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Firenze, 15-17 Gennaio 2024
Centro Congressi Hotel Albani

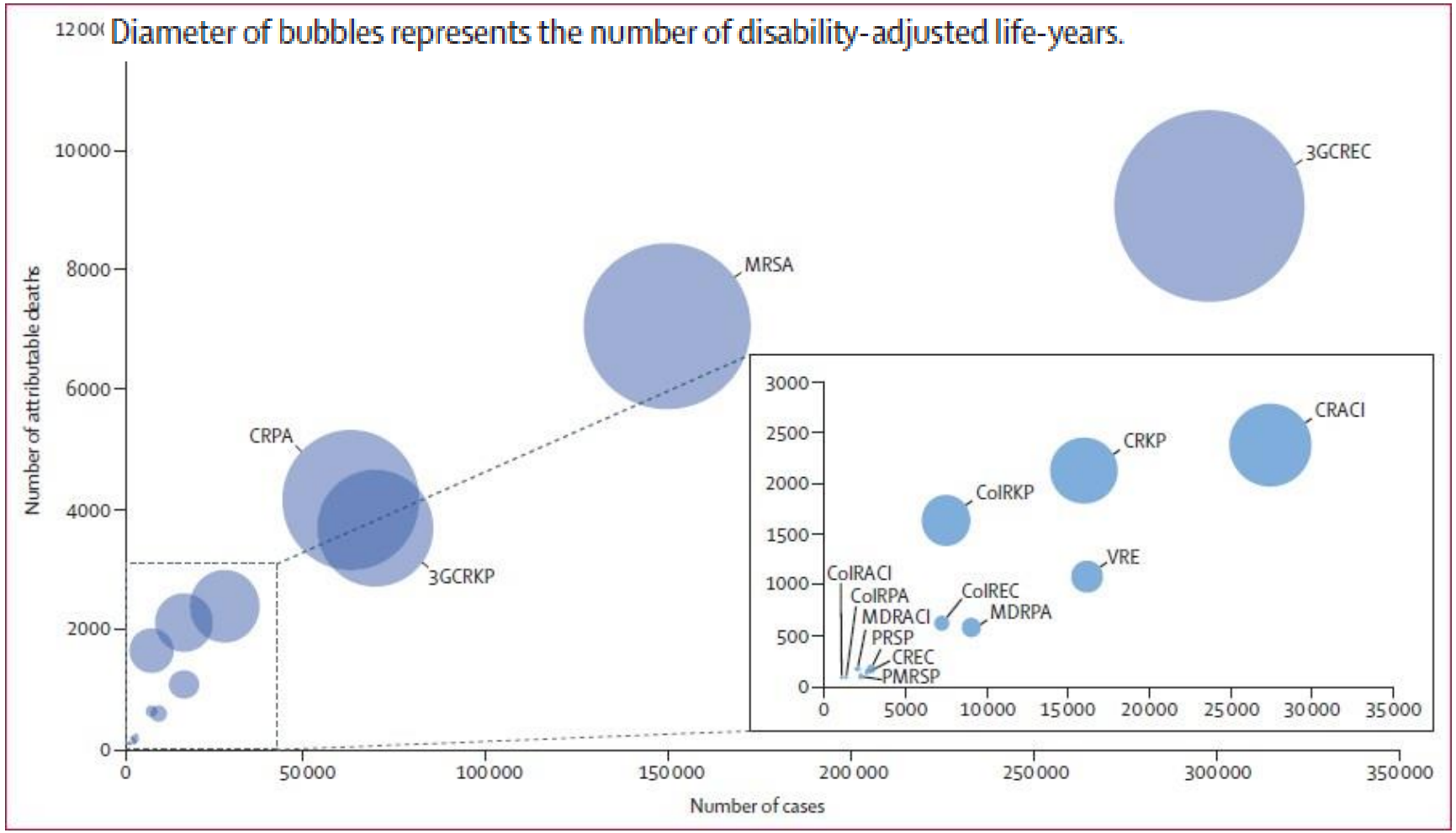
Infezioni da enterobatteri MDR

Mario Tumbarello

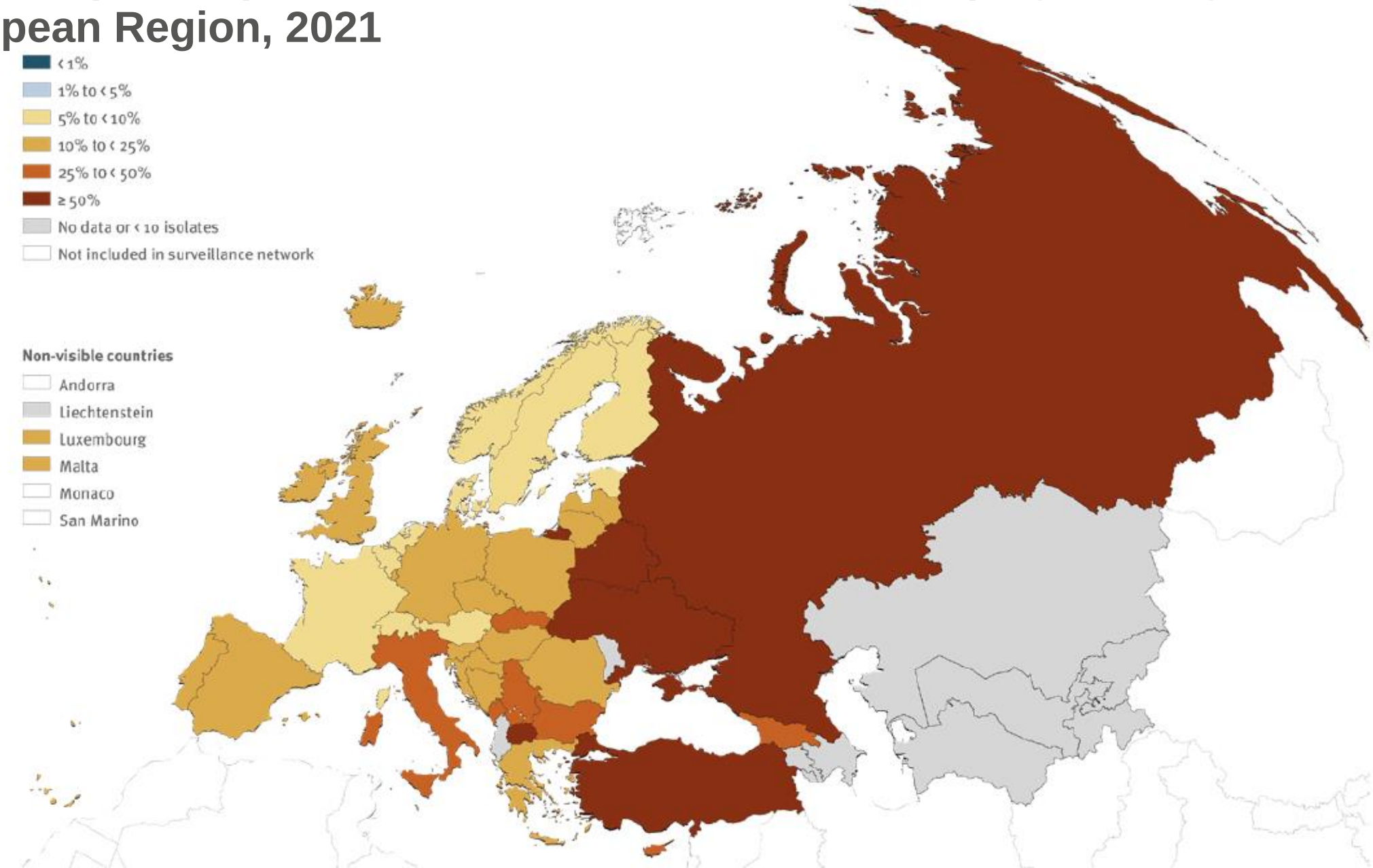
Azienda ospedaliero-universitaria Senese
UNIVERSITÀ DI SIENA 1240

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**



E. coli: percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country/area, WHO European Region, 2021



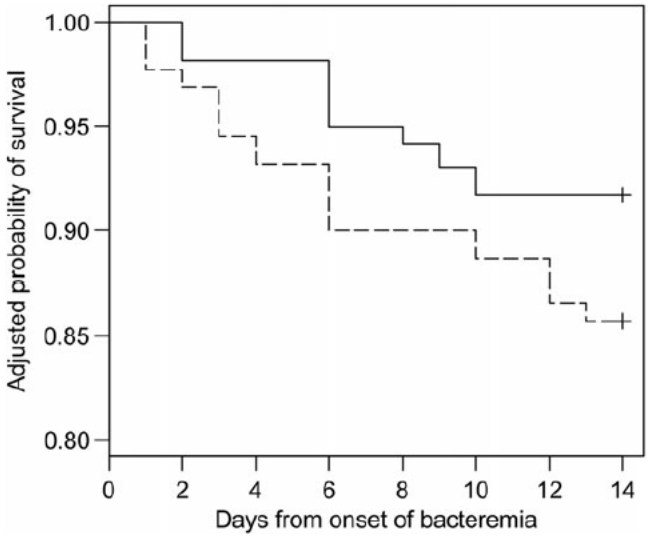
ESBL (Extended Spectrum beta-Lactamases) and types

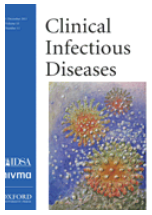
Type (Class)	Origins	No. Variants
TEM (A)	Mutants of TEM penicillinase, origins unknown	>100
SHV (A)	Mutants of SHV penicillinase, originated as a chromosomal type in K. pneumoniae	> 50
CTX-M (A)	Chromosomal ESBL in Kluyvara spp.	>40, 5 sub-classes
VEB (A)	Unknown	3
PER (A)	Unknown	2
OXA-15 (D)*	Mutant of OXA-2, a long-known penicillinase of uncertain origin	1
OXA-11, 14, 15, 16 17 (D)*	Mutant of OXA-10, a long-known penicillinase of uncertain origin	At least 5

* The definition of ESBLs is sometimes stretched to include Class D β-lactamase mutants that hydrolyse

Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients With Extended-Spectrum β-Lactamase Bacteremia

Pranita D. Tamma,[1] Jennifer H. Han,[2] Clare Rock,[3] Anthony D. Harris,[3] Ebbing Lautenbach,[2] Alice J. Hsu,[4] Edina Avdic,[4] and Sara E. Cosgrove[5]; for the Antibacterial Resistance Leadership Group





2015

Table 2. Fourteen-Day Mortality for 213 Patients With Extended-Spectrum β-Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy in a Stabilized Inverse Probability–Weighted Cohort[a]

	Univariable Analysis			Multivariable Analysis		
Characteristic	HR	95% CI	*P* Value	Adjusted HR[a]	95% CI	*P* Value
Piperacillin-tazobactam	1.78	1.00–3.13	.05	1.92	1.07–3.45	.03
Age (per 10-y increase)	1.28	1.09–1.50	.11	1.18	0.99–1.41	.07
Pitt bacteremia score	1.55	1.39–1.72	<.001	1.49	1.28–1.72	<.001
Intensive care unit level care, day 1	4.49	2.53–7.98	<.001	4.25	1.86–9.71	<.001
Immunocompromised	1.09	0.62–1.93	.76	. . .	. . .	. . .
Inadequate source control[b]	1.18	0.81–1.72	.39	. . .	. . .	. . .

PTZ is inferior to carbapenem therapy for the treatment of ESBL bacteremia.

For patients at high risk of invasive ESBL infections, early carbapenem therapy should be considered.

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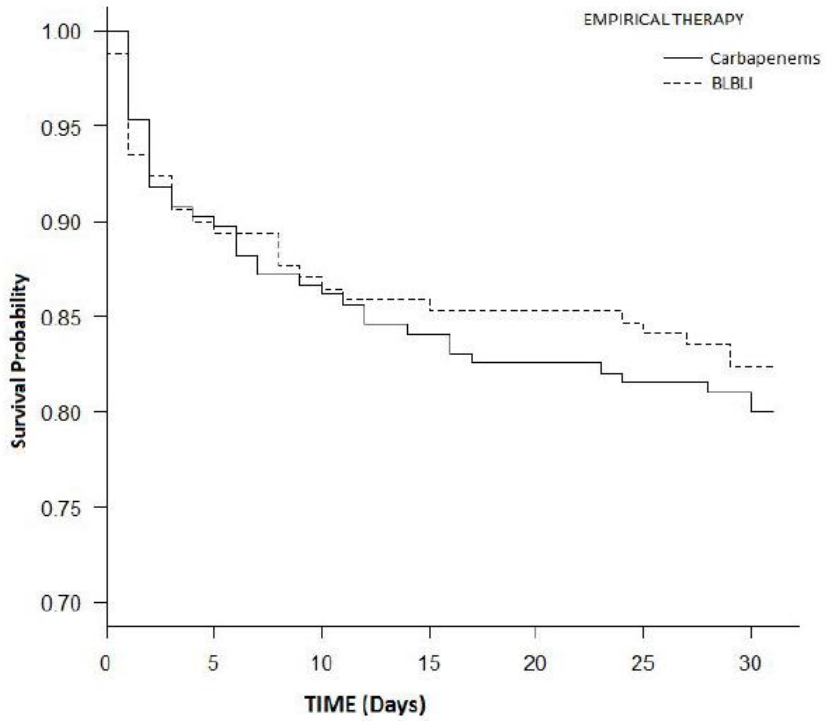
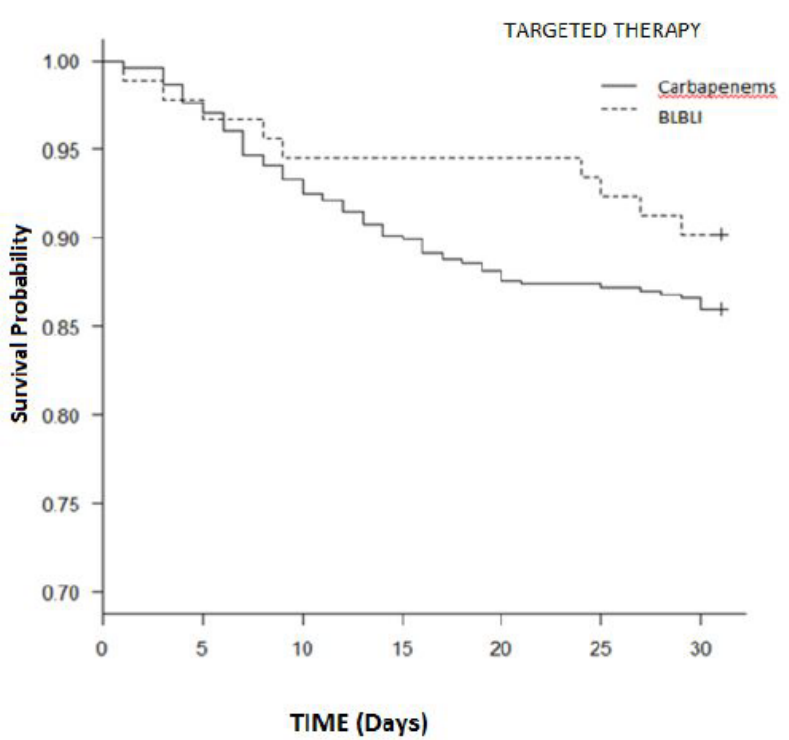
A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*





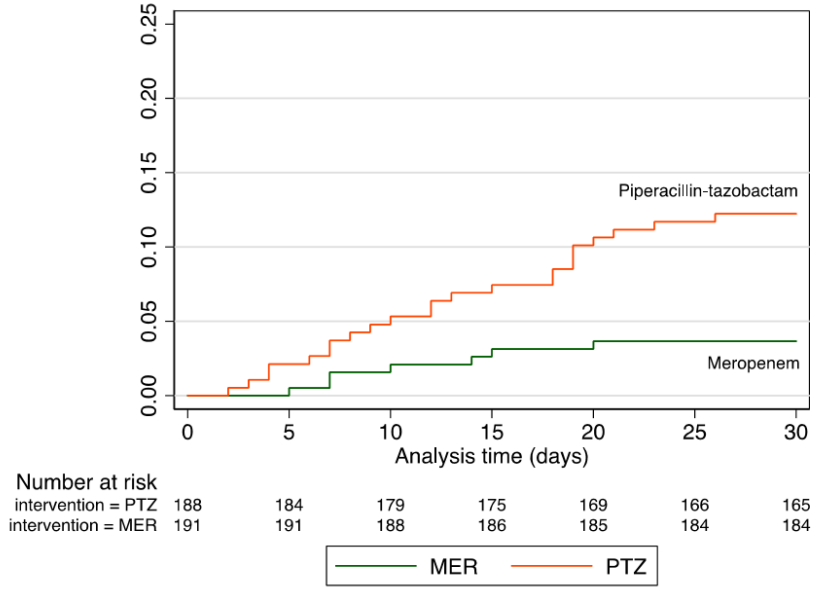
BLBLI, if active in vitro, appear as effective as carbapenems for ET and TT of BSI due to ESLB-E regardless of the source and specific species.
These data may help to avoid the overuse of carbapenems.

Gutiérrez-Gutiérrez B et al AAC 2016

Key Points

Question Can piperacillin-tazobactam be used as carbapenem-sparing therapy in patients with bloodstream infections caused by ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae*?

Findings In this noninferiority randomized clinical trial that included 391 patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, the 30-day mortality rate for patients treated with piperacillin-tazobactam compared with meropenem was 12.3% vs 3.7%, respectively. The difference did not meet the noninferiority margin of 5%.



JAMA. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

Merino limitations:

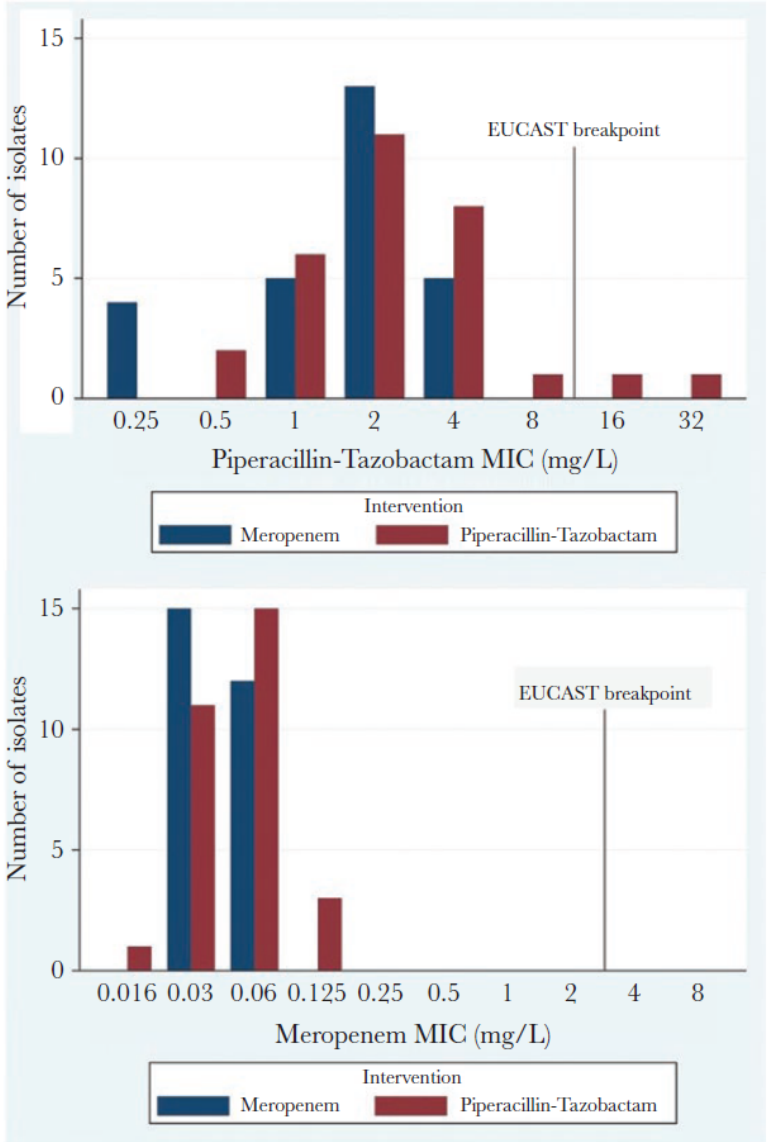
External validity:

- Only 3% mortality in meropenem arm
- High number of excluded patients after randomisation
- Piptazo not used in extended or continuous infusion
- No mention about use of generic products which may widely differ in in-vitro efficacy

- **Internal validity:**
- Geographical distribution of patients
- All mortality due to non-infection related causes
- Uncertainty in microbiological assessment of susceptibility and laboratory proficiency testing
- Discrepancy between low PIP-TAZO in vitro resistance (3.9%), but high (67.6%) OXA-1 co-production (which provides R to tazobactam) in isolates

Open Forum Infectious Diseases
MAJOR ARTICLE

Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)



- BSI due to AmpC producers. Patients were assigned 1:1 to receive piperacillin-tazobactam 4.5 g every 6 hours or meropenem 1 g every 8 hours.
- The primary efficacy outcome was a composite of death, clinical failure, microbiological failure, and microbiological relapse at 30 days.
- 72 patients underwent randomization and were included in the primary analysis population.
- Eleven of 38 patients (29%) randomized to piperacillin-tazobactam met the primary outcome compared with 7 of 34 patients (21%) in the meropenem group

Among patients with BSI due to AmpC producers, our pilot randomized trial was unable to show a difference in primary
outcome between the piperacillin-tazobactam and meropenem treatment groups; we found that piperacillin-tazobactam

STUDY PROTOCOL Open Access

Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ("MERINO-3"): study protocol for a multicentre, open-label randomised non-inferiority trial

This study will use a multicentre, parallel group open-label non-inferiority trial design comparing ceftolozane-tazobactam and meropenem in adult patients with bloodstream infection caused by ESBL or AmpC producing Enterobacterales.

Trial recruitment will occur in up to 40 sites in six countries (Australia, Singapore, Italy, Spain, Saudi Arabia and Pakistan).

Participants will have BSI due to third-generation cephalosporin non-susceptible E. coli and Klebsiella spp. or Enterobacter spp., Citrobacter freundii, Morganella morganii, Providencia spp. or Serratia marcescens.

They will be randomised 1:1 to ceftolozane-tazobactam 3 g versus meropenem 1 g, both every 8 h.

Secondary outcomes will be a comparison of 14-day all-cause mortality, clinical and microbiological success at day 5, functional bacteraemia score, microbiological relapse, new bloodstream infection, length of hospital stay, serious adverse events, C. difficile infection, multidrug-resistant organism colonisation.

The estimated trial completion date is December 2024.

Stewart *et al. Trials* (2021) 22:301
https://doi.org/10.1186/s13063-021-05206-8

Open Forum Infectious Diseases

MAJOR ARTICLE

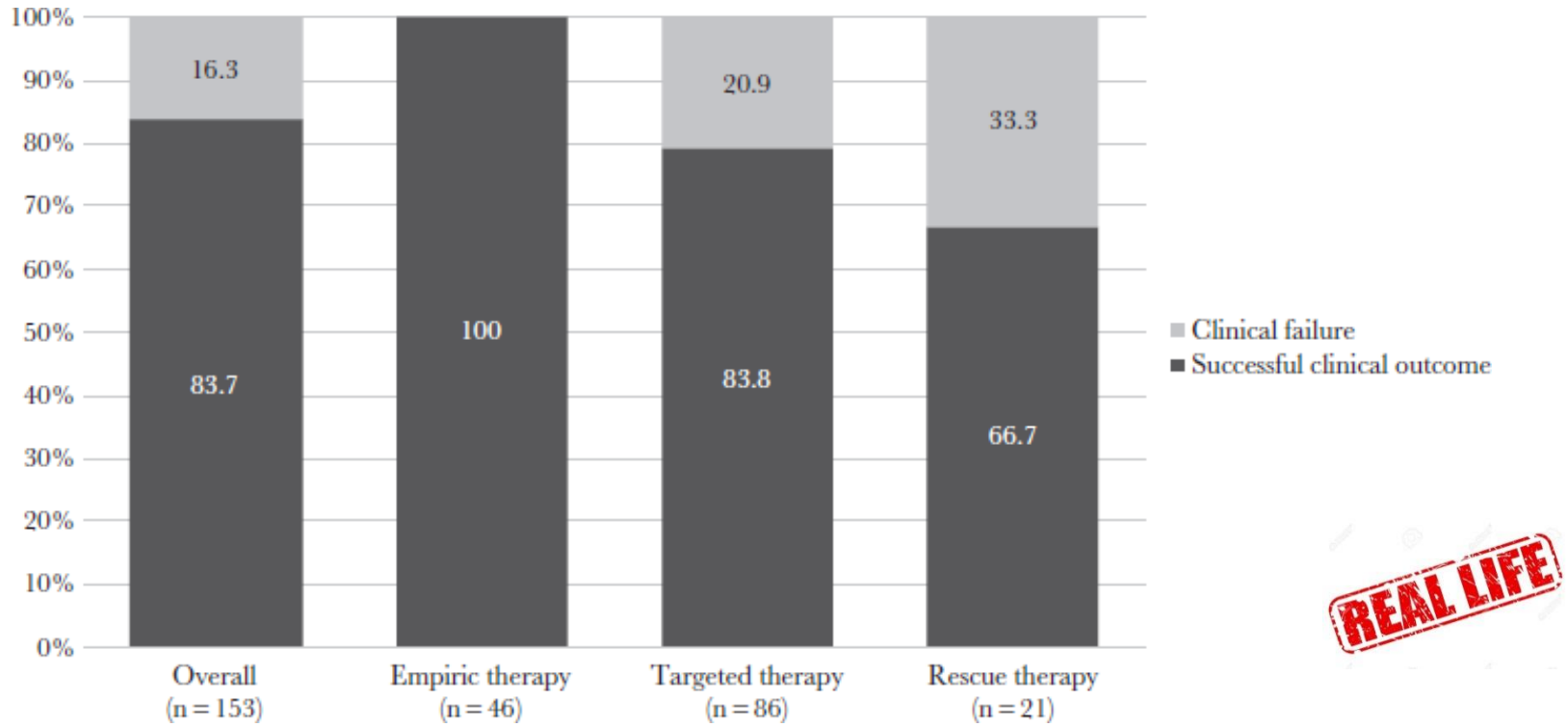
Ceftolozane/Tazobactam for Treatment of Severe ESBL-Producing *Enterobacterales* Infections: A Multicenter Nationwide Clinical Experience (CEFTABUSE II Study)

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 Mastroianni,[11] Gioacchino Angarano,[10] Mario Tumbarello,[12] Carlo Tascini,[8] Paolo Grossi,[7] Claudio Maria Mastroianni,[5] Cristina Mussini,[4] Pierluigi Viale,[3] Francesco Menichetti,[2] Claudio Viscoli,[1] and Alessandro Russo[2]; for the CEFTABUSE Study Group

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

153 patients. The most common diagnosis was pneumonia (n=46, 30%), followed by cUTI (n=34, 22%) cIAI (n=25, 16.3%) and BSI (n=16, 10%)



REAL LIFE

CI, confidence interval; CRRT, continuous renal replacement therapy; OR, odds ratio.

Bassetti M, et al. *Open Forum Infect Dis* 2020;7:ofaa139.

antibiotics

MDPI

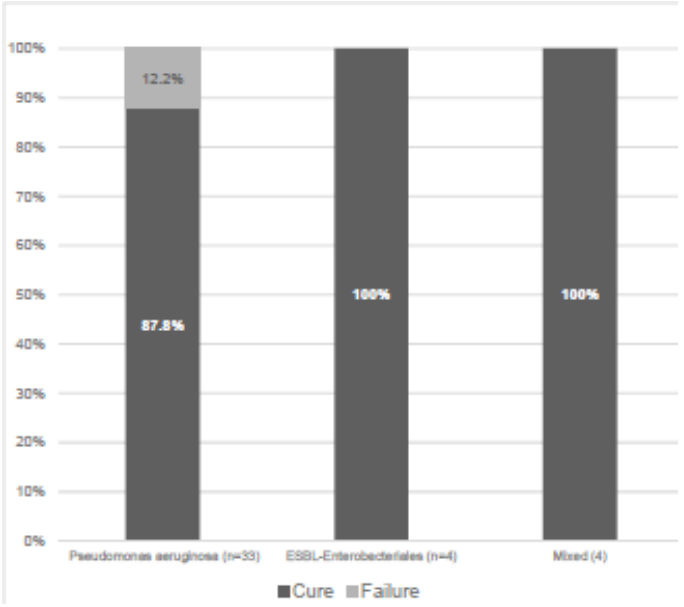
Article

Clinical Experience with Ceftazidime-Avibactam for the Treatment of Infections due to Multidrug-Resistant Gram-Negative Bacteria Other than Carbapenem-Resistant *Enterobacterales*

Antonio Vena [1,2], Daniele Roberto Giacobbe [1,2], Nadia Castaldo [3], Annamaria Cattelan [4], Cristina Mussini [5], Roberto Luzzati [6], Francesco Giuseppe De Rosa [7], Filippo Del Puente [1,2], Claudio Maria Mastroianni [8], Antonio Cascio [9], Sergio Carbonara [10], Alessandro Capone [11], Silvia Boni [12], Chiara Sepulcri [1,2], Marianna Meschiari [5], Francesca Raumer [4], Alessandra Oliva [8], Silvia Corcione [7], Matteo Bassetti [1,2,*] and for the Ceftabuse Study Group [†]

REAL LIFE

- All strains were susceptible to ceftazidime–avibactam
- Median length of therapy was 13 days
- Clinical success rates were 90.5%
- Ceftazidime–avibactam was mainly administered as a combination treatment (80.5%):
  - Colistin (n=12)
  - Aminoglycosides (n=11)
  - Carbapenems (n=5)
  - Fosfomycin (n=5)



Vena A, et al. *Antibiotics* 2020;9:71.

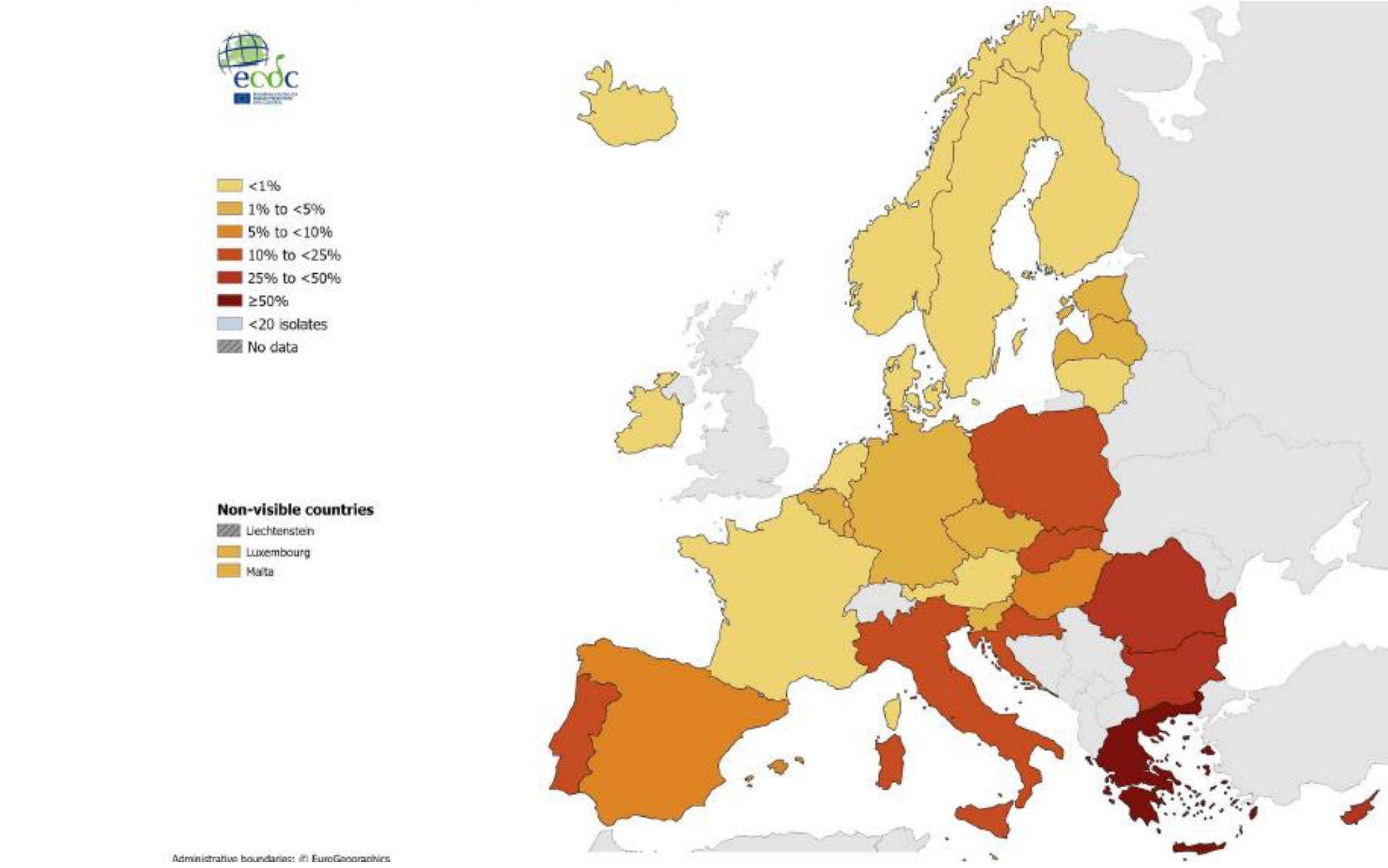
Klebsiella pneumoniae: percentage of invasive isolates with resistance to carbapenems

- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

2009 → 2014

- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

Klebsiella pneumoniae. Percentage of invasive isolates resistant to carbapenems (imipenem / meropenem), by country, EU/EEA, 2022



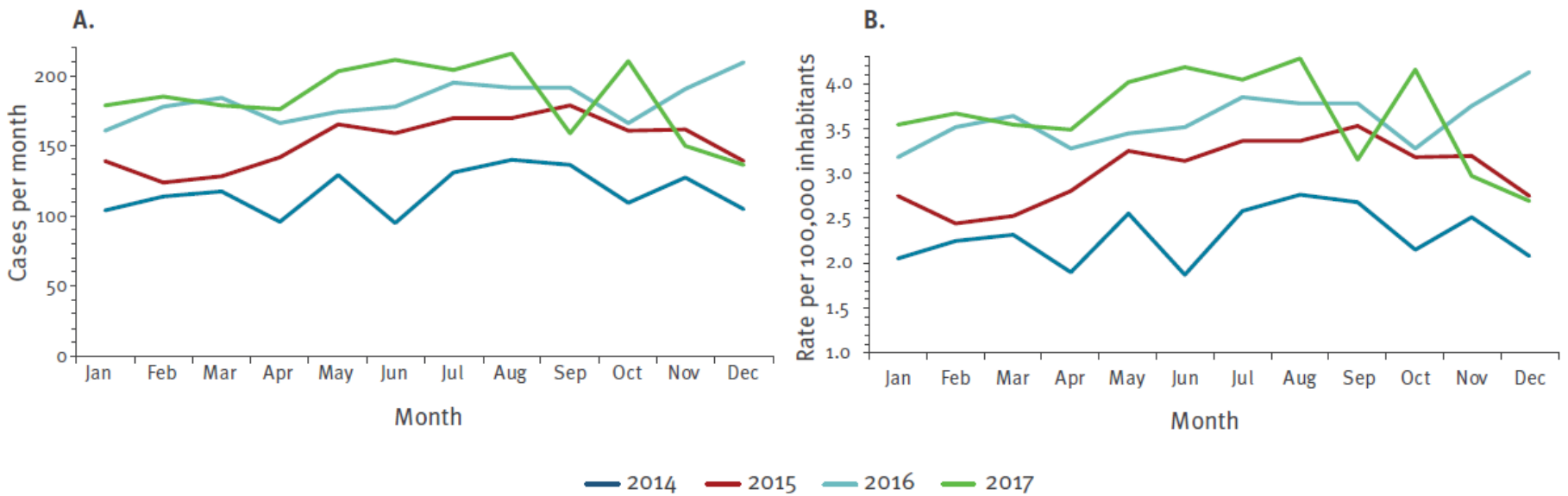
Bloodstream infections due to carbapenemase-producing Enterobacteriaceae in Italy: results from nationwide surveillance, 2014 to 2017

Simone Iacchini[1], Michela Sabbatucci[1,2], Carlo Gagliotti[3], Gian Maria Rossolini[4,5], Maria Luisa Moro[3], Stefania Iannazzo[6], Fortunato D'Ancona[1], Patrizio Pezzotti[1], Annalisa Pantosti[1]

Carbapenemase enzyme	*Klebsiella pneumoniae*		*Escherichia coli*		Total	
	N	%	N	%	N	%
KPC	4,323	95.2	57	81.4	4,380	95.0
MBL[a]	87	1.9	12	17.1	99	2.1
KPC + MBL[b]	43	0.9	0	0.0	43	0.9
OXA-48	55	1.2	1	1.4	56	1.2
MBL[c] + OXA-48	15	0.3	0	0.0	15	0.3
KPC + OXA-48	3	0.1	0	0.0	3	0.1
ND[d]	16	0.4	0	0.0	16	0.3
Not indicated	2,948	–	72	–	3,020	–
Total	7,490	–	142	–	7,632	–

Characteristics		N	%
Pathogen	*Klebsiella pneumoniae*	7,490	98.1
	Escherichia coli	142	1.9
Sex[a]	Female	2,817	37.3
	Male	4,731	62.7
Age group (years)[a]	0–19	101	1.4
	20–39	411	5.6
	40–59	1,642	22.2
	60–79	3,677	49.7
	≥ 80	1,569	21.2
Nationality	Italian	7,631	96.4
	Other	271	3.6
Patient location at symptom onset[a]	Hospital	6,386	87.2
	Other[b]	937	12.8
Total		**7,632**	**100**

(A) Frequency and (B) incidence rate per 100,000 inhabitants by month and year of bloodstream infections due to carbapenemase-producing Enterobacteriaceae reported to the national surveillance system, Italy, 2014–2017



Ceftazidime-avibactam Phase III clinical trial programme

Seven prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3: Adults with cIAI

Double-blind randomisation (1:1):
- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg IV q8h *or*
- MER 1000 mg IV + placebo q8h

Primary objective:
- RECLAIM 1 and 2:
  - Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
- RECLAIM 3:
  - Proportion of patients with clinical cure at TOC visit (CE populations)

RECAPTURE 1 and 2: Adults with cUTI (including acute pyelonephritis)

Double-blind randomisation (1:1) :
- CAZ 2000 mg + AVI 500 mg q8h IV *or*
- DOR 500 mg + placebo q8h IV

Primary objective:
Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:
1) Resolution of UTI-specific symptoms
2) Resolution/improvement of flank pain
3) Per-patient microbiol eradication and symptomatic resolution

REPRISE Adults with CAZ-resistant pathogens

Open-label randomisation (1:1) :
- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg q8h IV *or*
- Best available therapy

Primary objective:
Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens

REPROVE Adults with nosocomial pneumonia (including VAP)

Double-blind randomisation (1:1) :
- CAZ 2000 mg + AVI 500 mg q8h IV *or*
- MER 1000 mg + placebo q8h IV

Plus open-label empiric linezolid + aminoglycoside

Primary objective:
Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

AVI, avibactam; CAZ, ceftazidime; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; DOR, doripenem; IV, intravenous; MER, meropenem; mMITT, microbiological modified intent-to-treat; q8h, every 8 h; TOC, test of cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Zavicefta EMA EPAR. April 2016. Accessed Nov 2017 (www.ema.europa.eu, ceftazidime-avibactam PI)

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

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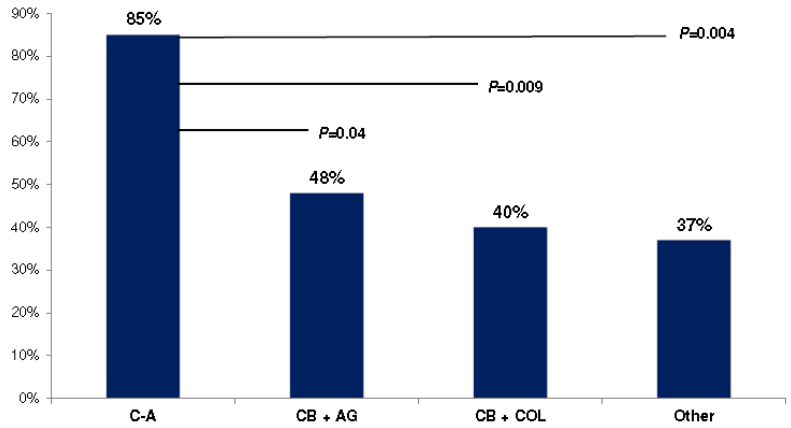
Figure 1. Rates of 30 day clinical success across treatment regimens



Thirty-day mortality rates was 28% (31/109).
Treatment regimens included C-A (n=**13**), CB+AG (n=25), CB+COL (n=30), and others (n=41); the corresponding clinical success rates by regimen were 85% (11/13), 48% (12/25), 40% (12/30), and 37% (15/41), respectively.
C-A was administered as monotherapy (n=8) or in combination with gentamicin (n=5); corresponding success rates were 75% (6/8) and 100% (5/5), respectively.

- **Ceftazidime-avibactam treatment of carbapenem-resistant *K. pneumoniae* bacteremia was associated with higher rates of clinical success (*P*=0.006) and survival (*P*=0.01) than other regimens.**
- **Aminoglycoside- and colistin-containing regimens were associated with increased rates of nephrotoxicity (*P*=0.002).**

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

Clinical Infectious Diseases
CID 2018:66 (15 January) • 163

Thirty-eight patients were treated first with CAZ-AVI and 99 with colistin.
Most patients received additional anti-CRE agents as part of their treatment.
BSI (n = 63; 46%) and respiratory (n = 30; 22%) infections were most common.
In patients treated with CAZ-AVI versus colistin, hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (*P* = .001).

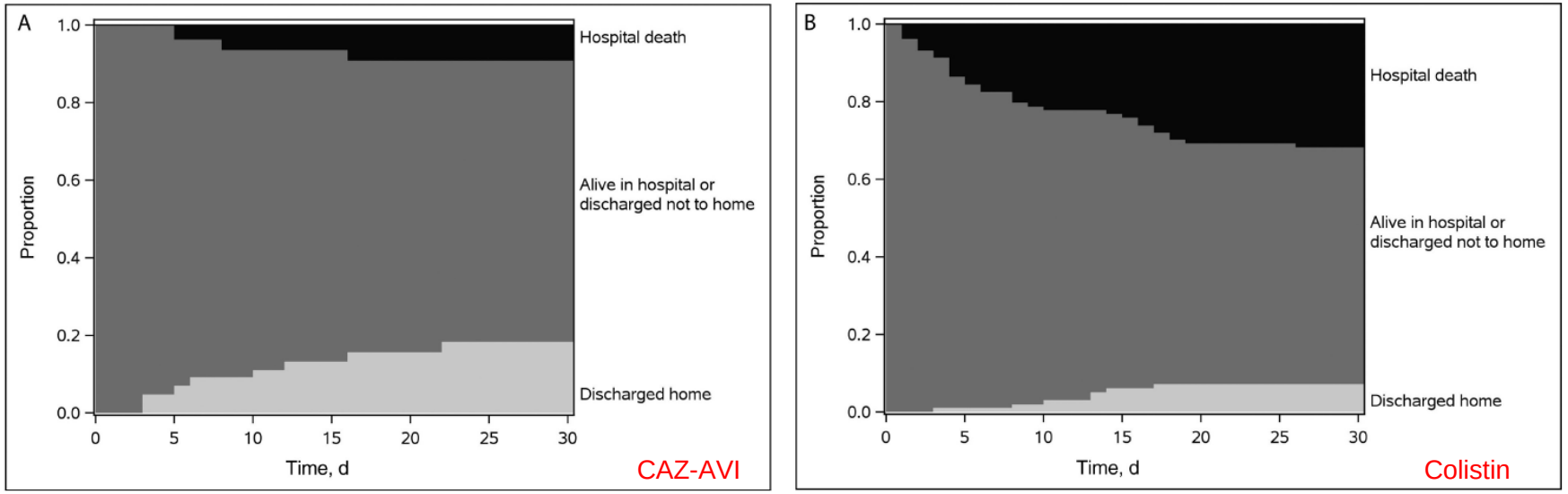


Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A,* Ceftazidime-avibactam group (n = 38). *B,* Colistin group (n = 99).

Clinical Infectious Diseases
MAJOR ARTICLE 2018

Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae*

Mario Tumbarello,[1,a] Enrico Maria Trecarichi,[1,a] Alberto Corona,[2] Francesco Giuseppe De Rosa,[3] Matteo Bassetti,[4] Cristina Mussini,[5] Francesco Menichetti,[6] Claudio Viscoli,[7] Caterina Campoli,[8] Mario Venditti,[9] Andrea De Gasperi,[10] Alessandra Mularoni,[11] Carlo Tascini,[12] Giustino Parruti,[13] Carlo Pallotto,[14] Simona Sica,[15] Ercole Concia,[16] Rosario Cultrera,[17] Gennaro De Pascale,[18] Alessandro Capone,[19] Spinello Antinori,[20] Silvia Corcione,[3] Elda Righi,[4] Angela Raffaella Losito,[1] Margherita Digaetano,[5] Francesco Amadori,[6] Daniele Roberto Giacobbe,[7] Giancarlo Ceccarelli,[9] Ernestina Mazza,[10] Francesca Raffaelli,[1] Teresa Spanu,[21] Roberto Cauda,[1] and Pierluigi Viale[8]

- 138 patients treated with CAZ-AVI salvage therapy after a first-line treatment with other antimicrobials.
- CAZ-AVI was administered with at least 1 other active antibiotic in 78.9% cases.
- Thirty days after infection onset **34.1% of the 138 patients had died**.
- Thirty-day mortality among the 104 patients with bacteremic KPC-Kp infections was significantly lower than that of a matched cohort whose KPC-Kp bacteremia had been treated with drugs other than CAZ-AVI (36.5% vs 55.8%, *P* = .005).

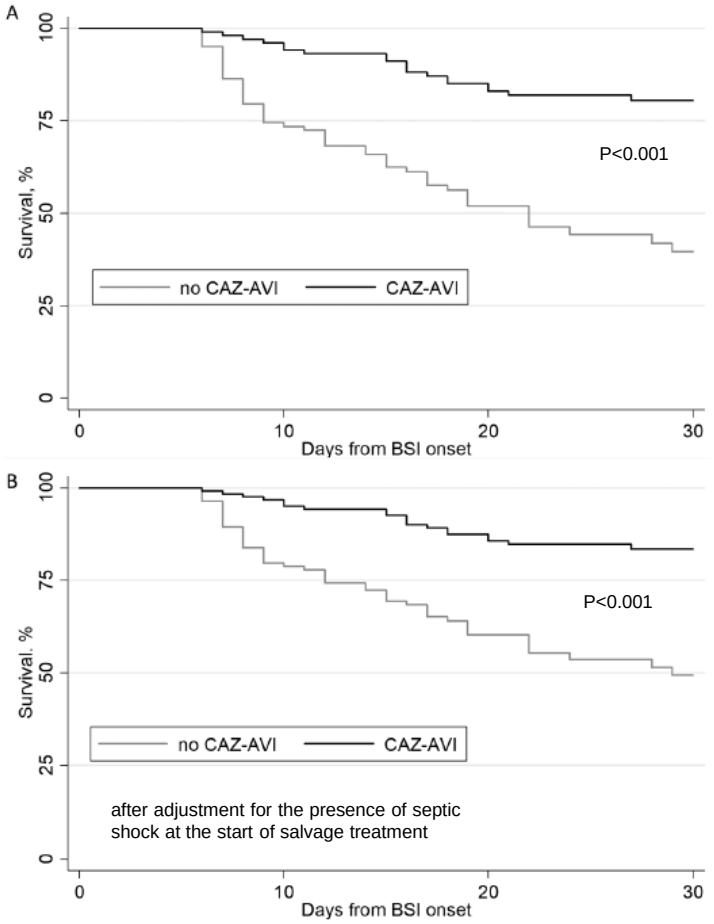


Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia

	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
Variable	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index ≥3	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia	.01	3.22 (1.25–8.29)	.03	3.36 (1.25–8.75)
Septic shock	.002	2.95 (1.46–5.94)	.003	2.94 (1.46–5.92)
Any regimen that included CAZ-AVI	<.001	0.25 (.13–.51)	.001	0.27 (.13–.57)

J Antimicrob Chemother
doi:10.1093/jac/dky295

Journal of Antimicrobial Chemotherapy

OXA-48

Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Adrian Sousa[1,2], María Teresa Pérez-Rodríguez[1,2]*, Adriana Soto[1], Lorena Rodríguez[1], Antonio Pérez-Landeiro[3], Lucia Martínez-Lamas[4], Andrés Nodar[1,2] and Manuel Crespo[1,2]

- 57 patients were treated with CAZ–AVI. The median age was 64 years, 77% were male and the median Charlson index was 3
- The most frequent sources of infection were intra-abdominal (28%), followed by respiratory (26%) and urinary (25%). 31 (54%) patients had a severe infection (defined as presence of sepsis or septic shock)
- Most patients received CAZ–AVI as monotherapy (81%) and the median duration of treatment was 13 days
- Mortality at 14 days was 14%
- There was no association between mortality and monotherapy with CAZ–AVI
- The recurrence rate at 90 days was 10%
- CAZ–AVI resistance was not detected

CAZ–AVI, ceftazidime–avibactam.

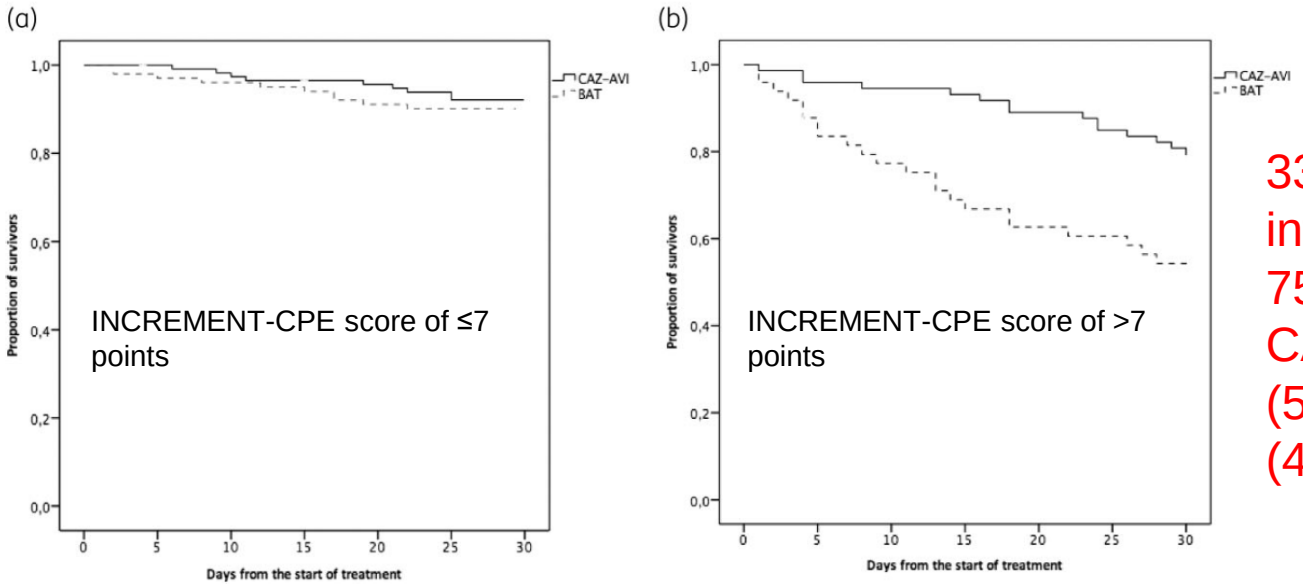
Sousa A, et al. *J Antimircob Chemother* 2018;73:3170–3175.

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

Journal of Antimicrobial Chemotherapy

OXA-48

Juan José Castón[1,2,3,4]*, Angela Cano[1,2,3,4], Inés Pérez-Camacho[5], Jose M. Aguado[4,6,7], Jordi Carratalá[4,8,9], Fernando Ramasco[10], Alex Soriano[4,11], Vicente Pintado[12], Laura Castelo-Corral[13], Adrian Sousa[14], María Carmen Fariñas[4,15,16], Patricia Muñoz[4,17,18,19,20], Vicente Abril López De Medrano[21], Óscar Sanz-Peláez[22], Ibai Los-Arcos[4,23,24], Irene Gracia-Ahufinger[3,25], Elena Pérez-Nadales[1,2,3], Elisa Vidal[1,2,3,4], Antonio Doblas[1], Clara Natera[1,2], Luis Martínez-Martínez[3,4,25,26] and Julian Torre-Cisneros[1,2,3,4]



339 patients with CPE infections.
75% OXA-48.
CAZ-AVI was used in 189 (55.8%) patients and 150 (44.2%) received BAT

Table 3. Multivariate analysis of factors associated with 30 day mortality in the 339 patients with infections caused by CPE

	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

Ceftazidime-Avibactam To Treat Life-Threatening Infections by Carbapenem-Resistant Pathogens in Critically Ill Mechanically Ventilated Patients

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'ch 2020 Volume 64 Issue 3 e02320-19

- 41 patients that received CAZ–AVI (the CAZ–AVI group) were compared to 36 patients that received antibiotics other than CAZ–AVI
- There was a significant improvement in SOFA score on days 4 and 10 in the CAZ–AVI group compared to that in the control group (P=0.006, and P=0.003, respectively)
- Clinical cure was observed in 33/41 (80.5%) vs 19/36 (52.8%) patients (P=0.010), respectively

TABLE 4 Multivariate analysis to determine predictors of 28-day survival and clinical cure in the CAZ-AVI and control groups of patients[a]

	Values for predictors of 28-day survival			Values for predictors of clinical cure		
Variable	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
SOFA score on admission	0.906	0.677–1.213	0.507	0.976	0.788–1.209	0.827
Charlson comorbidity index	0.830	0.655–1.053	0.124	0.880	0.704–1.101	0.263
SOFA score at infection onset	0.805	0.684–0.948	0.010	0.887	0.772–1.019	0.091
CAZ-AVI containing regime	5.575	1.469–21.162	0.012	5.123	1.680–15.619	0.004

[a]CAZ-AVI, ceftazidime-avibactam; control, best available therapy; BSI, bloodstream infection; SOFA, Sequential Organ Failure Assessment; CI, confidence interval.

Ceftazidime-Avibactam To Treat Life-Threatening Infections by Carbapenem-Resistant Pathogens in Critically Ill Mechanically Ventilated Patients Tsolaki V, et al.

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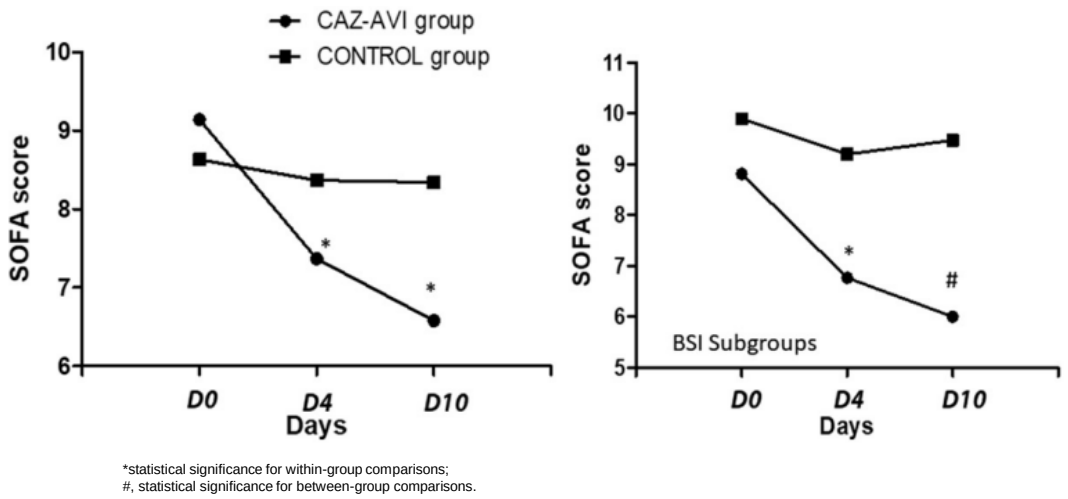
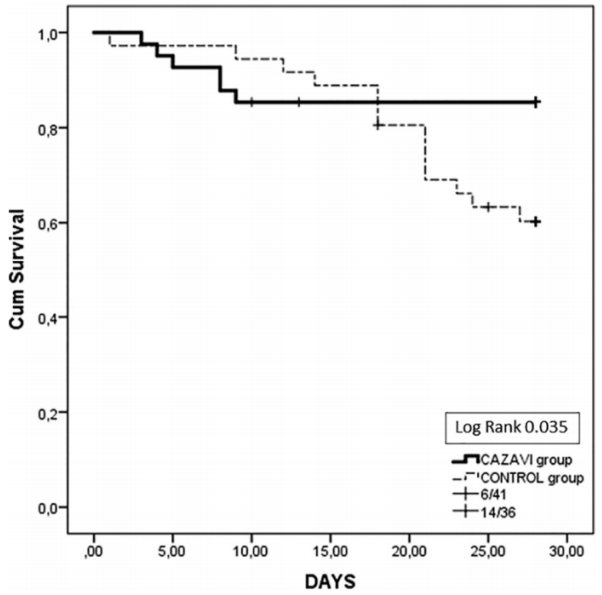
March 2020 Volume 64 Issue 3 e02320-19

SOFA score change during the first 10 days of treatment in the two main study groups and the two BSI subgroups



*statistical significance for within-group comparisons;
#, statistical significance for between-group comparisons.

Twenty-eight-day survival in the whole study group



BSI, bloodstream infections; CAZ–AVI, ceftazidime–avibactam; SOFA, sequential organ failure assessment score

Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

Ryan K. Shields,[a,b] M. Hong Nguyen,[a,b] Liang Chen,[c] Ellen G. Press,[a] Barry N. Kreiswirth,[c] Cornelius J. Clancy[a,b,d]

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May 2018 Volume 62 Issue 5 e02497-17

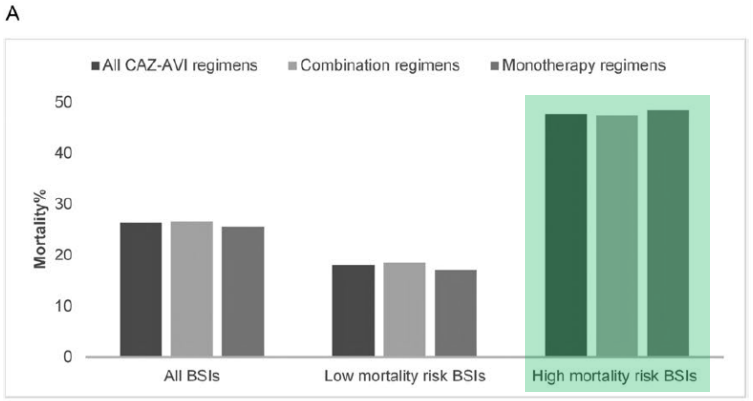
- **Ceftazidime-avibactam was used to treat 77 patients with CRE infections.**
- **33 (43%) infections were pneumonia (26, 79% VAP), 20 (26%) were bacteremia, 8 (10%) UTI, 7 (9%) intra-abdominal infections, 6 (8%) skin/soft tissue infection, and 3 other infections.**
- **Thirty-day survival rate was 81%.**
- **Success rates were lowest for pneumonia (36%) and higher for bacteremia (75%) and urinary tract infections (88%).**
- **Ceftazidime-avibactam resistance emerged in 10% of patients**

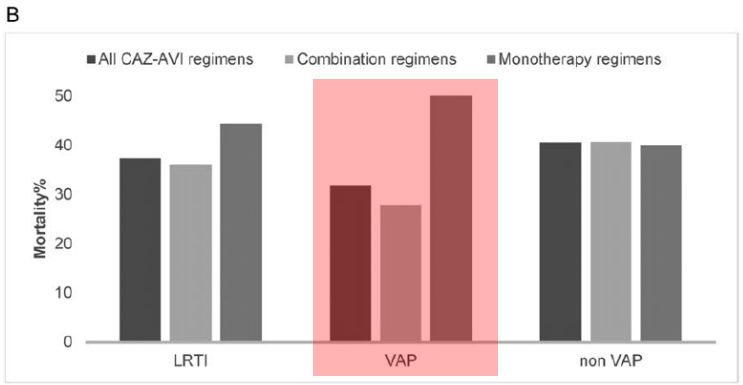
Risk factors associated with R to C-A (N=8 pts)	N/total R (%)	P value
KPC-3	8/8 (100)	0.003
Pneumoniae	7/8 (88)	0.09
Renal replacement therapy	5/8 (63)	0.006

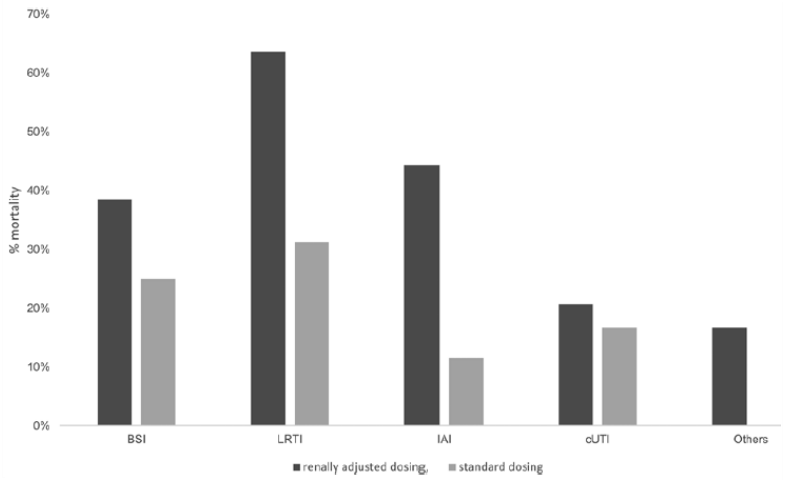
Clinical Infectious Diseases
MAJOR ARTICLE

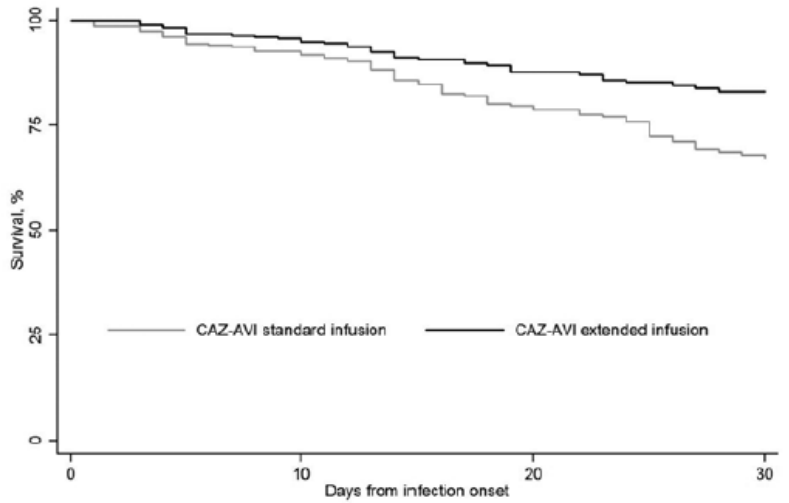
Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase–Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

- 577 adults with bloodstream infections (391) or nonbacteremic infections involving mainly the urinary tract, lower respiratory tract, and intra-abdominal structures.
- All received treatment with CAZ-AVI alone (165) or with ≥1 other active antimicrobials (412).
- The all-cause mortality rate 30 days after infection onset was 25%









Infect Dis Ther
https://doi.org/10.1007/s40121-018-0214-1

ORIGINAL RESEARCH

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Published online: 01 October 2018

M–V (n = 32)
BAT (n = 15)
Total (N = 47)

- **A Phase 3, multinational, openlabel, randomized controlled trial (TANGO II) was conducted from 2014 to 2017 to evaluate the efficacy/safety of meropenem–vaborbactam monotherapy (2 g/2 g administered every 8 h over 3-h intravenous infusion) versus best available therapy (BAT) for CRE.**

- **Day-28 all-cause mortality was 15.6% (5/32) and 33.3% (5/15) for meropenem–vaborbactam versus BAT, respectively**

Infect Dis Ther
https://doi.org/10.1007/s40121-018-0214-1

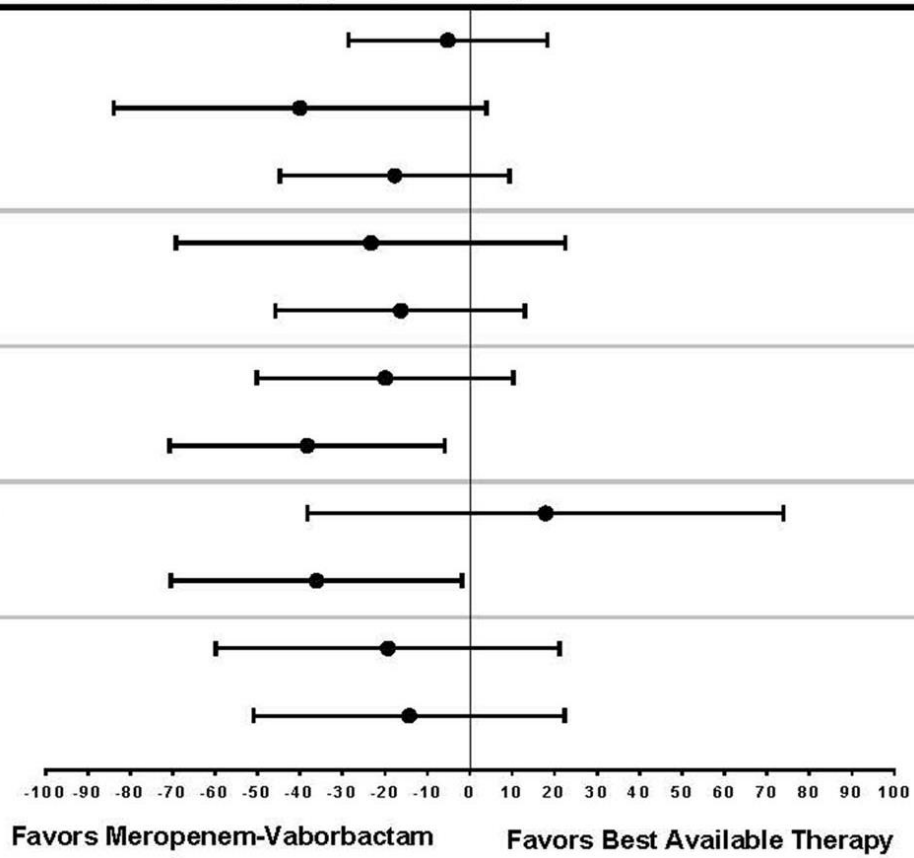
ORIGINAL RESEARCH

M–V (n = 32)
BAT (n = 15)
Total (N = 47)

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Published online: 01 October 2018

B Day 28 all-cause mortality by subgroup (mCRE-MITT)



		Meropenem-Vaborbactam	Best Available Therapy	Difference (95% CI)
Age	<65 years	1/17 (5.9%)	1/9 (11.1%)	-5.2 (-28.6, 18.2)
	≥65 years	4/15 (26.7%)	4/6 (66.7%)	-40.0 (-83.9, 3.9)
	All	5/32 (15.6%)	5/15 (33.3%)	-17.7 (-44.7, 9.3)
SIRS Status	Yes	4/15 (26.7%)	3/6 (50.0%)	-23.3 (-69.2, 22.5)
	No	1/17 (5.9%)	2/9 (22.2%)	-16.3 (-45.7, 13.0)
Charlson Comorbidity Score Category	≥4	5/27 (18.5%)	5/13 (38.5%)	-19.9 (-50.2, 10.3)
	≥6	1/14 (7.1%)	5/11 (45.5%)	-38.3 (-70.7, -5.9)
Creatinine Clearance	<50 mL/min	3/7 (42.9%)	1/4 (25.0%)	17.9 (-38.2, 73.9)
	≥50 mL/min	2/24 (8.3%)	4/9 (44.4%)	-36.1 (-70.4, -1.8)
Immuno-compromised	Yes	2/11 (18.2%)	3/8 (37.5%)	-19.3 (-59.9, 21.2)
	No	3/21 (14.3%)	2/7 (28.6%)	-14.3 (-50.9, 22.4)

Conclusions: Monotherapy with M-V for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with BAT.

Clinical Infectious Diseases

BRIEF REPORT

Early Experience With Meropenem-Vaborbactam for Treatment of Carbapenem-resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,2,3] Erin K. McCreary,[3] Rachel V. Marini,[3] Ellen G. Kline,[1] Chelsea E. Jones,[1] Binghua Hao,[1,2] Liang Chen,[4] Barry N. Kreiswirth,[4] Yohei Doi,[1] Cornelius J. Clancy,[1,2,5] and M. Hong Nguyen[1,2,3]

CRE infection types included bacteremia (n=8), pneumonia (n=6; 83% [5/6] ventilator-associated), tracheobronchitis (n=2; 50% [1/2] ventilator-associated), skin/soft tissue (n=2), pyelonephritis (n=1), and peritonitis with intra-abdominal abscess (n=1).

Twenty patients with carbapenem-resistant Enterobacteriaceae infections were treated with meropenem-vaborbactam.

Thirty day clinical success and survival rates were 65% (13/20) and 90% (18/20), respectively.

Thirty-five percent of patients had microbiologic failures within 90 days. One patient developed a recurrent infection due to meropenem-vaborbactam–nonsusceptible, *ompK36* porin mutant *Klebsiella pneumoniae*.

Real-world Multicenter Analysis of Clinical Outcomes and Safety of Meropenem-Vaborbactam in Patients Treated for Serious Gram-Negative Bacterial Infections

Sara Alosaimy,[1] Sarah C. J. Jorgensen,[1,a] Abdalhamid M. Lagnf,[1] Sarah Melvin,[1] Ryan P. Mynatt,[2,b] Travis J. Carlson,[3,c] Kevin W. Garey,[3] David Allen,[4] Veena Venugopalan,[5] Michael Veve,[6,7] Vasilios Athans,[8] Stephen Saw,[8] Christine N. Yost,[9] Susan L. Davis,[1,10] and Michael J. Rybak[1,2,11]

Open Forum Infectious Diseases

BRIEF REPORT 2020

Fourty patients were treated with meropenem-vaborbactam (MEV) for serious Gram-negative bacterial (GNB) infections.

Carbapenem-resistant *Enterobacteriaceae* (CRE) comprised 80.0% of all GNB infections.

The most common sources of infection were pneumonia (32.5%, 13/40), urinary tract (20.0%, 8/40), intra-abdominal (12.5%, 5/40), and skin and soft tissue (SST; 12.5%, 5/40). Blood cultures were positive in 27.5% (11/40) of patients

Clinical success occurred in 70.0% of patients.

Mortality and recurrence at 30 days were 7.5% and 12.5%, respectively.

One patient experienced a probable rash due to MEV.

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CLINICAL THERAPEUTICS

Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections

Renee Ackley,[a] Danya Roshdy,[a] Jacqueline Meredith,[a] Sarah Minor,[b] William E. Anderson,[c] Gerald A. Capraro,[d] Christopher Polk[e]

131 patients
105 ceftazidime-avibactam
26 meropenem-vaborbactam
40% had bacteremia.

TABLE 4 Clinical outcomes[a]

	Ceftazidime-avibactam group (n = 105)	Meropenem-vaborbactam group (n = 26)	P value
No. of clinical successes[b] (%)	65 (61.9)	18 (69.2)	0.49
No. of failures to resolve signs and symptoms of infection (%)	4 (3.8)	1 (3.8)	1.0
Failure to sterilize blood cultures within 7 days of treatment initiation [no. of failures/no. of bacteremias (%)]	1/44 (2.3)	1/9 (11.1)	0.31
No. of 30-day mortalities (%)	20 (19.1)	3 (11.5)	0.57
No. of 90-day mortalities (%)	30 (28.6)	7 (26.9)	0.48
Median length of hospital stay[c] (days) (IQR)	15.3 (9.3–28.5)	15.6 (9.5–33.1)	0.99
Median length of ICU stay (days) (IQR)	15.0 (5.0–32.0)	12.0 (5.0–22.0)	0.53
No. of recurrences of CRE infection (%)	15 (14.3)	3 (11.5)	1.0
No. of increases in study drug MIC in mg/liter (%)	6 (40.0)	0	0.51
No. of emergences of study drug resistance (%)	3 (20.0)	0	1.0

No significant difference in clinical success was observed between groups (62% versus 69%)
Patients in the ceftazidime-avibactam arm received combination therapy more often than patients in the meropenem-vaborbactam arm (61% versus 15%).
No difference in 30- and 90-day mortality resulted, and rates of AE were similar between

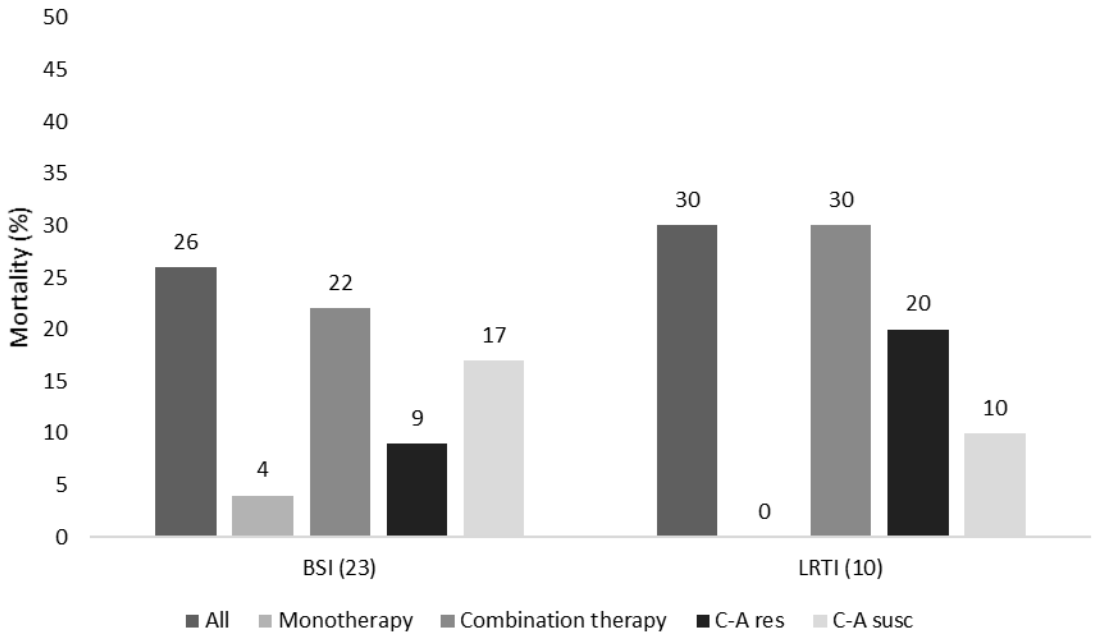
Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: a multicentre study

Mario Tumbarello[1,2*], Francesca Raffaelli[3], Antonio Cascio[4], Marco Falcone[5], Liana Signorini[6], Cristina Mussini[7], Francesco Giuseppe De Rosa[8], Angela Raffaella Losito[3], Gennaro De Pascale[9,10], Renato Pascale[11], Daniele Roberto Giacobbe[12,13], Alessandra Oliva[14], Alberto Farese[15], Paola Morelli[16,17], Giusy Tiseo[5], Marianna Meschiari[7], Paola Del Giacomo[3], Francesca Montagnani[1,2], Massimiliano Fabbiani[2], Joel Vargas[10], Teresa Spanu[3,10], Matteo Bassetti[12,13], Mario Venditti[14] and Pierluigi Viale[11]

37 KPC-Kp infections
BSIs, *n*=23
LRTIs, *n*=10
CZA res. n=22

Clinical cure was achieved in 28 (75.6%) cases. Nine patients (24.3%) died in hospital with persistent signs of infection. Most were aged over 60 years, with high comorbidity burdens and INCREMENT scores ≥8.

Outcomes were unrelated to the isolate's ceftazidime/avibactam susceptibility status.

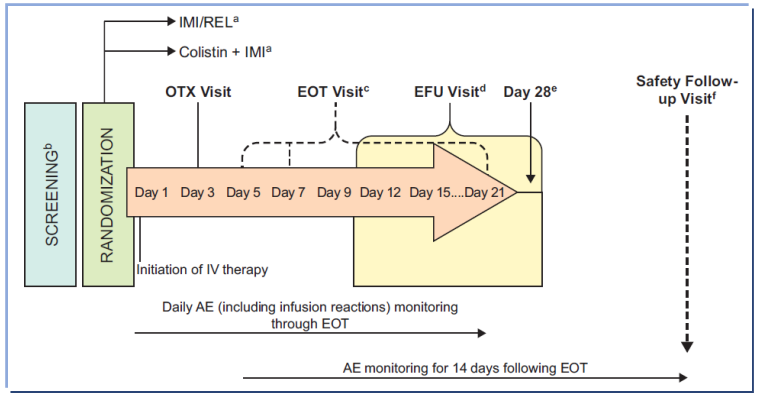


JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac022

Clinical Infectious Diseases
MAJOR ARTICLE

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

Johann Motsch,[1] Cláudia Murta De Oliveira,[2] Viktor Stus,[3] Iftihar Köksal,[4] Olexiy Lyulko,[5] Helen W. Boucher,[6] Keith S. Kaye,[7] Thomas M. File Jr,[8] Michelle L. Brown,[9] Ireen Khan,[9] Jiejun Du,[9] Hee-Koung Joeng,[9] Robert W. Tipping,[9] Angela Aggrey,[9] Katherine Young,[9] Nicholas A. Kartsonis,[9] Joan R. Butterton,[9] and Amanda Paschke[9]



Pseudomonas aeruginosa (77%), *Klebsiella* spp. (16%), other Enterobacteriaceae (6%)

31 patients received imipenem/relebactam and 16 colistin+imipenem

Favorable overall response was observed in 71% imipenem/relebactam and 70% colistin+imipenem patients, day 28 favorable clinical response in 71% and 40%, and 28-day mortality in 10% and 30%, respectively. Serious adverse events occurred in 10% of imipenem/relebactam and 31% of colistin+imipenem patients,

Table 2. Primary and Secondary Prospective Efficacy Endpoints (in the Modified Microbiologic Intent-to-Treat Population) and Secondary Prospective Safety Endpoints (in the Safety Population)

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	−7.3	(−27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		−27.3 (−52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	−20.5	−17.3	(−46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		−45.9 (−69.1, −18.4)	

Open Forum Infectious Diseases

BRIEF REPORT

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

Nicholas Rebold,[1] Taylor Morrisette,[1,2,3] Abdalhamid M. Lagnf,[1] Sara Alosaimy,[1] Dana Holger,[1] Katie Barber,[4,5] Julie Ann Justo,[6,7] Kayla Antosz,[7] Travis J. Carlson,[8] Jeremy J. Frens,[9] Mark Biagi,[10,11] Wesley D. Kufel,[12,13] William J. Moore,[14] Nicholas Mercuro,[15,16] Brian R. Raux,[2] and Michael J. Rybak[1,17,18]

- Multicenter, retrospective, observational case series
- 21 patients were treated with imipenem-cilastatin-relebactam.
- There were mixed infection sources, with pulmonary infections (11/21,52%) composing the majority.
- The primary pathogen was *Pseudomonas aeruginosa* (16/21, 76%), and 15/16 (94%) isolates were multidrug-resistant.
- Thirty-day survival occurred in 14/21 (67%) patients
- Two patients experienced adverse effects.

Real-world effectiveness of imipenem/cilastatin/relebactam for the treatment of gram-negative infections

Ryan K. Shields[1]; Vladimir Turzhitsky[2]; Emre Yucel[2]; Sanjay Merchant[2]; Alexandre H. Watanabe[2]

[1]Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA; [2]Merck & Co., Inc., Rahway, NJ, USA

REAL LIFE

- A total of 160 patients from 63 hospitals were included in the analysis (Figure 1)
- The median (IQR) age was 59 (46-68) years, and patients were acutely and chronically ill (Table 1)
  - Common comorbid conditions included renal disease (43.1%), diabetes (37.5%), congestive heart failure (34.4%), and chronic pulmonary disease (26.9%)
  - The median (IQR) age-adjusted Charlson Comorbidity Index was 5 (2-8), and 20.6% of patients had a COVID ICD-10 diagnosis code
  - During the index hospitalization, 60.6% of patients were in the intensive care unit (ICU), 40.6% had septic shock, and 55.0% required mechanical ventilation

Type of infection, n (%)	
HABP/VABP	86 (53.8)
cUTI	27 (16.9)
cIAI	6 (3.8)

Table 2. Microbiology characteristics stratified by infection type[a]

	Overall (N=37)	HABP/VABP (n=24)	cUTI (n=4)	cIAI (n=3)
Polymicrobial infections, n (%)	13 (35.1)	11 (45.8)	–	–
Pathogen, n (%)				
P. aeruginosa	33 (89.2)	21 (87.5)	3 (75.0)	3 (100.0)
E. coli	4 (10.8)	4 (16.7)	–	–
K. pneumoniae	7 (18.9)	4 (16.7)	1 (25.0)	–
E. cloacae	4 (10.8)	4 (16.7)	–	–
K. (Enterobacter) aerogenes	1 (2.7)	1 (4.2)	–	–
K. oxytoca	1 (2.7)	1 (4.2)	–	–
S. marcescens	2 (5.4)	2 (8.3)	–	–
Resistant infection, n (%)				
CRE	1 (2.7)	1 (4.2)	–	–
ESBL	4 (10.8)	4 (16.7)	–	–
MDR PSA	28 (75.7)	18 (75.0)	2 (50.0)	2 (66.7)

Table 4. Patient outcomes

	Overall (N=160)	HABP/VABP (n=86)
Median hospital LOS, days (IQR)	25 (13, 44)	32 (18, 59)
Median ICU LOS, days (IQR)	27 (13, 38)	29 (16, 49)
All-cause in-hospital mortality, n (%)	39 (24.4)	34 (39.5)
All-cause 30-day mortality[a], n (%)	34 (21.3)	27 (31.4)
Readmission in 30 days, n (%)	28 (17.5)	8 (9.3)
In-hospital mortality among COVID+ patients, n (%)	19/33 (57.6)	17/28 (60.7)
In-hospital mortality among non-COVID+ patients, n (%)	20/127 (15.7)	17/58 (29.3)

33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

CORRESPONDENCE

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

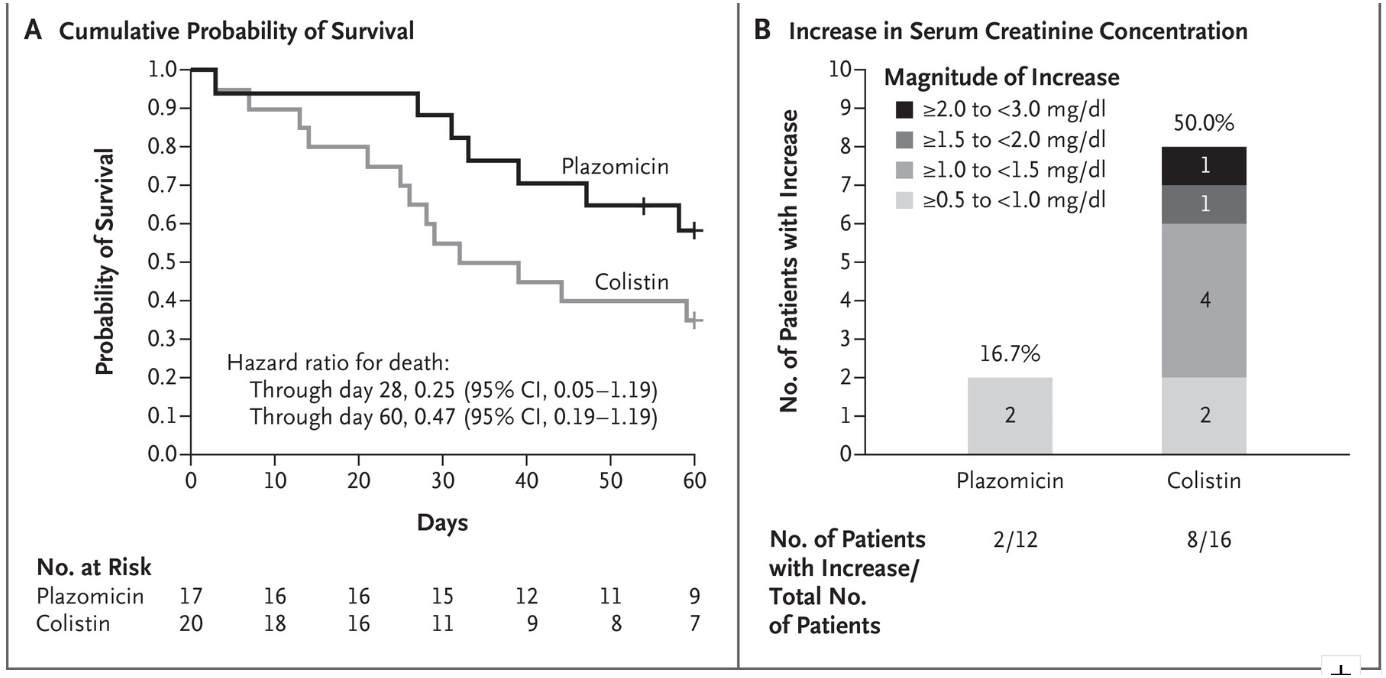
14 Citing Articles

TO THE EDITOR:

February 21, 2019
N Engl J Med 2019; 380:791-793
DOI: 10.1056/NEJMc1807634
Metrics

Eligible patients received plazomicin (15 mg per kilogram of body weight once daily) or colistin (5 mg colistin base per kilogram per day), in combination with adjunctive meropenem or tigecycline.

The microbiologic modified intention-to-treat population included 37 patients with confirmed CRE (29 with bloodstream infection and 8 with hospital-acquired or ventilator-associated bacterial pneumonia



Combating Antibiotic-Resistant Enterobacteriaceae trial (CARE; ClinicalTrials.gov number, NCT01970371

MBL

Journal of Antimicrobial Chemotherapy

Reversal of carbapenemase-producing *Klebsiella pneumoniae* epidemiology from bla_{KPC}- to bla_{VIM}-harbouring isolates in a Greek ICU after introduction of ceftazidime/avibactam

Matthaios Papadimitriou-Olivgeris ✉, Christina Bartzavali, Anastasia Lambropoulou, Anastasia Solomou, Ekaterini Tsiata, Evangelos D Anastassiou, Fotini Fligou, Markos Marangos, Iris Spiliopoulou, Myrto Christofidou ✉

Journal of Antimicrobial Chemotherapy, dkz125,
https://doi.org/10.1093/jac/dkz125
Published: 19 April 2019 **Article history** ▾

ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; VIM, Verona integron-encoded metallo-β-lactamase.

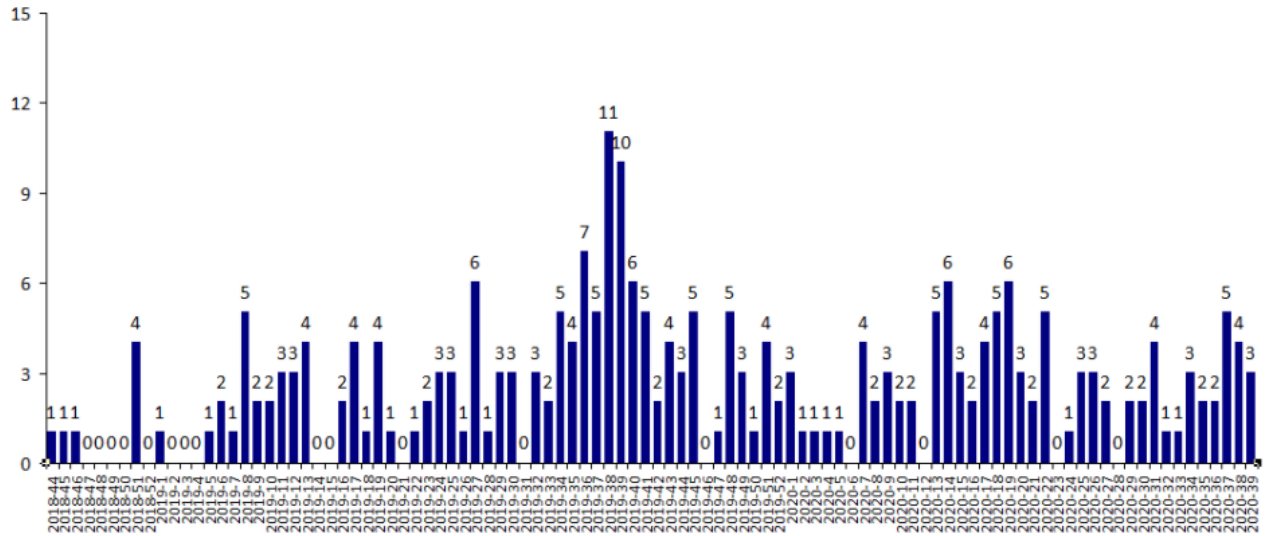
Tags Ndm

12/10/2020

L'**ARS** partecipa all'**unità di crisi**, costituita a maggio 2019 dall'Assessorato alla salute, per monitorare la diffusione significativa - in particolare nell'area nord-occidentale della **Toscana** - di **enterobatteri NDM**, diffusione osservata a partire da novembre 2018. L'ARS è impegnata nel monitoraggio continuo del fenomeno, in stretta collaborazione con l'assessorato e le aziende sanitarie della Toscana: sul nostro sito l'aggiornamento dei dati.

Aggiornamento 12 ottobre 2020

Casi NDM in Toscana, per settimana, 29 ottobre 2018-27 settembre 2020



Tra **novembre 2018** e il **23 agosto 2020** i **batteri NDM** sono stati **isolati nel sangue di 254 pazienti**.
I **casi** sono risultati **letali nel 25% dei pazienti con sepsi** (non necessariamente si tratta di decessi dovuti all'infezione specifica), percentuale paragonabile alla letalità per questa condizione causata da altri batteri resistenti agli antibiotici carbapenemici.

AAC Accepted Manuscript Posted Online 30 September 2019
Antimicrob. Agents Chemother. doi:10.1128/AAC.01426-19

1 **Searching for the Optimal Treatment for Metallo- and Serine-β-Lactamase Producing**
2 **Enterobacteriaceae: Aztreonam in Combination with Ceftazidime-avibactam or**
3 **Meropenem-vaborbactam**
4
5 Biagi M[1], Wu T[1], Lee M[1], Patel S[1], Butler D[1], Wenzler E[1]
6 [1]College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

- 8 clinical Enterobacteriaceae strains (4 *Escherichia coli* and 4 *Klebsiella pneumoniae*) co-producing NDM and at least one serine β-lactamase were used for all experiments.

- All strains were resistant to ceftazidime-avibactam and meropenem-vaborbactam and 7/8 (87.5%) strains were resistant to aztreonam.

- Aztreonam combined with ceftazidime-avibactam was synergistic against all 7 aztreonam-resistant strains.

- Aztreonam combined with meropenem-vaborbactam was synergistic against all aztreonam-resistant strains with the exception of an OXA-232-69 producing *K. pneumoniae* strain.

Clinical Infectious Diseases

MAJOR ARTICLE

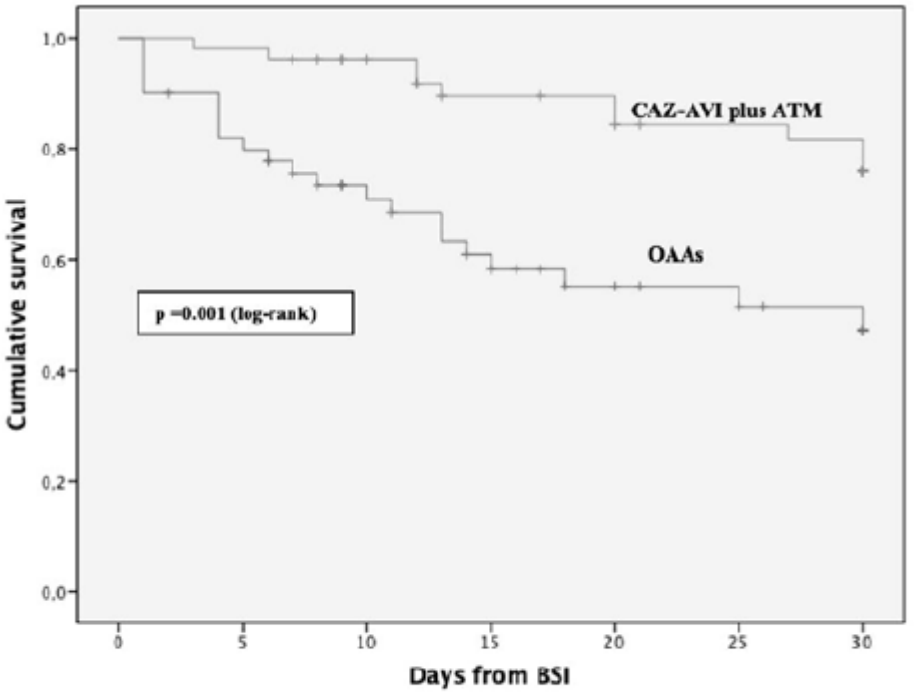
Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Marco Falcone,[1] George L. Daikos,[2] Giusy Tiseo,[1] Dimitrios Bassoulis,[2] Cesira Giordano,[3] Valentina Galfo,[1] Alessandro Leonildi,[3] Enrico Tagliaferri,[1] Simona Barnini,[3] Spartaco Sani,[4] Alessio Farcomeni,[5] Lorenzo Ghiadoni,[6] and Francesco Menichetti[1]

102 patients with BSI

82 had infections caused by NDM-producing and 20 by VIM-producing strains.

The 30-day mortality rate was 19.2% in the CAZ-AVI + ATM group vs 44% in the OAA group (*P* = .007).



Number at risk

CAZ-AVI *plus* ATM	52	51	50	47	45	45	42
OAAs	50	40	36	31	30	29	28

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	< .001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	< .001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	< .001

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

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

- **Cefiderocol had similar clinical and microbiological efficacy to best available therapy in this heterogeneous patient population with infections caused by CR Gram-neg. bacteria.**
- **Numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp infections.**

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3
Without *Acinetobacter* spp	0/3	0/1
Stenotrophomonas maltophilia	4/5 (80%)	NA
Without *Acinetobacter* spp	2/3 (67%)	NA

Data are n/N (%). NA=not available. *Includes *Acinetobacter baumannii* (for 39 patients assigned cefiderocol and 17 assigned best available therapy), *Acinetobacter nosocomialis* (for two patients assigned cefiderocol), and *Acinetobacter radioresistens* (for one patient assigned cefiderocol).

Table 6: **All-cause mortality at the end of study by most frequent baseline pathogen in the safety population**

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=30)	Best available therapy (n=17)	Cefiderocol (n=26)	Best available therapy (n=10)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9–39·5)	3 (14%; 2·9–34·9)	5 (17%; 5·6–34·7)	1 (6%; 0·1–28·7)	3 (12%; 2·4–30·2)	2 (20%; 2·5–55·6)	19 (19%; 11·7–27·8)	6 (12%; 4·6–24·8)
Day 28	14 (31%; 18·2–46·6)	4 (18%; 5·2–40·3)	7 (23%; 9·9–42·3)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	25 (25%; 16·7–34·3)	9 (18%; 8·8–32·0)
End of study	19 (42%; 27·7–57·8)	4 (18%; 5·2–40·3)	11 (37%; 19·9–56·1)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	34 (34%; 24·6–43·8)	9 (18%; 8·8–32·0)

Data are n (%; 95% CI) by clinical diagnosis and overall. Percentages were calculated using n as the denominator, where n was the number of patients in the safety population who had the specified clinical diagnosis and known vital status at each timepoint.

Table 5: **All-cause mortality in the safety population**

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

Objectives: To assess the impact of carbapenem resistance on mortality in *Klebsiella pneumoniae* bloodstream infection (BSI) in the era of novel β-lactam/β-lactamase inhibitor combinations.

Material and methods: Retrospective study of patients with *K. pneumoniae* BSI between January and August 2020 in 16 centres.

Results: 426 patients were included: 107/426 (25%) had carbapenem-resistant *K. pneumoniae* (CR-Kp) BSI and 319/426 (75%) had carbapenem-susceptible *K. pneumoniae* (CS-Kp) BSI.

Despite the observation of a large difference in crude cumulative 30 day mortality between CR-Kp BSI and CS-Kp BSI (33.8% versus 20.7%, respectively), **carbapenem resistance was not found independently associated with an increased mortality in *K. pneumoniae* BSI** after adjustment for other prognostic factors.

Ceftazidime/avibactam was the most frequently used appropriate therapy for CR-Kp BSI (80/107; 74.7%).

In a propensity score-matched analysis, there was **no difference in mortality between patients appropriately treated with ceftazidime/avibactam for CR-Kp BSI and patients appropriately treated with other agents** (mainly meropenem monotherapy or piperacillin/tazobactam monotherapy) for CS-Kp BSI (HR 1.07; 95% CI 0.50–2.29, $P = 0.866$).

Giacobbe et al. 2023 Oct 3;78(10):2505-2514. doi: 10.1093/jac/dkad262.

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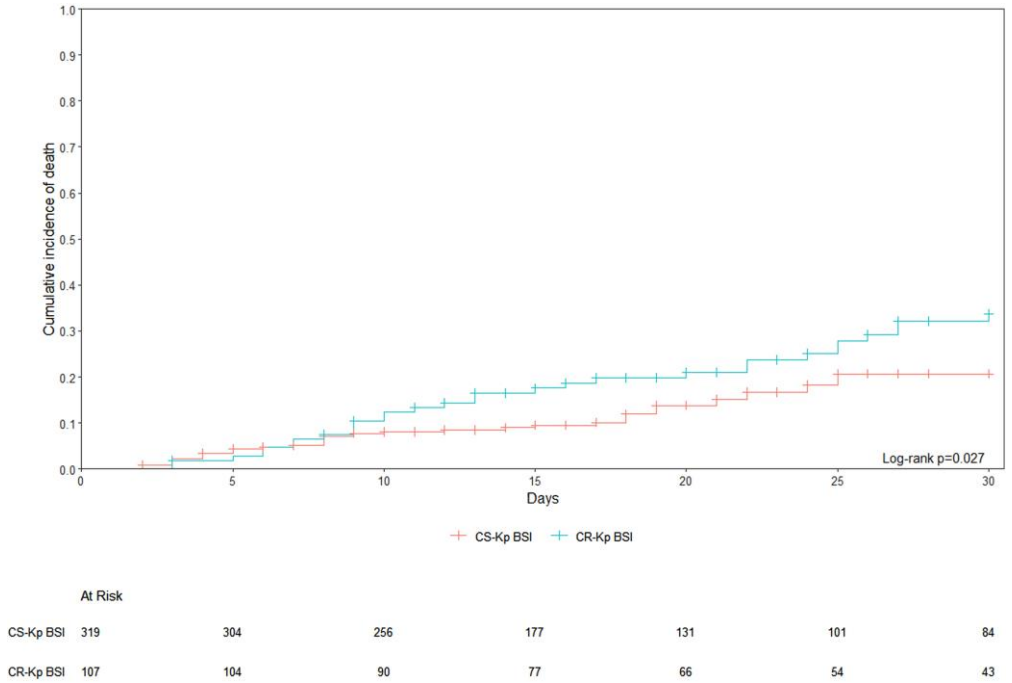
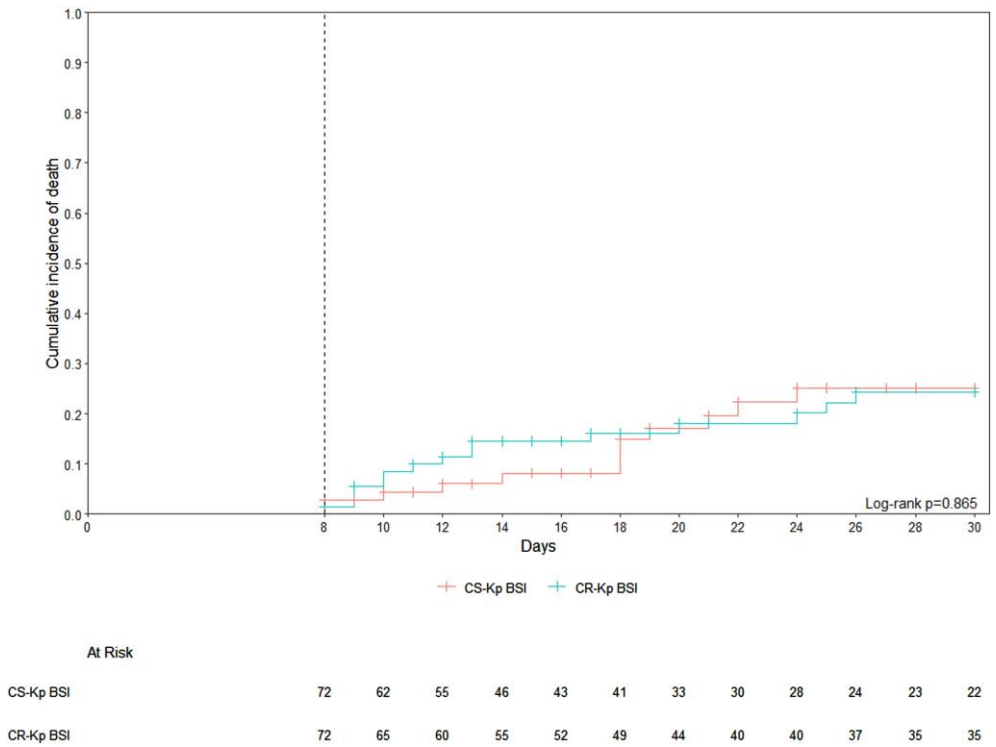
Mortality in KPC-producing Klebsiella pneumoniae bloodstream infections: a changing landscape

Unadjusted cumulative mortality up to Day 30 in patients with CR-Kp BSI and CS-Kp BSI.



Cumulative mortality up to Day 30 in pts with CR-Kp BSI receiving appropriate therapy with CAZ_AVI (cases) versus pts with CS-Kp BSI receiving appropriate therapy with agents other than CAZ-AVI (controls).



Our study suggests that ***the increased mortality of CR-Kp BSI compared with CS-Kp BSI is not (or no longer) dependent on the type of therapy in areas where ceftazidime/avibactam susceptible KPC-producing isolates are the prevalent type of CR-Kp and ceftazidime/avibactam is employed for treating most cases of CR-Kp BSI***

Giacobbe et al. 2023 Oct 3;78(10):2505-2514. doi: 10.1093/jac/dkad262.