



Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

13° CONGRESSO NAZIONALE

PADOVA | 23-24 novembre 2023

Infezioni da KPC e terapia

Mario Tumbarello



Azienda ospedaliero-universitaria Senese



UNIVERSITÀ DI SIENA 1240



Klebsiella pneumoniae: percentage of invasive isolates with resistance to carbapenems



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

2009

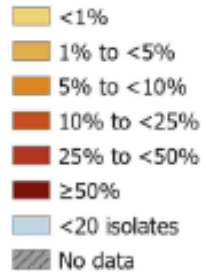


2014

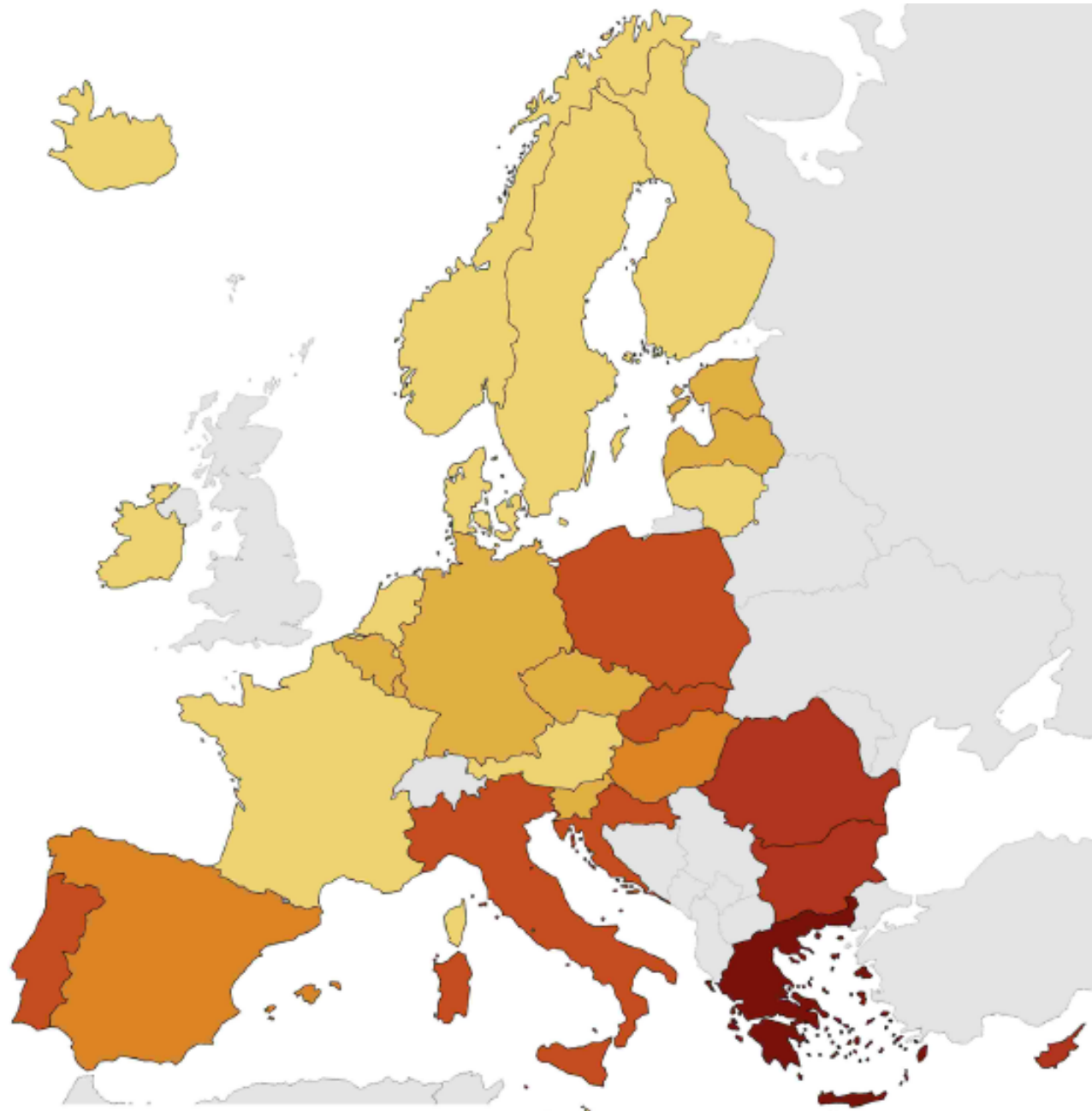
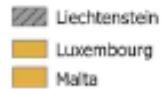


- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- Grey: No data reported or less than 10 isolates
- White: Not included

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



Non-visible countries



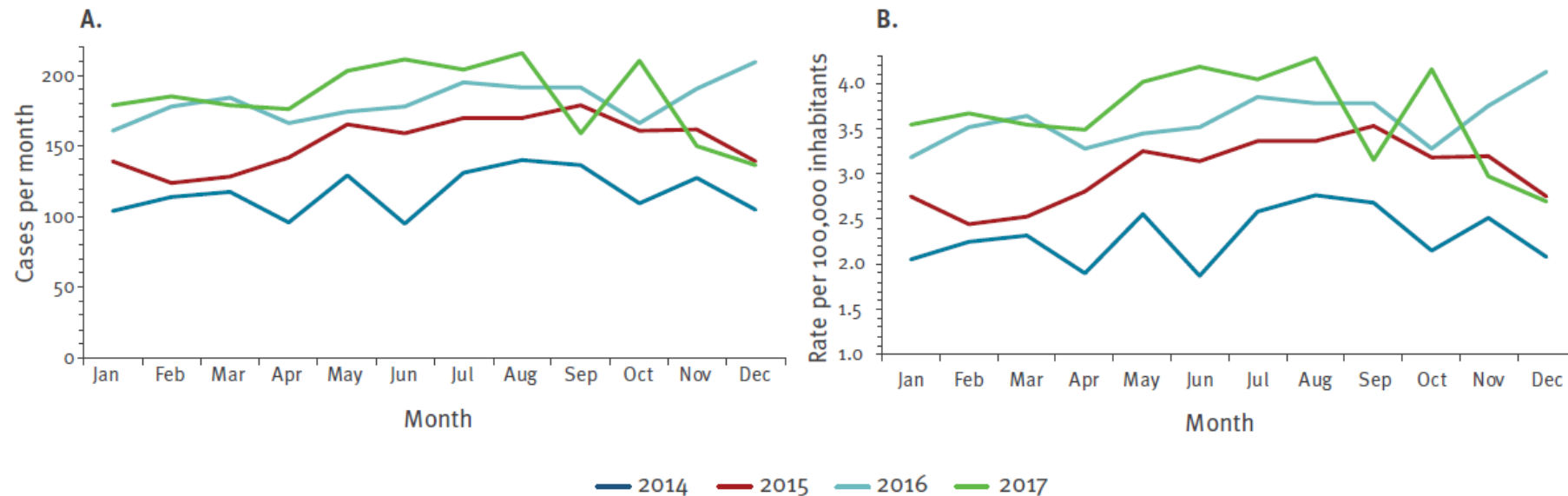
Bloodstream infections due to carbapenemase-producing Enterobacteriaceae in Italy: results from nationwide surveillance, 2014 to 2017

Simone Iacchini¹, Michela Sabbatucci^{1,2}, Carlo Gagliotti³, Gian Maria Rossolini^{4,5}, Maria Luisa Moro³, Stefania Iannazzo⁶, Fortunato D'Ancona¹, Patrizio Pezzotti¹, Annalisa Pantosti¹

Carbapenemase enzyme	<i>Klebsiella pneumoniae</i>		<i>Escherichia coli</i>		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	<i>Klebsiella pneumoniae</i>	7,490	98.1
	<i>Escherichia coli</i>	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

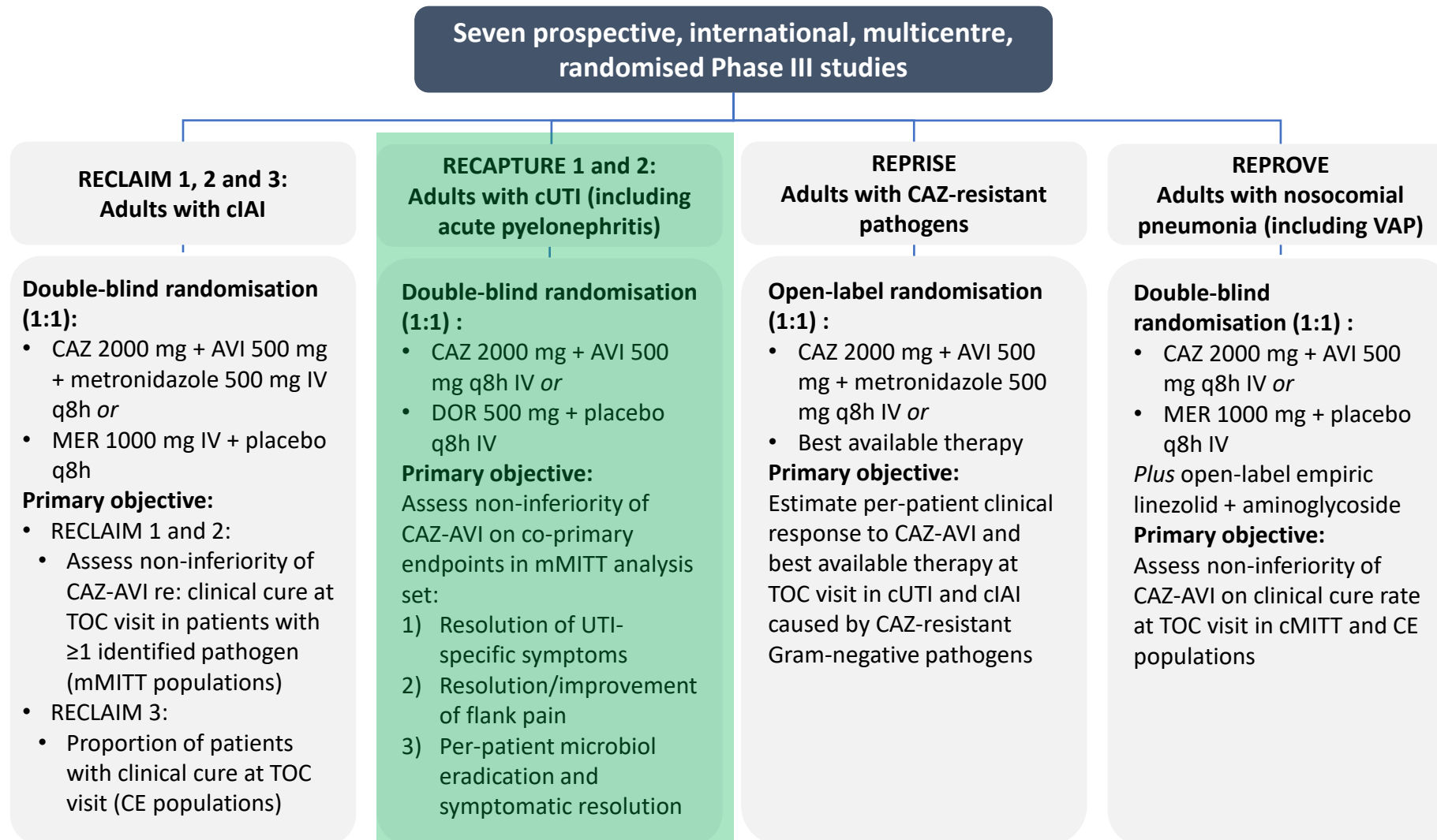
(A) Frequency and (B) incidence rate per 100,000 inhabitants by month and year of bloodstream infections due to carbapenemase-producing Enterobacteriaceae reported to the national surveillance system, Italy, 2014–2017



cUTI



Ceftazidime-avibactam Phase III clinical trial programme



Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

In this non inferiority randomized trial that included 550 patients with **complicated urinary tract infection, including acute pyelonephritis**, the difference in the composite outcome of complete resolution or improvement of symptoms along with microbial eradication met the **non inferiority** margin of 15% when comparing meropenem-vaborbactam vs piperacillin-tazobactam (98.4%vs 94.0%).

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

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

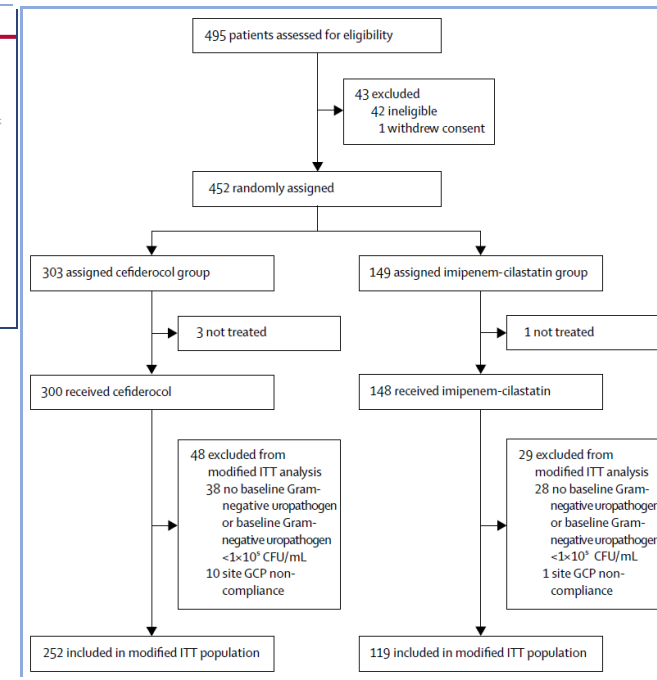
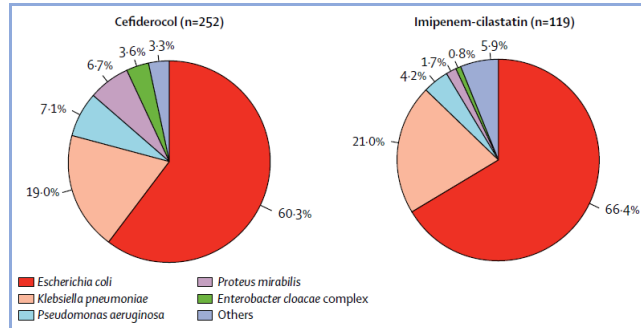
Characteristic	M–V (n = 32)	BAT (n = 15)	Total (N = 47)
Age, mean (SD), years	63.5 (14.1)	60.2 (13.0)	62.5 (13.7)
Infection type, n (%)			
Bacteremia	14 (43.8)	8 (53.3)	22 (46.8)
cUTI/AP	12 (37.5)	4 (26.7)	16 (34.0)
HABP/VABP	4 (12.5)	1 (6.7)	5 (10.6)
cIAI	2 (6.3)	2 (13.3)	4 (8.5)
Baseline pathogen, n (%) ^b			
<i>Klebsiella pneumoniae</i>	29 (90.6)	12 (80.0)	41 (87.2)
<i>Escherichia coli</i>	3 (9.4)	1 (6.7)	4 (8.5)
<i>Enterobacter cloacae</i> sp.	1 (3.1)	2 (13.3)	3 (6.4)
<i>Proteus mirabilis</i>	0 (0)	2 (13.3)	2 (4.3)
<i>Serratia marcescens</i>	1 (3.1)	1 (6.7)	2 (4.3)

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

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial



Simon Portsmouth, David van Veenhuizen, Roger Echols, Mitsuki Machida, Juan Camilo Arjona Ferreira, Mari Ariyasu, Peter Tenke, Tsutae Den Nagata



	n/N (%)		Treatment difference* (95% CI)
	Cefiderocol	Imipenem-cilastatin	
Analysis population			
mITT population	183/252 (73)	65/119 (55)	18.58 (8.23-28.92)
Microbiologically evaluable population	182/228 (80)	65/106 (61)	19.35 (8.87-29.82)
Age, years			
<65	87/113 (77)	32/54 (60)	17.73 (2.50-32.96)
≥65	96/139 (69)	33/65 (51)	18.30 (3.92-32.67)
Sex			
Men	84/119 (71)	25/48 (52)	18.50 (2.17-34.84)
Women	99/133 (74)	40/71 (56)	18.10 (4.38-31.81)
Clinical diagnosis			
cUTI with or without pyelonephritis	129/187 (69)	41/84 (49)	20.17 (7.60-32.75)
Acute uncomplicated pyelonephritis	54/65 (83)	24/35 (69)	14.51 (-3.37-32.38)

← Favours imipenem-cilastatin Favours cefiderocol →

Once-Daily Plazomicin for Complicated Urinary Tract Infections

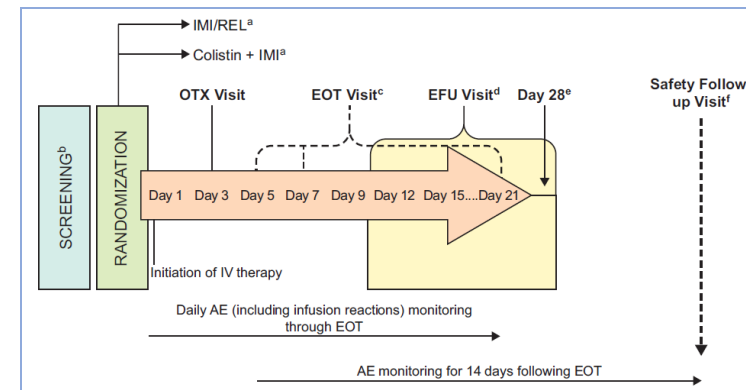
Florian M.E. Wagenlehner, M.D., Daniel J. Cloutier, Pharm.D.,
Allison S. Komirenko, Pharm.D., Deborah S. Cebrik, M.S., M.P.H.,
Kevin M. Krause, M.B.A., Tiffany R. Keepers, Ph.D., Lynn E. Connolly, M.D., Ph.D.,
Loren G. Miller, M.D., M.P.H., Ian Friedland, M.D., and Jamie P. Dwyer, M.D.,
for the EPIC Study Group*

Table 2. Primary and Additional Efficacy End Points (Microbiologic Modified Intention-to-Treat Population).*

Time of Assessment and End Point	Plazomicin (N=191) <i>number (percent)</i>	Meropenem (N=197) <i>number (percent)</i>	Difference (95% CI) [†] <i>percentage points</i>
Day 5			
Primary end point: composite cure at day 5	168 (88.0)	180 (91.4)	-3.4 (-10.0 to 3.1)
Clinical cure	171 (89.5)	182 (92.4)	-2.9 (-9.1 to 3.3)
Microbiologic eradication	188 (98.4)	193 (98.0)	0.5 (-3.1 to 4.1)
End of intravenous therapy			
Composite cure	179 (93.7)	187 (94.9)	-1.2 (-6.5 to 4.0)
Clinical cure	184 (96.3)	190 (96.4)	-0.1 (-4.6 to 4.3)
Microbiologic eradication	186 (97.4)	192 (97.5)	-0.1 (-4.1 to 3.9)
Test-of-cure visit			
Primary end point: composite cure at 15 to 19 days after start of therapy	156 (81.7)	138 (70.1)	11.6 (2.7 to 20.3)
Clinical cure	170 (89.0)	178 (90.4)	-1.4 (-7.9 to 5.2)
Microbiologic eradication	171 (89.5)	147 (74.6)	14.9 (7.0 to 22.7)
Late follow-up[‡]			
Composite cure	147 (77.0)	119 (60.4)	16.6 (7.0 to 25.7)
Sustained clinical cure [§]	169 (88.5)	168 (85.3)	3.2 (-4.0 to 10.3)
Sustained eradication [¶]	161 (84.3)	128 (65.0)	19.3 (10.4 to 27.9)
Clinical relapse	3 (1.6)	14 (7.1)	Not calculated
Microbiologic recurrence	7 (3.7)	16 (8.1)	Not calculated

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 İftihar 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. Butters,⁹ and Amanda Paschke⁹



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

21 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)

Endpoint	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference ^a	
	n	% (95% CI) ^b	n	% (95% CI) ^a		%	%
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)	

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Keith S. Kaye,¹ Louis B. Rice,² Aaron L. Dane,³ Viktor Stus,⁴ Olexiy Sagan,⁵ Elena Fedosiuk,⁶ Anita F. Das,⁷ David Skarinsky,^{8a} Paul B. Eckburg,^{8a} and Evelyn J. Ellis-Grosse^{8a}

Baseline Pathogen	Clinical Cure	
	ZTI-01, n/N (%)	PIP-TAZ, n/N (%)
<i>Escherichia coli</i>	120/133 (90.2)	120/133 (90.2)
<i>Klebsiella pneumoniae</i>	25/27 (92.6)	25/25 (100)
<i>Proteus mirabilis</i>	8/9 (88.9)	3/5 (60.0)
<i>Enterobacter cloacae</i> species complex	8/9 (88.9)	3/3 (100)
<i>Klebsiella oxytoca</i>	2/3 (66.7)	2/2 (100)
<i>Raoultella ornithinolytica</i>	1/1 (100)	1/1 (100)
<i>Serratia marcescens</i>	1/1 (100)	1/1 (100)
<i>Morganella morganii</i>	0/0 (...)	1/1 (100)
<i>Citrobacter amalonaticus/farmer</i>	1/1 (100)	0/0 (...)
<i>Pseudomonas aeruginosa</i>	8/8 (100)	9/9 (100)
<i>Acinetobacter baumannii-calcoaceticus</i> species complex	2/2 (100)	0/0 (...)
<i>Enterococcus faecalis</i>	2/3 (66.7)	6/7 (85.7)
<i>Staphylococcus aureus</i>	1/1 (100)	0/0 (...)
<i>Staphylococcus saprophyticus</i>	0/0 (...)	1/1 (100)

EDITORIAL COMMENTARY

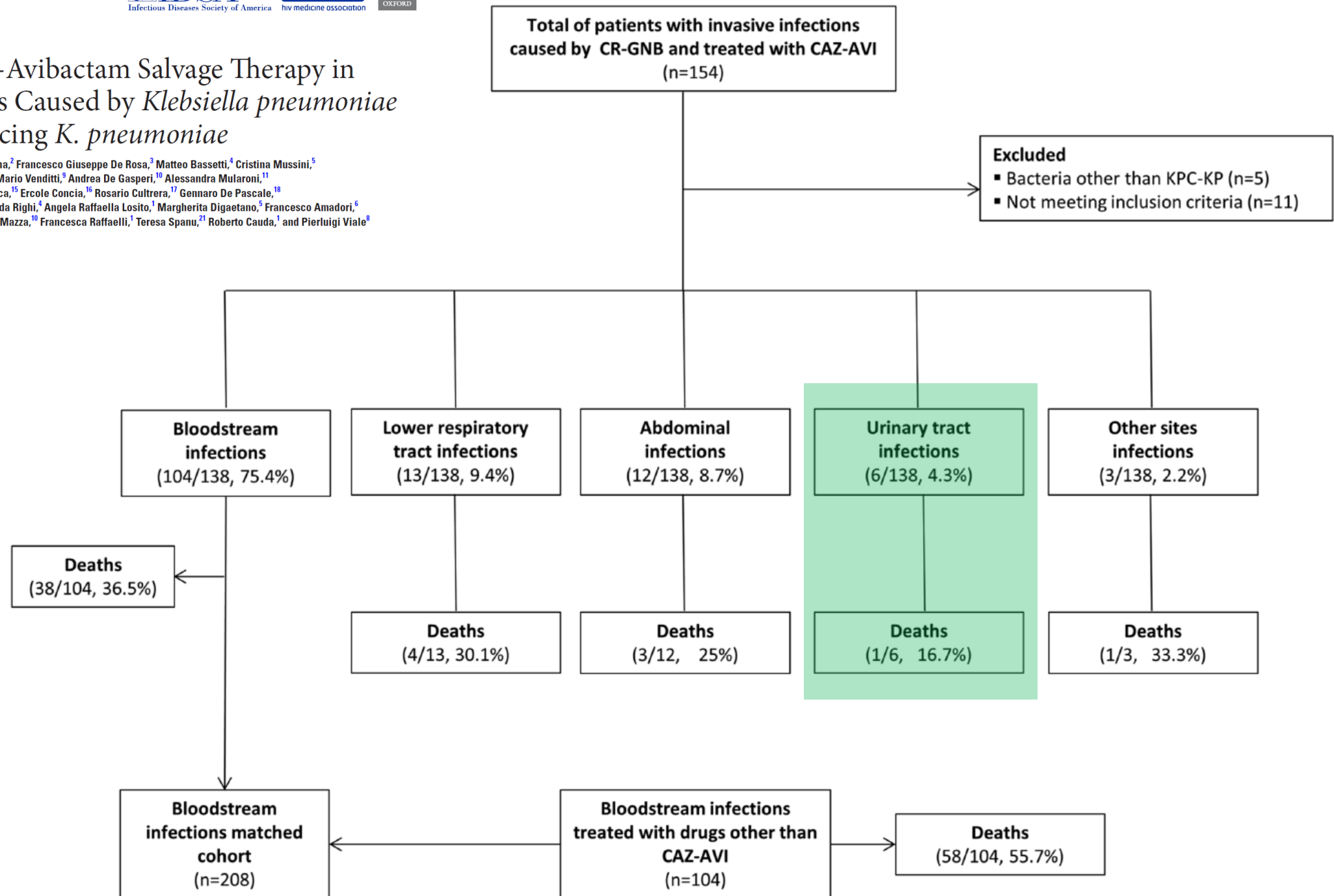
233 treated with 6 g q8h of fosfomycin ev
231 treated with 4.5 g q8h of PIP-TAZ.
Fixed 7-day course (14 for bacteremic).

Fosfomycin met the primary objective of NI compared with PIP-TAZ in treatment of hospitalized patients with cUTI/AP.

By ZEUS! Can We Use Intravenous Fosfomycin for Complicated Urinary Tract Infections?

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

Mario Tumbarello,^{1,4} Enrico Maria Treccarichi,^{1,4} 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 Viale⁸



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

Mario Tumbarello,^{1,2,3} Francesca Raffaelli,¹ Maddalena Giannella,⁴ Elisabetta Mantengoli,⁵ Alessandra Mularoni,⁶ Mario Venditti,⁷ Francesco Giuseppe De Rosa,⁸ Loredana Sarmati,⁹ Matteo Bassetti,^{10,11} Gaetano Brindicci,¹² Marianna Rossi,¹³ Roberto Luzzati,¹⁴ Paolo Antonio Grossi,¹⁵ Alberto Corona,¹⁶ Alessandro Capone,¹⁷ Marco Falcone,¹⁸ Cristina Mussini,¹⁹ Enrico Maria Trecarichi,²⁰ Antonio Cascio,²¹ Elena Guffanti,²² Alessandro Russo,²³ Gennaro De Pascale,²⁴ Carlo Tascini,²⁵ Ivan Gentile,²⁶ Angela Raffaella Losito,¹ Linda Bussini,⁴ Giampaolo Corti,^{5,27} Giancarlo Ceccarelli,⁷ Silvia Corcione,^{8,28} Mirko Compagno,²⁹ Daniele Roberto Giacobbe,^{10,11} Annalisa Saracino,¹² Massimo Fantoni,¹² Spinello Antinori,³⁰ Maddalena Peghin,³¹ Paolo Bonfanti,^{13,32} Alessandra Oliva,⁷ Andrea De Gasperi,²² Giusy Tiseo,¹⁸ Cristina Rovelli,¹⁵ Marianna Meschieri,¹⁵ Nour Shbaklo,⁸ Teresa Spanu,^{1,34} Roberto Cauda,¹² and Pierluigi Viale⁴

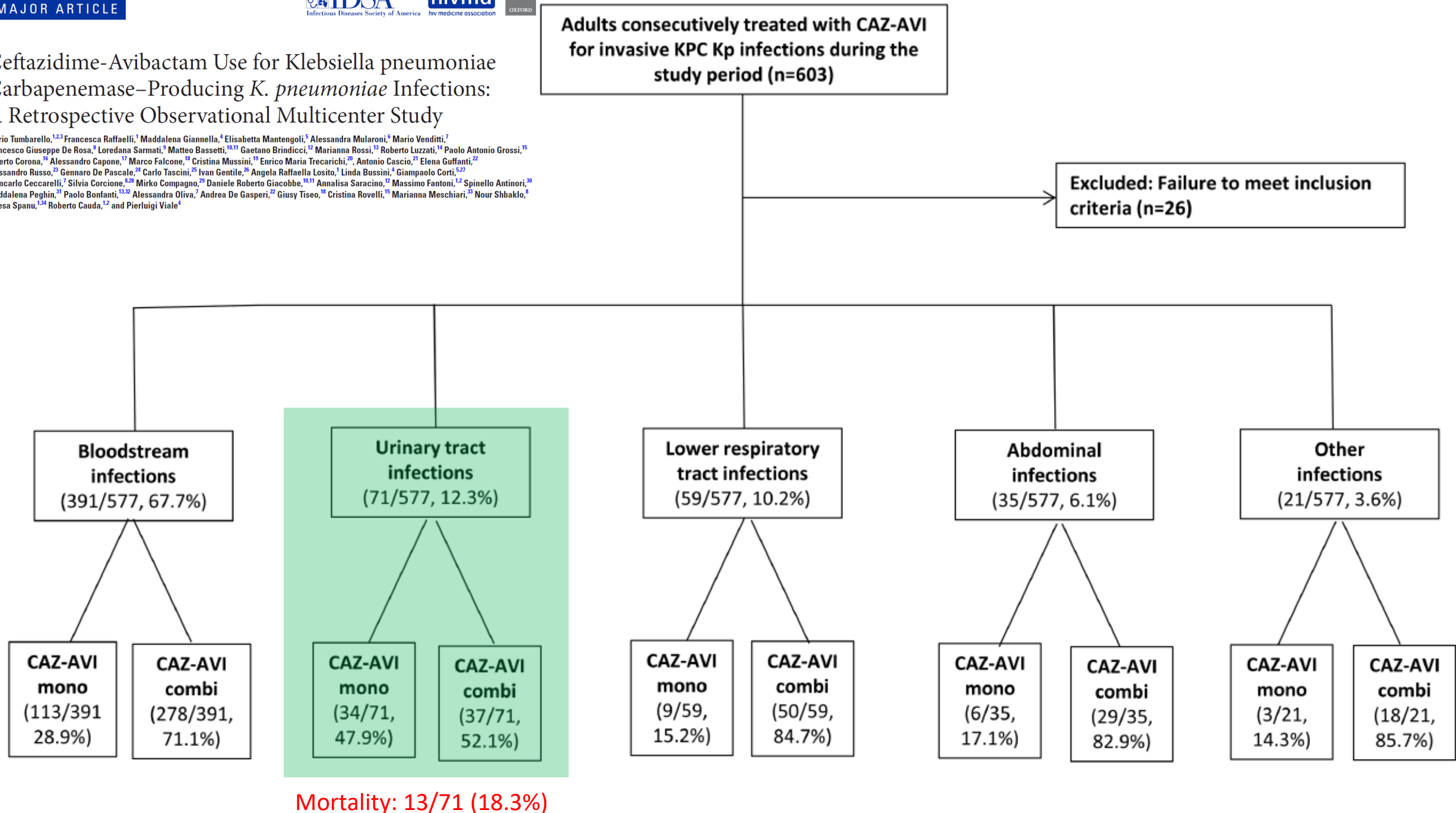




Table 4 Ceftazidime–avibactam usage by indication

Characteristic	cIAI (<i>n</i> = 90)	cUTI (<i>n</i> = 103)	HAP/VAP (<i>n</i> = 114)	Other (<i>n</i> = 209) ^a	Total (<i>n</i> = 516)
Use of ceftazidime–avibactam overall, <i>n</i> (%)					
Monotherapy	26 (28.9)	68 (66.0)	25 (21.9)	39 (18.7)	158 (30.6)
Combination therapy	64 (71.1)	35 (34.0)	89 (78.1)	170 (81.3)	358 (69.4)
Gram-negative coverage	22 (24.4)	17 (16.5)	43 (37.7)	94 (45.0)	176 (34.1)
Other coverage ^b	17 (18.9)	8 (7.8)	19 (16.7)	20 (9.6)	64 (12.4)
Gram-negative and other coverage	25 (27.8)	10 (9.7)	27 (23.7)	56 (26.8)	118 (22.9)
Total duration of administration of ceftazidime–avibactam (days), <i>n</i> (%)					
Mean (SD)	13.6 (12.5)	9.3 (5.7)	10.3 (6.6)	13.3 (14.3)	11.9 (11.4)

ORIGINAL RESEARCH

The Use and Effectiveness of Ceftazidime–Avibactam in Real-World Clinical Practice: EZTEAM Study

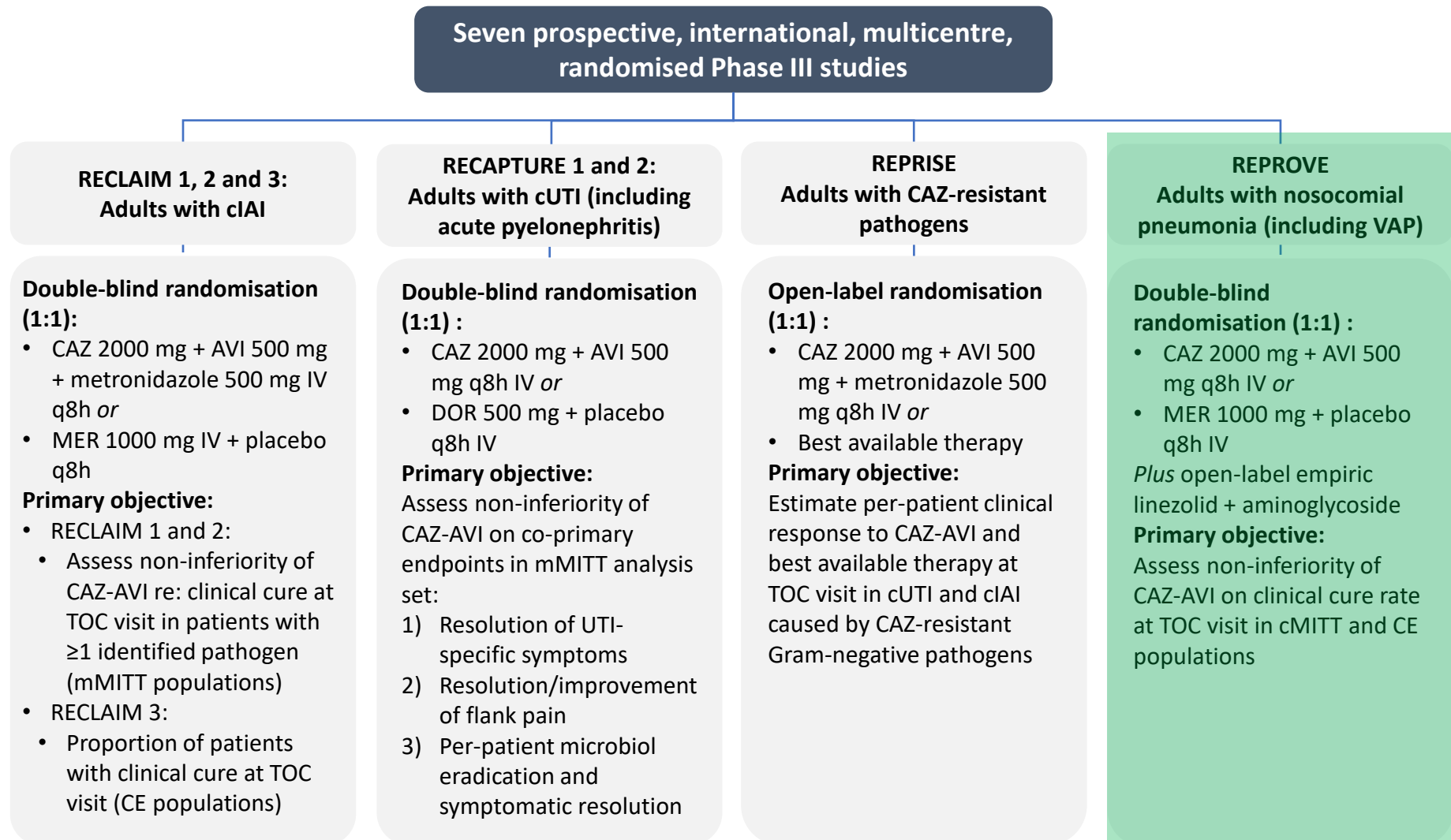
Alex Soriano · Philippe Montravers · Matteo Bassetti · Galina Klyasova · George Daikos · Paurus Irani · Gregory Stone · Richard Chambers · Pascale Peeters · Mitesh Shah · Claire Hulin · Natalia Albuquerque · Efim Basin · Benjamin Gaborit · Irene Kourbeti · Francesco Menichetti · María Teresa Perez-Rodriguez · Mathias W. Pletz · Marisa Sanchez · Ivan Trompa · Anita Verma · Maria Lavinea N. de Figueiredo · Claudie Charbonneau

- 516 patients were treated for at least 72 h (354 patients from Europe and 162 patients from LATAM);
- Infection sources were intra-abdominal, urinary, respiratory, bloodstream infections, and other infections (approximately 20% each).
- *K. pneumoniae* was the most common microorganism identified (59.3%).
- The common MDR mechanisms for *K. pneumoniae* were KPC carbapenemase (33.9%), oxacillinase 48 (25.2%), ESBL (21.5%), or MBL (14.2%) production.
- Without prior patient exposure, 17 isolates (mostly *K. pneumoniae*) were resistant to ceftazidime–avibactam.
- Treatment success was achieved in 77.3% of patients overall.
- In-hospital mortality rate was 23.1%.
- Adverse events were reported for six of the 569 patients enrolled.



HAP/VAP

Ceftazidime-avibactam Phase III clinical trial programme





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 Evans², for the Antibacterial Resistance Leadership Group

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 ($P = .001$).

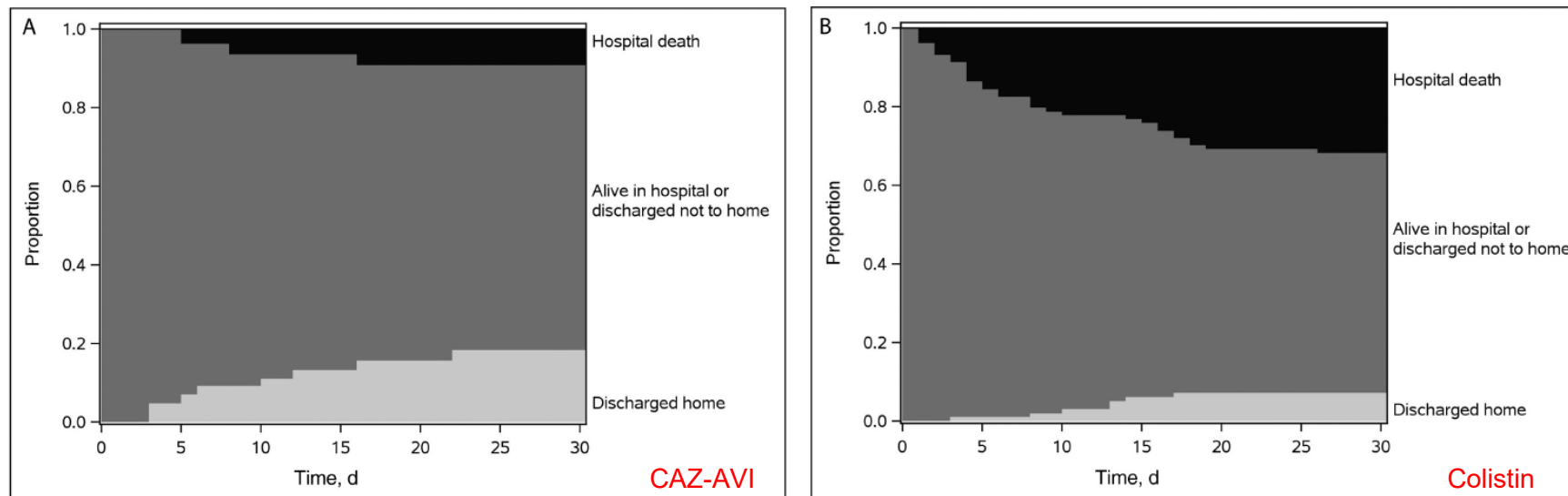


Figure 1. Inverse probability of treatment weighting (IPTW)-adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

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

- 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

REAL LIFE

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

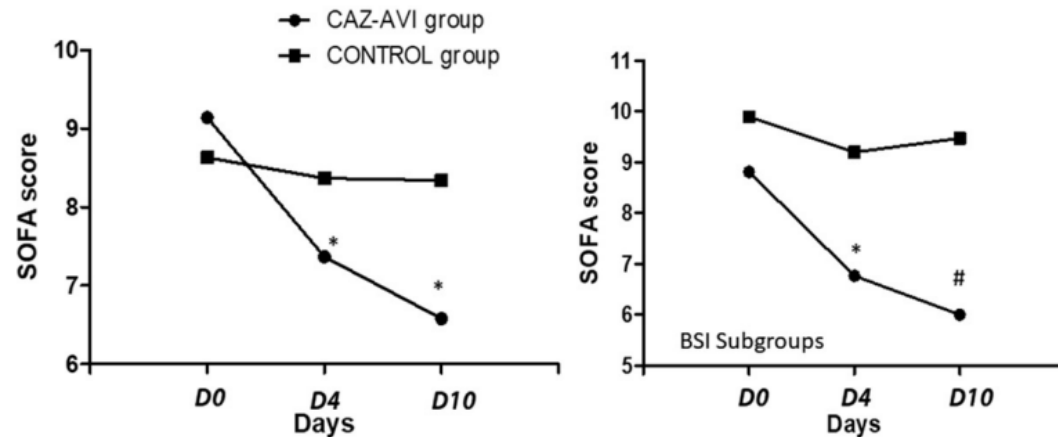
Variable	Values for predictors of 28-day survival			Values for predictors of clinical cure		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
SOFA score on admission	0.906	0.677–1.213	0.507	0.976	0.788–1.209	0.827
Charlson comorbidity index	0.830	0.655–1.053	0.124	0.880	0.704–1.101	0.263
SOFA score 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

^aCAZ-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

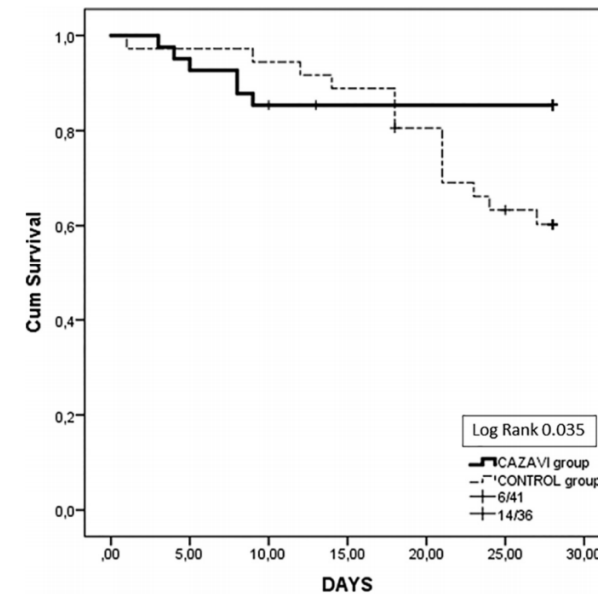
Tsolaki V, et al.

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

Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections

Sarah C. J. Jorgensen,¹ Trang D. Trinh,^{1,2} Evan J. Zasowski,^{1,2} Abdalhamid M. Lagnf,¹ Sahil Bhatia,¹ Sarah M. Melvin,¹ Molly E. Steed,⁴ Samuel P. Simon,⁵ Sandra J. Estrada,^{6,7} Taylor Morrisette,^{1,8} Kimberly C. Claeys,⁹ Joshua R. Rosenberg,² Susan L. Davis,^{1,10} and Michael J. Rybak^{1,11,12}

- **203 patients**
- CRE and *Pseudomonas* spp. were isolated from 117 (57.6%) and 63 (31.0%) culture specimens, respectively
- The most common infection sources were **respiratory (37.4%)**, urinary (19.7%), and intra-abdominal (18.7%)
- Clinical failure, **30-day mortality**, and 30-day recurrence occurred in 59 (29.1%), **35 (17.2%)**, and 12 (5.9%) patients, respectively

Table 5. Multivariable Logistic Regression Model for Clinical Failure^a

Variable	Adjusted Odds Ratio (95% CI)	P Value
Primary bacteremia or respiratory tract infection	2.270 (1.115–4.620)	<.001
SOFA score	1.234 (1.118–1.362)	.0238
CZA within 48 hours of culture collection	0.409 (0.180–0.930)	.0329

CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; CZA, ceftazidime-avibactam; OR, odds ratio; SOFA, sequential organ failure assessment score.

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}

- 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

Novel β -lactam- β -lactamase inhibitor combinations: expectations for the treatment of carbapenem-resistant Gram-negative pathogens

Ilias Karaiskos, Irene Galani, Maria Souli & Helen Giamarellou



Table 2. Pharmacokinetic parameters of novel combinations of β -lactam/ β -lactamase inhibitors [31,42–44,78,82,100–101].

Parameters	Ceftazidime/Avibactam ^a	Meropenem/Vaborbactam ^b	Imipenem/cilastatin/Relebactam ^c
C _{max} (mg/L)	90.4/14.6	43.4/55.6	30.5/15.8
T _{1/2} (hours)	2.7/2.7	1.22/1.68	1.13/1.63
V _d (L)	17/22.2	20.2/18.6	19.6/20.8
AUC _{0-inf} (mg*h/L)	291/38.2	138/196	130/81.2
Cl (L/h)	6.9/13.1	15.1/10.9	12.1/8.9
Protein binding (%)	21/8	2/33	20/20
Elimination (%)	Renal (83/>97)	Renal (40–60/75–95)	Renal (49.8/>95)
ELF penetration (%)	20/25–30	65/79	55/54

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

264 imipenem/cilastatin/relebactam and 267 piperacillin/tazobactam; 48.6% had ventilated HAP/VABP, 66.1% were in the ICU.

The most common pathogens were *K. pneumoniae* (25.6%) and *P. aeruginosa* (18.9%).

Table 2. Primary, Key Secondary, and Other Prespecified Secondary Efficacy Endpoints

Endpoint	IMI/REL, no./No. (%) ^a	PIP/TAZ, no./No. (%) ^a	Adjusted Difference ^b , % (95% CI)
Primary endpoint			
Day 28 all-cause mortality (MITT)	42/264 (15.9)	57/267 (21.3)	-5.3 (-11.9 to 1.2) ^c
Key secondary endpoint			
Favorable clinical response at EFU (MITT)	161/264 (61.0) ^d	149/267 (55.8) ^d	5.0 (-3.2 to 13.2) ^e
Other secondary endpoints			
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	-3.5 (-10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9) ^d	135/218 (61.9) ^d	6.2 (-2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	-3.7 (-13.6 to 6.4)

Imipenem/cilastatin/relebactam was **non-inferior** ($P < .001$) to piperacillin/tazobactam for both endpoints: day 28 all-cause mortality and favorable clinical response at early follow-up.

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. Shields¹; Vladimir Turzhitsky²; Emre Yucel²; Sanjay Merchant²; Alexandre H. Watanabe²

¹Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA; ²Merck & 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

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 (%)				
<i>P. aeruginosa</i>	33 (89.2)	21 (87.5)	3 (75.0)	3 (100.0)
<i>E. coli</i>	4 (10.8)	4 (16.7)	–	–
<i>K. pneumoniae</i>	7 (18.9)	4 (16.7)	1 (25.0)	–
<i>E. cloacae</i>	4 (10.8)	4 (16.7)	–	–
<i>K. (Enterobacter) aerogenes</i>	1 (2.7)	1 (4.2)	–	–
<i>K. oxytoca</i>	1 (2.7)	1 (4.2)	–	–
<i>S. marcescens</i>	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)

Type of infection, n (%)

HABP/VABP	86 (53.8)
cUTI	27 (16.9)
cIAI	6 (3.8)

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)

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

Open Forum Infectious Diseases

BRIEF REPORT 2020

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}



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.

Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial



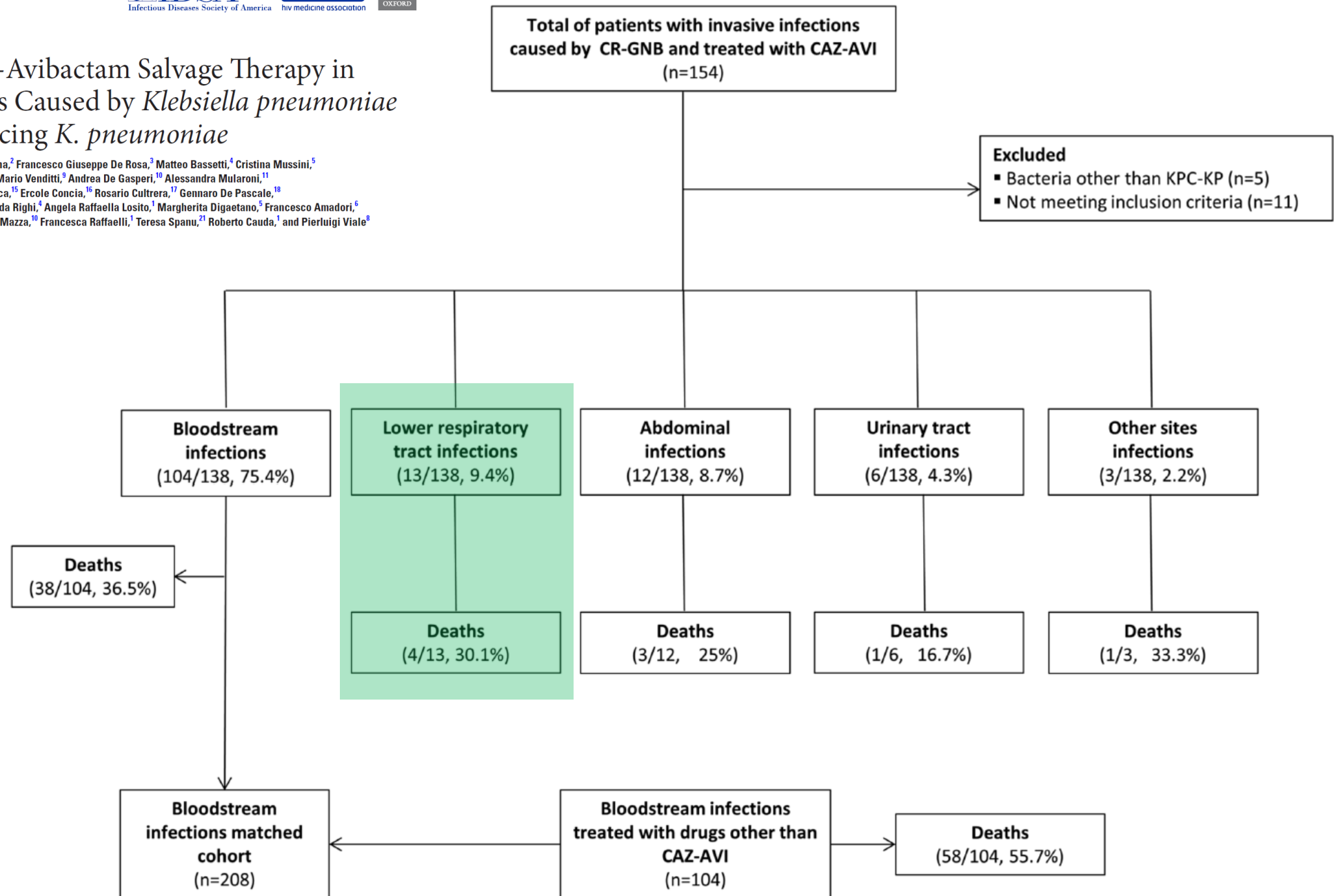
Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata

	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Clinical cure			
All patients	94/145 (65%)	98/147 (67%)	-1.8 (-12.7 to 9.0)
HAP	33/59 (56%)	41/60 (68%)	-12.4 (-29.7 to 4.9)
VAP	39/59 (66%)	36/64 (56%)	9.9 (-7.3 to 27.0)
HCAP	22/27 (82%)	21/23 (91%)	-9.8 (-28.5 to 8.8)
Top five baseline pathogens			
<i>Klebsiella pneumoniae</i>	31/48 (65%)	29/44 (66%)	-1.3 (-20.8 to 18.1)
<i>Pseudomonas aeruginosa</i>	16/24 (67%)	17/24 (71%)	-4.2 (-30.4 to 22.0)
<i>Acinetobacter baumannii</i>	12/23 (52%)	14/24 (58%)	-6.2 (-34.5 to 22.2)
<i>Escherichia coli</i>	12/19 (63%)	13/22 (59%)	4.1 (-25.8 to 33.9)
<i>Enterobacter cloacae</i>	5/7 (71%)	4/8 (50%)	21.4 (NA)
Microbiological eradication			
All patients	59/145 (41%)	61/147 (42%)	-0.8 (-12.1 to 10.5)
HAP	21/59 (36%)	27/60 (45%)	-9.4 (-26.9 to 8.1)
VAP	25/59 (42%)	22/64 (34%)	8.0 (-9.2 to 25.2)
HCAP	13/27 (48%)	12/23 (52%)	-4.0 (-31.8 to 23.8)
Top five baseline pathogens			
<i>K pneumoniae</i>	21/48 (44%)	22/44 (50%)	-6.3 (-26.6 to 14.1)
<i>P aeruginosa</i>	9/24 (38%)	11/24 (46%)	-8.3 (-36.1 to 19.5)
<i>A baumannii</i>	9/23 (39%)	8/24 (33%)	5.8 (-21.7 to 33.2)
<i>E coli</i>	10/19 (53%)	11/22 (50%)	2.6 (-28.0 to 33.3)
<i>E cloacae</i>	4/7 (57%)	3/8 (38%)	19.6 (NA)

Cefiderocol was **non-inferior** to high-dose, extended-infusion meropenem in terms of all-cause mortality on day 14 in patients with Gram-negative nosocomial pneumonia, with similar tolerability

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

Mario Tumbarello,^{1,4} Enrico Maria Treccarichi,^{1,4} 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 Viale⁸



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

Mario Tumbarello,^{1,2,3} Francesca Raffaelli,¹ Maddalena Giannella,⁴ Elisabetta Mantengoli,⁵ Alessandra Mularoni,⁶ Mario Venditti,⁷ Francesco Giuseppe De Rosa,⁸ Loredana Sarmati,⁹ Matteo Bassetti,^{10,11} Gaetano Brindicci,¹² Marianna Rossi,¹³ Roberto Luzzati,¹⁴ Paolo Antonio Grossi,¹⁵ Alberto Corona,¹⁶ Alessandro Capone,¹⁷ Marco Falcone,¹⁸ Cristina Mussini,¹⁹ Enrico Maria Trecarichi,²⁰ Antonio Cascio,²¹ Elena Guffanti,²² Alessandro Russo,²³ Gennaro De Pascale,²⁴ Carlo Tascini,²⁵ Ivan Gentile,²⁶ Angela Raffaella Losito,¹ Linda Bussini,⁴ Giampaolo Corti,^{5,27} Giancarlo Ceccarelli,⁷ Silvia Corcione,^{8,28} Mirko Compagno,²⁹ Daniele Roberto Giacobbe,^{10,11} Annalisa Saracino,¹² Massimo Fantoni,¹² Spinello Antinori,³⁰ Maddalena Peghin,³¹ Paolo Bonfanti,^{13,32} Alessandra Oliva,⁷ Andrea De Gasperi,²² Giusy Tiseo,¹⁸ Cristina Rovelli,¹⁵ Marianna Meschiari,¹⁵ Nour Shbaklo,⁸ Teresa Spanu,^{1,34} Roberto Cauda,¹² and Pierluigi Viale⁴

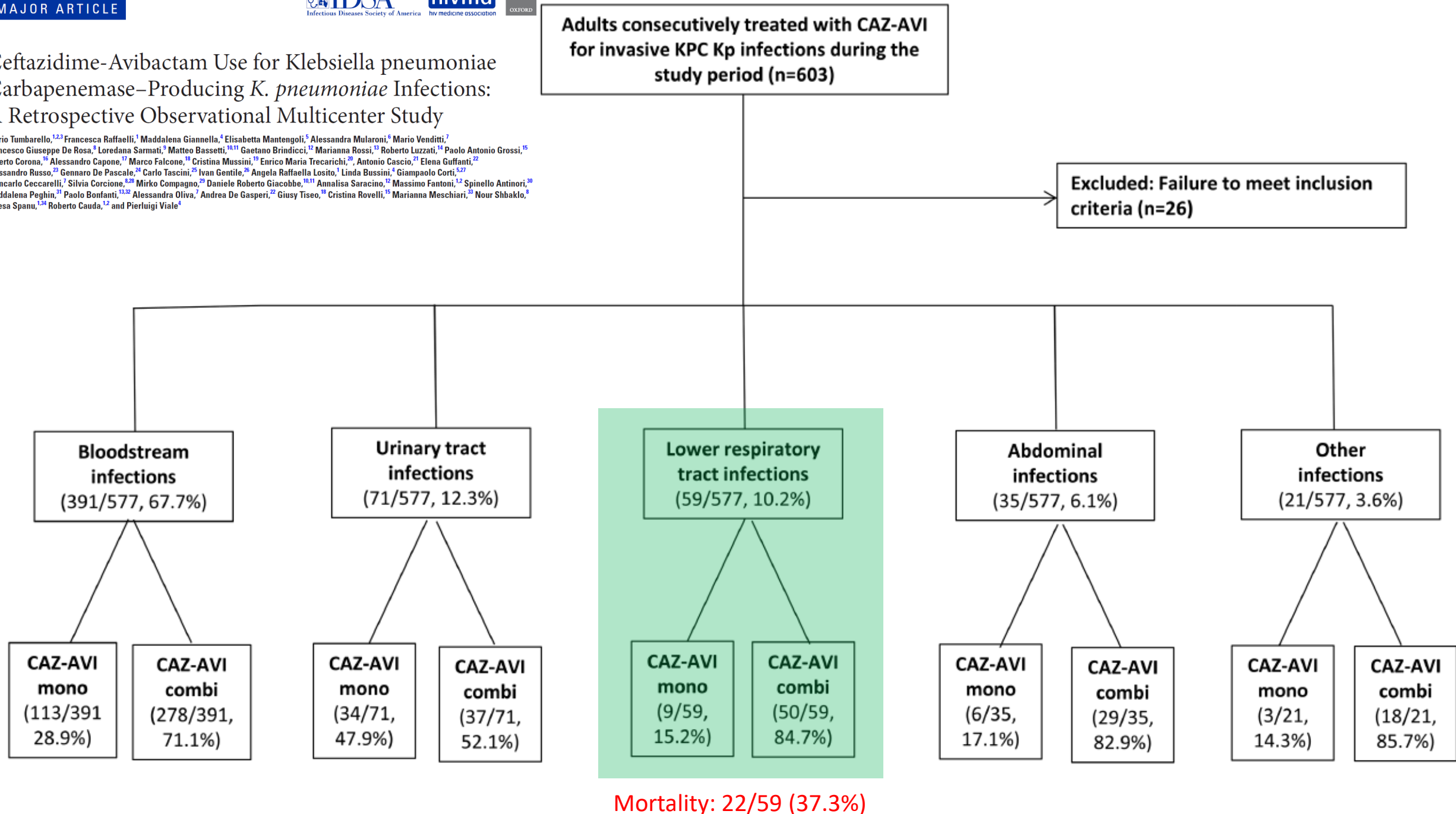




Table 4 Ceftazidime–avibactam usage by indication

Characteristic	cIAI (<i>n</i> = 90)	cUTI (<i>n</i> = 103)	HAP/VAP (<i>n</i> = 114)	Other (<i>n</i> = 209) ^a	Total (<i>n</i> = 516)
Use of ceftazidime–avibactam overall, <i>n</i> (%)					
Monotherapy	26 (28.9)	68 (66.0)	25 (21.9)	39 (18.7)	158 (30.6)
Combination therapy	64 (71.1)	35 (34.0)	89 (78.1)	170 (81.3)	358 (69.4)
Gram-negative coverage	22 (24.4)	17 (16.5)	43 (37.7)	94 (45.0)	176 (34.1)
Other coverage ^b	17 (18.9)	8 (7.8)	19 (16.7)	20 (9.6)	64 (12.4)
Gram-negative and other coverage	25 (27.8)	10 (9.7)	27 (23.7)	56 (26.8)	118 (22.9)
Total duration of administration of ceftazidime–avibactam (days), <i>n</i> (%)					
Mean (SD)	13.6 (12.5)	9.3 (5.7)	10.3 (6.6)	13.3 (14.3)	11.9 (11.4)

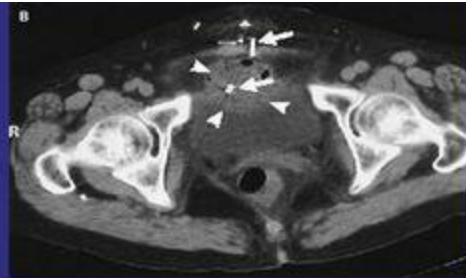
ORIGINAL RESEARCH

The Use and Effectiveness of Ceftazidime–Avibactam in Real-World Clinical Practice: EZTEAM Study

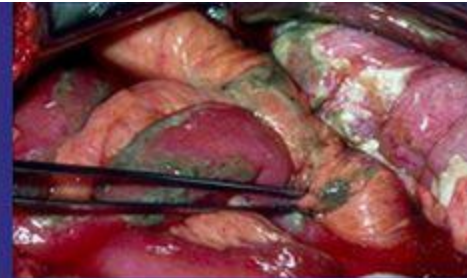
Alex Soriano · Philippe Montravers · Matteo Bassetti · Galina Klyasova · George Daikos · Paurus Irani · Gregory Stone · Richard Chambers · Pascale Peeters · Mitesh Shah · Claire Hulin · Natalia Albuquerque · Efim Basin · Benjamin Gaborit · Irene Kourbeti · Francesco Menichetti · María Teresa Perez-Rodriguez · Mathias W. Pletz · Marisa Sanchez · Ivan Trompa · Anita Verma · Maria Lavinea N. de Figueiredo · Claudie Charbonneau

- 516 patients were treated for at least 72 h (354 patients from Europe and 162 patients from LATAM);
- Infection sources were intra-abdominal, urinary, respiratory, bloodstream infections, and other infections (approximately 20% each).
- *K. pneumoniae* was the most common microorganism identified (59.3%).
- The common MDR mechanisms for *K. pneumoniae* were KPC carbapenemase (33.9%), oxacillinase 48 (25.2%), ESBL (21.5%), or MBL (14.2%) production.
- Without prior patient exposure, 17 isolates (mostly *K. pneumoniae*) were resistant to ceftazidime–avibactam.
- Treatment success was achieved in 77.3% of patients overall.
- In-hospital mortality rate was 23.1%.
- Adverse events were reported for six of the 569 patients enrolled.

cIAI



Abscess Formation¹

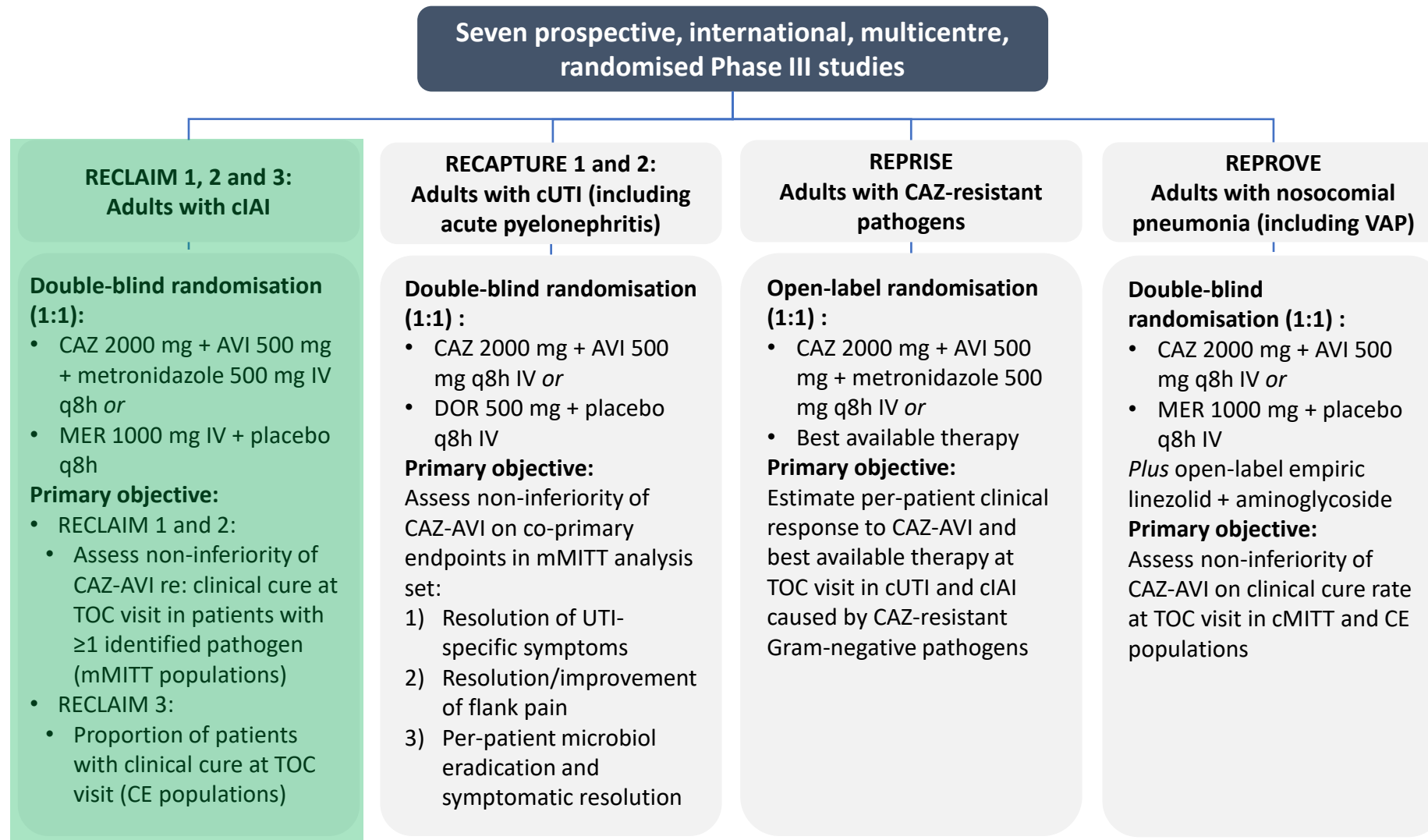


Peritonitis

Complicated intra-abdominal infections:

- Extend beyond the hollow viscus of origin into the peritoneal space and are associated either with abscess formation or with peritonitis²
- Require either surgery or percutaneous drainage for source control as well as **antimicrobial therapy**^{3,4}

Ceftazidime-avibactam Phase III clinical trial programme



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 Soto¹, Lorena Rodríguez¹, Antonio Pérez-Landeiro³,
Lucía Martínez-Lamas⁴, 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

IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections

Joseph S. Solomkin,¹ Janis Gardovskis,² Kenneth Lawrence,³ Philippe Montravers,^{4,5,6} Angie Sway,⁷ David Evans,⁸ and Larry Tsai³

Table 2. Pathologies: Microbiological Intent-to-Treat Population

Pathology	Eravacycline (N = 195)	Meropenem (N = 205)
Actual primary disease diagnosis		
Complicated appendicitis, n (%)	94 (48.2)	90 (43.9)
Other complicated intra-abdominal infection	101 (51.8)	115 (56.1)
Diagnosed and enrolled preoperatively	7 (3.6)	11 (5.4)
Diagnosed intra-/postoperatively	188 (96.4)	194 (94.6)
Intra-abdominal abscess(es) ^a	119 (63.3)	110 (56.7)
Peritonitis	94 (50.0)	95 (49.0)
Gastric/duodenal perforation	11 (5.9)	12 (6.2)
Complicated cholecystitis	40 (21.3)	45 (23.2)
Perforation of small intestine	7 (3.7)	7 (3.6)
Complicated appendicitis	93 (49.5)	91 (46.9)
Perforation of large intestine	8 (4.3)	12 (6.2)
Diverticulitis with perforation, peritonitis, or abscess	5 (2.7)	7 (3.6)
Other	0	2 (1.0)

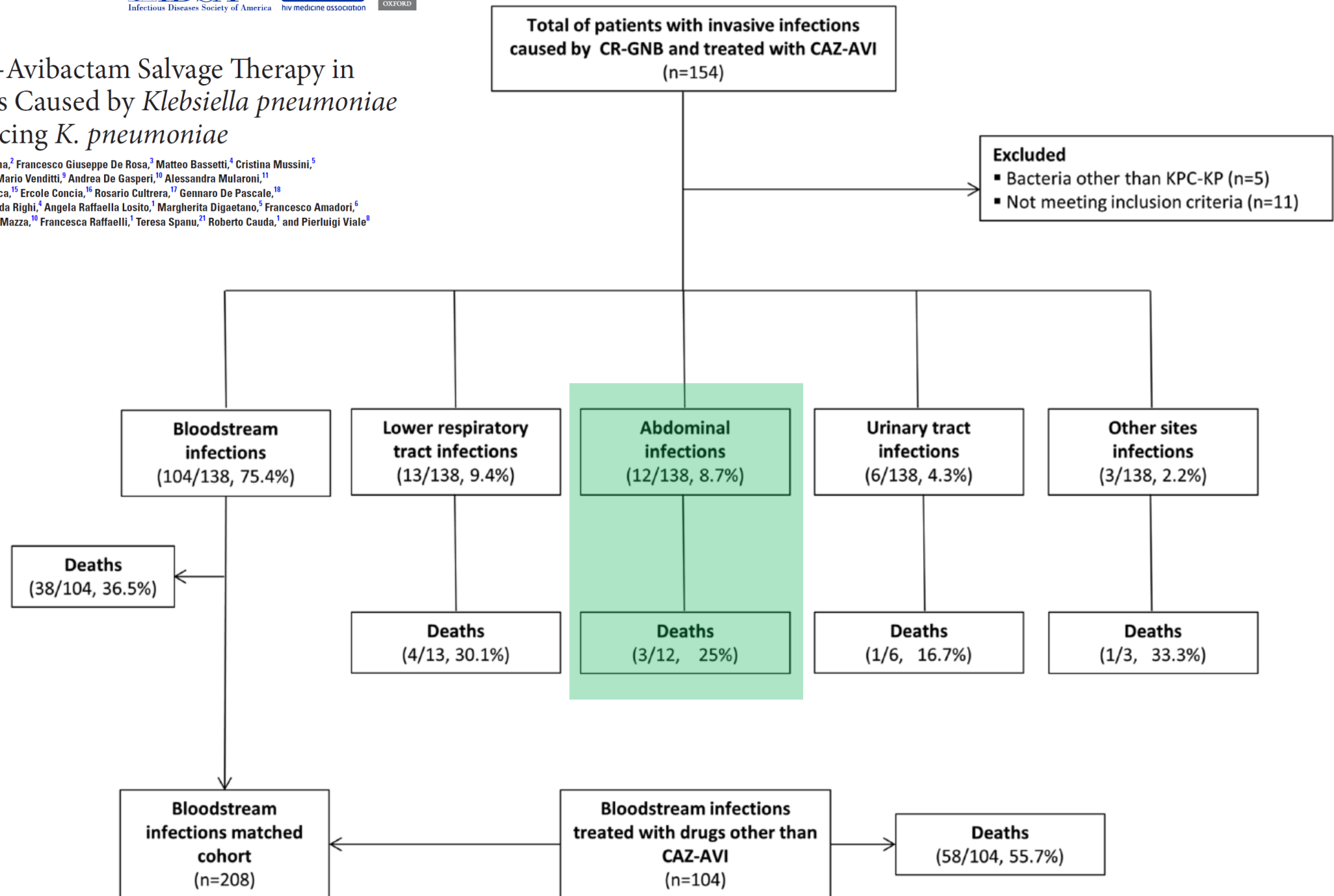
Table 7. Extended Spectrum Beta-lactamases

	Eravacycline (Cured/Total)	Meropenem (Cured/Total)
<i>Citrobacter freundii</i>	0	1/1
CTX-M-15	0	1/1
<i>Enterobacter cloacae/asburiae</i>	3/3	1/1
CTX-M-15	2/2	1/1
<i>Escherichia coli</i>	8/10	5/7
CTX-M-15	7/8	3/5
CTX-M-3	0/1	1/1
CTX-M-32	1/1	0
CTX-M-5	0	1/1
SHV-12	0	1/1
<i>Klebsiella pneumoniae</i>	5/5	5/6
CTX-M-15	5/5	3/4
CTX-M-2	0	1/1
SHV-12	0	1/1
<i>Serratia marcescens</i>	0	1/1
CTX-M-15	0	1/1

Treatment with **eravacycline was noninferior to meropenem** in adult patients with cIAI, including infections caused by resistant pathogens

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

Mario Tumbarello,^{1,4} Enrico Maria Treccarichi,^{1,4} 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 Viale⁸

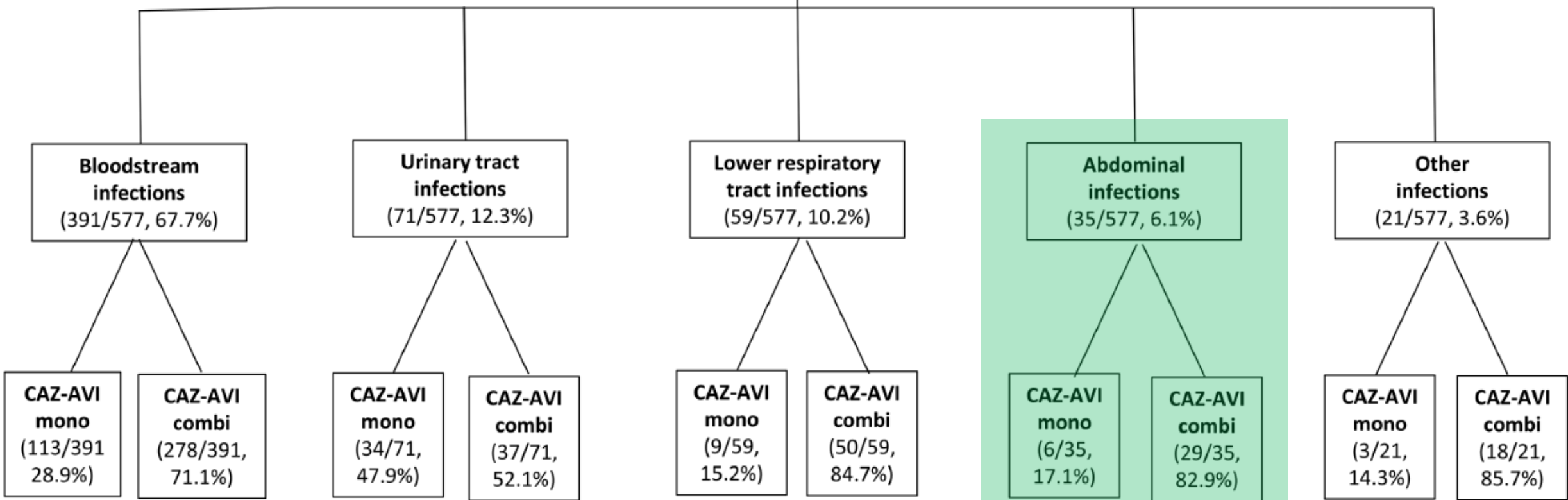


Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase-Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

Mario Tumbarello,^{1,2,3} Francesca Raffaelli,¹ Maddalena Giannella,⁴ Elisabetta Mantengoli,⁵ Alessandra Mularoni,⁶ Mario Venditti,⁷ Francesco Giuseppe De Rosa,⁸ Loredana Sarmati,⁹ Matteo Bassetti,^{10,11} Gaetano Brindicci,¹² Marianna Rossi,¹³ Roberto Luzzati,¹⁴ Paolo Antonio Grossi,¹⁵ Alberto Corona,¹⁶ Alessandro Capone,¹⁷ Marco Falcone,¹⁸ Cristina Mussini,¹⁹ Enrico Maria Trecarichi,²⁰ Antonio Cascio,²¹ Elena Guffanti,²² Alessandro Russo,²³ Gennaro De Pascale,²⁴ Carlo Tascini,²⁵ Ivan Gentile,²⁶ Angela Raffaella Losito,¹ Linda Bussini,⁴ Giampaolo Corti,^{5,27} Giancarlo Ceccarelli,⁷ Silvia Corcione,^{8,28} Mirko Compagno,²⁹ Daniele Roberto Giacobbe,^{10,11} Annalisa Saracino,¹² Massimo Fantoni,¹² Spinello Antinori,³⁰ Maddalena Peghin,³¹ Paolo Bonfanti,^{13,32} Alessandra Oliva,⁷ Andrea De Gasperi,²² Giusy Tiseo,¹⁸ Cristina Rovelli,¹⁵ Marianna Meschiari,¹⁵ Nour Shbaklo,⁸ Teresa Spanu,^{1,34} Roberto Cauda,¹² and Pierluigi Viale⁴

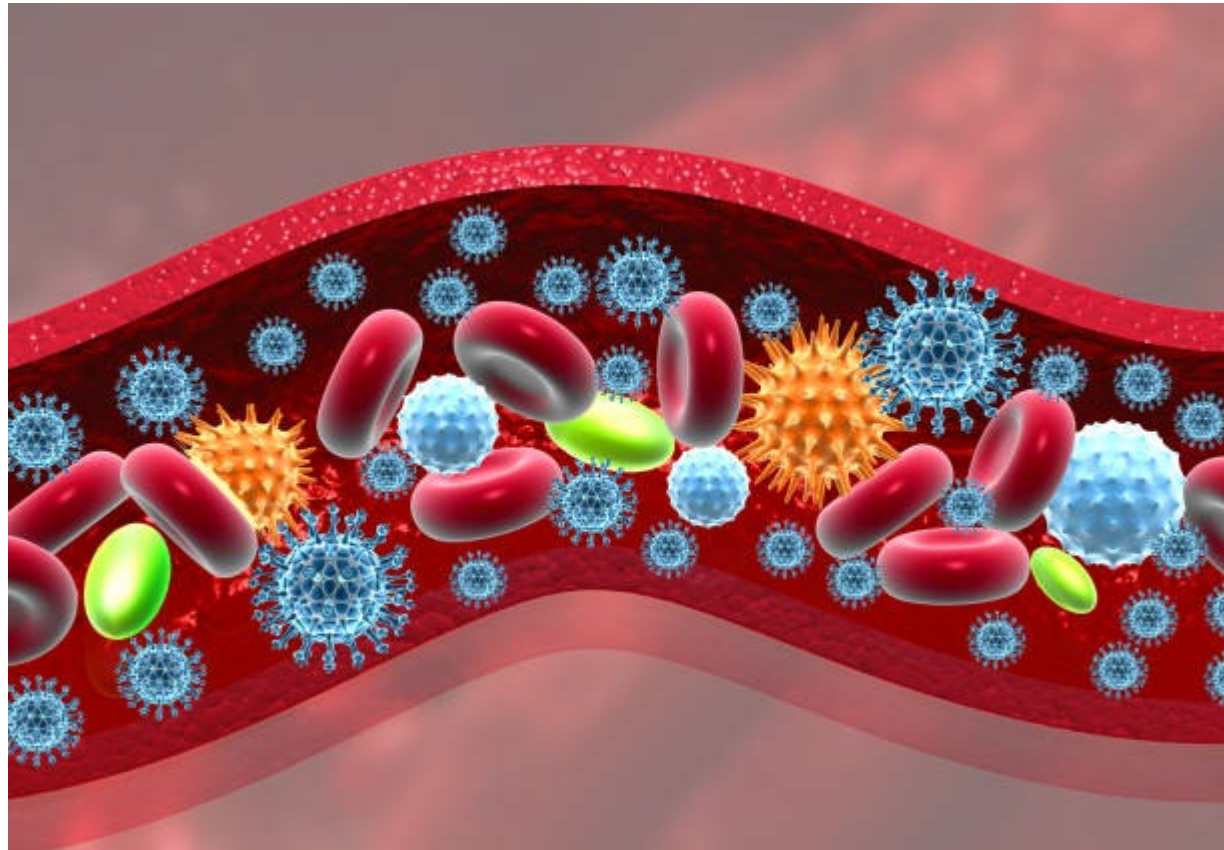
Adults consecutively treated with CAZ-AVI for invasive KPC Kp infections during the study period (n=603)

Excluded: Failure to meet inclusion criteria (n=26)



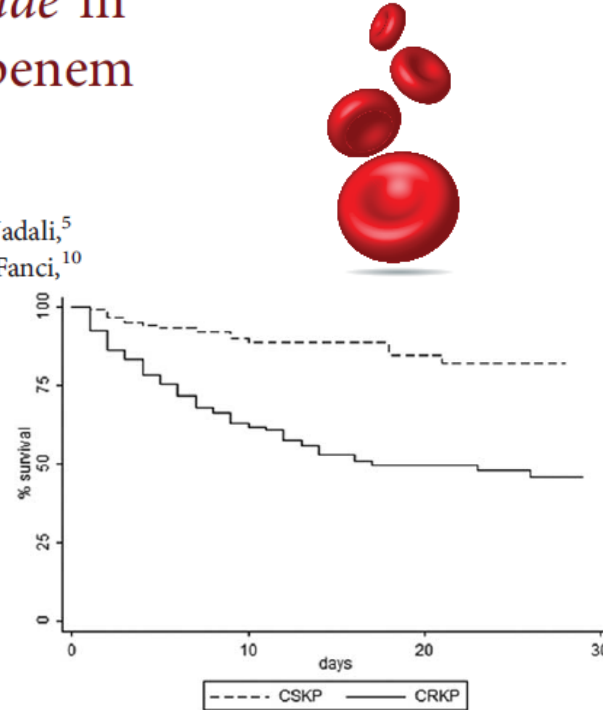
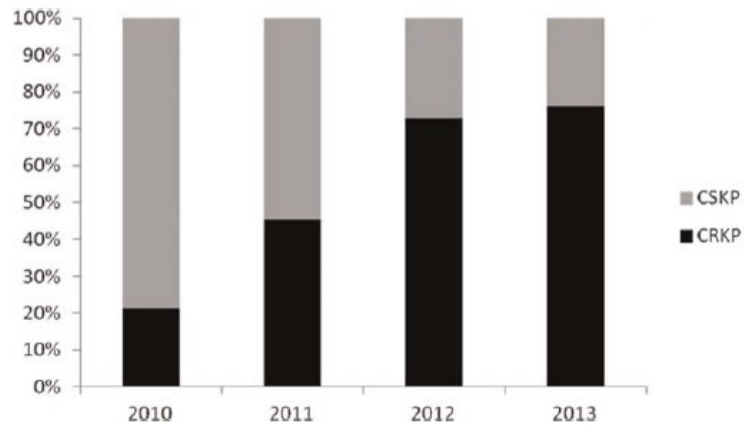
Mortality: 7/35 (20%)

BSI



Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey

Enrico Maria Trecarichi,^{1*} Livio Pagano,² Bruno Martino,³ Anna Candoni,⁴ Roberta Di Blasi,² Gianpaolo Nadali,⁵ Luana Fianchi,² Mario Delia,⁶ Simona Sica,² Vincenzo Perriello,⁷ Alessandro Busca,⁸ Franco Aversa,⁹ Rosa Fanci,¹⁰ Lorella Melillo,¹¹ Federica Lessi,¹² Maria Ilaria Del Principe,¹³ Chiara Cattaneo,¹⁴ and Mario Tumbarello,¹



Prospective cohort study on KP BSI in 13 Italian hematological units.

161/278 (57.9%) of KP BSI were CR.

Mortality was significantly higher for patients with CRKP BSI (84/161, 52.2%) than for those with BSI caused by CSKP (17/117, 14.5%; $P < 0.001$)

Variables	HR	(95% IC)	P values
MODEL (A)			
Septic shock	3.86	(2.47–6.02)	<0.001
Acute respiratory failure	2.32	(1.45–3.70)	<0.001
Initial inadequate antimicrobial therapy	1.87	(1.08–2.22)	0.02
Carbapenem-resistance by KP isolate	1.85	(1.01–3.42)	0.04
MODEL (B)			
Septic shock	2.64	(1.57–4.45)	<0.001
Acute respiratory failure	2.83	(1.63–4.92)	<0.001
Combination therapy	0.32	(0.19–0.54)	<0.001

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

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

Characteristic	M–V (n = 32)	BAT (n = 15)	Total (N = 47)
Age, mean (SD), years	63.5 (14.1)	60.2 (13.0)	62.5 (13.7)
Infection type, n (%)			
Bacteremia	14 (43.8)	8 (53.3)	22 (46.8)
cUTI/AP	12 (37.5)	4 (26.7)	16 (34.0)
HABP/VABP	4 (12.5)	1 (6.7)	5 (10.6)
cIAI	2 (6.3)	2 (13.3)	4 (8.5)
Baseline pathogen, n (%) ^b			
<i>Klebsiella pneumoniae</i>	29 (90.6)	12 (80.0)	41 (87.2)
<i>Escherichia coli</i>	3 (9.4)	1 (6.7)	4 (8.5)
<i>Enterobacter cloacae</i> sp.	1 (3.1)	2 (13.3)	3 (6.4)
<i>Proteus mirabilis</i>	0 (0)	2 (13.3)	2 (4.3)
<i>Serratia marcescens</i>	1 (3.1)	1 (6.7)	2 (4.3)

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

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

- 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 BAT for CRE.
- Mortality was **15.6%** vs 33.3% for meropenem–vaborbactam versus BAT.
- Cure rates was **65.6%** vs 33.3%
- Renal related AE was **4%** vs 24%



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 groups.

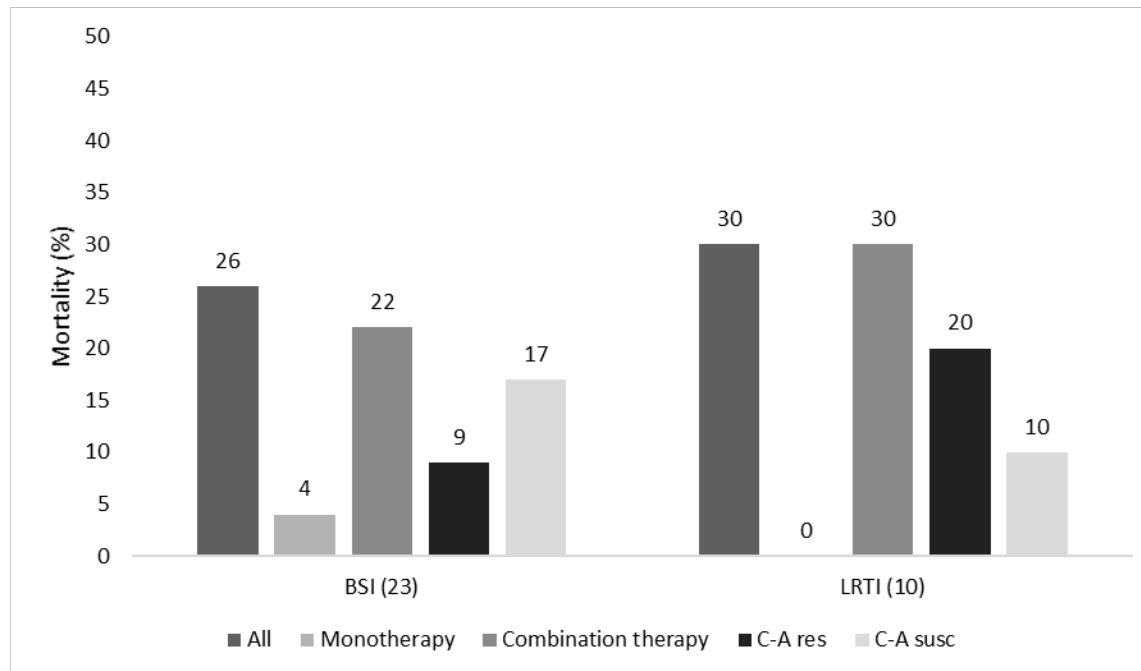
Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: a multicentre study

Mario Tumbarello ^{1,2*}, Francesca Raffaelli³, Antonio Cascio⁴, Marco Falcone ⁵, Liana Signorini⁶, Cristina Mussini⁷, Francesco Giuseppe De Rosa ⁸, Angela Raffaella Losito³, Gennaro De Pascale^{9,10}, Renato Pascale ¹¹, Daniele Roberto Giacobbe ^{12,13}, Alessandra Oliva ¹⁴, Alberto Faresè¹⁵, Paola Morelli^{16,17}, Giusy Tiseo⁵, Marianna Meschiari ⁷, Paola Del Giacomo³, Francesca Montagnani^{1,2}, Massimiliano Fabbiani², Joel Vargas¹⁰, Teresa Spanu^{3,10}, Matteo Bassetti^{12,13}, Mario Venditti¹⁴ and Pierluigi Viale¹¹

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.



Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae



14 Citing Articles

TO THE EDITOR:

February 21, 2019

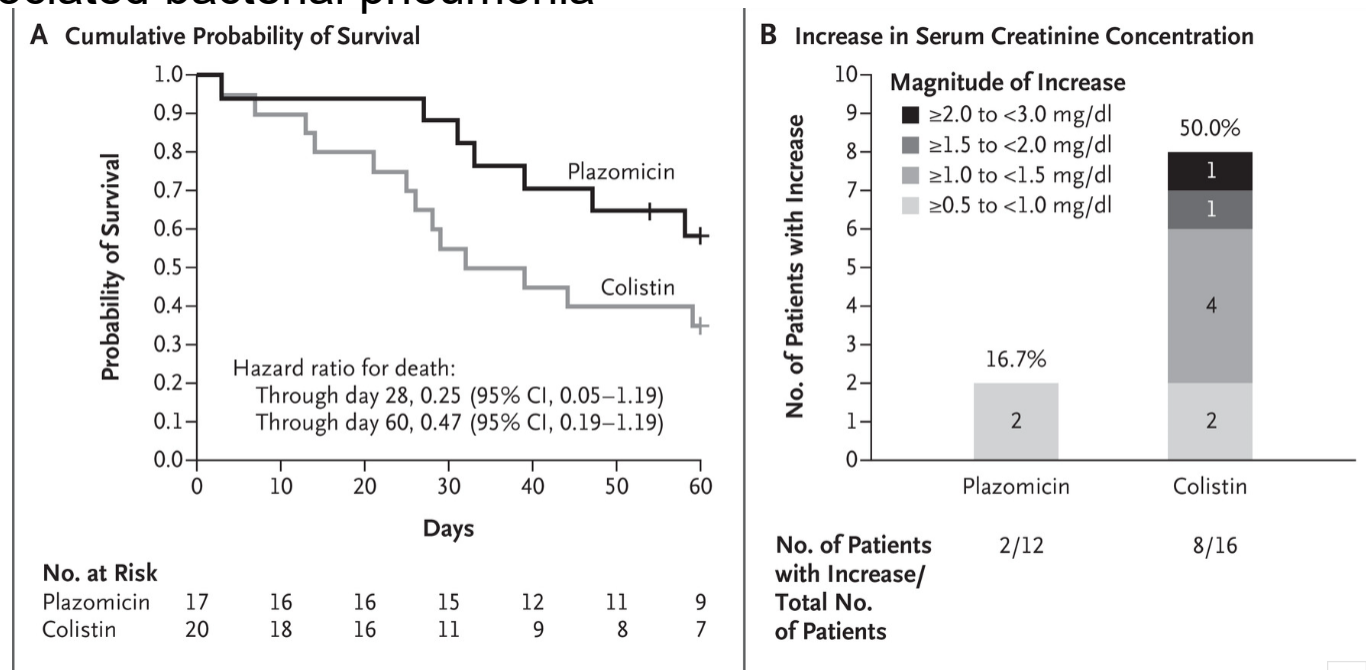
N Engl J Med 2019; 380:791-793

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

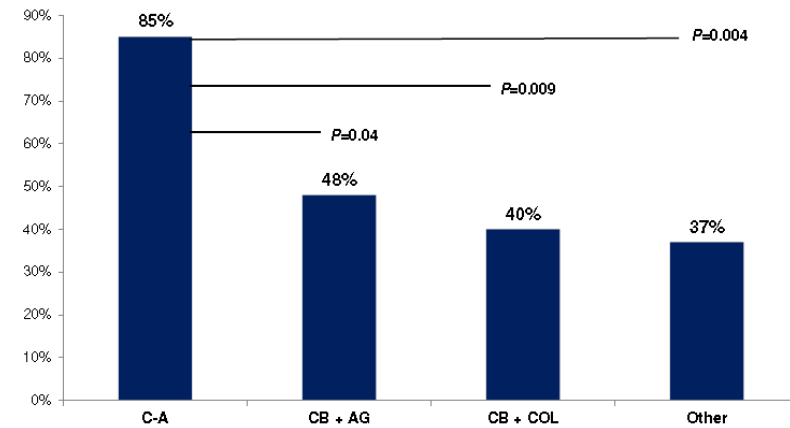


Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

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}



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 ($P=0.002$).**



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 Evans², for the Antibacterial Resistance Leadership Group

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 ($P = .001$).

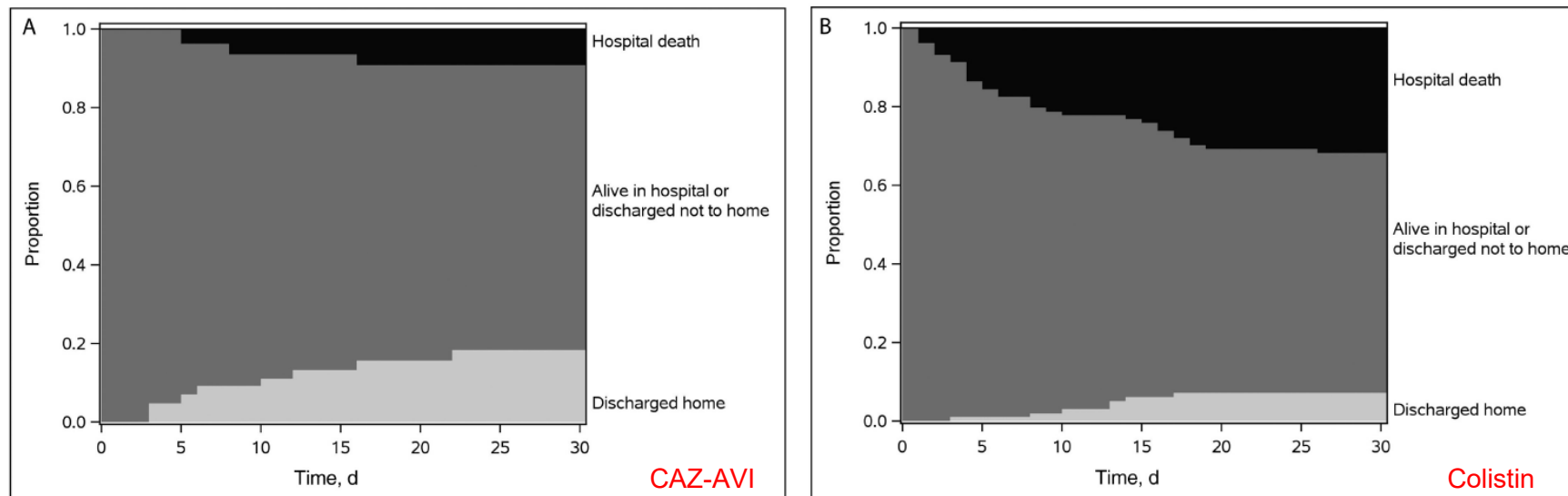
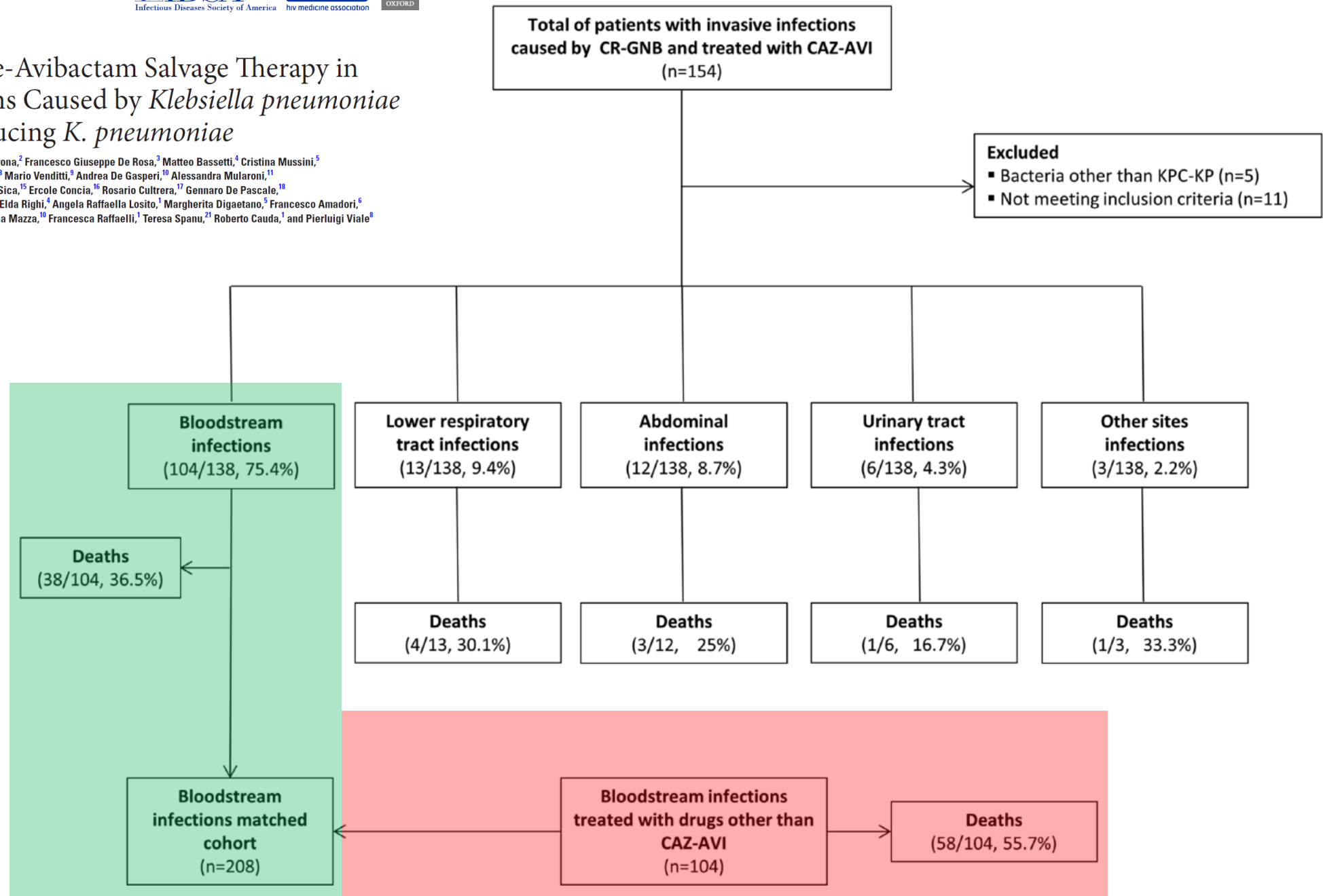


Figure 1. Inverse probability of treatment weighting (IPTW)-adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

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

Mario Tumbarello,^{1,4} Enrico Maria Trecaichi,^{1,4} 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 Viale⁸



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- 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%, $P = .005$).

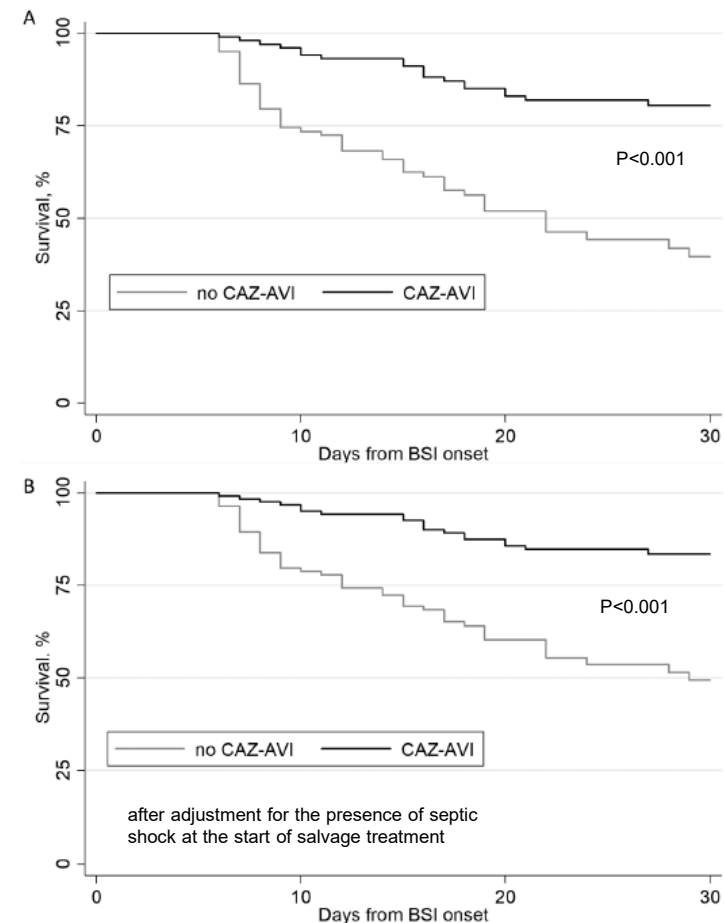


Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae* Bacteremia

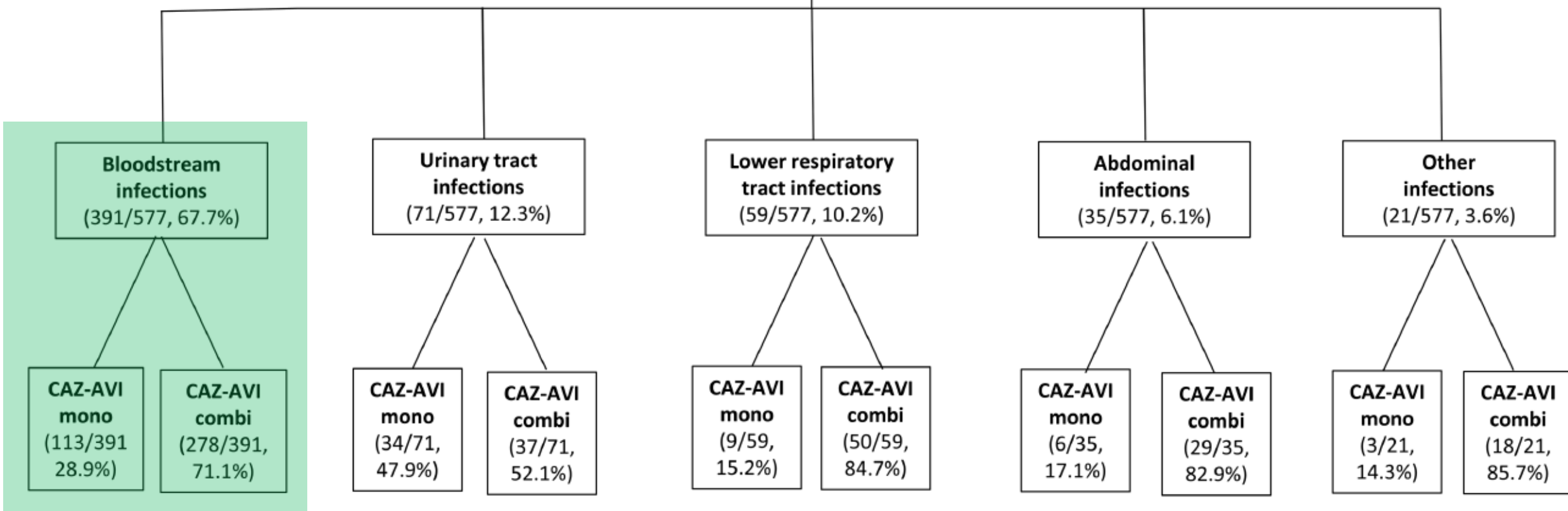
Variable	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
	P Value	OR (95% CI)	P Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index ≥ 3	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia	.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)

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

Mario Tumbarello,^{1,2,3} Francesca Raffaelli,¹ Maddalena Giannella,⁴ Elisabetta Mantengoli,⁵ Alessandra Mularoni,⁶ Mario Venditti,⁷ Francesco Giuseppe De Rosa,⁸ Loredana Sarmati,⁹ Matteo Bassetti,^{10,11} Gaetano Brindicci,¹² Marianna Rossi,¹³ Roberto Luzzati,¹⁴ Paolo Antonio Grossi,¹⁵ Alberto Corona,¹⁶ Alessandro Capone,¹⁷ Marco Falcone,¹⁸ Cristina Mussini,¹⁹ Enrico Maria Trecarichi,²⁰ Antonio Cascio,²¹ Elena Guffanti,²² Alessandro Russo,²³ Gennaro De Pascale,²⁴ Carlo Tascini,²⁵ Ivan Gentile,²⁶ Angela Raffaella Losito,¹ Linda Bussini,⁴ Giampaolo Corti,^{5,27} Giancarlo Ceccarelli,⁷ Silvia Corcione,^{8,28} Mirko Compagno,²⁹ Daniele Roberto Giacobbe,^{10,11} Annalisa Saracino,¹² Massimo Fantoni,¹² Spinello Antinori,³⁰ Maddalena Peghin,³¹ Paolo Bonfanti,^{13,32} Alessandra Oliva,⁷ Andrea De Gasperi,²² Giusy Tiseo,¹⁸ Cristina Rovelli,¹⁵ Marianna Meschieri,¹⁵ Nour Shbaklo,⁸ Teresa Spanu,^{1,34} Roberto Cauda,¹² and Pierluigi Viale⁴

Adults consecutively treated with CAZ-AVI for invasive KPC Kp infections during the study period (n=603)

Excluded: Failure to meet inclusion criteria (n=26)

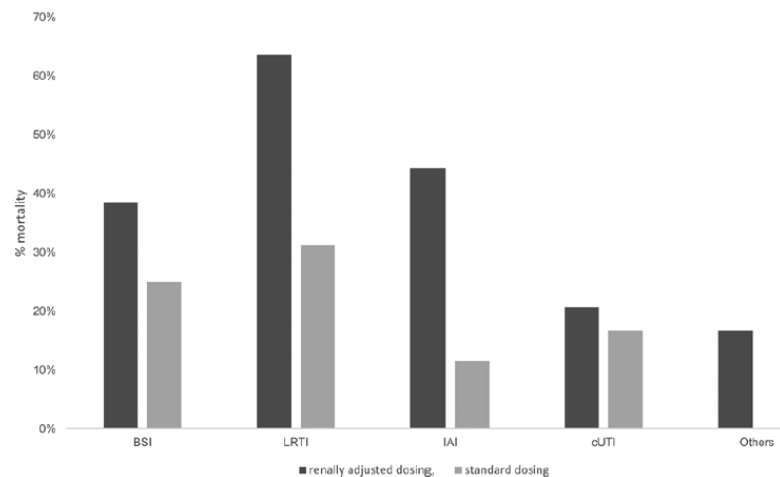


Mortality: 103/391 (26%)

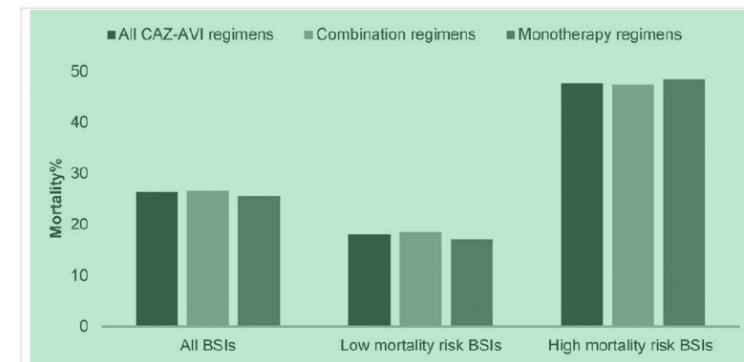
Ceftazidime-Avibactam Use for *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

Mario Tumbarello,^{1,2,3} Francesca Raffaelli,¹ Maddalena Giannella,⁴ Elisabetta Mantengoli,⁵ Alessandra Mularoni,⁶ Mario Venditti,⁷ Francesco Giuseppe De Rosa,⁸ Loredana Sarmati,⁹ Matteo Bassetti,^{10,11} Gaetano Brindicci,¹² Marianna Rossi,¹³ Roberto Luzzati,¹⁴ Paolo Antonio Grossi,¹⁵ Alberto Corona,¹⁶ Alessandro Capone,¹⁷ Marco Falcone,¹⁸ Cristina Mussini,¹⁹ Enrico Maria Treccarichi,²⁰ Antonio Cascio,²¹ Elena Guffanti,²² Alessandro Russo,²³ Gennaro De Pascale,²⁴ Carlo Tascini,²⁵ Ivan Gentile,²⁶ Angela Raffaella Losito,¹ Linda Bussini,⁴ Giampaolo Corti,^{5,27} Giancarlo Ceccarelli,⁷ Silvia Corcione,^{8,28} Mirko Compagno,²⁹ Daniele Roberto Giacobbe,^{10,11} Annalisa Saracino,¹² Massimo Fantoni,¹² Spinello Antinori,³⁰ Maddalena Peghin,³¹ Paolo Bonfanti,^{13,32} Alessandra Oliva,⁷ Andrea De Gasperi,²² Giusy Tiseo,¹⁸ Cristina Rovelli,¹⁵ Marianna Meschiari,³³ Nour Shbaklo,⁸ Teresa Spanu,^{1,34} Roberto Cauda,¹² and Pierluigi Viale⁴

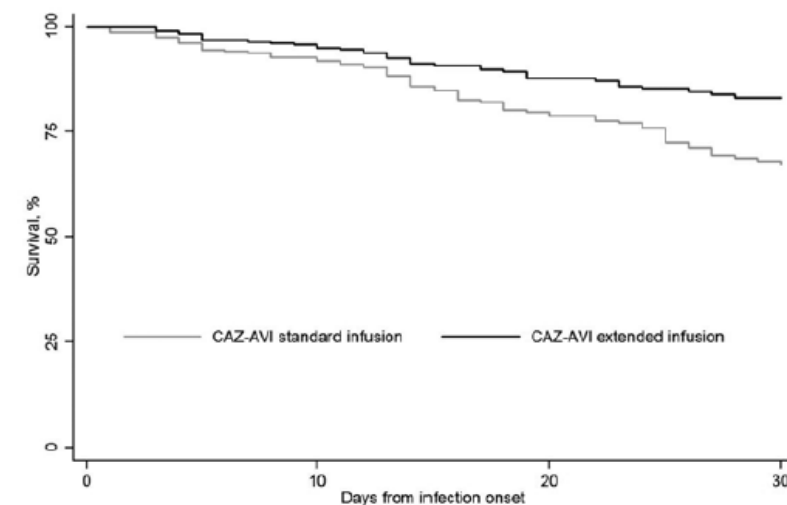
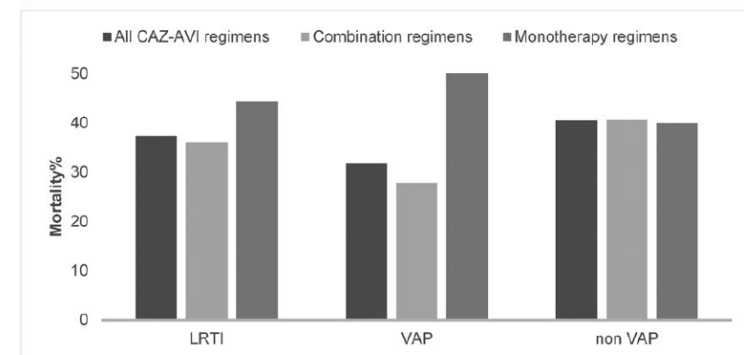
- 577 adults with **bloodstream infections (391)** or nonbacteremic infections involving mainly the urinary tract, lower respiratory tract, and intra-abdominal structures.
- All received treatment with CAZ-AVI alone (165) or with ≥ 1 other active antimicrobials (412).
- The all-cause mortality rate after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



A



B



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 Toyozumi, 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)
<i>Acinetobacter</i> spp*	21/42 (50%)	3/17 (18%)
<i>Acinetobacter baumannii</i>	19/39 (49%)	3/17 (18%)
<i>Klebsiella pneumoniae</i>	8/34 (24%)	4/16 (25%)
Without <i>Acinetobacter</i> spp	6/28 (21%)	4/15 (27%)
<i>Pseudomonas aeruginosa</i>	6/17 (35%)	2/12 (17%)
Without <i>Acinetobacter</i> spp	2/11 (18%)	2/11 (18%)
<i>Escherichia coli</i>	1/6 (17%)	0/3
Without <i>Acinetobacter</i> spp	0/3	0/1
<i>Stenotrophomonas maltophilia</i>	4/5 (80%)	NA
Without <i>Acinetobacter</i> 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.

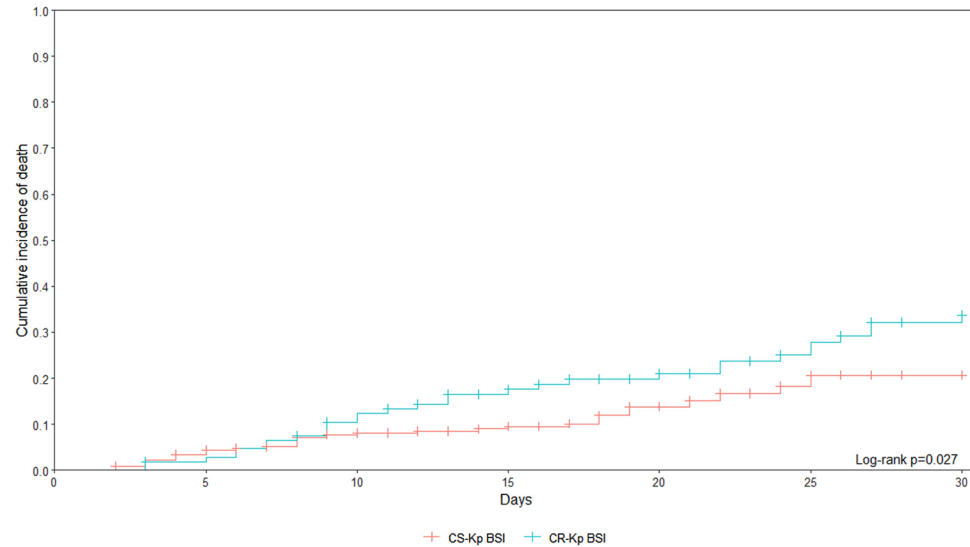
Despite the observation of a large difference in crude cumulative 30 day mortality between CR-Kp BSI and CS-Kp BSI (33.8% versus 20.7%, respectively), **carbapenem resistance was not found independently associated with an increased mortality in *K. pneumoniae* BSI** after adjustment for other prognostic 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, $P = 0.866$).

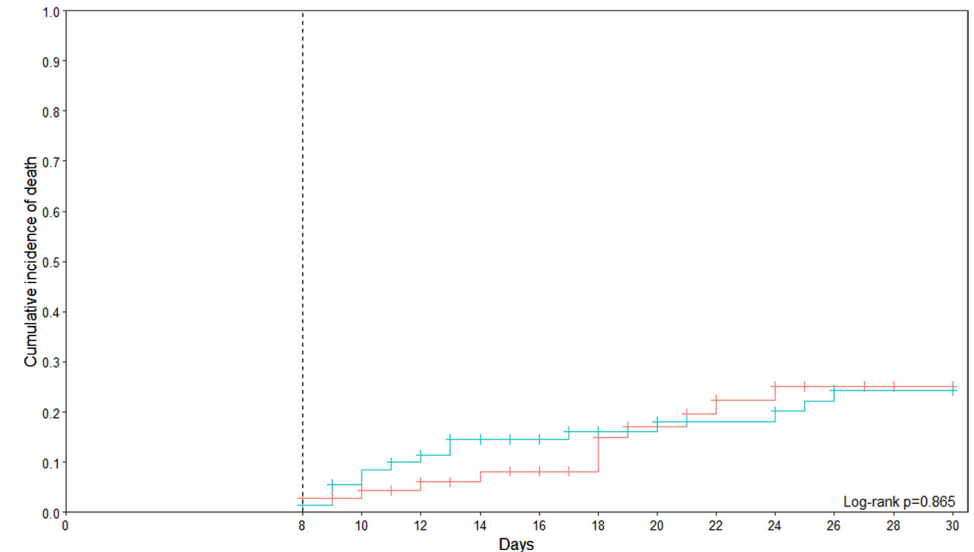
Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape

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



	0	5	10	15	20	25	30
CS-Kp BSI	319	304	256	177	131	101	84
CR-Kp BSI	107	104	90	77	66	54	43

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).



	0	8	10	12	14	16	18	20	22	24	26	28	30
CS-Kp BSI		72	62	55	46	43	41	33	30	28	24	23	22
CR-Kp BSI		72	65	60	55	52	49	44	40	40	37	35	35

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

Ceftazidime-avibactam

Meropenem-vaborbactam

Imipenem-relebactam

Cefiderocol



Fosfomicina

Aminoglicosidi

Altro ?