CONVEGNO ECM

Antimicrobico-resistenza: cure e ambiente #6

L'eclettismo dell'antibiotico-resistenza

7 giugno 2023

ORE 9.15-17.20

Auditorium di Sant'Apollonia
via S. Gallo, 25a - Firenze

antibiotico-resistenza: sconfiggiamola insieme!

Nuovi antibiotici per la cura di infezioni da Gram negativi MDR in oncoematologia

Mario Tumbarello

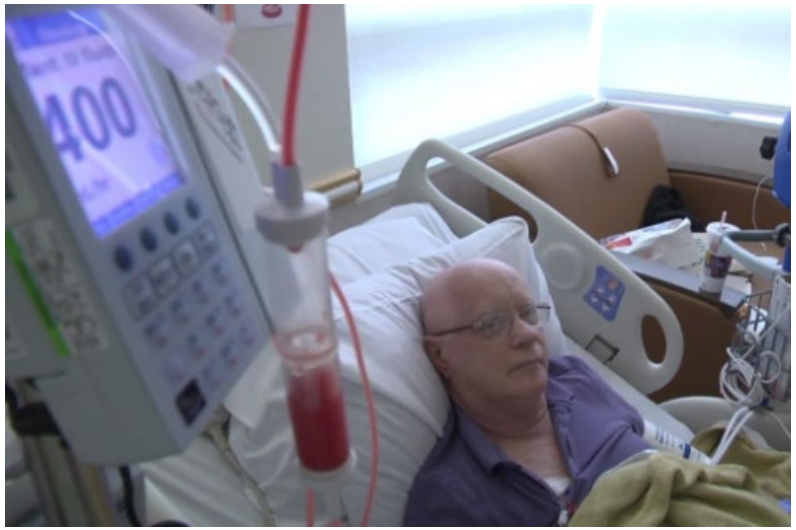
Azienda ospedaliero-universitaria Senese

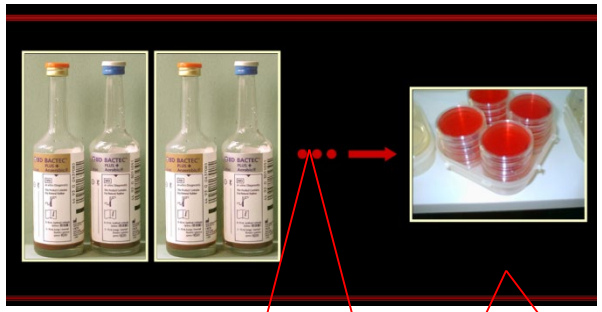
UNIVERSITÀ DI SIENA 1240

Il sottoscritto Mario Tumbarello
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario





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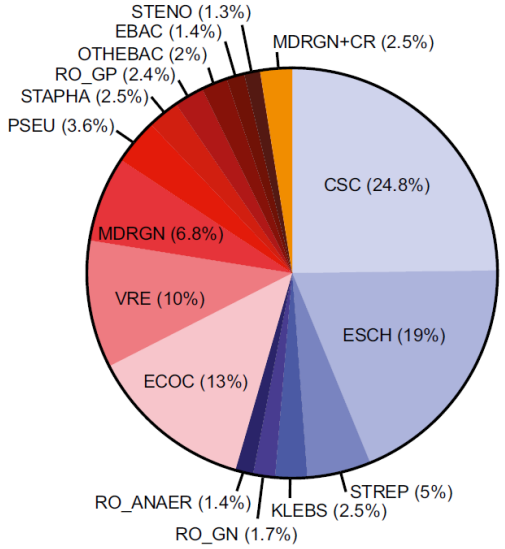
Annals of Hematology (2021) 100:1593–1602
https://doi.org/10.1007/s00277-021-04541-9

ORIGINAL ARTICLE

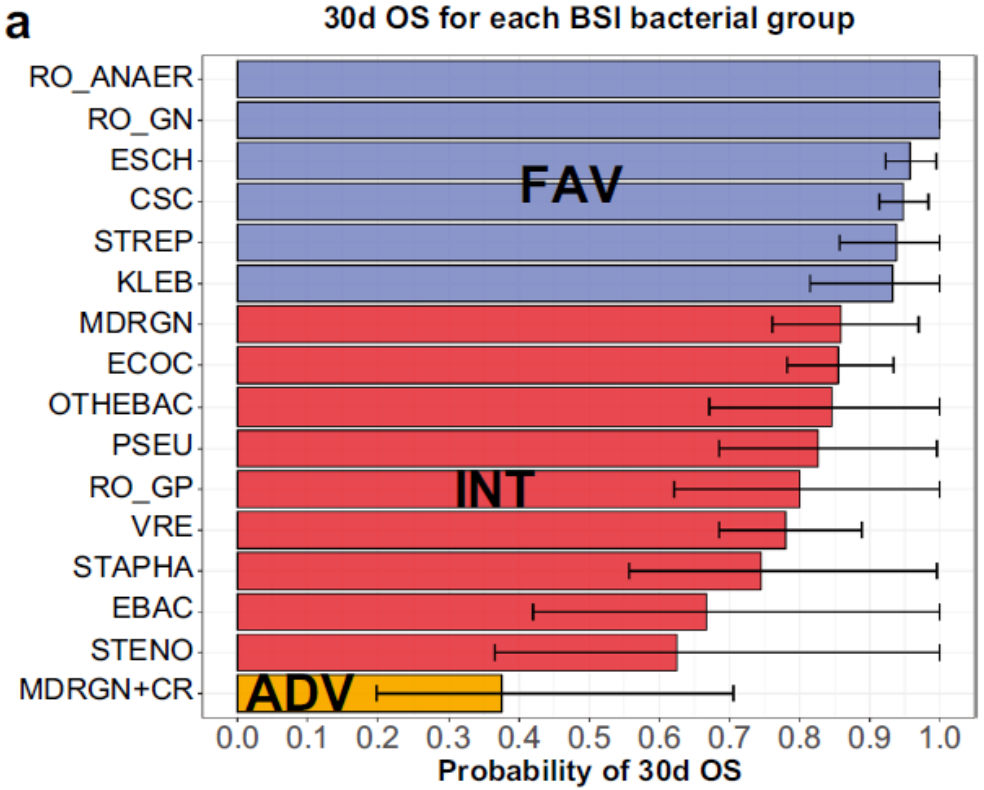
Profiling of bacterial bloodstream infections in hematological and oncological patients based on a comparative survival analysis

Sarah Weber[1,2] · Aaron Magh[1] · Michael Hogardt[2,3,4] · Volkhard A. J. Kempf[2,3,4] · Maria J. G. T. Vehreschild[2,5,6] · Hubert Serve[1,2] · Sebastian Scheich[1,2] · Björn Steffen[1,2]



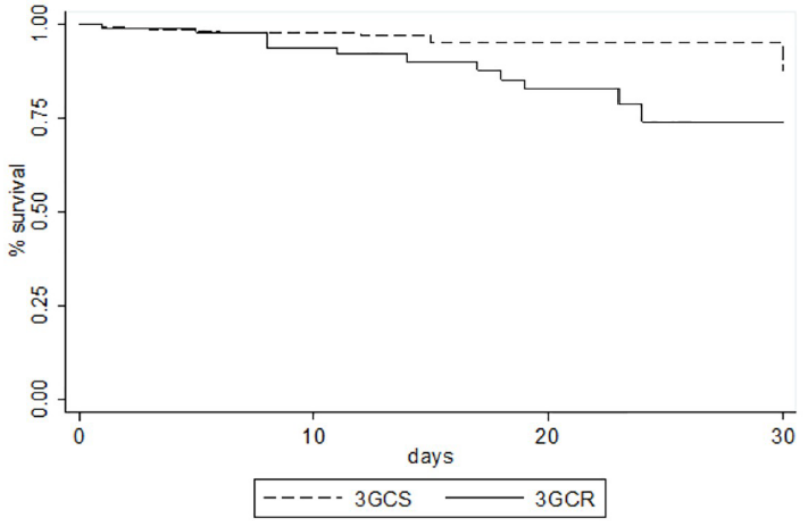
637 bacterial BSI episodes in hematological and oncological patients

Polymicrobial BSI (different organisms
on the first day of a BSI episode) and sequential BSI (another BSI before the respective BSI episode) were associated witha worse 30d OS.



Bloodstream infections caused by *Escherichia coli* in onco-haematological patients: Risk factors and mortality in an Italian prospective survey

Enrico Maria Trecarichi[1]*, Gabriele Giuliano[2], Chiara Cattaneo[3], Stelvio Ballanti[4], Marianna Criscuolo[5], Anna Candoni[6], Francesco Marchesi[7], Marica Laurino[8], Michelina Dargenio[9], Rosa Fanci[10], Mariagiovanna Cefalo[11], Mario Delia[12], Angelica Spolzino[13], Laura Maracci[14], Gianpaolo Nadali[15], Alessandro Busca[16], Maria Ilaria Del Principe[17], Rosa Daffini[3], Edoardo Simonetti[4], Giulia Dragonetti[5], Maria Elena Zannier[6], Livio Pagano[5,18☯], Mario Tumbarello[2,19☯], for the Haematologic Malignancies Associated Bloodstream Infections Surveillance (HEMABIS) registry–Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne (SEIFEM) group, Italy[¶]



15 Italian haematological wards
342 cases of EC BSI were collected during the study period.
The rate of resistance to 3GC among EC isolates was 25.7% (8

SEIFEM

Table 2. Multivariate analysis of risk factors for 3rd generation cephaloporins in patients with hematological malignancies and BSI caused by *Escherichia coli*.

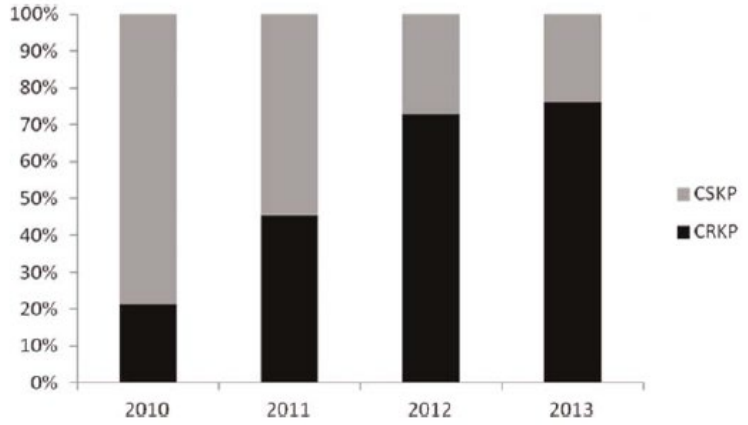
Variables	OR	(95% IC)	P values
Recent endoscopic procedures	3.68	(1.23–11.04)	0.02
MDR bacteria culture-positive surveillance rectal swabs	2.81	(1.59–4.95)	<0.001
Antibiotic prophylaxis with fluoroquinolones	1.95	(1.16–3.28)	0.01
PMN < 500/mmc for at least 10 days	1.82	(1.08–3.06)	0.02

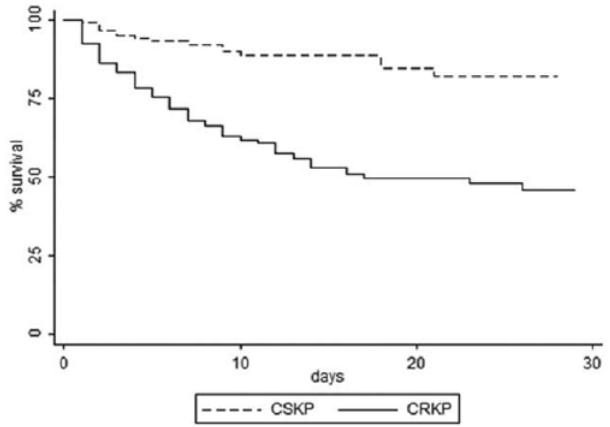
PLOS ONE | https://doi.org/10.1371/journal.pone.0224465 October 29, 2019

AJH

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

American Journal of Hematology, 2016

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Bloodstream infections due to Gram-negative bacteria in patients with hematologic malignancies: updated epidemiology and risk factors for multidrug-resistant strains in an Italian perspective survey

E.M. Trecarichi, G. Giuliano, C. Cattaneo et al.

International Journal of Antimicrobial Agents 61 (2023) 106806

811 BSI episodes.
There was a shift to a reduced use of fluoroquinolone prophylaxis and increased rates of susceptibility to fluoroquinolones in almost all isolates and to almost all antibiotics tested among P. aeruginosa isolates, compared to our previous survey.

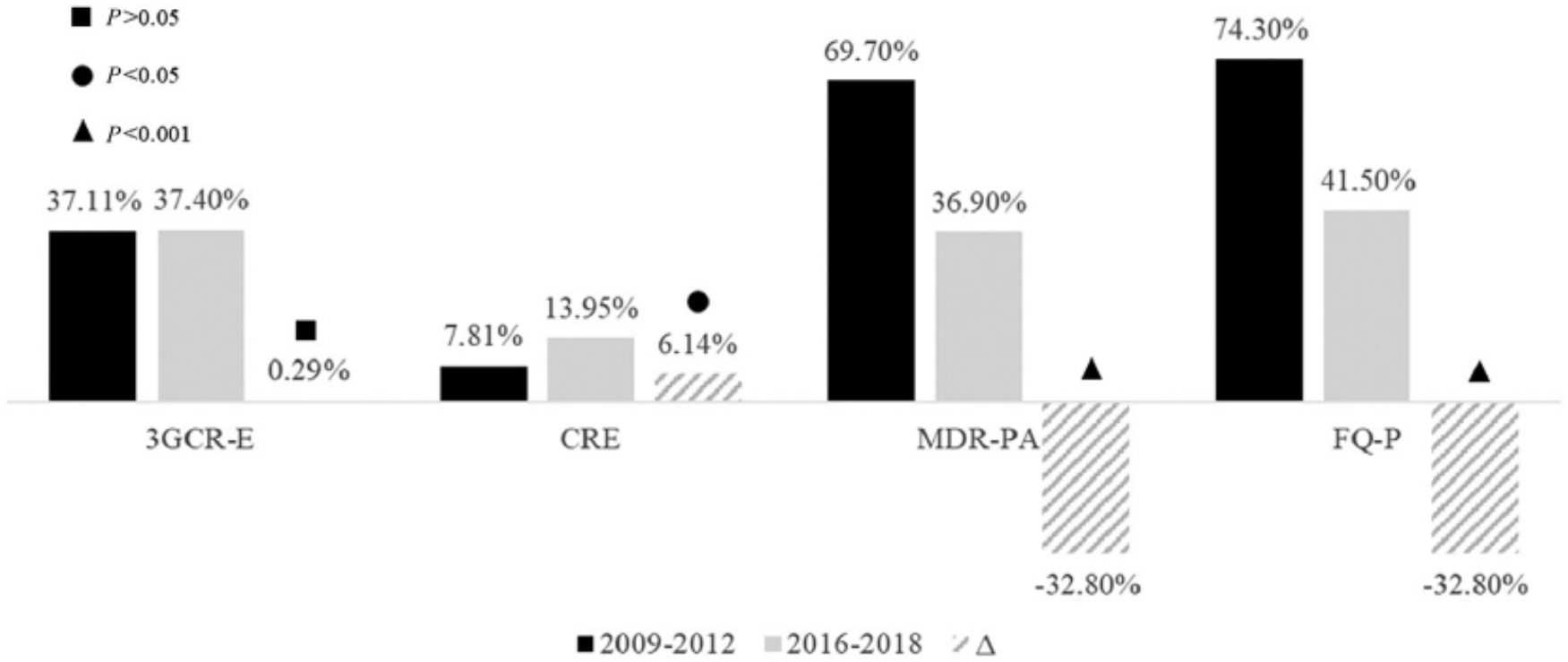


Figure 1. Correlation between percentages of third-generation cephalosporin-resistant Enterobacterales (3GCR-E), carbapenem-resistant Enterobacterales (CRE), MDR *P. aeruginosa* (MDR-PA) isolates and fluoroquinolone prophylaxis (FQ-P) during 2009-2012 [9] and 2016-2018 and their percentage differences (Δ).

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections

Yohei Doi[1,2]

Table 1. Activity and Indications of New Agents Against Carbapenem-resistant Gram-negative Pathogens

	Activity							
	Enterobacteriaceae							
Agent	Class A Carbapenemase (eg, KPC)	Class B Carbapenemase (eg, NDM)	Class D Carbapenemase (eg, OXA-48)	*P. aeruginosa*	*A. baumannii*	*S. maltophilia*	Indications (Including Expected)	Pathogen-directed Trial (Including Expected)
Ceftazidime-avibactam	Yes	No	Yes	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	No
Ceftolozane-tazobactam	No	No	No	Yes	No	No	cUTI/AP, cIAI, NP	No
Meropenem-vaborbactam	Yes	No	No	No[a]	No	No	cUTI/AP	Yes
Imipenem-cilastatin-relebactam	Yes	No	No	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	Yes
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	cUTI/AP, HABP/VABP	Yes
Plazomicin	Yes	Variable[b]	Yes	Variable	No	No	cUTI/AP	Yes
Eravacycline	Yes	Yes	Yes	No	Yes	Yes	cIAI	No
Fosfomycin	Yes	Yes	Yes	Variable	No	No	cUTI/AP	No

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study

Benjamin Miller,[a] Myra W. Popejoy,[b] Ellie Hershberger,[b] Judith N. Steenbergen,[b] John Alverdy[c]

- **Clinical cure in the microbiologically evaluable population was 100% for ceftolozane/tazobactam plus metronidazole and 93.1% for meropenem.**
- **These findings support the use of ceftolozane/tazobactam in the management of cIAI when *Psa* is suspected or confirmed.**

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

Lancet 2015; 385: 1949–56

levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis.

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

www.thelancet.com/infection Published online September 25, 2019 https://doi.org/10.1016/S1473-3099(19)30403-7

- **Patients received either 3 g ceftolozane–tazobactam or 1 g meropenem as 1-h intravenous infusions every 8 h for 8–14 days.**

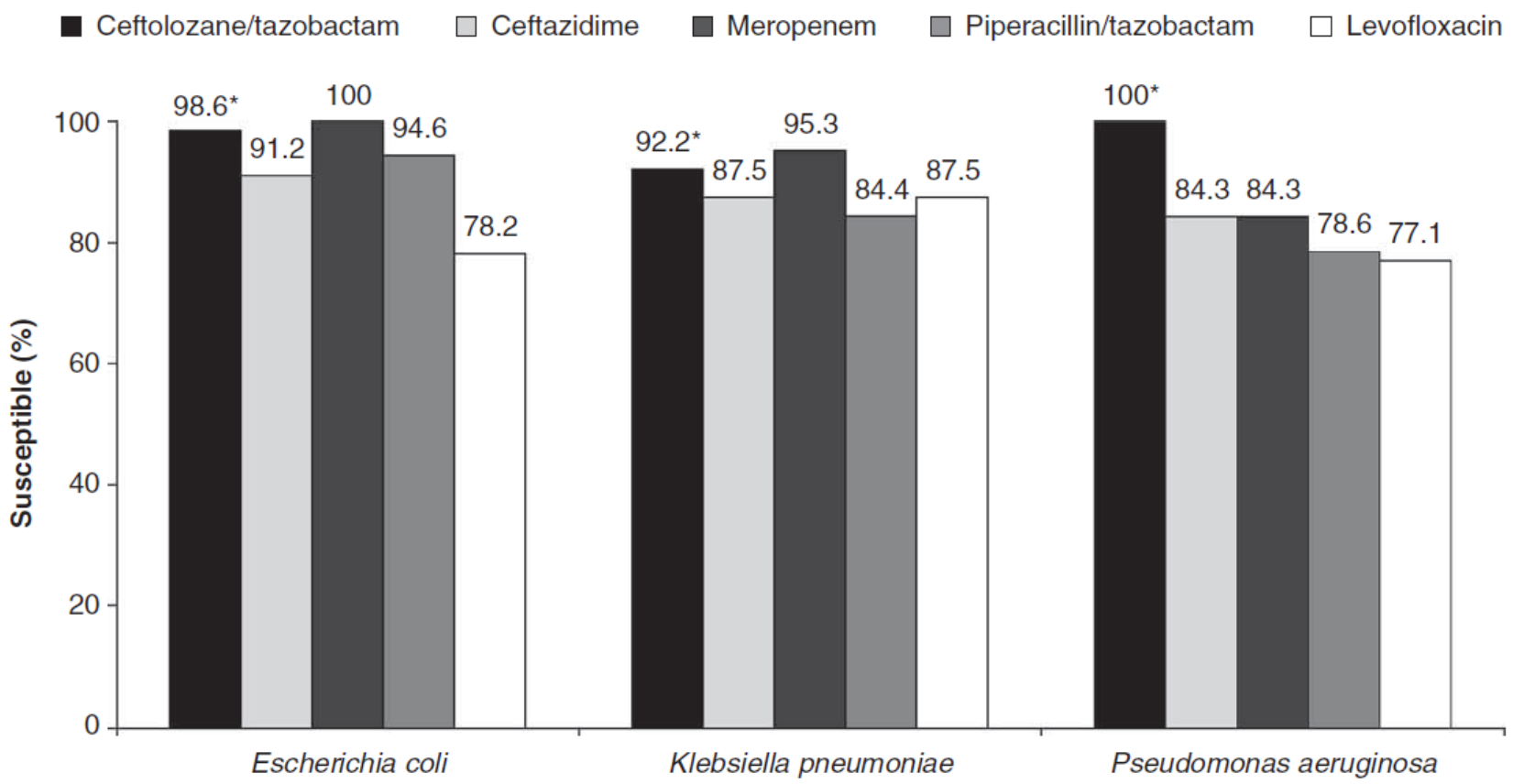
	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)	3·5 (–5·1 to 12·1)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)	4·8 (–5·1 to 14·5)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)	–4·5 (–19·3 to 10·7)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	–2·9 (–19·4 to 13·8)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)	–0·4 (–31·2 to 31·7)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)	0·0 (–43·6 to 40·3)

Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

Table 3: Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population

- **High-dose ceftolozane–tazobactam is an efficacious and well tolerated treatment for Gram-negative nosocomial pneumonia in mechanically ventilated patients, a high-risk, critically ill population.**

In vitro activity of ceftolozane/tazobactam versus comparator agents in Gram-negative isolates causing cIAI



International Journal of Antimicrobial Agents 53 (2019) 408–415

Contents lists available at ScienceDirect

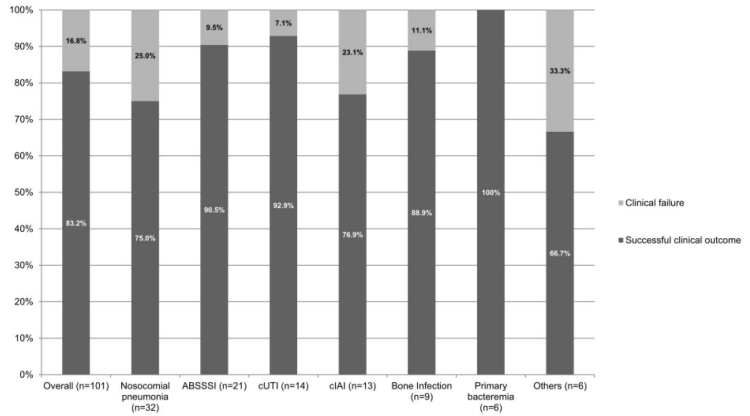
International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Ceftolozane/tazobactam for the treatment of serious *Pseudomonas aeruginosa* infections: a multicentre nationwide clinical experience

Matteo Bassetti[a,*], Nadia Castaldo[a], Annamaria Cattelan[b], Cristina Mussini[c], Elda Righi[a], Carlo Tascini[d], Francesco Menichetti[e], Claudio Maria Mastroianni[f], Mario Tumbarello[g], Paolo Grossi[h], Stefania Artioli[i], Novella Carannante[d], Ludovica Cipriani[b], Davide Coletto[b], Alessandro Russo[a], Margherita Digaetano[c], Angela Raffaella Losito[g], Maddalena Peghin[a], Alessandro Capone[j], Stefano Nicolè[b], Antonio Vena[a,k,*], for the CEFTABUSE Study Group

101 patients with diverse infections caused by *P. aeruginosa*



- **Almost half of *P.aeruginosa* strains were XDR (51%), with 78% of the isolates resistant to at least one carbapenem.**
- **Concomitant antibiotics was reported in 35% of patients.**
- **The overall clinical success was 83.2%.**
- **No differences in the clinical success rate with respect to the type of C/T treatment: monotherapy versus combination therapy or primary versus second or later line therapy.**

Open Forum Infectious Diseases

MAJOR ARTICLE

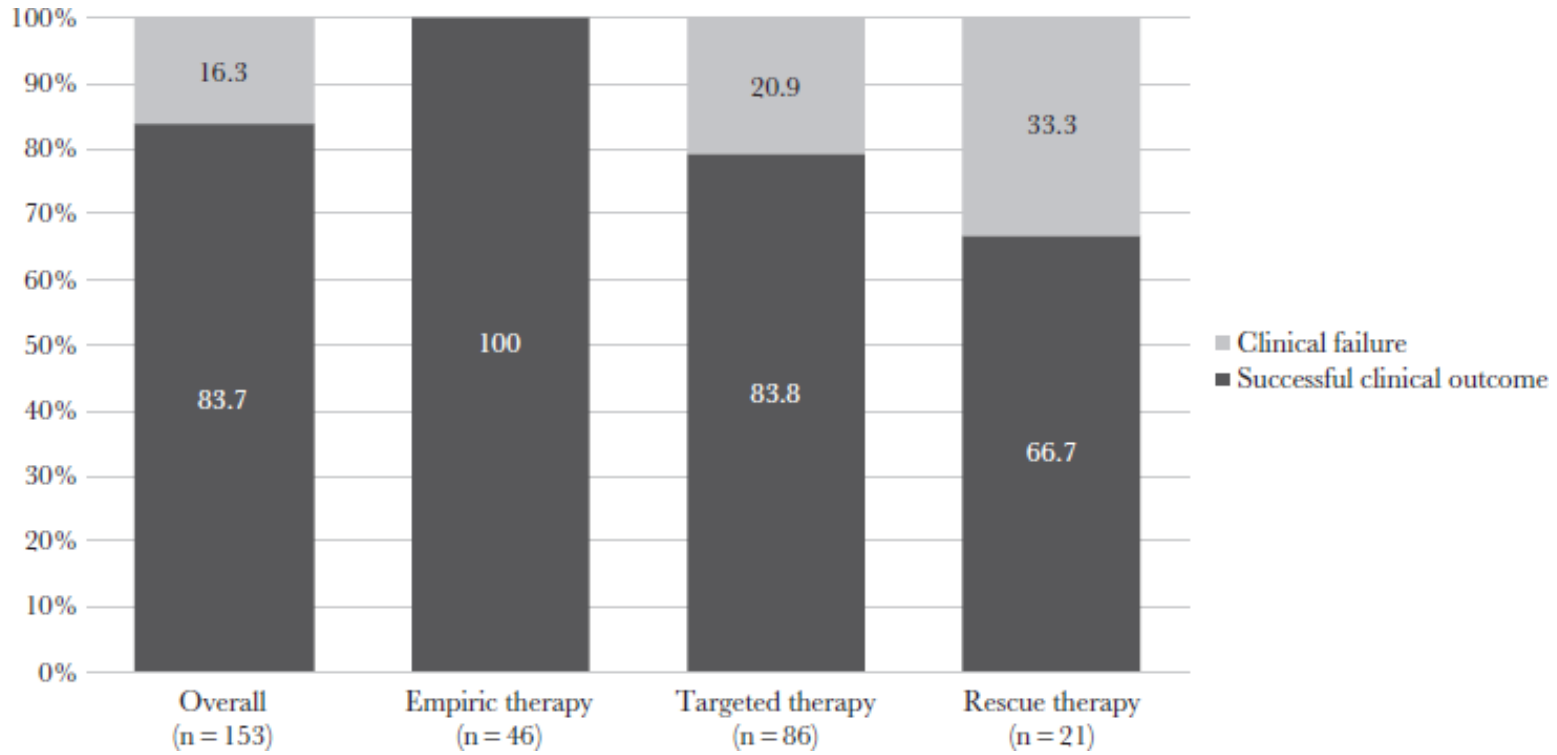
Ceftolozane/Tazobactam for Treatment of Severe ESBL-Producing *Enterobacterales* Infections: A Multicenter Nationwide Clinical Experience (CEFTABUSE II Study)

Matteo Bassetti,[1] Antonio Vena,[1] Daniele Roberto Giacobbe,[1] Marco Falcone,[2] Giusy Tiseo,[2] Maddalena Giannella,[3] Renato Pascale,[3] Marianna Meschiari,[4] Margherita Digaetano,[4] Alessandra Oliva,[5,6,©] Cristina Rovelli,[7] Novella Carannante,[8] Angela Raffaella Losito,[9] Sergio Carbonara,[10] Michele Fabiano Mariani,[10] Antonio Mastroianni,[11] Gioacchino Angarano,[10] Mario Tumbarello,[12] Carlo Tascini,[8] Paolo Grossi,[7] Claudio Maria Mastroianni,[5] Cristina Mussini,[4] Pierluigi Viale,[3] Francesco Menichetti,[2] Claudio Viscoli,[1] and Alessandro Russo[2]; for the CEFTABUSE Study Group

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

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

- 153 patients; the most common diagnosis was pneumonia (n=46, 30%), followed by complicated urinary tract infections (n=34, 22%)



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

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

Open Forum Infectious Diseases
MAJOR ARTICLE March 2021.

A Multicenter Evaluation of Ceftolozane/Tazobactam Treatment Outcomes in Immunocompromised Patients With Multidrug-Resistant *Pseudomonas aeruginosa* Infections

Delaney E. Hart,[1] Jason C. Gallagher,[2] Laura A. Puzniak,[3] and Elizabeth B. Hirsch[1]; for the C/T Alliance to deliver Real-world Evidence (CARE)

69 immunocompromised patients treated with C/T for MDR *P. aeruginosa*,
clinical cure was achieved in 68%
and mortality was 19%,

Table 2. Clinical Outcomes

Outcome	
Clinical cure, all infection sources (n = 69), No. (%)	47 (68)
Pneumonia, receiving pneumonia dosing (n = 28)	21 (75)
Pneumonia, receiving nonpneumonia dosing (n = 10)	3 (30)
30-d all-cause mortality, all infection sources (n = 69), No. (%)	13 (19)
Pneumonia, receiving pneumonia dosing (n = 28)	5 (18)
Pneumonia, receiving nonpneumonia dosing (n = 10)	3 (30)
Length of C/T therapy, mean ± SD, d	13 ± 11
Length of hospital stay, median (IQR), d	38 (54)

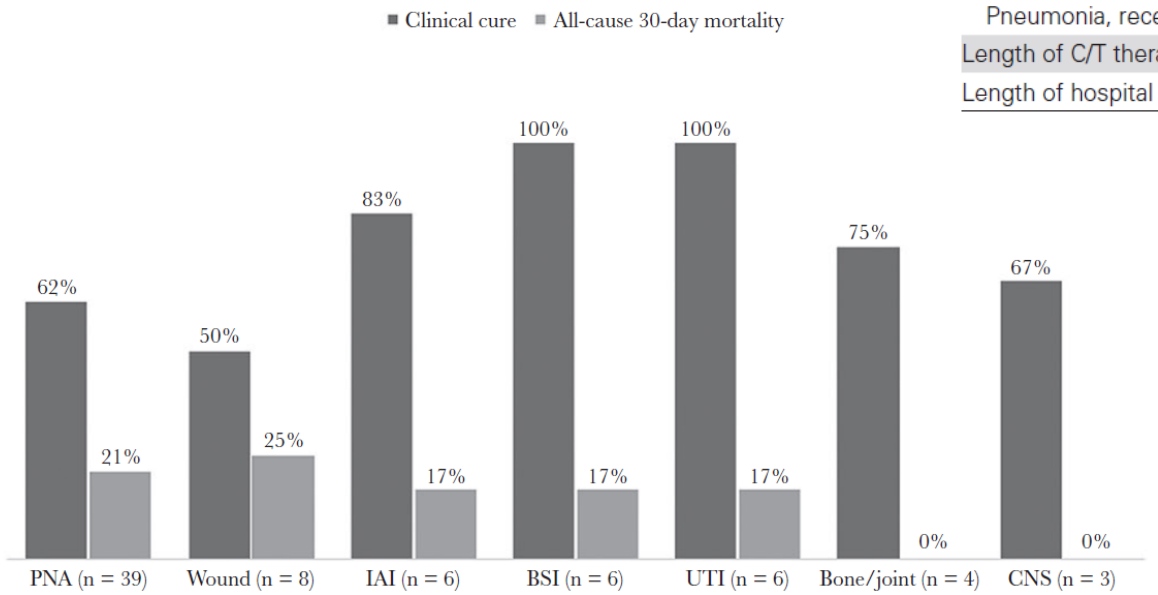


Figure 1. Clinical outcomes by source of infection. Abbreviations: BSI, primary bloodstream infection; CNS, central nervous system; IAI, intra-abdominal infection; PNA, pneumonia; UTI, urinary tract infection.

European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:1457–1461
https://doi.org/10.1007/s10096-019-03573-4

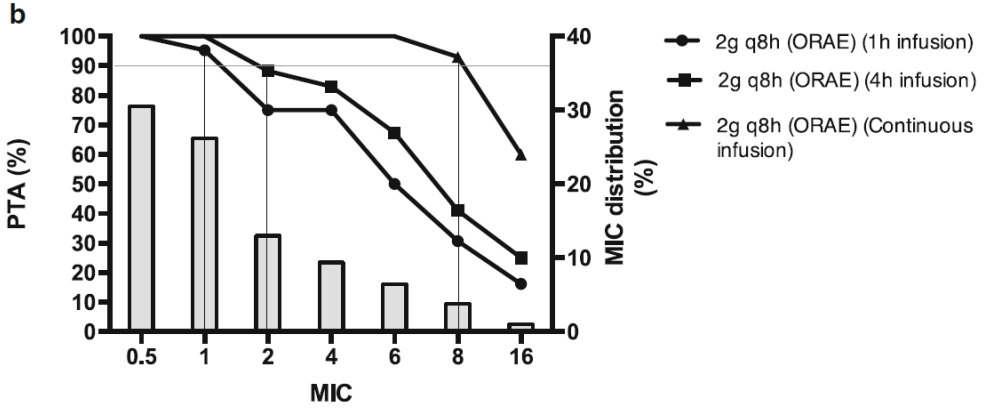
ORIGINAL ARTICLE

Continuous infusion of ceftolozane/tazobactam is associated with a higher probability of target attainment in patients infected with *Pseudomonas aeruginosa*

Benoît Pilmis[1,2] · Grégoire Petitjean[3,2] · Philippe Lesprit[4] · Matthieu Lafaurie[5] · Najoua El Helali[3,6] · Alban Le Monnier[3,2,6] · on behalf the ATB PK/PD study group

- 72 patients were enrolled, 79% were hospitalized in ICU, 51.4% were immunosuppressed
- The major site of infection was the respiratory tract (66.7%).
- In-hospital mortality rate was 15.2%.
- The PK/PD objectives (100% ƒT>4 MIC) were achieved for all patients infected with strains with CTZ/TZ MICs < 4 mg/L, regardless of the mode of administration.
- In contrast, intermittent bolus administration and prolonged infusion did not achieve the PK/PD objectives when the CTZ/TZ MICs were ≥ 4 mg/L.
- However, the PK/PD objectives (100% ƒT>4 MIC) were achieved for strains with MICs up to 8 mg/L in patients receiving continuous infusion of CTZ/TZ.

Prospective multicenter cohort study to compare prolonged or continuous infusion versus intermittent administration of CTZ/TZ for the treatment of MDR
P. aeruginosa infections



A dosing regimen of 2 g/1 g CTZ/TZ administered every 8 h as a 1-h intravenous infusion, as currently recommended, did not provided adequate coverage to achieve a sufficient probability of target
attainment for P. aeruginosa strains with MICs ≥4 mg/L.

Clinical Infectious Diseases

MAJOR ARTICLE

Clinical Infectious Diseases® 2020;

Modifiable Risk Factors for the Emergence of Ceftolozane-tazobactam Resistance

Pranita D. Tamma,[1] Stephan Beisken,[2] Yehudit Bergman,[3] Andreas E. Posch,[4] Edina Avdic,[5] Sima L. Sharara,[6] Sara E. Cosgrove,[7] and Patricia J. Simner[8]

Table 2. Comparison of 28 Patients with MDR *Pseudomonas aeruginosa* Treated with at Least 72 Hours of Ceftolozane-tazobactam (TOL-TAZ) with at Least a 4-Fold Increase in TOL-TAZ MICs on Subsequent *P. aeruginosa* Isolates Compared to Patients Who Did Not Have at Least a 4-Fold Increase in TOL-TAZ MICs on Subsequent *P. aeruginosa* Isolates

Variable	Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	No Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	*P*-value
Demographics			
Age in years (median, IQR)	56 (40–65)	56 (48–60)	.95
Female	5 (36%)	3 (21%)	.40
Weight in kilograms (median, IQR)	62 (56–79)	63 (56–76)	.87
Renal replacement therapy	4 (29%)	1 (7%)	.14
Underlying medical condition			
Cystic fibrosis	2 (14%)	1 (7%)	.54
Chronic ventilator dependence	3 (21%)	4 (29%)	.66
Burn	1 (7%)	1 (7%)	.99
Active immunosuppressive therapy	8 (57%)	5 (36%)	.26
Complex cardiovascular disease with foreign material[a]	3 (21%)	1 (7%)	.28
Site of infection			
Pneumonia	9 (64%)	10 (71%)	.69
Bacteremia	4 (29%)	1 (7%)	.14
Intra-abdominal infection	1 (7%)	3 (21%)	.28
Treatment data			
3 grams IV every 8 hours of TOL-TAZ	12 (86%)	14 (100%)	.14
1.5 grams IV every 8 hours of TOL-TAZ	2 (14%)	0	.14
1-hour TOL-TAZ infusion	14 (100%)	10 (71%)	.04
3-hour TOL-TAZ infusion	0	4 (29%)	.04
Duration of TOL-TAZ therapy	15 (8–22)	8.5 (6–14)	.32
Combination therapy for > 48 hours	6 (43%)	4 (29%)	.43
No source control[a]	4 (29%)	0	.04

Our results forewarn of the potential emergence of TOL-TAZ resistance during therapy and suggest extending TOL-TAZ infusions may be protective

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

Real-Life Use of Ceftolozane/Tazobactam for the Treatment of Bloodstream Infection Due to *Pseudomonas aeruginosa* in Neutropenic Hematologic Patients: a Matched Control Study (ZENITH Study)

May/June 2022 Volume 10 Issue 3

- **Objective:** to assess the characteristics and outcomes of neutropenic hematologic patients with *Pseudomonas aeruginosa* bloodstream infection (BSI) treated with ceftolozane/tazobactam (C/T)

- **Study Design:** multicenter, international, case-control study of episodes of *P. aeruginosa* BSI in neutropenic hematologic patients who received C/T as empirical and/or definitive treatment from 2016-2020
  - Controls were patients with *P. aeruginosa* BSI treated with other antibiotics, matched according to closest BSI date, underlying disease, polymicrobial etiology, and antibiotic susceptibility profile

- **Primary Outcome:** overall 30-day mortality

Results

Baseline Characteristics

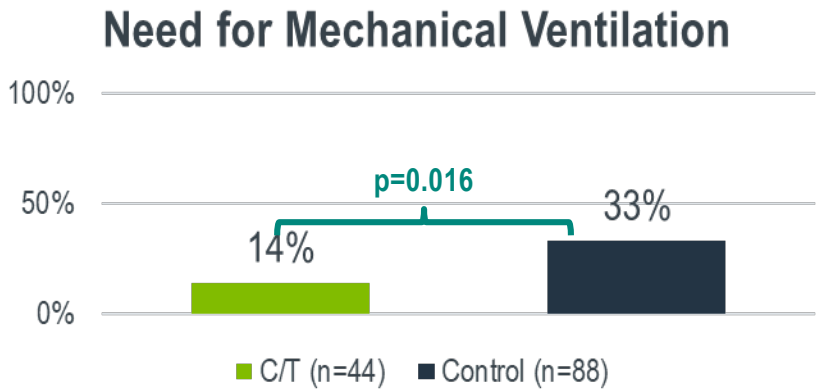
Patient Characteristics

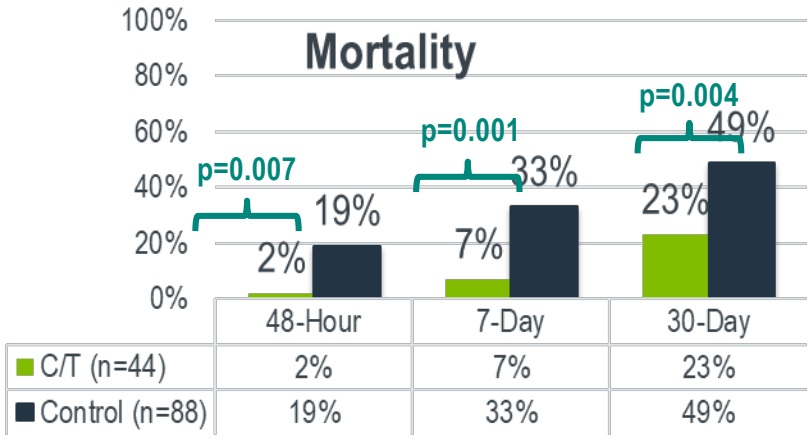
- No significant differences between groups: Cases (n=44) vs. Controls (n=88)
- **Most common underlying disease:** acute myeloid leukemia (AML), 49%
- **37%** of patients were **allogeneic** hematopoietic stem cell transplant recipients
- **64%** of patients had **profound neutropenia** (defined as <0.1 × 10^9/L, equivalent to ANC <100/uL)

Infection Characteristics

- **91%** of all episodes caused by **multidrug-resistant (MDR)** strains
- **Origin of infection:** endogenous (32%), pneumonia (26%)
- **32%** of patients presented with **septic shock**

Results
Primary Endpoint





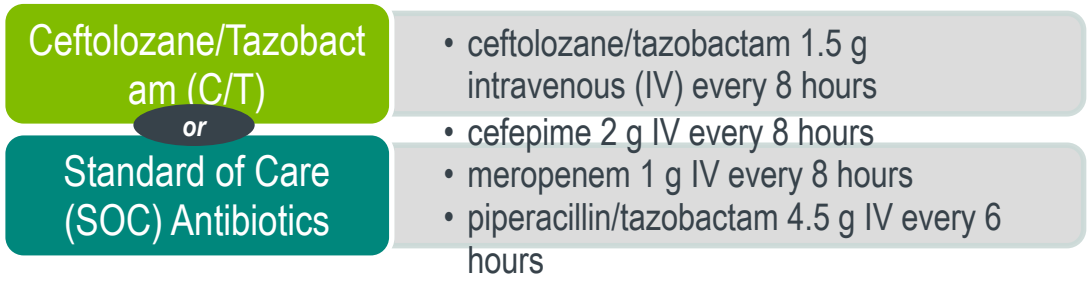
Results:

- **Lower mortality found among patients treated with C/T (aOR 0.19; IC95% 0.07-0.55; p=0.002)**
- Numerically fewer cases developed nephrotoxicity (18% vs. 33%; p=0.082)
- Independent risk factors for 30-day mortality:
  - Pneumonia
  - Profound neutropenia
  - Persistent BSI

A Prospective Randomized Study Comparing Ceftolozane/Tazobactam to Standard of Care in the Management of Neutropenia and Fever in Patients with Hematological Malignancies

Chaftari A, et al. *Open Forum Infect Dis.* 14 February 2022; ofac079, https://doi.org/10.1093/ofid/ofac079.

- **Study Design:** This is a single-center, prospective, randomized, open-label comparative study conducted from May 2018 to October 2020 in 100 patients randomized to receive either:



  - Eligible patients were age ≥18 years, had hematologic malignancies (HM), presented to the emergency center with febrile neutropenia, and required hospitalization for intravenous (IV) empiric antibiotic therapy

Results
Treatment Characteristics

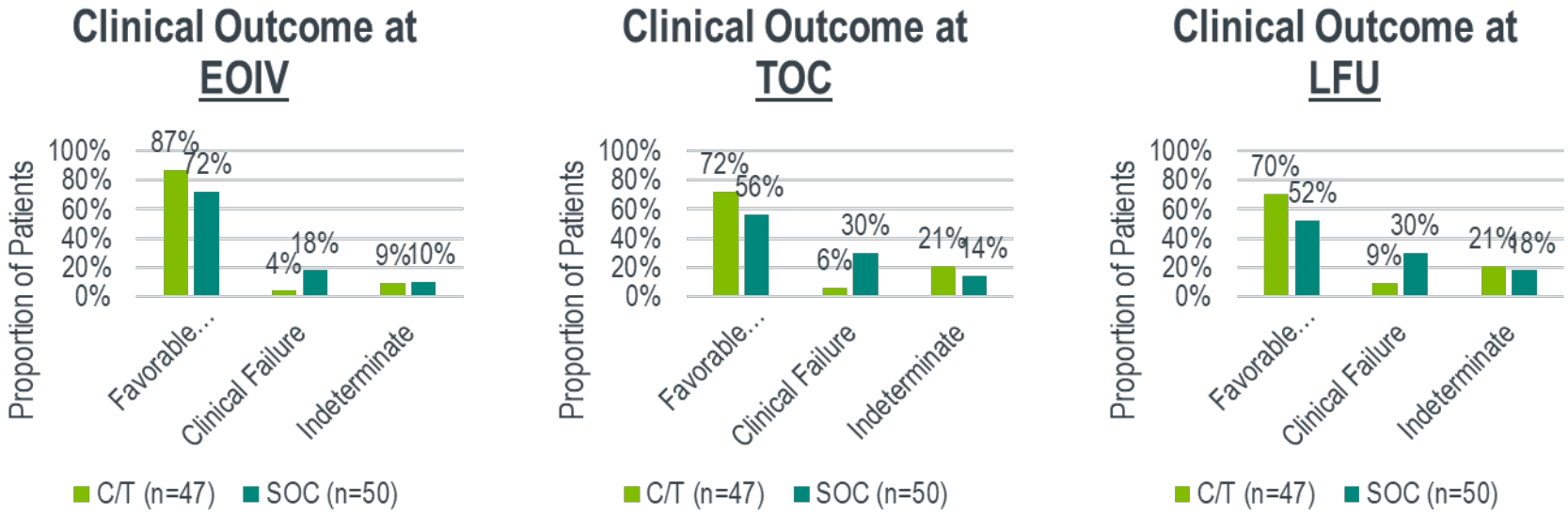
- Most commonly used antibiotics in the SOC group:
  - Cefepime: 76% (n=38/50)
  - Piperacillin/tazobactam: 20% (n=10/50)
  - Meropenem: 4% (n=2/50)

- In both groups, >90% of the patients received Gram-positive coverage
  - Linezolid was the most commonly used agent

- De-escalation at end of IV study drug occurred similarly in both groups:
  - 94% in C/T and 84% in SOC; p=0.14

- Patients on C/T were more likely to de-escalate to IV study drug compared to SOC
  - 55% vs. 21%

Results
Clinical Outcomes



- **Other Clinical Outcomes:**
  - Infection-related mortality: 0 in both groups
  - 30-day all-cause mortality: 2 (4%) in both groups

EOIV, end of IV therapy; TOC, test of cure; LFU, late follow-up.

Ceftazidime-avibactam Phase III clinical trial programme

Seven prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3: Adults with cIAI

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

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

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

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

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

REPRISE Adults with CAZ-resistant pathogens

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

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

REPROVE Adults with nosocomial pneumonia (including VAP)

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

Plus open-label empiric linezolid + aminoglycoside

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

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

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

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

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

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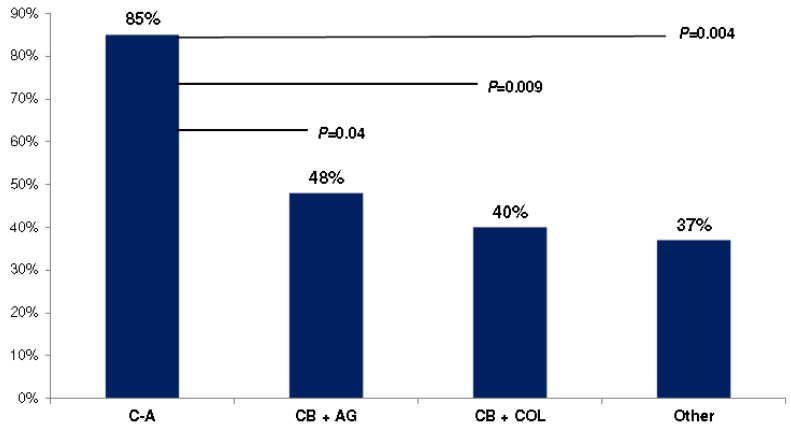
Figure 1. Rates of 30 day clinical success across treatment regimens



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

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

Clinical Infectious Diseases
MAJOR ARTICLE

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

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

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

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

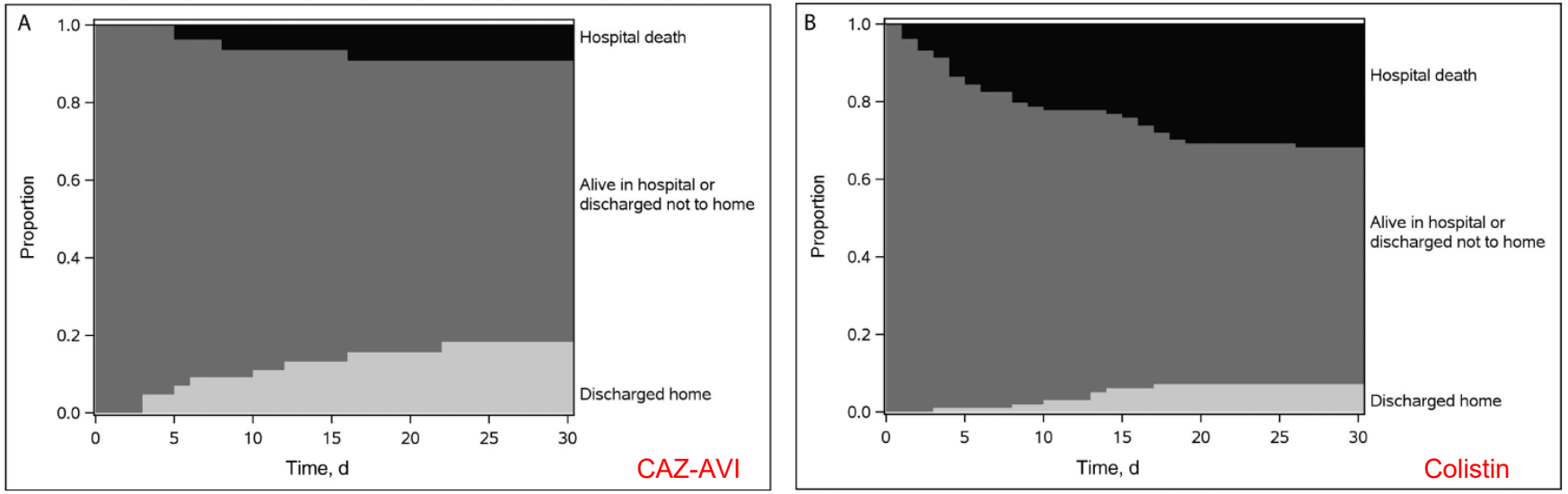


Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

Clinical Infectious Diseases
MAJOR ARTICLE 2018

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

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

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

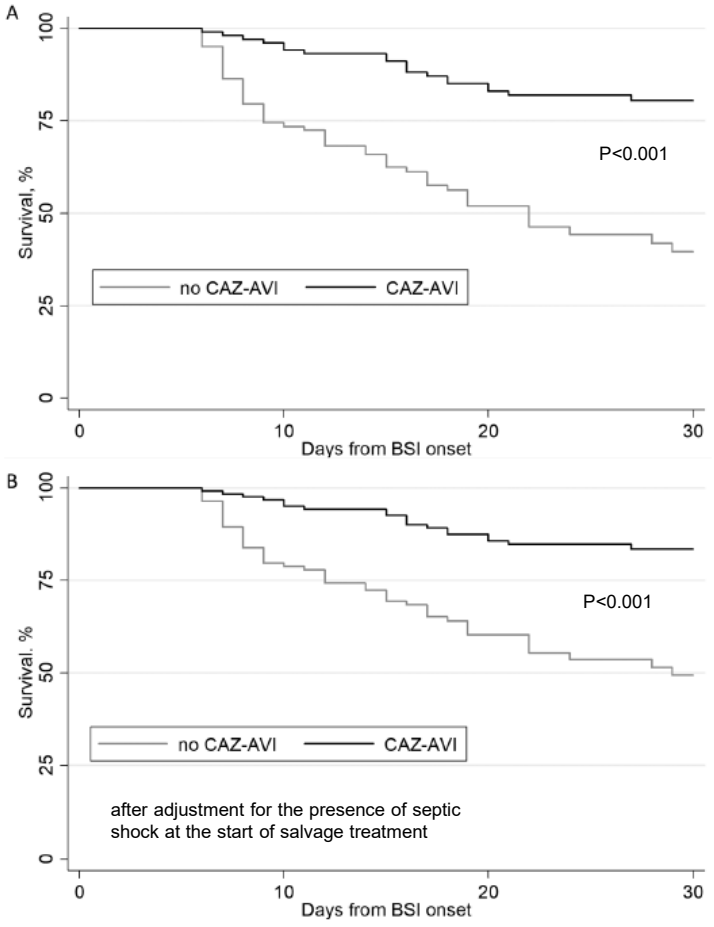


Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia

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

J Antimicrob Chemother
doi:10.1093/jac/dky295

Journal of Antimicrobial Chemotherapy

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

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

OXA-48

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

CAZ–AVI, ceftazidime–avibactam.

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

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

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

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May 2018 Volume 62 Issue 5 e02497-17

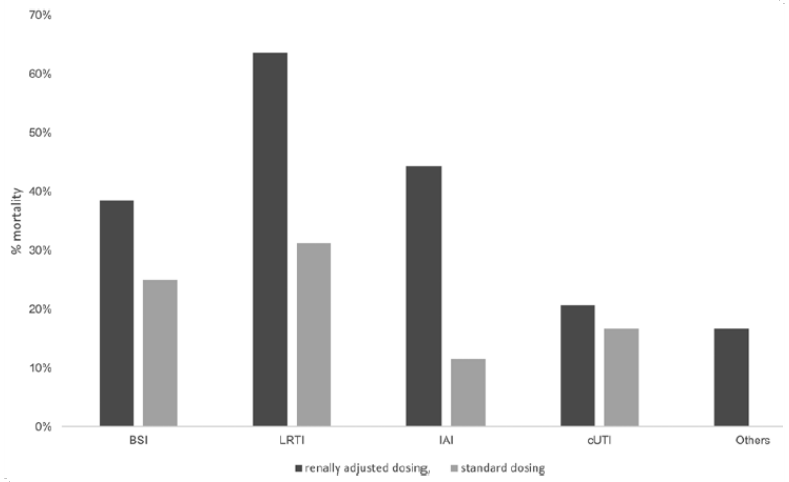
- **Ceftazidime-avibactam was used to treat 77 patients with CRE infections.**
- **33 (43%) infections were pneumonia (26, 79% VAP), 20 (26%) were bacteremia, 8 (10%) UTI, 7 (9%) intra-abdominal infections, 6 (8%) skin/soft tissue infection, and 3 other infections.**
- **Thirty-day survival rate was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

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

Clinical Infectious Diseases
MAJOR ARTICLE

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

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



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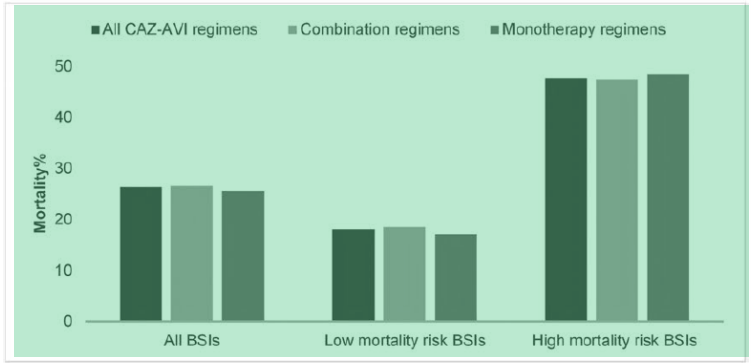

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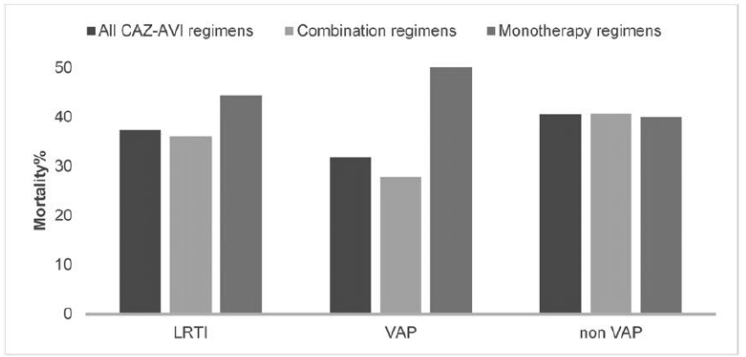
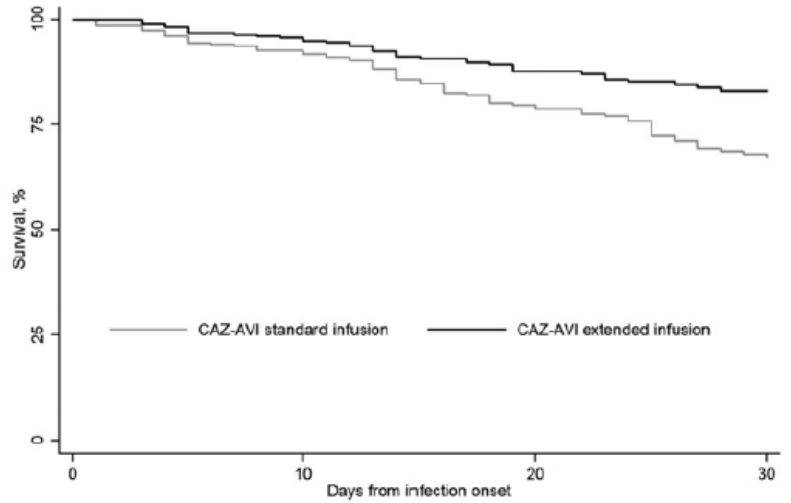




Infect Dis Ther
https://doi.org/10.1007/s40121-023-00762-9

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

Table 4 Ceftazidime–avibactam usage by indication

Characteristic	cIAI (n = 90)	cUTI (n = 103)	HAP/VAP (n = 114)	Other (n = 209)[a]	Total (n = 516)
Use of ceftazidime–avibactam overall, n (%)					
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), n (%)					
Mean (SD)	13.6 (12.5)	9.3 (5.7)	10.3 (6.6)	13.3 (14.3)	11.9 (11.4)

- 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.

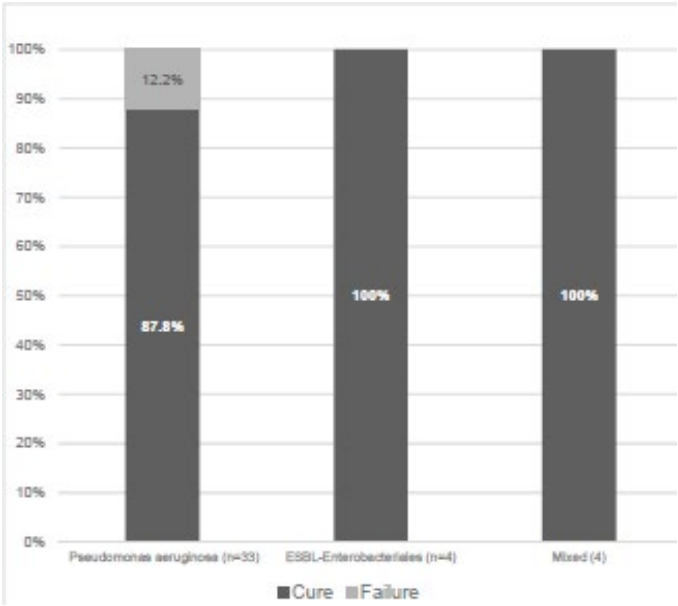
antibiotics

MDPI

Article

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

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



- The main causative agents were P. aeruginosa (33/41; 80.5%) and ESBL-producing Enterobacterales (4/41, 9.8%)
- All strains were susceptible to ceftazidime–avibactam
- Median length of therapy was 13 days
- Clinical success rates were 90.5%
- No association between clinical failures and type of primary infection, microbiological isolates, and monotherapy with ceftazidime–avibactam
- Resistance to ceftazidime–avibactam was not detected in any case during the whole follow-up period
- No adverse events related to ceftazidime–avibactam were observed in the study population

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

Stefano Di Bella[a,*], Daniele Roberto Giacobbe[b], Alberto Enrico Maraolo[c], Valentina Viaggi[d], Roberto Luzzati[a], Matteo Bassetti[b,e], Francesco Luzzaro[d], Luigi Principe[d,1]

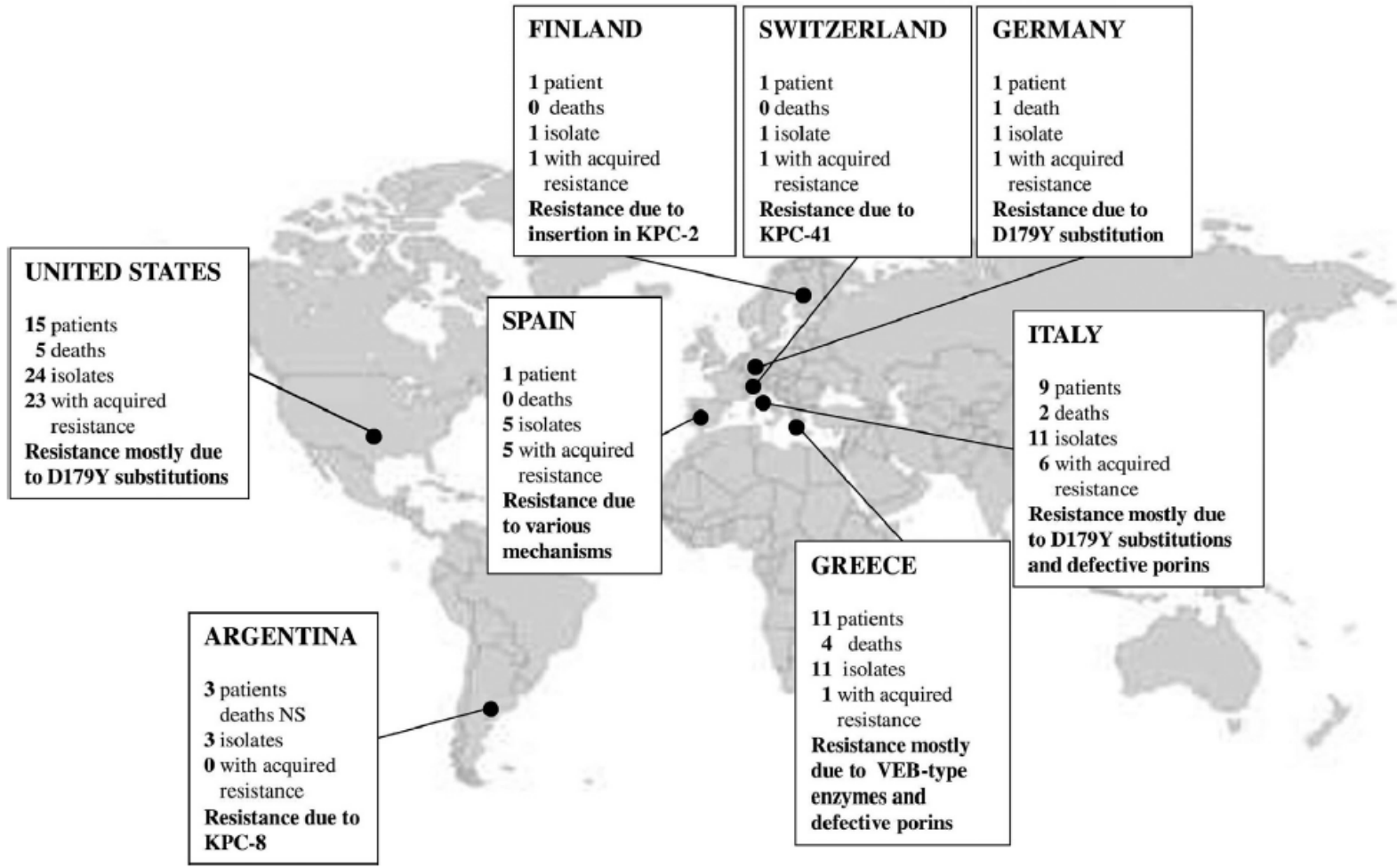


Fig. 2. Country-wise distribution of ceftazidime/avibactam-resistant cases and most relevant features.

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

ORIGINAL RESEARCH

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

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

Published online: 01 October 2018

- 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%

Wunderink IDT 2018

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

ORIGINAL RESEARCH

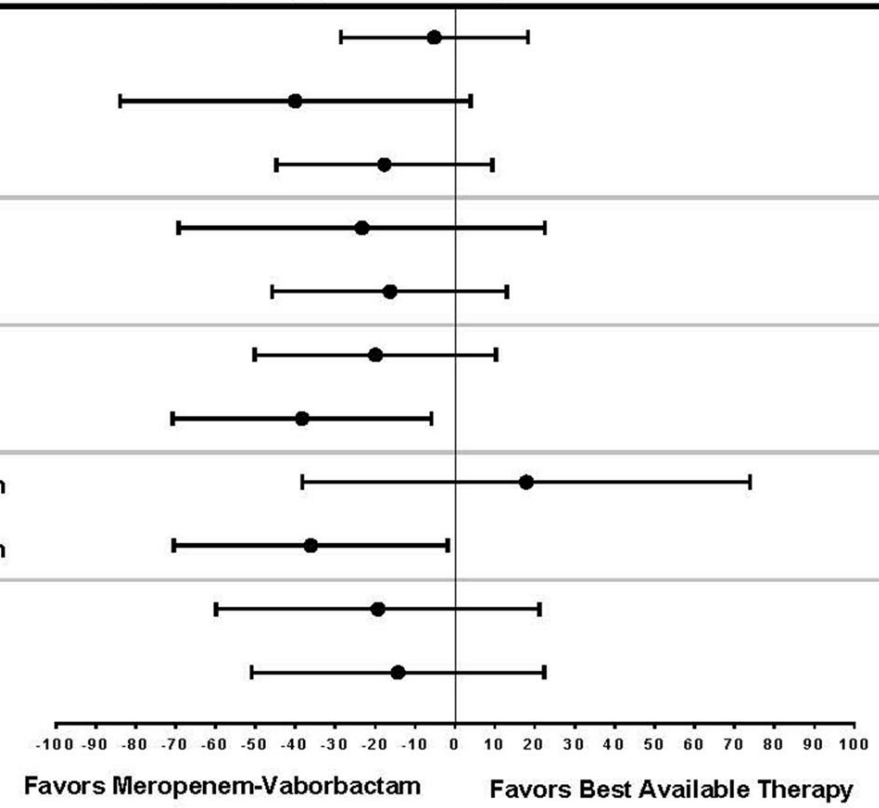
M–V (n = 32)
BAT (n = 15)
Total (N = 47)

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

Published online: 01 October 2018

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

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



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

Wunderink IDT 2018

Clinical Infectious Diseases

BRIEF REPORT

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

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

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

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

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

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

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

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

Open Forum Infectious Diseases

BRIEF REPORT 2020

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

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

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

Clinical success occurred in 70.0% of patients.

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

One patient experienced a probable rash due to MEV.

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

JAC-Antimicrobial Resistance

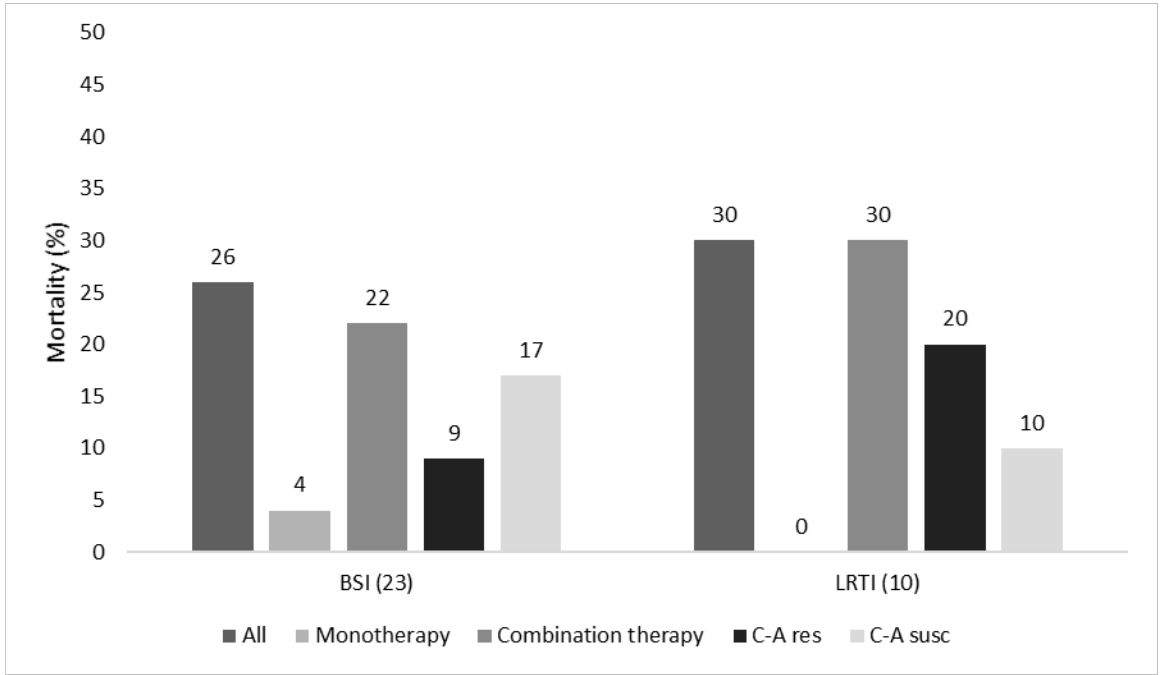
Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: a multicentre study

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

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

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

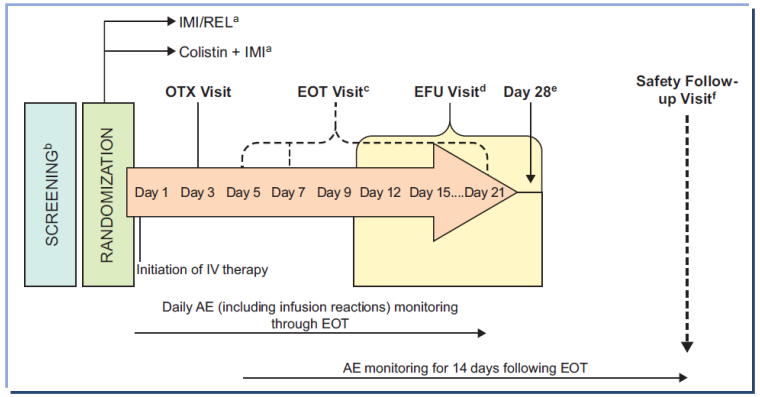
Outcomes were unrelated to the isolate's ceftazidime/avibactam susceptibility status.



Clinical Infectious Diseases
MAJOR ARTICLE

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

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



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

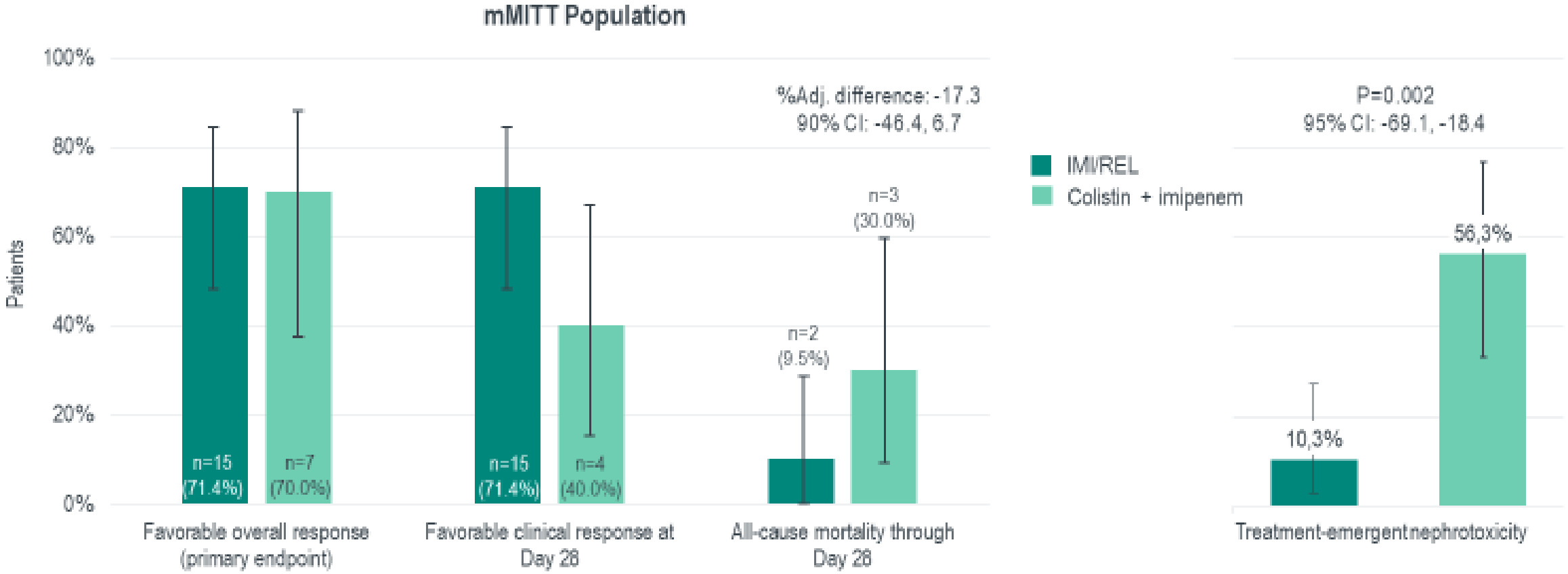
31 patients received imipenem/relebactam and 16 colistin+imipenem

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

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

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

RESTORE-IMI-1: Response to IMI/REL in mMITT Population



Motsch J, et al. *Clin Infect Dis* 2020;70:1799–808 (RESTORE-IMI-1)

Clinical Infectious Diseases

MAJOR ARTICLE

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 HABP/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 noninferior ($P < .001$) to piperacillin/tazobactam for both endpoints: day 28 all-cause mortality and favorable clinical response at early follow-up.

Open Forum Infectious Diseases

BRIEF REPORT

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

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

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

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

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

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

REAL LIFE

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

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

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

Table 4. Patient outcomes

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

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Clinical Infectious Diseases

SUPPLEMENT ARTICLE

In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria

Yoshinori Yamano

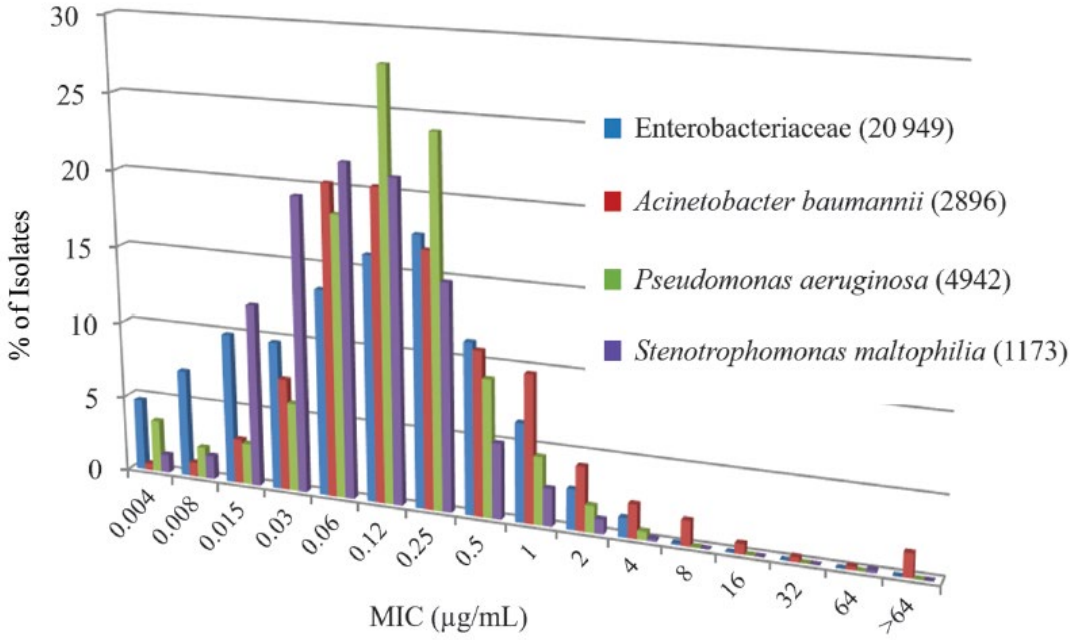
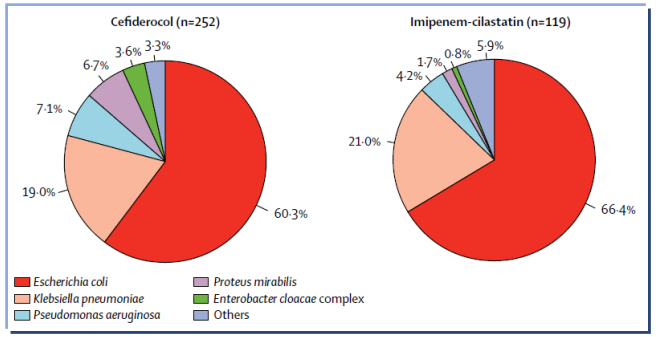


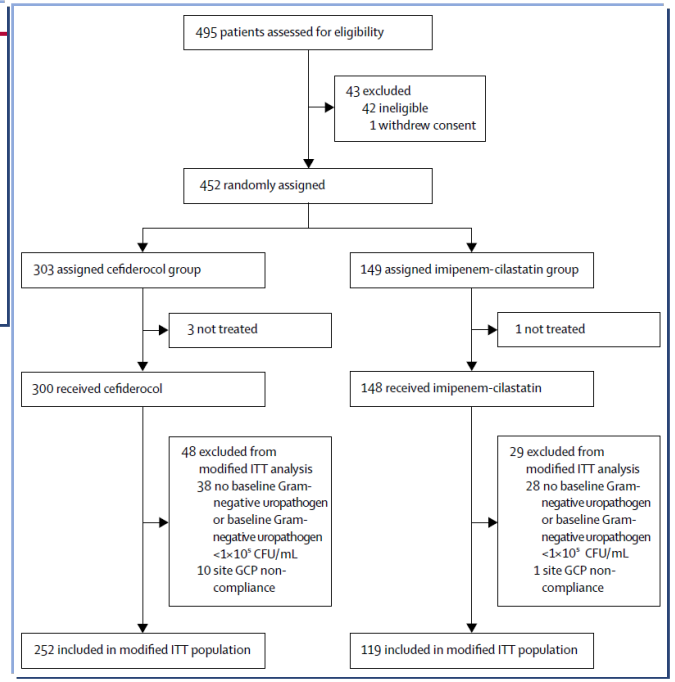
Table 2. Susceptibility Ratio to Cefiderocol and Comparators of Carbapenem-resistant Isolates From the SIDERO-CR-2014/2016 Study

	Ratio of Susceptible Strains[a], (%)				
Species (No. of Strains)	Cefiderocol	Ceftazidime-avibactam	Ceftolozane-tazobactam	Ciprofloxacin	Colistin
Carbapenem-nonsusceptible strains[b]					
Enterobacteriaceae (1022)	97.0	77.0	1.7	11.5	77.8[c]
Pseudomonas aeruginosa (262)	99.2	36.3	24.1	1.2	99.6
Acinetobacter baumannii (368)	90.9	NA	NA	0	94.6
Stenotrophomonas maltophilia (217)	100[e]	NA	NA	NA	NA

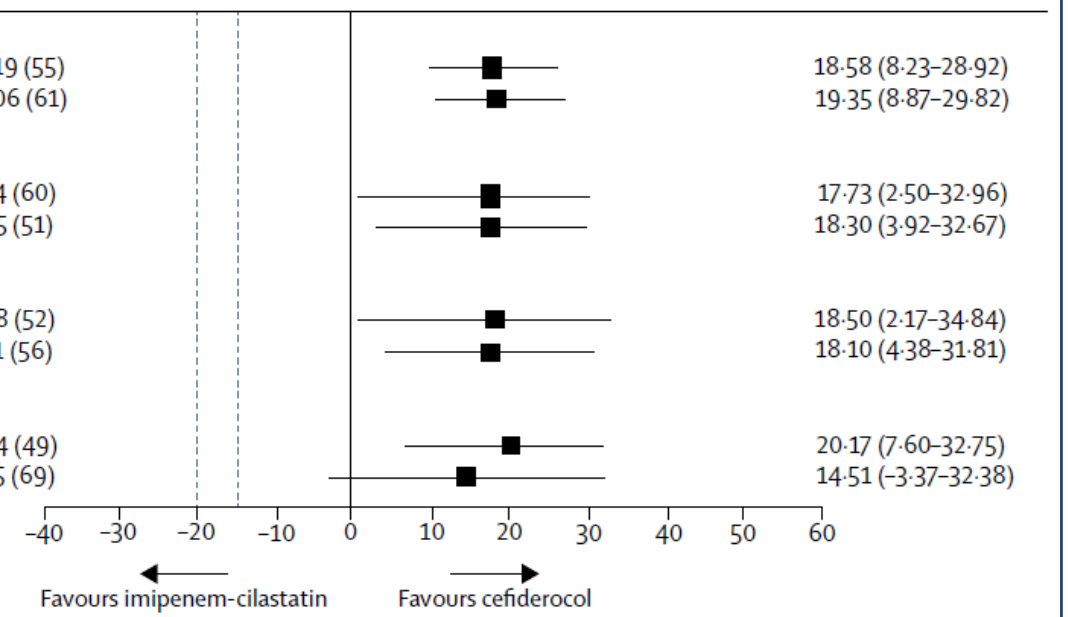
Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

Simon Portsmouth, David van Veenhuyzen, Roger Echols, Mitsuaki 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)



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

Lancet Infect Dis 2021; 21: 213–25

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			
Klebsiella pneumoniae	31/48 (65%)	29/44 (66%)	-1·3 (-20·8 to 18·1)
Pseudomonas aeruginosa	16/24 (67%)	17/24 (71%)	-4·2 (-30·4 to 22·0)
Acinetobacter baumannii	12/23 (52%)	14/24 (58%)	-6·2 (-34·5 to 22·2)
Escherichia coli	12/19 (63%)	13/22 (59%)	4·1 (-25·8 to 33·9)
Enterobacter cloacae	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			
K pneumoniae	21/48 (44%)	22/44 (50%)	-6·3 (-26·6 to 14·1)
P aeruginosa	9/24 (38%)	11/24 (46%)	-8·3 (-36·1 to 19·5)
A baumannii	9/23 (39%)	8/24 (33%)	5·8 (-21·7 to 33·2)
E coli	10/19 (53%)	11/22 (50%)	2·6 (-28·0 to 33·3)
E cloacae	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 and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

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

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

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

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

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

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

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

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

Open Forum Infectious Diseases

BRIEF REPORT

REAL LIFE

Cefiderocol for Extensively Drug-Resistant Gram-Negative Bacterial Infections: Real-world Experience From a Case Series and Review of the Literature

Sandra Zingg,[1,a] G. Jacopo Nicoletti,[2,a] Sabine Kuster,[1] Milena Junker,[2] Andreas Widmer,[1] Adrian Egli,[3,4] Vladimira Hinic,[3] Parham Sendi,[1,5] Manuel Battegay,[1] Veronika Bättig,[1] Nina Khanna,[1,©] and Sarah Tschudin-Sutter[1,6,©]

Table 2. Characteristics of the 3 Cases Treated at our Institution, as Well as the Cases Identified by the Literature Search

Case	Age, y	Sex	Exposition	Diagnosis	Pathogen(s) and Carbapenemases	Days on Cefiderocol	Concomitant Antibiotic Therapy[a]	Adverse Events	Outcome
Case 1	29	M	Columbia	Acute osteomyelitis	*A. baumannii* (OXA-23) *E. cloacae* (KPC) *P. aeruginosa* (VIM)	14	Ceftazidim/ avibactam, colistin	None	Cured
Case 2	64	M	Serbia	Postoperative implant-associated surgical site infection	*A. baumannii* (OXA-40, NDM)	54	Ceftazidim/ avibactam (6d), colistin (14d)	None	Cured
Case 3	62	M	Thailand	Pleural empyema	*A. baumannii* (OXA-23, OXA-58)	42	Colistin	None	Cured
Stevens et al. [6]	46	M	USA	Tertiary peritonitis	*P. aeruginosa* (no carbapenemase detected)	28	None	None reported	Cured
Contreras et al. [7]	68	M	USA	Postoperative intra-abdominal infection	*K. pneumoniae* (2 strains; OXA-232, NDM-1, CTX-M-15)	13	Polymixin B, ceftazidim/ avibactam	None reported	Died[b]
Edgeworth et al. [8]	78	F	Kuwait	Native valve endocarditis	*P. aeruginosa* (no carbapenemase detected)	23	Colistin, meropenem (7d)	Neutropenia	Cured
Trecarichi et al. [9]	Adult	M	Italy	Ventilator-associated pneumonia	*A. baumannii* (no carbapenemase reported), *K. pneumoniae*	14	None	None reported	Cured
Alamarat et al. [10]	15	M	Nigeria	Chronic implant-associated osteomyelitis	*P. aeruginosa* (NDM-1)	95	Aztreonam (13d)	Neutropenia	Cured

Cefiderocol as Rescue Therapy for *Acinetobacter baumannii* and Other Carbapenem-resistant Gram-negative Infections in Intensive Care Unit Patients

Marco Falcone,[1] Giusy Tiseo,[1] Manuela Nicastro,[2] Alessandro Leonildi,[3] Alessandra Vecchione,[3] Costanza Casella,[2] Francesco Forfori,[2,4] Paolo Malacarne,[2] Fabio Guarracino,[2] Simona Barnini,[3] and Francesco Menichetti[1]

Ten critically ill patients with either bacteremia or ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, or New Delhi metallo-β-lactamase–producing *Klebsiella pneumoniae* received cefiderocol.
All strains had minimum inhibitory concentration ≤2 µg/mL. Thirty-day clinical success and survival rates were 70% and 90%, respectively.

Age/ Sex	Underlying Diseases	Cause of ICU Admission	SOFA Score	APACHE II Score	Isolated Pathogen	CFDC MIC, µg/mL	Type of Infection	Initial Treatment Regimen	CFDC Dosage	CFDC Mono-therapy	CRRT	Clinical Outcome at 30 d
76/F	Hypertension Bipolar disorder	Burn (40% TBSA)	12	44	*A. baumannii*	0.25	BSI	COL + TGC	2 g q8h	Yes	Yes	Failure
82/M	Cerebrovascular disease Bladder cancer	Burn (22% TBSA)	12	43	*A. baumannii*	0.5	BSI	COL + TGC + FOS	2 g q8h	Yes	No	Success
65/F	Hypertension Obesity	Burn (36% TBSA)	12	46	*A. baumannii*	0.5	BSI	COL	2 g q8h	Yes	No	Failure
33/F	IV drug user	Burn (Lyell syn-drome, 90% TBSA)	12	34	*A. baumannii*	0.5	BSI	COL + TGC	2 g q6h	Yes	No	Success
82/F	Hypertension Previous stroke	Colonic perforation, hemicolectomy	8	25	*A. baumannii*	0.25	BSI	COL + TGC + MEM	1.5 g q8h	Yes	No	Success
75/F	Hypertension Ischemic cardiomyopathy	COVID-19	11	29	*A. baumannii*	0.5	BSI	TGC + SAM	2 g q6h	Yes	No	Success
79/F	Hypertension	COVID-19	10	39	NDM-producing Kp *Stenotrophomonas maltophilia*	1/0.5	VAP	CAZ-AVI + ATM + FOS	2g q6h	Yes	No	Success
44/M	Hypertension Obesity	COVID-19	9	40	NDM-producing Kp	1	VAP	COL + FOS	2g q6h	Yes	No	Success
77/M	Hypertension	COVID-19	9	36	*A. baumannii* + NDM-producing Kp	0.12/ 2	VAP	COL + CAZ-AVI + ATM	1.5 g q8h	No[a]	Yes	Failure
72/M	Hypertension	COVID-19	11	30	*A. baumannii*	0.5	VAP	COL + TGC	2g q6h	Yes	No	Success

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Research note

Cross-resistance to cefiderocol and ceftazidime–avibactam in KPC β-lactamase mutants and the inoculum effect

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- Because of the structural similarities between cefiderocol and ceftazidime, we hypothesized that resistance to CAZ-AVI in KPC-producing members of the Enterobacterales could lead to cross resistance to cefiderocol.

- We used 37 KPC mutants (carrying either bla_{KPC-2} or bla_{KPC-3}) with increased CAZ-AVI MICs.

- We observed that most of the CAZ-AVI -resistant KPC variants have a possible impact on cefiderocol by increasing the cefiderocol MICs.

- In addition, cefiderocol is greatly impacted by the inoculum effect, suggesting that precautions should be taken when treating infections with a suspected high inoculum.

Ceftazidime-avibactam, Meropenem-vaborbactam and Imipenem-relebctam have a strong activity against KPC-producing Enterobacterales.

The activity of meropenem–vaborbactam and imipenem-relebactam would not be expected to differ from that of meropenem or imipenem alone in the presence of MBL and/or oxacillinase producers.

PK / PD characteristics suggests that meropenem/vaborbactam and imipenem-relebactam may be important treatment options for both ICU and non-ICU HP, including VAP, caused by Enterobacterales in regions with a high prevalence of KPCs.

Cefiderocol is effective against several MDR isolates of Pseudomonas and Acinetobacter and can also be used against CRE