Nuovi antibiotici per il trattamento delle infezioni da Gram negativi MDR

Matteo Bassetti
Clinica Malattie Infettive, Università di Genova
Ospedale Policlinico San Martino-IST
Genova, Italy

UNIVERSITÀ DEGLI STUDI DI GENOVA

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Disclosures
(past 5 years)

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

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	🔴	🔴	🔴	🔴	🟢	🔴

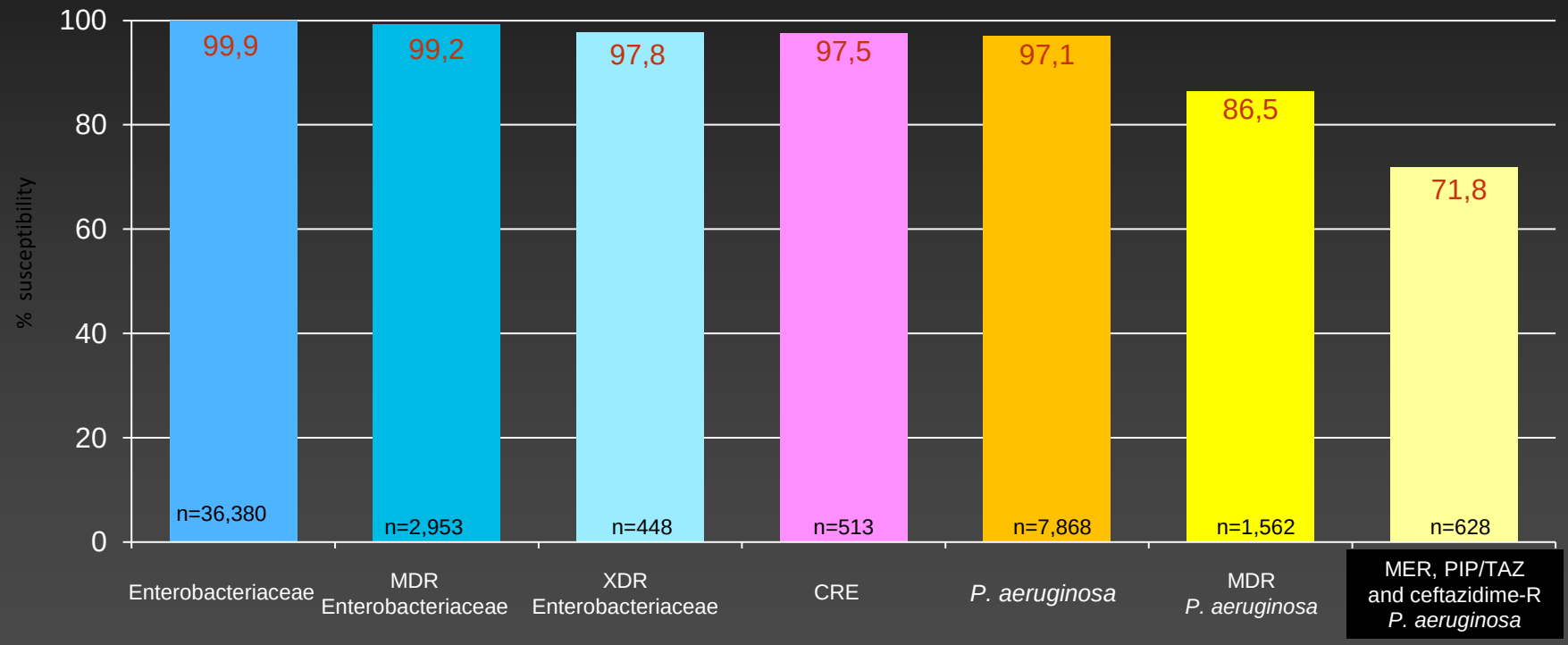
🔴 No activity or intrinsic or acquired resistance. 🟢 Activity. Abbreviations: BL/BLI, β-lactam/β-lactamase Inhibitor CRE, carbapenem resistant Enterobacteriacae; ESBL, extended-spectrum beta-lactamase; MBLs, metallo-β-lactamases; OMPTA, outer membrane protein targeting antibiotics. 1. Decreased activity 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

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Antimicrobial activity of ceftazidime–avibactam against MDR Enterobacteriaceae and *P. aeruginosa* isolates from US medical centers (2013–2016)



CRE, carbapenem-resistant Enterobacteriaceae; MDR, multidrug resistant; PIP/TAZ, piperacillin/tazobactam; MER, meropenem; R, resistant; XDR, extensively drug resistant.

Adapted from Sader, HS, et al. Antimicrob Agents Chemother 2017;61:e01045.

Ceftazidime–avibactam: real-world data

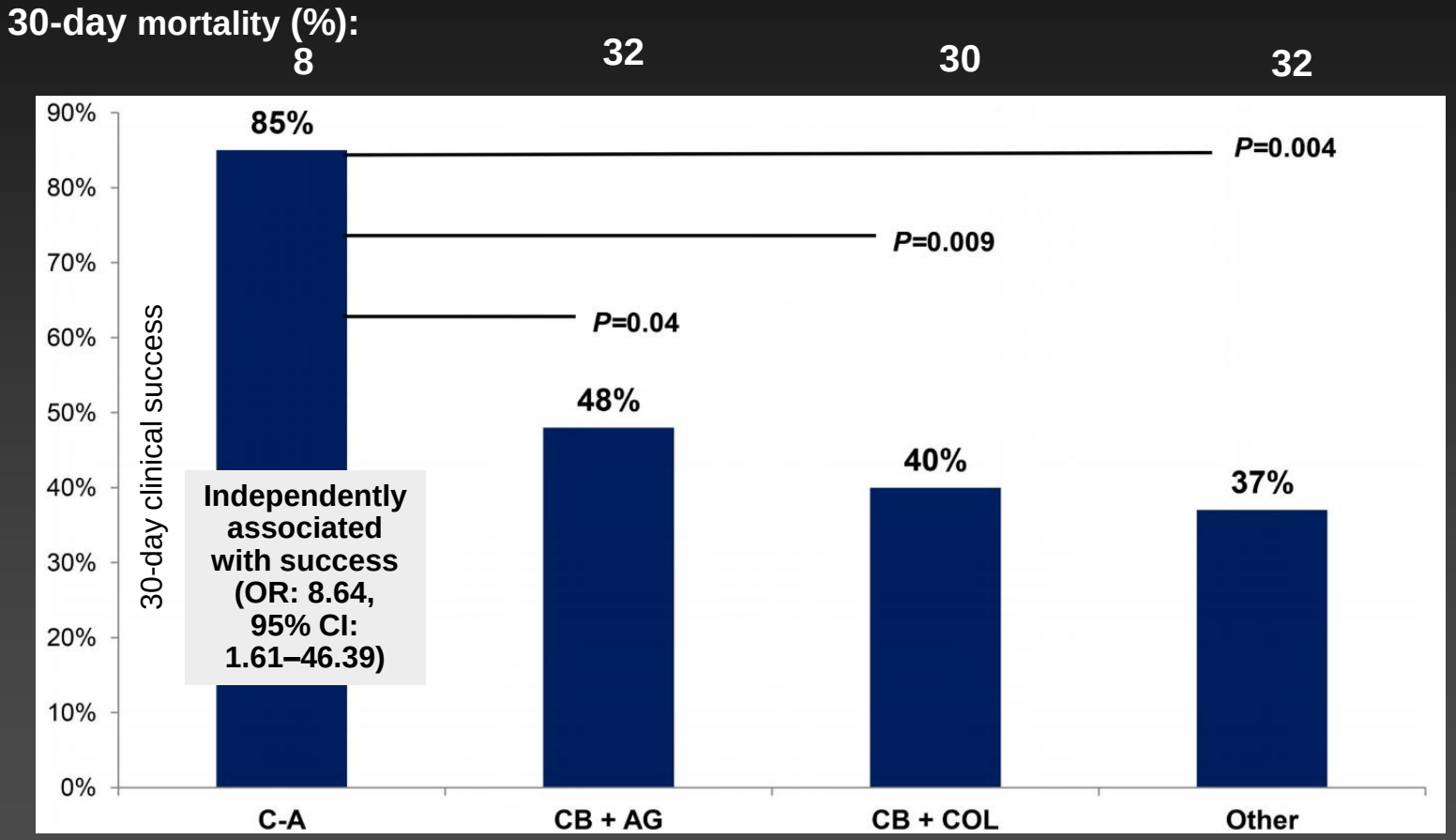
More than 17 observational studies!

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 as salvage therapy for KPC-producing *Klebsiella pneumoniae*

Table 4. Multivariate analysis of factors associated with 30-day mortality in the 208 patients with KPC-Kp bacteremia.

	Without propensity score adjustment		Adjusted for the propensity score for therapy with CAZ-AVI	
Variables	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Mechanical ventilation	<0.001	4.25 (1.99-9.09)	<0.001	4.31 (1.99-9.33)
Charlson comorbidity index >3	0.001	3.31 (1.61-6.77)	0.001	3.30 (1.61-6.77)
Neutropenia	0.01	3.22 (1.25-8.29)	0.03	3.36 (1.25-8.75)
Septic shock	0.002	2.95 (1.46-5.94)	0.003	2.94 (1.46-5.92)
Any regimen that included CAZ-AVI	<0.001	0.25 (0.13-0.51)	0.001	0.27 (0.13-0.57)

Tumbarello M, et al. Clin Infect Dis 2018. doi: 10.1093/cid/ciy492.

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

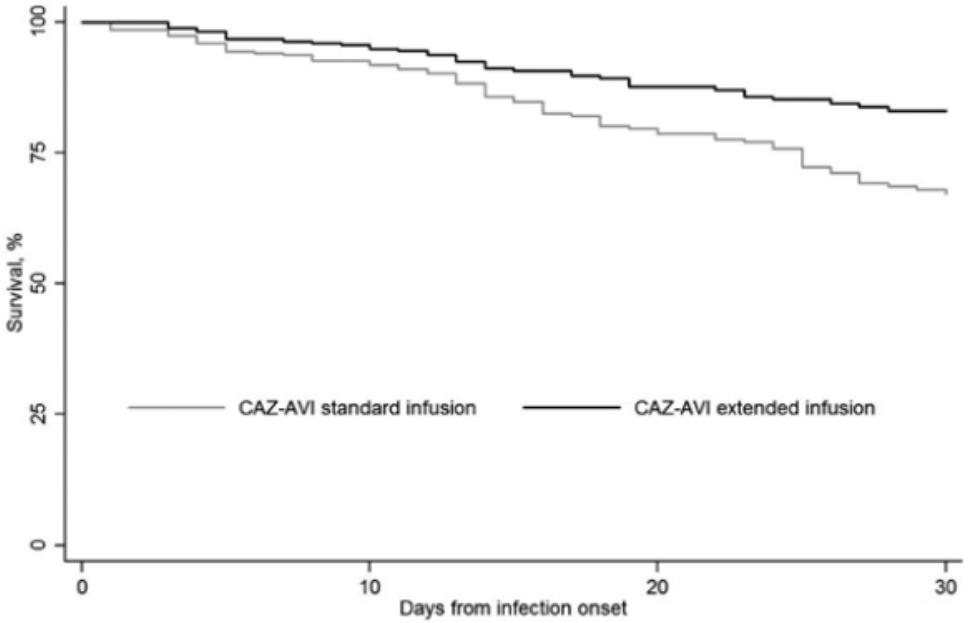


Figure 3. Kaplan-Meyer analysis of the impact of CAZ-AVI infusion times on 30-day survival. Significantly better survival was observed when CAZ-AVI was administered by prolonged infusion (standard dose given over ≥3 hours) versus standard infusion ($P < .001$). Abbreviation: CAZ-AVI, ceftazidime-avibactam.

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

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Clinical Infectious Diseases
MAJOR ARTICLE

Objective

- To compare the outcome of patients with BSIs due to metallo β-lactamase (MBLs) producing *Enterobacteriales* treated either with CAZ-AVI + AZT or other active antibiotics (OAAs)

Methods: **Observational prospective study (2018-19)**

- All adult patients diagnosed with MBL producing *Enterobacteriales* who received therapy ≥1 antimicrobial showing in vitro activity against the MBL-producing isolate for at least 48 hours.

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

Results

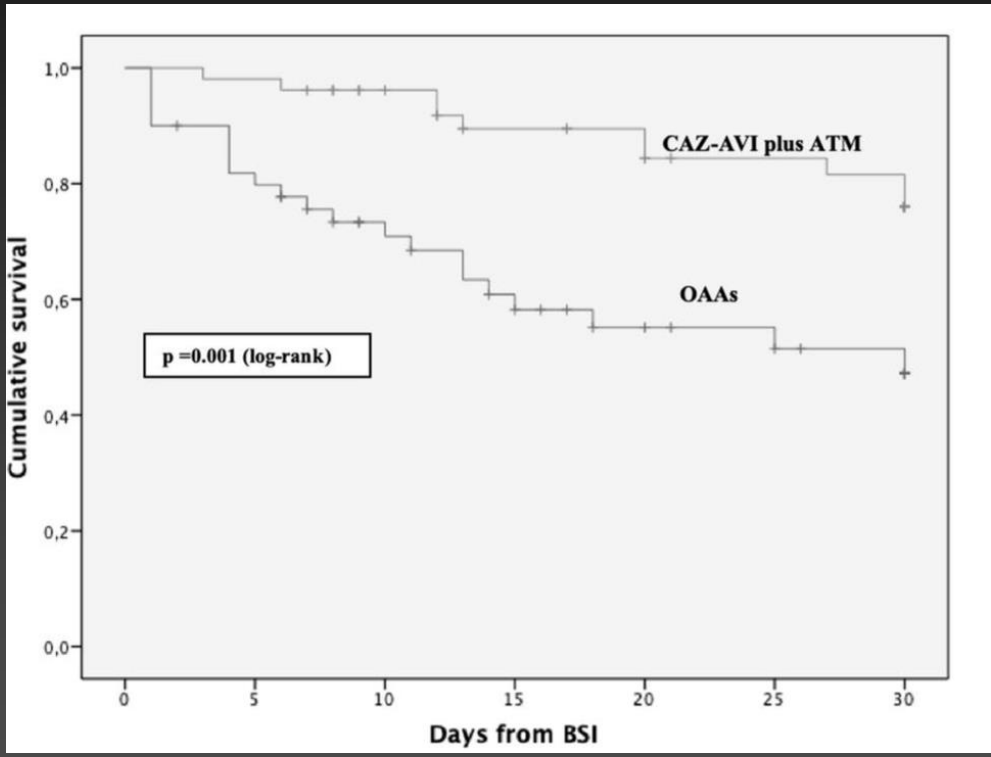
- 102 adults with *MBL Enterobacteriales* BSI
  - **82 NDM and 20 VIM**
- **52 (51%)** patients treated with CAZ-AVI+ATM vs **50 (49%)** treated with OAAs.

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.

What about ceftazidime-avibactam for *P.aeruginosa* infection?

- **Retrospective multicenter study**
- All patients who received >72 h of ceftazidime-avibactam for GNB other than CRE
- **41 patients** (age 62 yo, 68% male)
  - *P. aeruginosa* (33/41; 80.5%)
  - ESBL-producing *Enterobacterales* (4/41, 9.8%).
  - Four patients had polymicrobial infections.
- All strains were susceptible to ceftazidime-avibactam.
- Most common site of infection: **nosocomial pneumonia** (48.8%), **primary bacteremia** (17.1%), **IAI** (9.8%)
- Combination treatment 33 patients; median length of therapy 13 d.

Vena A, Giacobbe DR, Bassetti M and Ceftabuse study group Antibiotics 2020

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

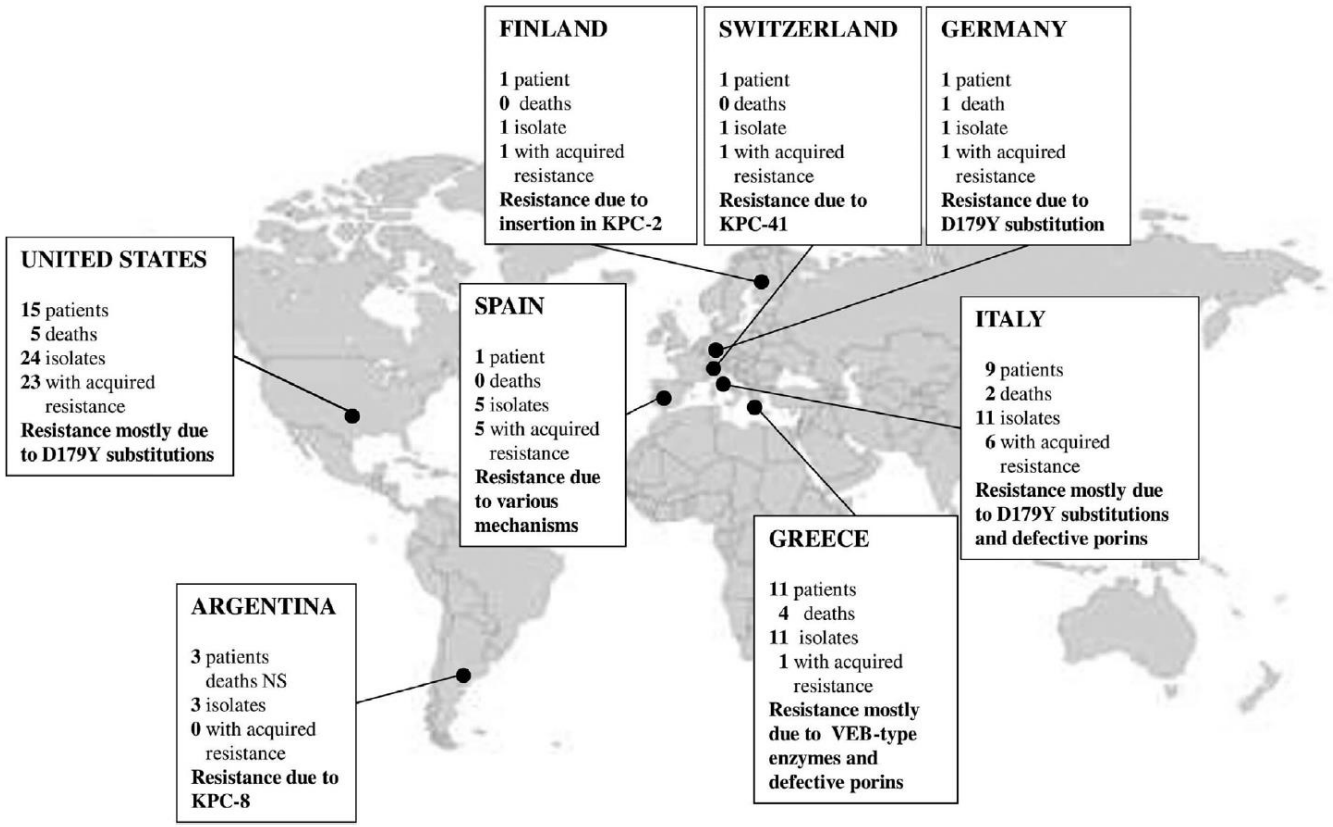


Fig. 2. Country-wise distribution of ceftazidime/avibactam-resistant cases and most relevant features.

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]

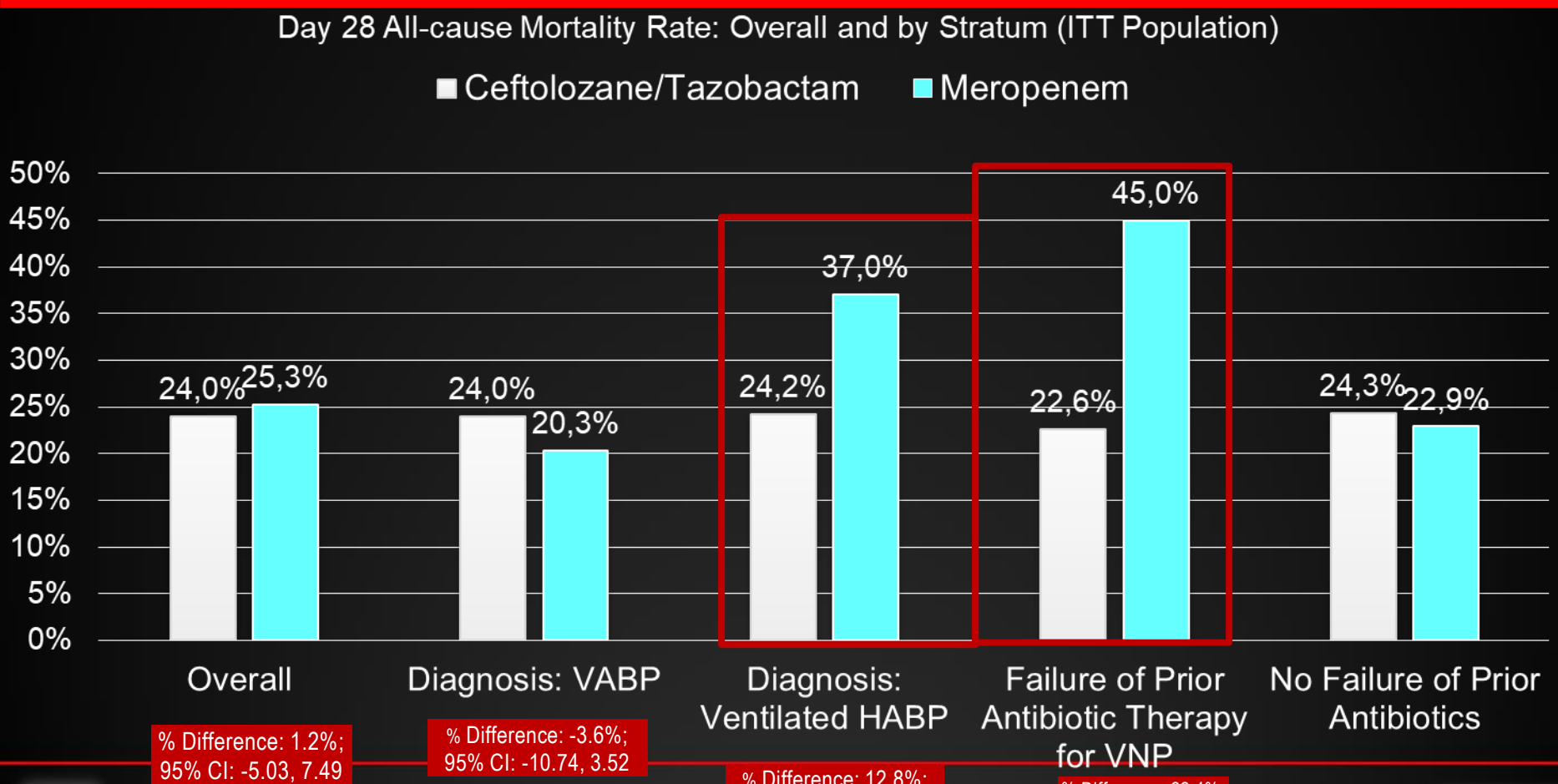
Resistance Mechanisms	Outer Membrane Porin Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	●	●	●	●
Ceftazidime	◐	○	●	○
Cefepime	●	○	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

○ 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

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

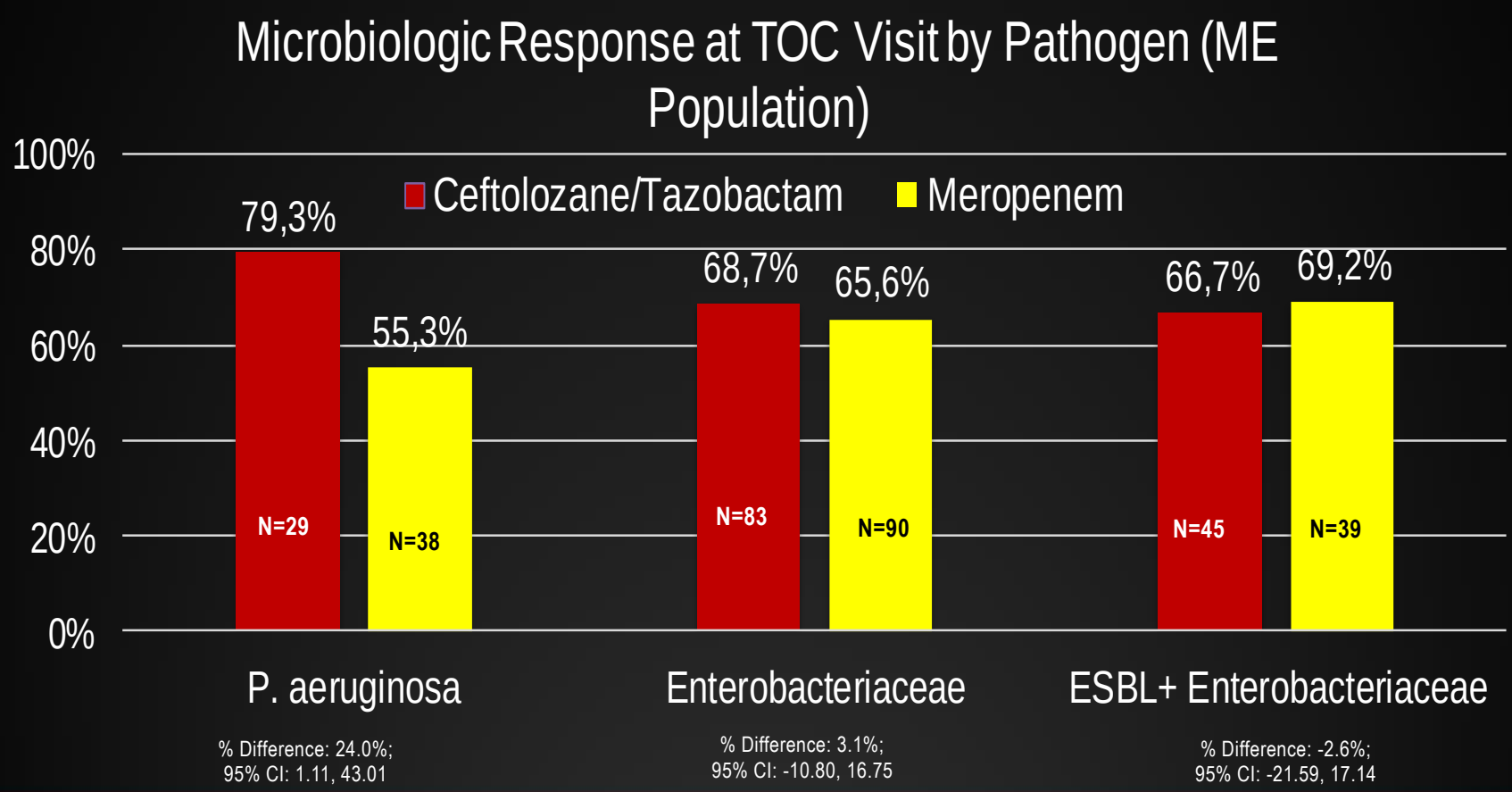


Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Kollef M et al. Lancet Infect Dis. 2019

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



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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

ASPECT-NP: vHABP subset analysis

Factors Assessed for Inclusion in MVA

- Age
- Creatinine clearance (CrCL)
- APACHE-II score
- SOFA score
- Clinical Pulmonary Infection Score (CPIS)
- PaO_2/FiO_2
- Failed antibacterial therapy for the current pneumonia episode
- ≥5 days prior hospitalization
- Baseline bacteremia
- All baseline pathogens susceptible to randomized study drug
- Baseline *P. aeruginosa*
- Baseline ESBL-positive Enterobacterales
- Adjunctive gram-negative therapy
- Concomitant vasopressor use
- Treatment arm

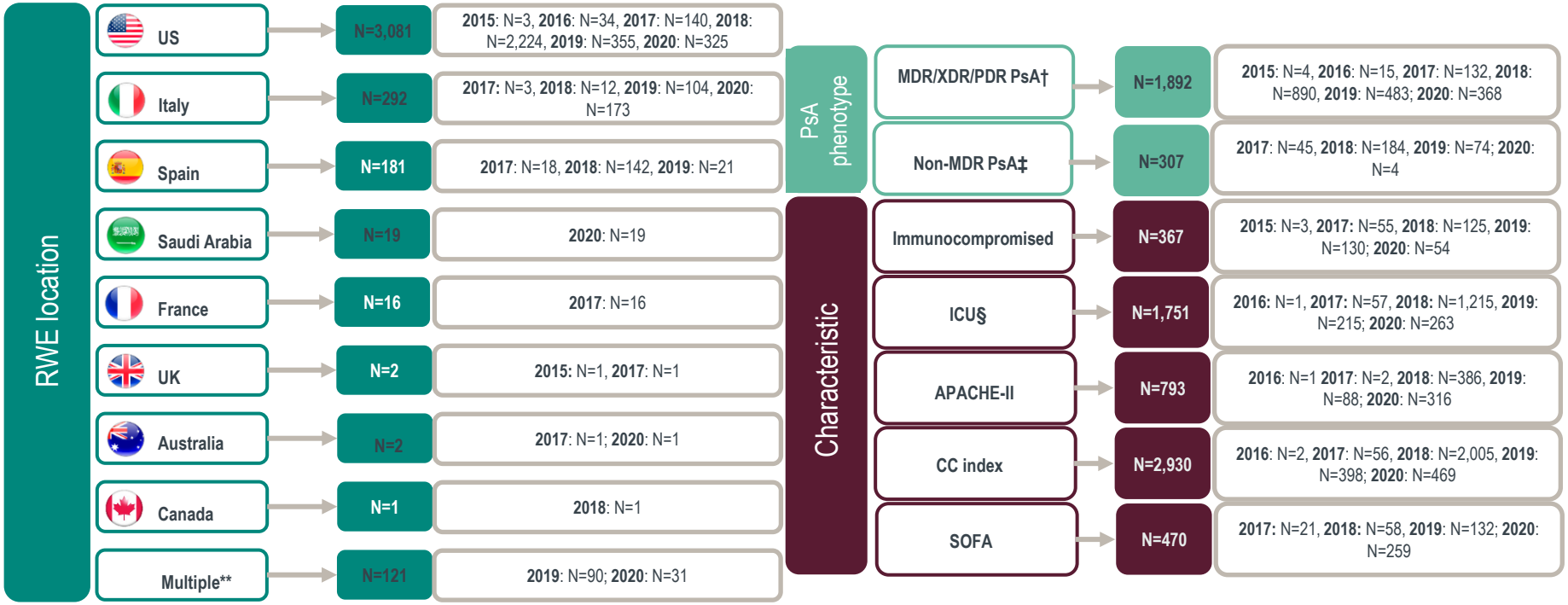
Odds Ratio Estimates for Factors Associated with Increased Mortality in MVA

Patient characteristic	Odds ratio for 28-day ACM (95% CI)
Concomitant vasopressor use	**5.4** (2.6, 11.0)
Baseline bacteremia	**2.7** (1.1, 7.1)
Meropenem treatment	**2.3** (1.2, 4.5)

Timsit J-F et al. Crit Care 2021 Aug 11;25(1): 290

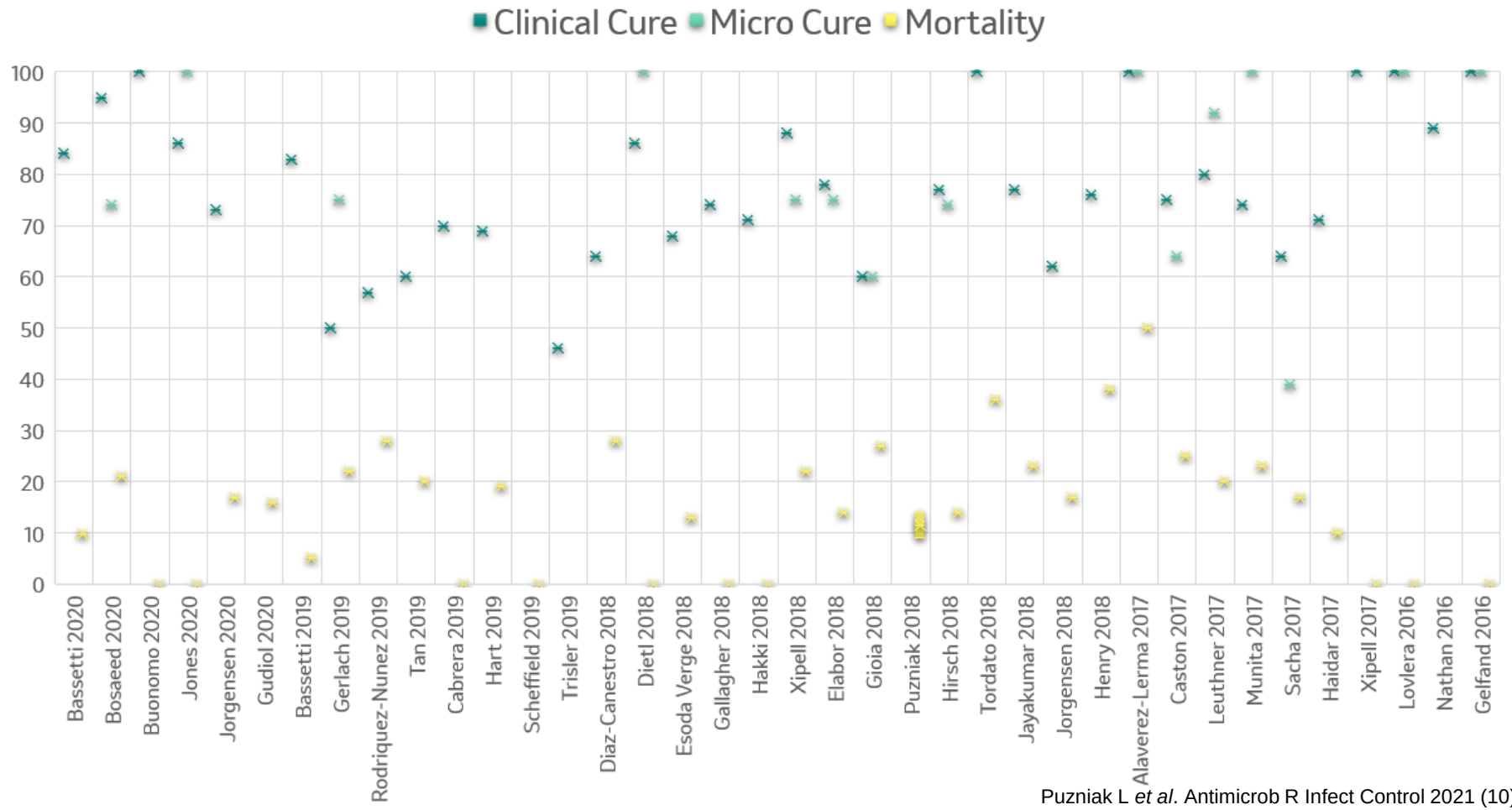
Summary of C/T Real World Effectiveness described in published literature

Eighty-three publications were captured.* Across these publications, 3,701 patients were reported to have infections that were treated by C/T. The majority of infections were caused by PsA and several studies included critically ill patients.



Puzniak L *et al*. Antimicrob R Infect Control 2021 (10): 68

Clinical Cure, Microbiologic Cure & Mortality from C/T Real World Effectiveness Studies 2016-2020



Puzniak L *et al*. Antimicrob R Infect Control 2021 (10): 68

Open Forum Infectious Diseases
MAJOR ARTICLE

Ceftolozane/Tazobactam for Treatment of Severe ESBL-Producing *Enterobacterales* Infections: A Multicenter Nationwide Clinical Experience (CEFTABUSE II Study)

Matteo Bassetti,[1] Antonio Vena,[1] Daniele Roberto Giacobbe,[1] Marco Falcone,[2] Giusy Tiseo,[2] Maddalena Giannella,[3] Renato Pascale,[3] Marianna Meschiari,[4] Margherita Digaetano,[4] Alessandra Oliva,[5,6] Cristina Rovelli,[7] Novella Carannante,[8] Angela Raffaella Losito,[9] Sergio Carbonara,[10] Michele Fabiano Mariani,[10] Antonio Mastro[illegible]anni,[11] Giacchino Angarano,[10] Mario Tumbarello,[12] Carlo Tascini,[8] Paolo Grossi,[7] Claudio Maria Mastroianni,[5] Cristina Mussi[illegible] CEFTABUSE Study Group

[1]Department of Health Sciences, University of Genoa, G[illegible] and Surgical Sciences, University of Bologna, Bologna, Italy, [4]Infectio[illegible]us Diseases, 'Sapienza' University of Rome, Rome, Italy, [6]IRCCS Neur[illegible]lo-Fondazioni Macchi, Varese, Italy, [8]First Division of Infectious Diseases, Cotu[illegible]CCS, Roma, Italy, [10]Clinic of Infectious Diseases, University of Bari, Bari, I[illegible]ico Universitario

Table 2. Etiology of Infection and Antimicrobial Susceptibility Pattern of ESBL-Producing *Enterobacterales* Isolates

100%

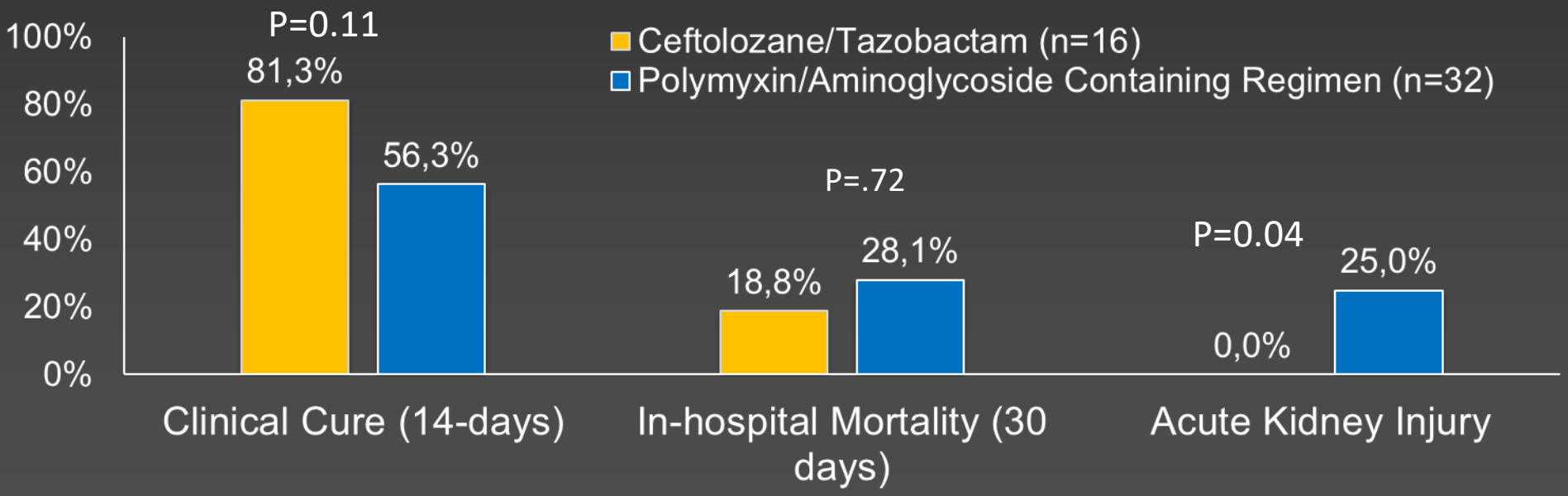
Table 5. Multivariate Analysis of Risk Factors for Clinical Failure of C/T Therapy Among Patients With Enterobacterales Infection

Variable	OR	95% CI	*P* Value
Charlson comorbidity index >4	2.3	1.9–3.5	.02
Septic shock	6.2	3.8–7.9	<.001
Empiric therapy displaying in vitro activity	0.12	0.01-0-34	<.001
CRRT	3.1	1.9–5.3	.001
Adequate source control of the infection	0.42	0.14–0.55	<.001

Abbreviations: C/T, ceftolozane/tazobactam; CI, confidence interval; CRRT, continuous renal replacement therapy; OR, odds ratio.

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

- Combination of **meropenem** and **vaborbactam**
  - Well-matched pharmacokinetics
  - Vaborbactam is a potent KPC inhibitor
  - Standard dosing = 4g IV q 8h over a 3 hour infusion
- FDA approved indications (approved in 2017)
  - cUTI
- EMA approved indications
  - cUTI/AP, cIAI, HAP/VAP
  - Bacterial infections due to Gram-negative organisms with limited treatment options

Meropenem-vaborbactam: TANGO II

- Phase III, open-label randomized trial comparing the efficacy and safety of meropenem-vaborbactam* to best available therapy for patients with CRE infections

27 hospitals in 8 countries

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

Meropenem-vaborbactam: TANGO II

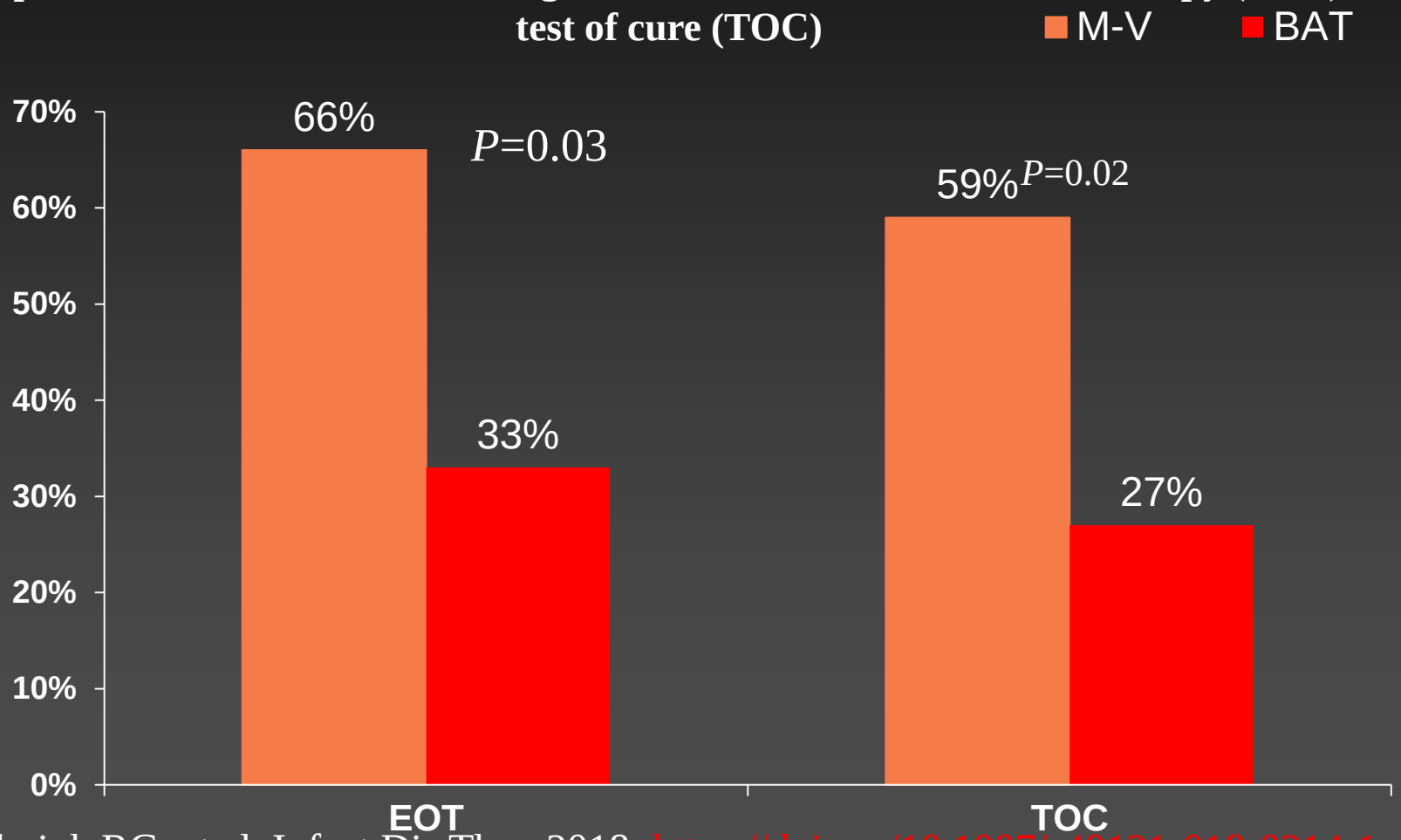
Baseline Characteristics	Meropenem/ vaborbactam N=32, n (%)	Best available therapy N=15, n (%)
Mean age (SD)	63.5 (14.1)	60.2 (13.0)
Charlson Score ≥5	25 (78.1)	12 (80.0)
Immunocompromised	11 (34.4)	8 (53.3)
SIRS	15 (46.9)	6 (40.0)
ICU admission	5 (15.6)	3 (20.0)
Prior Treatment Failure	**9 (28.1)**	**0/15 (0)**
Infection types • Bacteremia • cUTI/AP • HABP/VABP • cIAI	 14 (43.8) 12 (37.5) 4 (12.5) 2 (6.3)	 8 (53.3) 4 (26.7) 1 (6.7) 2 (13.3)
Pathogens • K. pneumoniae • E. coli • E. cloacae • Other	 29 (90.6) 3 (9.4) 1 (3.1) 1 (3.1)	 12 (80.0) 1 (6.7) 2 (13.3) 3 (20.0)

BAT Regimen	All (N=15*), n (%)
Monotherapy	**4 (26.7)**
Aminoglycoside	1 (6.7)
Carbapenem	1 (6.7)
Ceftazidime-Avibactam	1 (6.7)
Polymyxin B/Colistin	1 (6.7)
Dual Therapy	**7 (46.7)**
Carbapenem + Aminoglycoside	1 (6.7)
Carbapenem + PolymyxinB/Colistin	1 (6.7)
Carbapenem + Tigecycline	2 (13.3)
PolymyxinB/Colistin + Aminoglycoside	3 (20.0)
Triple Therapy	**1 (6.7)**
Carbapenem + Polymyxin/Colistin+Tigecycline	1 (6.7)
4 or More Drugs	**2 (13.3)**
Carbapenem+Colistin+Tigecycline+Aminoglycoside	2 (13.3)

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

Meropenem-vaborbactam: TANGO II

Meropenem-vaborbactam showed higher clinical cure rates at end of therapy (EOT) and test of cure (TOC)



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.

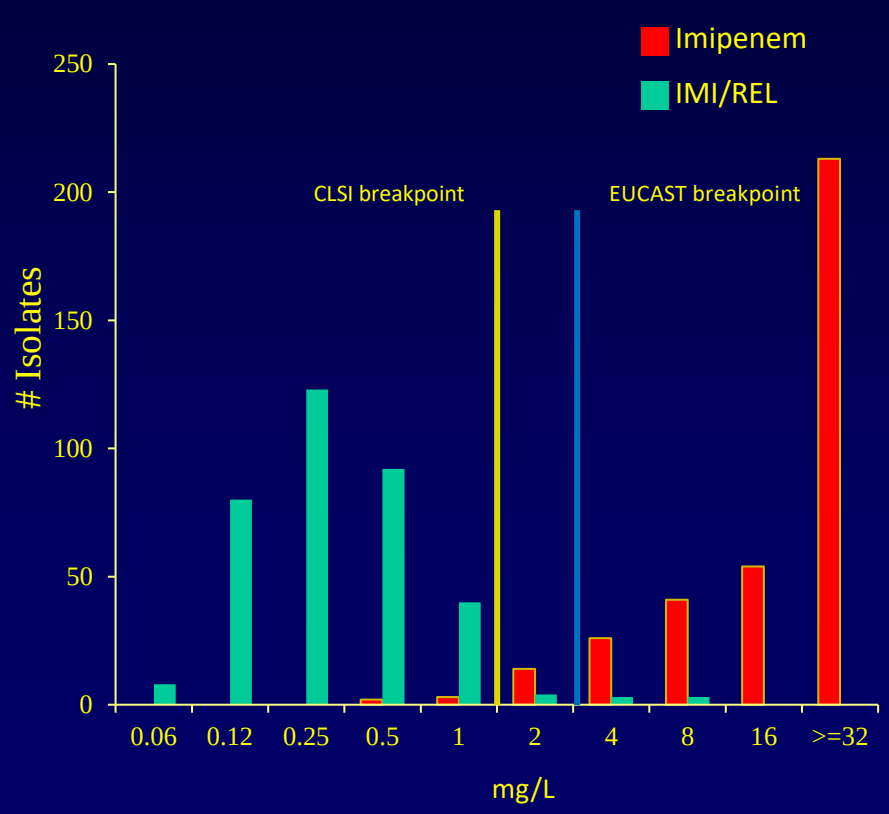
IMIPENEM/RELEBACTAM

- Fixed-dose combination of a β-lactam antibiotic, imipenem (IMI), with a β-lactamase inhibitor, relebactam (REL)
- REL is an inhibitor of **Class A and C β-lactamases** and restores activity to IMI in resistant Gram-negative bacteria
- Active *in vitro* against enterics producing *Klebsiella pneumoniae* carbapenemases (KPC, Class A) and extended-spectrum β-lactamases (ESBL)
- Active in vitro against Amp-C-producing *Pseudomonas aeruginosa* (Class C)
- Activity confirmed in in vitro and in vivo animal models

IMIPENEM/RELEBACTAM: In Vitro Activity – Enterobacteriaceae

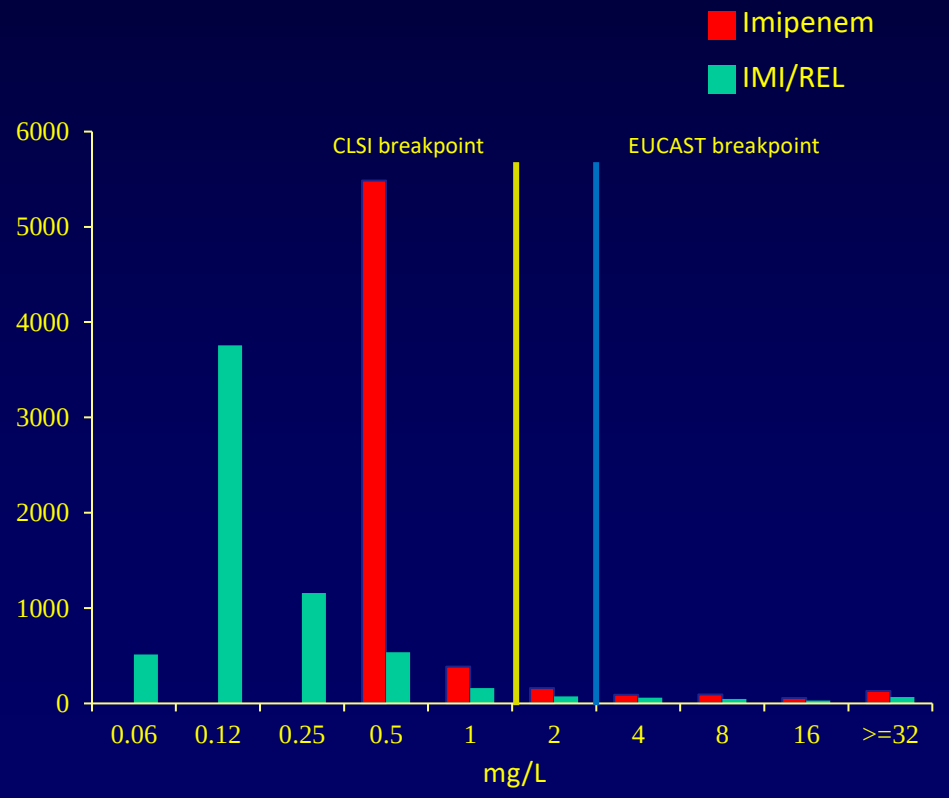
Effect of REL on IMI Susceptibility of KPC-Expressing Enterobacteriaceae

Increased susceptibility to IMI from 5% in the absence of REL to 98% in presence of 4 mg/L REL
N=353 from SMART surveillance 2016



Effect of REL on IMI Susceptibility of ESBL- and Amp-C-Expressing Enterobacteriaceae

Increased susceptibility to IMI from 94% in the absence of REL to 97% in presence of 4 mg/L REL
N=6406 from SMART surveillance 2016



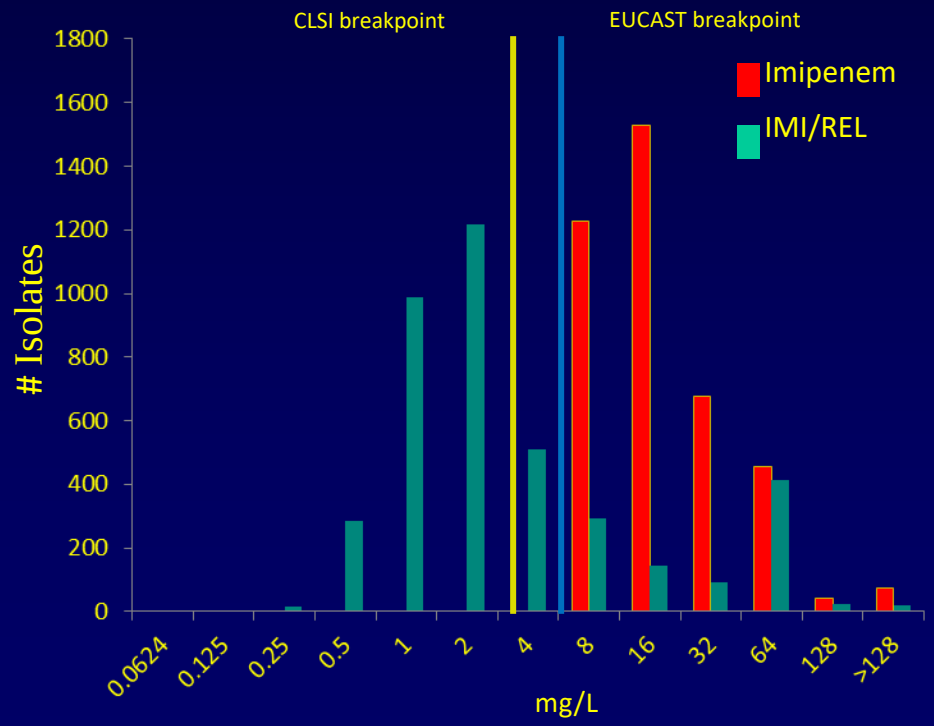
IMIPENEM/RELEBACTAM:
In Vitro Activity – *P. aeruginosa*

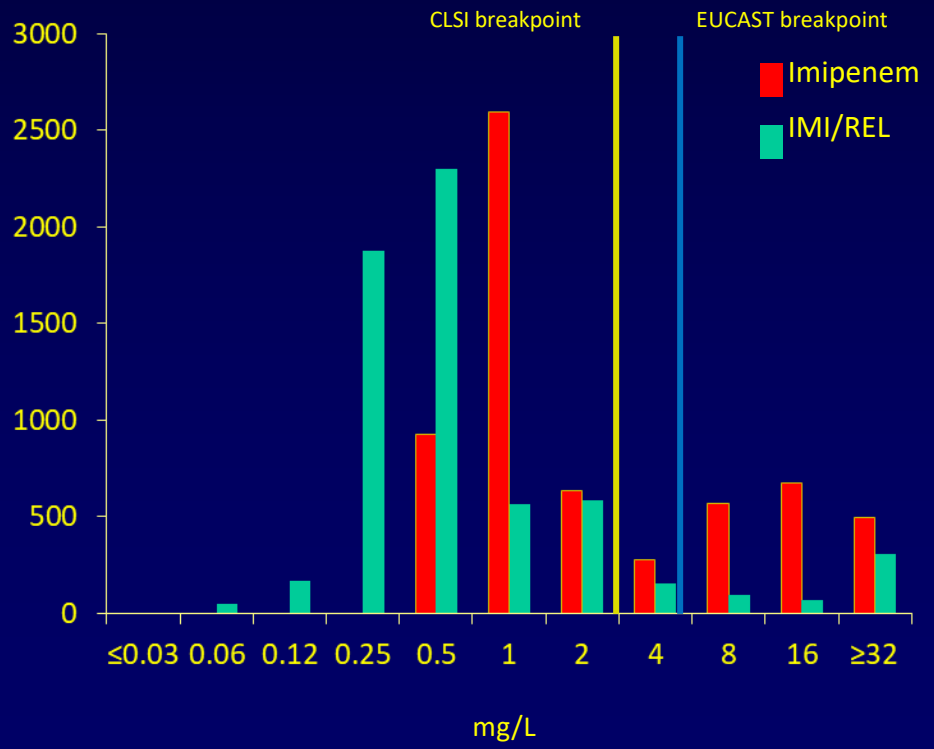
Effect of REL on IMI Susceptibility of IMI-NS *P aeruginosa*

Increased susceptibility to IMI from 0% in the absence of REL to 75% in presence of 4 mg/L REL
N=4002 IMI-NS *P aeruginosa* from challenge panels and surveillance studies

Effect of REL on IMI Susceptibility of Surveillance *P aeruginosa*

Increased susceptibility to IMI from 73% in the absence of REL to 93% in presence of 4 mg/L REL
N= 6165 SMART Surveillance Isolates 2016





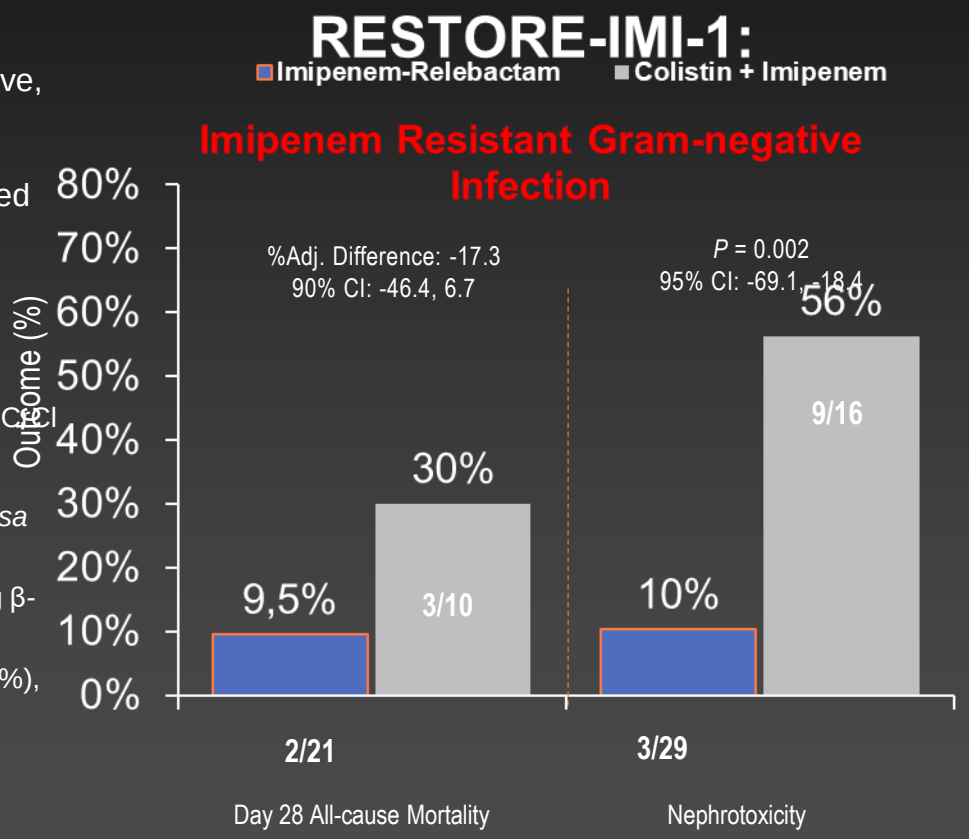
Two double-blind, randomized studies, including a small Phase 3 study (PN013) in various IMI-resistant infections and a large Phase 3 study in HABP/VABP

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)

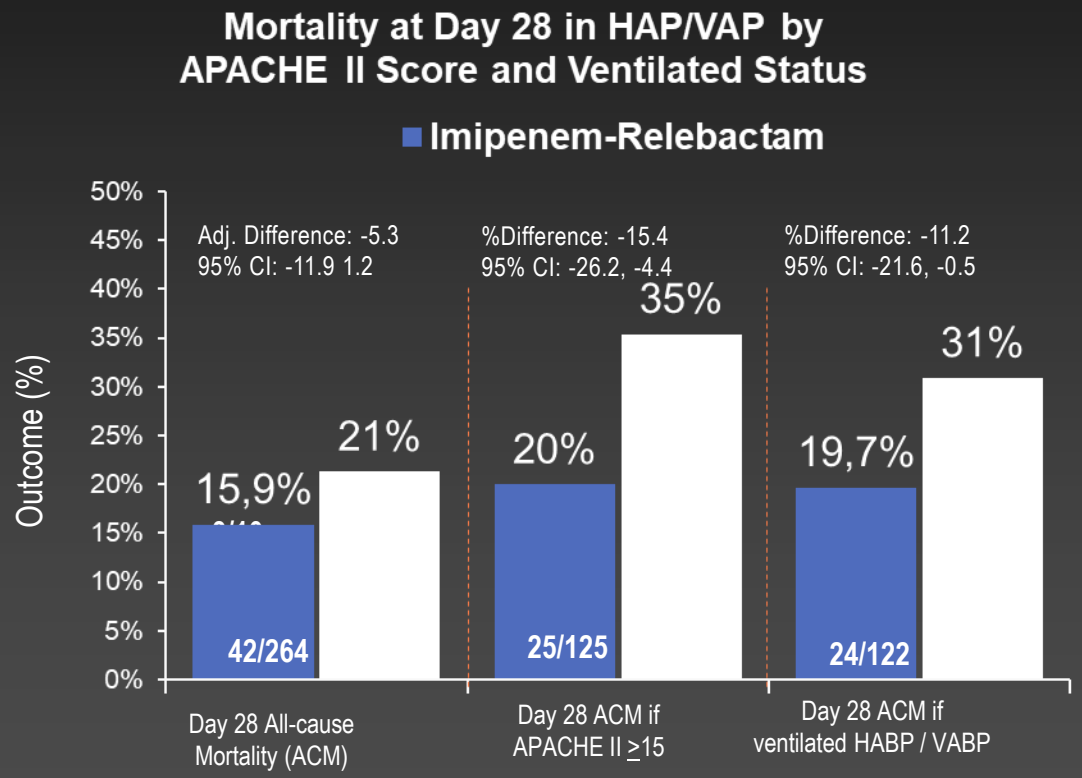


Adjusted difference, based on Miettinen and Numiren method stratified by infection site
Motsch J et al..Clin Infect Dis Clin Infect Dis. 2020;70(9):1799-1808 (RESTORE-IMI-1)

RESTORE-IMI-2: Efficacy of Imipenem/Relebactam in Hospital-Acquired or Ventilator-Associated Pneumonia

Patient Population	Study Design

Adults (>18 years) with either HAP or VAP	• Double-blind, randomized study
	• 2 treatment arms, both given IV every 6 hrs[a]:
	  ○ IMI/REL 500/250 mg
	  ○ PIP/TAZ 4 g/500 mg
	• Concurrent linezolid IV therapy (600 mg BID) as empirical MRSA therapy
	• Primary endpoint: Day 28 all-cause mortality



Titov I et al. Clin Infect Dis 2020 Aug 12:ciaa803. doi: 10.1093/cid/ciaa803 (RESTORE-IMI-2)

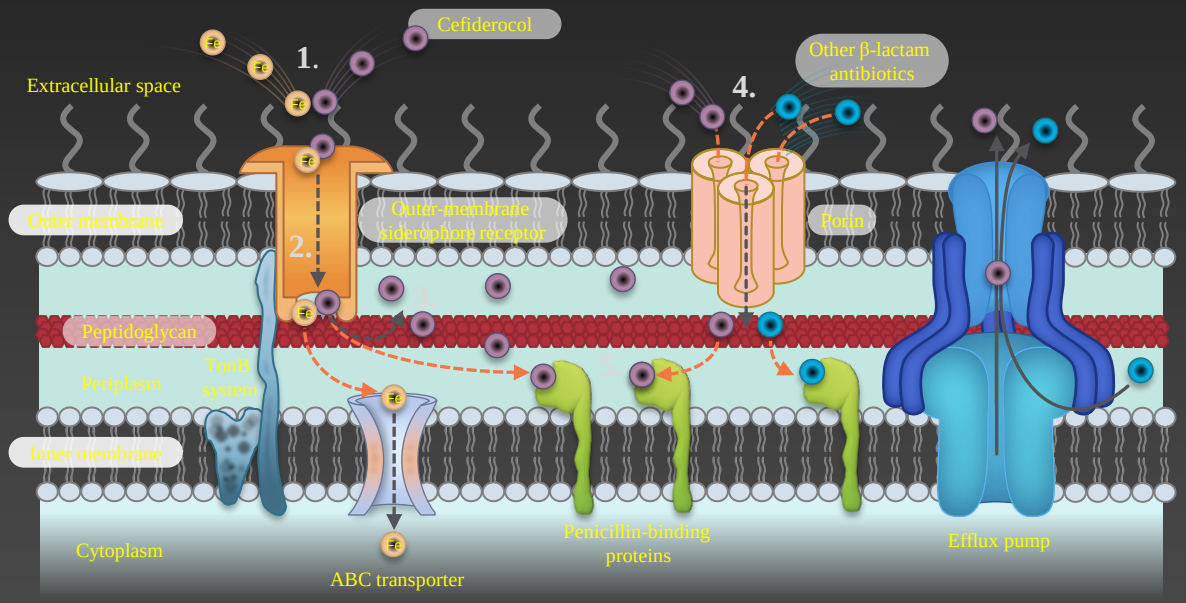
Cefiderocol mechanism of action

- Cefiderocol is a beta-lactam antibiotic and therefore inhibits bacterial cell wall synthesis[1]
- Cefiderocol is highly resistant to hydrolysis by various types of carbapenemases[2]
- Trojan horse mechanism of entry into the bacterial cell circumvents efflux pump- and porin-mediated mechanisms of resistance[3]

1. Bush K, et al. *Cold Spring Harb Perspect Med* 2016;6:a025247; 2. Ito A, et al. *J Antimicrob Chemother* 2016;71:670–7;
3. Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–401; 4. Tsuji M, et al. Poster P0808 ECCMID 2016; Amsterdam, Netherlands.

Novel mechanism of cefiderocol entry into the periplasm

Cefiderocol is actively transported across the outer membrane via an iron-uptake mechanism[1,2]



1. Cefiderocol chelates extracellular iron
2. Chelated complex is actively transported into the periplasm by outer-membrane receptors
3. Once in the periplasm, cefiderocol dissociates from iron ions
4. Like other beta-lactam antibiotics, cefiderocol also enters the periplasm via diffusion through porins
5. Once inside the periplasm, cefiderocol binds and inhibits PBPs

Cefiderocol's unique mechanism of entry enables it to overcome resistance mediated by changes to porin channels and efflux-pump overexpression

.

1. Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–401; 2. Ito A, et al. Poster Saturday-114 presented at ASM Micr

Summary of global SIDERO study results

SIDERO-WT-2014-2016[1]

Cefiderocol demonstrated potent inhibition against a range of GN strains, including those non-susceptible to carbapenem

Proportion of strains with cefiderocol MIC ≤4 mg/L		
Enterobacteriaceae	99.9%	n=6,087
CarbNS-Enterobacteriaceae	97.0%	n=169
P. aeruginosa	99.9%	n=1,530
CarbNS-*P. aeruginosa*	100%	n=353
A. baumannii	97.6%	n=1,148
CarbNS-*A. baumannii*	96.9%	n=768
S. maltophilia	100%	n=428
B. cepacia complex	93.8%	n=12

Based on MIC_{90}s, the *in vitro* activity of cefiderocol was superior to that of comparators, including against colistin-resistant isolates

SIDERO-CR-2014-2016[2]

Cefiderocol inhibited 96.2% of all CR-GN isolates tested at MIC ≤4 mg/L

Proportion of strains with cefiderocol MIC ≤4 mg/L		
Enterobacteriaceae	97.0%	n=1,022
MDR *P. aeruginosa*	99.2%	n=262
MDR *A. baumannii*	89.7%	n=368
S. maltophilia	100%	n=217

Based on MIC_{90}s, cefiderocol was found to be a more potent *in vitro* antimicrobial agent than comparators against a range of CR-GN isolates, including those non-susceptible to colistin

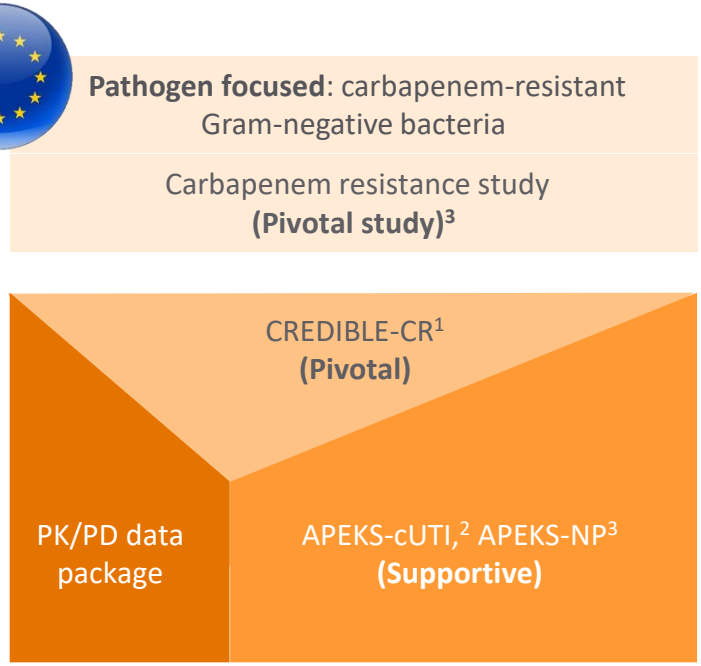
[a]Published data are only available from the SIDERO-WT-2014 and -2015 studies.

1. Hackel MA, et al. *Antimicrob Agents Chemother* 2017;61:e00093-17; 2. Hackel MA, et al. *Antimicrob Agents Chemother* 2018;62:e01968-17.

Approval process for cefiderocol: different approaches – pathogen focused in Europe and infection site/organism led in the USA

Pathogen focused: carbapenem-resistant Gram-negative bacteria

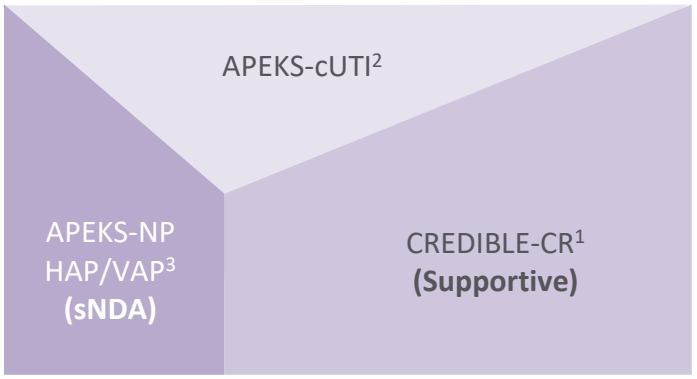
Carbapenem resistance study
(Pivotal study)[3]



Aerobic Gram-negative organisms with limited treatment options[4]

Infection site specific: carbapenem-susceptible cUTI, HAP/VAP Gram-negative infection

Establish clinical efficacy and safety profile of cefiderocol 2000 mg q8h[3]



cUTI, HAP/VAP[5]

CR, carbapenem resistant; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MAA, marketing authorisation application; NDA, new drug application; NP, nosocomial pneumonia; PD, pharmacodynamic; PK, pharmacokinetic; sNDA, supplemental NDA; q8h, every 8 hours; VAP, ventilator-associated pneumonia.

1. Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9; 2. .Portsmouth S, et al. *Lancet Infect Dis* 2018;18:1319-28; 3. Wunderink RG, et al. Lancet Infect Dis 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731-3; 4. Fetcroja (cefiderocol). Summary of Product Characteristics. Shionogi BV. https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf [Accessed Jan 2021]; 5. Fetroja (cefiderocol). Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf [Accessed Jan 2021]

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

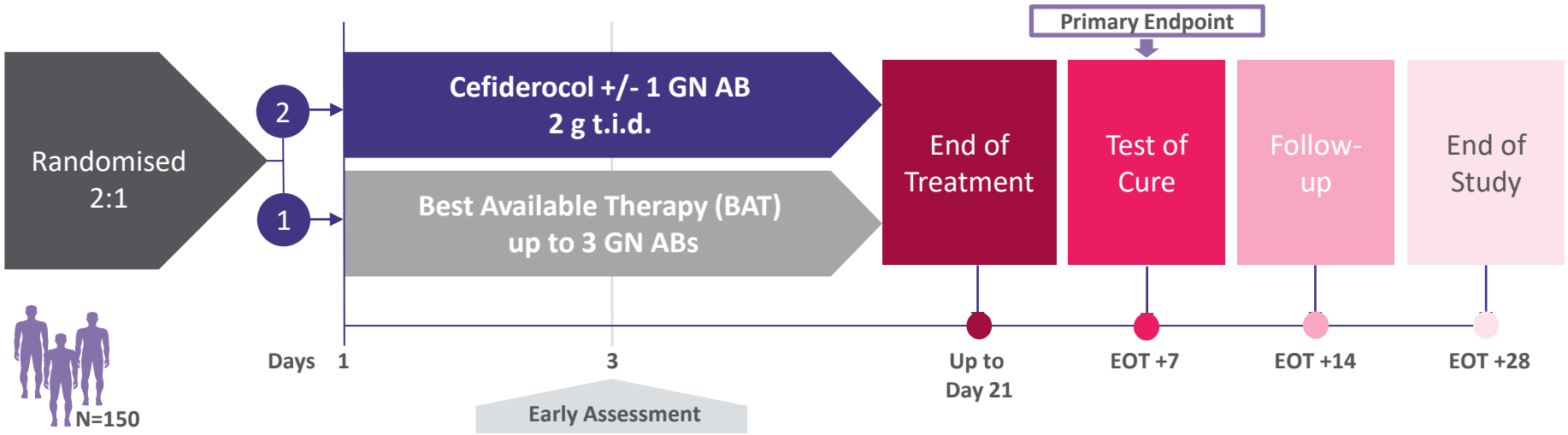
Open-label design

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

CREDIBLE-CR: baseline demographic and clinical characteristics were broadly similar between the two treatment groups[a]

	Cefiderocol (N=101)	BAT (N=49)
Sex, male n(%)	66 (65)	35 (71)
Median age, years (range)	69 (19–92)	62 (19–92)
Clinical diagnosis n(%)		
HAP/VAP/HCAP	45 (45)	22 (45)
BSI/sepsis	30 (30)	17 (35)
cUTI	26 (26)	10 (20)
Median CrCl (range) mL/min	59 (9–540)	69 (5–271)
APACHE II >15 score n(%)		
16-19	17 (17)	9 (18)
≥20	29 (29)	13 (27)
Median CPIS score (range)	5 (2–9)	5 (0–7)
Median SOFA score (range)	4 (0–17)	4 (0–16)

More cefiderocol-treated patients were aged >65 years and were in the ICU at randomisation

[a]ITT and safety populations

APACHE, Acute Physiology and Chronic Health Evaluation; BAT, best available therapy; BSI, bloodstream infection; CPIS, Clinical Pulmonary Infection Score; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; ITT, intention to treat; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-acquired pneumonia.

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

CREDIBLE-CR: baseline CR Gram-negative pathogens – *A. baumannii* the most commonly identified resistant pathogen[a,b]

	Cefiderocol (n=80) n (%)	BAT (n=38) n (%)
CR *A. baumannii*	37 (46)	17 (45)
CR *K. pneumoniae*	27 (34)	12 (32)
CR *P. aeruginosa*	12 (15)	10 (26)
S. maltophilia	5 (6)	0

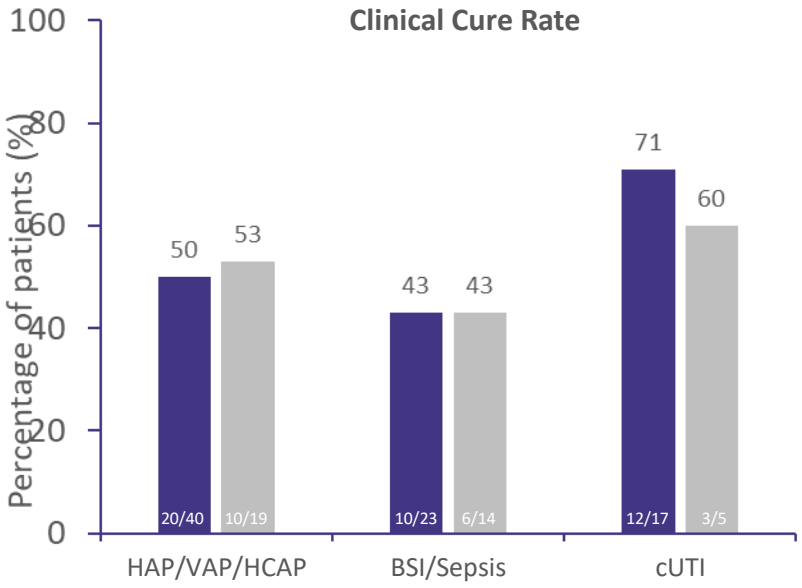
[a]CR micro-ITT population

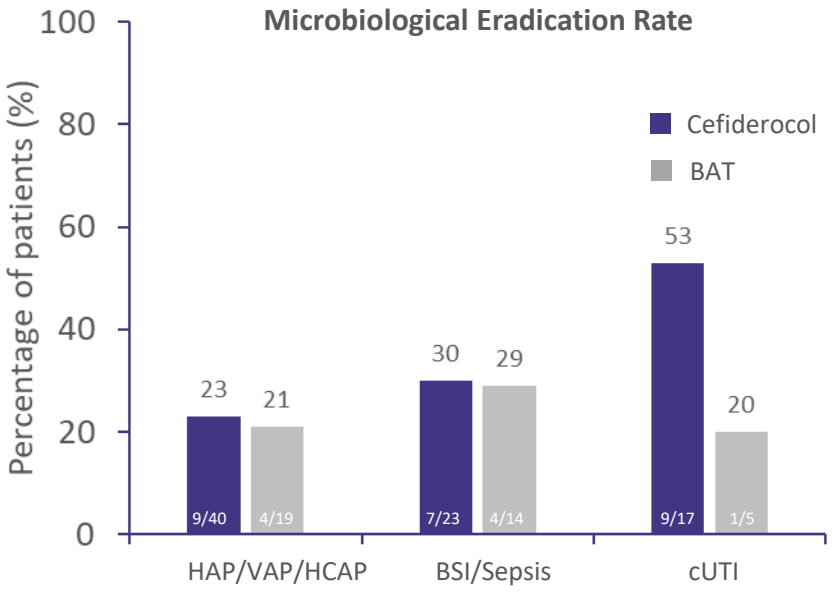
[b]Data reflects isolated resistant pathogens; patients may have had mixed infections and infections with >1 CR pathogen

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

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

CREDIBLE-CR: similar clinical and microbiological rates at TOC for all types of infection[a]





[a]CR micro-ITT population

BAT, best available therapy; BSI, bloodstream infection; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; 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

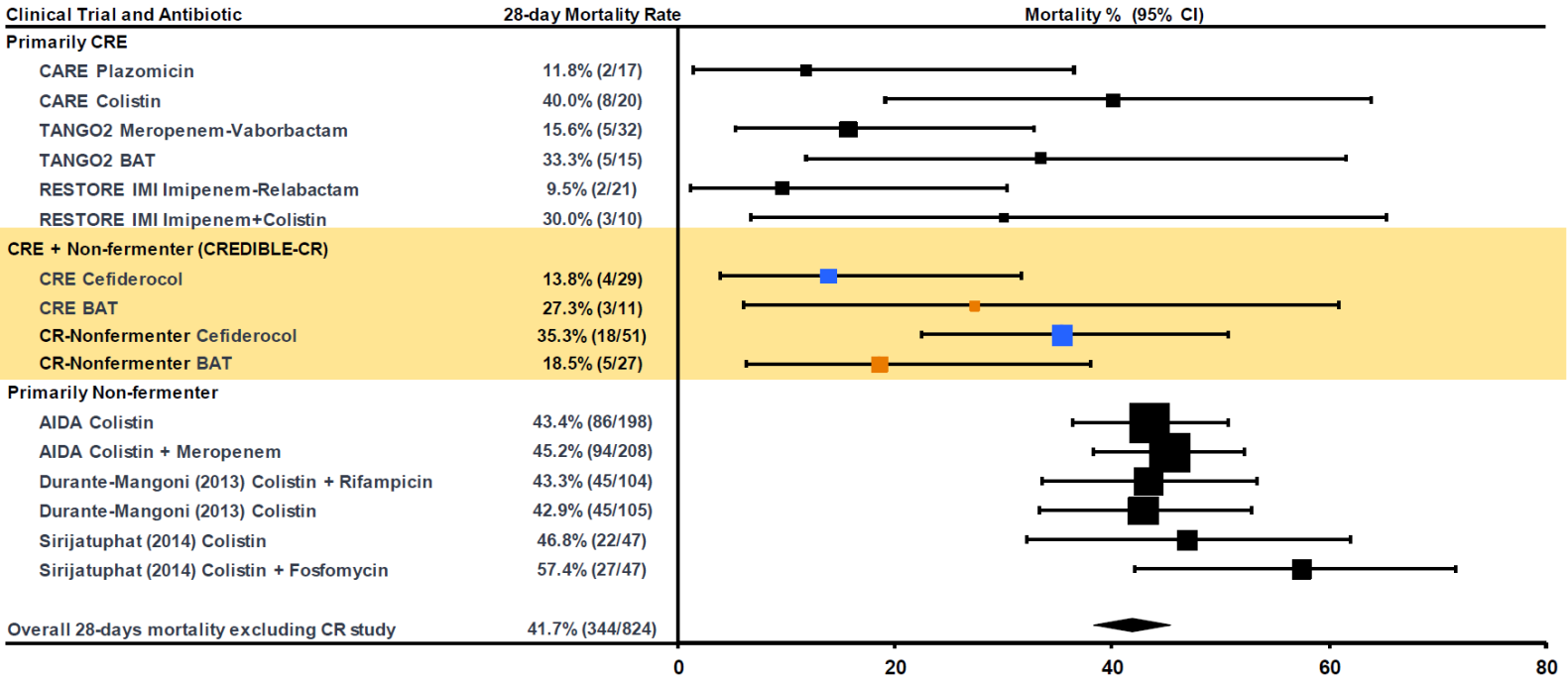
BAT, best available therapy.

[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

CREBIBLE-CR study

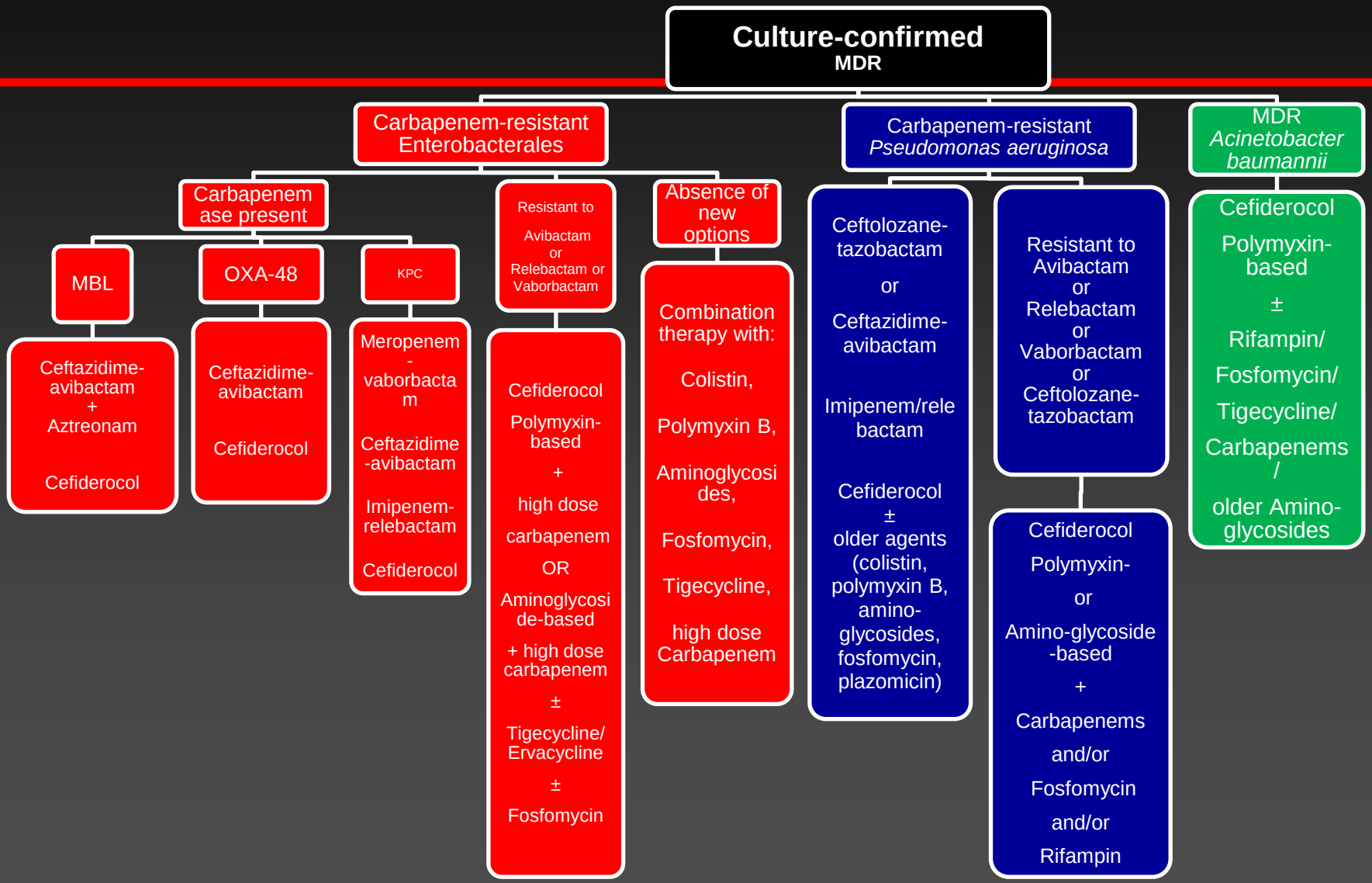
Day-28 Mortality in Recently Completed Pathogen-Focused Studies



BU-1616

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%



Bassetti M, Garau J. JAC 2021

HTIDE

Hot Topics in Infectious DisEases

To get the slides and to be part of the HTIDE community

Register at

www.htide.net