Current and emerging treatment options for Gram-negative infections

Yehuda Carmeli, MD, MPH

National Institute for Antibiotic Resistance and Infection Control, Tel Aviv, Israel

Disclaimer

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- Roche Pharmaceuticals
- Tetraphase Pharmaceuticals Inc
- VenatoRx Pharmaceuticals, Inc.

Priority pathogens

WHO, World Health Organization.

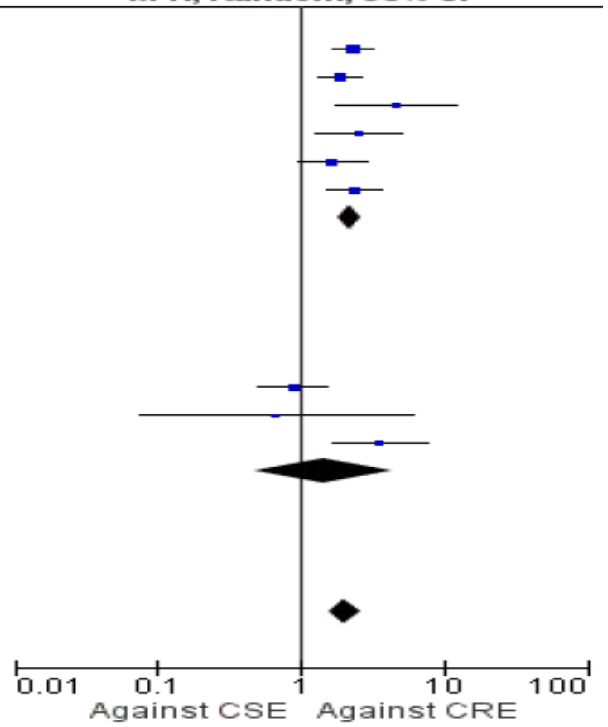
WHO 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Accessed October 2019.

Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

Matthew E. Falagas,[1] Giannoula S. Tansarli,[1] Drosos E. Karageorgopoulos,[1] and Konstantinos Z. Vardakas[1]

CRE Bacteremia mortality 131/222= 60%

Study or Subgroup	Carba-resistant Events	Total	Carba-susceptible Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Bacteremia						
Ben-David 2012	29	42	45	150	18.4%	2.30 [1.68, 3.16]
Chang 2011	16	17	17	34	17.3%	1.88 [1.32, 2.69]
Daikos 2007	7	13	5	43	6.0%	4.63 [1.76, 12.16]
Daikos 2009	6	14	25	148	9.3%	2.54 [1.26, 5.12]
Mouloudi 2010	25	37	9	22	12.2%	1.65 [0.95, 2.86]
Patel 2008	48	99	20	99	14.9%	2.40 [1.54, 3.73]
Subtotal (95% CI)		**222**		**496**	**78.1%**	**2.19 [1.82, 2.63]**
Total events	131		121			
Heterogeneity: Tau² = 0.00; Chi² = 4.53, df = 5 (P = 0.48); I² = 0%						
Test for overall effect: Z = 8.30 (P < 0.00001)						
1.1.2 Bacteremia or other infections						
Falagas 2007	16	53	18	53	12.1%	0.89 [0.51, 1.55]
Gaviria 2011	1	19	3	38	1.4%	0.67 [0.07, 5.99]
Schwaber 2008	21	48	7	56	8.4%	3.50 [1.63, 7.51]
Subtotal (95% CI)		**120**		**147**	**21.9%**	**1.46 [0.47, 4.49]**
Total events	38		28			
Heterogeneity: Tau² = 0.68; Chi² = 8.68, df = 2 (P = 0.01); I² = 77%						
Test for overall effect: Z = 0.65 (P = 0.51)						
Total (95% CI)		**342**		**643**	**100.0%**	**2.05 [1.56, 2.69]**
Total events	169		149			
Heterogeneity: Tau² = 0.08; Chi² = 16.49, df = 8 (P = 0.04); I² = 51%						
Test for overall effect: Z = 5.17 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.49), I² = 0%						



CI, confidence interval; CRE, carbapenem-resistant *Enterobacteriaceae*;
M-H, Mantel-Haenszel random effects model.

Falagas ME, et al. *Emerg Infect Dis*. 2014;20:1170–5.

Efficacy against common MDR GNR

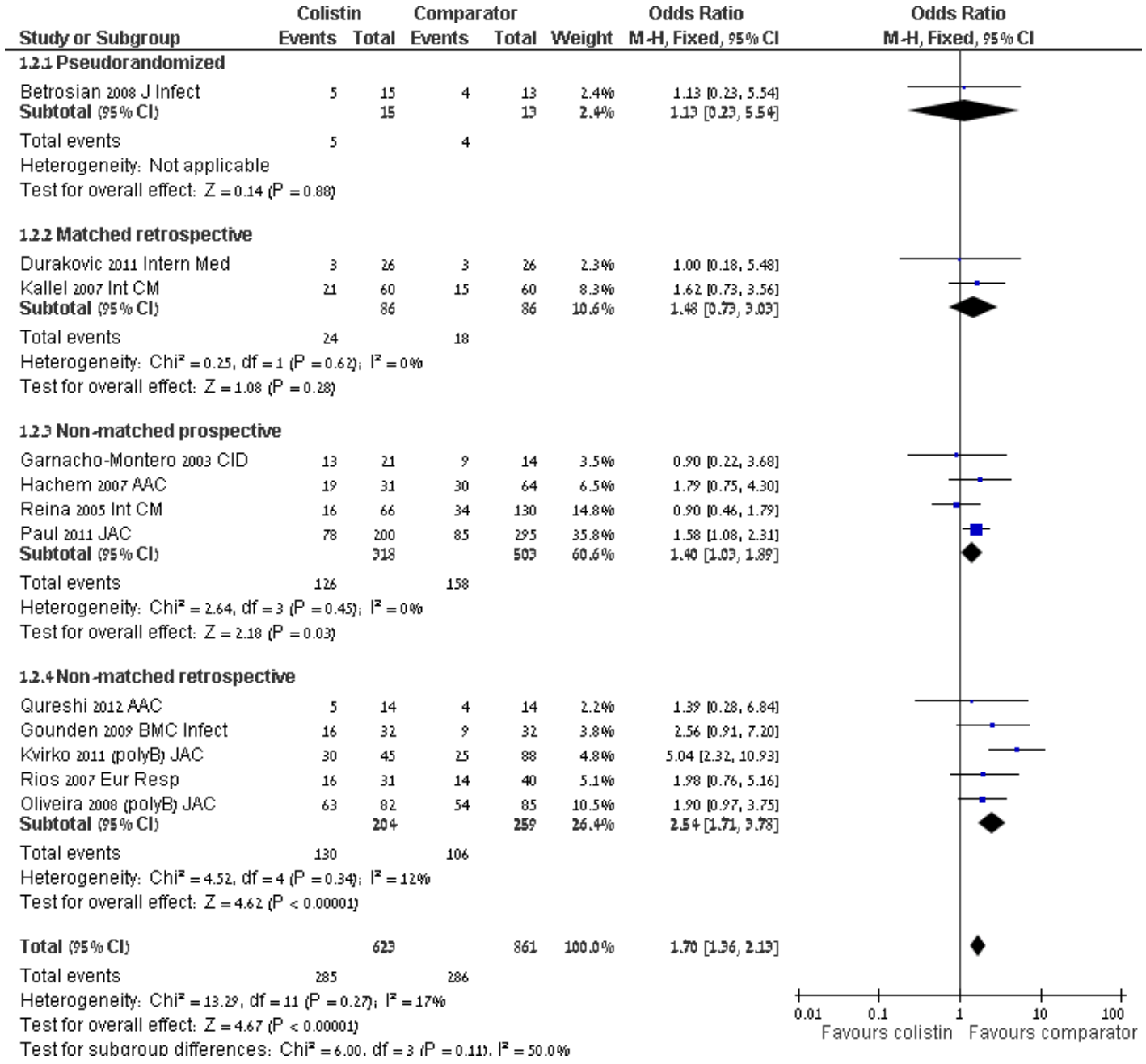
Agent	MDR-E (ESBL)	CR-PA	CR-AB	CRE –Serine KPC	CRE –Serine OXA-48	CR-metallo-enzyme
Piperacillin/tazobactam	++	-/+	-	-	-	-
Carbapenem	+++++	-	-	-/+	-	-
Ceftolozane/tazobactam	++++	+++++	-	-	-	-
Ceftazidime/avibactam	+++++	++++	-	++++	++++	-
Meropenem/vabrobactam	+++++	-/+		++++	-	
Imipenem/relebactam	+++++	++		++++	-	
Cefiderocol	++	++	++	++	++	++
Colistin	-/+	+	+	+	+	+

MDR, multidrug resistance; GNR, Gram-negative; CR-PA, carbapenem resistant *Pseudomonas aeruginosa;* CR-AB, carbapenem resistant *Acinetobacter baumannii.*

Colistin

- Used for almost two decade as the go-to agent to treat carbapenem-resistant GNR
- Correct dosing was figured out only in the last decade
- Accurate susceptibility testing – still unsolved
- Its efficacy is doubtful
- It has serious side effects

All-cause mortality: colistin vs. comparator antibiotics for sepsis



CI, confidence interval; M-H, Mantel-Haenszel random effects model.

Clinical Microbiology and Infection 2012 18, 18-29DOI: (10.1111/j.1469-0691.2011.03734.x)

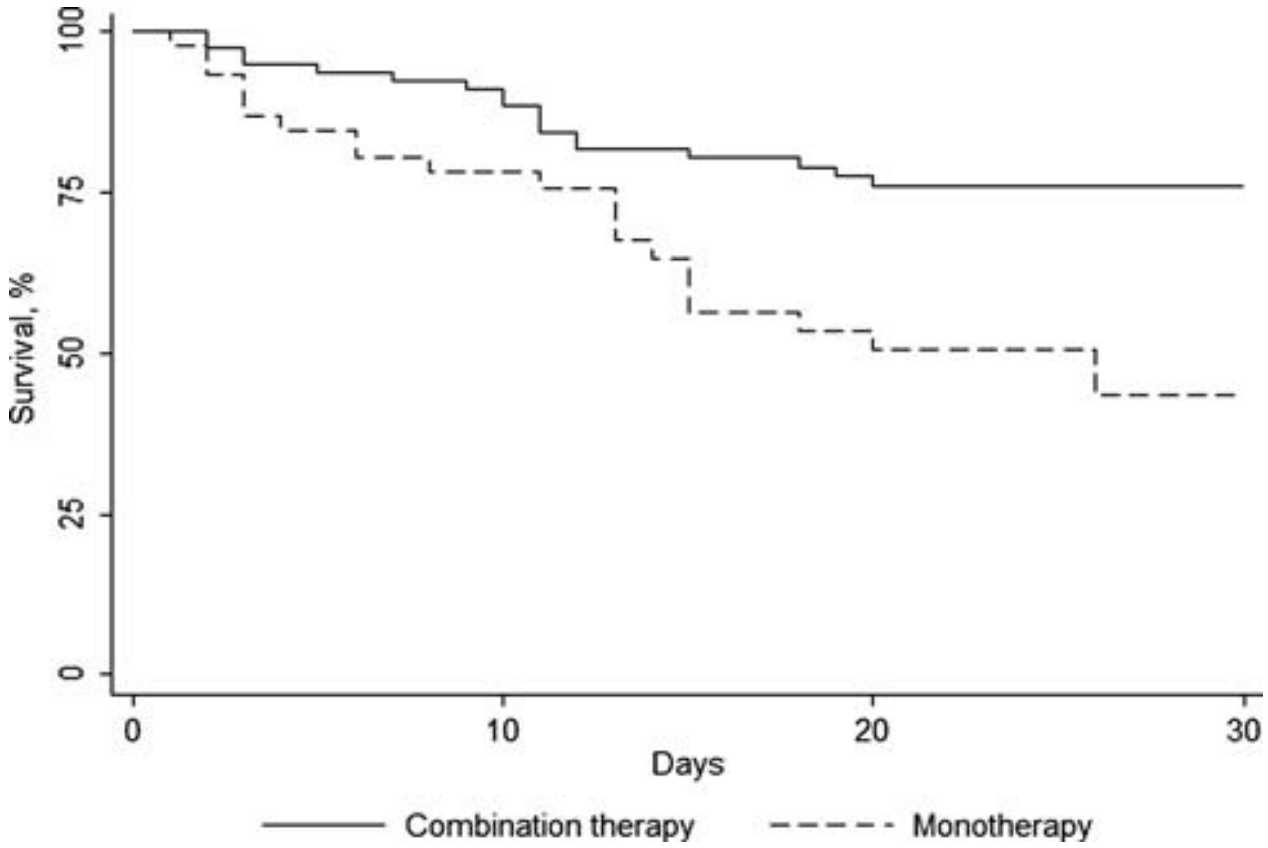
Combination therapy

- Rational for combination therapy
  - Colistin unsatisfactory efficacy
  - Hetero-resistance to colistin
  - Time to reach appropriate levels
- Various agents has been recommended
  - Rifampicin, carbapenems, quinolones, various beta-lactams, tetracycline, aminoglycosides, tigecycline
- Variable in vitro and in vivo results may reflect strain to strain variation
- Human data are limited and difficult to interpret
  - Two large randomized trials are being conducted

Carmeli Y. Personal opinion.

KPC-producing Kp

- 125 patients with BSI
- The overall 30-day mortality rate was 41.6%
  - Monotherapy: 54.3%
  - Combination: 34.1%
  - KPC-Kp BSIs are associated with high mortality

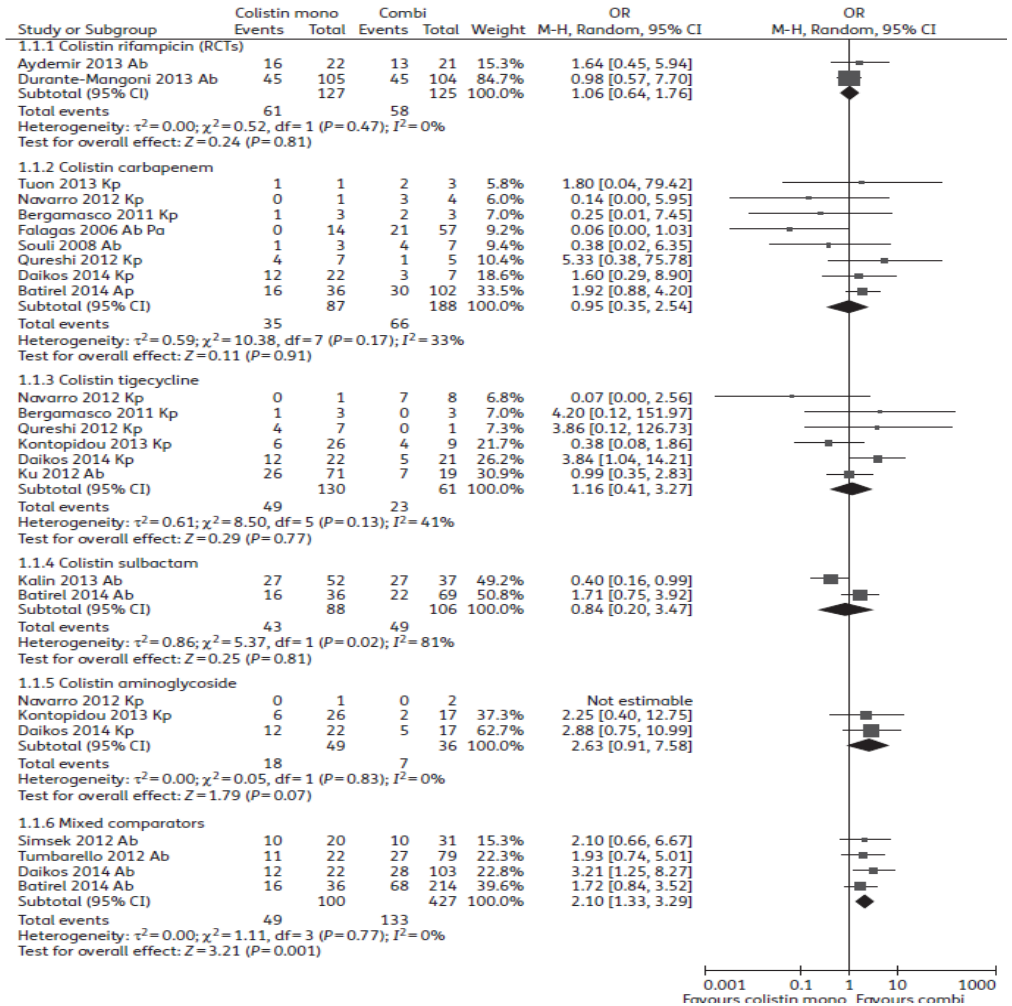


BSI, bloodstream infection; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *Klebsiella pneumoniae*

Tumbarello M, et al. *Clin Infect Dis.* 2012;55:943–50.

Combination therapy for carbapenem-resistant Gram-negative bacteria

Mical Paul[1]*, Yehuda Carmeli[2], Emanuele Durante-Mangoni[3], Johan W. Mouton[4], Evelina Tacconelli[5], Ursula Theuretzbacher[6], Cristina Mussini[7] and Leonard Leibovici[8,9]



Colistin/rifampicin

Colistin/carbapenem

Colistin/tigecycline

Colistin/sulbactam

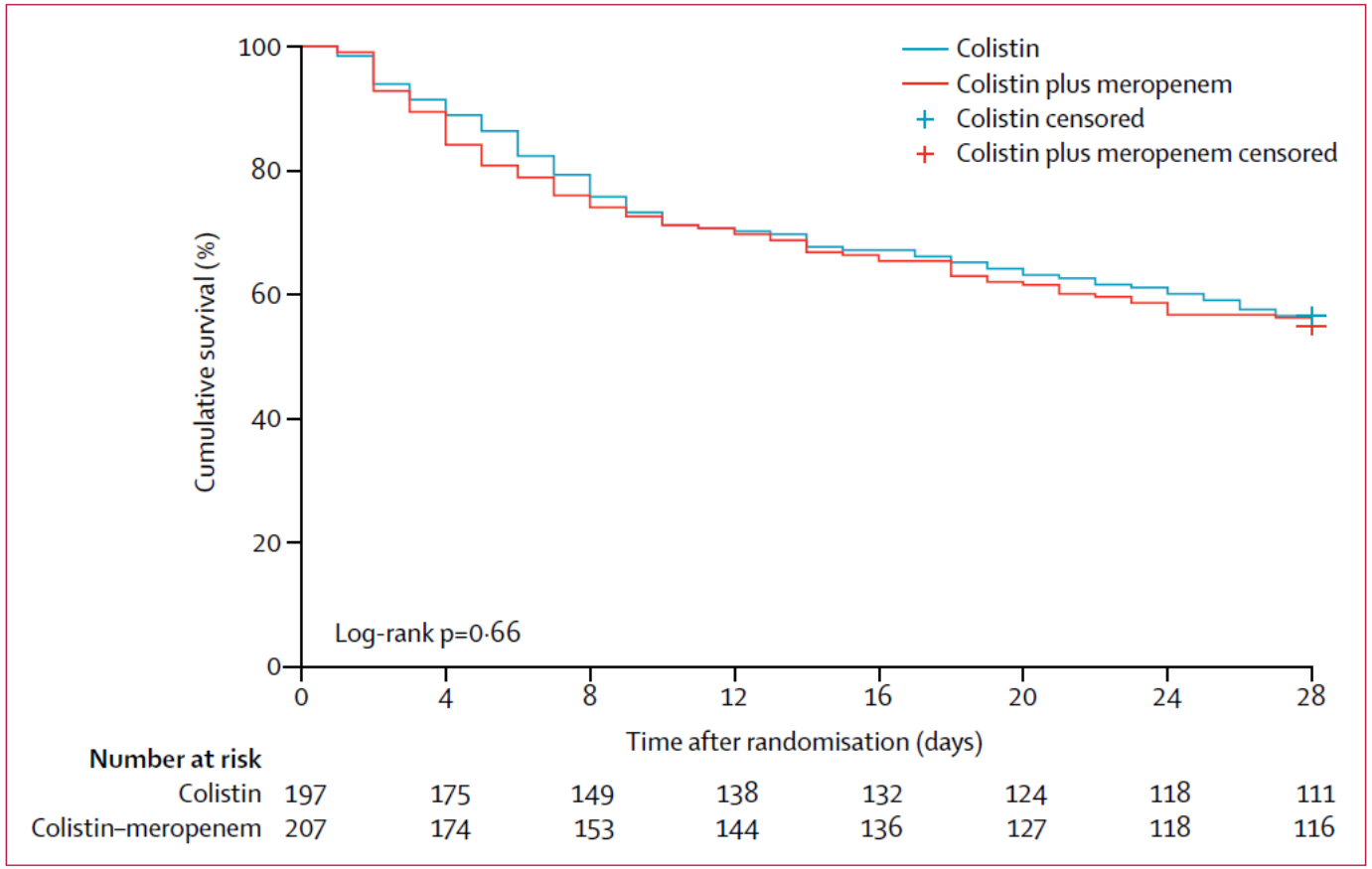
Colistin/aminoglycosides

Colistin/mixed comparator

Paul M, et al. *J Antimicrob Chemother*. 2014;69:2305–9.

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton,

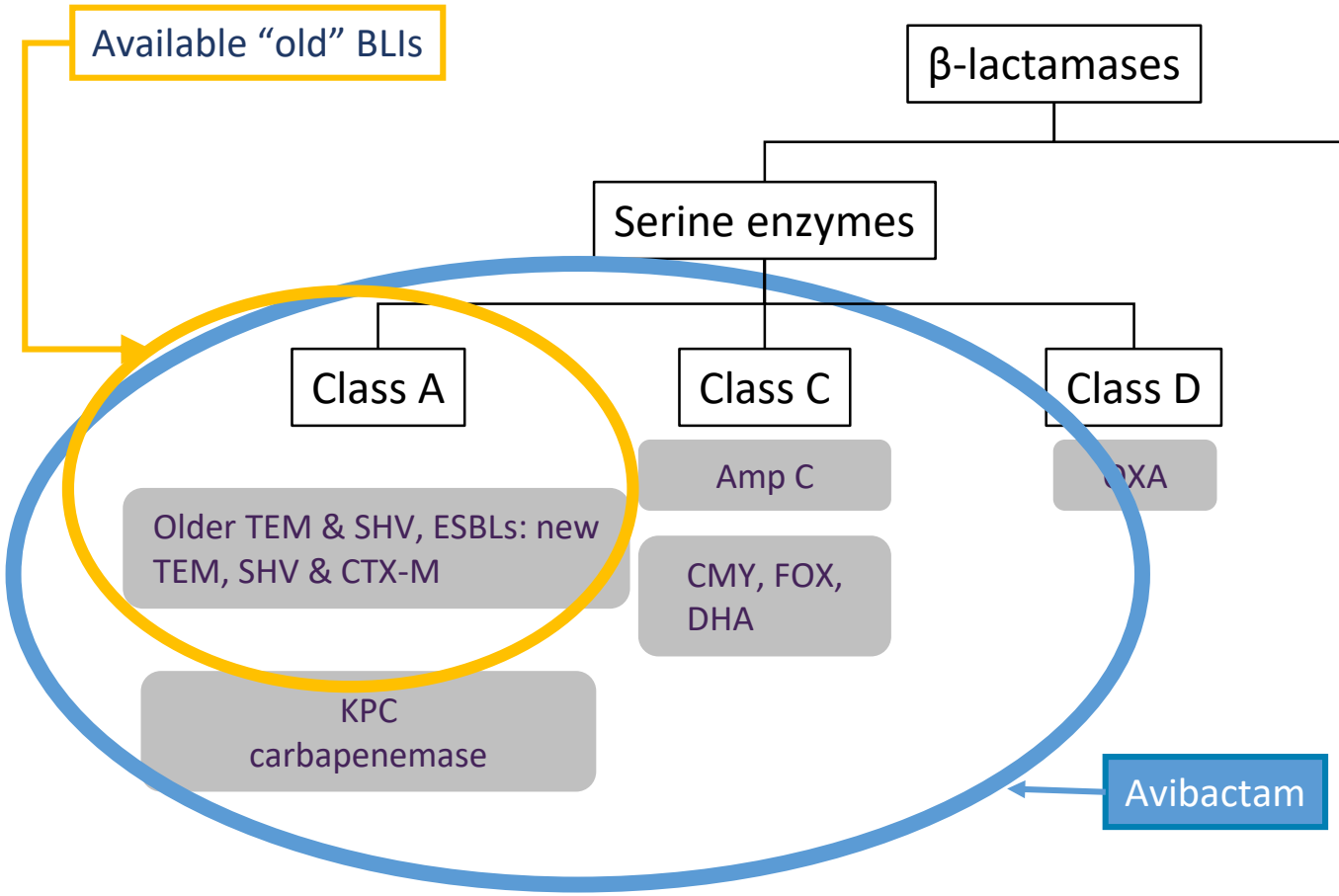


Number at risk								
Colistin	197	175	149	138	132	124	118	111
Colistin–meropenem	207	174	153	144	136	127	118	116

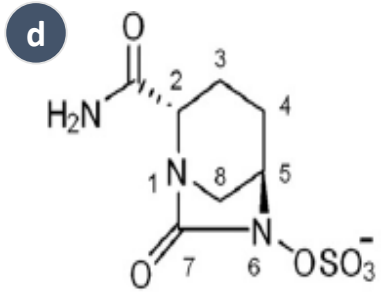
Figure 2: Survival analysis to day 28 after randomisation

Paul M, et al. *Lancet Infect Dis.* 2018;18:391–400.

Avibactam – Novel BLI - spectrum of β-lactamase inhibition



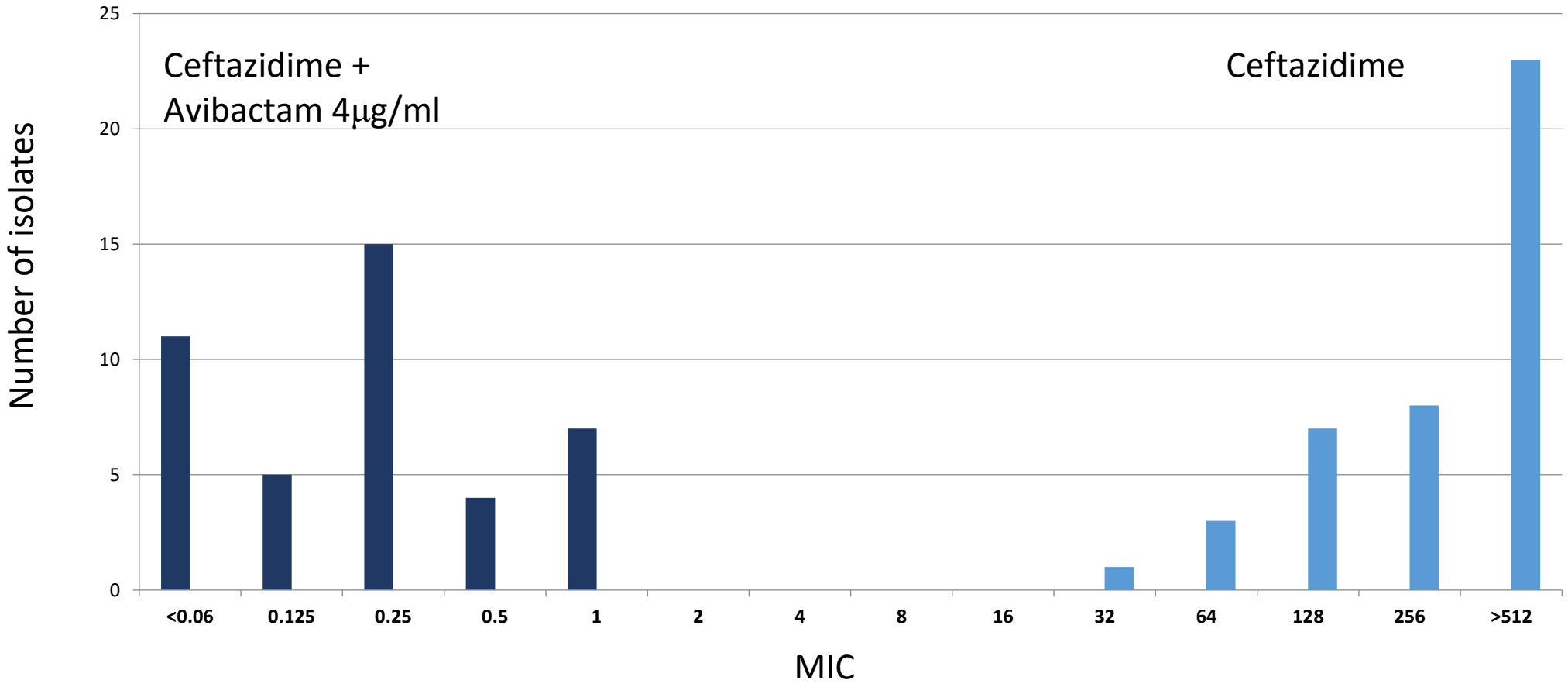
Avibactam



BLI, ß-lactam inhibitor; KPC, *K. pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; VIM, Verona Integron-encoded-β- lactamase.

Lagacé-Wiens P, et al. *Core Evid*. 2014;9:13–25; Bush K. Int J Antimicrob Agents. 2015;46:483–93; Zavicefta Summary of Product Characteristics.

MIC of 42 KPC producing *K. pneumoniae* collected in the US



KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration.

Endimiani A, et al. *Antimicrob Agents Chemother*. 2009;53:3599–601.

Ceftazidime avibactam *in vitro* activity on 36,380 Enterobacteriaceae and 7,868 *Pseudomonas aeruginosa*

Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers, 2013 to 2016

Helio S. Sader, Mariana Castanheira, Dee Shortridge, Rodrigo E. Mendes, Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA

- Isolates from all 9 U.S. Census divisions collected from 2013–2016

Organism category and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)		CLSI[b]		EUCAST	
	MIC_{50}	MIC_{90}	%S	%R	%S	%R
Enterobacteriaceae						
All isolates (36,380)						
Ceftazidime-avibactam	0.12	0.25	99.9	0.1*	99.9	0.1
Ceftriaxone	≤0.06	>8	85.3	13.6	85.3	13.6
Ceftazidime	0.25	8	88.8	9.9	86.2	11.2
Cefepime	≤0.12	2	91.2	6.7	89.8	7.7
Piperacillin-tazobactam	2	16	92.7	4.1	89.8	7.3
Meropenem	≤0.06	≤0.06	98.5	1.3	98.7	0.7
Levofloxacin	≤0.12	>4	82.6	15.6	78.7	18.8
Gentamicin	≤1	2	91.2	7.6	90.2	8.8
Amikacin	2	4	99.2	0.2	98.4	0.8
Tigecycline	0.25	1	98.0	0.1*	92.7	2.0
Colistin	≤0.5	>8			78.2	21.8
CRE (513)						
Ceftazidime-avibactam	0.5	2	97.5	2.5*	97.5	2.5
Ceftriaxone	>8	>8	2.1	97.5	2.1	97.5
Ceftazidime	>32	>32	4.3	93.0	2.3	95.7
Cefepime	>16	>16	8.4	77.9	3.2	87.1
Piperacillin-tazobactam	>64	>64	3.1	91.2	2.7	96.9
Meropenem	>8	>8	2.7	89.7	10.3	52.4
Levofloxacin	>4	>4	23.4	72.9	15.0	81.3
Gentamicin	8	>8	49.5	33.9	44.4	50.5
Amikacin	8	32	68.2	7.0	51.5	31.8
Tigecycline	0.5	1	98.8	0.0*	90.3	1.2
Colistin	≤0.5	>8			79.1	20.9

CLSI, Clinical Labroatory Standards Institute; CRE, carbapenem-resistant Enterobacteriaceae; EUCAST, The European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration

Sader, HS, et al. Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant Enterobacteriaceae and Pseudomonas aeruginosa Isolates from U.S. Medical Centers, 2013 to 2016. Antimicrob Agents Chemother 2017;61(11):e01045.

In vitro activity of CAZ-AVI & ATM-AVI against OXA-48-carrying Enterobacteriaceae

- Kazmierczak KM, Bradford PA, Stone GG, de Jonge BLM, Sahm DF. 2018. In vitro activity of ceftazidime-avibactam and aztreonam-avibactam against OXA-48-carrying Enterobacteriaceae isolated as part of the International Network for Optimal resistance Monitoring (INFORM) global surveillance program from 2012 to 2015. Antimicrob agents Chemother 62:e00592-18.

A total of 45,872 *Enterobacteriaceae* clinical isolates collected in 39 countries as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance study in 2012 to 2015

Organism subset (*n*) and agent[a]	MIC (μg/ml)[b]			% susceptible[c]
	Range	MIC_{50}	MIC_{90}	
All OXA-48-like-positive *Enterobacteriaceae* (68)				
Ceftazidime	16 to >128	>128	>128	0.0
Ceftazidime-avibactam	0.06 to >128	1	>128	89.7
Aztreonam	0.05 to >128	128	>128	4.4
Aztreonam-avibactam	0.03 to 8	0.25	4	NA
Cefepime	2 to >16	>16	>16	1.5
Meropenem	0.015 to >8	2	>8	33.8
Imipenem	0.12 to >8	2	>8	29.4
Piperacillin-tazobactam	4 to >128	>128	>128	1.5
Amikacin	1 to >32	8	>32	64.7
Tigecycline	0.12 to 4	0.5	2	92.6
Colistin (52)	0.25 to >4	0.5	1	94.2

CAZ-AVI – Ceftazidime avibactam; ATM-AVI – Aztreonam avibactam

Kazmierczak KM, et al. Antimicrob agents Chemother 62 2018:e00592-18.

Pseudomonas aeruginosa Antimicrobial Susceptibility Results from Four Years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States

Helio S. Sader, Michael D. Huband, Mariana Castanheira, Robert K. Flamm

Resistance group	No. of isolates (%) susceptible to drug(s):			
	CAZ-AVI	CAZ	MEM	PT
All (n = 7,452)	7,228 (97.0)	6,284 (84.3)	6,096 (82.0)	5,996 (80.5)
CAZ-NS (≥16 mg/liter; n = 1,168)	946 (81.0)	0 (0.0)	516 (44.3)	95 (8.1)

CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; NS, non-susceptible; MEM, meropenem; PT, piperacillin-tazobactam.

Sader HS, et al. *Antimicrob Agents Chemother*. 2017;61(3). pii: e02252-16.

Ceftazidime–avibactam* in ICU patients

- Ceftazidime–avibactam, infused over 2 h, in 10 ICU patients
- Two pts with ARC, 6 patients with normal RF, two patients with moderate RI

TABLE 3. POPULATION PHARMACOKINETIC PARAMETERS FOR CEFTAZIDIME AND AVIBACTAM IN ADULT INTENSIVE CARE UNIT PATIENTS

Pharmacokinetic parameter	*Mean (SD)*
Ceftazidime	
Model derived parameters	
V_d	34.78 (10.49)
CL_i	1.15 (0.63)
CL_s	0.043 (0.016)
Calculated parameters	
CL	6.14 (3.80)
$t_{1/2}$	4.84 (2.15)
Avibactam	
Model derived parameters	
V_d	50.81 (14.32)
CL_i	0.89 (0.58)
CL_s	0.10 (0.03)
Calculated parameters	
CL	11.09 (6.78)
$t_{1/2}$	4.09 (2.13)

Higher Vd and longer $t_{1/2}$

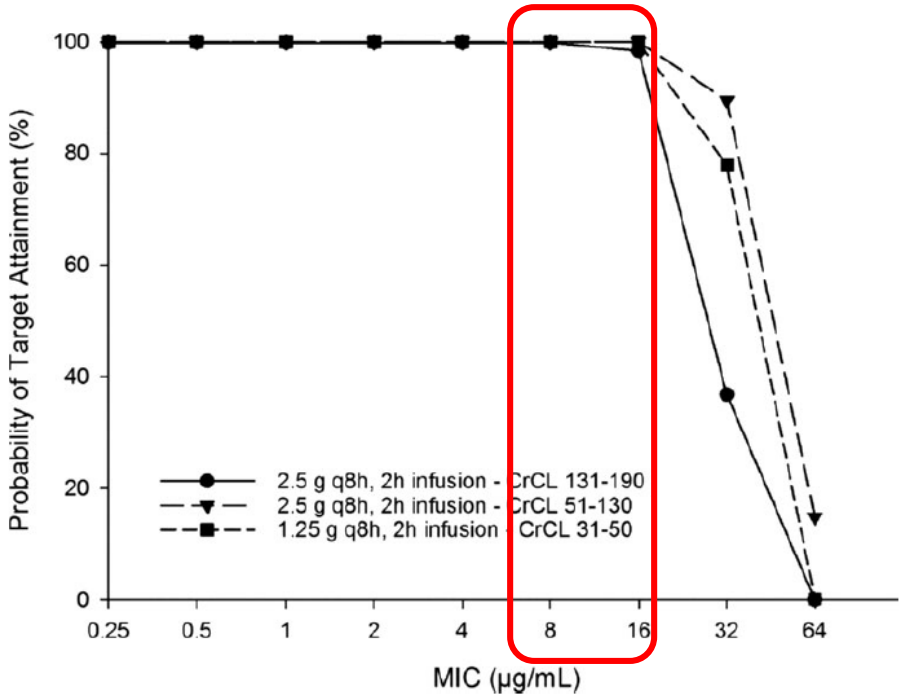
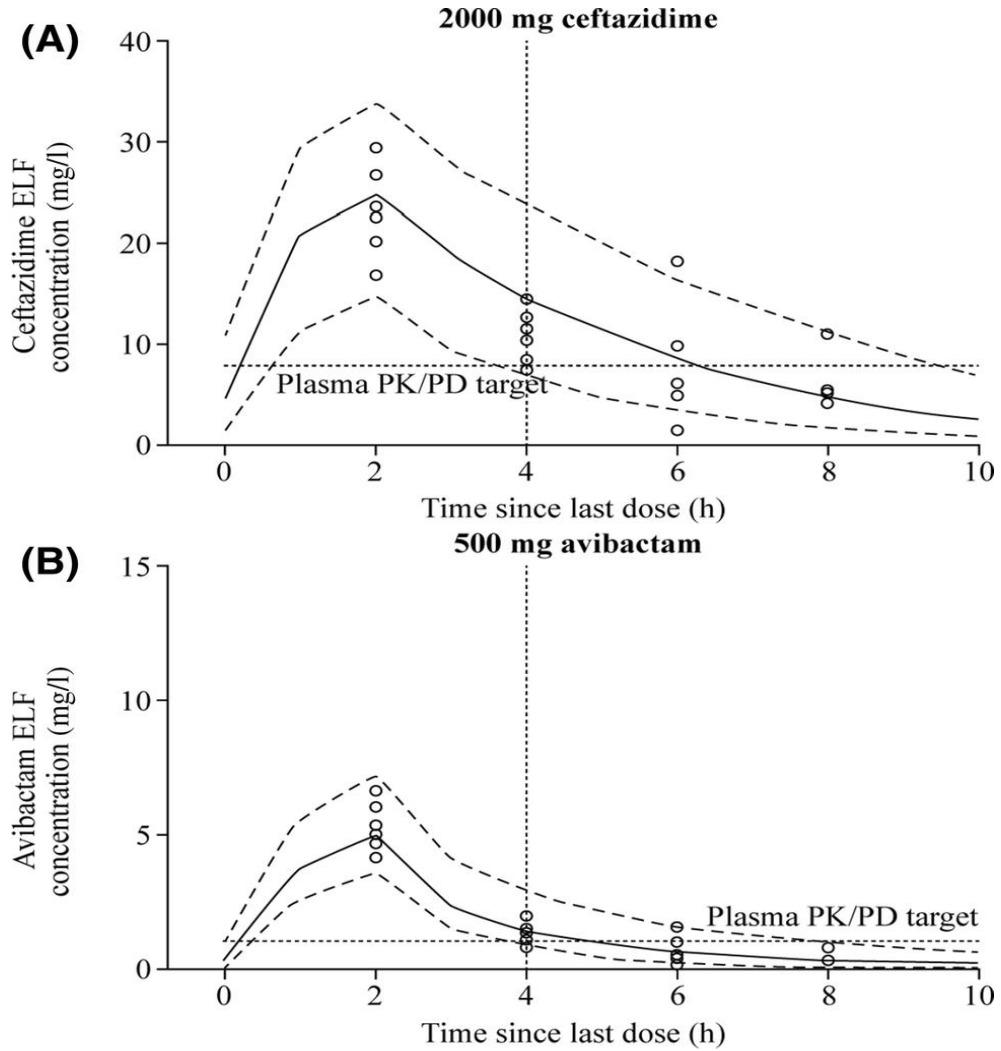


FIG. 1. Probability of target attainment (PTA) at a pharmacodynamic target of 50% $fT > MIC$ for ceftazidime and 50% $fT > 1$ mg/L for avibactam CrCL = creatinine clearance (mL/min) calculated by Cockcroft-Gault; q8h = every 8 h; MIC = minimum inhibitory concentration.

ARC, augmented renal clearance; CL, clearance; ICU, intensive care unit; MIC, minimum inhibitory concentration; PTA, probability of target attainment; RF, renal function; RI, renal impairment; t1/2, half-life; Vd, volume of distribution.

Stein GE, et al. *Surg Infect*. 2019;20:55–61.

Plasma and ELF concentration–time profiles



ELF, epithelial lining fluid; SD, standard deviation.

Dimelow R. Population PK modeling. Drugs in R&D 2018

Phase III clinical trials of ceftazidime – avibactam

Seven prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3[1-2]: Adults with cIAI

Double-blind randomisation (1:1):

- CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g IV q8h *or*
- Meropenem 1 g 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[3]: Adults with cUTI (including acute pyelonephritis)

Double-blind randomisation (1:1):

- CAZ 2 g + AVI 0.5 g q8h IV *or*
- Doripenem 0.5 g + placebo q8h IV

Primary objective:

- Assess non-inferiority of CAZ-AVI on
- co-primary endpoints in mMITT analysis set:
  - Resolution of UTI-specific symptoms
  - Resolution/improvement of flank pain
  - Per-patient microbioogical eradication and symptomatic resolution

REPRISE[4] Adults with CAZ-resistant bacteria

Open-label randomisation (1:1):

- CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g 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 bacteria

REPROVE[5] Adults with HAP (including VAP)

Double-blind randomisation (1:1):

- CAZ 2 g + AVI 0.5 g q8h IV *or*
- Meropenem 1 g q8h IV

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; IV, intravenous; mMITT, microbiological modified intent-to-treat; q8h, every 8 h; TOC, test of cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

1. Mazuski JE, et al. *Clin Infect Dis*. 2016;62:1380–9; 2. ClinicalTrails.gov. NCT01726023; 3. Wagenlehner F, et al. *Clin Infect Dis.* 2016;63:754–62; 4. Carmeli Y, et al. *Lancet Infect Dis*. 2016;16:661–73; 5. Torres A, et al. *Lancet Infect Dis*. 2018;18:285–95.

Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program

Florian M. Wagenlehner,[1] Jack D. Sobel,[2] Paul Newell,[3] Jon Armstrong,[3] Xiangning Huang,[4] Gregory G. Stone,[5] Katrina Yates,[3,a] and Leanne B. Gasink[6,b]

[1]Justus-Liebig-University, Giessen, Germany; [2]Detroit Medical Center, Michigan; [3]AstraZeneca, Alderley Park, Cheshire, and [4]AstraZeneca, Cambridge, United Kingdom; [5]AstraZeneca, Waltham, Massachusetts; and [6]AstraZeneca, Wilmington, Delaware

Endpoint	Patients, No. (%)		
	Ceftazidime-Avibactam (n = 393)	Doripenem (n = 417)	Difference, % (95% CI)
FDA co-primary endpoints			
Patient-assessed symptomatic resolution[a] at day 5[b]	276 (70.2)	276 (66.2)	4.0 (–2.39 to 10.42)
Combined patient-assessed symptomatic resolution[c] and favorable per-patient microbiological response at TOC[b]	280 (71.2)	269 (64.5)	6.7 (.30 to 13.12)
Per-patient favorable microbiological response at TOC	304 (77.4)	296 (71.0)	6.4 (.33 to 12.36)
Patient-reported symptomatic resolution at TOC	332 (84.5)	360 (86.3)	–1.9 (–6.78 to 3.02)
EMA primary endpoint			
Per-patient favorable microbiological response at TOC[d]	304 (77.4)	296 (71.0)	6.4 (.33 to 12.36)

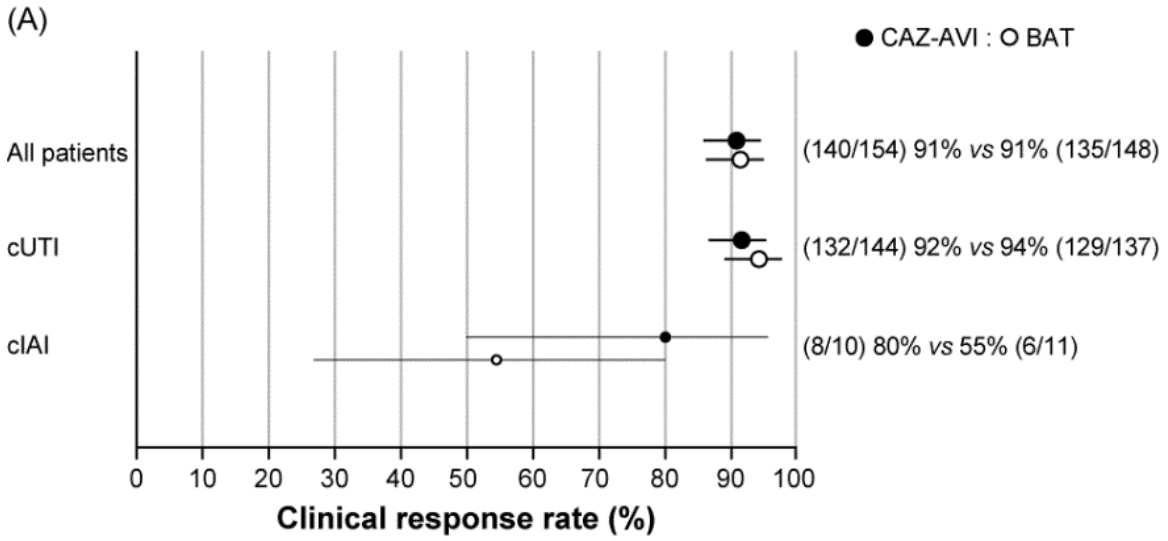
CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; TOC, test of cure.

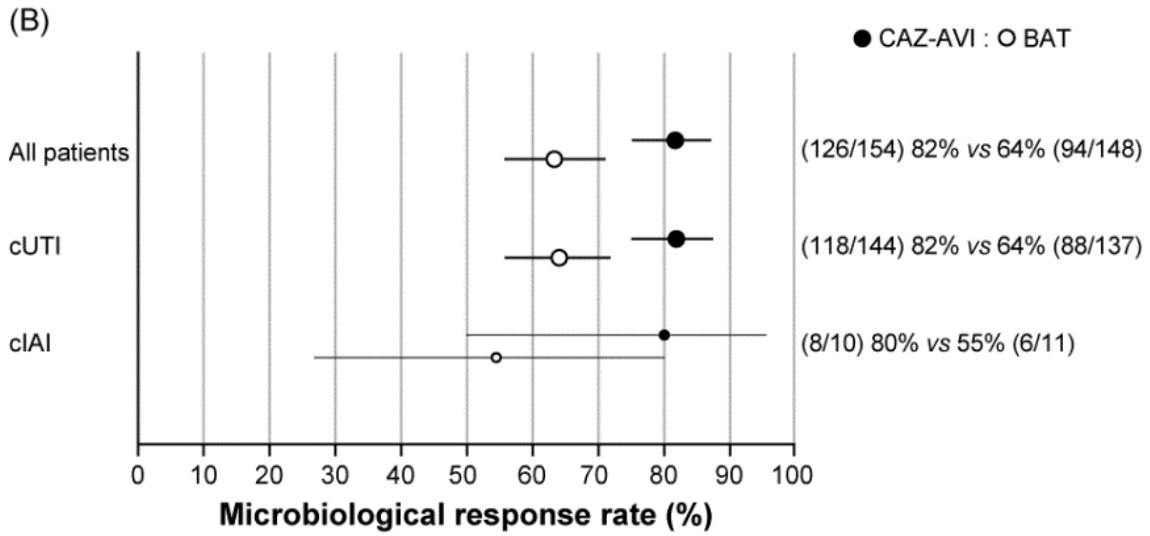
Wagenlehner F, et al. *Clin Infect Dis.* 2016;63:754–62.

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

Yehuda Carmeli, Jon Armstrong, Peter J Laud, Paul Newell, Greg Stone, Angela Wardman, Leanne B Gasink

Open-label Phase 3 study : 97% of BAT included carbapenems

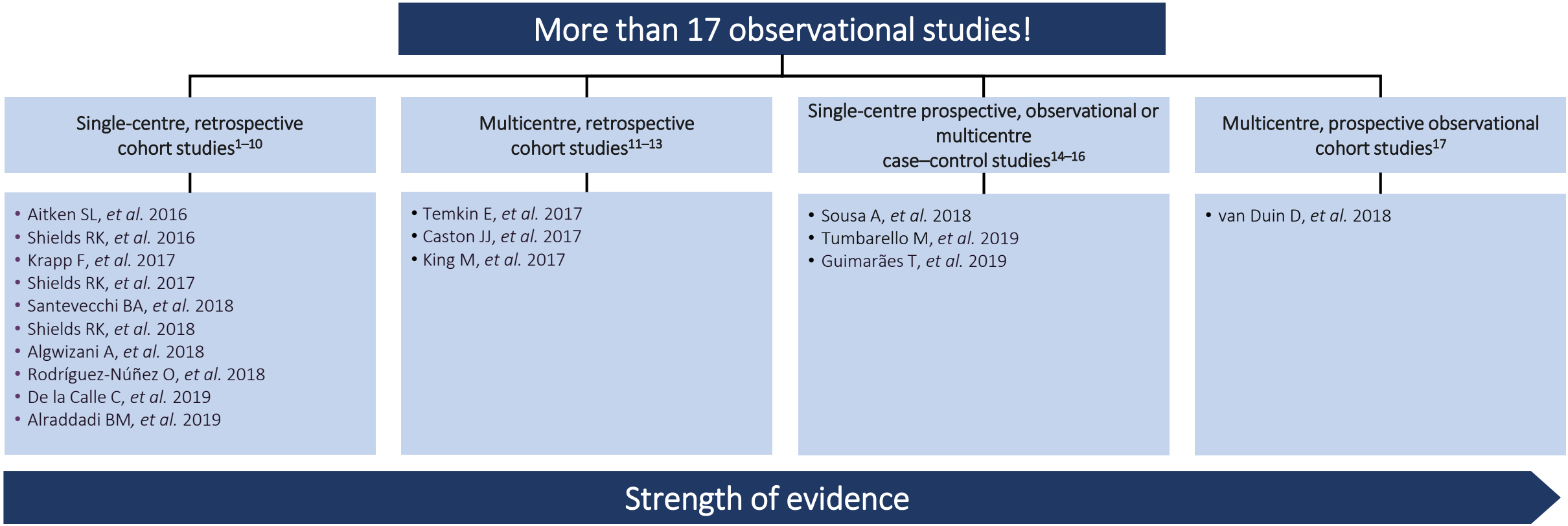




BAT, best available therapy; CAZ-R, ceftazidime-resistant; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection.

Carmeli Y, et al. *Lancet Infect Dis*. 2016;16:661–73.

Ceftazidime–avibactam: real-world data



1. Aitken SL, et al. *Clin Infect Dis* 2016;63:954–8; 2. Shields RK, et al. *Clin Infect Dis* 2016;63:1615–8; 3. Krapp F, et al. *Int J Antimicrob Agents* 2017;49:770–3;
4. Shields RK, et al. *Antimicrob Agents Chemother* 2017;61:e00883–17; 5. Santevecchi BA, et al. *Int J Antimicrob Agents* 2018;51:629–35; 6. Shields RK, et al. *Antimicrob Agents Chemother* 2018;62:e02497–18;
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17. van Duin D, et al. *Clin Infect Dis* 2018;66:163–71.

Salvage therapy with ceftazidime–avibactam

Survey of physicians who prescribed ceftazidime–avibactam for compassionate use

38 patients with multiple comorbidities included

Predominantly CRE infections caused by KPC and OXA-48

95% received antibiotics prior to ceftazidime–avibactam

TABLE 3 Characteristics of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Characteristic	Value (n = 38)[a]
Demographic characteristics	
Age in yr, median (IQR[b])	61 (47–67)
Male sex	25 (65.8)
Location before hospitalization	
Home	33 (86.8)
Transferred from another hospital	5 (13.2)
Comorbidities	
Transplant recipient	5 (13.2)
Diabetes mellitus	8 (21.1)
Immunosuppression[c]	10 (26.3)
Renal disease	7 (18.4)
Cardiovascular disease	11 (28.9)
McCabe score of >1	19 (50.0)
Infection characteristics	
Organism and carbapenemase	
Klebsiella pneumoniae	
KPC	22
OXA-48	12
Klebsiella oxytoca (KPC)	1
Escherichia coli (OXA-48)	1
Pseudomonas aeruginosa	2
Hospital-acquired infection	34 (89.5)
Bacteremia	26 (68.4)
Polymicrobial infection	11 (29.0)
Life-threatening infection (high risk of death within 30 days)	23 (60.5)
Antibiotics before CAZ-AVI	
Received antibiotics before CAZ-AVI for this infection	36 (94.7)
Days of antibiotic treatment before CAZ-AVI, median (IQR)	13 (7–31)
No. of antibiotics before CAZ-AVI, median (IQR)	3 (3–4)

CAZ–AVI, ceftazidime–avibactam; CRE, carbapenem-resistant Enterobacteriaceae; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; OXA, oxacillinase.

Temkin E, et al. Antimicrob Agents Chemother 2017;61(2):e01964.

Salvage therapy with ceftazidime–avibactam

74% of patients with clinical and/or microbiologic cure[1]

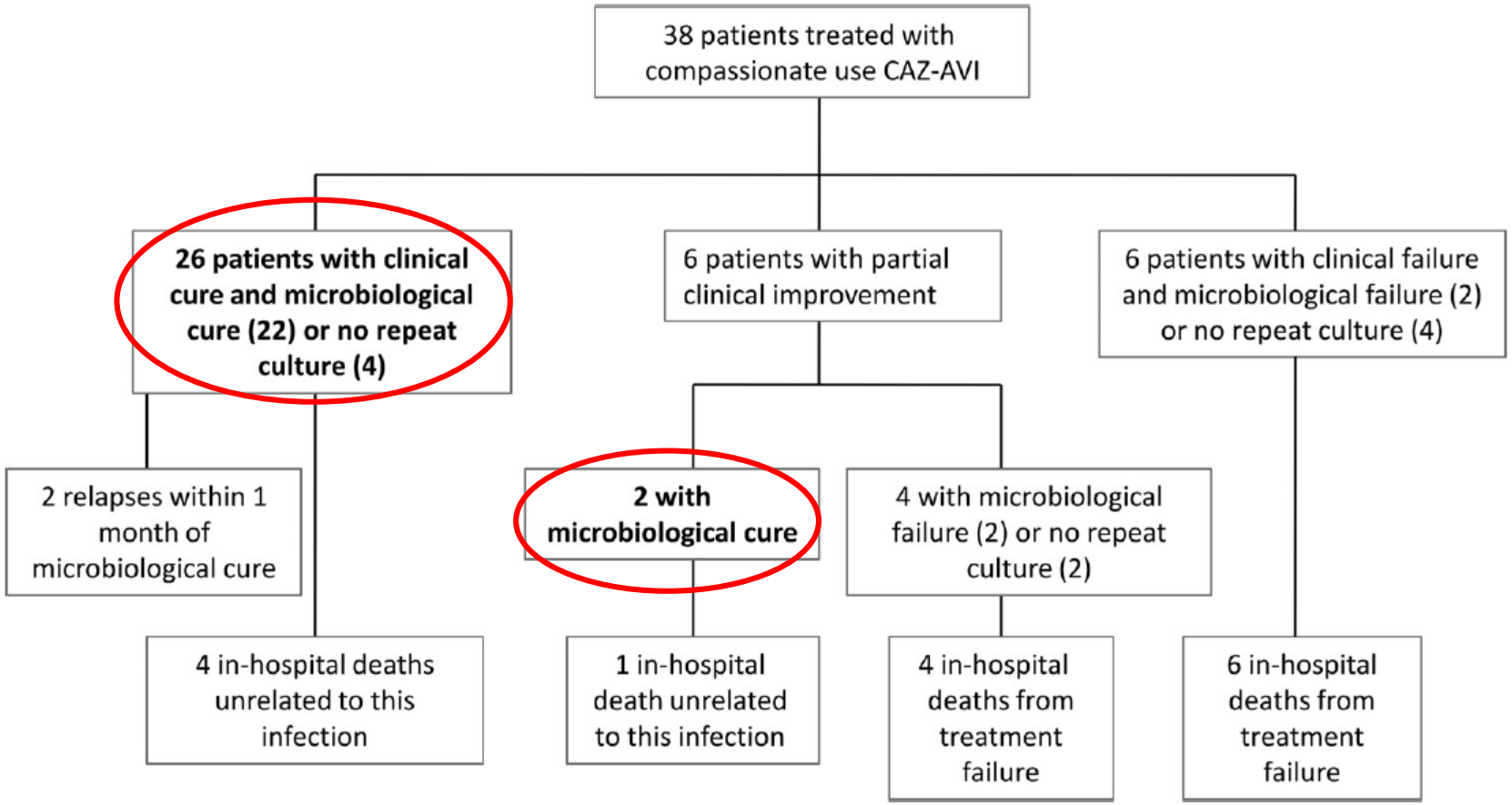


FIG 1 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI.

CAZ–AVI, ceftazidime–avibactam

Temkin E, et al. *Antimicrob Agents Chemother*. 2017;61(2). pii: e01964-16.

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

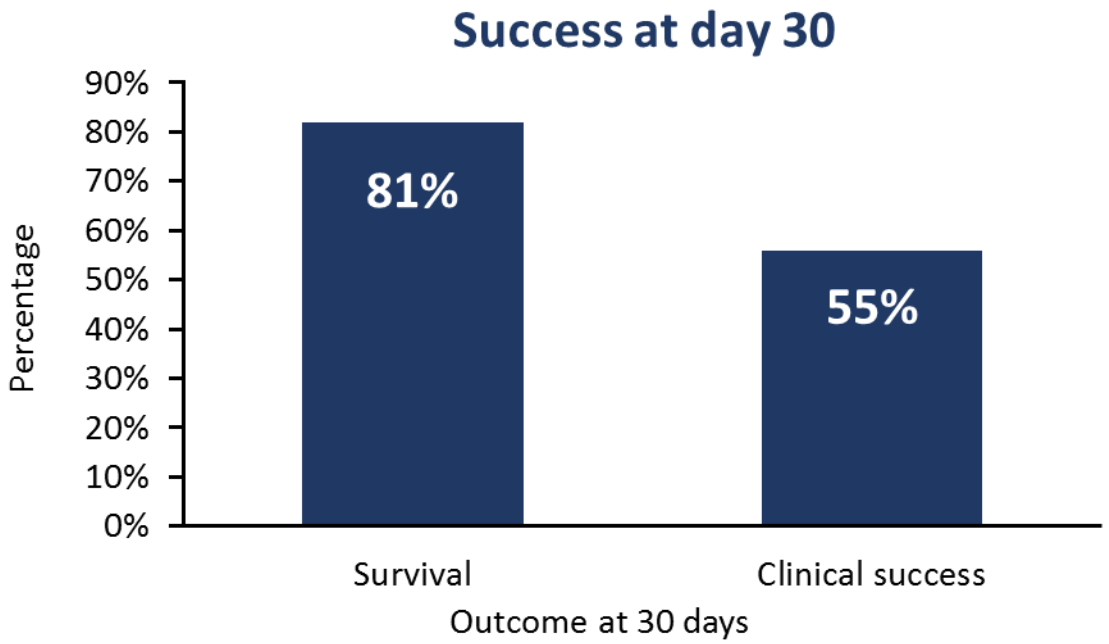
Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[6] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

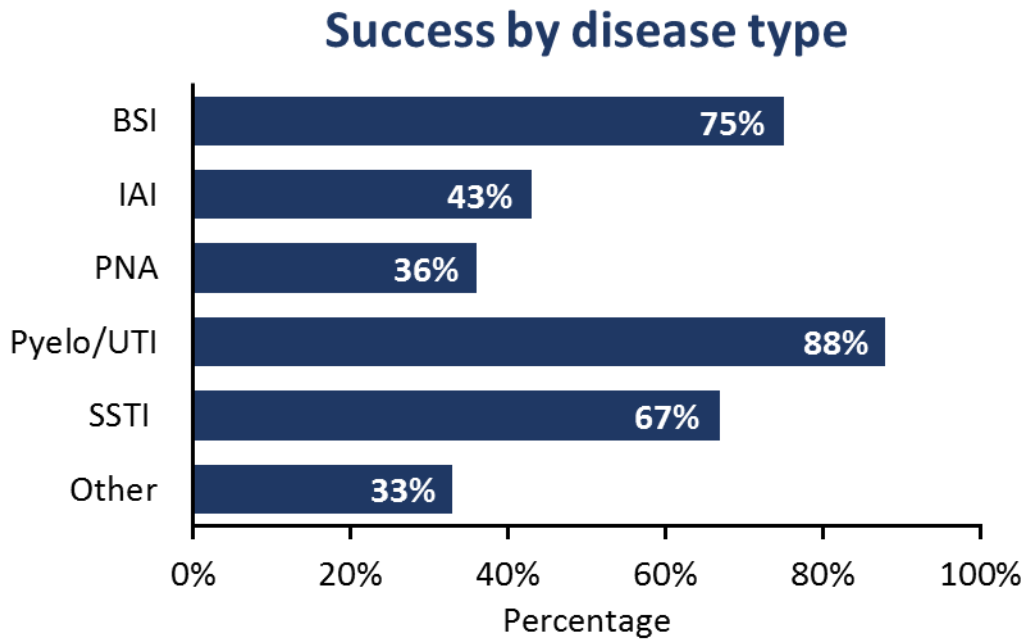
- 37 patients, median age 64 y, 30% transplant recipients
- 12 pneumonia, 10 bacteremia
- Ceftazidime/avibactam monotherapy 70%
- 30d survival 76%, 90d survival 62%
- Failure
  - Death 9, reoccurrence 4, non clinical cure 2
- Microbiology failure 27%
  - 3 patient emergence of resistance (10-19 days of treatment)

Shields R, et al. *Clin Infect Dis*. 2016;63:1615–8.

Real-world data from the USA

- 77 patients were treated with ceftazidime–avibactam for CRE infections between April 2015 and April 2017
  - 60 *K. pneumoniae*, nine *E. coli*, six *Enterobacter* spp., one *S. marcescens*, one *K. oxytoca*

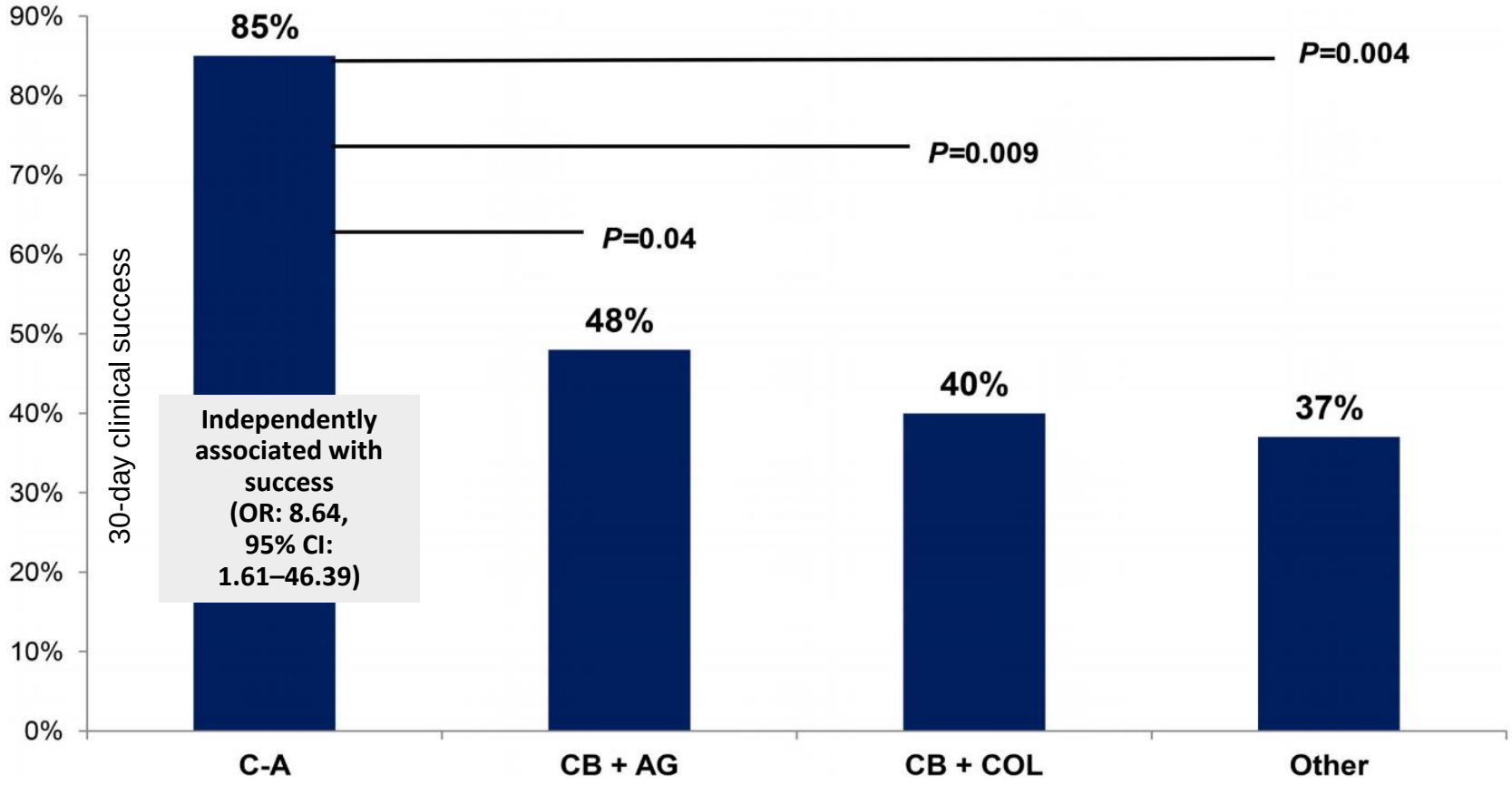




BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; IAI, intra-abdominal infection; PNA, pneumonia; Pyelo, pyelonephritis; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

Shields RK, et al. *Antimicrob Agents Chemother* 2018;62:e02497–17.

Mortality rate in KPC-producing *K. pneumoniae* bacteraemia experience with ceftazidime–avibactam

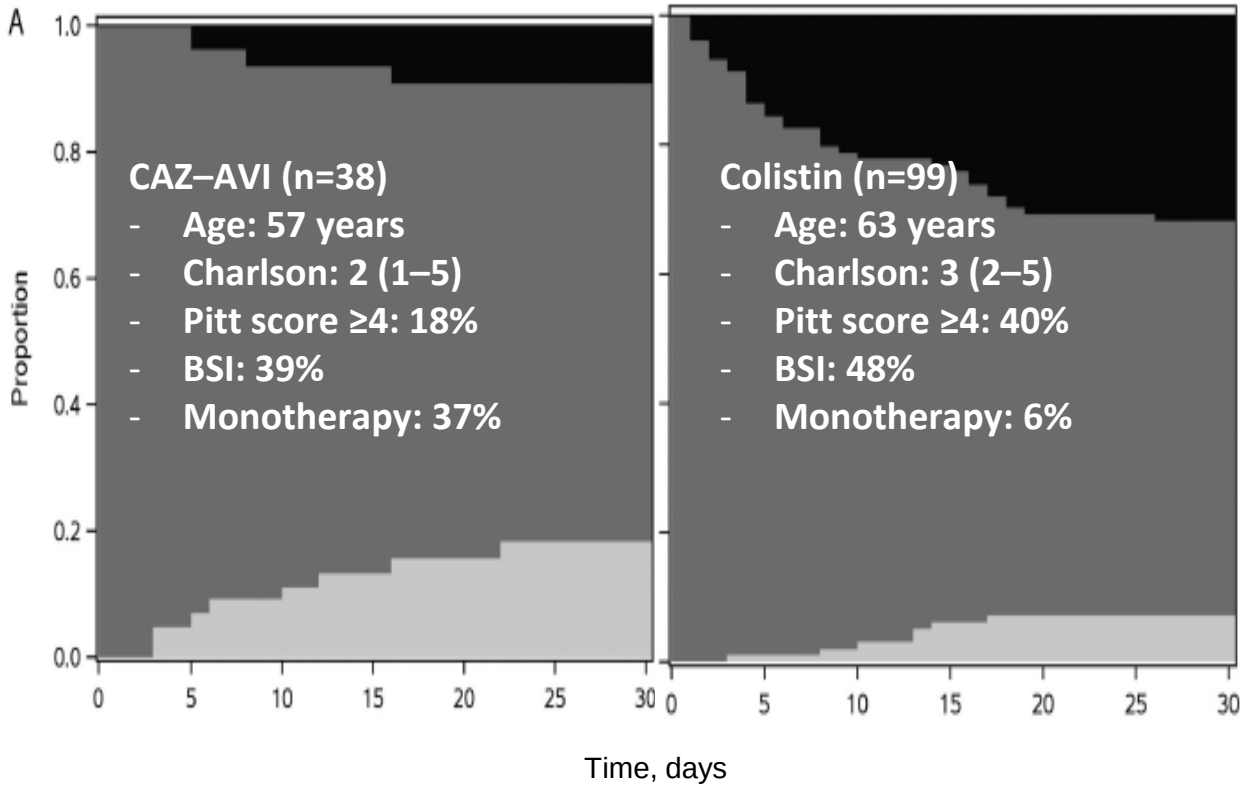


Secondary bacteremia resulted from abdominal (46%), respiratory tract (13%), urinary tract (13%).

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

Shields RK, et al. *Antimicrob Agents Chemother*. 2017;61:e00883-17.

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



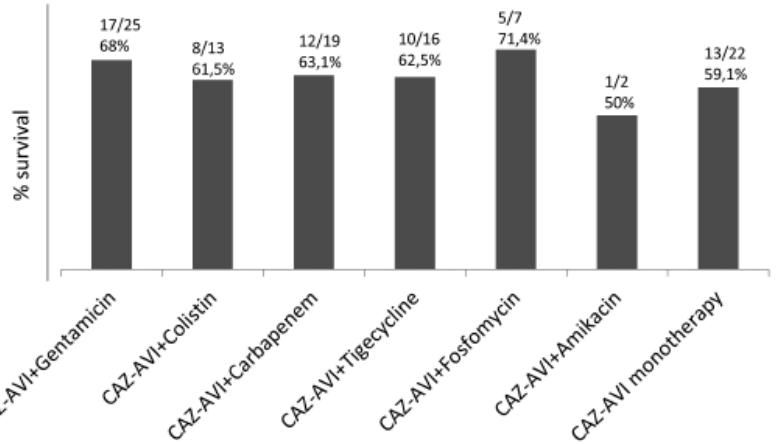
- Incident renal failure was 5% for CAZ–AVI versus 13% for colistin
- IPTW-adjusted all-cause mortality at 30 days was 9% for CAZ–AVI versus 32% for colistin
- CAZ–AVI had an IPTW-adjusted 64% probability of a better outcome versus colistin

BSI, blood stream infection; CAZ-AVI, Ceftazidime–avibactam; CI, confidence interval; IPTW, inverse probability of treatment weighting; MDR, multi-drug resistant.

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

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]



Overall 30 days survival CR-KP BSI

- 104 patients treated with CAZ-AVI 36.5%
- 104 matched patients treated with other agents 55.8%

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

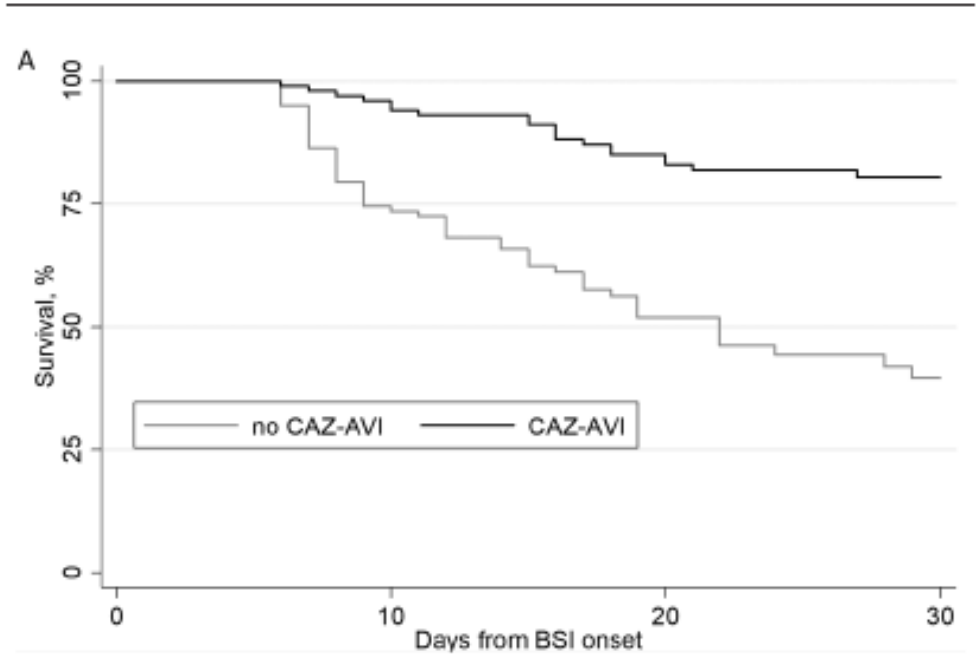
	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
Variable	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index ≥3	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia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

BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; CR-Kp, carbapenem-resistant *Klebsiella pneumoniae*; OR, odds ratio.

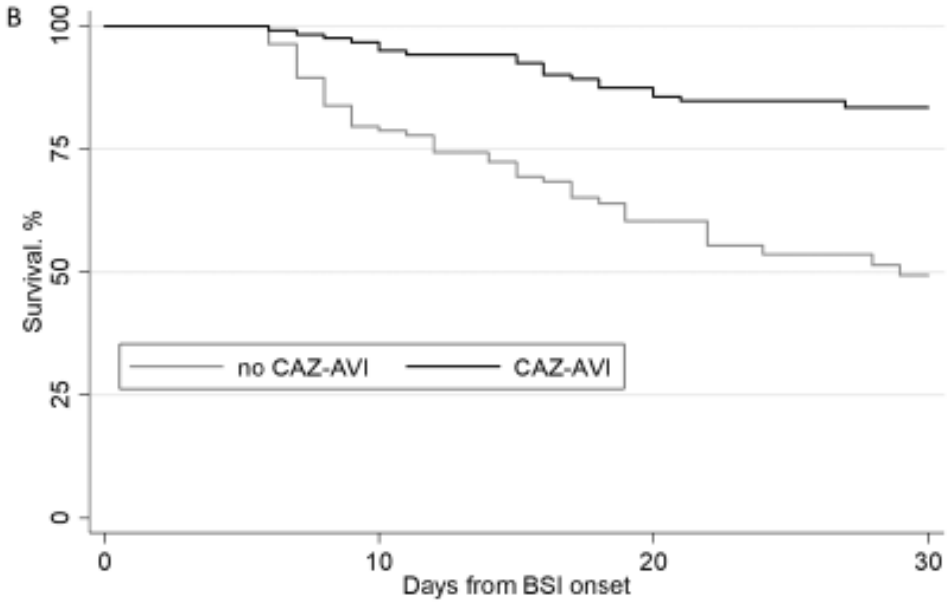
Tumbarello M, et al. *Clin Infect Dis.* 2019;68:355–64.

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

Unadjusted



Adjusted for the presence of septic shock at start of salvage regimen



BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam.

Tumbarello M, et al. *Clin Infect Dis.* 2019;68:355–64.

P2469 Impact of ceftazidime-avibactam on mortality of OXA-48-producing *Klebsiella pneumoniae* bacteraemia

Olalla Lima*[1], Adrian Sousa[1], María Teresa Pérez-Rodríguez[1,2], Rebeca Longueira[1], Patricia Diéguez[1], Milagros Suárez[1], Francisco Vasallo Vidal[1], Antonio Pérez-Landeiro[1], Manuel Crespo[1,2]

Table. Characteristics of patients analysed

	CAZ-AVI (n = 21)	Other * (n = 63)	P
Age >70 years, (%)	7 (33)	31 (49)	0.311
Sex male, n (%)	10 (48)	48 (76)	0.027
Charlson >3	10 (48)	36 (57)	0.461
Nosocomial acquisition, n (%)	18 (86)	45 (71)	0.251
Source of infection, n (%)			
- Urinary	4 (19)	30 (48)	0.023
- Catheter	9 (43)	15 (24)	0.104
- Respiratory	2 (10)	9 (14)	0.723
- Abdominal	4 (19)	4 (6)	0.103
- Unknown	2 (10)	5 (8)	1
Pitt index >2, n (%)	10 (48)	26 (41)	0.621
Increment score >11, n (%)	12 (57)	35 (56)	1
Adequate empirical therapy, n (%)	9 (43)	22 (35)	0.603
Outcome			
- Cure	20 (95)	43 (68)	0.018
- Recurrence	4 (19)	5 (8)	0.218
- 14-day mortality	1 (5)	18 (29)	0.033
- 30-day mortality	3 (14)	19 (30)	0.251

*** Other therapies: carbapenem + colistina (n=34); carbapenem + 2 active drugs (n=13); others (n=16)**

CAZ-AVI, ceftazidime-avibactam.

Lima O, et al. Abstract P2469. Presented at ECCMID 2019, Amsterdam, Netherlands.

Ceftazidime–avibactam as salvage therapy for infections due to OXA-48 CPE

- Prospectively collected cohort of adults with OXA-48 CPE infections
  - 57 patients were treated with ceftazidime–avibactam
  - The most frequent sources of infection were intra-abdominal (28%), respiratory (26%) and urinary (25%)
  - 54% patients had a severe infection (defined as presence of sepsis or septic shock)
  - 81% patients received ceftazidime–avibactam monotherapy
  - Median duration of treatment was 13 days
- 77% had clinical cure
- The emergence of resistance to ceftazidime–avibactam was not observed

Sousa A, et al. J Antimicrob Chemother. 2018 Aug 7. doi: 10.1093/jac/dky295. [Epub ahead of print].

Emergence of resistance

- Emergence of ceftazidime-avibactam resistance was noticed in one study in 10% of the patients with KPC infection.
  - Mostly transplant center, in patients with renal replacement therapy
  - Resistance due to de-novo mutations which usually result in regaining in carbapenem susceptibility
- In other studies emergence of ceftazidime-avibactam resistance is uncommon
  - Recent experience with 203 CRE patients (62 with repeated cultures) 1 case of emergence of resistance

Shields RK, et al. Antimicrob Agents Chemother 2017;61:pii: e02097-16.
Jorgenson SCJ. OFID 2019. in press.

CRE, carbapenem-resistant *Enterobacteriaceae*.

Summary

- In an era of increasing drug resistance new treatment modalities are important
- Ceftazidime/avibactam is a promising agent, proved in treatment of ceftazidime resistant GNR
- Experience with treatment of severe infections in hard to cure carbapenem-resistant *Enterobacteriaceae* is accumulating, showing 60-80% success and superiority compared to BAT
- Events of emergence of resistance in KPC-3 producers may occur occasionally primarily in transplant patient with renal replacement therapy

BAT, best available therapy; GNR, Gram-negative rods;
KPC, *Klebsiella pneumoniae* carbapenemase.