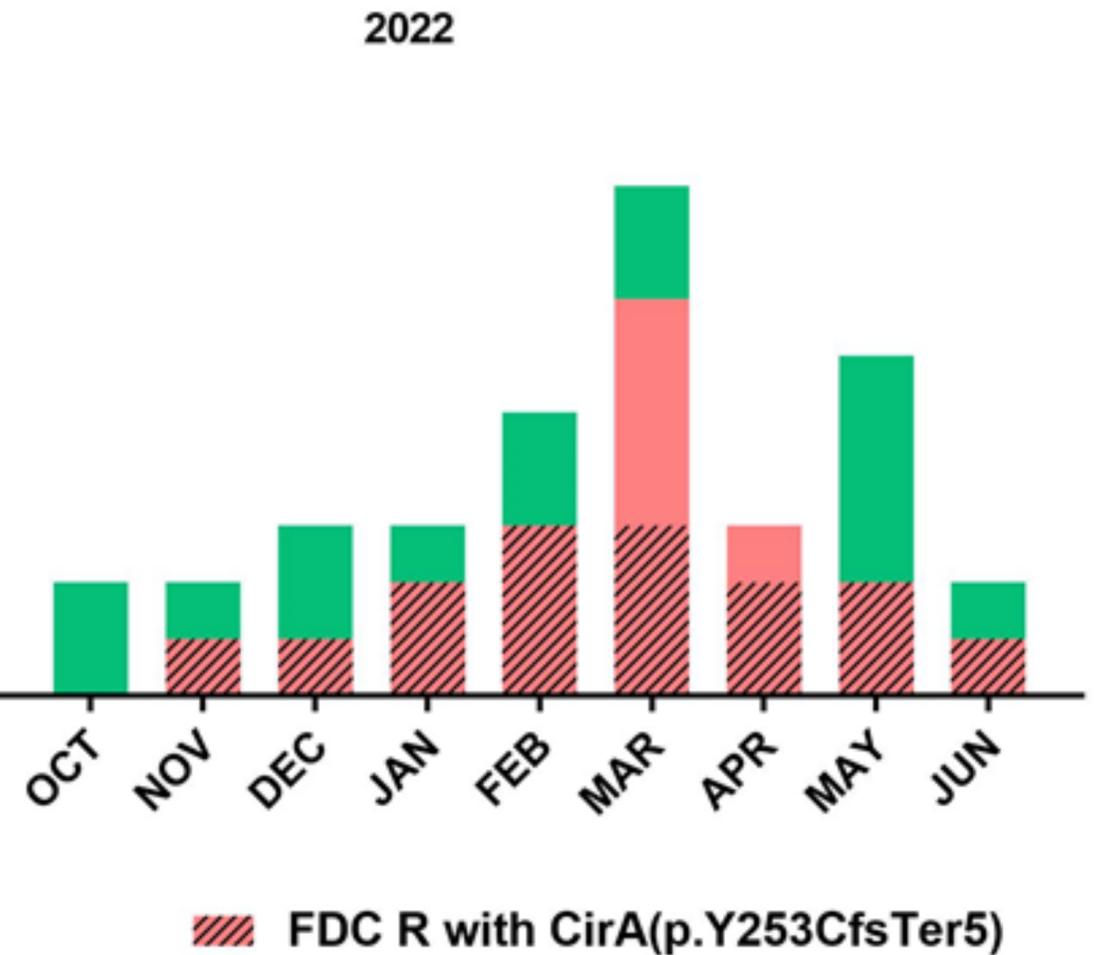
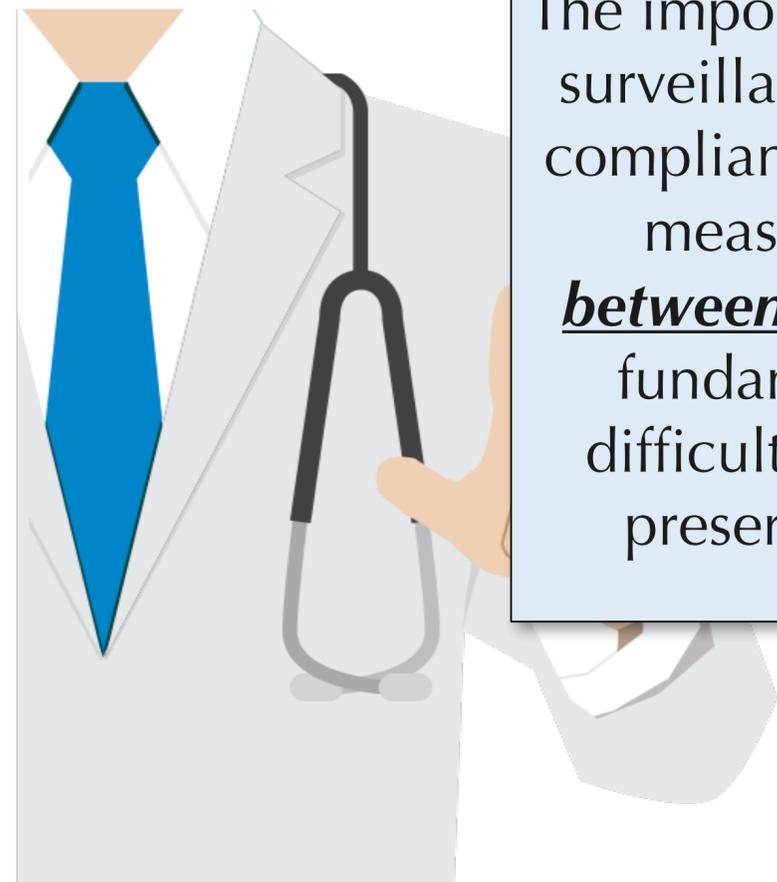
A nosocomial outbreak by cefiderocol (FDC)-resistant NDM-1-producing *Klebsiella pneumoniae* (NDM-Kp) occurred in a large tertiary care hospital from August 2021–June 2022 in Florence, Italy, an area where NDM-Kp strains have become endemic.

Retrospective analysis of NDM-Kp from cases observed in January 2021–June 2022 revealed that **21/52 were FDC-resistant**.

The outbreak was mostly sustained **by clonal expansion of a mutant with inactivated cirA siderophore receptor gene**, which exhibited high-level resistance to FDC (MIC ≥ 32 mg/L) **and spread independently of FDC exposure**

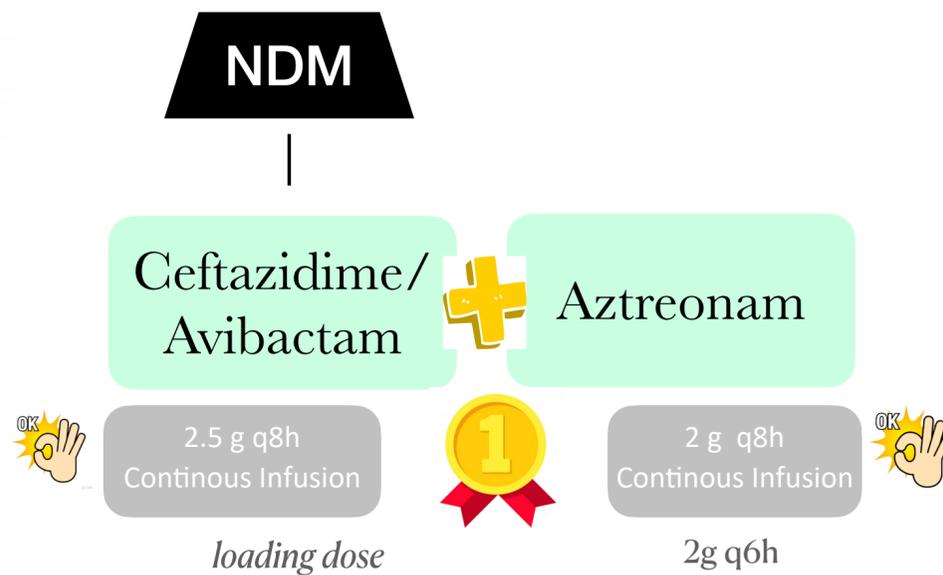
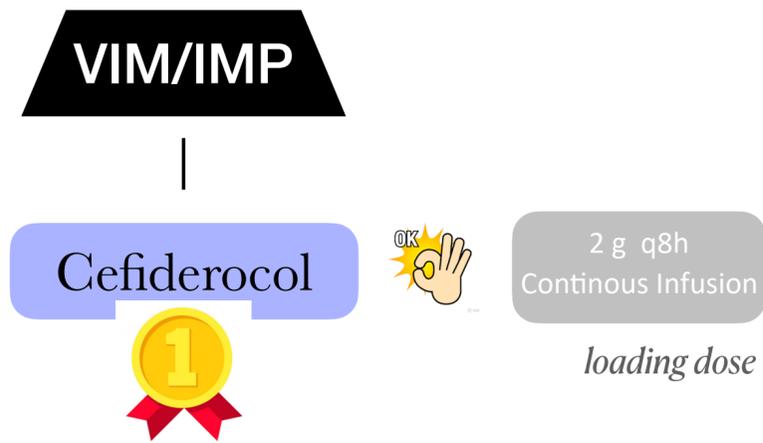
CONCLUSION

The importance of surveillance, including genomic surveillance and active surveillance, and of strict compliance with infection prevention and control measures – **based on a tight collaboration between clinical and laboratory personnel** – are fundamental to avoid further spread of these difficult-to-treat Gram-negative bacteria and to preserve the activity of novel antimicrobials

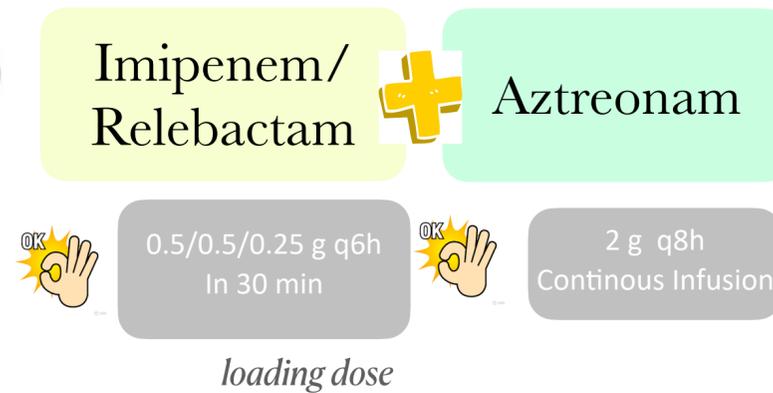


Algorithms for targeted therapy of IVACs/BSIs caused by *Enterobacterales* **MBL+** in critically ill adult patients

bla_{NDM-1}, bla_{CTX-M-15}, Δ cirA



MAYBE?



Conventional anti-CPE
(Fosfomicin + genta?
+ meropenem HD? + colistin?)

Antibiotico	MIC mg/l
Amoxi/clav	>64 R
Piperacillina/tazobactam	128 R
Ceftriaxone	≥4 R
Ceftazidime	>64 R
Cefepime	>16 R
Imipenem	>16 R
Meropenem	>16R
C/T	>32R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>4 R
CAZ/AVI	>64 R
MEM/VAB	ND
I/R	ND
Cefiderocol	128 R

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P

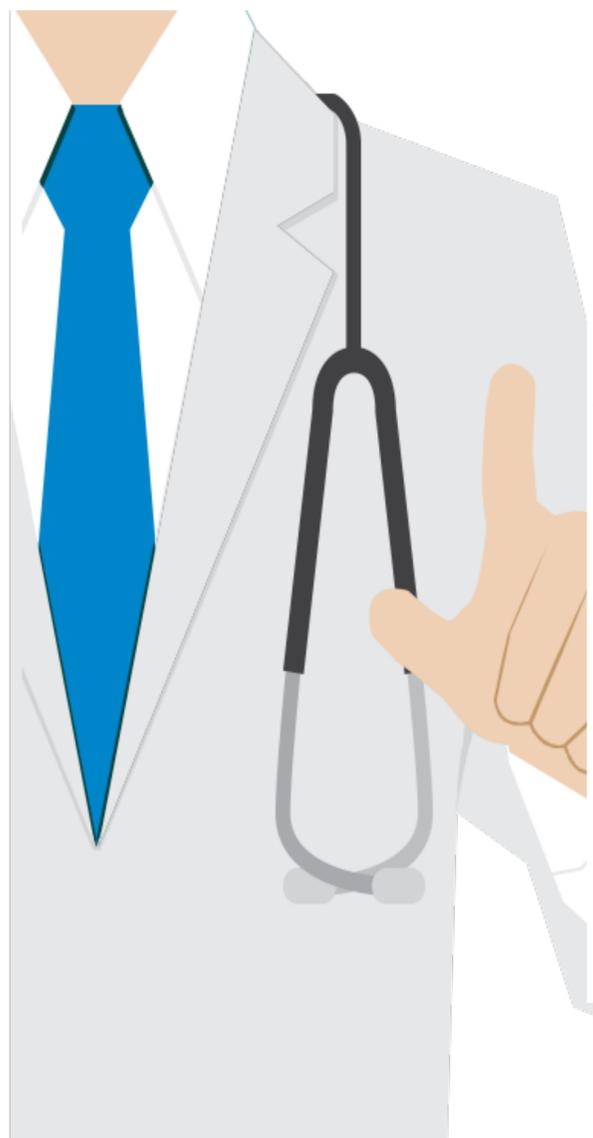
Exp Rev Anti Infect Ther Sep 2022

Infect Drug Resist Jun 2021

Antibiotics dec 2021

Identifying Effective Durations of Antibiotic Therapy for the Treatment of Carbapenem-resistant *Enterobacterales* Bloodstream Infections: A Multicenter Observational Study

Soto CL. et al. *Clin Infect Dis* 2023; DOI: 10.1093/cid/ciad476 1



RESULTS: 66 (36%) received a short-course of active antibiotics; and 117 (64%) received a prolonged-course of active antibiotics. The most common CRE were *Klebsiella pneumoniae* (96 [52%]) and *Enterobacter cloacae* complex (66 [36%]). Of the 183 isolates, 64 (35%) had a carbapenemase gene; all belonged to the *bla_{KPC}* family. Common treatment regimens included ceftazidime-avibactam (75, 41%); meropenem-vaborbactam (19, 11%); and high-dose extended-infusion meropenem with or without an aminoglycoside, fluoroquinolone, or polymyxin (89, 49%). The addition of an aminoglycoside, fluoroquinolone, or polymyxin to a beta-lactam/beta-lactam inhibitor was administered to 15% of patients. No patients received imipenem-cilastatin-relebactam or cefiderocol. All patients with a *bla_{KPC}* identified received a beta-lactam/beta-lactamase inhibitor

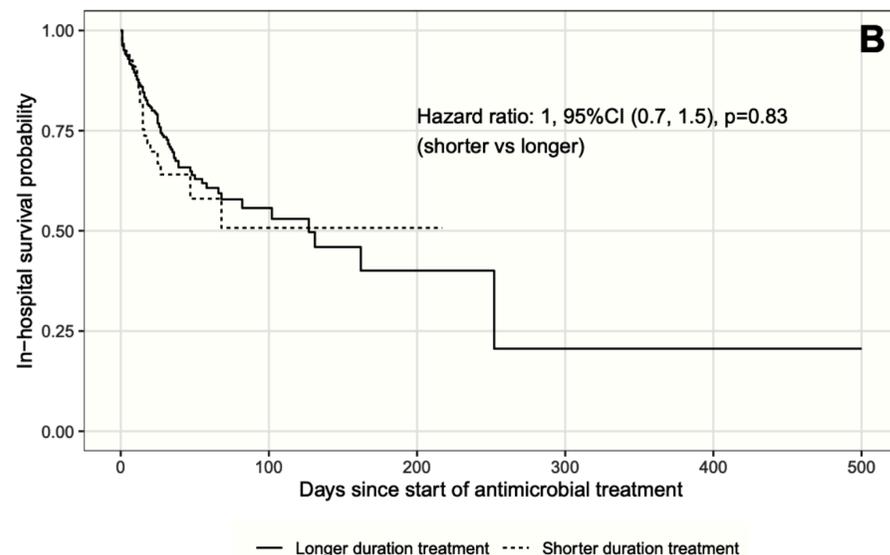
In a propensity-score-weighted cohort of 183 adults with carbapenem-resistant *Enterobacterales* bacteremia at 24 United States hospitals, patients receiving short-courses of active therapy (7-10 days, median 9 days) experienced similar odds of recurrent bacteremia or death within 30 days as those receiving prolonged courses of active therapy (14-21 days, median 14 days)

CONCLUSION
there were no differences with regards to all-cause mortality (3.4% versus 4.6%) or recurrent bacteremia (6.1% versus 5.7%) within 30 days between the short-course and the prolonged-course groups



The effect of duration of antimicrobial treatment for bacteremia in critically ill patients on in-hospital mortality – Retrospective double center analysis

Zuercher P. et al. *J Crit Care* 2023; doi.org/10.1016/j.jcrc.2023.154257



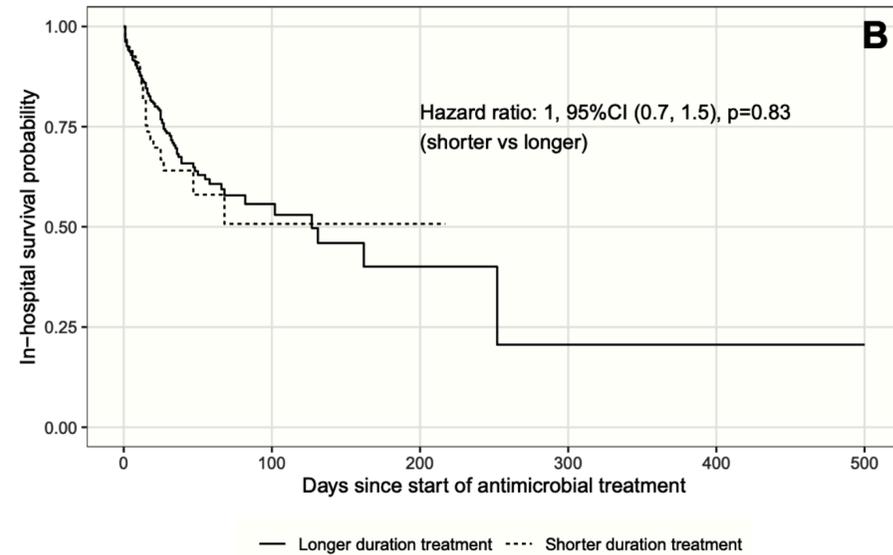
Conclusions: we found no evidence for a survival benefit of longer (>10 days) versus shorter treatment course in ICU patients with bacteremia

Background: the primary outcome of interest was the time from start of antimicrobial treatment to in-hospital death or hospital discharge, whichever comes first. The predictor of interest was adequate antimicrobial treatment duration, further divided into shorter (≤ 10 days) and longer (> 10 days) durations

Results: Out of the 707 patients with positive blood cultures, 382 were included into the primary analysis. Median duration of antibiotic therapy was **14 days** (IQR, 7–20). Most bacteremia (**84%**) were monomicrobial; **18%** of all episodes were primary bacteremia. Respiratory (28%), intra-abdominal (23%) and catheter infections (17%) were the most common sources of secondary bacteremia. Using methods to mitigate the risk of confounding associated with antibiotic treatment durations, shorter versus longer treatment groups showed no differences in in-hospital survival (time-dependent Cox-model: HR 1.5, 95% CI (0.8, 2.7), $p = 0.20$; Cloning approach: HR 1.0, 95% CI (0.7, 1.5) $p = 0.83$). Sensitivity analyses showed that the interpretation did not change when using a 7 days cut-off

The effect of duration of antimicrobial treatment for bacteremia in critically ill patients on in-hospital mortality – Retrospective double center analysis

Zuercher P. et al. *J Crit Care* 2023; doi.org/10.1016/j.jcrc.2023.154257



Reducing antibiotic treatment duration for ventilator-associated pneumonia (REGARD-VAP): a trial protocol for a randomised clinical trial

Mo Y. et al. *BMJ Open* apr 2021

Open access Protocol

BMJ Open Reducing antibiotic treatment duration for ventilator-associated pneumonia (REGARD-VAP): a trial protocol for a randomised clinical trial

Yin Mo^{1,2,3,4} Timothy Eoin West^{5,6} Graeme MacLaren⁷ Suchart Booraphun⁸ Andrew Yunkai Li^{3,4} Gyan Kayastha⁹ Yie Hui Lau¹⁰ Yin Tze Chew¹⁰ Ploenchai Chetchotsakd¹¹ Paul Anantharajah Tambyah^{3,4,12} Direk Limmathrotsakul² Ben Cooper^{1,2}

ABSTRACT
Introduction Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in intensive care units (ICUs). Using short-course antibiotics to treat VAP caused by Gram-negative non-fermenting bacteria has been reported to be associated with excess pneumonia recurrences. The "Reducing Antibiotic Treatment Duration for Ventilator-Associated Pneumonia" (REGARD-VAP) trial aims to provide evidence for using a set of reproducible clinical criteria to shorten antibiotic duration for individualised treatment duration of VAP.
Methods and analysis This is a randomised controlled hierarchical non-inferiority-superiority trial being conducted in ICUs across Nepal, Thailand and Singapore. The primary outcome is a composite endpoint of death and pneumonia recurrence at day 60. Secondary outcomes include ventilator-associated events, multidrug-resistant organism infection or colonisation, total duration of antibiotic exposure, mechanical ventilation and hospitalisation. Adult patients who satisfy the US Centers for Disease Control and Prevention National Healthcare Safety Network VAP diagnostic criteria are enrolled. Participants are assessed daily until fever subsides for >48 hours and have stable blood pressure, then randomised to a short duration treatment strategy or a standard-of-care duration arm. Antibiotics may be stopped as early as day 3 if respiratory cultures are negative, and day 5 if respiratory cultures are positive in the short-course arm. Participants receiving standard-of-care will receive antibiotics for at least 8 days. Study participants are followed for 60 days after enrolment. An estimated 460 patients will be required to achieve 80% power to determine non-inferiority with a margin of 12%. All outcomes are compared by absolute risk differences. The conclusion of non-inferiority, and subsequently superiority, will be based on unadjusted and adjusted analyses in both the intention-to-treat and per-protocol populations.
Ethics and dissemination The study has received approvals from the Oxford Tropical Research Ethics Committee and the respective study sites. Results will be disseminated to patients, their caregivers, physicians, the funders, the critical care societies and other researchers.
Trial registration number NCT03382548.

Strengths and limitations of this study

- ▶ The "Reducing Antibiotic Treatment Duration for Ventilator-Associated Pneumonia" (REGARD-VAP) trial is a randomised controlled hierarchical non-inferiority-superiority trial which compares a short duration treatment strategy versus a standard-of-care duration for ventilator-associated pneumonia (VAP).
- ▶ The short treatment strategy allows for individualisation of antibiotic duration recommendations according to the patients' clinical responses, that is, antibiotics can be stopped after 48 hours of defervescence and stable haemodynamics parameters.
- ▶ The trial will update treatment duration guidelines for VAP predominantly caused by Gram-negative non-fermenting bacilli, which were previously reported to be associated with more frequent recurrences.
- ▶ To overcome the anticipated issue of non-adherence to allocated treatment, which potentially may increase type 1 error and bias the study estimates, multiple analysis approaches will be performed in both intention-to-treat and per-protocol populations including inverse probability weighting.
- ▶ The REGARD-VAP trial excludes patients with concurrent infections from other sources and who are immunocompromised.

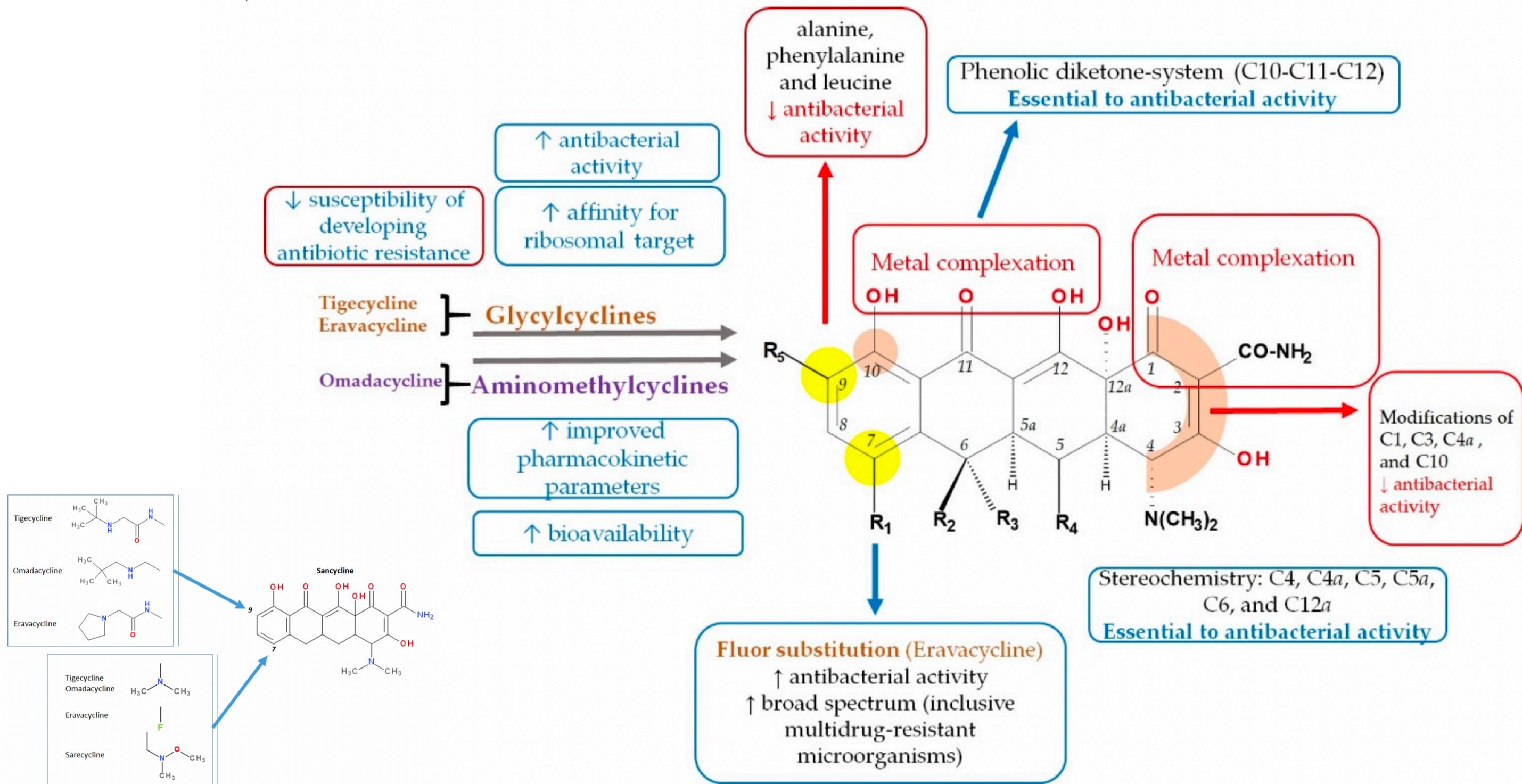
INTRODUCTION
 Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection in patients admitted to the intensive care unit (ICU).¹ Estimates of all-cause mortality in patients with VAP range from 20% to 50%,^{2,3} and can be as high as 94% in low-income and middle-income countries.⁴ Given its high prevalence and frequent association with multidrug-resistant organisms, the treatment of VAP is likely to be a key driver of antimicrobial resistance (AMR) in ICUs.

Participants are assessed daily until fever subsides for >48 hours and have stable blood pressure, then randomised to a **short duration treatment strategy** or a **standard-of-care duration arm**. Antibiotics may be stopped as early as **day 3** if respiratory cultures are negative, and **day 5** if respiratory cultures are positive in the short-course arm. Participants receiving standard-of-care will receive antibiotics for at least 8 days. Study participants are followed for 60 days after enrolment



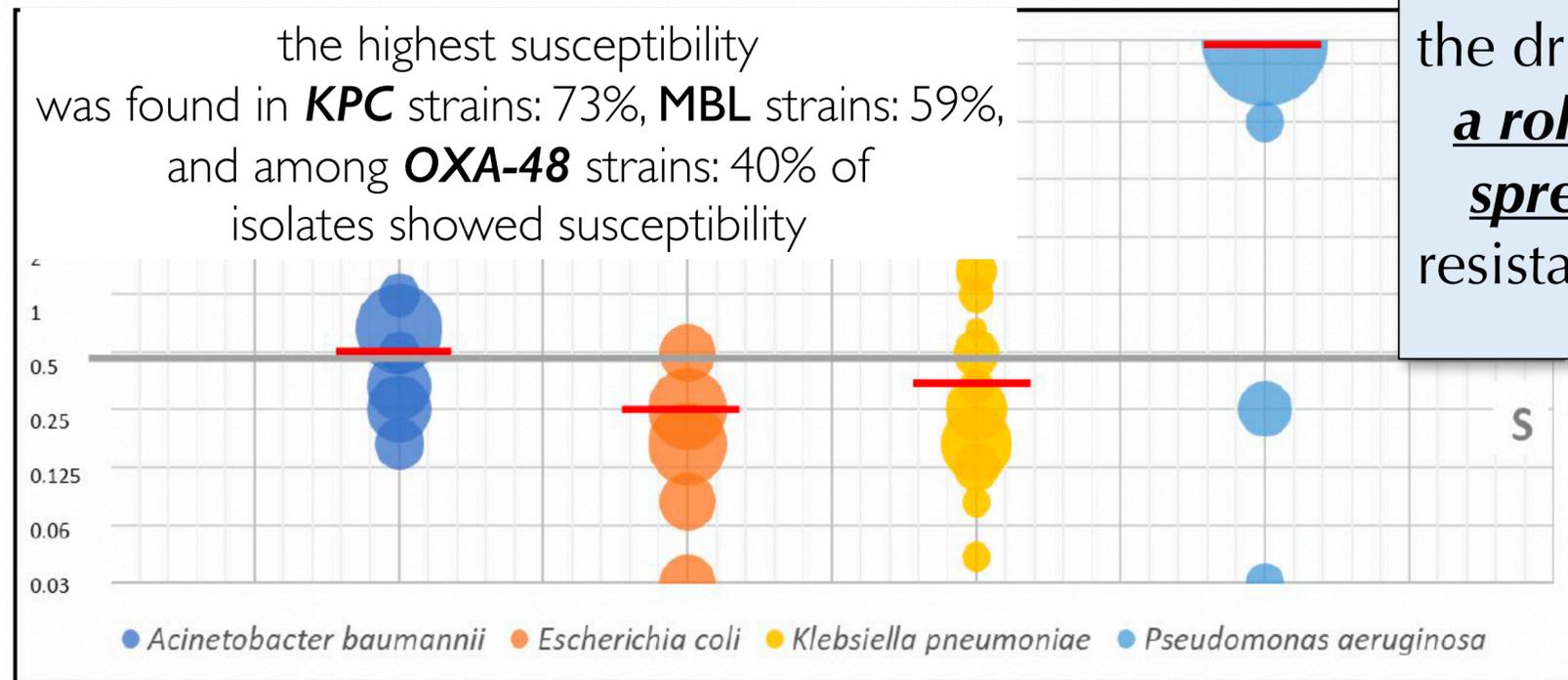
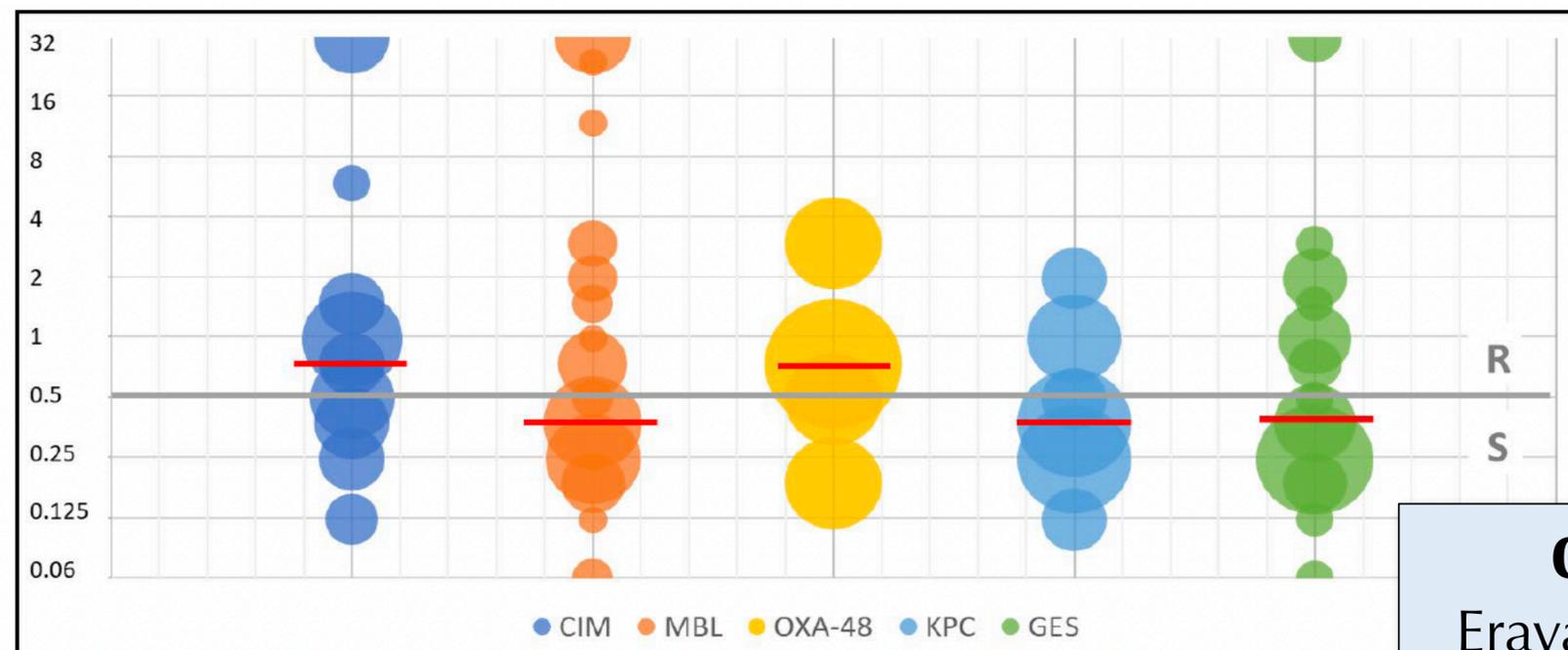
The Development of *Third-Generation Tetracycline Antibiotics* and New Perspectives

Rusu A. et al. *Pharmaceutics* 2021; 13:2085



In Vitro Activity of **Eravacycline** against Carbapenemase-Producing Gram-Negative Bacilli Clinical Isolates in Central Poland

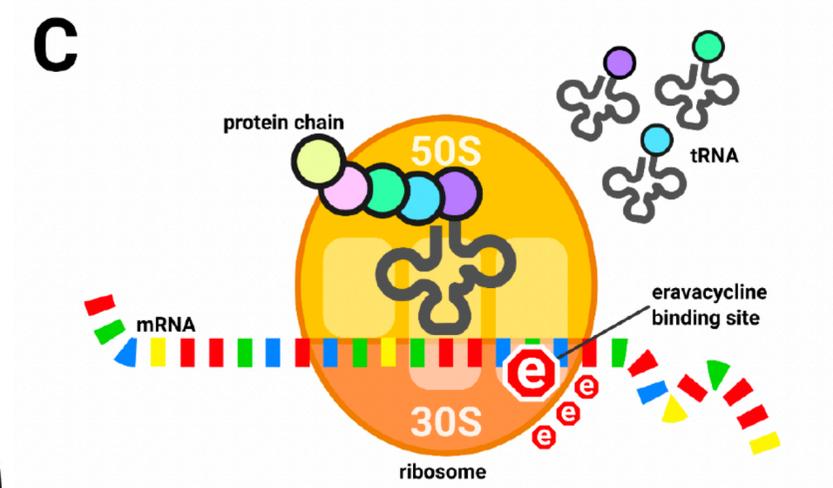
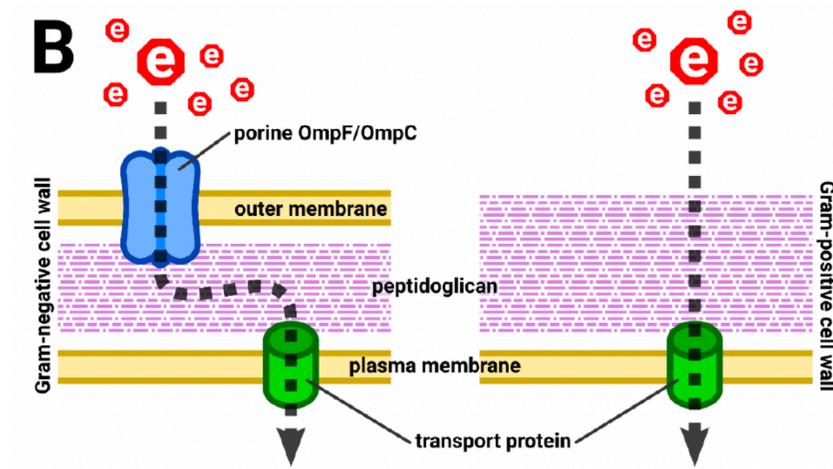
Brauncajs M. et al. *biomedicines* 2023; 11:1784



CONCLUSION
Eravacycline is one of the drugs that ***could play a role in reducing the spread of*** multidrug-resistant microorganisms



We analyzed **102** strains producing **KPC**, **MBL**, **OXA-48**, **GES**, and other carbapenemases. Eravacycline susceptibility was determined following the EUCAST guidelines. The highest susceptibility was found in **KPC (73%)** and **MBL (59%)** strains



inhibits protein synthesis by binding to the 30S subunit of the bacterial ribosome, preventing the amino-acyl tRNA from binding to the acceptor site on the mRNA-ribosome complex

Impact of Acquired Broad Spectrum β -Lactamases on Susceptibility to Novel Combinations Made of β -Lactams (Aztreonam, Cefepime, Meropenem, and Imipenem) and Novel β -Lactamase Inhibitors in *Escherichia coli* and *Pseudomonas aeruginosa*

Le Terrier C. et al. *Antimicrob Agents Chemother* 2023

gene primers - into plasmid pUCp24 that is capable of replicating in both *E. coli* and *P. aeruginosa*  the MICs were determined via broth microdilution

it is worth highlighting that meropenem-nacubactam significantly decreased the MICs of some of the class β -lactamase producers (NDM-1, NDM-7, NDM-9, DIM-1, GIM-1, IMP-1), and this was likely due to the *intrinsic activity of nacubactam*, as previously suggested

As expected, **cefepime-taniborbactam** was active against all of the ESBL and carbapenemase producers, including MBL producers, **EXCEPT** when **IMP-1** and **NDM-9** were produced, and these results are in line with previous observations highlighting the lack of inhibitory activity of taniborbactam against IMP-1 and NDM-9

Meropenem-nacubactam was also effective against most of the recombinant strains, with the **EXCEPTION** of the **MBL** producers, such as those producing **AIM-1**, **NDM-5**, **VIM-1**, **SPM-1**, and **IMP-1**, as expected

In contrast, this combination remained active against producers of class D-lactamases, as the latter enzymes *do not hydrolyze cefepime at a significant level*

As a result, resistance to **cefepime-zidebactam** was observed for the *P. aeruginosa* recombinant strains producing **VEB-1**, **KPC-like**, **NDM-like**, **VIM-like**, **IMP-1**, and **CMY-like** enzymes. A reduced susceptibility was observed among **SHV-1**, **PER-2**, **PER-6**, **PER-7**, and **OXA-23** producers;

Among the newly developed β -lactamase inhibitors, there are diazabicyclooctane (DBO) molecules, namely, **zidebactam** and **nacubactam**, that efficiently inhibit most **class A** and **class C** (also **class D** for **zidebactam**) β -lactamases. **Additionally, they possess an antibiotic effect on PBP2, compared to avibactam.** Another class of inhibitors corresponds to the boronic acid derivatives vaborbactam and **taniborbactam**, both of which inhibit **class A** and **class C** β -lactamases, with taniborbactam additionally being **an excellent inhibitor of the metallo- β -lactamases (MBLs) of most of the NDM- and VIM-types.** Finally, another class of inhibitors corresponds to penicillin-based sulfones, such as **enmetazobactam**, which is a derivative of tazobactam, and it is reported to be **an excellent inhibitor of class A** β -lactamases

Moreover, resistance to **cefepime-enmetazobactam** was observed for many recombinant strains, including those producing β -lactamases of class A (**SHV-1**, **SHV-2a**, **SHV-12**, **PER-1**, **PER-7**, **KPC-2**, **KPC-3**, **KPC-41**), class B (**NDM-type**, **VIM-type**, **SPM-1**, **AIM-1**), class C (**CMY-type**), and class D (**OXA-23**), whereas resistance to **cefepime-taniborbactam** was only observed for those producing β -lactamases of class A (**KPC-41**), class B (**VIM-1**, **AIM-1**, **NDM-type**, **IMP-1**, **SPM-1**), class C (**CMY-2**), and class D (**OXA-1**, **OXA-23**)

Impact of Acquired Broad Spectrum β -Lactamases on Susceptibility to Novel Combinations Made of β -Lactams (Aztreonam, Cefepime, Meropenem, and Imipenem) and Novel β -Lactamase Inhibitors in *Escherichia coli* and *Pseudomonas aeruginosa*

Le Terrier C. et al. *Antimicrob Agents Chemother* 2023

gene primers - into plasmid pUCp24 that is capable of replicating in both *E. coli* and *P. aeruginosa*  the MICs were determined via broth microdilution

Among the class A β -lactamase-producing *P. aeruginosa* strains, ***imipenem-relebactam***, cefepime-taniborbactam, and meropenem-nacubactam appeared to be the best options, whereas aztreonam and aztreonam-avibactam remained the best options against the class β producer

IMPORTANT MESSAGE

Therefore, our results highlight that the continuous spread of class β -lactamases (NDM, IMP, and VIM) and, more rarely, KPC-type enzymes in *P. aeruginosa* ***may still be considered a significant source of concern*** when considering treatment with newly available therapeutics

As expected, ***cefepime-taniborbactam*** was active against all of the ESBL and carbapenemase producers, including MBL producers, **EXCEPT** when ***IMP-1*** and ***NDM-9*** were produced, and these results are in line with previous observations highlighting the lack of inhibitory activity of taniborbactam against IMP-1 and NDM-9

it is worth highlighting that meropenem-nacubactam significantly decreased the MICs of some of the class β -lactamase producers (NDM-1, NDM-7, NDM-9, DIM-1, GIM-1, IMP-1), and this was likely due to the ***intrinsic activity of nacubactam***, as previously suggested

Meropenem-nacubactam was also effective against most of the recombinant strains, with the **EXCEPTION** of the ***MBL*** producers, such as those producing ***AIM-1***, ***NDM-5***, ***VIM-1***, ***SPM-1***, and ***IMP-1***, as expected

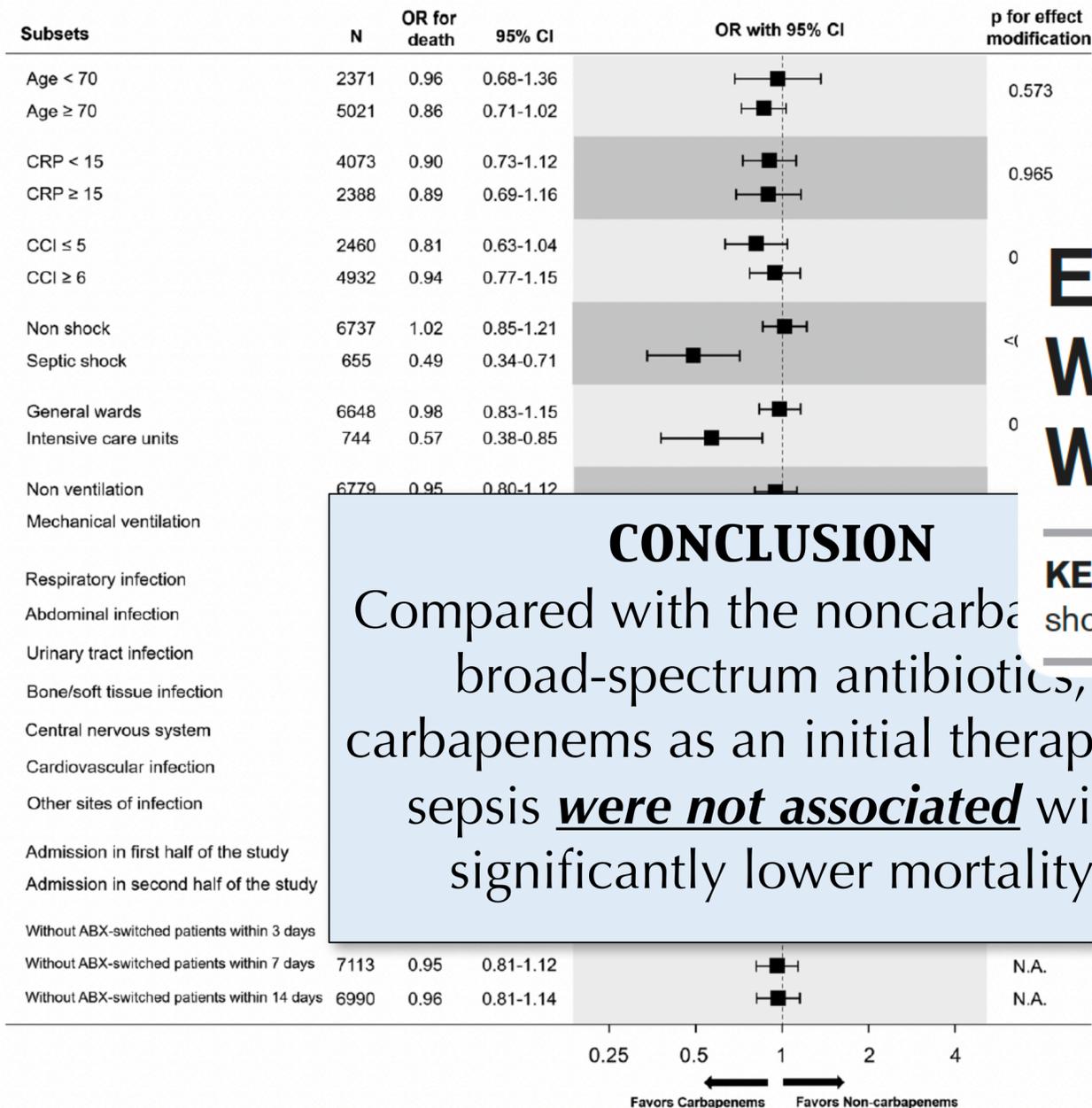
In contrast, this combination remained active against producers of class D-lactamases, as the latter enzymes ***do not hydrolyze cefepime at a significant level***

As a result, resistance to ***cefepime-zidebactam*** was observed for the *P. aeruginosa* recombinant strains producing ***VEB-1***, ***KPC-like***, ***NDM-like***, ***VIM-like***, ***IMP-1***, and ***CMY-like*** enzymes. A reduced susceptibility was observed among ***SHV-1***, ***PER-2***, ***PER-6***, ***PER-7***, and ***OXA-23*** producers;

Moreover, resistance to ***cefepime-enmetazobactam*** was observed for many recombinant strains, including those producing β -lactamases of class A (***SHV-1***, ***SHV-2a***, ***SHV-12***, ***PER-1***, ***PER-7***, ***KPC-2***, ***KPC-3***, ***KPC-41***), class B (***NDM-type***, ***VIM-type***, ***SPM-1***, ***AIM-1***), class C (***CMY-type***), and class D (***OXA-23***), whereas resistance to ***cefepime taniborbactam*** was only observed for those producing β -lactamases of class A (***KPC-41***), class B (***VIM-1***, ***AIM-1***, ***NDM-type***, ***IMP-1***, ***SPM-1***), class C (***CMY-2***), and class D (***OXA-1***, ***OXA-23***)

Efficacy of Carbapenems Compared With Noncarbapenem Broad-Spectrum Beta-Lactam Antibiotics as Initial Antibiotic Therapy Against Sepsis: A Nationwide Observational Study

Umemura Y. et al. *Crit Care Med* 2023; 51(9):1210-1221



CONCLUSION
 Compared with the noncarbapenem broad-spectrum antibiotics, carbapenems as an initial therapy for sepsis ***were not associated*** with significantly lower mortality

MEASUREMENTS AND MAIN RESULTS: this study used data of adult patients with sepsis extracted from a large-scale database in Japan. Patients were divided ***into two groups*** as follows: patients receiving carbapenems and patients receiving noncarbapenem broad-spectrum beta-lactam antibiotics as initial treatment. In-hospital mortality was compared between the groups by a logistic regression model adjusted by an inverse probability treatment weighting using propensity scores. Among 7,392 patients with sepsis, 3,547 patients received carbapenems, and 3,845 patients received noncarbapenem agents. The logistic model showed ***no significant association between carbapenem therapy***

Empiric Carbapenem Therapy for Sepsis: Are We Winning the Battle at the Expense of the War?*

Jeffrey F. Barletta, PharmD, FCCM

KEY WORDS: anti-bacterial agents; beta-lactams; carbapenems; sepsis; septic shock

Rapid diagnostic tests allow for timely modification of antimicrobial regimens, either toward expanding coverage (in the event of a resistant organism) or in streamlining therapy to a medication with a narrower spectrum

carbapenems and four cephalosporins, between meropenem and tazobactam/piperacillin, and between meropenem and a fourth-generation cephalosporin.



THANKS

bruno.viaggi@gmail.com