Nuovi antibiotici per la cura dei batteri MDR

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- Research grants
  - Astellas, Pfizer, MSD, Gilead
- Advisor/consultant/speaker bureau
  - Angelini, Astellas, Bayer, Biomerieux, Cidara, Gilead, Menarini, MSD, Pfizer, Shionogi

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Cambiano i tempi…..

- «Nei Paesi ad alto sviluppo socio-economico, le malattie infettive non rappresentano più una priorità»
- OMS, 1978

- «Senza un'azione immediata e coordinata di tutti , il mondo andrà verso un'era post-antibiotici, in cui le infezioni comuni e le ferite lievi fino ad ora curabili potranno tornare a diventare mortali»
- Dr. Keiji Fukuda, Vicedirettore per la Sicurezza Sanitaria OMS,2014

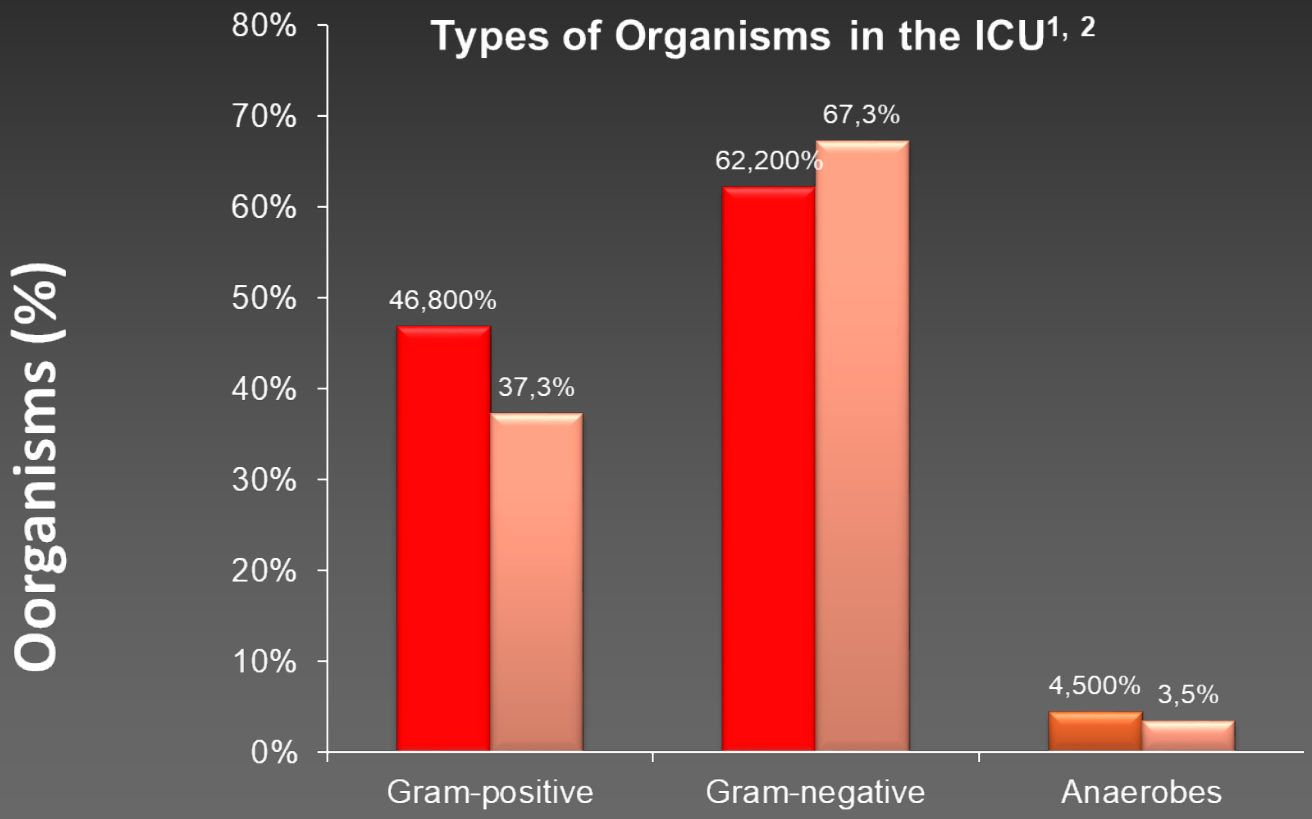
«La carenza di antibiotici efficaci è da considerarsi una minaccia per la pubblica sicurezza»

Dr. Tedros Adhanom Ghebreyesus , Direttore Generale OMS, 2018

«Il covid e l'uso estensivo e spesso ingiustificato di antibiotici ci ha fatto tornare indietro di 20 anni nella lotta ai batteri resistenti».

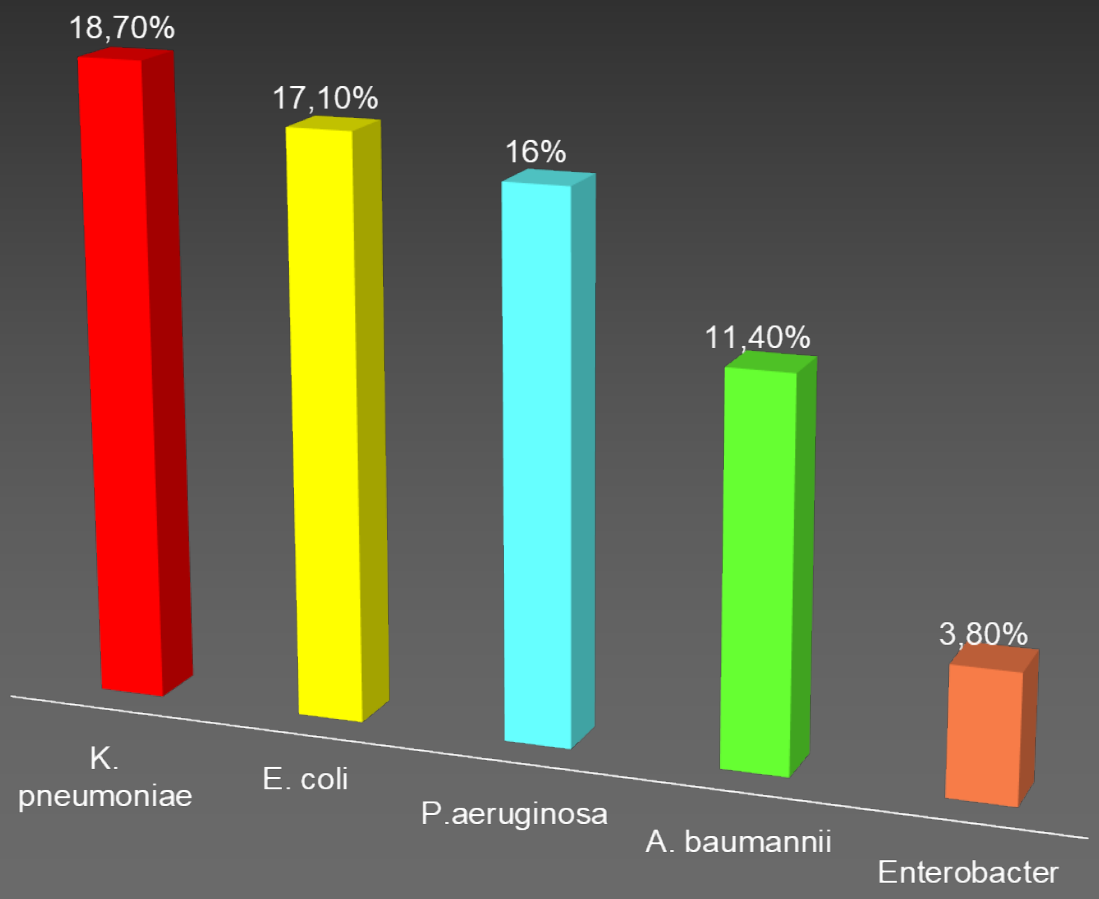
De Waele JJ, Derde L and Bassetti M. *Intensive Care Med.* 2020

Common Pathogens in critically ill patients



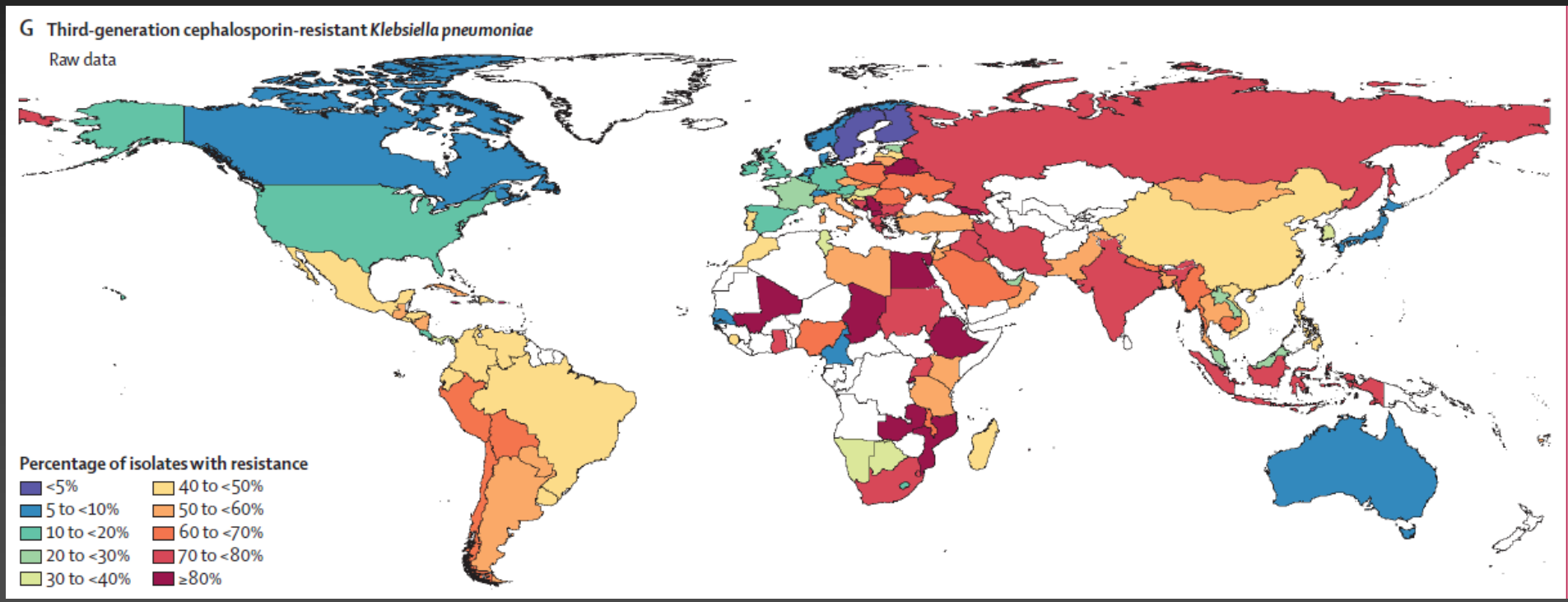
1. Data from the Extended Prevalence of Infection in Intensive Care (EPIC II) Study, a global, 1-day point prevalence study of 13,796 patients from 1,265 ICUs in 75 countries in 2007. Vincent et al. JAMA 2009; 302: 2323-2329.
2. Vincent et al. JAMA. 2020 Apr 21; 323(15): 1478–1487

Common Gram-negative bacteria in critically ill patients (EPIC III)



Vincent et al. JAMA. 2020 Apr 21; 323(15): 1478–1487

3rd gen. Resistant *Klebsiella pneumoniae* data worldwide



Antimicrobial Resistance Collaborators. *Lancet* 2022; **399**: 629–55

Emerging Carbapenemases in Gram-negatives

- KPC in *Klebsiella* and other enterics
- MBLs (IMP and VIM) in *P. aeruginosa*
- MBLs (VIM and NDM) in enterics
- OXA-23/24/58 in *Acinetobacter*
- OXA-48 in *K. pneumoniae* and *E. coli*

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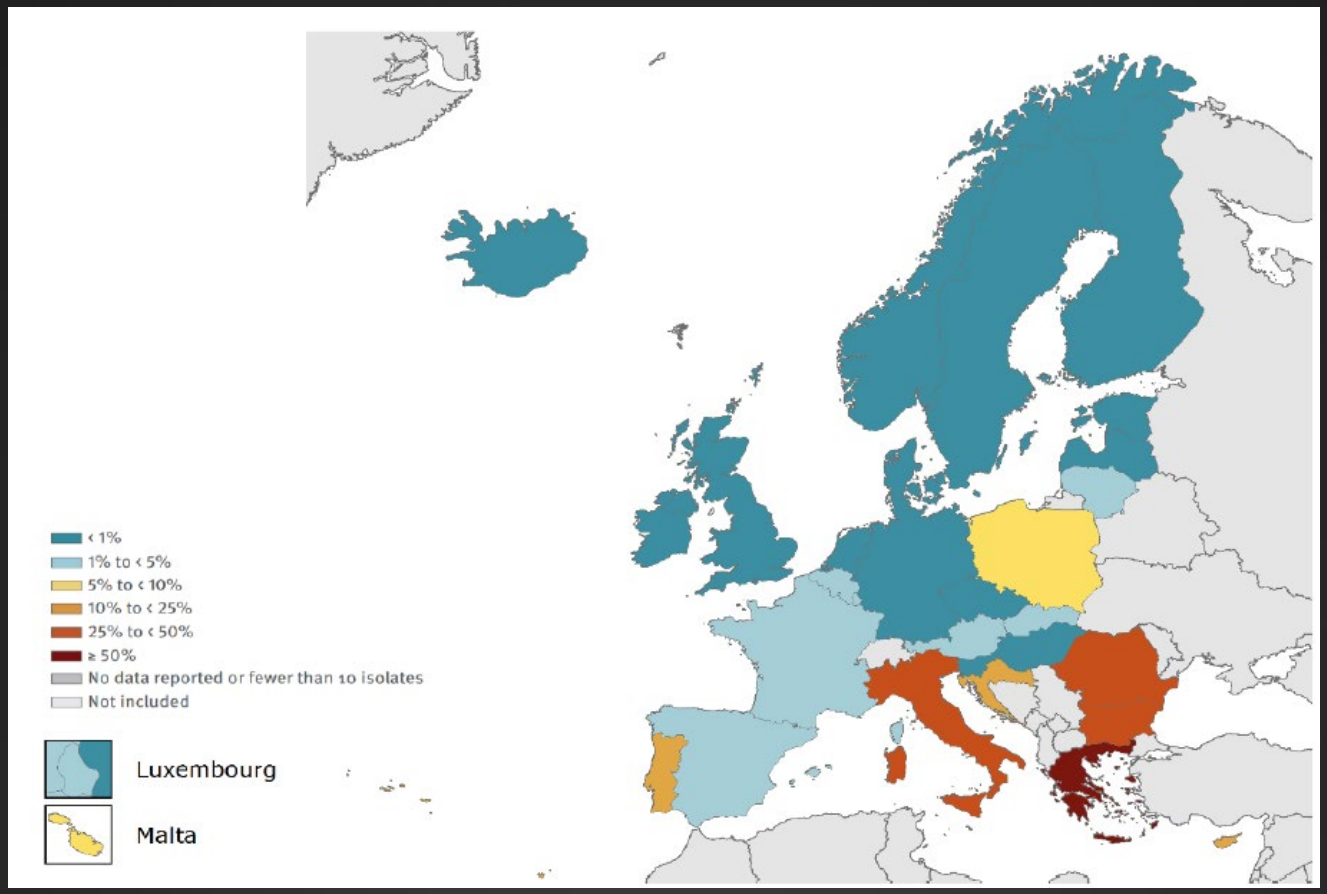
Klebsiella pneumoniae resistance to carbapenems (EARS-NET 2019)



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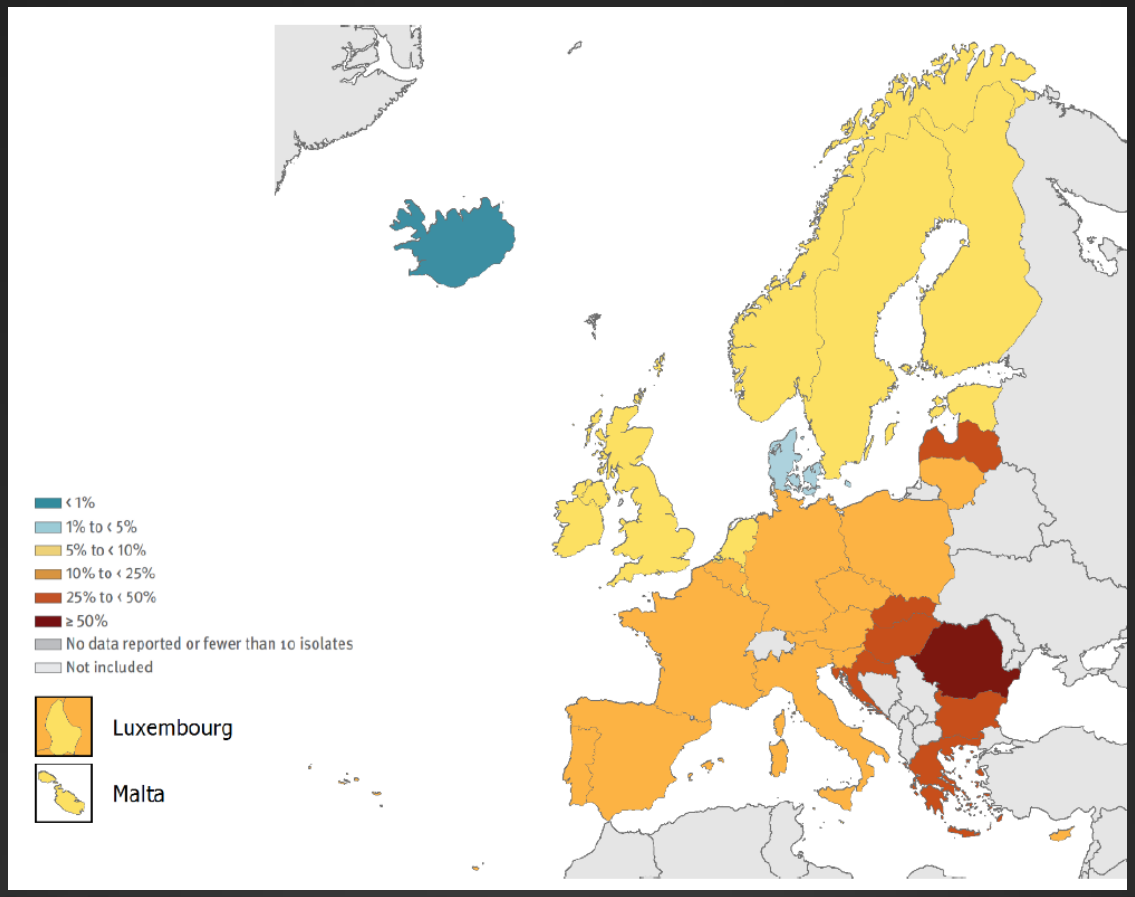
Pseudomonas aeruginosa resistance to carbapenems (EARS-NET 2019)



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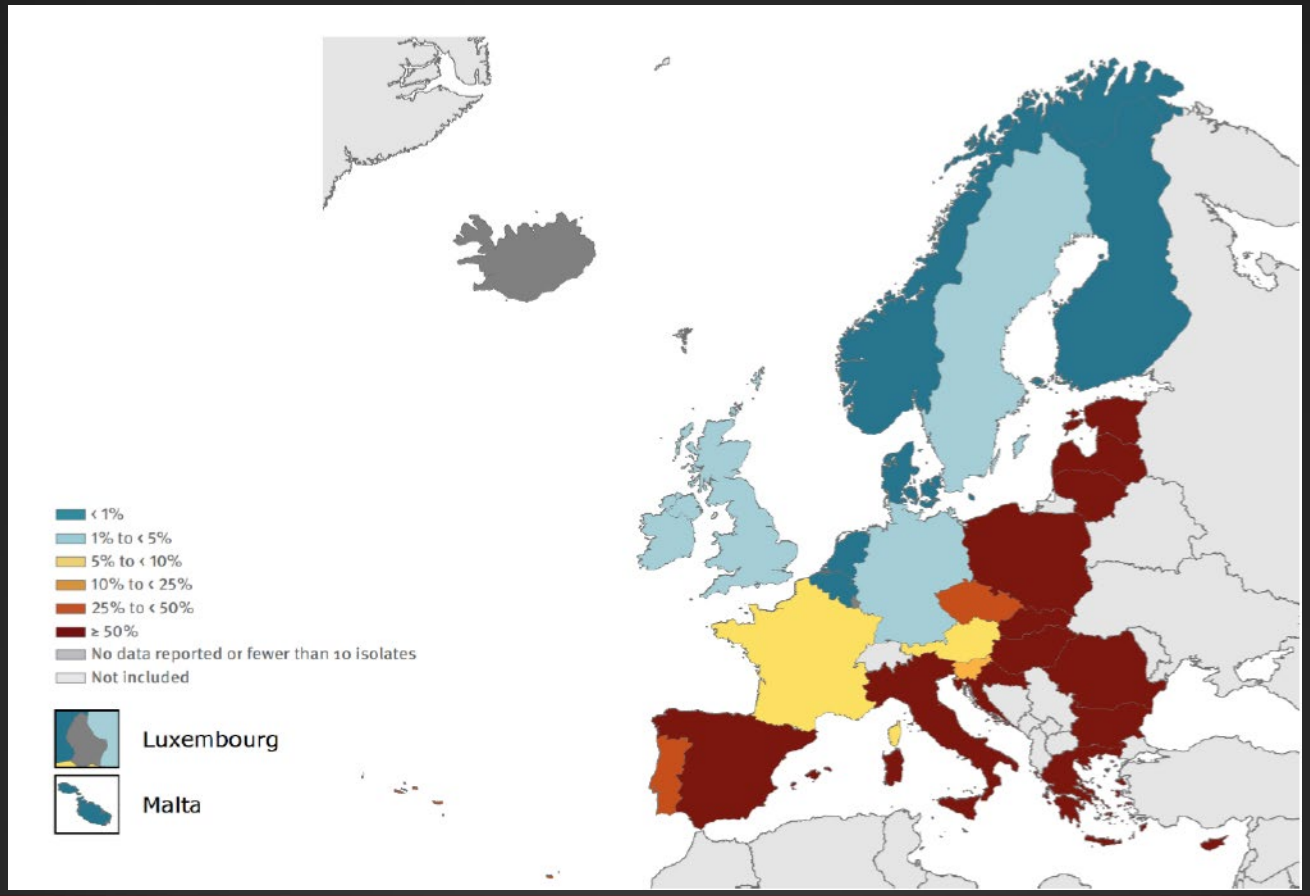
Acinetobacter baumannii resistance to carbapenems (EARS-NET 2019)



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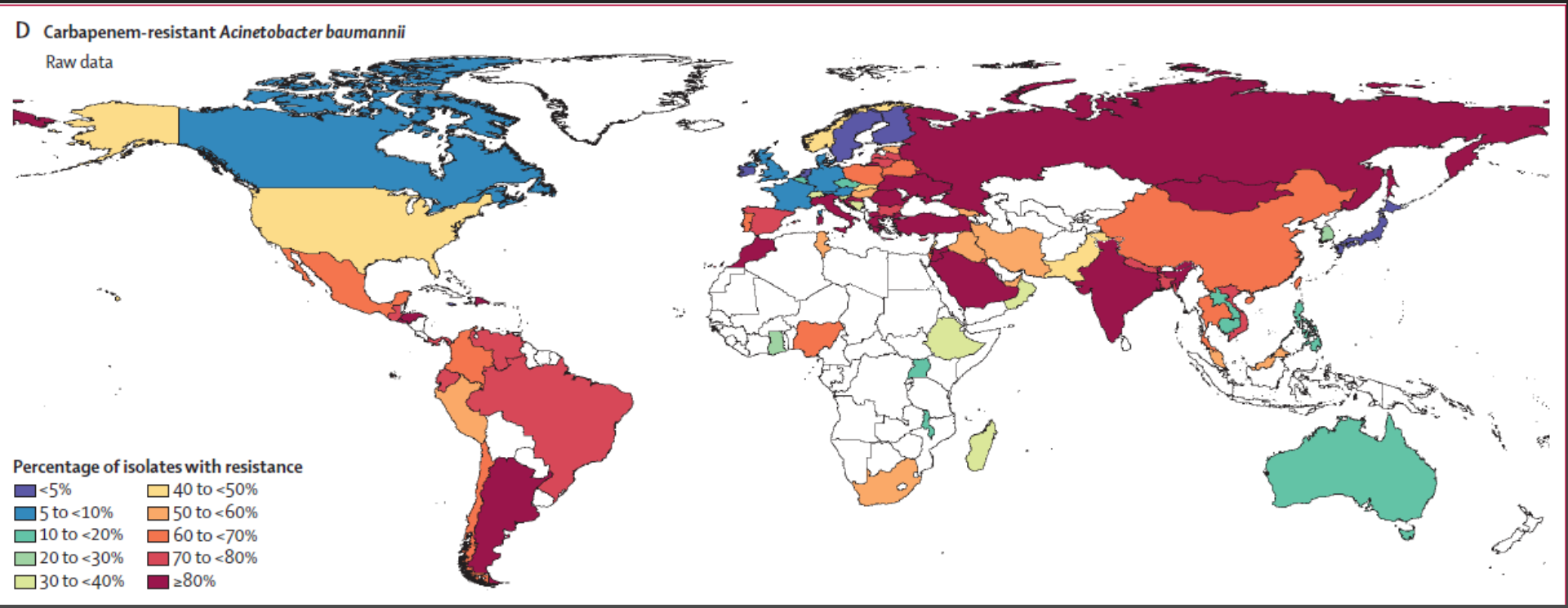
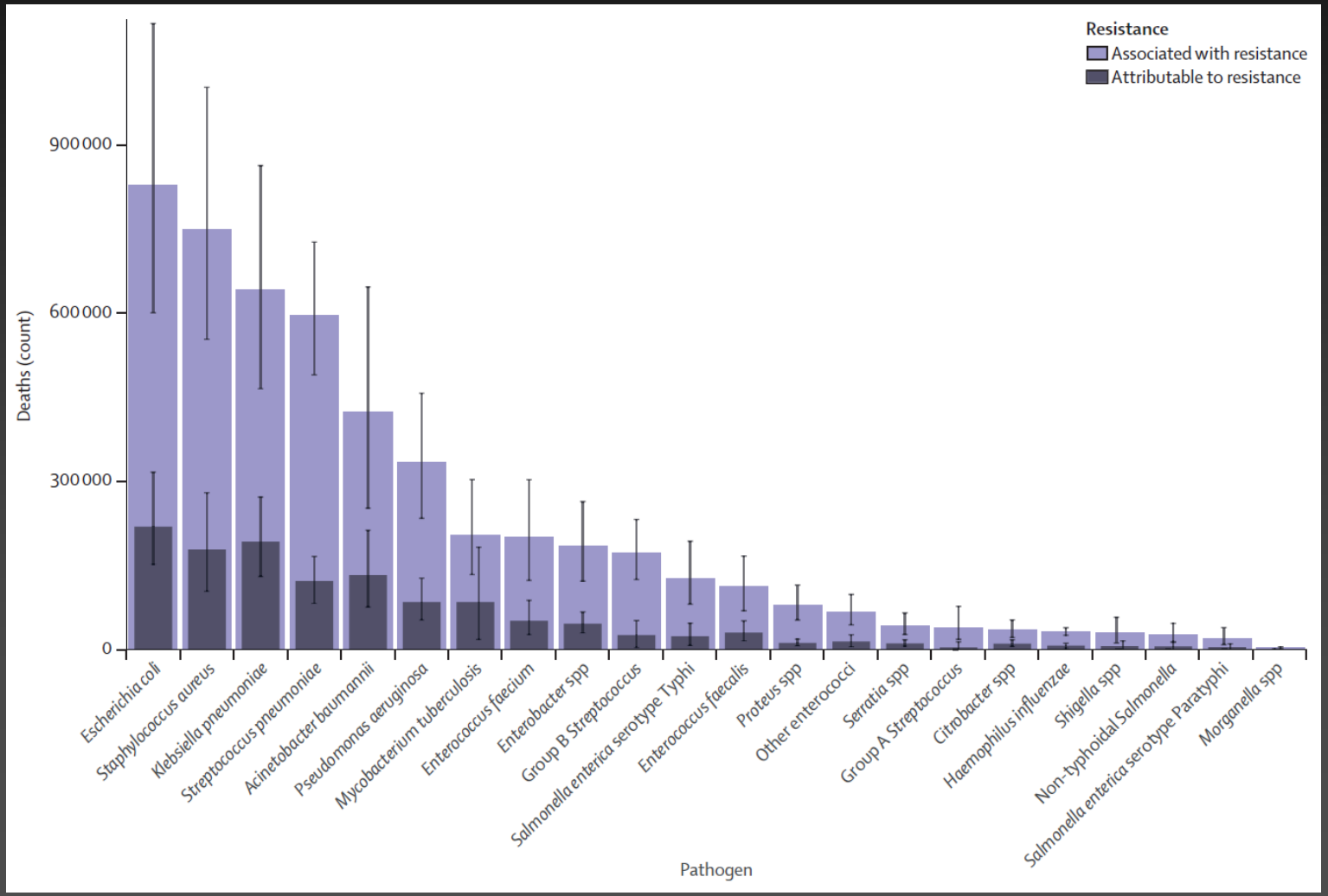
Carbapenem-resistant Acinetobacter baumannii data worldwide



Antimicrobial Resistance Collaborators. *Lancet* 2022; **399**: 629–55

Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019



Antimicrobial Resistance Collaborators. *Lancet* 2022; **399**: 629–55

Spectrum of activity of new antibiotics for difficult to treat (DTR) Gram-negative infections

	ESBL	CRE-KPC	CRE-OXA48	CRE-MBL	DTR *P. Aeruginosa*	DTR *Acinetobacter*
BL/BLI Combination						
• Ceftolozane/Tazobactam	🟢	🔴	🔴	🔴	1 🟢	🔴
• Ceftazidime-Avibactam	🟢	🟢	🟢	🔴	🟢	🔴
• Imipenem-Relebactam	🟢	🟢	2 🔴	🔴	3 🟢	🔴
• Meropenem-Vaborbactam	🟢	🟢	🔴	🔴	🔴	🔴
• Aztreonam-Avibactam	🟢	🟢	🟢	4 🟢	5 🔴	🔴
• Cefepime/Zidebactam	🟢	🟢	🟢	🟢	🟢	🟢
• Meropenem/Nacubactam	🟢	🟢	🟢	🔴	🔴	🔴
• Ceftaroline/Avibactam	🟢	🟢	🟢	🔴	🔴	🔴
Novel Cephalosporine						
• Cefiderocol	🟢	🟢	🟢	🟢	🟢	🟢
Novel Amynoglicoside						
• Plazomicin	🟢	🟢	6 🟢	7 🟢	8 🔴	8 🔴
Novel Tetracycline						
• Eravacyclin	🟢	🟢	🟢	🟢	🔴	🟢
• Murepavadin	🔴	🔴	🔴	🔴	🟢	🔴

🔴 No activity or intrinsic or acquired resistance. 🟢 Activity. Abbreviations: BL/BLI, β-lactam/β-lactamase Inhibitor CRE, carbapenem resistant Enterobacteriacae; ESBL, extended-spectrum beta-lactamase; MBLs, metallo-β-lactamases; OMPTA, outer membrane protein targeting antibiotics. 1. Decreased activity for carbapenemase- producing strains of CR *P. aeruginosa*; 2. Very weak activity; 3. Not have activity against MBL; 4. Reduced activity against certain NDM *Escherichia coli* isolates; 5. Activity comparable to aztreonam alone; 6. Activity against OXA-type CREs but increased resistance is observed; 7. Not active against many NDMs; 8. Activity toward *P. aeruginosa* and *A. baumannii* is overall comparable to existing aminoglycosides (tobramycin, amikacin, gentamicin).

Bassetti M et al. *Antibiotics* **2020**, 9, 632; doi:10.3390/antibiotics9090632

Ceftazidime–avibactam: real-world data

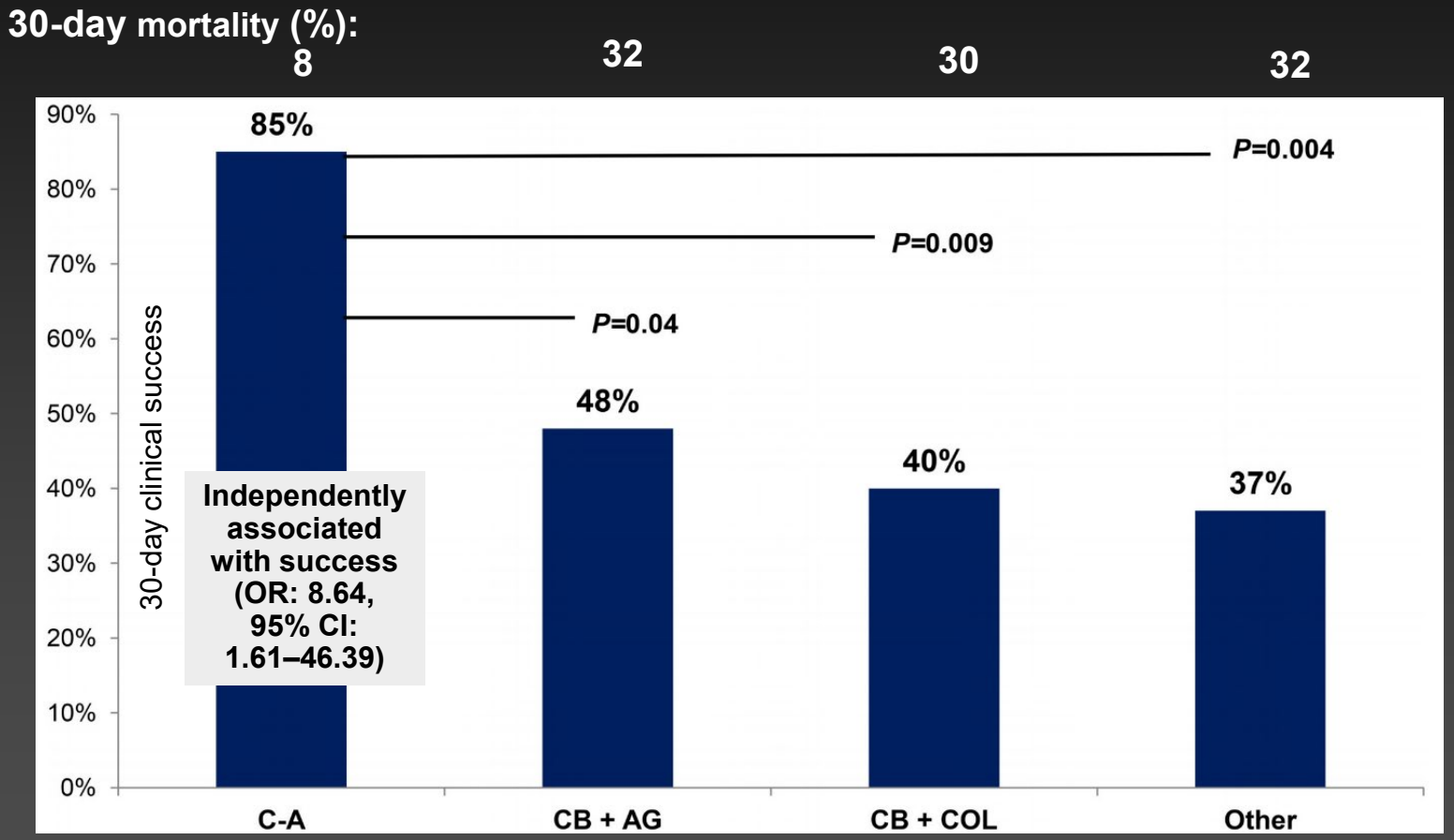
More than 17 observational studies!

Single-centre, retrospective cohort studies[1–10]	Multicentre, retrospective cohort studies[11–13]	Single-centre prospective, observational or multicentre case–control studies[14–16]	Multicentre, prospective observational cohort studies[17]
• Aitken SL, *et al.* 2016 • Shields RK, *et al.* 2016 • Krapp F, *et al.* 2017 • Shields RK, *et al.* 2017 • Santevecchi BA, *et al.* 2018 • Shields RK, *et al.* 2018 • Algwizani A, *et al.* 2018 • Rodríguez-Núñez O, *et al.* 2018 • De la Calle C, *et al.* 2019 • Alraddadi BM, *et al.* 2019	• Temkin E, *et al.* 2017 • Caston JJ, *et al.* 2017 • King M, *et al.* 2017	• Sousa A, *et al.* 2018 • Tumbarello M, *et al.* 2019 • Guimarães T, *et al.* 2019	• van Duin D, *et al.* 2018

Strength of evidence

1. Aitken SL, et al. Clin Infect Dis 2016;63:954–8; 2. Shields RK, et al. Clin Infect Dis 2016;63:1615–8; 3. Krapp F, et al. Int J Antimicrob Agents 2017;49:770–3; 4. Shields RK, et al. Antimicrob Agents Chemother 2017;61:e00883–17; 5. Santevecchi BA, et al. Int J Antimicrob Agents 2018;51:629–35; 6. Shields RK, et al. Antimicrob Agents Chemother 2018;62:e02497–18; 7. Algwizani A, et al. J Infect Public Health 2018;11:793–5; 8. Rodríguez-Núñez O, et al. J Glob Antimicrob Resist 2018;15:136–9; 9. De la Calle C, et al. Int J Antimicrob Agents 2018;53:520–4; 10. Alraddadi BM, et al. BMC Infect Dis. 2019;19:772; 11. Temkin E, et al. Antimicrob Agents Chemother 2017;61:e01964–16; 12. Caston JJ, et al. Int J Infect Dis 2017;59:118–23; 13. King M, et al. Antimicrob Agents Chemother 2017;61:e00449–17; 14. Sousa A, et al. J Antimicrob Chemother 2018;73:3170–5; 15. Tumbarello M, et al. Clin Infect Dis 2019;68:355–64; 16. Guimarães T, et al. Antimicrob Agents Chemother 2019 Epub ahead of print; 17. van Duin D, et al. Clin Infect Dis 2018;66:163–71.

Mortality rate in KPC-producing *K. pneumoniae* bacteraemia experience with CAZ–AVI



N=109

100% resistant to meropenem MIC≥16 mg/L (meropenem dose was not provided)

Secondary bacteremia resulted from abdominal (46%), respiratory tract (13%), urinary tract (13%).

AG, aminoglycoside; CAZ–AVI, ceftazidime-avibactam; CB, carbapenem-based; CI, confidence interval; COL, colistin; KPC, *K. pneumonia* carbapenemase; MIC, minimum inhibitory concentration; OR, odds ratio

Adapted from: Shields R, *et al. Antimicrob Agents Chemother.* 2017;61:e00883–17.

Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase–Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

- 577 infections of which 391 BSI
- All-cause 30-day mortality 25% (146/577)
- No difference in mortality between CAZAVI mono and CAZAVI in combo (26.1% vs. 25.0%, P=0.79)
- Mortality independently associated with septic shock, neutropenia, an INCREMENT score >8, LRTI, and CAZAVI dose adjustment for renal function
- Prolonged CAZAVI infusion was associated with reduced mortality

Tumbarello M, Raffaelli F, et al. Clin Infect Dis 2021 Feb 22;ciab176

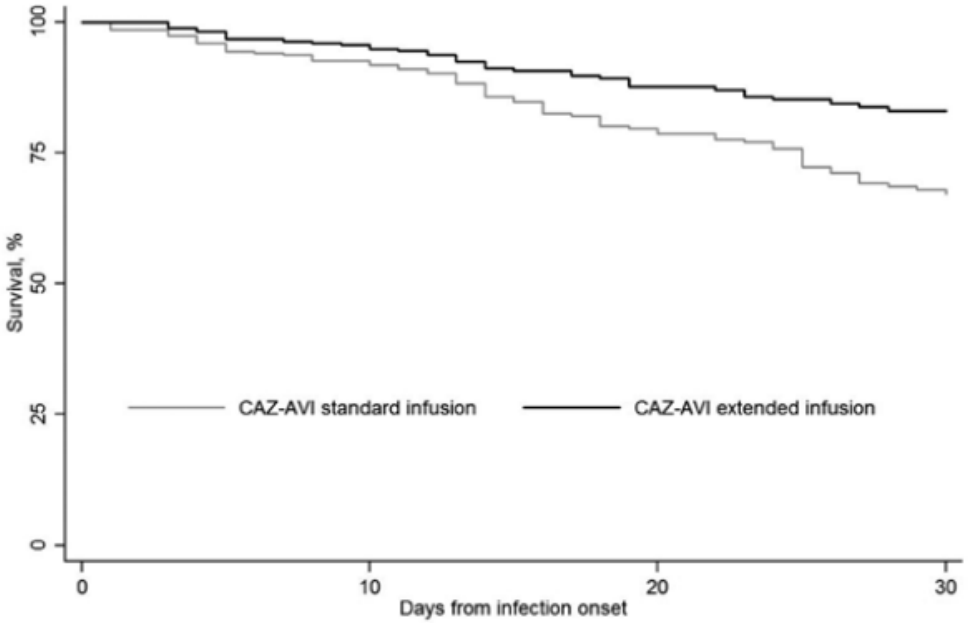


Figure 3. Kaplan-Meyer analysis of the impact of CAZ-AVI infusion times on 30-day survival. Significantly better survival was observed when CAZ-AVI was administered by prolonged infusion (standard dose given over ≥3 hours) versus standard infusion ($P < .001$). Abbreviation: CAZ-AVI, ceftazidime-avibactam.

Tumbarello M, Raffaelli F, et al. Clin Infect Dis 2021 Feb 22;ciab176

Results

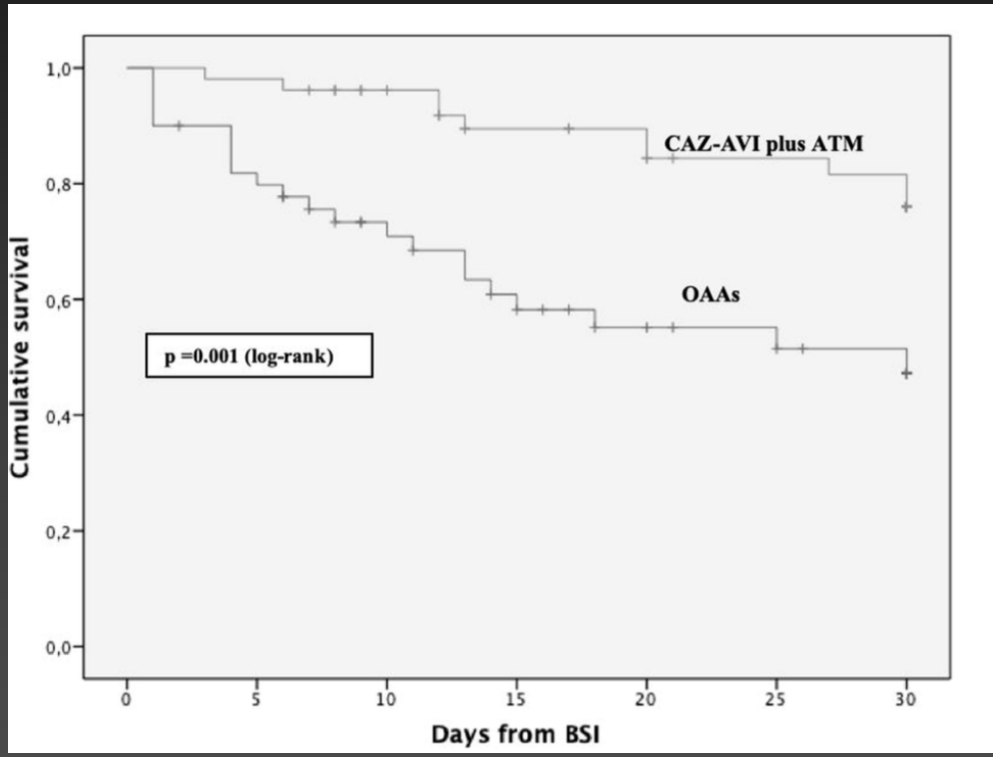
- 102 adults with *MBL Enterobacteriales* BSI
  - **82 NDM and 20 VIM**
- **52 (51%)** patients treated with CAZ-AVI+ATM vs **50 (49%)** treated with OAAs.

Falcone M et al. Clin Infect Dis. 2021 72:1871-1878.

Characteristic	CAZ-AVI + ATM (n = 52)	OAAs (n = 50)	*P* Value
Age, y, median (IQR)	69 (49.75–77)	70.5 (57.5–78)	.247
Male sex	36 (69.2)	33 (66)	.727
Ward of hospitalization			
Medical ward	21 (40.4)	28 (56)	.115
ICU ward	26 (50)	9 (18)	**.001**
Surgery	5 (9.6)	13 (26)	**.030**
Comorbidities			
Cardiovascular disease	22 (42.3)	19 (38)	.657
Solid cancer	16 (30.8)	19 (38)	.442
COPD	6 (11.5)	14 (28)	**.036**
Diabetes	20 (38.5)	14 (28)	.263
Chronic renal disease	8 (15.4)	7 (14)	.844
Chronic liver failure	3 (5.8)	7 (14)	.162
Solid organ transplantation	2 (3.8)	6 (12)	.126
Charlson comorbidity index, median (IQR)	4 (1–6)	4.5 (2–7)	.339
Immunosuppressive therapy, previous 30 d	10 (19.2)	25 (50)	**.001**
Source of infection			
Unknown	5 (9.6)	9 (18)	.219
Urinary tract	13 (25)	20 (40)	.105
Intravascular device	17 (32.7)	10 (20)	.146
Skin and soft tissue	9 (17.3)	3 (6)	.076
Respiratory tract	6 (11.5)	3 (6)	.324
Intra-abdominal	2 (3.8)	5 (10)	.219
Source control	34 (65.4)	24 (48)	.076
SOFA score, median (IQR)	4 (2–6)	5 (2–7.5)	.383
Septic shock	13 (25)	14 (28)	.731
Mechanical ventilation	17 (32.7)	14 (28)	.607
Time to in vitro active therapy ≤ 48 h	40 (76.9)	31 (62)	.101
Drug-induced AKI	1 (1.9)	10 (20)	**.003**
Duration of antibiotic therapy, d, median (IQR)	11 (8–14)	9 (5.75–12.5)	.081
Primary outcome			
30-d mortality	10 (19.2)	22 (44)	**.007**
Secondary outcome measures			
Clinical failure at day 14	13 (25)	26 (52)	**.005**
LOS after BSI[a], median (IQR)	14 (10–20.25)	23 (9.5–42.75)	.135

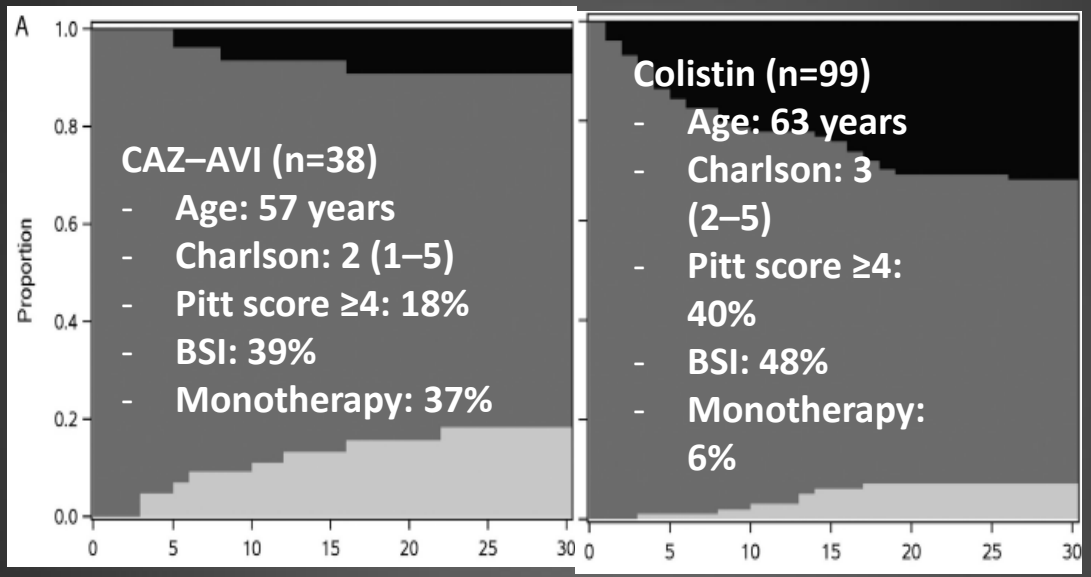
Factors Independently Associated With 30-Day Mortality

- Factors associated with mortality:
  - Cardiovascular disease (**HR 6.62**)
  - SOT (HR **3.52**)
  - SOFA score (HR **1.21**)
  - **CAZ-AVI+ATM** (HR 0.17)



Falcone M et al. Clin Infect Dis. 2021 72:1871-1878.

Outcomes of patients with MDR Gram-negative infections treated with colistin-based regimens

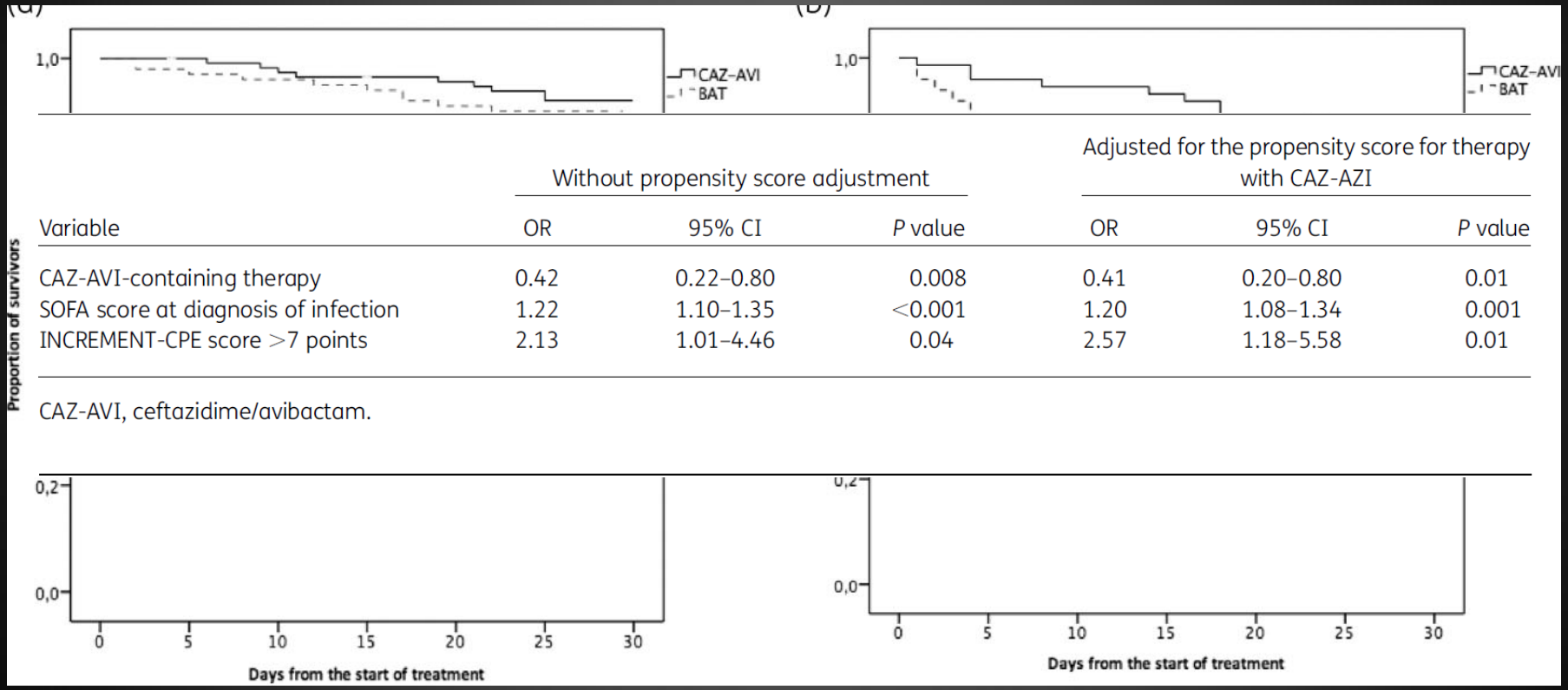


- Incident renal failure was 5% for CAZ–AVI versus 13% for colistin
- IPTW-adjusted all-cause mortality at 30 days was 9% for CAZ–AVI versus 32% for colistin
  - CAZ–AVI had an IPTW-adjusted 64% probability of a better outcome versus colistin

BSI, bloodstream infection; CAZ–AVI, ceftazidime-avibactam; IPTW, inverse probability of treatment weight; MDR, multidrug-resistant

Adapted from: Van Duin D, *et al. Clin Infect Dis.* 2018;66:163–71.

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)



	Without propensity score adjustment			Adjusted for the propensity score for therapy with CAZ-AZI		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
CAZ-AVI-containing therapy	0.42	0.22–0.80	0.008	0.41	0.20–0.80	0.01
SOFA score at diagnosis of infection	1.22	1.10–1.35	<0.001	1.20	1.08–1.34	0.001
INCREMENT-CPE score >7 points	2.13	1.01–4.46	0.04	2.57	1.18–5.58	0.01

CAZ-AVI, ceftazidime/avibactam.

Caston JJ et al. J Antimicrob Chemother 2022; 77: 1452–1460

Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacterales: a systematic review of observational clinical studies

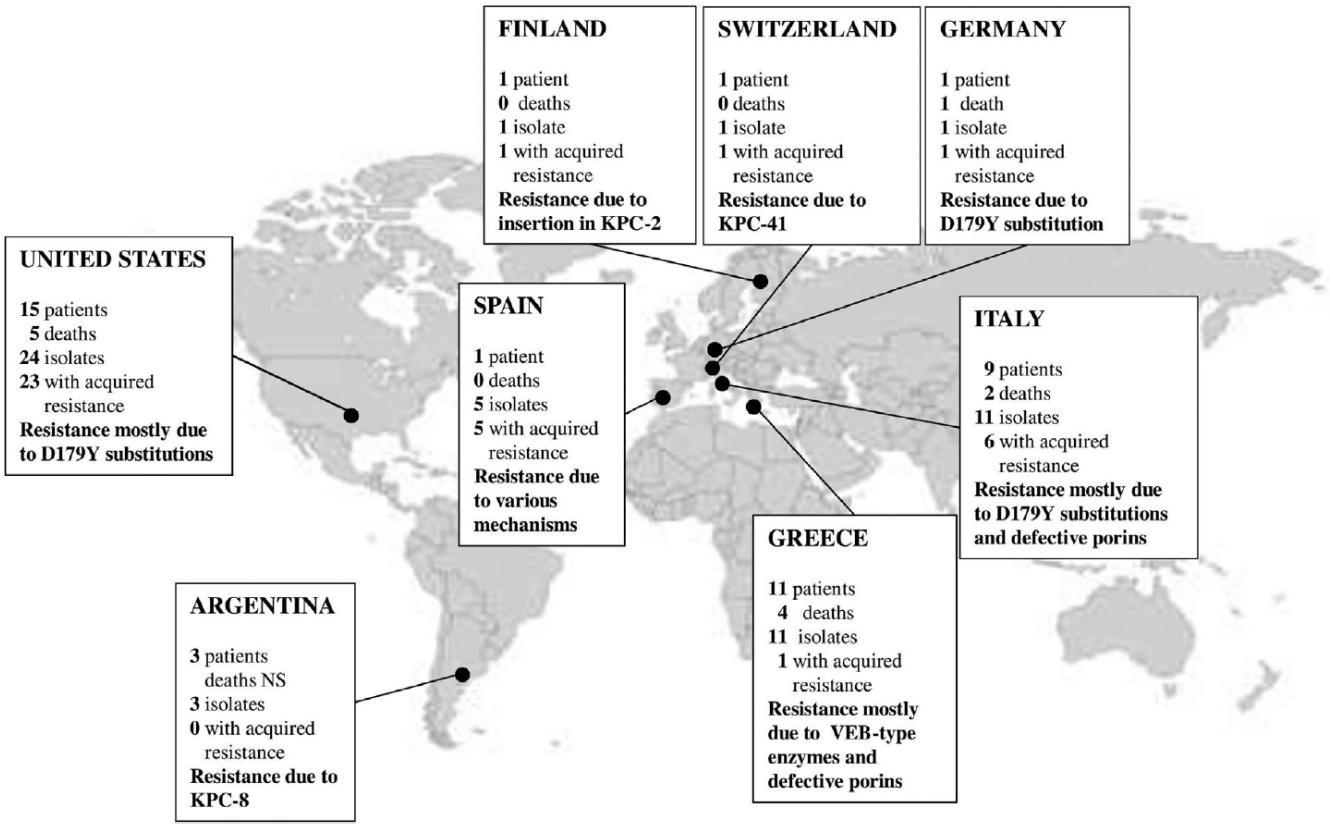


Fig. 2. Country-wise distribution of ceftazidime/avibactam-resistant cases and most relevant features.

Di Bella S, Giacobbe DR, et al. Journal of Global Antimicrobial Resistance 25 (2021) 268–281

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]

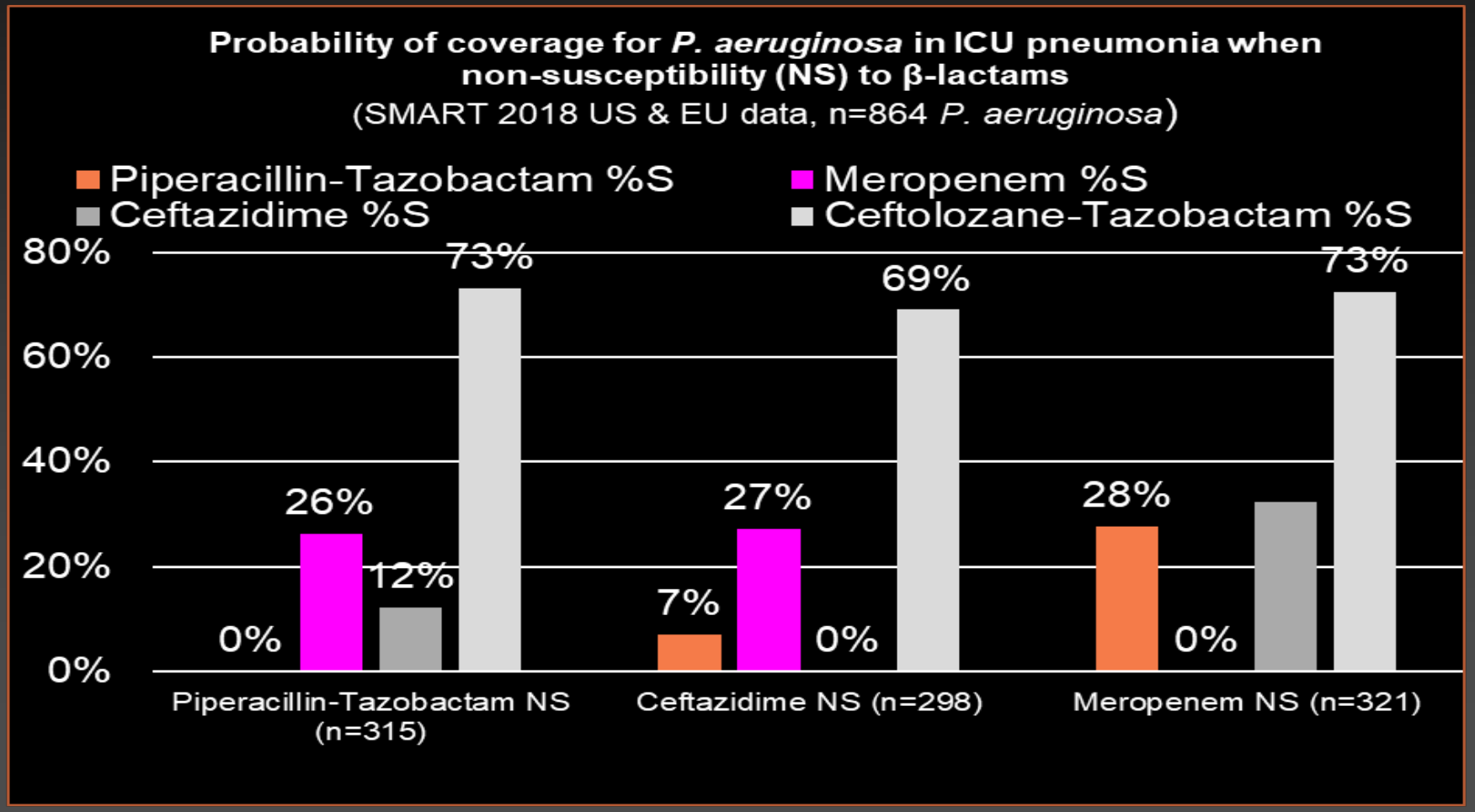
Resistance Mechanisms	Outer Membrane Porin Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	●	●	●	●
Ceftazidime	◐	○	●	○
Cefepime	●	○	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

○ Activity greatly decreased >> ● Retains activity

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

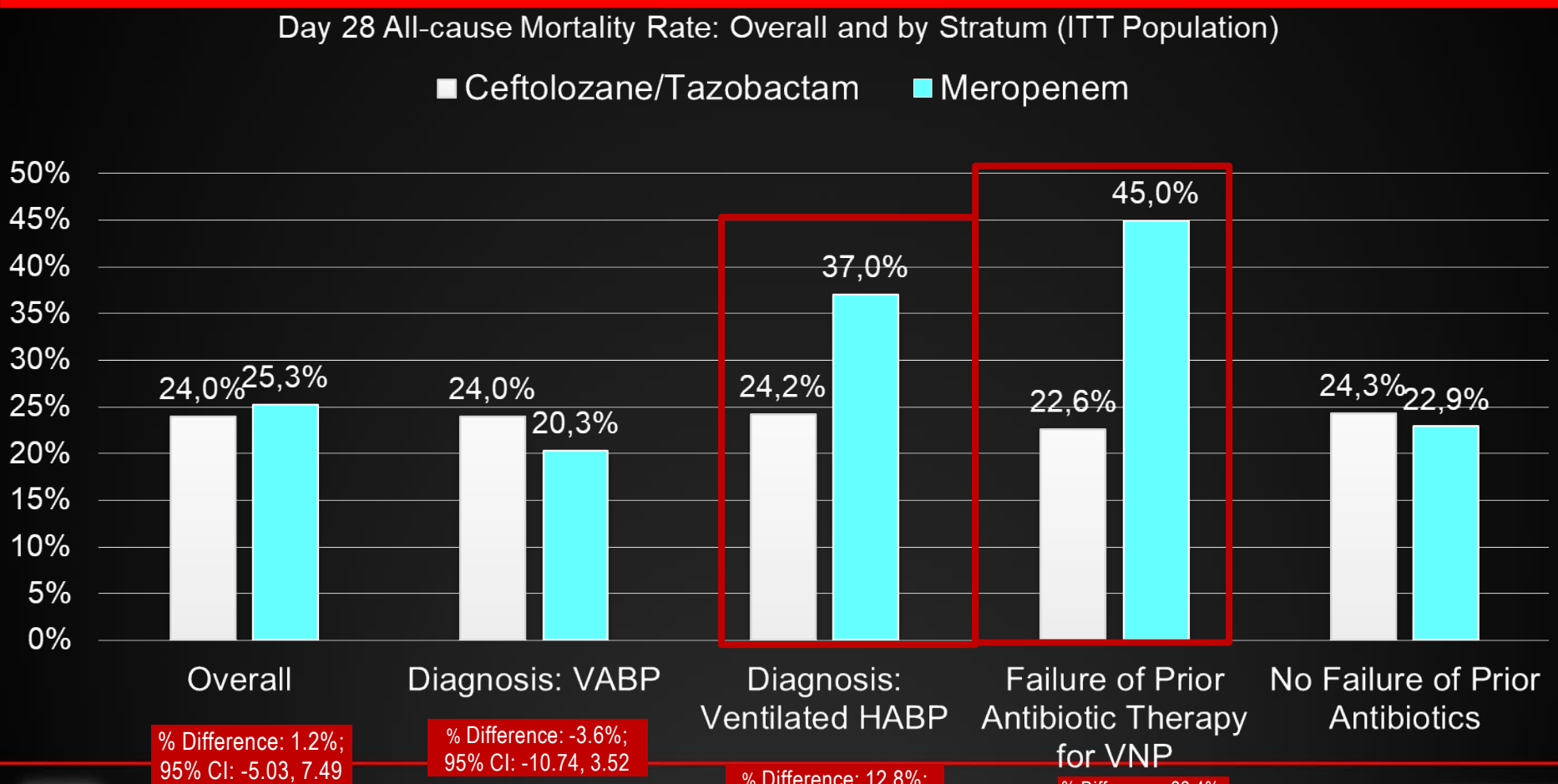
Table adapted from Castanheira M, et al. 2014

Co-Resistance in P. aeruginosa: New vs Old Antibiotics



Moise P et al Critical Care 2020, 24(Suppl 1):P425

Day 28 All Cause Mortality in Select at Risk Patients (ITT Population)



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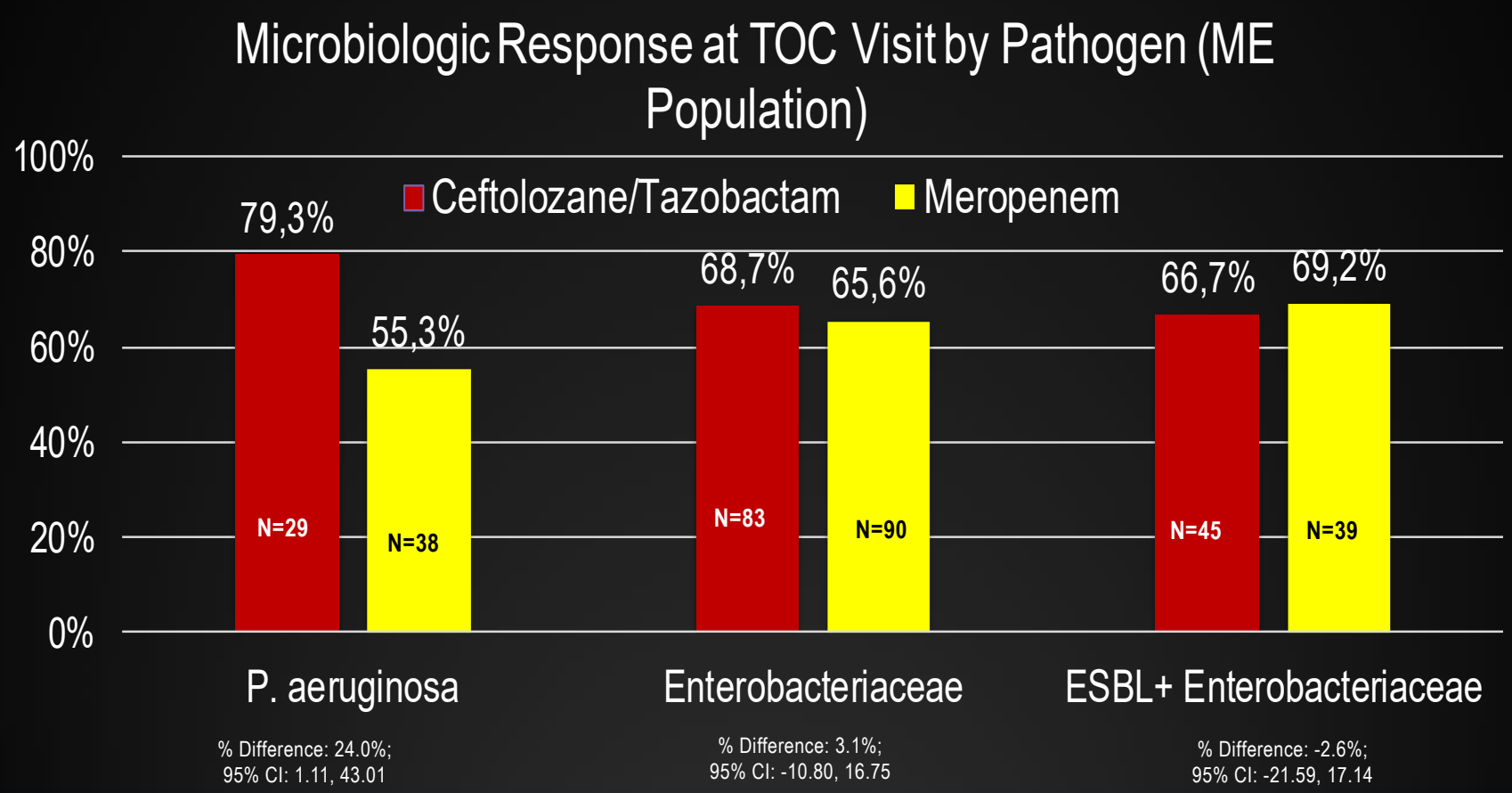
Kollef M et al. Lancet Infect Dis. 2019

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



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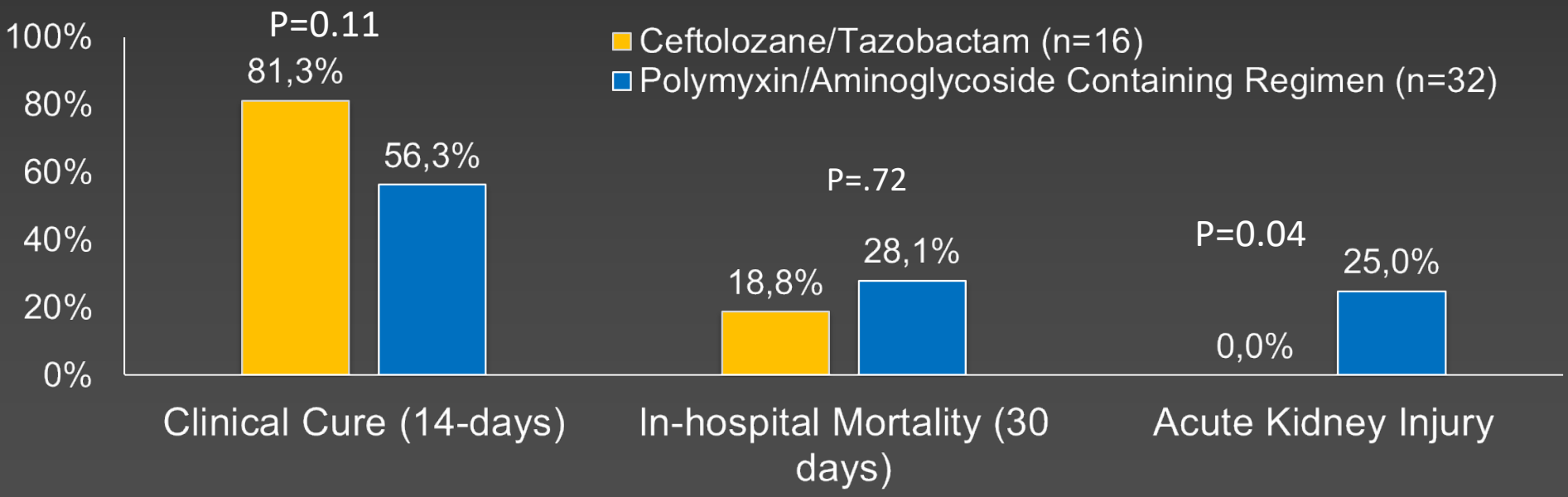
Kollef M et al. Lancet Infect Dis. 2019 Sep 25. pii: S1473-3099(19)30403-7

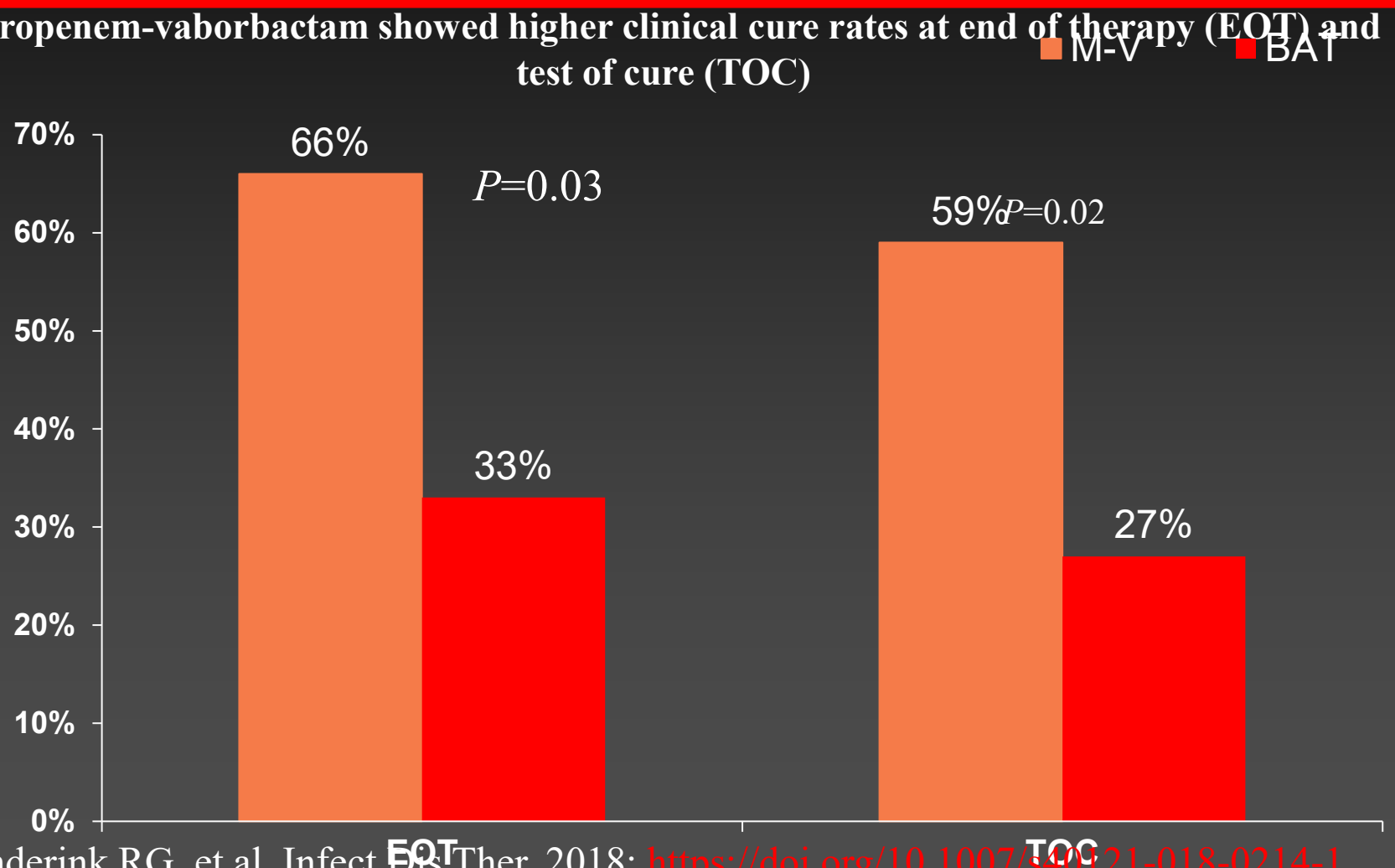
Comparative effectiveness of ceftolozane/tazobactam vs. polymyxin or aminoglycoside containing regimens (Italy)

- 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
  - A trend toward more favorable 14-day clinical cure rates with C/T (81% vs 56%, p=0.11)
  - An increased prevalence of acute kidney injury (25% vs 0%, p=0.04) with colistin/aminoglycoside containing regimens



Vena A et al. Clin Infect Dis 2020

Meropenem-vaborbactam: TANGO II



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

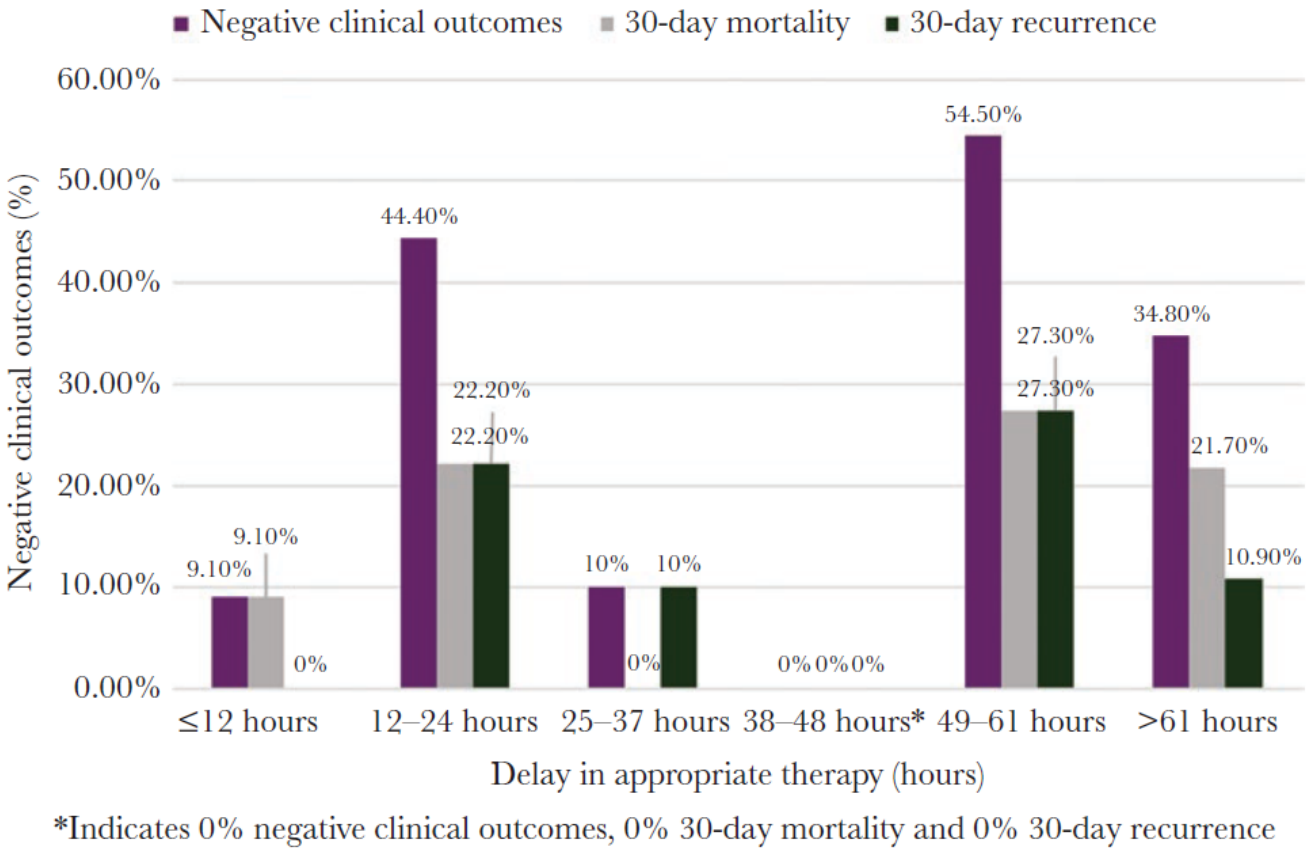
TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)

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.

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

Real-world, Multicenter Experience With MeropenemVaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant Enterobacterales and Pseudomonas aeruginosa



*Indicates 0% negative clinical outcomes, 0% 30-day mortality and 0% 30-day recurrence

Alosaimy S et al. Open Forum Infect Dis. 2021;8(8):ofab371

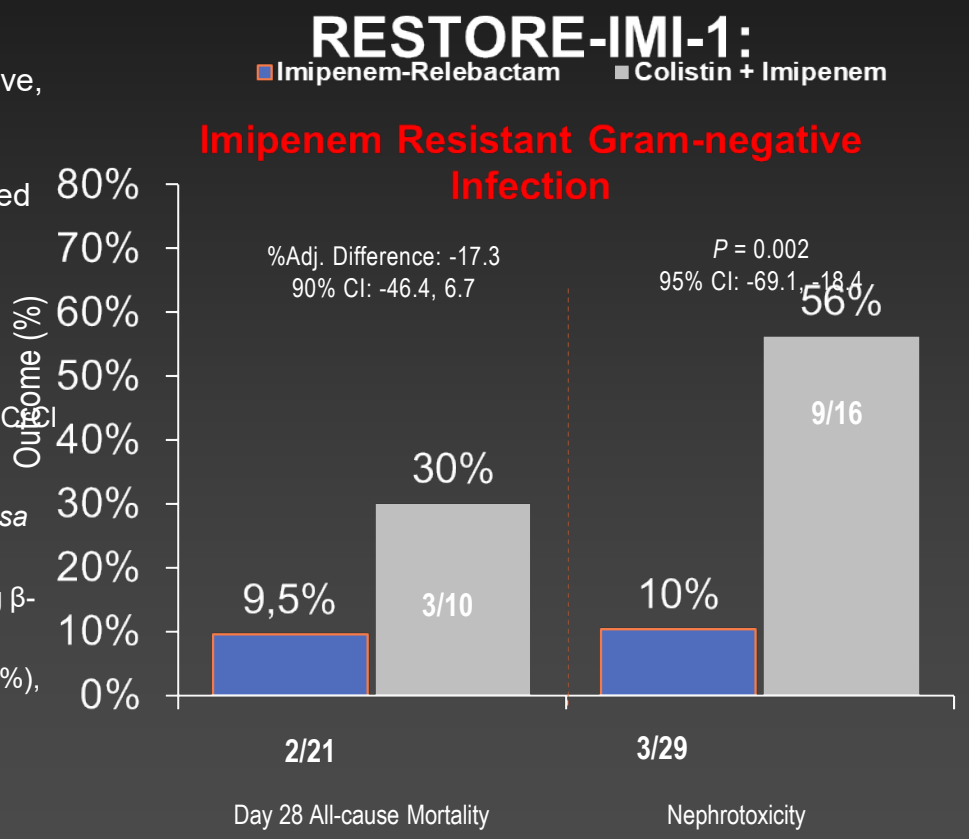
Two double-blind, randomized studies, including a small Phase 3 study (PN013) in various IMI-resistant infections and a large Phase 3 study in HABP/VABP

Study	Patient Population	Study Design	Sample Size
RESTORE-IMI 1	Patients with cUTI, cIAI, or HABP/VABP caused by **IMI-NS**, but IMI/REL- and colistin-susceptible isolates	• 2 treatment arms, randomized 2:1 – IMI/REL 500/250 mg, every 6 hours – Colistin (as CMS, 150 mg CBA every 12 hours after 300 mg loading dose) + IMI 500 mg every 6 hours • Primary endpoint: overall response, determined by relevant endpoint for each infection	50
RESTORE-IMI 2	Patients with either HABP or VABP	• 2 treatment arms, randomized 1:1 – IMI/REL 500/250 mg, every 6 hours – Piperacillin/tazobactam 4 g/500 mg, every 6 hours • Concurrent linezolid IV as empirical methicillin-resistant *Staphylococcus aureus* (MRSA) therapy • Primary endpoint: day 28 all-cause mortality	536 (268 per group)

Motsch J et al Clin Infect Dis. 2019

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 <60 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: pathogen-focused Phase 3 study

Population

High-risk, severely ill patients; infections include non-fermenter species such as *Acinetobacter* spp.

Patients were enrolled irrespective of infection type, comorbidities, pathogen species, or CR mechanism

Study drug

Cefiderocol (2 g) (n=101) (mostly monotherapy) or **best available therapy (BAT)** (n=49) that could include up to three antibiotics, dosed according to country's label

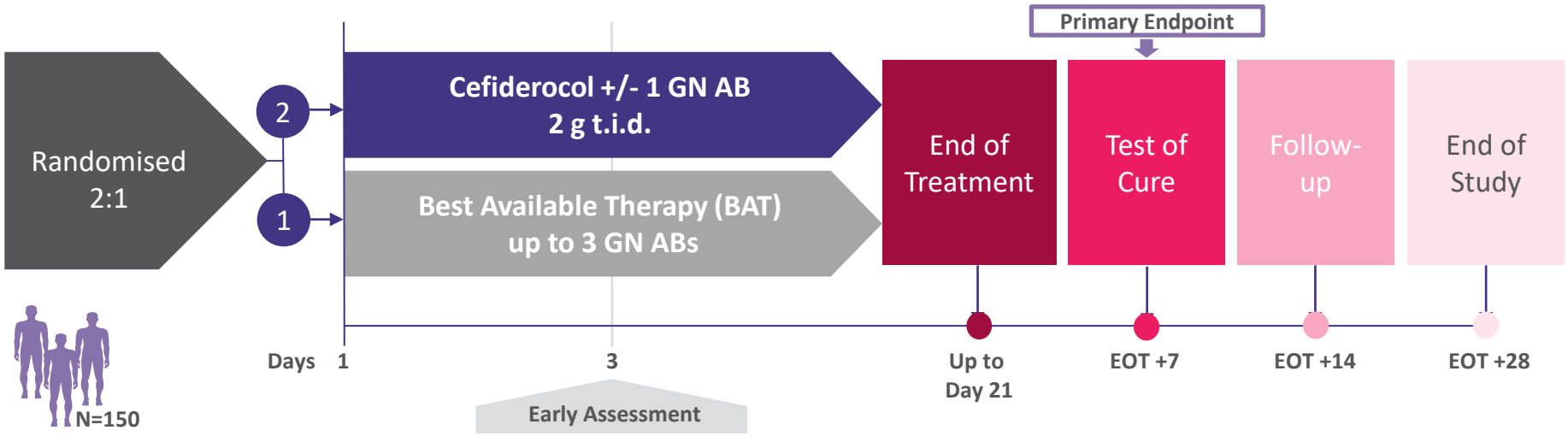
Open-label design

Randomised, pathogen-focused, **open-label, non-inferential, descriptive trial** to assess the efficacy and safety of cefiderocol or BAT.

BAT, best available therapy; CR, carbapenem resistant.

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

CREDIBLE-CR: a novel, pathogen-focused, open-label study to explore cefiderocol therapy and BAT in CR GN infections



Objectives

- **Primary endpoint at TOC:** HAP/VAP/HCAP and bloodstream infections/sepsis – clinical outcome; cUTI – microbiological outcome
- **Secondary endpoint:** clinical and microbiological outcomes at TOC, EOT and FU, and Day 14 and 28 ACM

ACM, all-cause mortality; AB, antibiotic; BAT, best available therapy; CR, carbapenem resistant; cUTI, complicated urinary tract infection; EOT, end of treatment; FU, follow-up; GN, Gram negative; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; t.i.d., three times daily dosing; TOC, test of cure; VAP, ventilator-associated pneumonia.

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

High rates of clinical cure and microbiological eradication with cefiderocol in CRE infections

Clinical cure

	Cefiderocol % (n/N)	BAT % (n/N)
CRE	66% (19/29)	45% (5/11)
CR non-fermenters	45% (22/49)	52% (13/25)
Mixed	50% (1/2)	50% (1/2)

Microbiological eradication

	Cefiderocol % (n/N)	BAT % (n/N)
CRE	48% (14/29)	18% (2/11)
CR non-fermenters	22% (11/49)	24% (6/25)
Mixed	0% (0/2)	50% (1/2)

BAT, best available therapy; CRE, carbapenem resistant Enterobacteriaceae; CR, carbapenem resistant

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

CREDIBLE-CR: all-cause mortality, Day 28 and End of Study[a]

Timing of death	Cefiderocol (n=101) n (%)	BAT (n=49) n (%)
Up to Day 28	25 (25)	9 (18)
Late: Day 29 to end of study	9 (9)	0 (0)
Overall mortality: end of study	34 (34)	9 (18)

[a]Safety population

BAT, best available therapy.

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

Mortality in CREDIBLE-CR was associated with *A. baumannii* infection, but characteristics of shock and infection severity may also contribute

The underlying reasons for the mortality imbalance in CREDIBLE may never be known, but mortality appears to be associated with *A. baumannii*

Patients infected with *A. baumannii* and treated with cefiderocol had a higher unadjusted mortality rates than patients without *A. baumannii* or treated with BAT; numbers were small

Characteristics of *A. baumannii* patients treated with cefiderocol

- Older (>65 years)
- More severely ill (APACHE II ≥16)
- Progressed to shock
- Resident in the ICU

But patient numbers were small

APACHE, Acute Physiology and Chronic Health Evaluation; BAT, BAT, best available therapy; ICU, intensive care unit.

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

CREDIBLE-CR: 49-day mortality rates, by most frequent baseline pathogen, appear to be associated with *Acinetobacter* spp infections[a]

	Cefiderocol (n=101) n (%)	BAT (n=49) n (%)
***Acinetobacter* spp.**[a]	21/42 (50)	3/17 (18)
A. baumannii	19/39 (49)	3/17 (18)
K. pneumoniae	8/34 (24)	4/16 (25)
without *Acinetobacter* spp.	6/28 (21)	4/15 (27)
P. aeruginosa	6/17 (35)	2/12 (17)
without *Acinetobacter* spp.	2/11 (18)	2/11 (18)
E. coli	1/6 (17)	0/3 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
S. maltophilia	4/5 (80)	–
without *Acinetobacter* spp.	2/3 (67)	–

[a]Safety population

Due to the small numbers, no conclusions can be drawn

BAT, best available therapy.

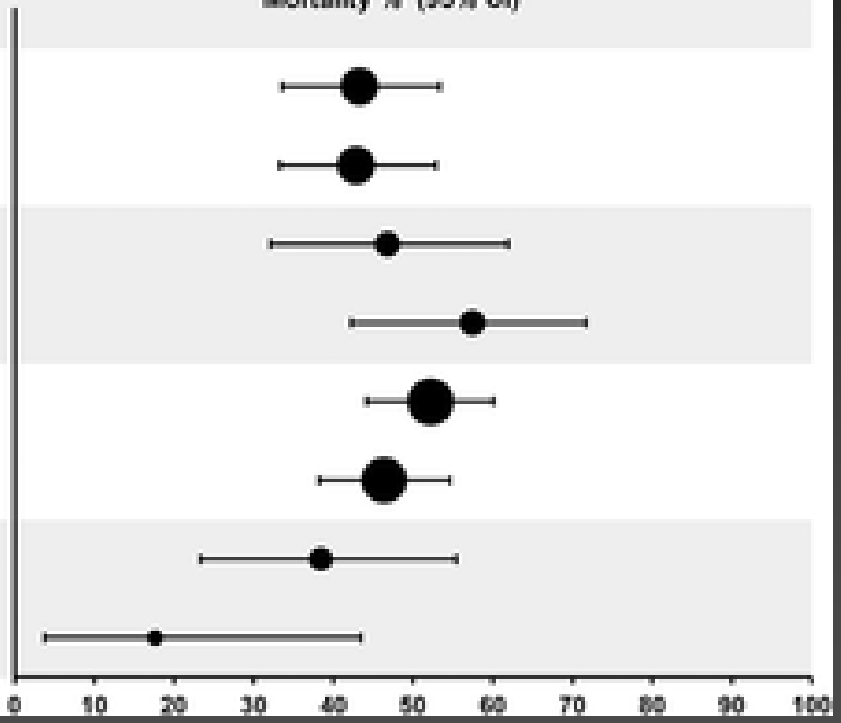
[a]*Acinetobacter* spp. includes *A. baumannii, A. nosocomialis* and *A. radioresistens.*

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

Day 28 all-cause mortality rates in carbapenem-resistant Acinetobacter spp. infections

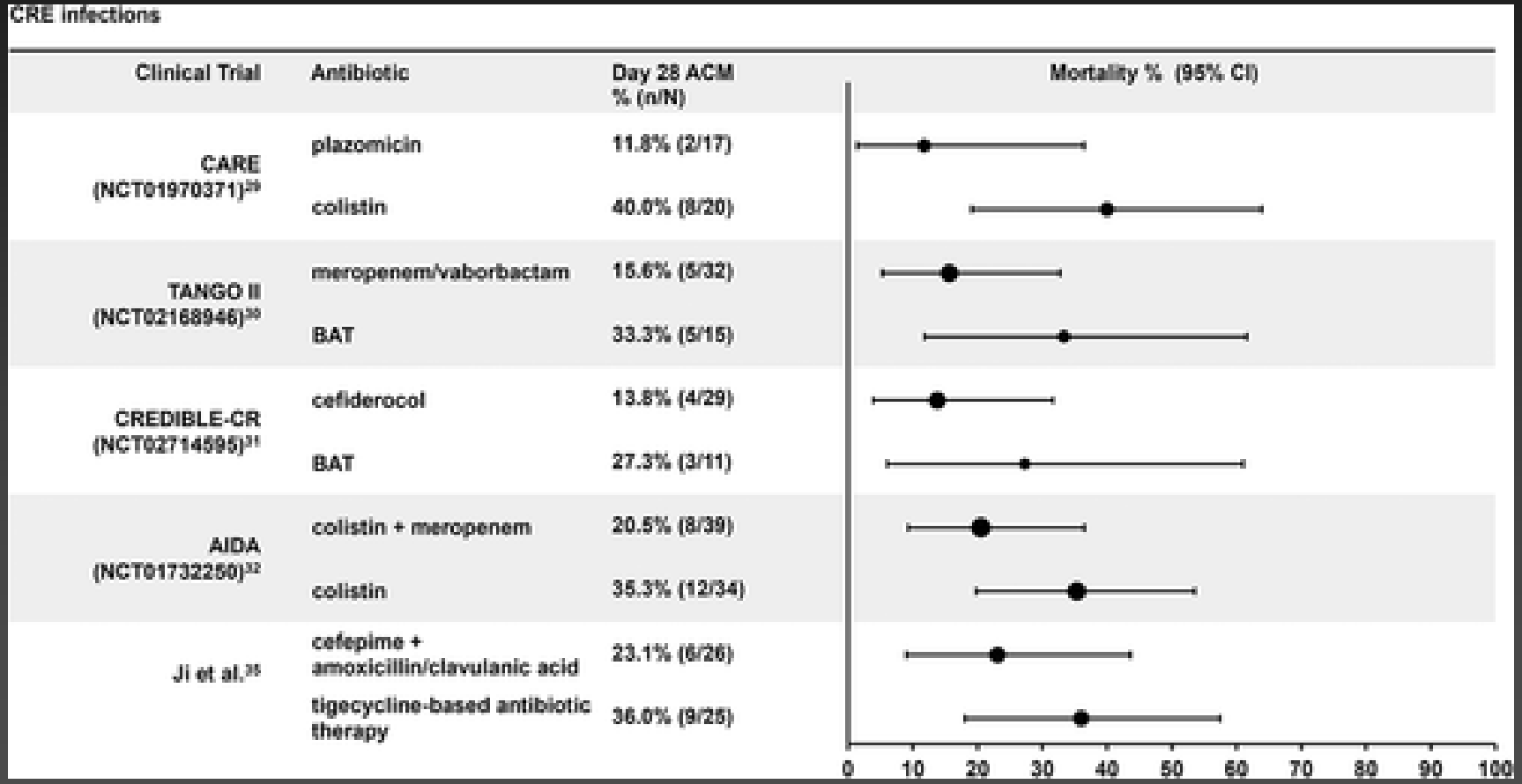
CR *Acinetobacter* spp. infections

Clinical Trial	Antibiotic	Day 28 ACM % (n/N)
Durante-Mangoni (NCT01577862)[33]	colistin + rifampicin	43.3% (45/104)
	colistin	42.9% (45/105)
Sirijatuphat (NCT01297894)[34]	colistin + fosfomycin	46.8% (22/47)
	colistin	57.4% (27/47)
AIDA (NCT01732250)[32]	colistin + meropenem	52.2% (84/161)
	colistin	46.4% (70/151)
CREDIBLE-CR* (NCT02714595)[31]	cefiderocol	38.5% (15/39)
	BAT	17.7% (3/17)



Lodise TP et al. *Expert Rev Anti Infect Ther* 2022 Jan 12;1-13

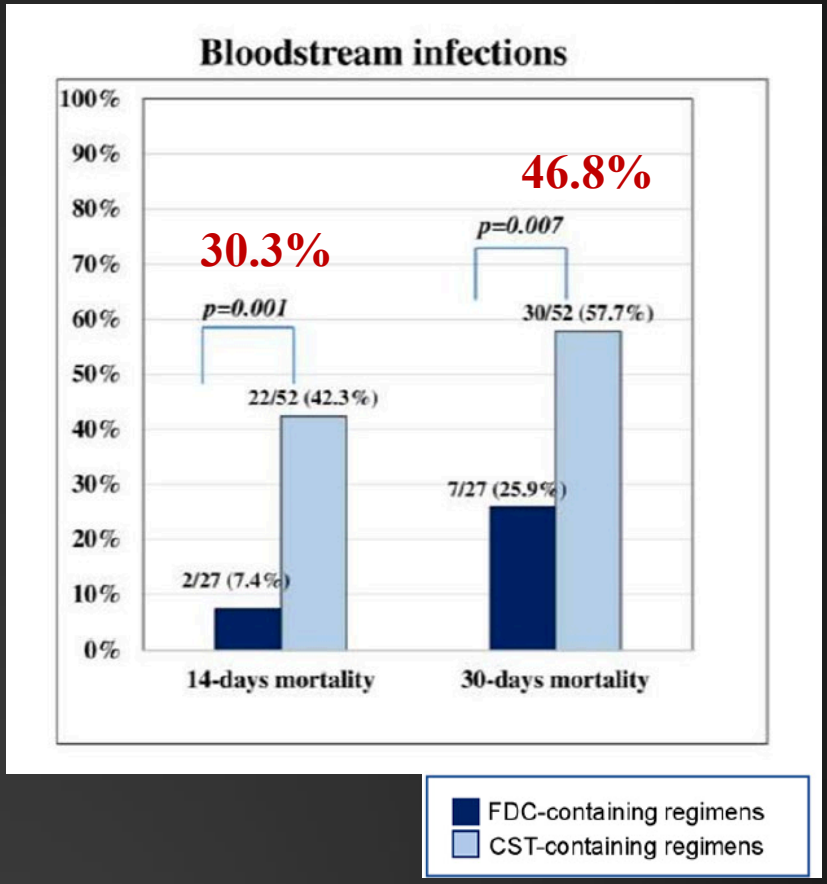
Day 28 all-cause mortality rates in carbapenem-resistant Enterobacterales infections.



Lodise TP et al. *Expert Rev Anti Infect Ther* 2022 Jan 12;1-13

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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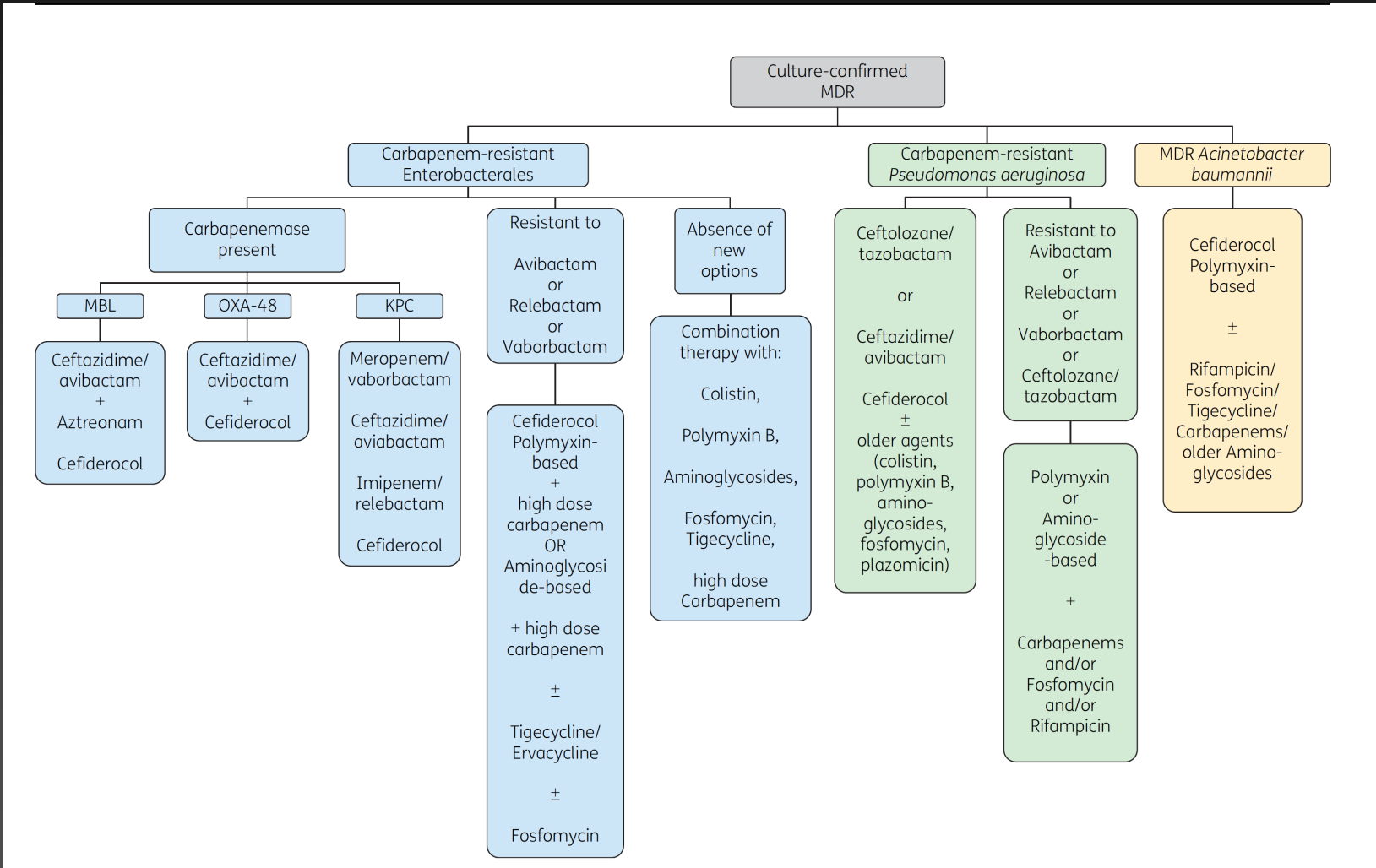
Genoa, Italy

Examples of clinical experience of «old style vs new style treatment» in CRE infections

Study	Treament	Mortality
OLD		
Shields, 2017	Ceftazidime/avibactam (mono or combo)	8%
Wunderink RG, 2018	Meropenem/vaborbactam	15.6%
Motsch, 2019	Imipenem/relabactam*	9.5%
Bassetti, 2021	Cefiderocol	13.8%

*Imipenem-relebactam is not yet registered in EMA

Suggested treatments for carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa, and multidrug-resistant Acinetobacter baumannii



Bassetti M, Garau X. . *J Antimicrob Chemother* 2021; **76** : iv23–iv37

Don’t forget…Tailoring Treatment also means

Adequate source control of the infection

Adequate lenght of therapy

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Recommendations are for non-colistin based regimens for MDR Gram-negatives: CRE Example

- 2020 IDSA "Resistance Guidance": Recommendations for Carbapenem-resistant Enterobacterales (CRE)

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Infections outside of the urinary tract Resistant to ertapenem, meropenem, AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Tamma PD, Aitken SL, Bonomo RA et al. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections. Available at https://www.idsociety.org/practice-guideline/amr-guidance/ Published by IDSA, 8-Sep-2020, Last accessed November 2020

Recommendations that we move away from colistin regimens to newer drugs for antimicrobial resistant Gram-negative infections: *P. aeruginosa* Example

- 2020 IDSA "Resistance Guidance": Recommendations for difficult-to-treat (DTR) *Pseudomonas aeruginosa*

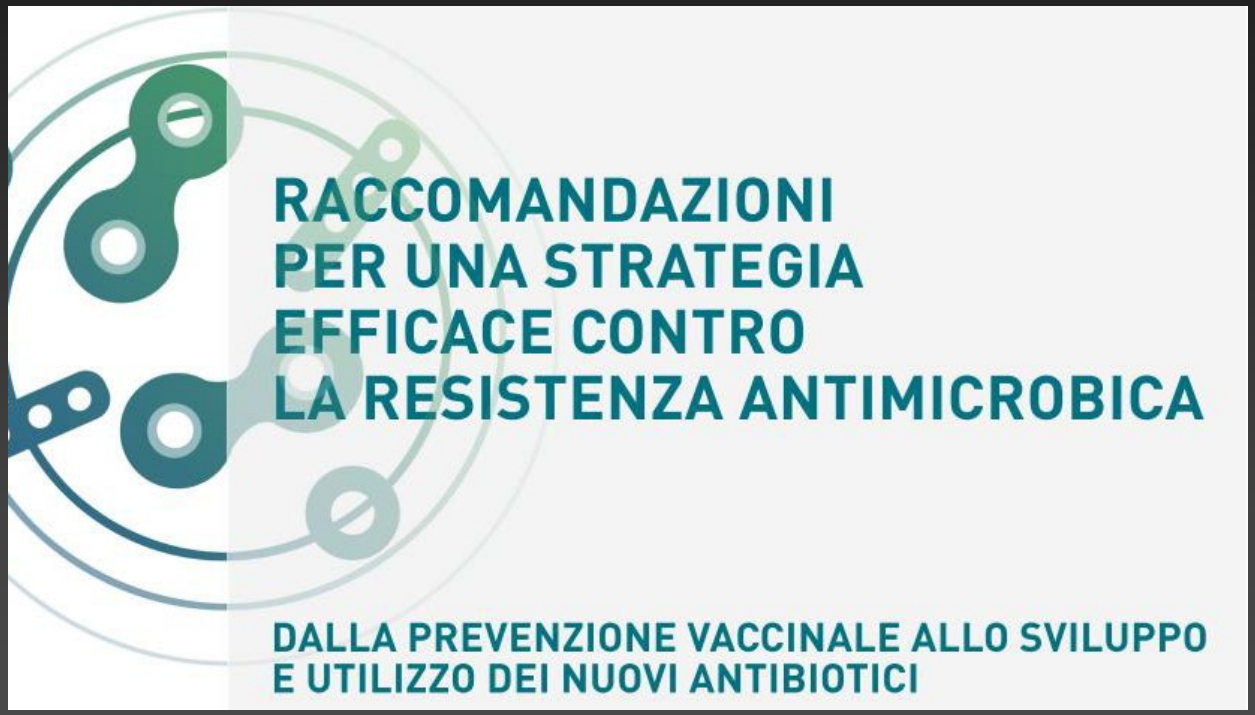
Source of Infection	**Preferred Treatment**	**Alternative Treatment** (when first-line options not available/tolerated)
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single-dose of an aminoglycoside	Colistin
Pyelonephritis or cUTI[1]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[2]

[1]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[2]Uncomplicated bloodstream infections include a bloodstream infection due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

Tamma PD, Aitken SL, Bonomo RA et al. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections. Available at https://www.idsociety.org/practice-guideline/amr-guidance/ Published by IDSA, 8-Sep-2020, Last accessed November 2020

Task force nazionale AMR



Valore, accesso e innovazione dei nuovi antibiotici contro le resistenze batteriche

- Metodologia di valutazione dei nuovi antibiotici contro i ceppi batterici resistenti
  - Adattare le attuali metodologie per la determinazione del valore degli antibiotici alle caratteristiche di questi farmaci, considerando il loro ruolo salvavita, tenendo presente che questo richiederà una prospettiva più ampia e l'analisi di scenari ed evidenze oltre a quelle necessarie per le attuali richieste di registrazione.

- Criteri per il conferimento dello status di farmaco "innovativo" ai nuovi antibiotici contro i ceppi batterici resistenti
  - Utilizzare indicatori specifici capaci di misurare efficacemente il grado di innovatività dei nuovi antibiotici, adattando, se necessario, gli attuali elementi di valutazione a supporto della richiesta di innovatività (bisogno terapeutico sulla base degli indicatori pubblicati annualmente dall'ECDC sui patogeni resistenti agli antibiotici, valore terapeutico aggiunto su patogeni resistenti agli antibiotici disponibili e robustezza delle prove scientifiche modulando la metodologia GRADE a seconda delle specificità dei nuovi antibiotici tenendo conto anche della capacità di contrastare efficacemente con meccanismi innovativi i principali meccanismi di resistenza batterica).

- Modelli di rimborso ad hoc per i nuovi antibiotici attivi per le resistenze batteriche
  - Visto che la stewardship antimicrobica fornisce indicazioni restrittive sull'uso dei nuovi antibiotici nel trattamento delle infezioni causate dai ceppi resistenti per ridurre la probabilità che si sviluppino nuove forme di resistenza, è necessario identificare delle modalità di rimborso che garantiscano agli sviluppatori un ritorno economico tale da aumentare e mantenere nel tempo gli investimenti in ricerca e sviluppo in quest'area.

Appropriatezza d'uso degli antibiotici

- Strutture sanitarie
  - Utilizzare le risorse previste per la Missione "Salute" del PNRR, per colmare le carenze strutturali, tecnologiche e organizzative che fino a oggi hanno rappresentato delle barriere per la completa attuazione delle azioni contenute nel PNCAR.
- Formazione degli operatori sanitari
  - Garantire che i fondi previsti dal PNRR in merito all'avvio di un piano straordinario di formazione sulle infezioni correlate all'assistenza a tutto il personale sanitario e non sanitario degli ospedali e delle cure primarie, siano indirizzati verso programmi specifici sulla stewardship antimicrobica e sul controllo delle infezioni.
- Team multidisciplinari
  - Garantire la presenza di un team multidisciplinare (medici specialisti, microbiologi, farmacisti ospedalieri, ecc.) all'interno delle strutture sanitarie con la responsabilità di definire i programmi di stewardship e la loro applicazione.

Appropriatezza d'uso degli antibiotici

- Governo dei nuovi antibiotici
- Garantire un accesso tempestivo ai nuovi antibiotici in situazioni di urgenza ed emergenza estendendo la prescrivibilità di questi farmaci "salvavita" ad altri specialisti, con competenze specifiche sull'uso degli antibiotici (intensivisti, ematologi, ecc.), prevedendola nell'ambito di progetti di stewardship antimicrobica.
- Inoltre, nel contesto di precise raccomandazioni terapeutiche potrebbe essere utile prevedere una "finestra di accesso libero e regolamentato" che permetta così ai pazienti di ricevere tempestivamente il trattamento necessario nelle prime decisive ore.

- Integrazione tra stewardship antibiotica e stewardship diagnostica
- Sviluppare programmi di stewardship antibiotica fortemente integrata con la stewardship diagnostica nella definizione del Percorso Diagnostico Terapeutico Assistenziale in maniera uniforme a livello nazionale.
- Potenziare, inoltre, l'utilizzo degli strumenti di diagnostica di primo livello (ad es. tampone faringeo per SBEGA, dosaggio PCR, strisce reattive per i test delle urine, otoscopia pneumatica, etc.) che, nell'ambito delle cure primarie, permette una maggiore precisione diagnostica e una conseguente maggiore appropriatezza prescrittiva.

- Informazione ai cittadini
- Promuovere campagne di comunicazione rivolte alla popolazione sull'uso appropriato e consapevole di antibiotici, puntando ad accrescere il livello di consapevolezza del cittadino.

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