Schemi di terapia delle infezioni da Gram-negativi con focus sulle carbapenemasi

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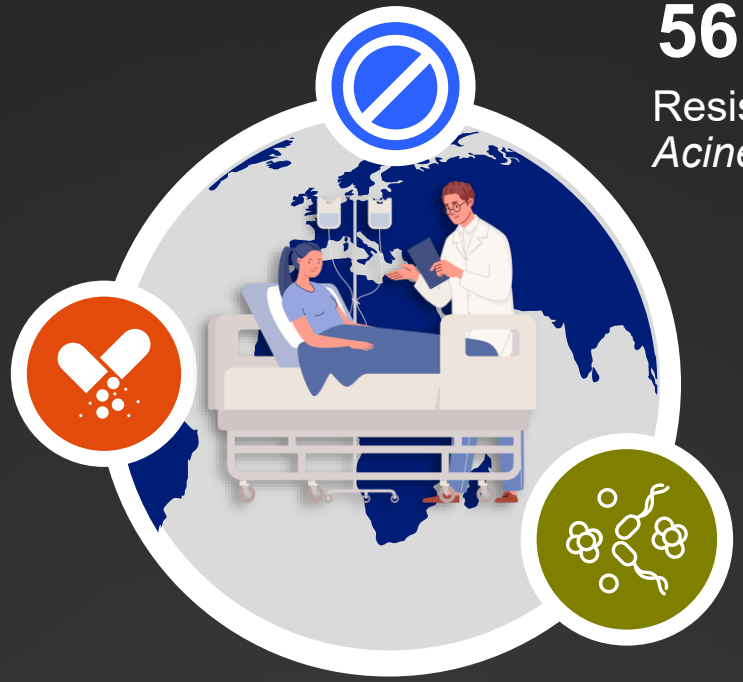
Disclosures (past 2 years)

- Advisor/consultant/speaker bureau
  - Adavanz, Angelini, Biomerieux, Cidara, Gilead, Menarini, Medscape, Mundipharma, MSD, Pfizer, Shionogi

Antimicrobial resistance is a globally unfolding crisis that every healthcare professional can act upon to avert

46%

Global increase in consumption of prescribed antibiotics between 2000 and 2018[1]



56%+*

Resistance in key pathogens: *Acinetobacter spp.* and *Klebsiella spp.*[2]

4.95 million

Deaths globally in 2019 associated with bacterial AMR[3]

AMR, antimicrobial resistance.

1. Browne AJ, et al. *Lancet Planet Health*. 2021;5(12):e893-e904.
2. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2022. 2022. https://www.who.int/publications/i/item/9789240062702;
3. Antimicrobial Resistance Collaborators. *Lancet*. 2022;399(10325):629-655.

* Data from the 2022 GLASS report covering 87 CTAs shows a global resistance rate of ≥56% in *Acinetobacter* spp. to carbapenem and aminoglycosides, and ≥57% in *Klebsiella pneumoniae* to third- and fourth-generation cephalosporins. This data accounts for varying testing coverage across different regions.

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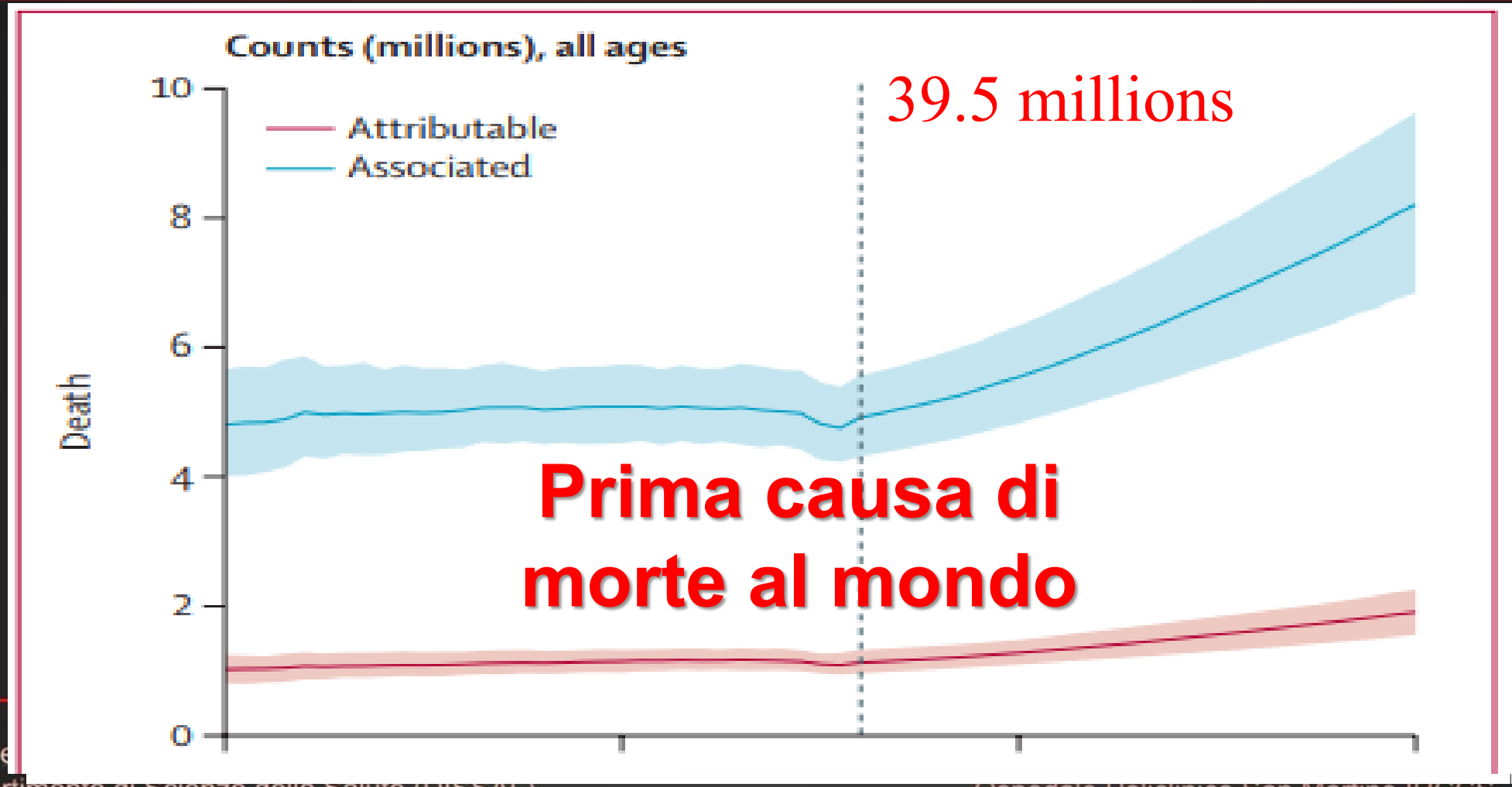
AMR Without intervention…..by 2050



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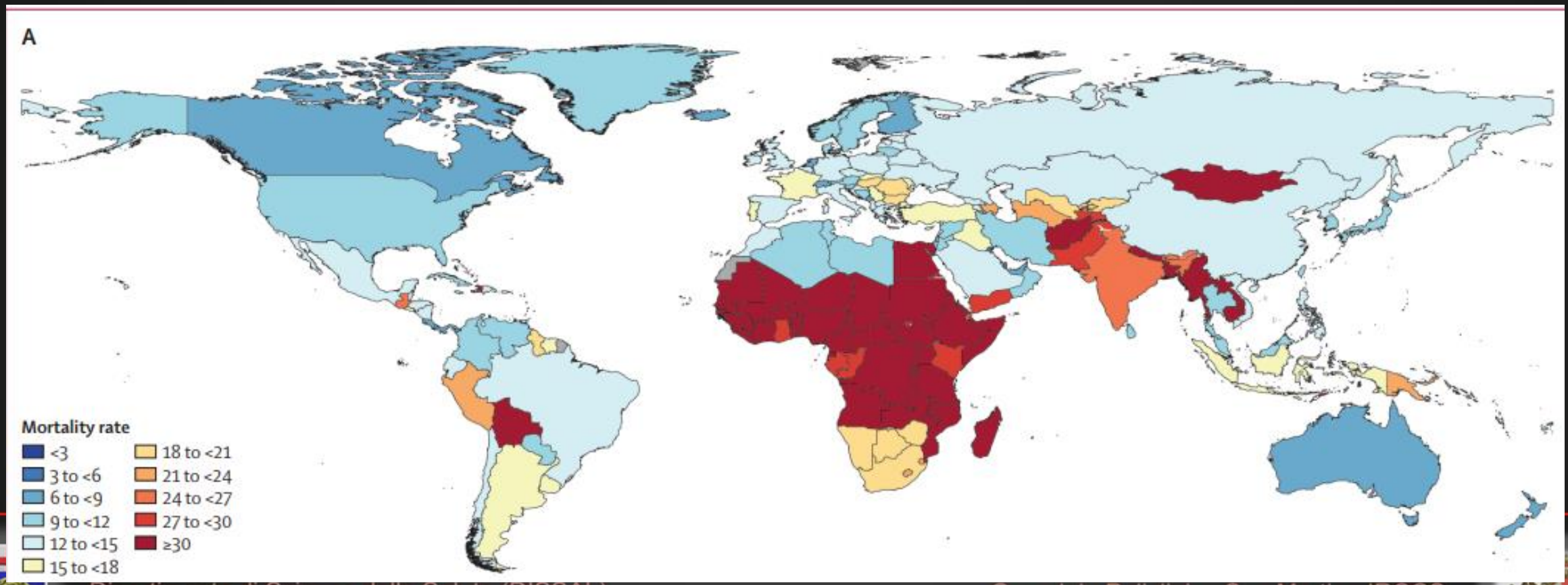
Bassetti M et al. *Intensive Care Med.* 2017 Jul 21. doi: 10.1007/s00134-017-4878-x

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet; Sept. 2024

Death rates per 100000 attributable to AMR, all ages, 1990, 2021, 2050

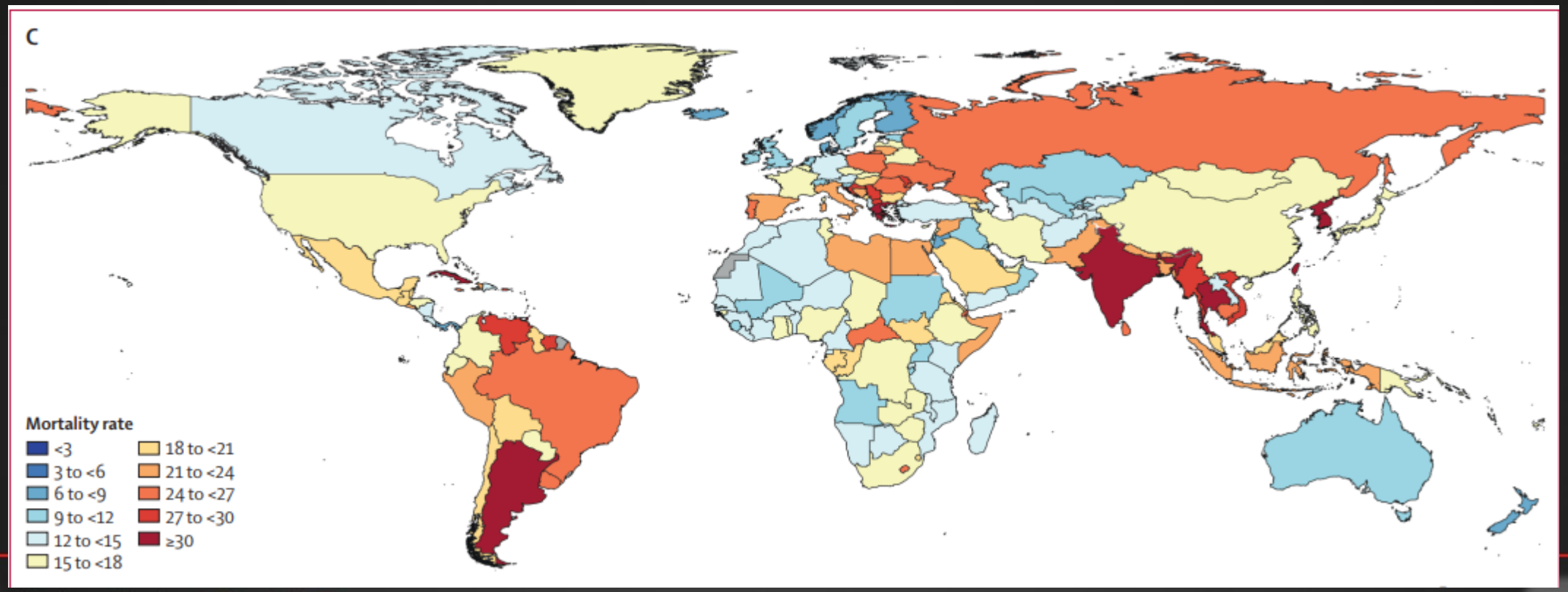
1990



Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet, Sept. 2024

Death rates per 100000 attributable to AMR, all ages, 1990, 2021, 2050

2050



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Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet, Sept. 2024

Gram-negative bacteria possess multiple modes of antibiotic resistance, including β-lactamases[1,2]

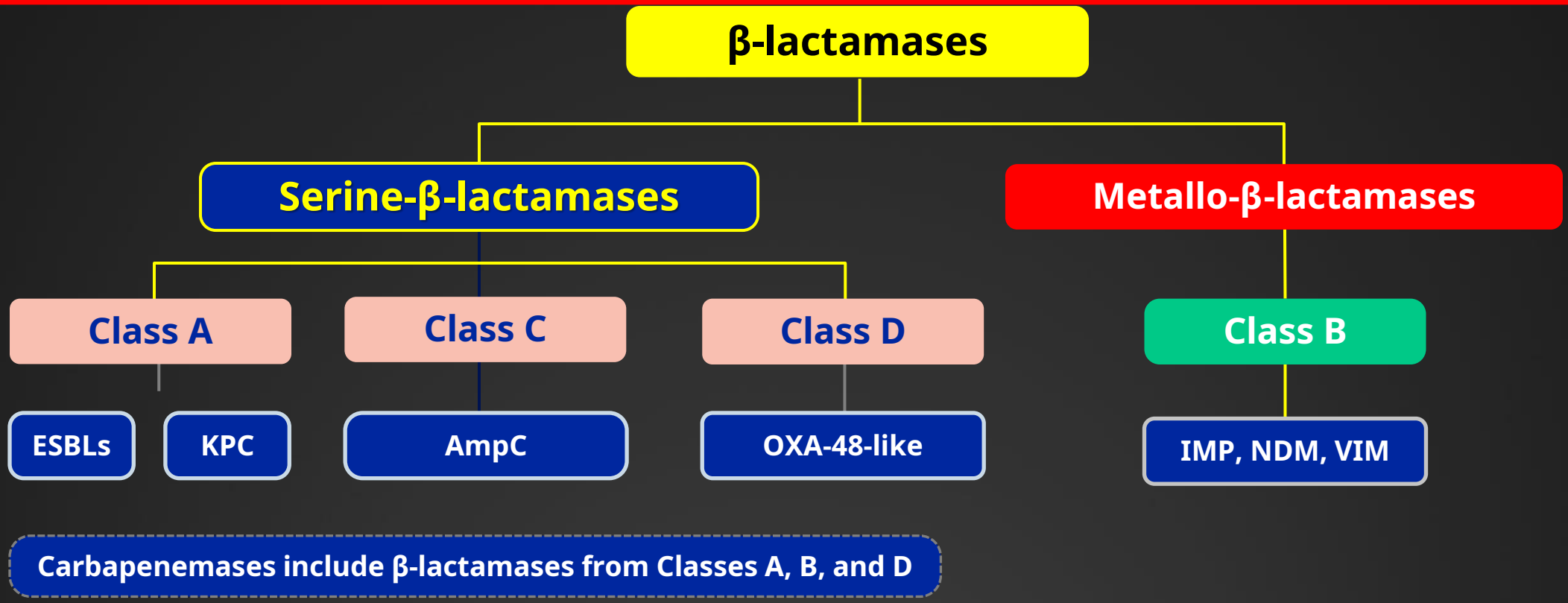


Figure adapted from 1. Bush K. *Antimicrob Agents Chemother.* 2018;62:e01076-18; 2. Reynolds D, et al. *Eur Respir Rev* 2022;31:220068.
AmpC, ampicillin class C β-lactamase; ESBL, extended-spectrum β-lactamase; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, OXA-β-lactamase; VIM, Verona integron-encoded m
1. Bush K. *Antimicrob Agents Chemother.* 2018;62:e01076-18; 2. Reynolds D, et al. *Eur Respir Rev* 2022;31:220068.

In 2023, WHO identified a major gap in activity of traditional antibiotics against MBL producers[1]

MBL genes are highly mobile, and accelerating their spread all over the world[2]

MBLs can hydrolyse almost all β-lactam antibiotics[3,4]

MBL-producing bacteria often co-harbour multiple resistance mechanisms, including SBLs (e.g., AmpC, ESBLs)[5,6]

- Infections caused by **MBL-producing Enterobacterales**, including those that produce NDM, VIM and IMP, are associated with **high mortality**[7-9]

***S. maltophilia* is intrinsically resistant to most β-lactam agents due to the production of two inducible β-lactamases (L1 and L2), along with other mechanisms[10]**

- L1 is an MBL that hydrolyses carbapenems and other β-lactams but not the monobactam aztreonam[10]

The 'big five' carbapenemases:[5,6]

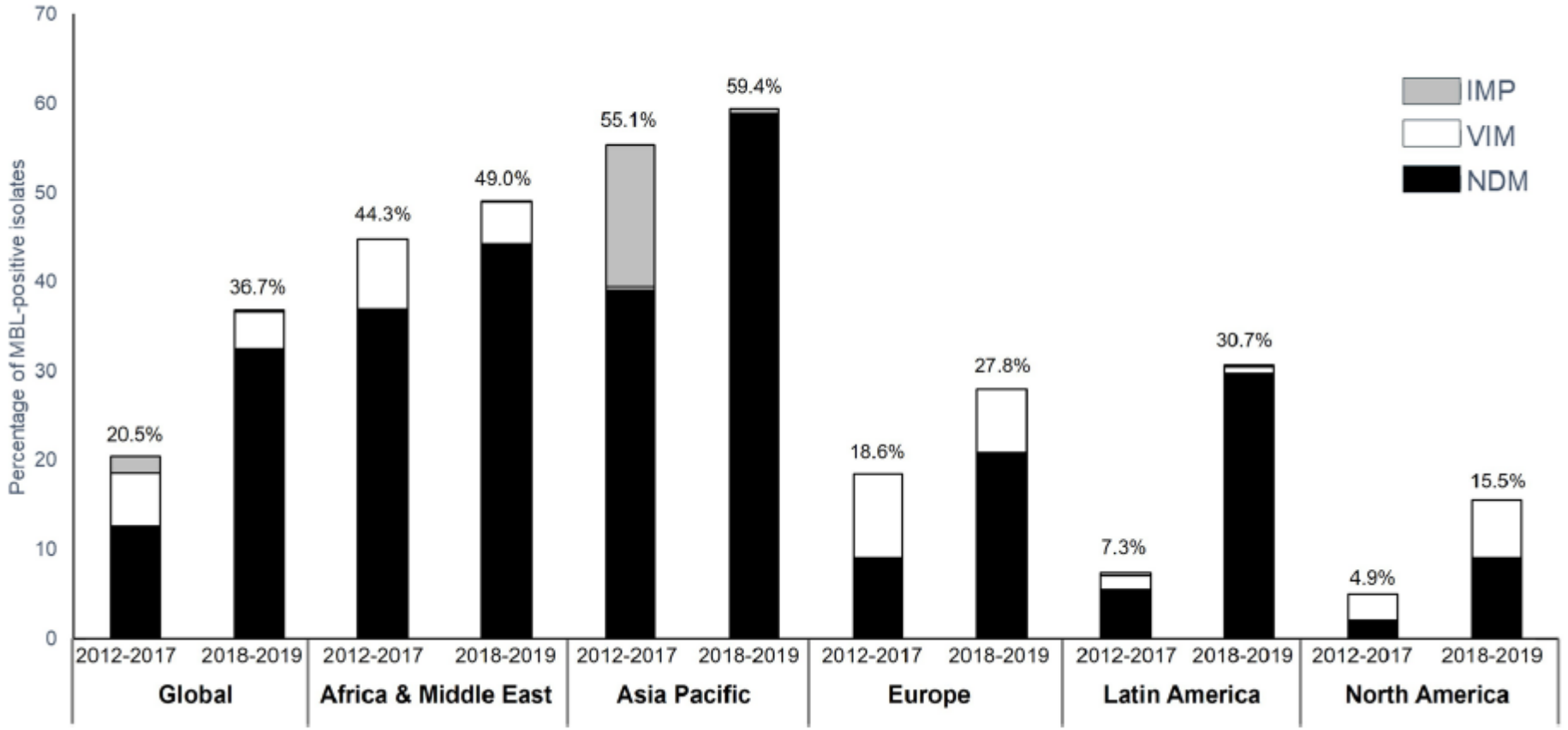
1. KPC
2. OXA-48
3. **IMP**
4. **VIM**
5. **NDM**

The most common carbapenemases reported in Enterobacterales globally[5,6]

AmpC, ampicillin class C β-lactamase; ESBL, extended-spectrum β-lactamase; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48; SBL, serine β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; WHO, World Health Organization.

1. World Health Organization. 2023 Antibacterial agents in clinical and preclinical development. 2023 Antibacterial agents in clinical and preclinical development: an overview and analysis (who.int) (Accessed August 2024); 2. Deshmuh DG, et al. *J Lab Physicians* 2011;3:93-7; 3. Mojica MF, et al. *Lancet Infect Dis* 2022;22:e28-34; 4. Tan X, et al. *Infect Drug Resist* 2021;14:125-42; 5. Han R, et al. *Front Cell Infect Microbiol* 2020;10:314; 6. Henderson J, et al. *J Hosp Infect* 2020;104:12-9; 7. de Jager P, et al. *PLoS One* 2015;10:e0123337; 8. Daikos GL, et al. *Antimicrob Agents Chemother* 2009;53:1868–73; 9. Hayakawa K, et al. *J Antimicrob Chemother* 2020;75:697–708; 10. Sader HS, et al. *Antimicrob Agents Chemother* 2020;64:e01433-20.

Distribution of MBL-positive Enterobacterales isolates among the carbapenem-nonsusceptible isolates collected globally



Grabein B et al. Infect Dis Ther (2024) 13:2423–2447

Mortality Doubles With Infections Caused by MDR - Pathogens

Infections caused by CR and MDR pathogens exacerbate an elevated risk of mortality[1,2]

Klebsiella pneumoniae[1]

Pooled mortality

Carbapenem-S	vs	Carbapenem-R
~21%		~42%
(n=2239)		(n=2462)

A systematic review and meta-analysis of 62 studies, involved 4701 patients, of whom 2462 had infection caused by CRKP.[1]

Pseudomonas aeruginosa[2]

30-day mortality

non-MDR	vs	MDR
~25%		~45%
(n=2388)		(n=813)

A meta-analysis of qualifying studies between 2006 and 2016 evaluated the risk of mortality in patients with infection caused by *P. aeruginosa*.

[a]MDR was defined as resistance to at least 3 different classes of antimicrobials, including carbapenems, antipseudomonal cephalosporins, fluoroquinolones, aminoglycosides, and β-lactams with inhibitors.[2]

CR, carbapenem-resistant; CRKP, carbapenem-resistant *Klebsiella pneumoniae;* CSKP, carbapenem-susceptible *Klebsiella pneumoniae;* KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; *P. aeruginosa, Pseudomonas aeruginosa*; VIM, Verona integron-encoded metallo-β-lactamase.

References: 1. Xu L et al. *Ann Clin Microbiol Antimicrob*. 2017;16:18. **2.** Matos ECO et al. *Rev Soc Bras Med Trop*. 2018;51(4):415-420.

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Infections caused by MBL-producing Enterobacterales are associated with increased mortality[1-3]

Design

Matched case-control study during a nosocomial outbreak of NDM-1-producers in an adult ICU in South Africa (n=38 cases vs n=68 controls)[1]

Prospective observational study of 162 patients in three tertiary-care hospitals located in the Athens metropolitan area (February 2004/2005 to March 2006)[2]

Multicentre prospective cohort study at 11 tertiary care facilities in Japan (1 October 2016 to 31 March 2018)[3]

Key results

In-hospital mortality

NDM-producing Enterobacterales

Non-NDM-producing Enterobacterales

Mean total length of hospital stay (P<0.001) **+30.7 days**

Mean total length of ICU stay (P<0.001) **+24.2 days**

AOR (in-hospital mortality)† (P=0.688) **11.29**

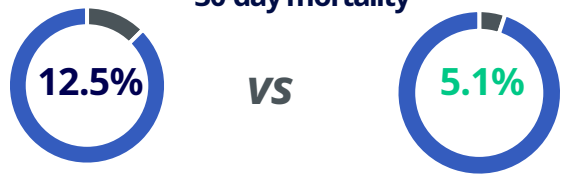
14-day mortality

VIM-positive *K. pneumoniae*

Non-VIM-positive *K. pneumoniae*

OR for all-cause 14-day mortality (P=0.20) **1.67**

Univariate analysis 30-day mortality



IMP-producing Enterobacterales

Non-IMP-producing Enterobacterales

P=0.349

Univariate analysis Length of hospital stay

40 days vs **29 days**

IMP-producing Enterobacterales

Non-IMP-producing Enterobacterales

P=0.143

*Adjusted for Chalrson co-morbidity index.[1] †Controlled for variable of 'infection (not colonization). OR for in-hospital death and 30-day mortality. The effect estimate for LOS after isolation of CPE/non-CPE, excluding cases who dies in hospital, was reported as the multiplicative effect (the antilog of the β coefficient).[3]

AOR, adjusted odds ratio; CPE, carbapenemase-producing Enterobacterales; ICU, intensive care unit; IMP, imipenemase; LOS, length of stay; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OR, odds ratio; VIM, Verona-integron-mediated metallo-β-lactamase.

1. de Jager P, et al. *PLoS One* 2015;10:e0123337; 2. Daikos GL, et al. *Antimicrob Agents Chemother* 2009;53:1868–73; 3. Hayakawa K, et al. *J Antimicrob Chemother* 2020;75:697–708.

Inhibition spectrum of β-lactamases inhibitors

Inhibitor	ESBL	AmpC	KPC	MBL	OXA-48-like	Intrinsic ATB activity
Clavulanic acid	++	-	+	-	-	-
Sulbactam	++	-	+	-	-	PBP2
Tazobactam	++	-	+	-	-	-
Enmetazobactam	**+++**	-/+	**++**	-	-	-
Avibactam	**+++**	**++**	**+++**	-	**+**	-
Relebactam	**+++**	**++**	**+++**	-	**+/-**	-
Vaborbactam	**+++**	**++**	**+++**	-	**+/-**	-
Zidebactam	+++	++	+++	-	?	PBP2
Taniborbactam	+++	++	+++	++ (except IMP)	?	?

Table adapted from Barbier et al. Annals of Intensive Care (2023) 13:65

Activity of new agents against Gram-negative pathogens.

Grey shading: variable activity; red shading: non-activity; green shading: activity. KPC: Klebsiella pneumoniae carbapenemases; OXA: OXA-β-lactamases; NDM: New Delhi metallo-β-lactamase.

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	Class B Carbapenemase (*e.g.* NDM)	Class D Carbapenemase (*e.g.* OXA-48)	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Ceftobiprole						
Ceftolozane-tazobactam						
Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicin						
Eravacycline						

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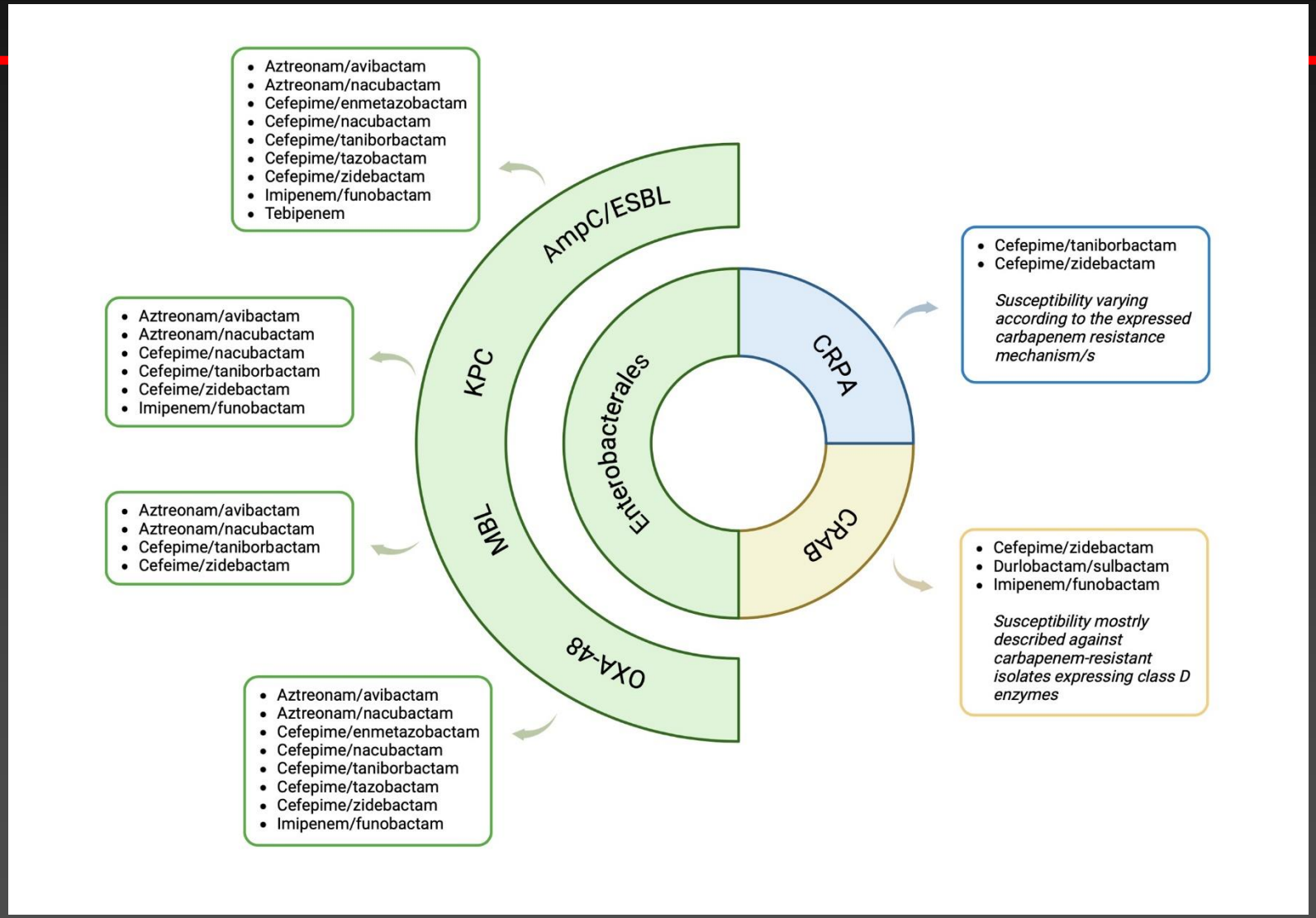
Bassetti M et al. Eur Respir Rev. 2022 Dec 31; 31(166): 220119

Activity according to *in vitro* studies



Bassetti M, et al. Current Opinion Infect Dis 2024

Ceftazidime/avibactam in Summary for KPC

Tumbarello, CID, 2019	*Tumbarello, CID, 2021*	***Falcone, Crit Care, 2020***	*Shields, CID, 2016*	*Van Duin, CID, 2018*	*Shields, AAC 2017*
Lower mortality rate in 104 BSI in targeted CAZ/AVI combo vs 104 BSI in targeted non CAZ/AVI combo	No differences in 165 CAZ/AVI mono vs 412 CAZ/AVI combo. Overall 25% mortality. **Prolunged infusion was protective**, **LRTI and CAZ/AVI renal dose adjustment were mortality risk factors**	102 BSI in CAZ/AVI vs COL-based showed lower mortality or nefrotoxicity. Time to appropriate therapy start was associated to survival. Primary BSI was mortality risk factor.	No differences in clinical success in 37 CAZ/AVI treated (70% mono vs 30% combo). **Lower clinical success in CRRT**	Higher probability of better outcome in 38 CAZ/AVI combo pts vs 99 COL-combo pts	Higher clinical success rate in 13 BSI in CAZ/AVI vs 25 CB+AG vs 30 CB + COL vs 41 other

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TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)

Endpoint/Statistics	MV N=32 n, (%)	Best Available Therapy N=15 n, (%)	Absolute Percent Difference (MV-BAT)	Relative Percent Difference [(MV-BAT)/BAT]
All-Cause Mortality Rate Day 28	5 (15.6)	5 (33.3)	-17.7	-53.2
Subjects Censored*	27 (84.4)	10 (66.7)		
Kaplan-Meier Estimate (95%CI)	15.6 (6.8 to 33.5)	33.3 (15.4 to 62.5)		

*Subjects whose survival status is unknown due to early termination or lost to follow up will be censored at the last day the subject was known to be alive.

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Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1

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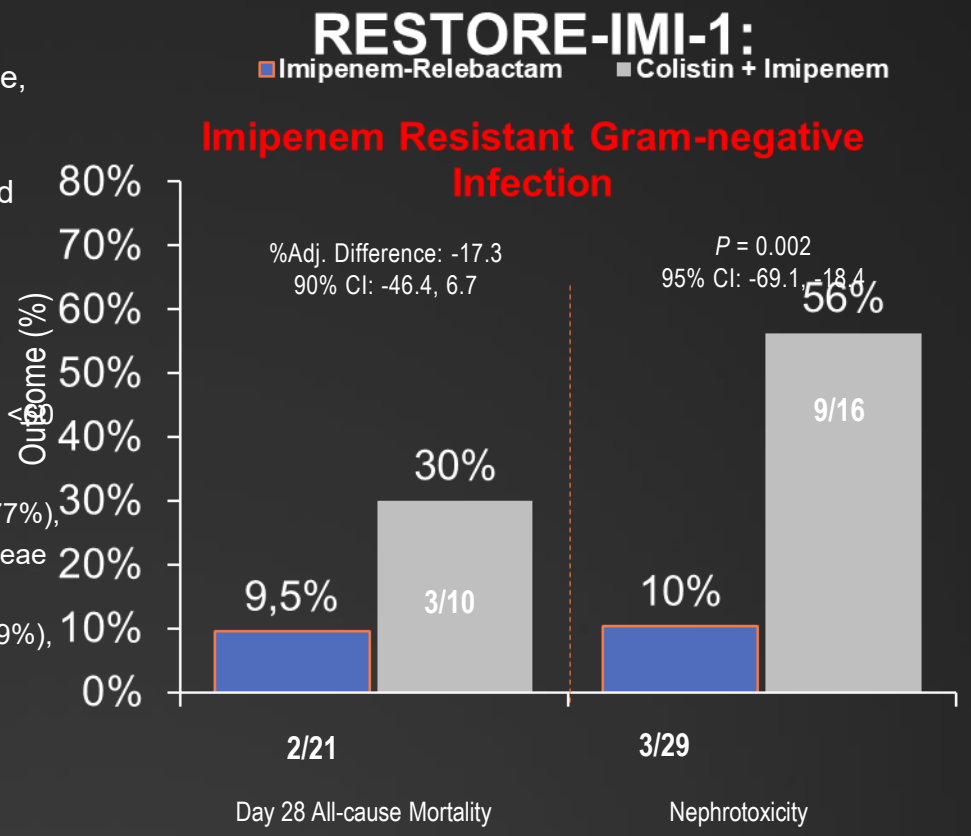
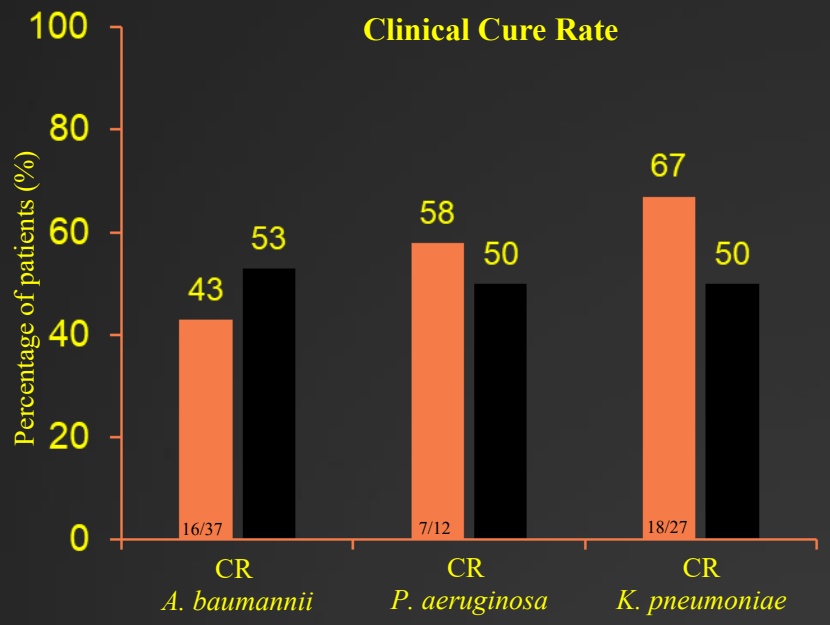
RESTORE-IMI-1: Efficacy & Safety of Imipenem-Relebactam (IMI-REL) in Patients with Imipenem-NS Infections

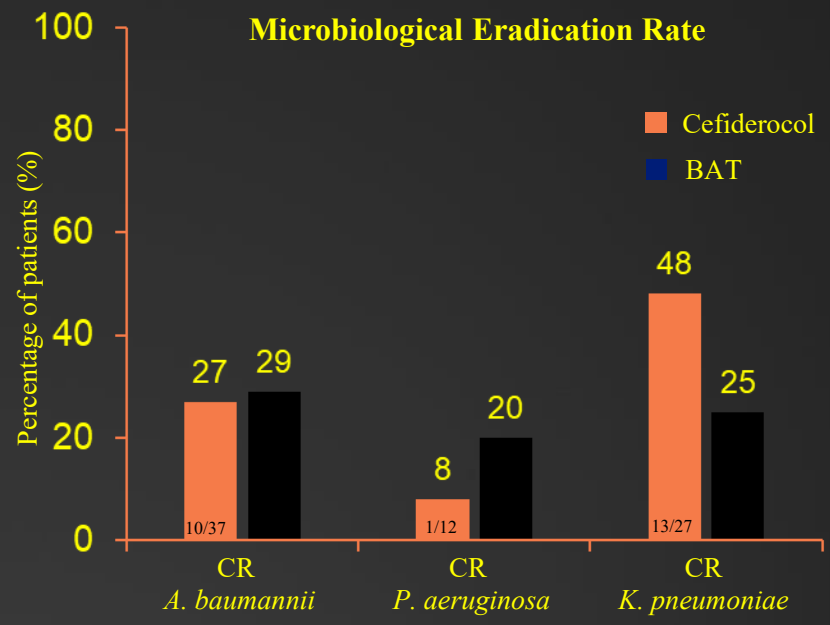
- RESTORE-IMI-1 is the first prospective comparative, randomized, double blind trial of a β-lactam/β-lactamase inhibitor as monotherapy (imipenem/relebactam) compared to dose optimized colistin + imipenem
  - 47 patients were randomized & treated (31 IMI/REL, 16 colistin+IMI), 31 of whom met mMITT criteria (11 HABP/VABP, 16 cUTI, and 4 cIAI)
    - 29% had APACHE-II scores >15, 23% had CrCl <50 mL/min, 35% were ≥65 yrs old.
    - Qualifying baseline pathogens: *P. aeruginosa* (77%), *Klebsiella* spp (16%), and other Enterobacteriaceae (6%), with the following β-lactamases detected: AmpC (84% of all qualifying isolates), ESBLs (39%), KPC (16%), OXA-48 (3%)
  - Efficacy defined by a favorable overall response (survival for HABP/VABP + clinical for cIAI, + clinical/micro for cUTI)



Adjusted difference, based on Miettinen and Numiren method stratified by infection site
Motsch J et al..Clin Infect Dis Clin Infect Dis. 2020;70(9):1799-1808 (RESTORE-IMI-1)

CREDIBLE-CR: similar rates at TOC by baseline pathogen, but higher for cefiderocol in Enterobacterales infection[a]





[a]CR micro-ITT population

BAT, best available therapy; CR, carbapenem resistant; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; TOC, test of cure.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

AZT/AVI is a combination of aztreonam and avibactam active against Enterobacterales that may co-produce SBLs and MBLs as well as *S. maltophilia*[1–7]

Colour coding adapted from Tamma PD, et al. *J Pediatric Infect Dis Soc* 2019;8:251–60.[5]

***In vitro* data, to be correlated clinically.**

*The breakpoint defines whether a species of bacteria is susceptive or resistant to the antibiotic. If the MIC is less than or equal to the susceptibility breakpoint, the bacteria are considered susceptible.[11,12]

ESBL, extended-spectrum β-lactamase; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; SBL, serine β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

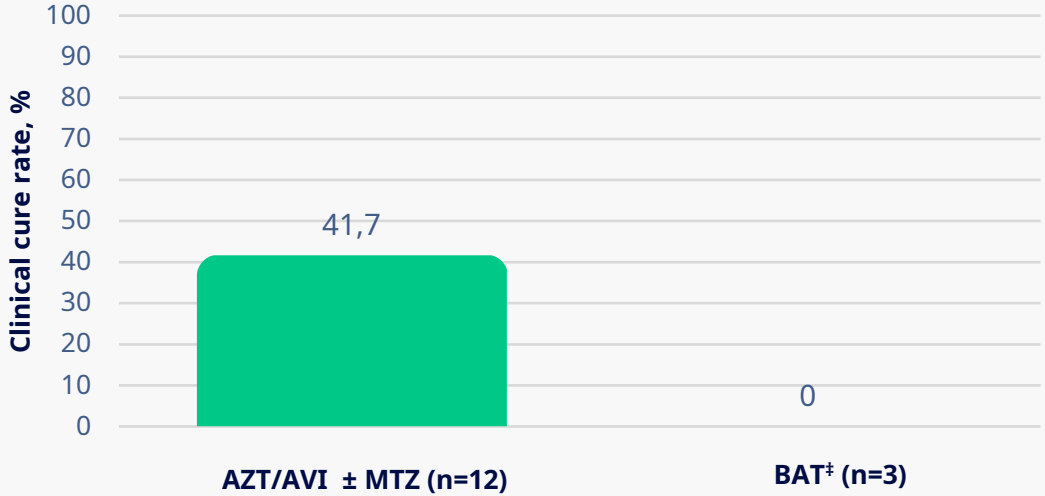
1. EMBLAVEO® (aztreonam–avibactam). Summary of Product Characteristics. Pfizer, 2024; 2. Rossolini GM et al. *J Glob Antimicrob Resist* 2022;30:214–21; 3. Karlowsky JA, et al. *Antimicrob Agents Chemother* 2017;61:e00472-17; 4. Biedenbach DJ, et al. *Antimicrob Agents Chemother* 2015;59:4239–48; 5. Tamma PD, et al. *J Pediatric Infect Dis Soc* 2019;8:251–60; 6. Rossolini GM, et al *J Glob Antimicrob Resist* 2024:36:123–31; 7. Wise MG, et al. *Eur J Clin Microbiol Infect Dis* 2023;42:1135–43; ; 8. Sader HS, et al. *JAC Antimicrob Resist* 2023;5:dlad032; 9. ATLAS surveillance program 2012–2022. https://atlas-surveillance.com/#/login (Accessed August 2024); 10. Biagi M, et al. *Antimicrob Agents Chemother* 2020;64(12):e00297-20; 11. European Committee on Antimicrobial Susceptibility Testing. EUCAST definitions of clinical breakpoints and epidemiological cut-off values. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/EUCAST_definitions_of_clinical_breakpoints_and_ECOFFs.pdf (Accessed August 2024); 12. Institute CaLS. Performance Standards for Antimicrobial Susceptibility Testing 34th Edition CLSI supplement M100: https://clsi.org/standards/products/microbiology/documents/m100/ (Accessed August 2024).

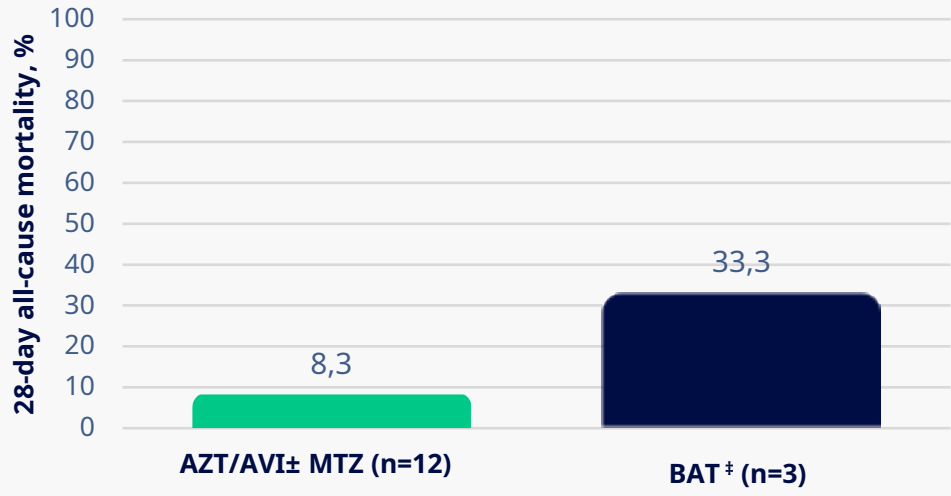
AZT/AVI was shown a favourable efficacy and safety profile in Phase II and Phase III studies in adult patients with serious Gram-negative infections

Phase	Trial	Objectives	Study design	Population	Results
Phase IIa	REJUVENATE (NCT02655419)[1]	Primary objectives: PK and overall safety profile Secondary objective: clinical efficacy	Prospective, open-label, multicentre trial enrolled adults with cIAI into sequential cohorts to receive IV EMBLAVEO (plus MTZ) for 5–14 days	Adults with cIAI	1. Overall safety profile of EMBLAVEO is in line with that of ATM alone; EMBLAVEO was well tolerated with no new safety findings 2. EMBLAVEO achieved favourable clinical response rates when combined with MTZ in adult patients with cIAI 3. PK results for ATM and AVI reported in REJUVENATE confirm the appropriate dosing regimen for the Phase 3 programme
Phase III	REVISIT (NCT03329092)[2,3]	Primary objective: clinical cure at TOC Secondary objectives: clinical cure at TOC by infection type, microbiological response at TOC, safety, and 28-day mortality	Prospective, randomised, multicentre, open-label, central assessor-blinded, comparative trial, conducted in 81 sites in 20 countries who received EMBLAVEO ± MTZ vs MER ± COL	Adults with cIAI or HAP/VAP caused by Gram-negative bacteria	1. EMBLAVEO (± MTZ) was effective in treating patients with cIAI and HAP/VAP, displaying similar efficacy to MER ± COL 2. EMBLAVEO was generally well tolerated, with no new safety findings
Phase III	ASSEMBLE (NCT03580044)[4-6]	Primary endpoint: clinical cure at TOC Secondary endpoints: 28-day mortality and safety	Prospective, randomised, multicentre, open-label, parallel-group, comparative trial conducted in 12 sites in 9 countries, to evaluate the efficacy safety and tolerability of EMBLAVEO versus best available therapy*	Hospitalised adults with cIAI, nosocomial pneumonia including HAP/VAP, cUTI or bloodstream infections due to MBL-producing Gram-negative bacteria	1. The ASSEMBLE data suggest a potential role for EMBLAVEO in treating serious infections caused by MBL-producing Gram-negative bacteria, for which there are few treatment options[†, ‡] 2. The safety profile of EMBLAVEO was consistent to that of ATM alone, with no serious adverse events deemed to be related to treatment reported.

*micro-ITT population.[6] [†]Given the small number of study participants, the findings should be interpreted accordingly.[6] [‡]The data from ASSEMBLE were first presented at ESCMID Global 2024.[6]
ATM, aztreonam; AVI, avibactam; cIAI, complicated intra-abdominal infection; COL, colistin; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; IV, intravenous; MBL, metallo-β-lactamase; MDR, multidrug-resistant; MTZ, metronidazole; MER, meropenem; PK, pharmacokinetics; TOC, test-of-cure; VAP, ventilator-associated pneumonia.
1. Cornely OA, et al. *J Antimicrob Chemother* 2020;75:618–27; 2. Carmeli Y, et al. Oral presentation 2893. Presented at: IDWeek, Boston, MA, USA, October 11–15, 2023; 3. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT03329092 (Accessed August 2024); 4. ClinicalTrials.gov. Efficacy, Safety, and Tolerability of ATM-AVI in the Treatment of Serious Infection Due to MBL-producing Gram-negative Bacteria - Full Text View - ClinicalTrials.gov (Accessed August 2024); 5. Pfizer. www.pfizer.com/news/press-release/press-release-detail/phase-3-studies-pfizers-novel-antibiotic-combination-offer (Accessed August 2024); 6. Daikos, G, et al. Poster 06184. Presented at the 34th ESCMID, Barcelona, Spain, April 27–30, 2024.

The ASSEMBLE data suggest a potential role for AZT/AVI for t serious infections caused by MBL-producing MDR Gram-ne bacteria[1,2]





Primary objective outcomes:[2]

- The overall clinical cure rates at for MBL-positive patients were 41.7% (5/12) and 0% (0/3) in the EMBLAVEO ± MTZ and BAT groups, respectively

Secondary objective outcomes:[2]

- All-cause 28-day mortality rates were 8.3% (1/12) and 33.3% (1/3) in the EMBLAVEO ± MTZ and BAT groups, respectively

Figures adapted from Daikos G, et al. Poster 06184. Presented at the 34th ESCMID, Barcelona, Spain, April 27–30, 2024.[2]
Given the small number of study participants, the findings should be interpreted accordingly.
*Clinical cure was defined as improvement in baseline signs and symptoms such that after study treatment, no further antimicrobial treatment for the index infection was required; no other failure criteria were met, and for cIAI subjects, no unplanned drainage or surgical intervention were necessary since the initial failure. Clinical responses were assessed by investigators, and independently by an adjudication committee; †Micro-ITT population constituted of patients with at least one MBL-positive, Gram-negative pathogen. ‡BAT regimens consisted of amikacin + polymyxin + meropenem (n=1) and amikacin + colistin (n=1).
BAT, best available therapy; MBL, metallo β-lactamase; MDR, multi-drug resistant; micro-ITT, microbiological intention-to-treat; MTZ, metronidazole; TOC, test-of-cure.
1. Pfizer. www.pfizer.com/news/press-release/press-release-detail/phase-3-studies-pfizers-novel-antibiotic-combination-offer (accessed August 2024); 2. Daikos, G, et al. Poster 06184. Presented at the 34th ESCMID, Barcelona, Spain, April 27–30, 2024.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad262

Journal of Antimicrobial Chemotherapy

Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape

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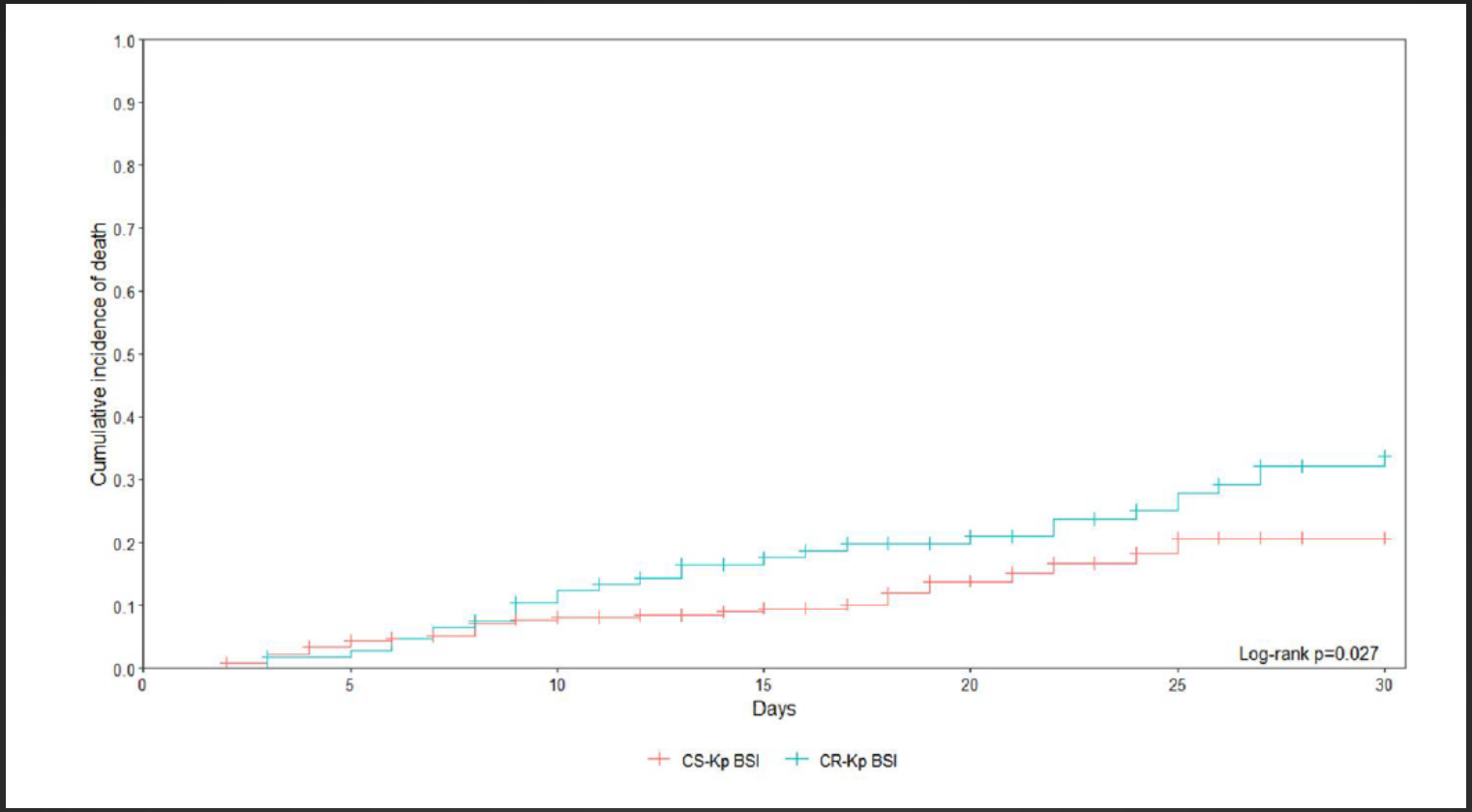
Cumulative mortality up to Day 30 in patients with CR-Kp BSI and CS-Kp BSI



Giacobbe DR et al. J Antimicrob Chemother. 2023 Aug 22:dkad262. doi: 10.1093/jac/dkad262.

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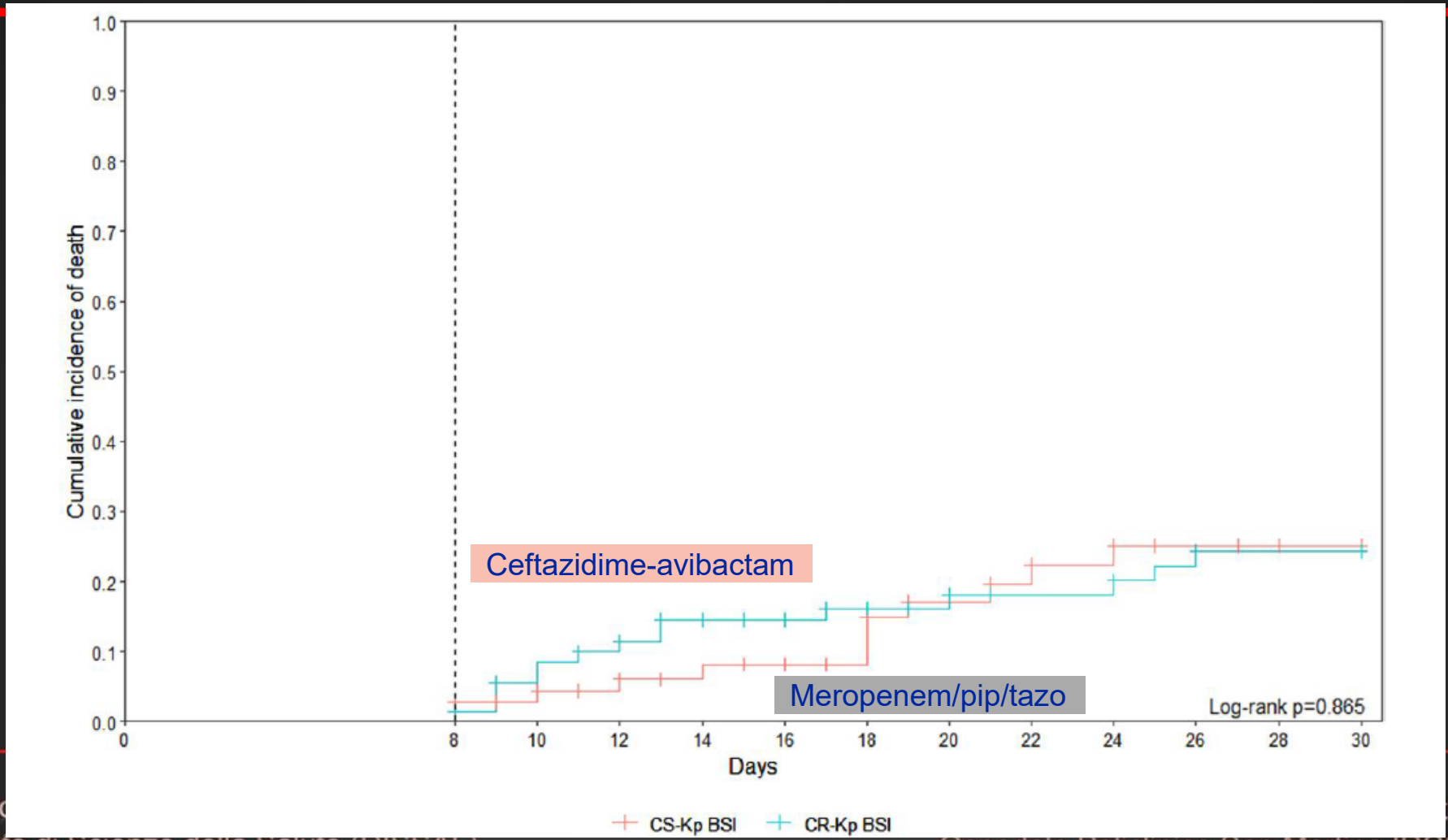
30-day mortality in patients with CR-Kp BSI receiving appropriate therapy with ceftazidime-avibactam (cases) vs patients with CS-Kp BSI receiving appropriate therapy with other agents (controls)



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Cefepime/enmetazobactam Activity

MoA

Agent	All Enterobacterales (n = 7,168)		ESBL-producing Enterobacterales (n = 801)	
	MIC_{90} (mg/l)	% susceptible	MIC_{90} (mg/l)	% susceptible
Cefepime	16	87.0/89.9	>64	12.0/26.1
Cefepime/enmetazobactam[a]	0.25	98.3/98.8[a]	0.5	98.9/99.9[a]
Meropenem	0.06	97.6	0.12	96.0
Piperacillin/tazobactam	32	87.4	256	71.4

Cefepime has broad Gram-positive and -negative activity, including to *P. aeruginosa* and AmpC-producing Enterobacterales. The addition of enmetazobactam extends cefepime's spectrum of activity further to include ESBL-producing Enterobacterales[2]

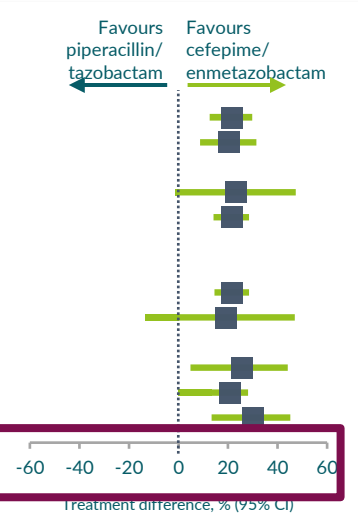
Notable gaps include Enterococci, anaerobes, *Acinetobacter spp., Stenotrophomonas maltophilia*, carbapenemase-producing Enterobacterales[2]

[a] Custom antimicrobial susceptibility testing plates (ThermoFisher Scientific, Cleveland, OH) were used to determine MICs by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines (40). Fixed concentrations of AAI101 (4 µg/ml and 8 µg/ml) and tazobactam (4 µg /ml) partnered with a -lactam antibiotic (piperacillin or cefepime) were used, along with cefepime, imipenem, and meropenem as comparators. The MIC endpoints were defined as the lowest concentration of -lactam (alone or partnered with a BLI) causing complete inhibition of growth; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration.

1. Papp-Wallace, KM et al. *Antimicrob Agents Chemother*. 2019;63(5):e00105-19; 2. Darlow, CA *et al.* Expert Opin Drug Metab Toxicol. 2024;

Favourable success rates were achieved for cefepime/enmetazobactam in the Subgroup analyses in the primary analysis set[1]

Subgroup	Cefepime/ enmetazobactam (n = 345) No./total (%)	Piperacillin/ tazobactam (n = 333) No./total (%)	Treatment difference[†], % (95% CI)
Baseline Charlson Comorbidity Index score			
<3	163/198 (82.3)	126/205 (61.5)	21.5 (12.6 to 29.8)
>3	109/145 (75.2)	69/125 (55.2)	20.4 (8.7 to 31.4)
Presence of concurrent bacteraemia at baseline			
Yes	27/38 (71.1)	14/28 (50.0)	23.3 (–1.5 to 45.9)
No	246/307 (80.1)	182/305 (59.7)	21.5 (14.2 to 28.5)
Race			
Black or African American	0/1	0	Not determined
White	260/327 (79.5)	186/316 (58.9)	21.6 (14.5 to 28.5)
Other (not including African descent)[a]	13/17 (76.5)	10/17 (58.8)	19.2 (–13.4 to 46.9)
Diabetes at baseline			
Yes	41/55 (74.5)	19/41 (46.3)	25.6 (4.8 to 44.1)
No	232/290 (80.0)	177/292 (60.6)	20.8 (13.4 to 28.1)
Enterobacterales baseline pathogen, ESBL-producing	56/76 (73.7)	34/66 (51.5)	30.2 (13.4 to 45.1)



[†] Treatment differences in the proportions of patients between the 2 treatment groups at day 14 were determined by the stratified Newcombe 2-sided 95%CIs. Treatment differences were not evaluated due to too low numbers for the Black race subgroup. [a] The "other" category indicates race was not identified. **CI:** confidence interval; **cUTI**: complicated urinary tract infection; **eGFR:** estimated glomerular filtration rate; **ESBL**: extended-spectrum β-lactamase.

1. Kaye KS, et al. Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA*. 2022;328:1304-14.

Cefepime-taniborbactam (VNRX-5133)

- Taniborbactam = boronic-acid-containing BLI

- *In vitro* activity against producers of class A, B (not IMP) and D carbapenemases
- Active against some CRPA and some KPC-3-producing CAZ-AVI resistant *Enterobacterales*

Hamrick JC et al. Antimicrob Agents Chemother 2019; 64:e01963-19. Yahav D, et al. Clin Microbiol Rev 2021; 34:e00115-20. Daigle D, et al. Open Forum Infect Dis 2018; 5:S419 –S420

CellPress

Med

Viewpoint

Cefepime-taniborbactam and CERTAIN-1: Can we treat carbapenem-resistant infections?

Matteo Bassetti[1,2,*] and Daniele Roberto Giacobbe[1,2]

Wagenlehner and colleagues[1] demonstrated non-inferiority and superiority with respect to a primary endpoint of composite success (microbiological plus clinical) of cefepime/taniborbactam vs. meropenem in treating complicated urinary tract infections and acute pyelonephritis caused by carbapenem-susceptible gram-negative bacteria in adults. A major area of interest in real-world application of cefepime/taniborbactam is its potential role in treating carbapenem-resistant infections, which deserves further investigation.

tion baseline of all core symptoms and signs, with no administration of additional antibacterials (for cUTIs or acute pyelonephritis), while microbiological success was defined as reduction of the bacterial load of gram-negative pathogens to less than 10^3 colony-forming units per milliliter. Both drugs were administered intravenously for 7 days (or up to 14 days in presence of bacteremia), and step down to oral agents was not permitted. Overall, the microITT population was composed of 293 and 143 patients randomized to cefepime/taniborbactam and meropenem arms, respectively, with a 2:1 ratio. Most infections were caused by Entero-

What Makes Ceftolozane/Tazobactam Different?
Activity vs. *Pseudomonas aeruginosa*

Ceftolozane

- Stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)[1]
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur[2]

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

○ Activity greatly decreased >> ● Retains activity

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1. Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-6850.
2. Ceftolozane/Tazobactam prescribing information.

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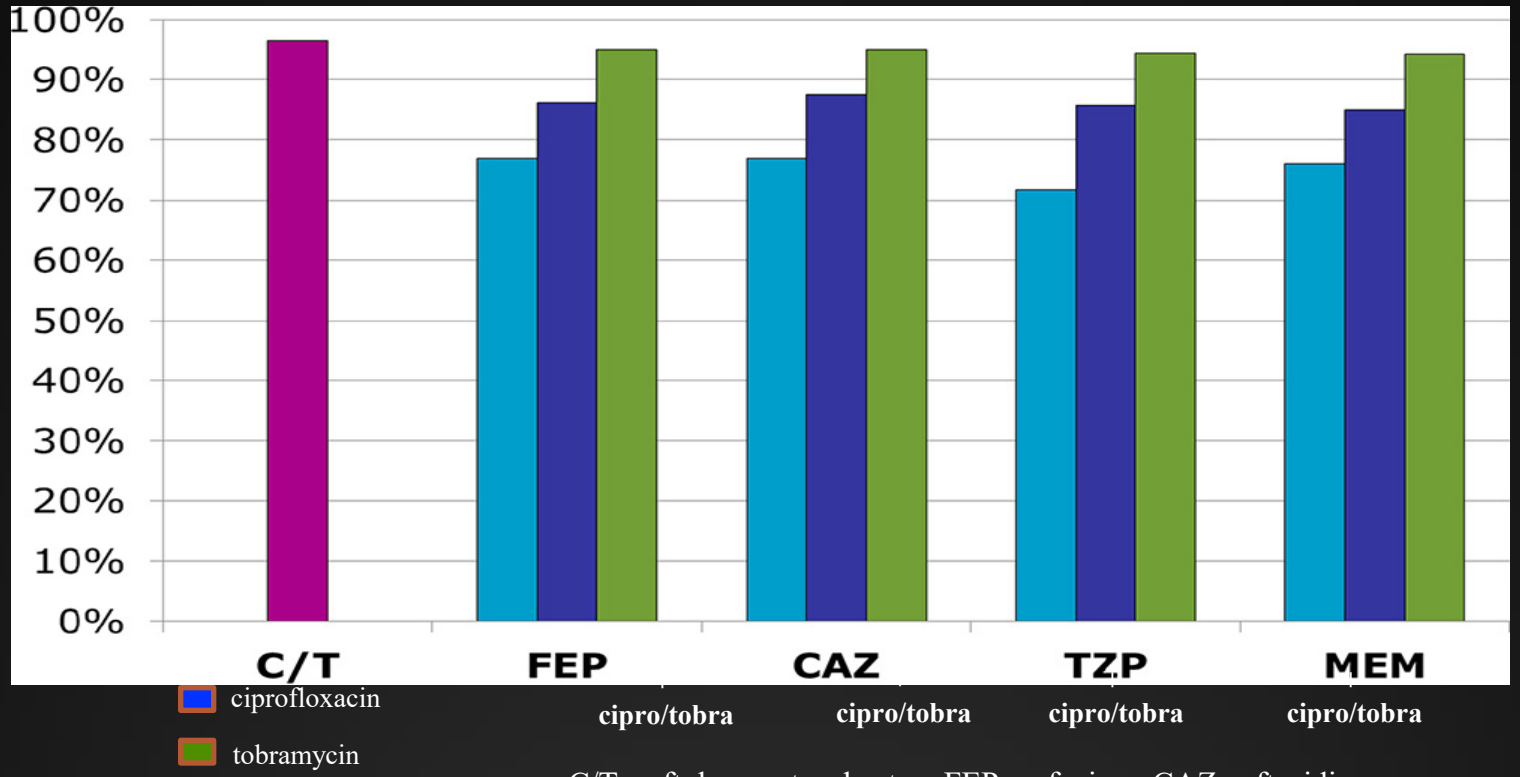
Table adapted from Castanheira M, et al. 2014

Percent susceptibility of all *P. aeruginosa* isolates (*n* = 1,257) to ceftolozane-tazobactam compared to B-lactams alone or in combination with ciprofloxacin and tobramycin



C/T- ceftolozane tazobactam,FEP- cefepime, CAZ-ceftazidime, TZP-piper tazo, MEM- meropenem

Source: Goodlet KJ, 2017. *In vitro* comparison of ceftolozane- tazobactam to traditional beta-lactams and ceftolozane-tazobactam as an alternative to combination antimicrobial therapy for *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 61:e01350-17

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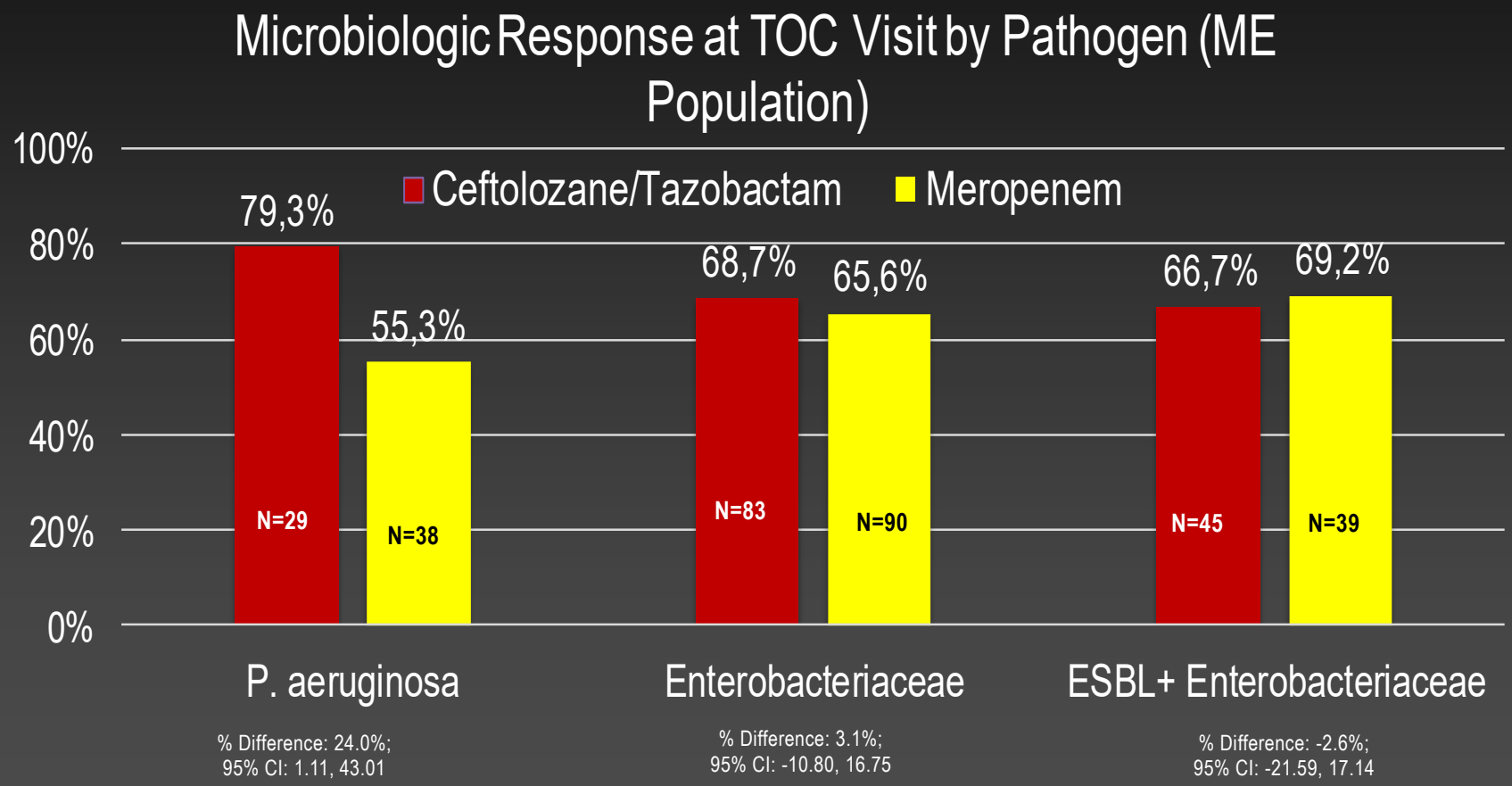
Per-Pathogen Microbiologic Response at Test of Cure (TOC)

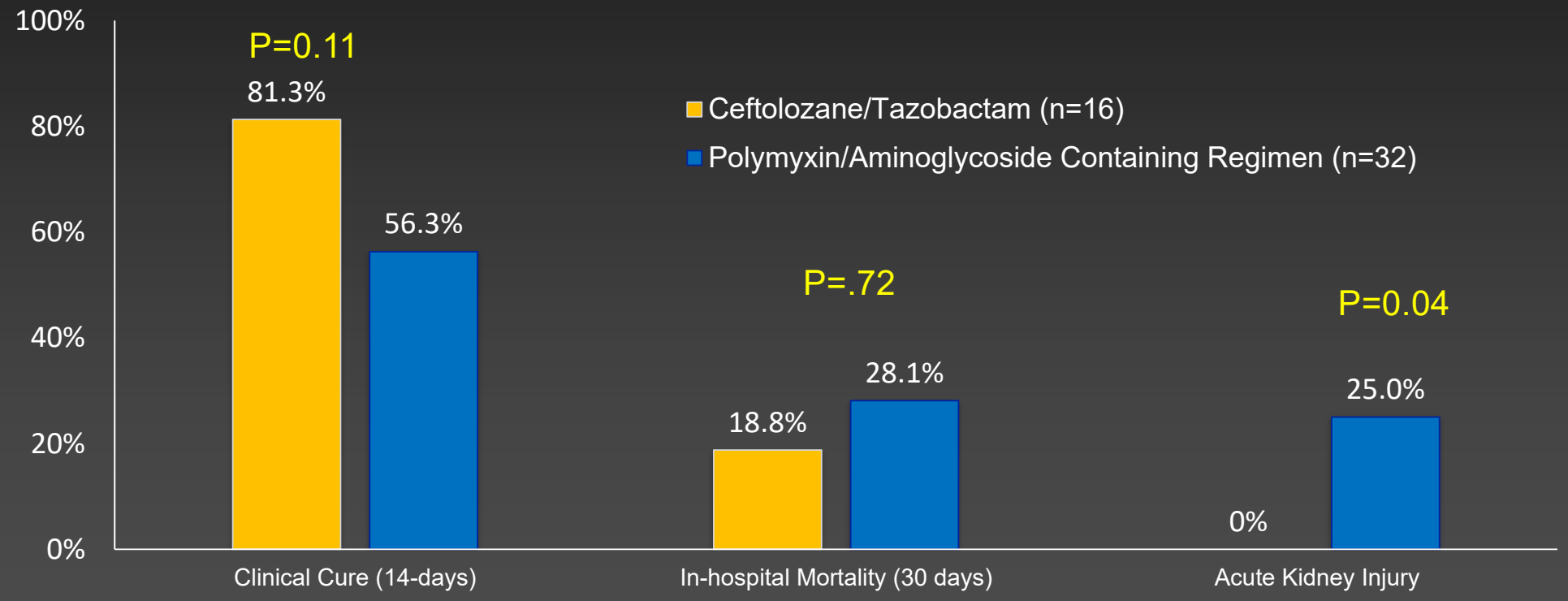


Kollef M et al. Lancet Infect Dis. 2019 Sep 25. pii: S1473-3099(19)30403-7

Comparative effectiveness of ceftolozane/tazobactam vs. polymyxin or aminoglycoside containing regimens (Italy)

C/T against Pseudomonas aeruginosa

- 1:2 matched case-control analysis at 9 centers in Italy
  - Patients with nosocomial pneumonia or bloodstream infections due to MDR or XDR *P. aeruginosa*



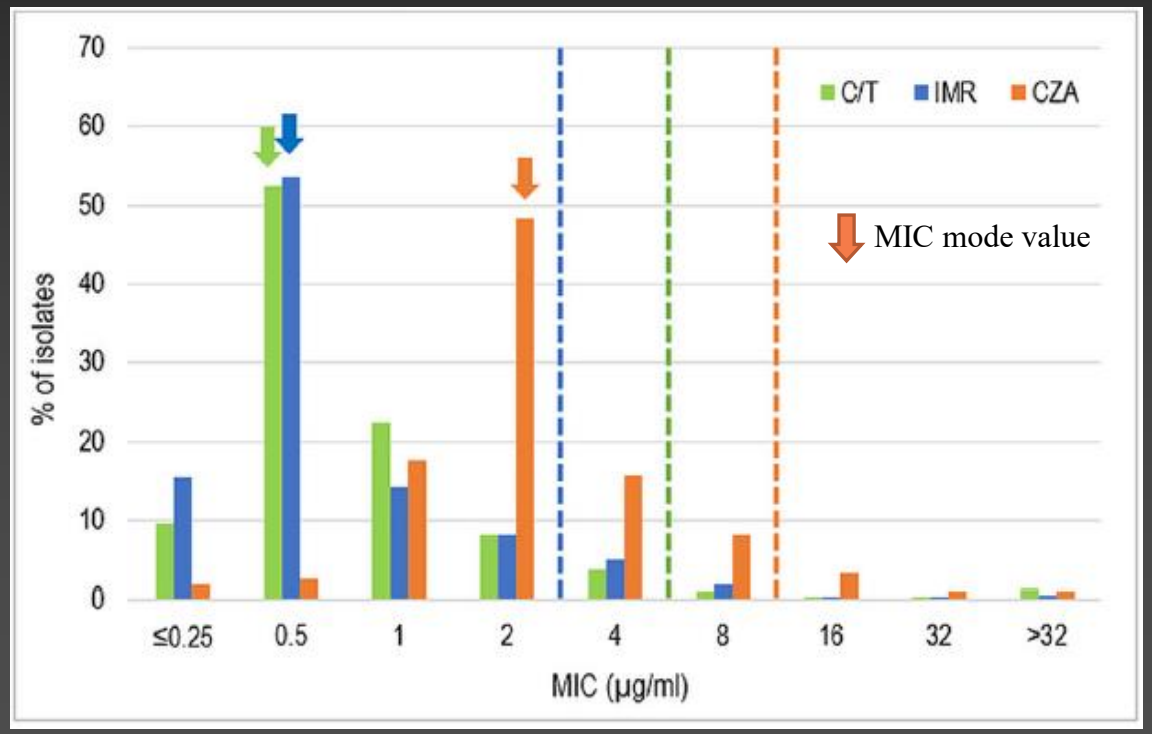
Vena A et al. Clin Infect Dis 2020

P. aeruginosa: In vitro activity of β-lactam / β-lactamase inhibitor combinations

US Hospitals (SMART Surveillance Program, 2018 to 2020)

C/T: Ceftolozane-tazobactam
IMR: Imipenem-relebactam
CZA: Ceftazidime-avibactam

Distribution of MIC values against all isolates (n=2531)



% of *P. aeruginosa* susceptible isolates:

C/T	96.4%
IMR	91.5%
CZA	94.4%

Cross-susceptibility to C/T, IMR, and CZA among *P. aeruginosa* isolates with different phenotypes

		Antimicrobial agent, % susceptible		
Phenotype	No. (% of all isolates)	C/T	IMR	CZA
C/T-NS	90 (3.6)	0	52.2	38.9
IMR-NS	214 (8.5)	79.9	0	64.0
CZA-R	141 (5.6)	61.0	45.4	0

Karlowsky JA et al. Antimicrob Agents Chemother. 2022 May 17;66(5):e0018922

* Data presented are for discussion purpose only and may not be consistent with the approved indication in Taiwan. Please refer to the local product label.

Imipenem-relebactam in real life

- Retrospective study in 8 hospitals USA, Jan 2020 - Aug 2021.
- Respiratory infections 11/21 (52%), UTI 3/21 (14%), prosthetic infections 3/21 (14%).
- Overall, positive blood cultures 29%
- ***P. aeruginosa* (16/21, 76%)**, *K. pneumonia* (3/21, 14%), and *Proteus mirabilis* (3/21, 14%),
- **15/16 (94%) *P. aeruginosa* MDR.**
- In combination 29% (6/21) (tobramycin more frequent)
- Mortality 7/21 (33%); Clinical cure 13/21 (62%)
- Microbiological recurrence 5/21 (24%). Development of resistance in 1 case (PA)
- Adverse effects: 1 G-I, 1 encephalopathy

Rebold et al. Open Forum Infect Dis. 2021 Dec; 8(12): ofab554

MIC for meropenem-resistant isolates: cefiderocol vs comparators

Attività in vitro di Cefiderocol e comparatori contro isolati italiani di *P. aeruginosa* dello studio SIDERO-WT-2014-2018 resistenti a meropenem (MIC> 8MG/L)

		MIC (mg/L)			
Specie (n)[a]	Antibiotico	Range	MIC_{50}	MIC_{90}	S%
Pseudomonas aeruginosa (39)	**Cefiderocol**	0,008-2	0,25	2	100
	Colistina	Da 0,5 a >8	1	1	94,9
	Ceftazidime/ avibactam	Da 4 a >64	8	>64	53,8
	Ceftolozane/ tazobactam	Da 0,5 a >64	4	>64	51,3

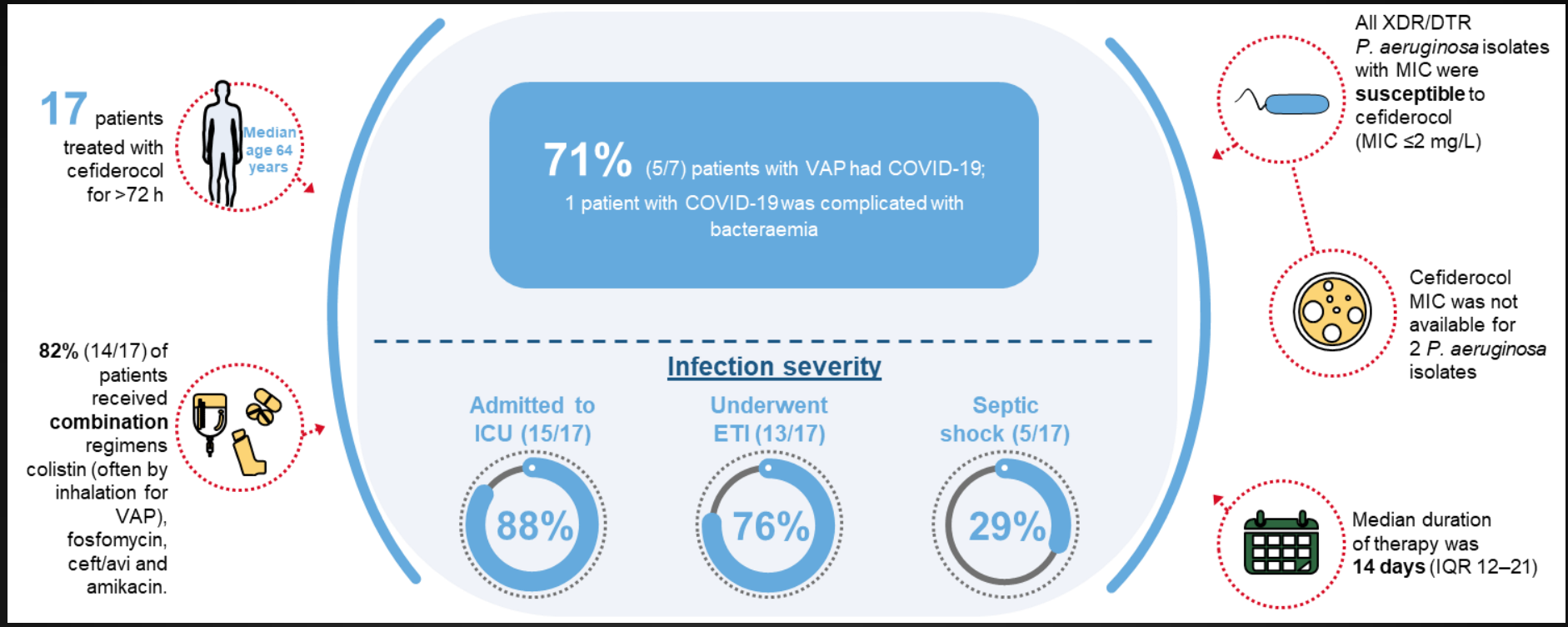
MIC, minima concentrazione inibente; MIC50/90, MIC per il 50% ed il 90% degli isolati testati, rispettivamente; S%, percentuale di suscettibilità

[a]Dove n ≥ 10 isolati

Stracquadanio S, et al. J Glob Antimicrob Resist 2021;25:390–8.

Cefiderocol in patients with XDR/DTR *P. aeruginosa* infection: a prospective, observational study

Prospective observational study including 17 pts (median age 64 yrs) with XDR and DTR *P.aeruginosa* infections, unresponsive to BAT w/o any other available treatment options.



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Meschiari M. et al. JAC Antimicrob Resist 2021;3:dlab188

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Old versus new antibiotics against *Acinetobacter baumannii*

OLD

- Colistin
- Tigecycline
- Ampicillin-sulbactam
- Fosfomycin

NEW

- Cefiderocol
- Durlobactam/sulbactam

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Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

- Small number of control group
- Abnormally low mortality in the control group.

Imbalance between groups.

- moderate or severe renal dysfunction
- ICU admission at randomisation
- ongoing shock at randomizati

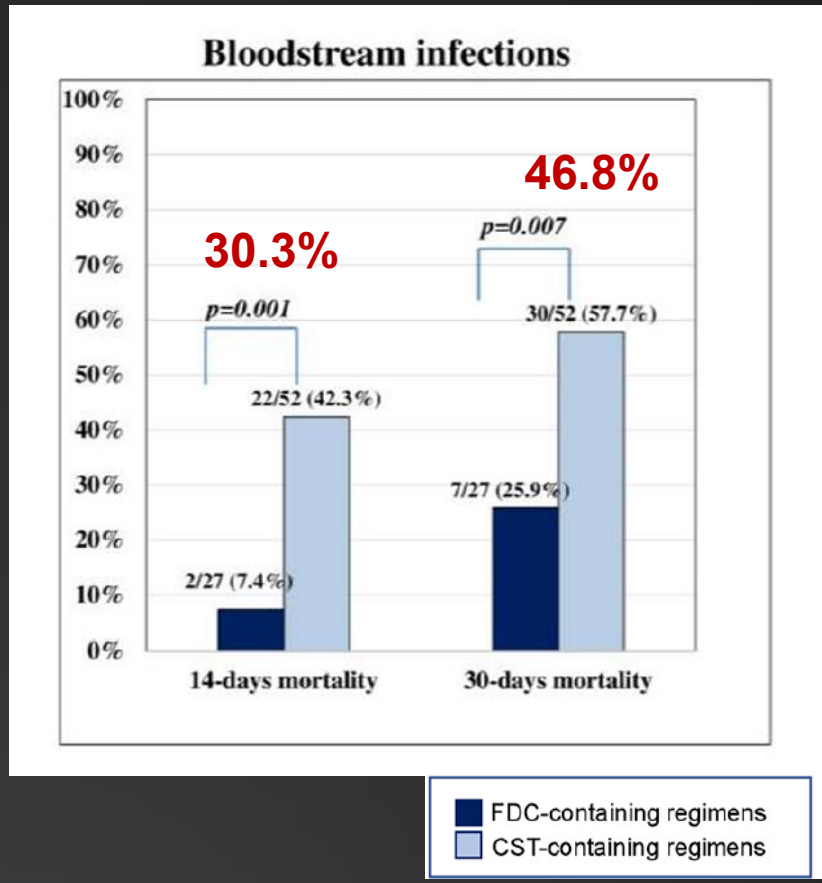
What is the avoidable mortality rate related to *A. baumannii* infections in this clinical context?

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

- **Study population**
  - 124 patients with *A. baumannii* infections
  - 47 (37.9%) FDC vs 77 (62.1%) CST-containing regimens

- **Risk factors for 30-day mortality**
  - Septic shock
  - SOFA score
  - Age were
  - Cefiderocol therapy (HR 0.44)

- **AEs:** 21.1% COL Vs 2.1%, FDC p<0.01.



Falcone M et al AAC. 2022

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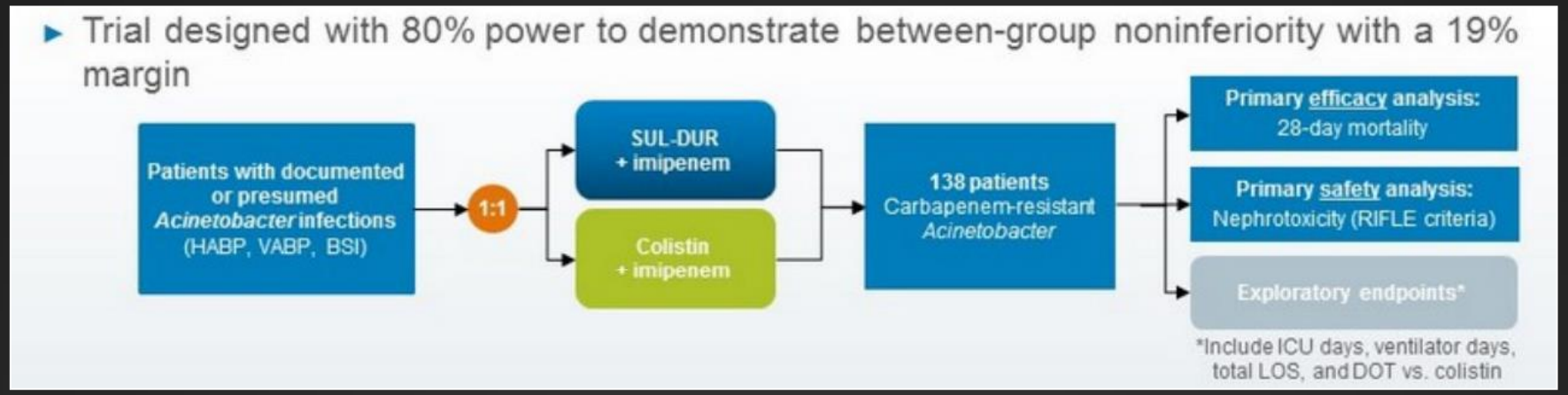
Durlobactam/sulbactam: ATTACK Phase III Trial



	SUL/DUR	COLISTIN	
28-day mortality	19%	32.3%	95% CI (-30.0, 3.5)
Clinical cure at TOC	61.9%	40.3%	95% CI (2.9, 40.3)
Nephrotoxicity	13.2%	37.6%	p<0.001

https://clinicaltrials.gov/ct2/show/NCT03894046

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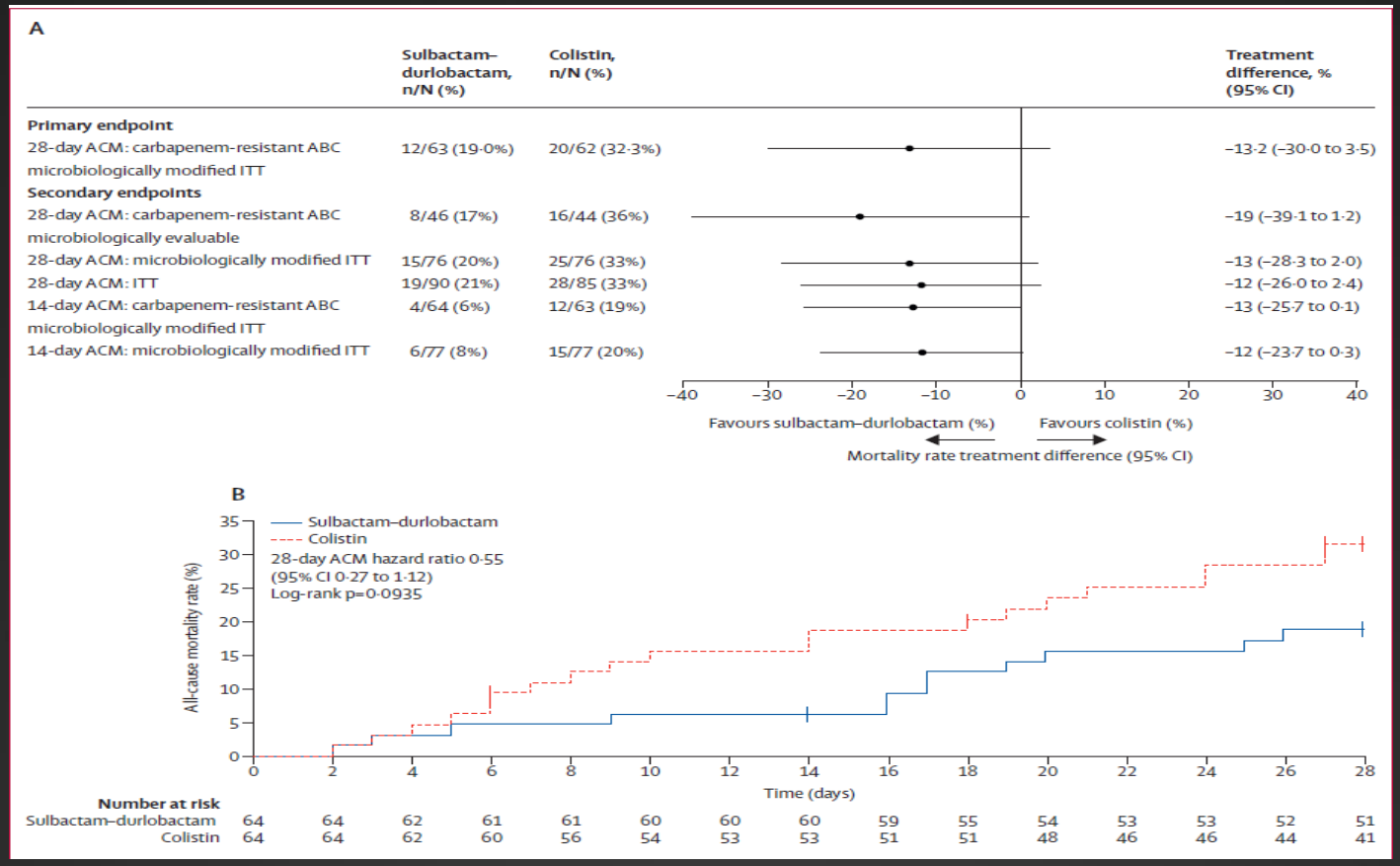
Sulbactam/durlobactam. The attack trial



Kaye KS et al. Lancet Infect Dis 2023

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Eravacycline activity vs Acinetobacter baumannii

A. baumannii	Eravacycline	1,600	0.5	1	≤0.015 - 16		NA	NA
	Amikacin	1,101	32	≥128	0.12 - ≥128		49.5	47.1
	Ampicillin-sulbactam	1,101	32	≥128	1 - ≥128		30.9	NA
	Aztreonam	1,600	≥32	≥32	≤0.5 - ≥32		NA	NA
	Cefepime	1,600	≥32	≥32	≤0.25 - ≥32		26.9	NA
	Ceftazidime	1,600	≥32	≥32	≤0.5 - ≥32		29.1	NA
	Ceftriaxone	1,600	≥64	≥64	≤0.5 - ≥64		12.6	NA
	Colistin	1,600	0.5	2	≤0.03 - ≥8		95.4	95.4
	Gentamicin	1,600	≥16	≥16	≤0.03 - ≥16		38.3	38.3
	Imipenem	499	≥16	≥16	≤0.25 - ≥16		37.3	37.3
	Levofloxacin	1,600	≥8	≥8	≤0.25 - ≥8		26.6	24.8
	Meropenem	1,101	32	≥128	≤0.03 - ≥128		32.2	32.2
	Minocycline	1,101	2	16	0.06 - ≥128		66.5	NA
	Piperacillin-tazobactam	1,600	≥128	≥128	≤0.5 - ≥128		24.3	NA
	Tetracycline	1,600	≥16	≥16	≤0.25 - ≥16		25.4	NA
	Tigecycline	1,600	2	4	0.06 - ≥32		NA	NA
	Trimethoprim-sulfamethoxazole	1,101	16	≥128	≤0.03 - ≥128		37.8	37.8

Morrissey I et al. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e01699-19.

Patient Case Report

Use of Eravacycline for *Acinetobacter baumannii* Infections: A Case Series

Journal of Pharmacy Practice
2023, Vol. 0(0) 1–5

DOI: 10.1177/08971900231196076
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Valerie Buckley, PharmD[1], MaiCuc Tran, PharmD, BCPS[1], Todd Price, MD[2], Sushma Singh, MD[2], and Stefanie Stramel, PharmD, BCIDP, MS[1]

Table 1. Patient Characteristics.

Case	Age, Sex	Culture Specimen	Infection Source	ERV Start, days	ERV Duration, days	ICU Stay, days	Prior Active Antimicrobial Therapy	Combination Antimicrobial Therapy with ERV	ERV MIC, µg/mL
1	59, F	Blood	Respiratory	1	9	0	FEP, VAN	Inhaled TOB, CST	0.5
2	43, F	Respiratory	Respiratory	9	10	14	FEP, VAN, ATM, CST, MEM	One dose ATM	0.5
3	84, F	Sacral wound	Skin/soft-tissue	8	13	0	MEM, VAN, FAM, AMK	VAN, FAM	1.0
4	68, F	Tracheal aspirate	Respiratory	24	4	0	FEP, VAN, MEM	FEP	0.5
5	26, F	Tracheal aspirate	Respiratory	14	11	27	CFZ, FEP, MEM, VAN, MFG	MEM, VAN, CST	1.0
6	47, M	Sputum	Respiratory	22	8	20	CRO, VAN, TZP, MEM, CST, MFG	MEM, CST, MFG	0.5
7	62, M	Blood	Respiratory	2	16	0	MEM, VAN	MEM, FAM, inhaled TOB, VAN, LVX, FEP	.38
8	68, M	Sputum	Respiratory	4	12	30	FEP, VAN, MEM	MEM, CST	0.5
9	68, M	Tracheal aspirate	Respiratory	4	6	7	FEP, VAN	FEP, CST	.75
10	45, M	Suprapubic aspirate	Urinary	4	3	0	MEM	MEM, CST	1.5

Note: Adapted from Early experience with eravacycline for complicated infections, by Alosaimy S, Molina KC, Claeys KC, et al., p. 3. Copyright 2020 by Open Forum Infectious Diseases. In the public domain.
Abbreviations: AMK, amikacin; ATM, aztreonam; CFZ, cefazolin; CRO, ceftriaxone; CST, colistimethate; ERV, eravacycline; FAM, ampicillin-sulbactam; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; MFG, micafungin; TOB, tobramycin; TZP, piperacillin-tazobactam; VAN, vancomycin.

A total of 10 patients were isolated for assessment of clinical course information. All patients had MDR CRAB isolated in cultures; 8 patients (80%) had *Acinetobacter* from a respiratory source, followed by skin (10%) and urinary (10%) sources. All patients were treated with eravacycline for non-FDA recommended infection types. Half of the patients (50%) were admitted to the ICU throughout their hospital stay. There were no patient deaths reported during the documented hospital stay after eravacycline use. A single patient had an MIC of .38 µg/mL (10%), 5 patients had an MIC of .5 µg/mL (50%), 1 with an MIC of .75 µg/mL (10%), 2 with an MIC of 1.0 µg/mL (20%), and one with an MIC of 1.5 µg/mL (10%).

Although there is currently little post-marketing data supporting the use of eravacycline in CRAB infections, this case series describes its clinical use and MIC breakpoint data for 10 patients. More high quality data is needed, however, to confirm the clinical utility of this agent in practice.

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Use of Colistin in Gram-negative infections

STOP IT!!!!

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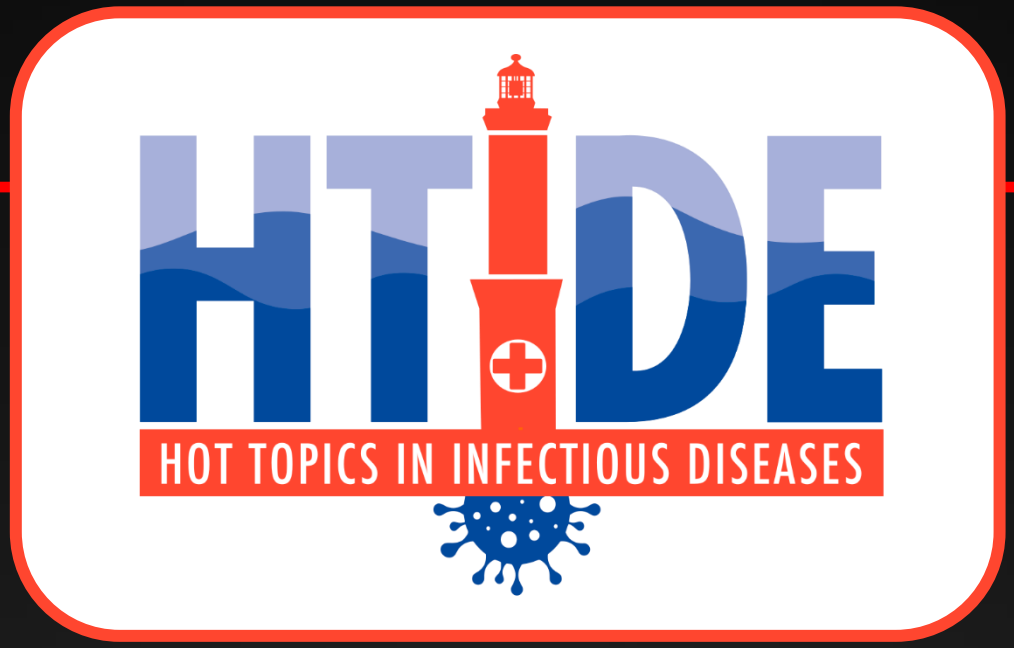
Who's the best?
New vs old

- ESBLs: equal or better (lower collateral damages)
  - C/T, C/A, C/E
- KPC/OXA-48: drugs of choice
  - C/A, M/V, I/R, second line cefiderocol
- MBL in enterobacterales:
  - A/V, cefiderocol
- P.aeruginosa (not MBL):
  - C/T, I/R
- P.aeruginosa MBL
  - cefiderocol
- A. baumannii:
  - cefiderocol, D/S, eravacycline



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