Imipenem/relebactam

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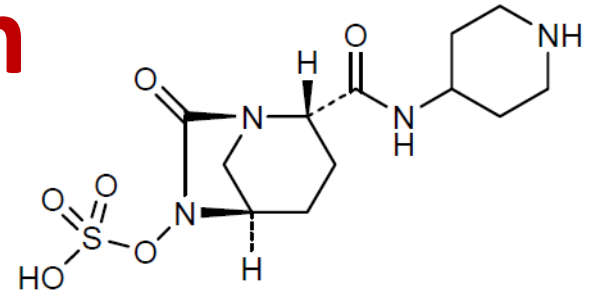
Conflicts of interest

- Grants from Pfizer, Shionogi and MSD as a speaker
- Grants from MSD as an advisory board member
- Grant from Pfizer for a research project

Imipenem/Relebactam



- Relebactam (REL) is a b-lactamase inhibitor that was designed to have **inhibitory activity against class A and C b-lactamases**.

- REL is not active against MBL and class D β-lactamases (OXA-48) and does not restore IMI susceptibility in *Acinetobacter baumannii* strains

- IMI/REL activity against *P. aeruginosa* is due also to the effect on **porin loss, efflux pumps as well as Pseudomonas-derived cephalosporinase**

In vitro activity of imipenem/relebactam against Gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme

Karlovsky JA et al. J Antimicrob Chemother 2018; 73: 1872–1879

In vitro activity of imipenem/relebactam against Gram-negative ESKAPE pathogens

Organism	Antimicrobial agent	MIC50 (mg/L)	MIC90 (mg/L)	MIC range	Susceptible (%)
P. aeruginosa (1705)	IMI-REL[a] IMI	0.25 1	2 16	≤0.03 to >32 ≤0.5 to >32	**94.7** **72**
IMI-non susceptible *P. aeruginosa* (477)	IMI-REL IMI	2 16	32 32	0.25 to >32 8 to >32	**81.1** **0**
K. *pneumoniae* (1591)	IMI-REL IMI	0.12 ≤0.5	1 4	≤0.03 to >32 ≤0.5 to >32	**94.8** **88.7**
IMI-non susceptible *K. pneumoniae* (179)	IMI-REL IMI	2 16	>32 >32	0.06 to >32 4 to >32	**54.2** **0**
A. baumannii (n=486)	IMI-REL IMI	32 32	>32 >32	0.12 to >32 ≤0.5 to >32	**10.3** **10.1**
IMI-non susceptible *A.baumannii* (n=437)	IMI-REL IMI	>32 32	>32 >32	0.5 to >32 4 to >32	**0.2** **0**

[a]For comparative purposes only, MICs of imipenem/relebactam were interpreted using imipenem EUCAST breakpoints

Imipenem-Relebactam Susceptibility in Enterobacterales Isolates Recovered from ICU Patients from Spain and Portugal (SUPERIOR and STEP Studies)

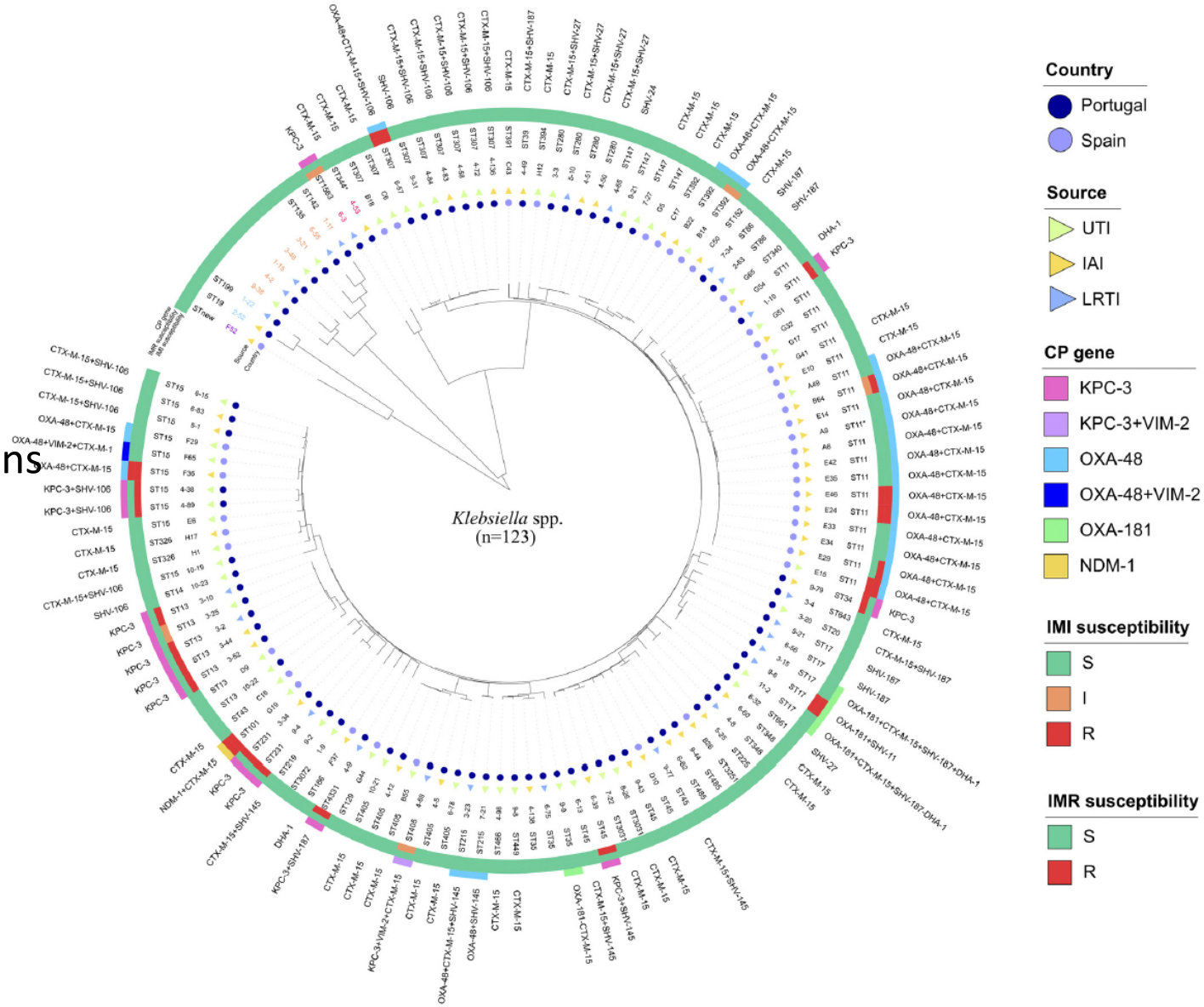
Henandez Garcia M et al. Microbiology Spectrum Oct 2022

- 747 Enterobacterales isolates
  - 378 *Escherichia coli*
  - 252 *Klebsiella* spp.
  - 64 *Enterobacter* spp.

- Imipenem-relebactam **98.7% susceptible**
  - **80.4% in CPE *K. pneumoniae***

- Imipenem-relebactam inactive against 10 strains
  - 9 *K. pneumoniae*
  - 1 *E. cloacae*

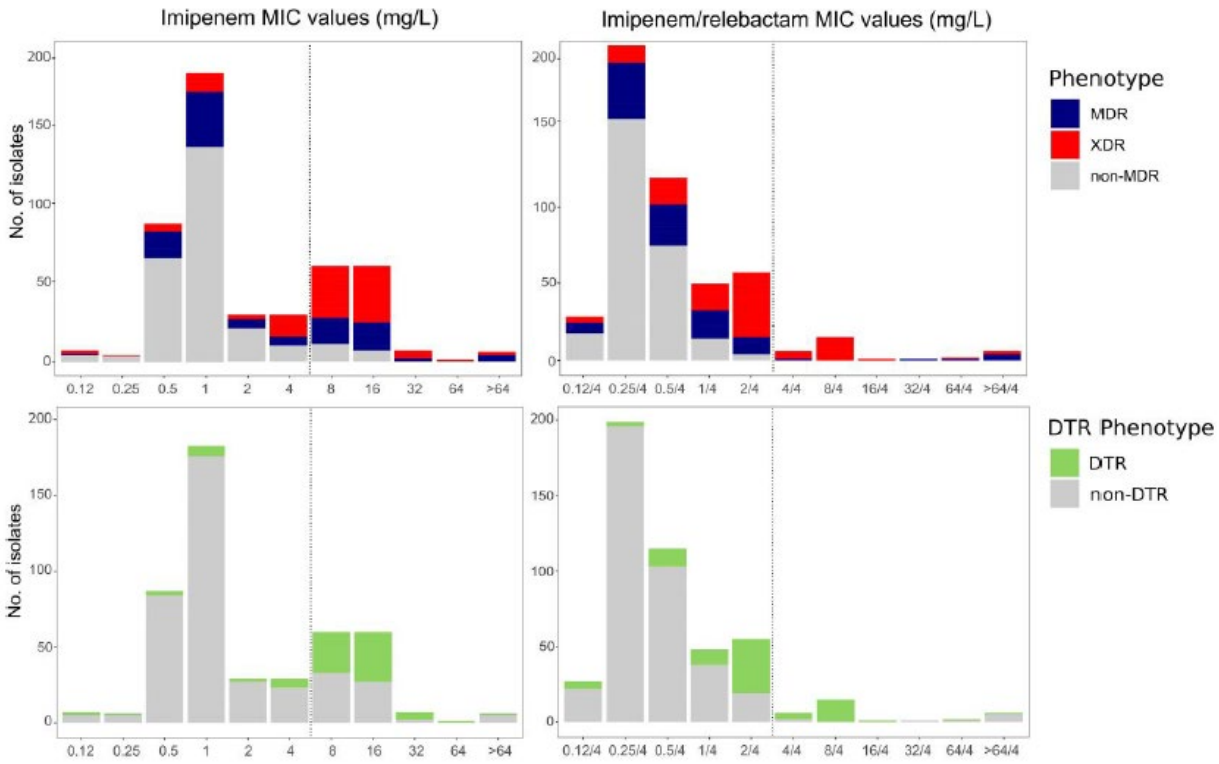
- 123 sequenced *K. pneumoniae*
  - 41 CPE
    - ✓ OXA-48 48.8%
    - ✓ KPC-3 34.1%
    - ✓ OXA-181 7.3%
    - ✓ NDM-1 2.4%



In vitro activity of imipenem/relebactam against *Pseudomonas aeruginosa* isolates recovered from ICU patients in Spain and Portugal (SUPERIOR and STEP studies)

Henandez Garcia M et al. J Antimicrob Chemother 2022; 77: 3163–3172

- *P. aeruginosa* isolates (n = 474) recovered from cUTI, cIAI and LRTI in 11 Portuguese and 8 Spanish ICUs
- Susceptibility to imipenem/relebactam 93.7%, ceftazidime/avibactam 93.5% and ceftolozane/tazobactam 93.2% was comparable
- Imipenem/relebactam **was inactive against all GES-13 producers and most of VIM producers (8/10)**
- Mutations in genes affecting porin inactivation, efflux pump overexpression and LPS modification might also be involved in imipenem/relebactam resistance

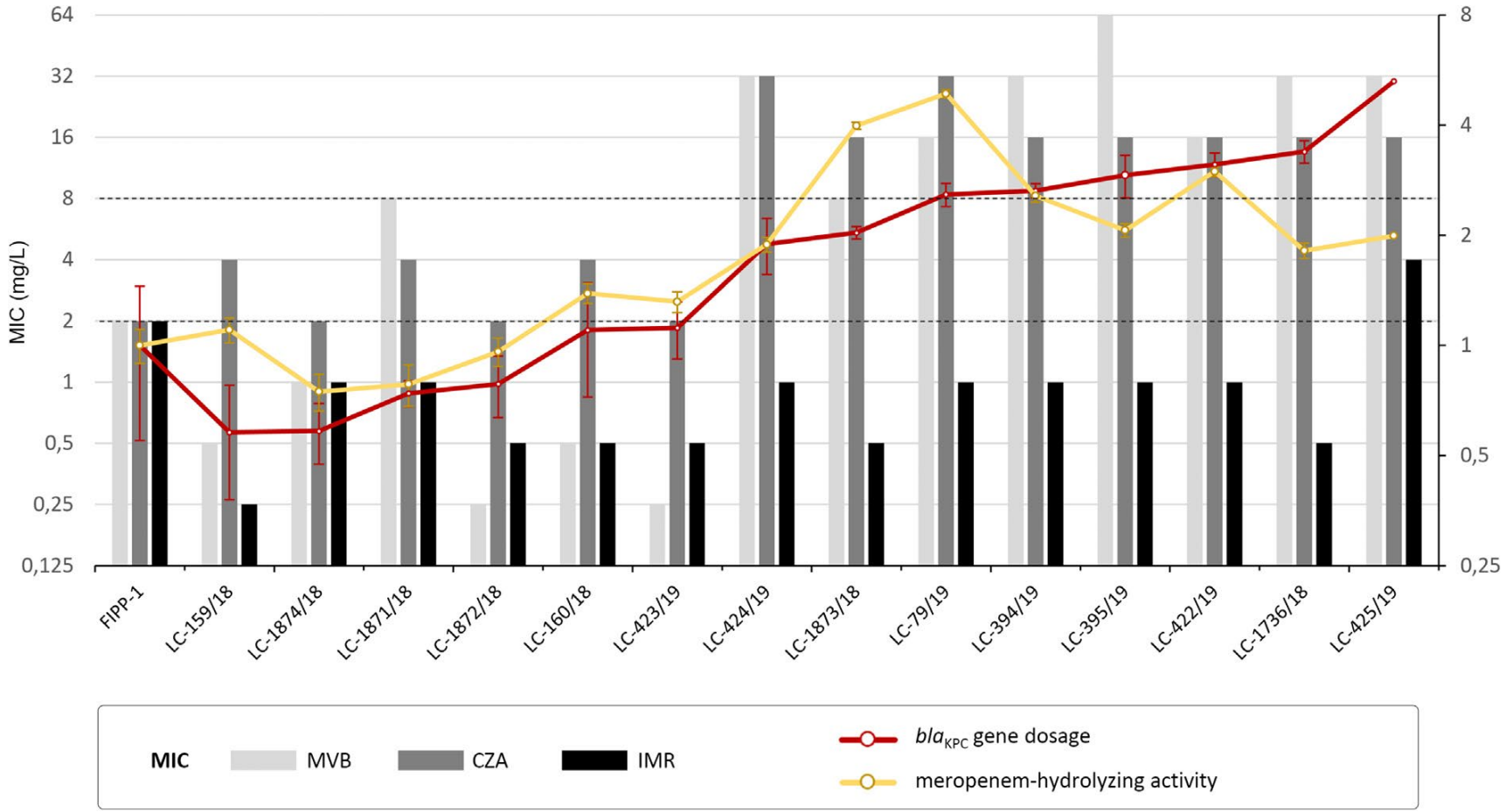


- Among strains resistant to ceftazidime/avibactam (31/474), ceftolozane/tazobactam (32/474) or both (14/474), the activity of imipenem/relebactam was 64.5% (20/31), 28.1% (9/32) and 35.7% (5/14)

Deciphering variable resistance to novel carbapenem-based b-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

- 15 KPC-Kp strains (9 CZA-R, 6 CZA-S) from an outbreak involving 6 patients in a neurorehabilitation facility



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Increased *bla*$_{KPC}$ Copy Number and OmpK35 and OmpK36 Porins Disruption Mediated Resistance to Imipenem/Relebactam and Meropenem/Vaborbactam in a KPC-Producing *Klebsiella pneumoniae* Clinical Isolate

Gaibani P et al. AAC 2022

	ST	Antimicrobial resistance determinants		Porins			bla$_{KPC}$ copy no.
		Beta-lactam	Aminoglycosides	ompK35	ompK36	Plasmid_replicons (InC)	
KPC-KP_TO1	512	bla$_{KPC-3}$, bla$_{TEM1A}$, bla$_{OXA-9}$	aadA2b, aac(6')-Ib-cr	Truncated at aa 41	GD insertion at aa 134-135	ColRNAI, IncFIB (pQIL), IncFII(K)	1
KPC-KP_TO3	512	bla$_{KPC-66}$, bla$_{TEM1A}$, bla$_{OXA-9}$	aadA2b, aac(6')-Ib-cr	Truncated at aa 41	GD insertion at aa 134-135	ColRNAI, IncFIB (pQIL), IncFII(K)	0,85
KPC-KP_TO5	**512**	**bla$_{KPC-3}$, bla$_{TEM1A}$, bla$_{OXA-9}$**	**aadA2b, aac(6')-Ib-cr**	**Truncated at aa 41**	**Truncated at aa 310**	**ColRNAI, IncFIB (pQIL), IncFII(K)**	**4,59**

CAZAVI, MIC 8
MER/VAB, MIC **≥256**
IMI/REL, MIC 8

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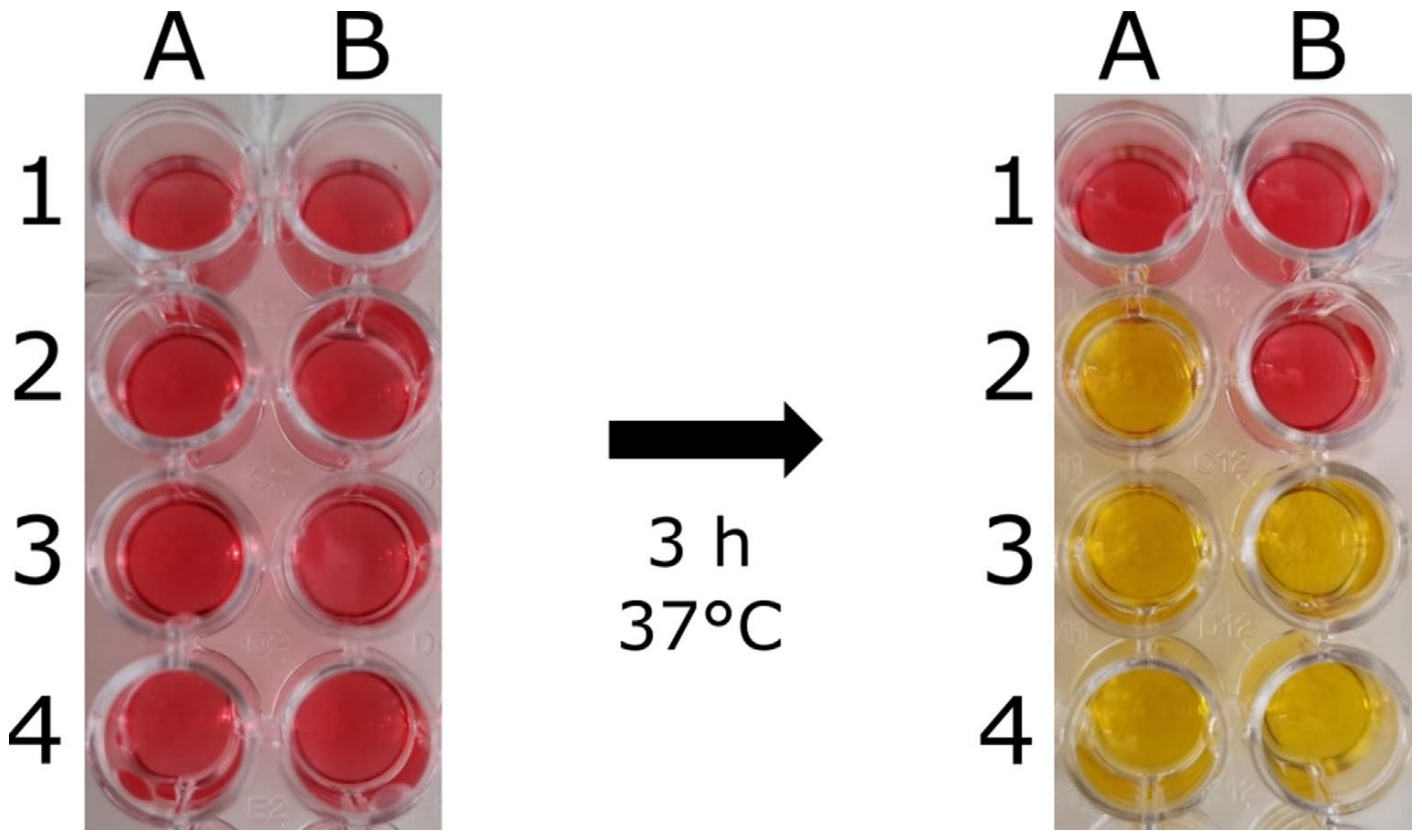
Rapid detection of imipenem/relebactam susceptibility/resistance in Enterobacterales

Bouvier M et al. Clin Microbiol Infect 2023

- 94 Enterobacterales including KPC, NDM, VIM-1, OXA, OXA and NDM co-producers, IMI-1, CTX-M-1, and a negative control without b-lactamase
- 44.7% (42/ 94) were resistant to IPR and 55.3% (52/94) were susceptible (BMD/EUCAST)
- All 52 IPR-susceptible strains were also negative for the Rapid test
- 40/42 IPR-resistant strains were correctly detected as positive by the Rapid IPR NP test. 2 FN OXA-48 MIC 8



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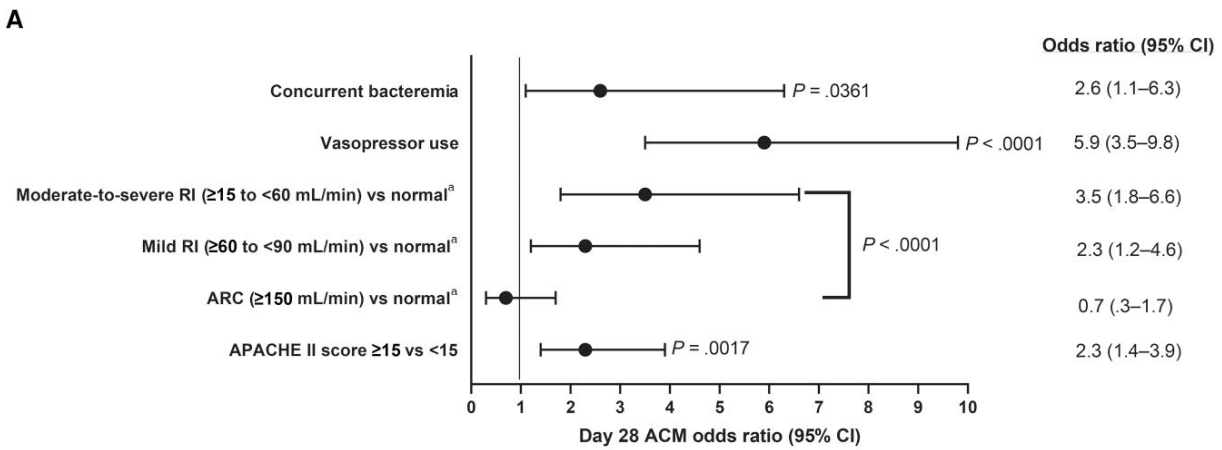
Imipenem-relebactam: clinical trials

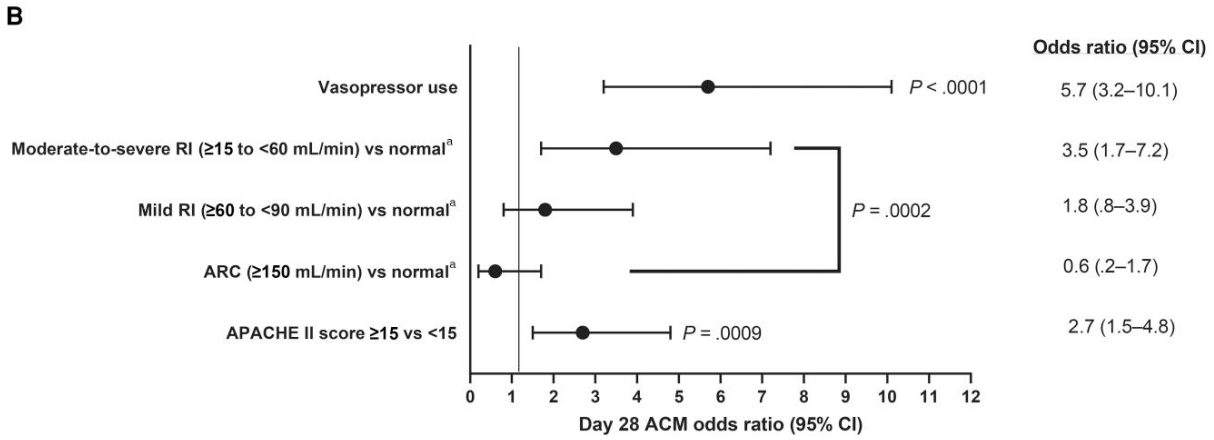
	DISEASE	DESIGN
MK-7655A Protocol 003-004 (phase II)	Complicated UTIs Complicated IAIs	Non inferiority vs IMI
RESTORE-IMI 1 study	IMI-R bacterial infections	Non inferiority vs IMI+COL
RESTORE-IMI 2 study	HAP including VAP	Non inferiority vs TZP

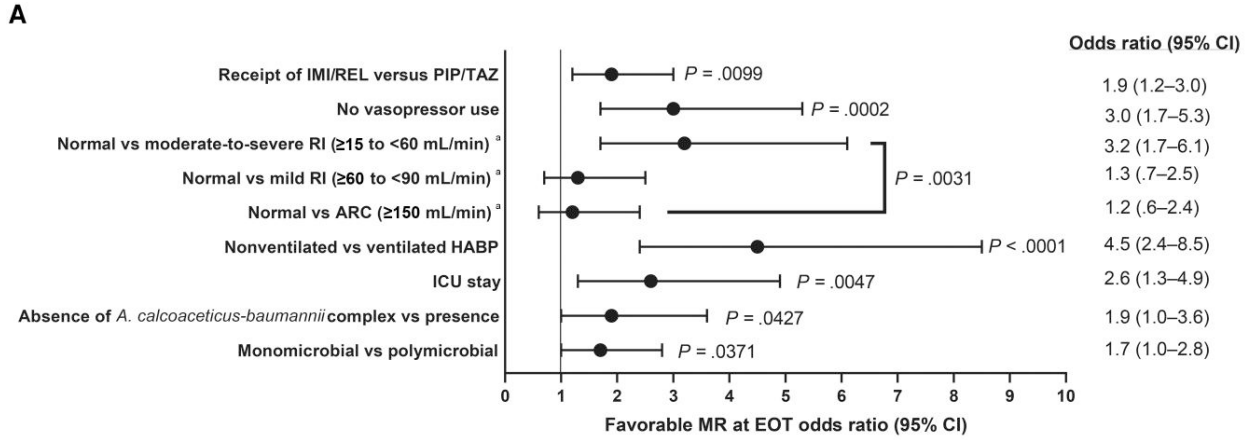
Sims M et al. J Antimicrob Chemother 2017; 72: 2616–2626
Antimicrob Agents Chemother.
2016;60(10):6234–43
Motsch J et al. . Clin Infect Dis 2020;70(9):1799–808
Titov I et al. Clin Infect Dis. 2020

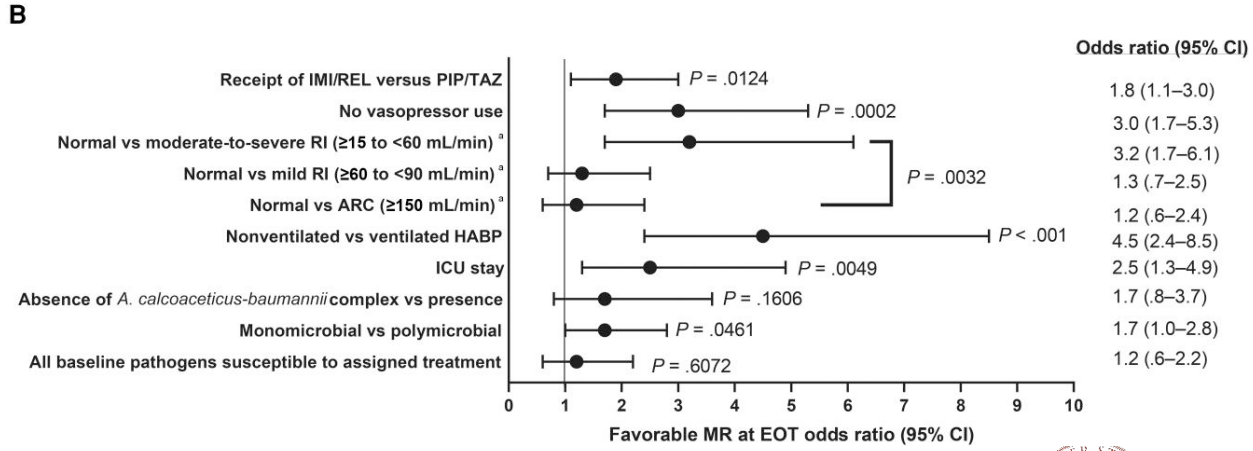
Participant- and Disease-Related Factors as Independent Predictors of Treatment Outcomes in the RESTORE-IMI 2 Clinical Trial: A Multivariable Regression Analysis

Martin-Loeches I et al. OFID 2023









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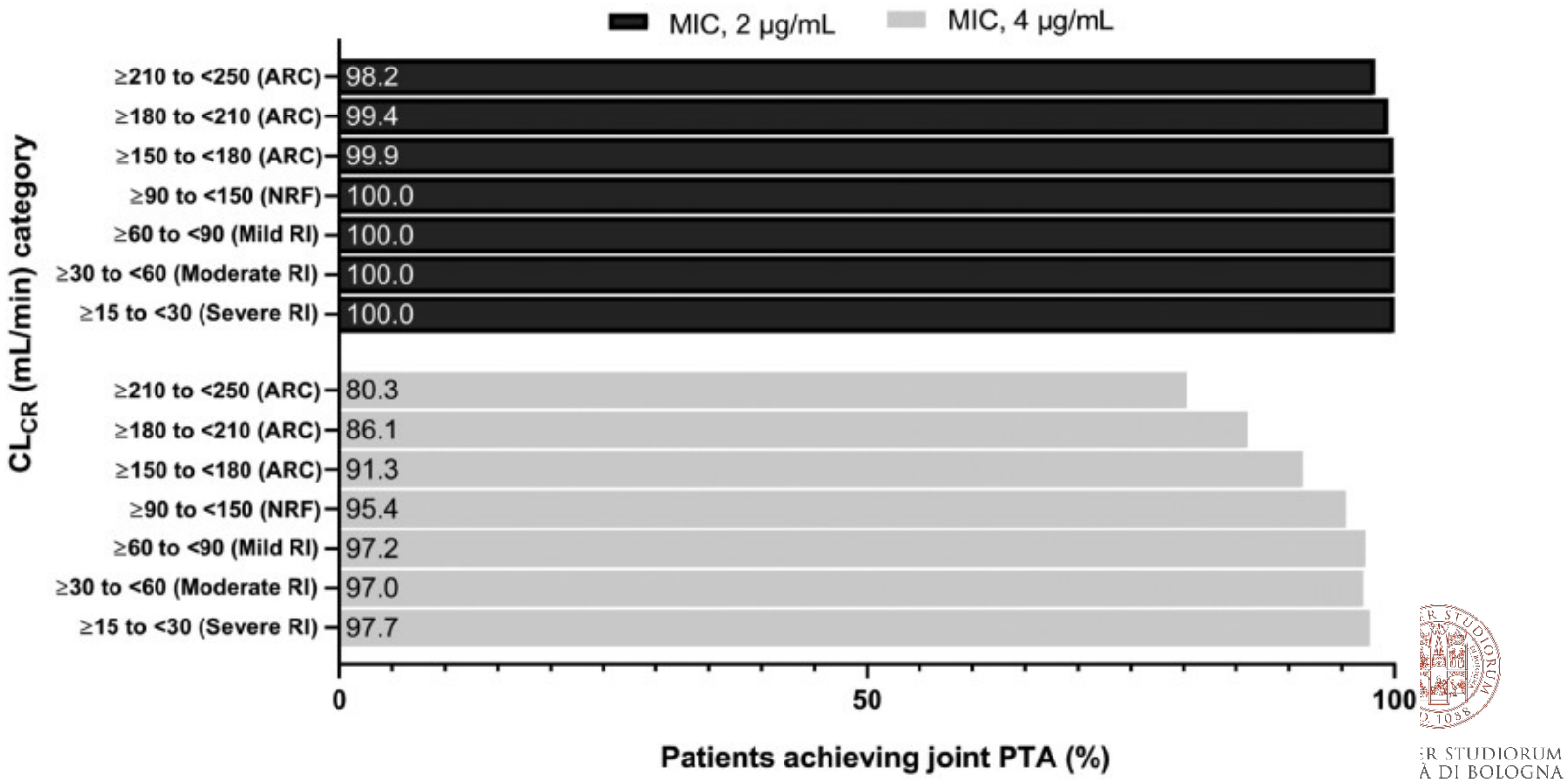
Imipenem/cilastatin/relebactam efficacy, safety and probability of target attainment in adults with hospital-acquired or ventilator-associated bacterial pneumonia among patients with baseline renal impairment, normal renal function, and augmented renal clearance

Roberts JA et al. JAC AMR 2023

CL_{CR} (mL/min)	IMI/REL dosing, q6h
≥15 to <30	0.5 g (200/200/100 mg)
≥30 to <60	0.75 g (300/300/150 mg)
≥60 to <90	1.0 g (400/400/200 mg)
≥90	1.25 g (500/500/250 mg)

- Targets for joint PTA evaluation were 40% $fT_{>MIC}$ for imipenem and fAUC/MIC = 8.0 for relebactam at steady state, which is associated with a 2-log kill in preclinical models



Early Multicenter Experience With Imipenem-Cilastatin-Relebactam for Multidrug-Resistant Gram-Negative Infections

Rebold N et al. Open Forum Infect Dis 2021;8:ofab554

- Twenty-one patients: median age 65 (IQR 48–75) years, 57% male
  - median CCI 4.0 (IQR 2.5–6.0)
  - 76% were admitted to ICU, median APACHE II 21.5 (13.0–28.0)
  - 67% received a renally adjusted dose of I-R due to AKI

- HAP and VAP (11/21, 52%), UTIs (3/21, 14%), and invasive prosthetic device (IPD) infections (3/21, 14%)

- *Pseudomonas aeruginosa* (16/21, 76%), *Klebsiella pneumoniae* (3/21, 14%), and *Proteus mirabilis* (3/21, 14%)
  - 3/8 patients with Enterobacterales having a CRE infection
  - nearly all (15/16, 94%) P. aeruginosa cases were MDR

- I-R was used for **polymicrobial bacterial infection 29%** of the time

- Only 52% of cases had I-R MICs performed primarily by Etest, MIC range of 0.125/4 to ≥32/4, where 8/11 or 73% were susceptible

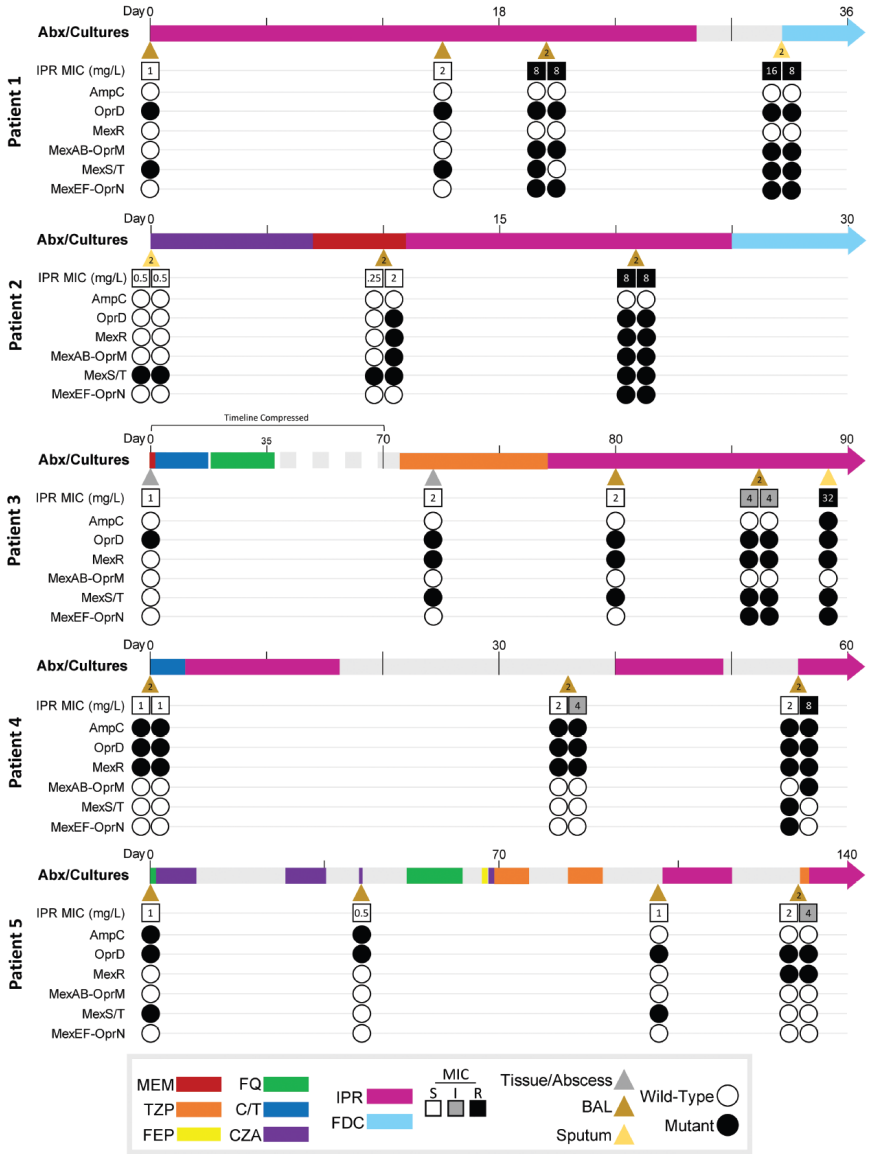
- I-R was used as combination therapy 29% (tobramycin 67%)

Early Multicenter Experience With Imipenem-Cilastatin-Relebactam for Multidrug-Resistant Gram-Negative Infections

Rebold N et al. Open Forum Infect Dis 2021;8:ofab554

- 30-day mortality occurred in 7/21 (33%) patients
- 7-day clinical cure occurred in 13/21 (62%) patients
- Non-susceptibility to I-R developed on treatment in only 1 case (1/21, 5%)
- Microbiological recurrence occurred in 5/21 (24%) patients
  - In 2 subsequent isolates showed increased I-R MICs relative to the index cultures

Evolution of Imipenem-Relebactam Resistance Following Treatment of Multidrug-Resistant Pseudomonas aeruginosa Pneumonia



Shields R et al. Clin Infect Dis 2022;75:710-714

- 19 patients treated with imipenem-relebactam for MDR P. aeruginosa infections
- Imipenem-relebactam nonsusceptible isolates were recovered from 26% (5/19) patients with HAP/VAP
- All had failed prior antibiotic regimens, including 2 with treatment emergent resistance to ceftolozane-tazobactam
- No patient received concomitant intravenous antibiotics with imipenem-relebactam
- **Imipenem-relebactam nonsusceptibility coincided with the emergence of mutations in efflux operons in all cases**

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Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. aeruginosa)

Tamma P et al. Clin Infect Dis. 2022 Apr 19:ciac268

	UTI	cUTI	non-UTI	Notes
ESBL	Nitrofurantoin TMP-SMX	ERTA, MEM, IMP FQs, TMP-SMX	CARBAPENEM	If BL/BLI was initiated as empiric therapy for UTI with clinical improvement no change is necessary
CRE-**KPC**	FQs, TMP-SMX, single dose AG, HD MEM (or new drugs)	FQs, TMP-SMX, single dose AG, HD MEM (or new drugs)	CAZ-AVI, MEM-VAB, **IMP-REL**	
DTR *P. aeruginosa*	TOL/TZB, CAZ/AVI, **IMP/REL**, CFD	TOL/TZB, CAZ/AVI, **IMP/REL**, CFD	TOL/TZB, CAZ/AVI, **IMP/REL**	If strain is susceptible to multiple traditional beta-lactams or FQs carbapenem-sparing options are preferred

Conclusions

- Optimal place in therapy for IMI-REL should be defined
- Prompt availability of the phenotypic pattern of susceptibility to IMI-REL for both KPC-producing Enterobacterales and DTR-P. aeruginosa strains is pivotal
- Patient setting: KPC carrier at high risk for DTR P. aeruginosa infection
- Infection type: cIAI, polymicrobial HAP/VAP