Terapie delle infezioni da Acinetobacter baumannii

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Tumbarello

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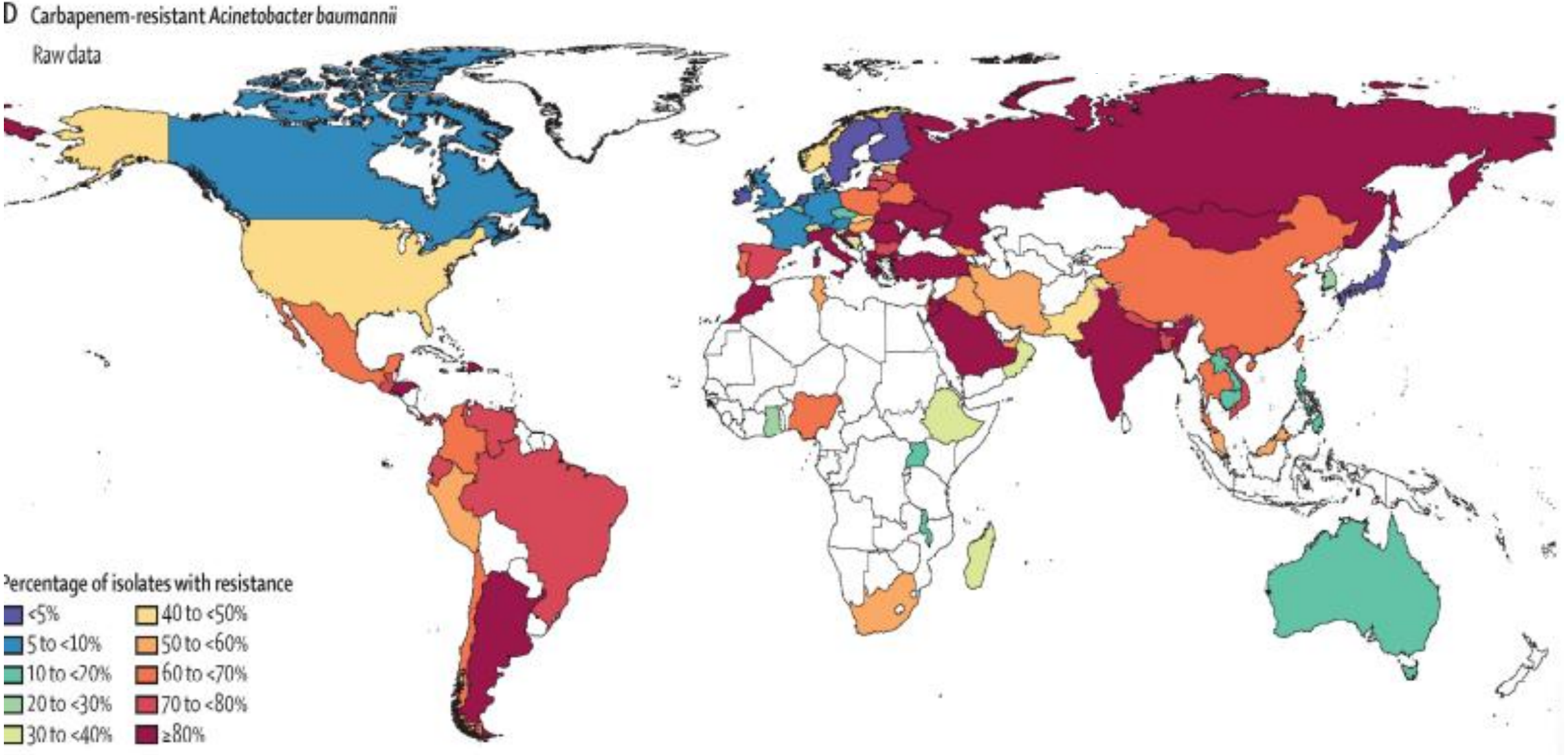
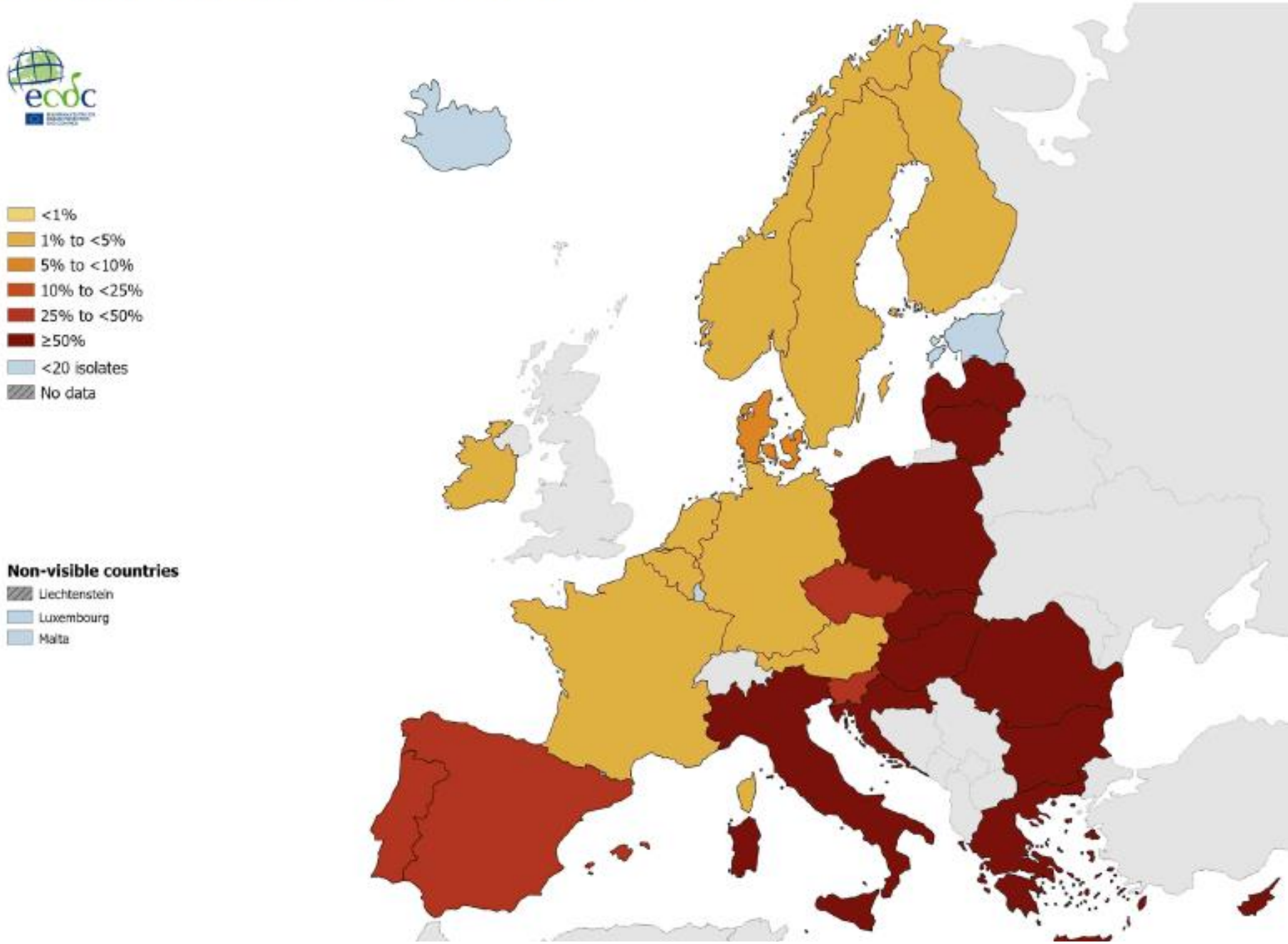


Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis; www.thelancet.com Vol 399 February 12, 2022

Figure 7. *Acinetobacter* **species. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, EU/EEA, 2022**

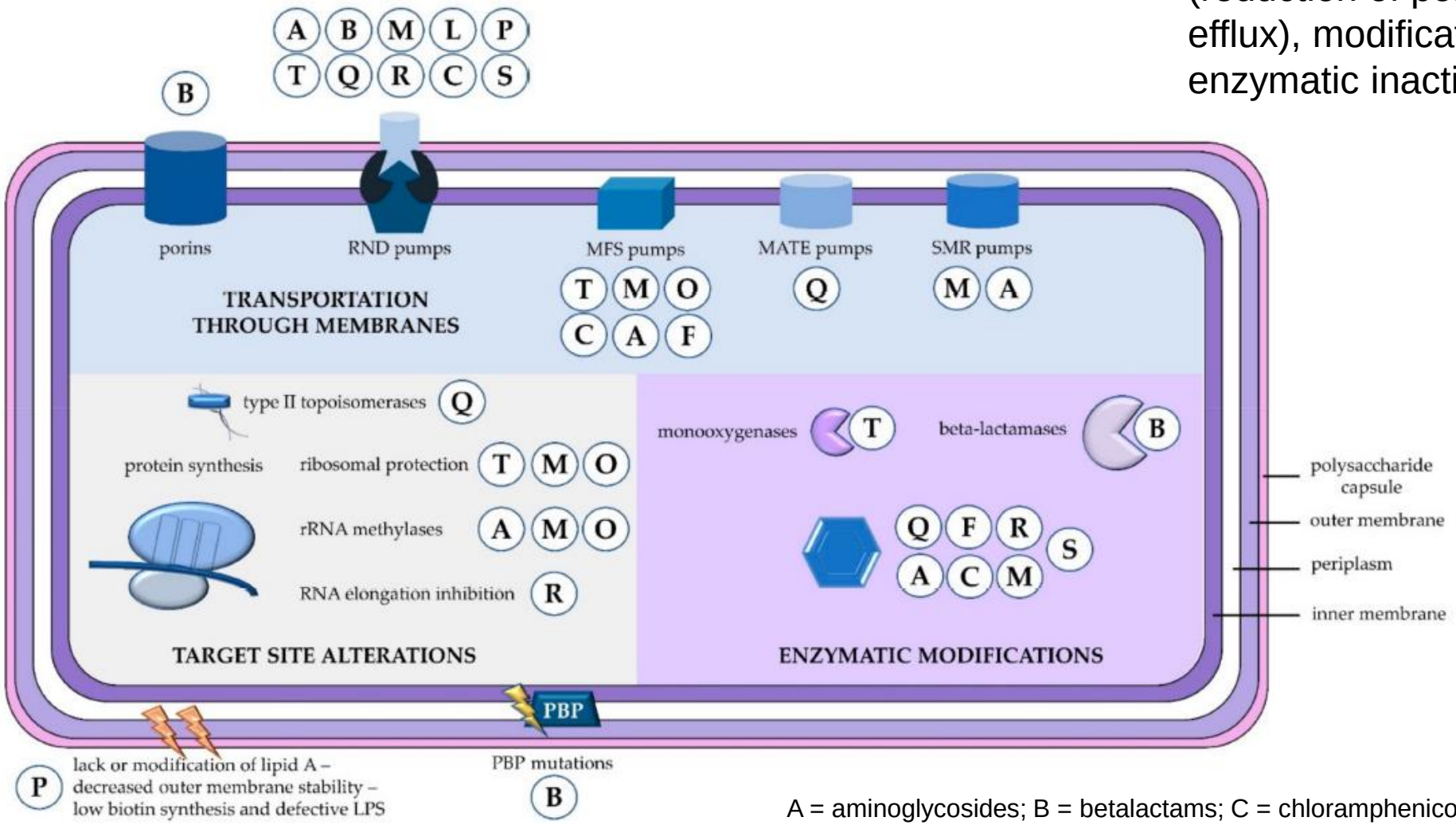


Review

Acinetobacter baumannii Antibiotic Resistance Mechanisms

Ioannis Kyriakidis [1,2,*], Eleni Vasileiou [1], Zoi Dorothea Pana [3] and Athanasios Tragiannidis [1]

Antibiotic resistance can be conferred through three main mechanisms, i.e., control of antibiotic transportation through membranes (reduction of porin permeability or increased efflux), modification of antibiotic targets, and enzymatic inactivation of the antibiotics.



A = aminoglycosides; B = betalactams; C = chloramphenicol; F = fosfomycin; L = lincosamides; M = macrolides; MATE = multidrug and toxic compound extrusion; MFS = major facilitator superfamily; O = oxazolidinones; P = polymyxins; PBP = penicillin binding protein; Q = fluoroquinolones; R = rifamycins; RND = resistance-nodulation-division; S = diaminopyrimidines and sulfonamides; SMR = small multidrug resistance family; T = tetracyclines.

Infect Dis Ther (2022) 11:683–694
https://doi.org/10.1007/s40121-022-00597-w

REVIEW

Carbapenem-resistant *Acinetobacter baumannii:* Colonization, Infection and Current Treatment Options

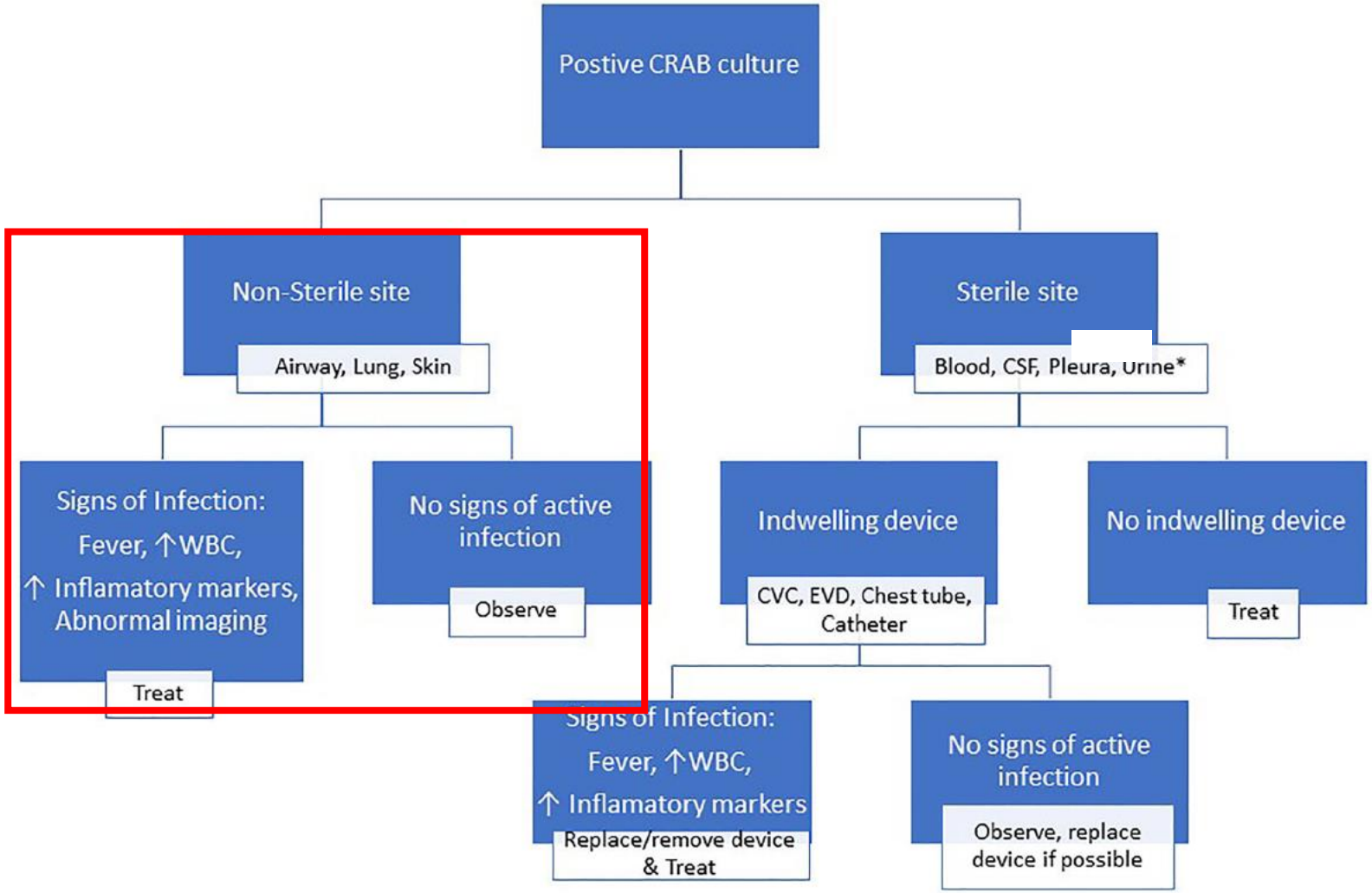


Fig. 1 Management algorithm of patients with a positive CRAB culture. *Most cultures in this setting represent colonization and not infection

Infection (2021) 49:1149–1161
https://doi.org/10.1007/s15010-021-01663-0

REVIEW

Systematic review and meta-analysis of the proportion and associated mortality of polymicrobial (vs monomicrobial) pulmonary and bloodstream infections by *Acinetobacter baumannii* complex

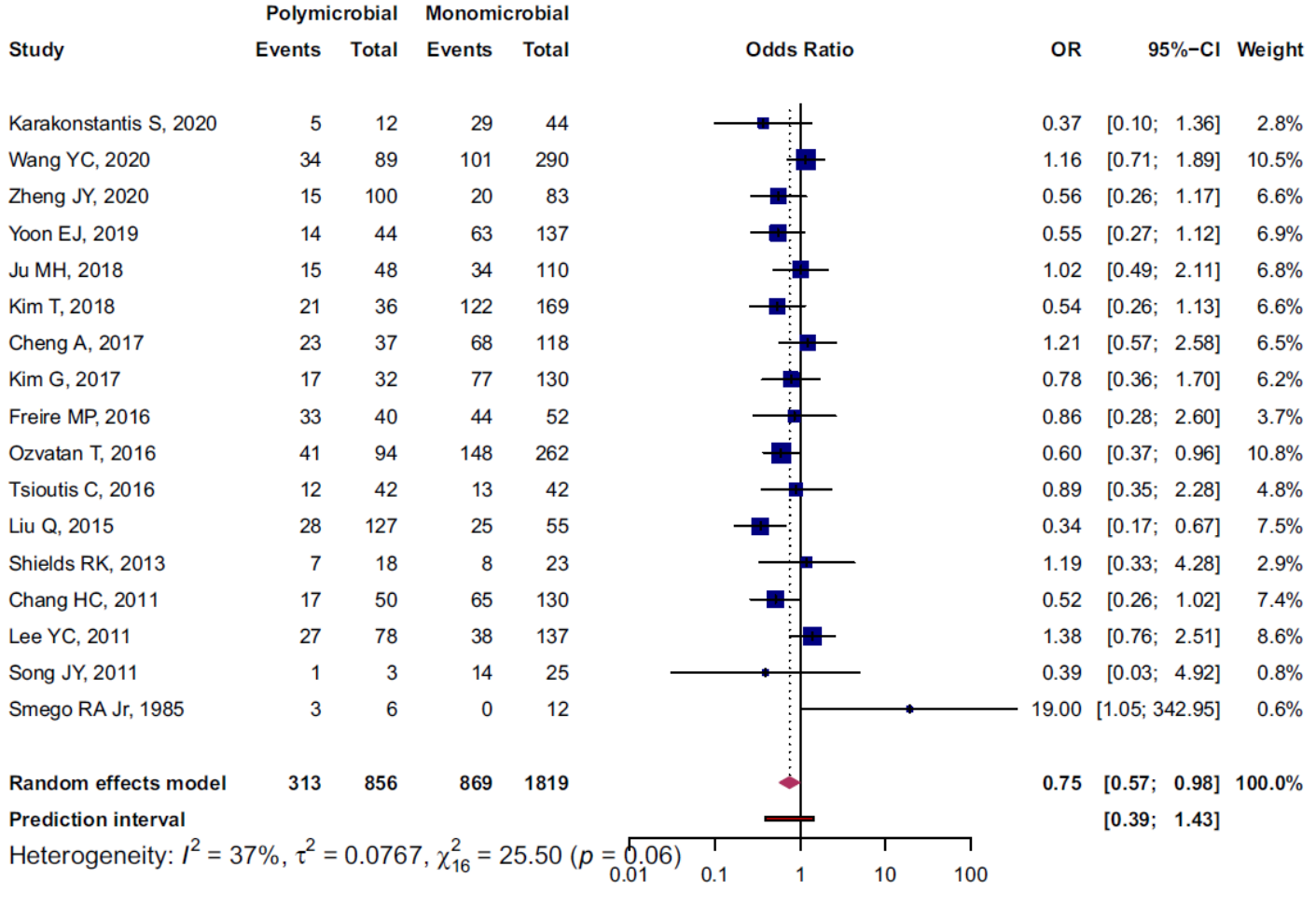
Stamatis Karakonstantis[1] · Evangelos I. Kritsotakis[2]

Differentiating *Acinetobacter baumannii* complex (ABC) infection from colonization remains difficult and further complicated in polymicrobial infections.

Considering a higher mortality of A. baumannii infections compared to other pathogens mortality of polymicrobial ABC infections should be similar to that of monomicrobial ABC infections or higher.

However, ***our meta-analysis showed a lower 28/30-day mortality in polymicrobial ABC infections.***

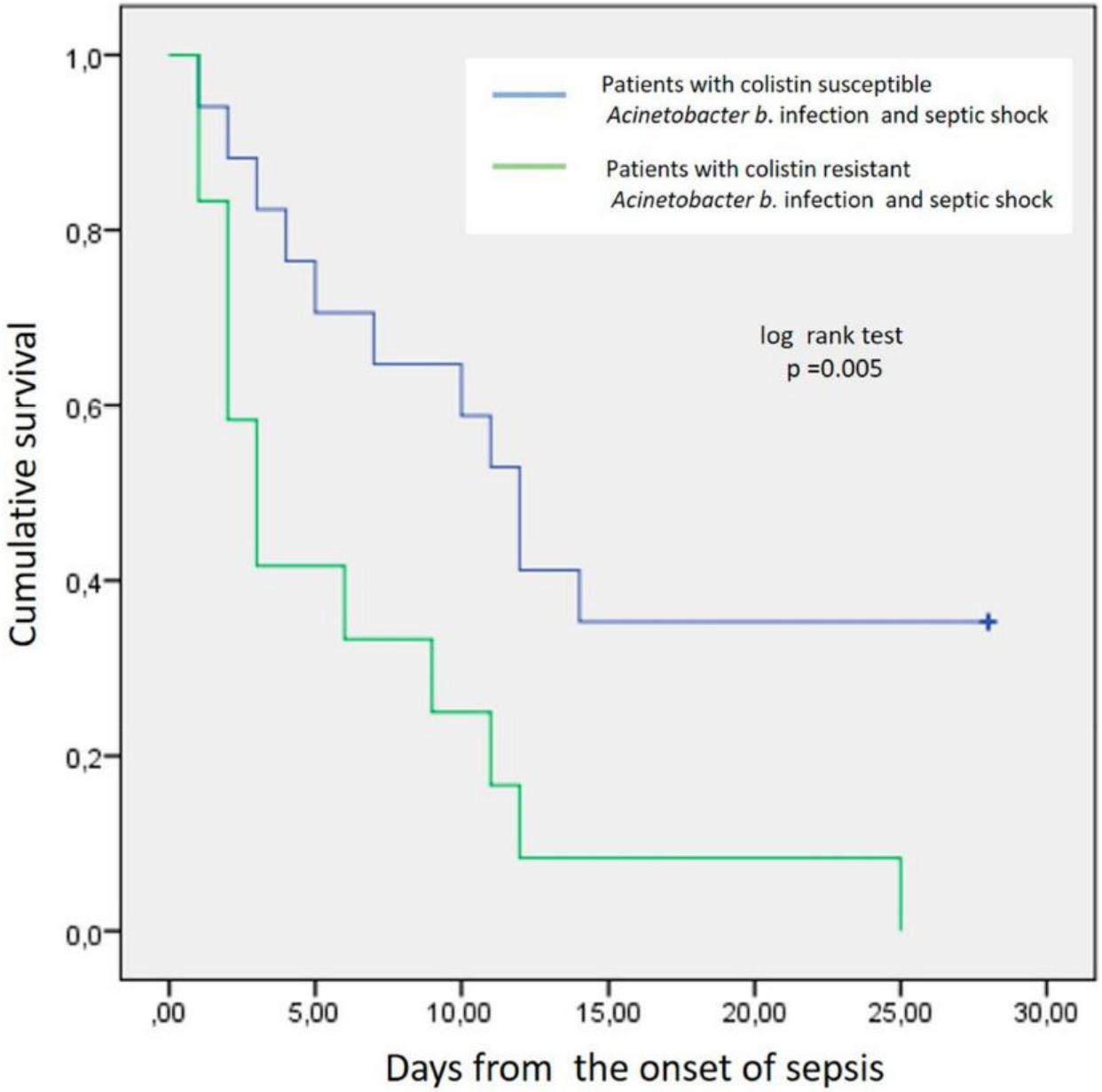
This supports the hypothesis that ***co-pathogens, which are usually more susceptible and more likely to be covered with effective antimicrobials, may represent the true pathogen in some polymicrobial ABC infections****, with ABC*



Article

Colistin-Resistant *Acinetobacter Baumannii* Bacteremia: A Serious Threat for Critically Ill Patients

Georgios Papathanakos [1,*], Ioannis Andrianopoulos [1], Athanasios Papathanasiou [1], Efthalia Priavali [2], Despoina Koulenti [3,4] and Vasilios Koulouras [1]



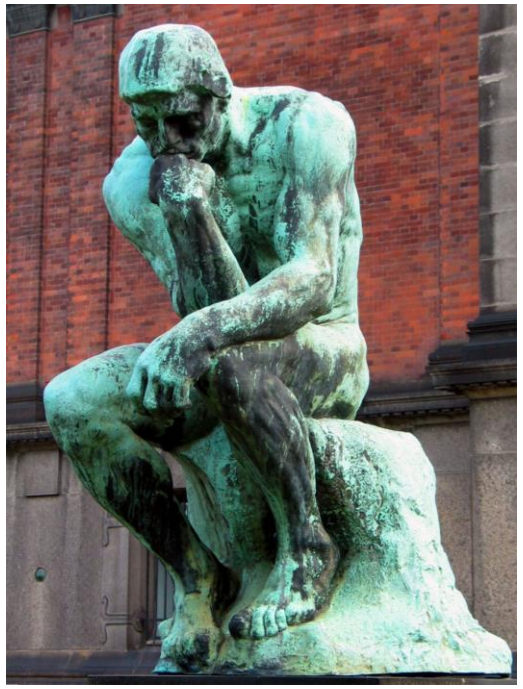


Table 1 Antibiotics used for the treatment of CRAB infections

Agent	Adult dosage (assuming normal renal and liver function)	Remarks	Major toxicities to consider
[a]Ampicillin-sulbactam	3 g every 4 h if intolerance or toxicities preclude the use of higher dosages or for mild infections		Hepatotoxicity (1%)
[a]Ampicillin-Sulbactam	9 g every 8 h, each dose given over 4 h 27-g continuous infusion over 24 h	High dose, suitable for ampicillin-sulbactam-resistant CRAB	
Cefiderocol	2 g every 8 h infused over 3 h		Elevated liver tests (2–16%) Hypokalemia (11%)
Colistin	As per international consensus guidelines[b]		Nephrotoxicity (1–18%) Neurotoxicity (1–7%)
Eravacycline	1 mg/kg/dose every 12 h		GI (2–7%)
[c]Imipenem-cilastatin	500 mg every 6 h infused over 3 h		Seizures (1%)
[c]Meropenem	2 g every 8 h infused over 3 h		Seizures (< 1%)
Minocycline	200 mg every 12 h		CNS (1–3%)
Tigecycline	200 mg once, then 100 mg every 12 h	High dose	Hepatotoxicity (2–5%) Pancreatitis (< 1%),

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Pranita D. Tamma,[1,©] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4,5] David van Duin,[6] and Cornelius J. Clancy[7]

Carbapenem-Resistant *Acinetobacter baumannii*

ESCMID Guidelines [1]	IDSA Guidance [2]
Sulbactam S (MIC $\leq$ 8/4) → Ampicillina/sulbactam Sulbactam R (MIC $>$ 8/4) → Polimixine o Tigeciclina ad alte dosi	Ampicillina/Sulbactam ad alte dosi* in combinazione con Tigeciclina o Colistina
Raccomandazione contro l'utilizzo di Cefiderocol	*6 – 9 grammi/die di sulbactam Cefiderocol solo se non ci sono alternative e, comunque, in regimi di combinazione

[1] European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine), Paul M. et al, Clinical Microbiology and Infection 28 (2022) 521e547

[2] Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections, Tamma P. et al., Clinical Infectious Diseases 2023

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**

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journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Carbapenem-Resistant *Acinetobacter baumannii*

- NO regimi di combinazione Meropenem/Polimixine
- Per infezioni severe, combinazione di DUE antibiotici attivi *in vitro* (polimixine, tigeciclina, ampicillina/sulbactam, aminoglicosidi)
- Se Meropenem mostra MIC <8 mg/L, si può tentare regime di combinazione utilizzandolo ad alte dosi in infusione prolungata

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Pranita D. Tamma,[1,@] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4,5] David van Duin,[6] and Cornelius J. Clancy[7]

Carbapenem-Resistant *Acinetobacter baumannii*

Vengono posti tutti i dubbi della “pratica clinica”:

- *Acinetobacter baumannii* colonizzante o patogeno?
- *Acinetobacter* CR ha già acquisito anche altre forme di resistenza (OXA-23, MBL, mutazioni a carico di PBPs, aminoglycoside modifying enzymes, mutazioni cromosomiche ai fluorchinoloni)
- Non esiste un vero “standard of care” con cui confrontarsi

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Pranita D. Tamma,[1,@] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4,5] David van Duin,[6] and Cornelius J. Clancy[7]

Carbapenem-Resistant *Acinetobacter baumannii*

- Usare Ampicillina/Sulbactam indipendentemente dall'antibiogramma
- Minociclina (400 mg/die, anche se PD suggerisce 700 mg/die) meglio di Tigeciclina
- Cefiderocol come "ultima spiaggia" e solo in terapia di combinazione
- NO associazione con antibiotici nebulizzati

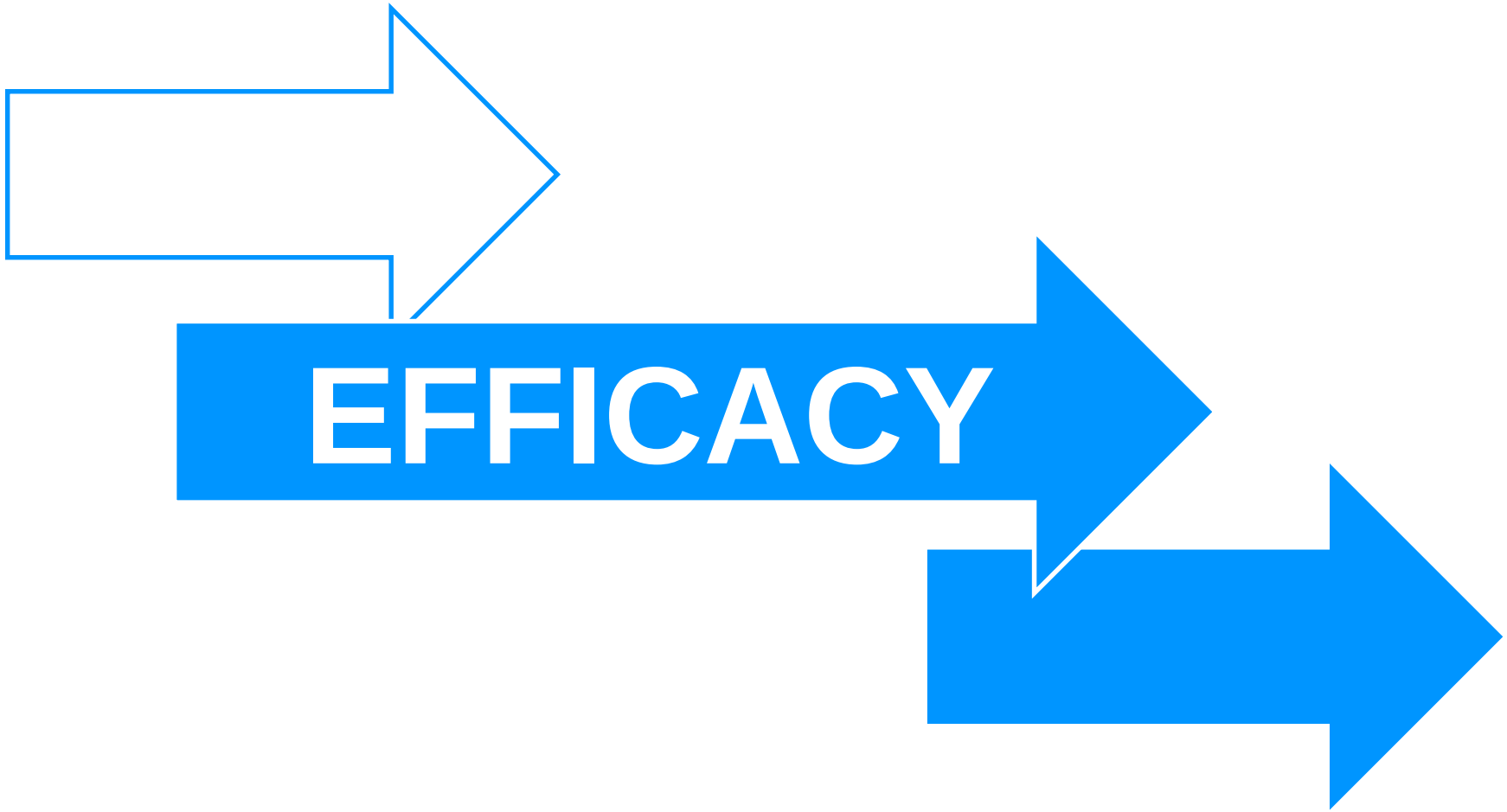
Diagnosi e management delle infezioni causate da batteri multiresistenti: linee guida della Società Italiana di Malattie Infettive e Tropicali (SIMIT), Società Italiana di Terapia Antinfettiva (SITA), Gruppo Italiano per la Stewardship Antimicrobica (GISA), Associazione Microbiologi Clinici Italiani (AMCLI), Società Italiana di Microbiologia (SIM)

Raccomandazione 7.1:			
Non esistono dati convincenti sulla terapia antibiotica ottimale per le infezioni da Acinetobacter baumannii resistente ai carbapenemi (CRAB). Si raccomanda la valutazione dello specialista infettivologo nei pazienti con infezioni da CRAB.			
Forza della raccomandazione:	**FORTE**	Livello di evidenza:	**MODERATO**

Tabella 8. Qualità degli studi sulla terapia antibiotica da utilizzare in caso di infezioni causate da carbapenem-resistant *Acinetobacter baumannii* (raccomandato per tutti i setting ospedalieri).

Trattamento antibiotico per CRAB	**Qualità degli studi**			**Livello complessivo di evidenza**
	Moderato	**Basso**	**Molto basso**	
Regimi contenenti colistina	[94, 101-103, 105]	[98-100, 104]		Moderato
FDC	[107-108]	[70*]	[106]	Basso

Raccomandazione 7.3:			
Il cefiderocol rappresenta un'opzione antibiotica promettente nei pazienti con infezioni da carbapenem-resistant Acinetobacter baumannii (CRAB). Sono necessari ulteriori studi per consolidare questa raccomandazione e per valutare l'uso di cefiderocol in monoterapia o in combinazione con altri antibiotici.			
Forza della raccomandazione:	**FORTE**	Livello di evidenza:	**BASSO**



Clinical efficacy
(trials or real life)

antibiotics

MDPI

Article

Effectiveness of First-Line Therapy with Old and Novel Antibiotics in Ventilator-Associated Pneumonia Caused by Carbapenem-Resistant *Acinetobacter baumannii*: A Real Life, Prospective, Observational, Single-Center Study

Lidia Dalfino [1,*,†], Monica Stufano [1,†], Davide Fiore Bavaro [2], Lucia Diella [2], Alessandra Belati [2], Stefania Stolfa [3], Federica Romanelli [3], Luigi Ronga [3], Rosa Di Mussi [1], Francesco Murgolo [1], Daniela Loconsole [4], Maria Chironna [4], Adriana Mosca [3], Maria Teresa Montagna [4], Annalisa Saracino [2] and Salvatore Grasso [1]

VAP

Overall, CRAB active iv regimens were colistin-based in 50 patients and cefiderocol-based in 40 patients, both always combined with inhaled colistin

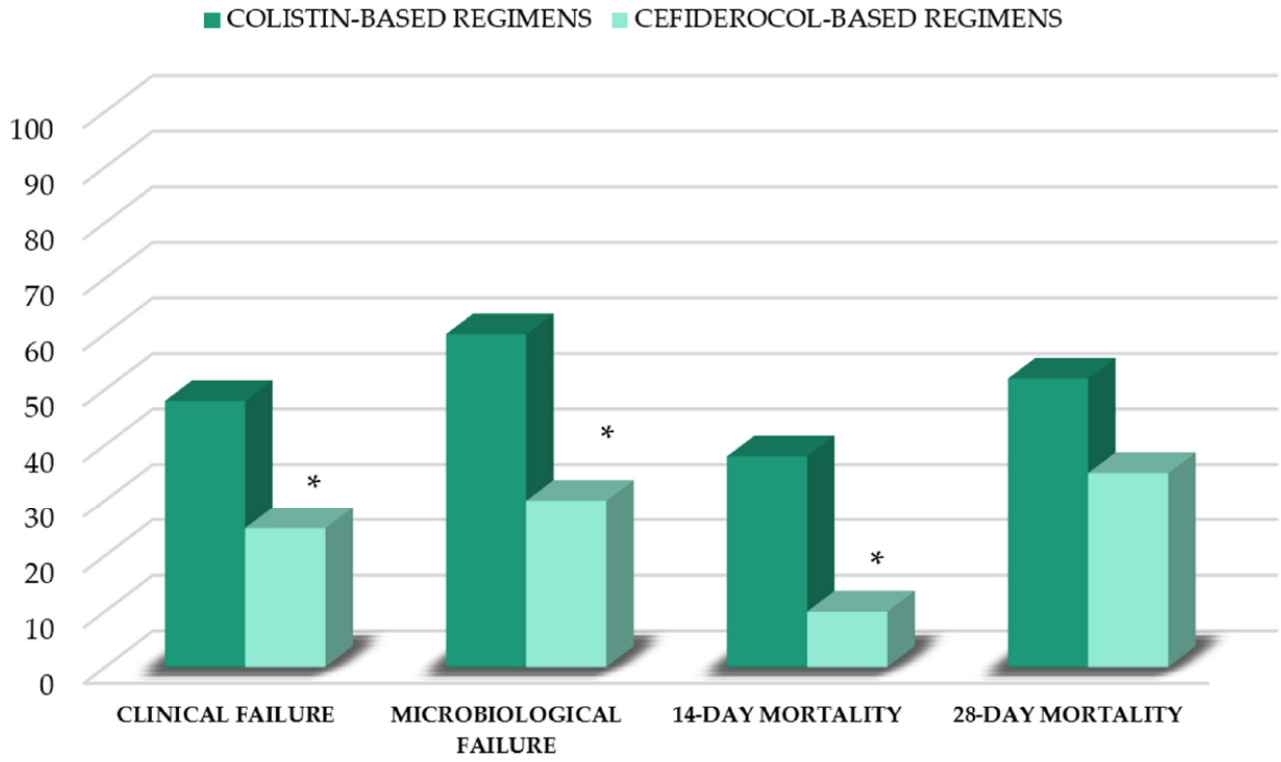


Figure 1. Outcomes of patients stratified by first-line therapy. * $p < 0.05$ vs. colistin group.

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlad085

JAC-Antimicrobial Resistance

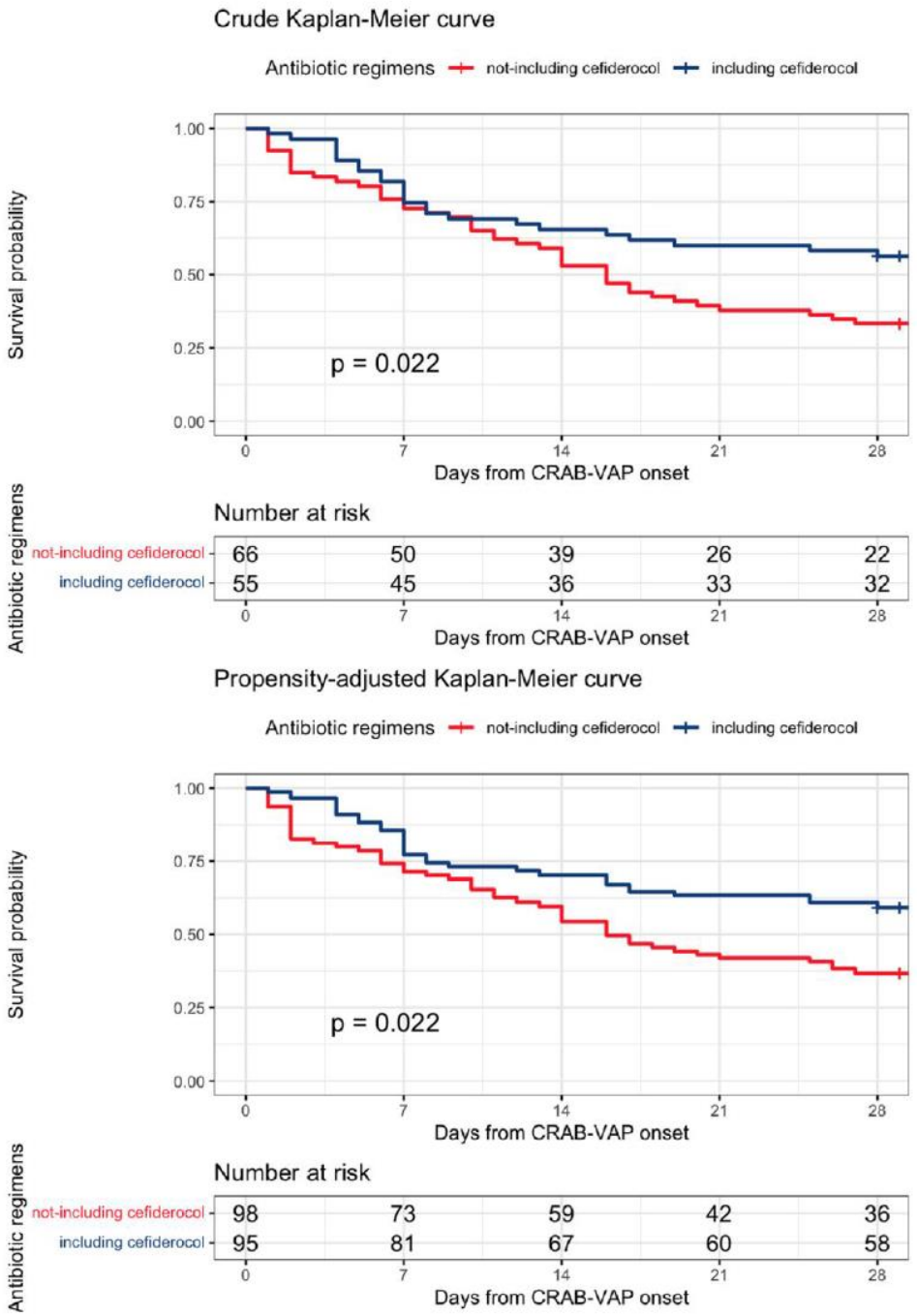
Cefiderocol-containing regimens for the treatment of carbapenem-resistant *A. baumannii* ventilator-associated pneumonia: a propensity-weighted cohort study

Emanuele Rando [1]*, Salvatore Lucio Cutuli[2], Flavio Sangiorgi[1], Eloisa Sofia Tanzarella[2], Francesca Giovannenze[3], Giulia De Angelis[3,4], Rita Murri[1,3], Massimo Antonelli[2,4], Massimo Fantoni[1,3] and Gennaro De Pascale[2,4]

121 patients were enrolled, 55 were treated with cefiderocol- and 66 with non-cefiderocol-containing regimens.

Statistically significant difference in 28-day mortality was found between cefiderocol- and non-cefiderocol-containing regimens groups (44% versus 67%, *P* = 0.011).

VAP



. Crude and propensity-adjusted Kaplan–Meier curves.

Infect Dis Ther (2023) 12:2147–2163
https://doi.org/10.1007/s40121-023-00854-6

ORIGINAL RESEARCH

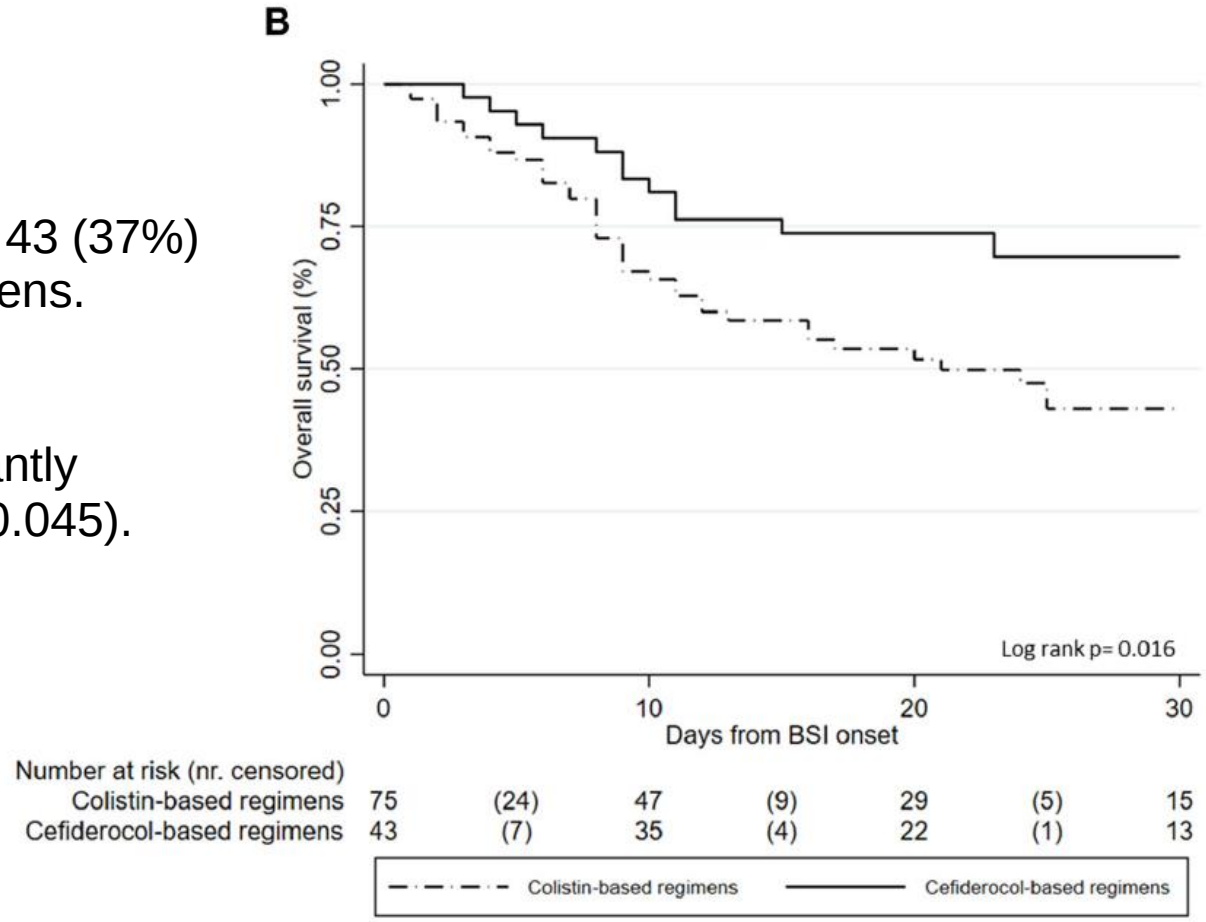
Cefiderocol Versus Colistin for the Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Complex Bloodstream Infections: A Retrospective, Propensity-Score Adjusted, Monocentric Cohort Study

Davide Fiore Bavaro · Roberta Papagni · Alessandra Belati · Lucia Diella · Antonio De Luca · Gaetano Brindicci · Nicolò De Gennaro · Francesco Di Gennaro · Federica Romanelli · Stefania Stolfa · Luigi Ronga · Adriana Mosca · Francesco Pomarico · Maria Dell'Aera · Monica Stufano · Lidia Dalfino · Salvatore Grasso · Annalisa Saracino

BSI

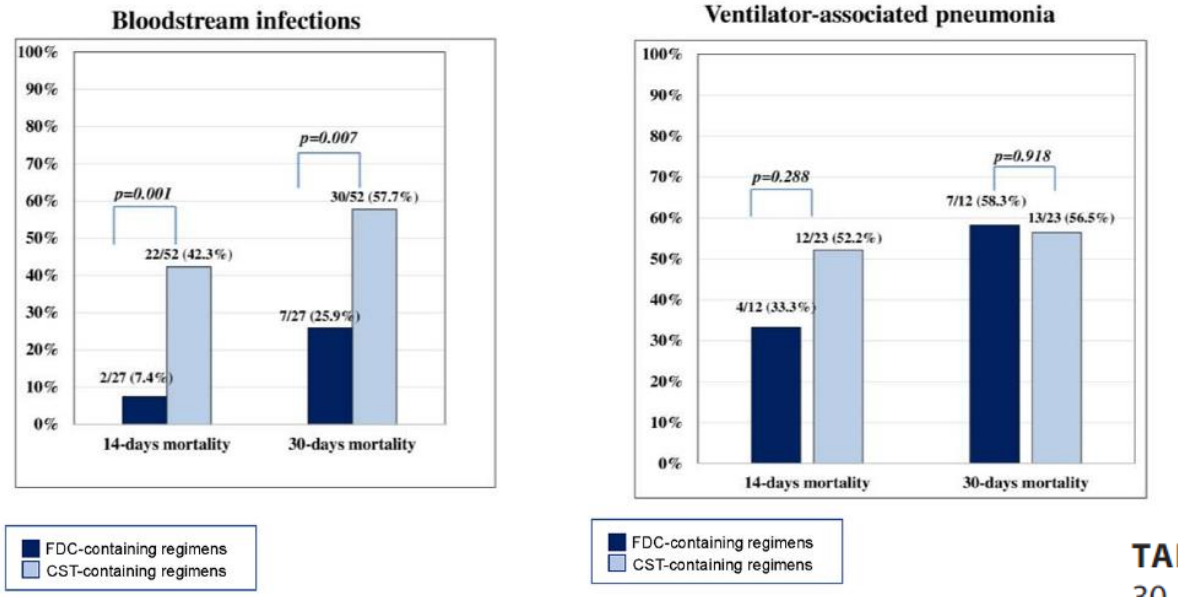
Overall 118 patients were enrolled, 75 (63%) and 43 (37%) treated with colistin- and cefiderocol-based regimens.

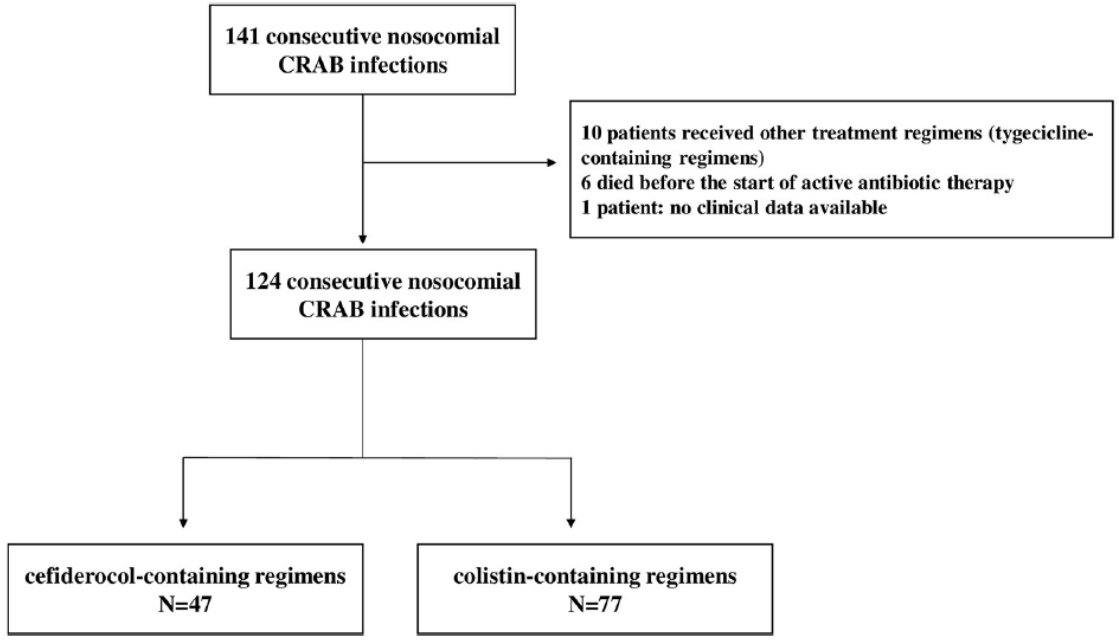
The 30-day all-cause mortality was 52%, significantly lower in the cefiderocol group (40% vs 59%, p = 0.045).



Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

Marco Falcone,[a] Giusy Tiseo,[a] Alessandro Leonildi,[b] Leonardo Della Sala,[a] Alessandra Vecchione,[b] Simona Barnini,[b] Alessio Farcomeni,[c] Francesco Menichetti[a]





79 (63.7%) patients had a BSI, 35 (28.5%) a ventilator-associated pneumonia and 10 (8.1%) other infections.

TABLE 5 Cox regression multivariable analysis of factors independently associated with 30-day mortality

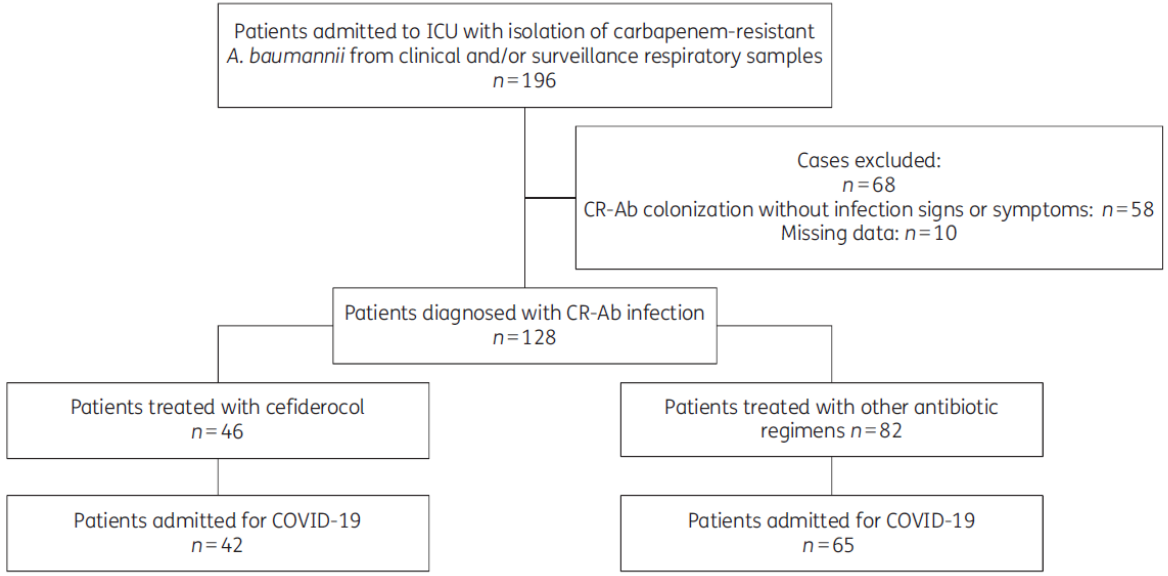
Analysis and factor	aHR[a] (95% CI)	p[b]
Cox regression multivariable analysis		
Septic shock	2.56 (1.11–5.94)	***0.028***
SOFA score	1.15 (1.05–1.27)	***0.003***
Age	1.05 (1.02–1.07)	***0.001***
Cefiderocol-containing regimens (colistin-containing regimens as reference variable)	0.32 (0.18–0.57)	***<0.001***
Propensity score analysis		
Cefiderocol-containing regimens (IPTW-adjusted)	0.44 (0.22–0.66)	***<0.001***

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlab174

JAC-Antimicrobial Resistance

Cefiderocol treatment for carbapenem-resistant *Acinetobacter baumannii* infection in the ICU during the COVID-19 pandemic: a multicentre cohort study

Renato Pascale[1], Zeno Pasquini[1], Michele Bartoletti[1], Luca Caiazzo[2], Giacomo Fornaro[1], Linda Bussini[1], Francesca Volpato[1], Elisa Marchionni[1], Matteo Rinaldi [1], Filippo Trapani[1], Chiara Temperoni[2], Paolo Gaibani [3], Simone Ambretti[3], Francesco Barchiesi[2,4], Pierluigi Viale[1] and Maddalena Giannella[1]*



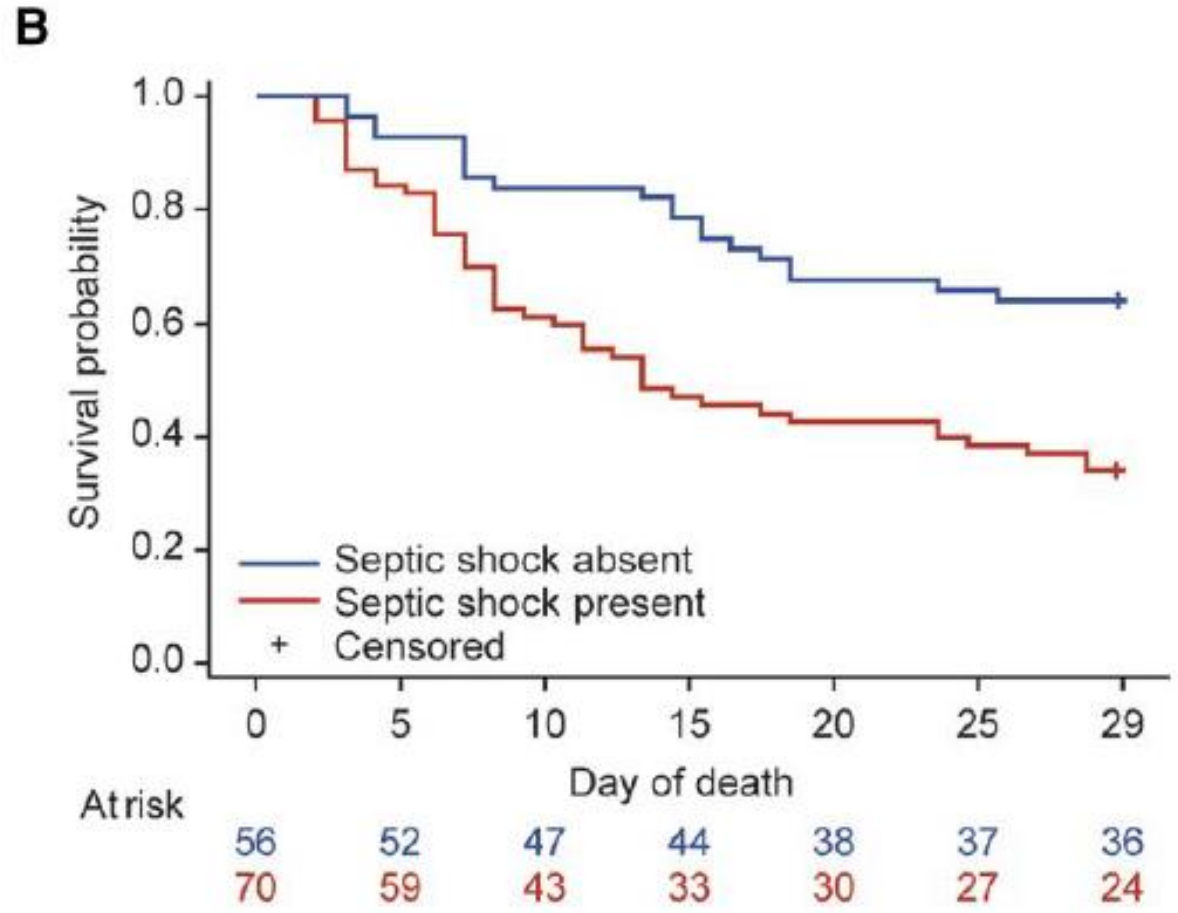
Cefiderocol was administered to 42 patients and as monotherapy in all cases.
The remaining patients received colistin, mostly (82%) administered as combination therapy.

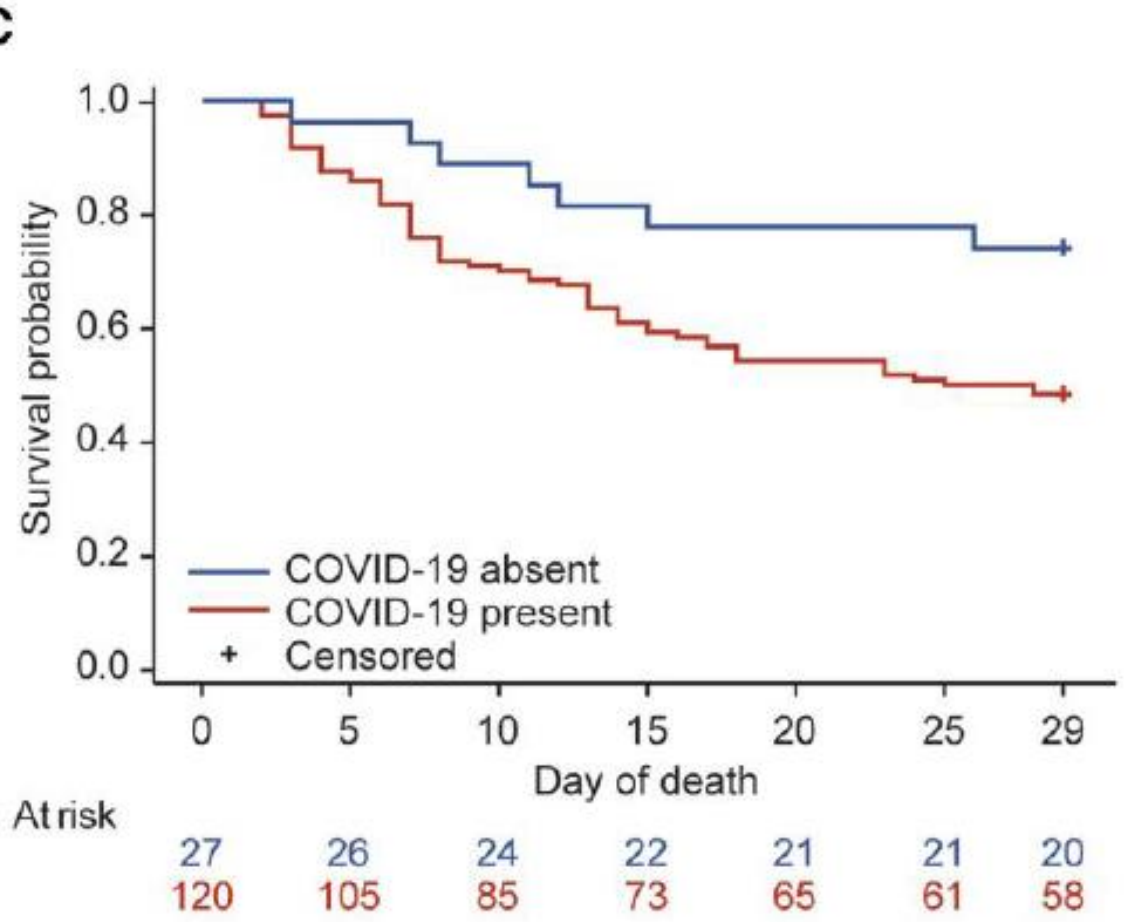
All-cause 28 day mortality rate was 57%, without differences between groups (cefiderocol 55% versus colistin 58%).
In multivariable analysis, the independent risk factor for mortality was SOFA score (HR 1.24, 95% CI 1.15–1.38, P,0.001).
Cefiderocol was associated with a non-significant lower mortality risk (HR 0.64, 95% CI 0.38–1.08, P=0.10).

Carbapenem-Resistant *Acinetobacter* spp Infection in Critically Ill Patients With Limited Treatment Options: A Descriptive Study of Cefiderocol Therapy During the COVID-19 Pandemic

Maddalena Giannella,[1,2] Stefano Verardi,[3] Andreas Karas,[3] Hasania Abdel Hadi,[4] Hervé Dupont,[5] Alex Soriano,[6,7] Anne Santerre Henriksen,[3] Andrew Cooper,[8] and Marco Falcone,[9] for the ARES Study Group

Despite use in complex patients with limited treatment options and high septic shock/COVID-19 rates, cefiderocol treatment was associated with an overall clinical success rate of 53%.





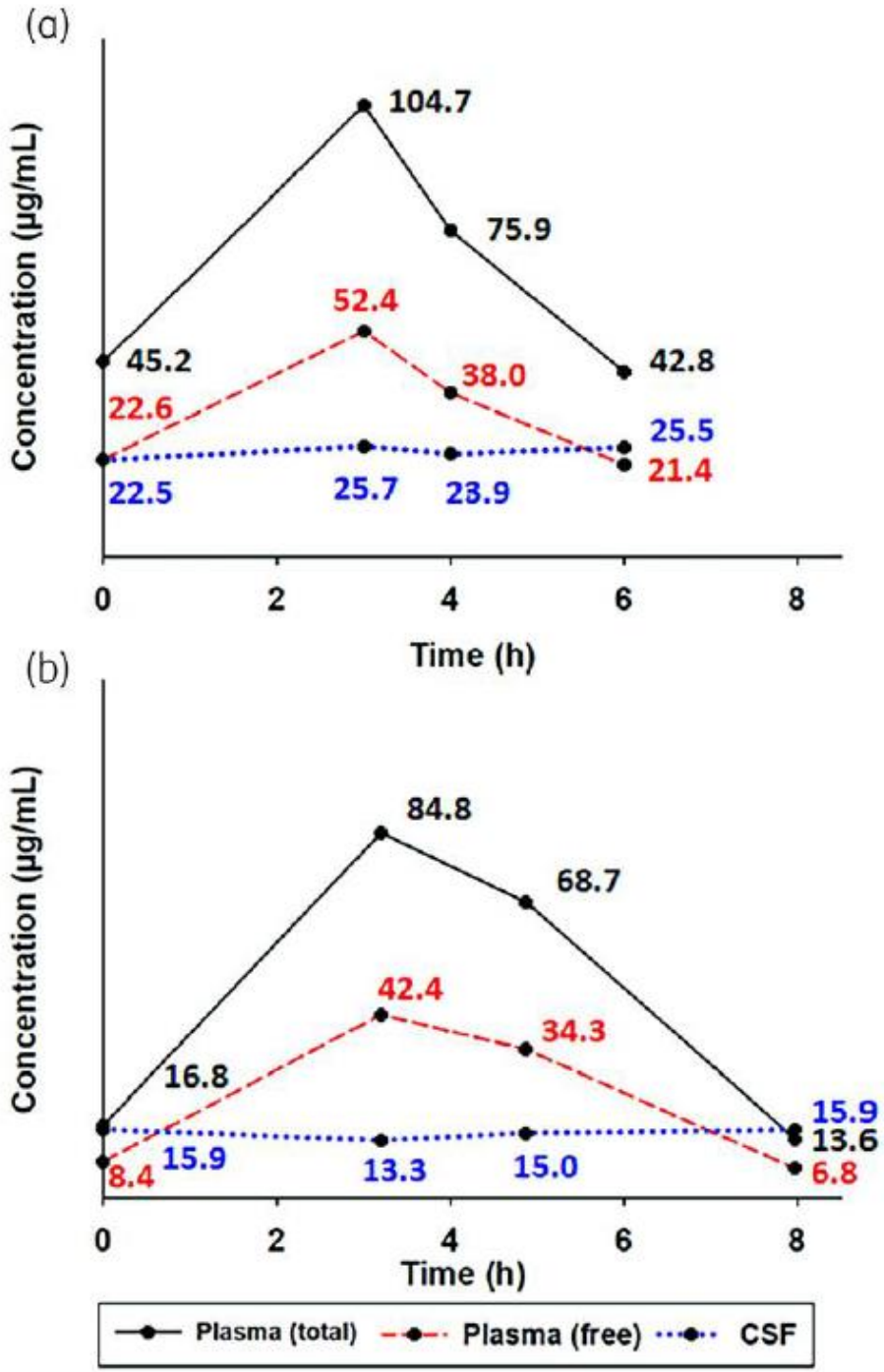
J Antimicrob Chemother 2022; **77**: 2737–2741
https://doi.org/10.1093/jac/dkac248 Advance Access publication 23 July 2022

Journal of Antimicrobial Chemotherapy

Plasma and cerebrospinal fluid concentrations of cefiderocol during successful treatment of carbapenem-resistant *Acinetobacter baumannii* meningitis

Wesley D. Kufel [1,2,3]*, Yasmeen Abouelhassan[4], Jeffrey M. Steele[2,3], Ramiro L. Gutierrez[2], Talha Perwez[2], George Bourdages[5] and David P. Nicolau[4,6]

Cefiderocol, when given as 2 g q8h and 2 g q6h, attained CSF concentrations that exceeded the organism-specific MIC and the CLSI susceptible breakpoint (≤4 mg/L) for 100% of the dosing interval.



Carbapenem-Resistant *Acinetobacter baumannii*

Cefiderocol?

In monoterapia o in combinazione?

Se in combinazione, con quale antibiotico?

Penetrazione a livello polmonare?

Relativamente rapida insorgenza di resistenze?

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

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

Lancet Infect Dis 2021; 21: 213–25

	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

Open Forum Infect Dis. 2019 Oct; 6(Suppl 2): S325. PMCID: PMC6811113
Published online 2019 Oct 23. doi: 10.1093/ofid/ofz360.791

723. Synergistic Effect of Cefiderocol Combined With Other Antibiotics Against Cefiderocol High MIC Isolates From the Multi-National SIDERO-WT Studies

Yoshinori Yamano, PhD,[1] Masakatsu Tsuji, PhD,[1] and Roger Echols, MD[2]

28 Acinetobacter spp. NON sensibili a Cefiderocol (PER produttori e NDM)

Hanno mostrato effetto sinergico nei confronti dei ceppi non-NDM:

Cefiderocol + Ceftazidime/Avibactam

Cefiderocol + Ceftolozane/Tazobactam

Cefiderocol + Meropenem

antibiotics

MDPI

Article

Synergistic Activity of Cefiderocol in Combination with Piperacillin-Tazobactam, Fosfomycin, Ampicillin-Sulbactam, Imipenem-Relebactam and Ceftazidime-Avibactam against Carbapenem-Resistant Gram-Negative Bacteria

Marta Palombo [1], Federica Bovo [2], Stefano Amadesi [1] and Paolo Gaibani [1,*]

Table 1. Genotypic characteristics of CR strains included in this study.

Isolates	ST [a]	β-Lactamase	Multidrug Efflux Pumps	Major Porins
				OmpK35
CRE 1	512	KPC-66, TEM, SHV-11, OXA-10, OXA-181, CMY-16	*emrD, oqxA, oqxB*	OmpK35, truncated at aa 41; OmpK36, INS135GD
CRE 2	307	KPC-3, TEM-1, SHV-28,	*emrD, oqxA, oqxB19*	OmpK35, truncated at aa 229; OmpK36, truncated at aa 183
CR-Ab 1	2	ADC-73, OXA-23, OXA-66	*adeC, amvA*	carO, variant III, Y245F; oprD, wt
CR-Ab 2	2	ADC-73, TEM-1, OXA-23, OXA-66, ftsl	*adeC, amvA*	carO, variant III, Y245F; oprD, wt
CR-Pa 1	298	OXA-848, BEL, PDC-16	*mexA, mexE, mexX*	oprD, variant C2, G425A; oprF, wt
CR-Pa 2	235	OXA-2, OXA-488, PDC-35, PER-1	*mexA, mexE, mexX*	oprD, variant C2, stop codon at aa 64, G425A; oprF, wt

[a] ST, Sequence Type.

antibiotics

MDPI

Article

Synergistic Activity of Cefiderocol in Combination with Piperacillin-Tazobactam, Fosfomycin, Ampicillin-Sulbactam, Imipenem-Relebactam and Ceftazidime-Avibactam against Carbapenem-Resistant Gram-Negative Bacteria

Marta Palombo [1], Federica Bovo [2], Stefano Amadesi [1] and Paolo Gaibani [1,*]

Isolates	MIC (mg/L) [1]							
	CFD [2]	SULB [3]	PIP-TAZ [4]	IMI-REL [5]	MER-VAB [6]	CAZ-AVI [7]	AMP-SULB [8]	FOS [9]
CRE 1	16	>256	>256 [a]	4 [b]	16 [c]	48 [d]	>256 [e]	>256
CRE 2	0.032	>256	>256 [a]	0.25 [b]	4 [c]	3 [d]	>256 [e]	8
CR-Ab 1	>256	>256	>256 [a]	>32 [b]	>256 [c]	>256 [d]	>256 [e]	32
CR-Ab 2	0.125	64	>256 [a]	>32 [b]	>256 [c]	48 [d]	>256 [e]	>256
CR-Pa 1	0.5	>256	12 [a]	2 [b]	16 [c]	24 [d]	>256 [e]	>256
CR-Pa 2	0.125	>256	8 [a]	>32 [b]	32 [c]	8 [d]	>256 [e]	>256

Table 3. FICI values obtained from CFD in combination with PIP-TAZ, FOS, CAZ-AVI, IMI-REL, MER-VAB and AMP-SULB against CR strains included in this study. FICI values in synergistic range are reported in bold.

Isolates	CFD/PIP-TAZ [1]	CFD/FOS [2]	CFD/CAZ-AVI [3]	CFD/IMI-REL [4]	CFD/MER-VAB [5]	CFD/AMP-SULB [6]
CRE 1	1.25	**0.50**	**0.38**	0.63	0.63	0.88
CRE 2	1.00	0.86	0.83	1.00	0.75	1.47
CR-Ab 1	2.00	**0.44**	2.00	2.00	2.00	2.00
CR-Ab 2	1.50	1.01	1.75	2.00	2.00	1.50
CR-Pa 1	1.00	1.00	**0.50**	0.63	1.25	**0.50**
CR-Pa 2	2	1.75	2	0.63	1.26	2

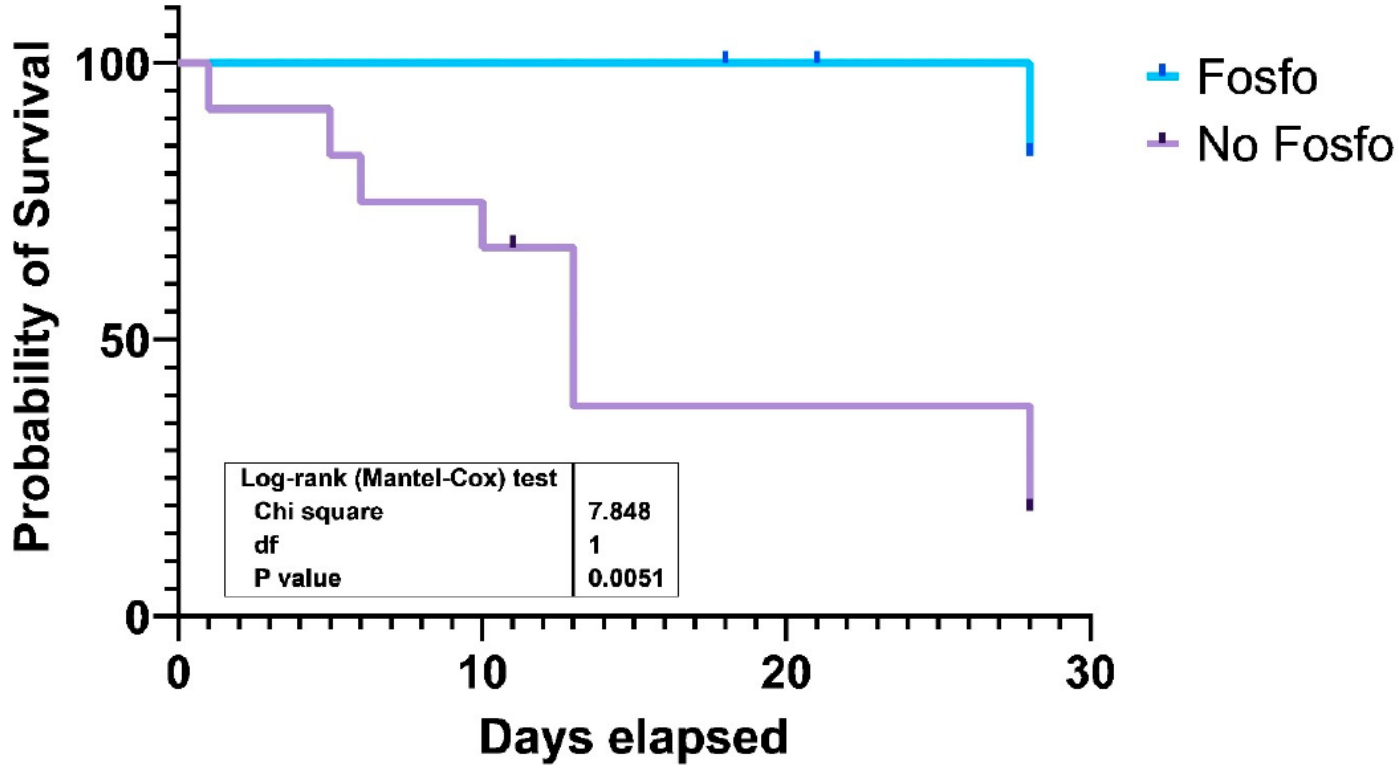
pathogens

MDPI

Brief Report

Efficacy of Fosfomycin-Containing Regimens for Treatment of Bacteremia Due to Pan-Drug Resistant *Acinetobacter baumannii* in Critically Ill Patients: A Case Series Study

Stelios F. Assimakopoulos [1,*,†], Vassilis Karamouzos [1,2,†], Gerasimos Eleftheriotis [1], Maria Lagadinou [1], Christina Bartzavali [3], Fevronia Kolonitsiou [3], Fotini Paliogianni [3], Fotini Fligou [2] and Markos Marangos [1]



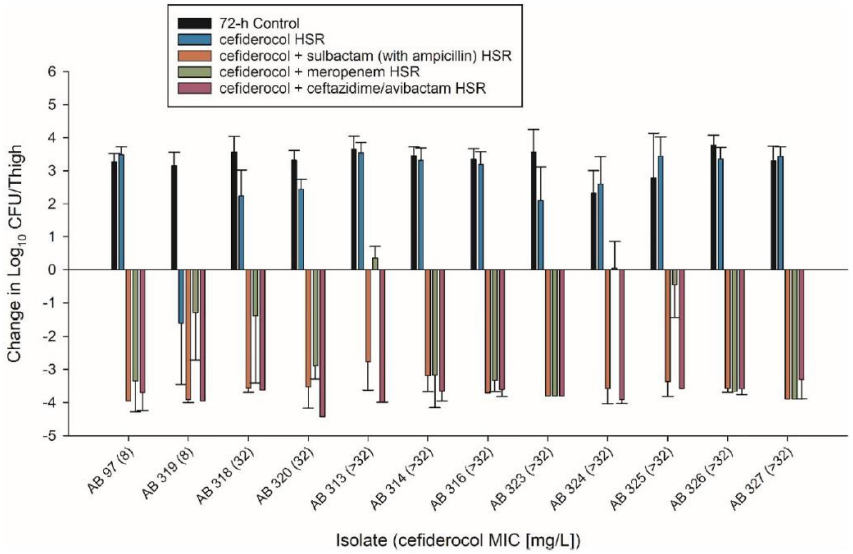
J Antimicrob Chemother 2023; **78**: 983–990
https://doi.org/10.1093/jac/dkad032 Advance Access publication 13 February 2023

Journal of Antimicrobial Chemotherapy

In vivo efficacy & resistance prevention of cefiderocol in combination with ceftazidime/avibactam, ampicillin/sulbactam or meropenem using human-simulated regimens versus *Acinetobacter baumannii*

Christian M. Gill[1]*, Debora Santini[1], Miki Takemura[2], Christopher Longshaw[3], Yoshinori Yamano[2], Roger Echols[4] and David P. Nicolau[1,5]

Evaluate the *in vivo* efficacy and resistance prevention of cefiderocol in combination with ceftazidime/avibactam, ampicillin/sulbactam and meropenem using human-simulated regimens (HSR) in the murine infection model.



Against cefiderocol-non-susceptible isolates, cefiderocol + ceftazidime/avibactam or ampicillin/sulbactam HSR produced *in vivo* kill against all 12 cefiderocol-non-susceptible isolates

(a)

BMD Modal MIC	Cefiderocol + ceftazidime/avibactam — Stacked disc diffusion diameter																							
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
>32																							
32																							
16																							
8																							
4											3	3											
2						1			3														
1											2	1	2	2	4	1							
0.5																1	2						
0.25																1	4		1				
0.125													1	1	1								
0.06																1		2					

(b)

BMD Modal MIC	Cefiderocol + sulbactam (with ampicillin) — Stacked disc diffusion diameter																							
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
>32																							
32																							
16																							
8									1	1	2	7	1										
4								1	2	2	1	3	2	1									
2												3	3		1								
1												2	1				2		1				
0.5																							
0.25																							
0.125																							
0.06																							

(c)

BMD Modal MIC	Cefiderocol + meropenem — Stacked disc diffusion diameter																							
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
>32	7		1	1		2	1																
32	3																						
16	6		3	1		1	4	1															
8																							
4	1		2																				
2																							
1											1	1			1								
0.5																							
0.25																							
0.125																							
0.06																							

Clinical Infectious Diseases
MAJOR ARTICLE

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

Joseph S. Solomkin,[1] Janis Gardovskis,[2] Kenneth Lawrence,[3] Philippe Montravers,[4,5,6] Angie Sway,[7] David Evans,[8] and Larry Tsai[3]

Open Forum Infectious Diseases
MAJOR ARTICLE

Efficacy and Safety of Eravacycline in Obese Patients: A Post Hoc Analysis of Pooled Data From the IGNITE1 and IGNITE4 Clinical Trials

Tomefa E. Asempa,[1,©] Sergey Izmailyan,[2,a] Kenneth Lawrence,[2] and David P. Nicolau[1,3,©]

Infect Dis Ther (2020) 9:1017–1028
https://doi.org/10.1007/s40121-020-00351-0

ORIGINAL RESEARCH

A Real-World Assessment of Clinical Outcomes and Safety of Eravacycline: A Novel Fluorocycline

RESEARCH ARTICLE

Clinical Outcomes of Eravacycline in Patients Treated Predominately for Carbapenem-Resistant *Acinetobacter baumannii*

ANTIBIOTIC ACTIVITY

Aerobic Bacteria		Anaerobic Bacteria	
Gram-positive bacteria	Gram-negative bacteria	Gram-positive bacteria	Gram-negative bacteria
Enterococcus faecalis	*Citrobacter freundii*	*Clostridium perfringens*	*Bacteroides caccae*
Enterococcus faecium	*Enterobacter cloacae*		***Bacteroides fragilis***
Staphylococcus aureus	***Escherichia coli***		*Bacteroides ovatus*
Streptococcus anginosus group	*Klebsiella oxytoca*		*Bacteroides thetaiotaomicron*
Streptococcus salivarius group	***Klebsiella pneumoniae***		*Bacteroides uniformis*
	Citrobacter koseri		*Bacteroides vulgatus*
	Enterobacter aerogenes		*Parabacteroides distasonis*

SCHEDA PER RICHIESTA DI ACQUISTO DI FARMACI

(a cura del personale sanitario richiedente)

Regione Toscana

SST Servizio Sanitario della Toscana

1.Dati del Richiedente

Data della richiesta

Nome e Cognome del richiedente

Telefono E-mail

Unità Operativa (UO)

Responsabile Unità Operativa

2.Dati del farmaco

Il farmaco è esclusivo?

Si ○

No ◉

farmaco non ancora valutato ai fini della rimborsabilità (definita dall'AIFA come classe Cnn, cioè classe C non

Journal of Global Antimicrobial Resistance 30 (2022) 445–450

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

In vitro activity of sulbactam-durlobactam against carbapenem-resistant *Acinetobacter baumannii* and mechanisms of resistance

Jacqueline Findlay[a,*], Laurent Poirel[a,b,c,d], Maxime Bouvier[b], Patrice Nordmann[a,b,c,d]

Durlobactam, a New Diazabicyclooctane β-Lactamase Inhibitor for the Treatment of *Acinetobacter* Infections in Combination With Sulbactam

*Adam B. Shapiro, Samir H. Moussa, Sarah M. McLeod, Thomas Durand-Réville and Alita A. Miller**

Sulbactam ha capacità battericide nei confronti di *Acinetobacter spp*. in quanto inibisce le PBPs, ma viene degradato dalle più comuni β-lattamasi.

Durlobactam ha un ampio spettro d'azione nei confronti delle β-lattamasi appartenenti alle classi A, C e D di Amber, incluse le OXA normalmente espresse da ABC resistenti ai carbapenemi. E' quindi in grado di ristabilire l'attività di Sulbactam nei confronti di ABC.

- Durlobactam is a new member of the diazabicyclooctane class of β-lactamase inhibitors with broad spectrum activity against Ambler class A, C, and D serine b-lactamases.

- Sulbactam is a first generation β-lactamase inhibitor with activity limited to a subset of class A enzymes that also has direct-acting antibacterial activity against Acinetobacter spp.

- The latter feature is due to sulbactam's ability to inhibit certain penicillin-binding proteins, essential enzymes involved in bacterial cell wall synthesis in this pathogen.

- Because sulbactam is also susceptible to cleavage by numerous b-lactamases, its clinical utility for the treatment of contemporary Acinetobacter infections is quite limited. However, when combined with durlobactam, the activity of sulbactam is effectively restored against these notoriously multidrug-resistant strains.

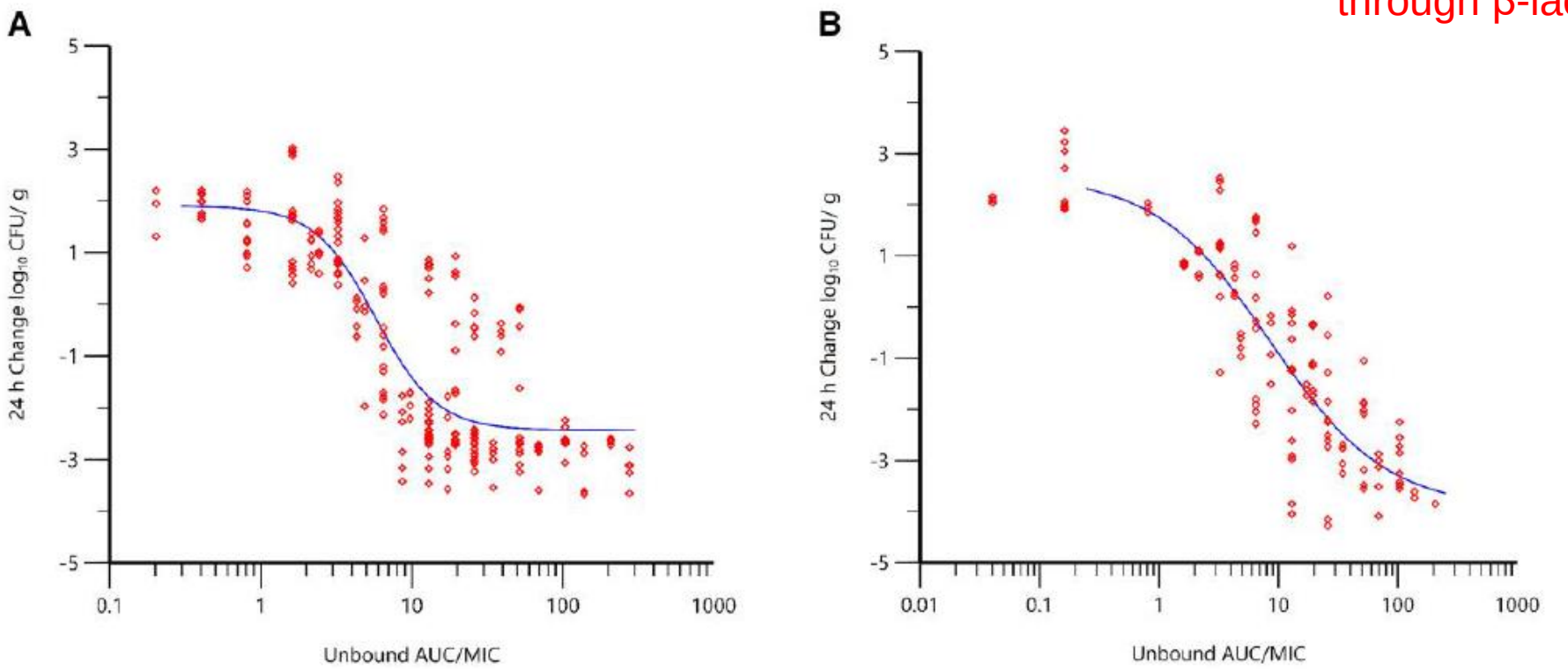
Clinical Infectious Diseases

SUPPLEMENT ARTICLE

The Pharmacokinetics/Pharmacodynamic Relationship of Durlobactam in Combination With Sulbactam in In Vitro and In Vivo Infection Model Systems Versus *Acinetobacter baumannii-calcoaceticus* Complex

John P. O'Donnell[1] and Sujata M. Bhavnani[2]

When combined with sulbactam, durlobactam effectively restores the susceptibility of resistant isolates through β-lactamase inhibition



Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

181 patients were randomly assigned to sulbactam–durlobactam or colistin (176 hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, or ventilated pneumonia; and five bloodstream infections)

28-day all-cause mortality was 12 (19%) of 63 in the sulbactam–durlobactam group and 20 (32%) of 62 in the colistin group.

Incidence of nephrotoxicity was significantly ($p<0{\cdot}001$) lower with sulbactam–durlobactam than colistin.

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

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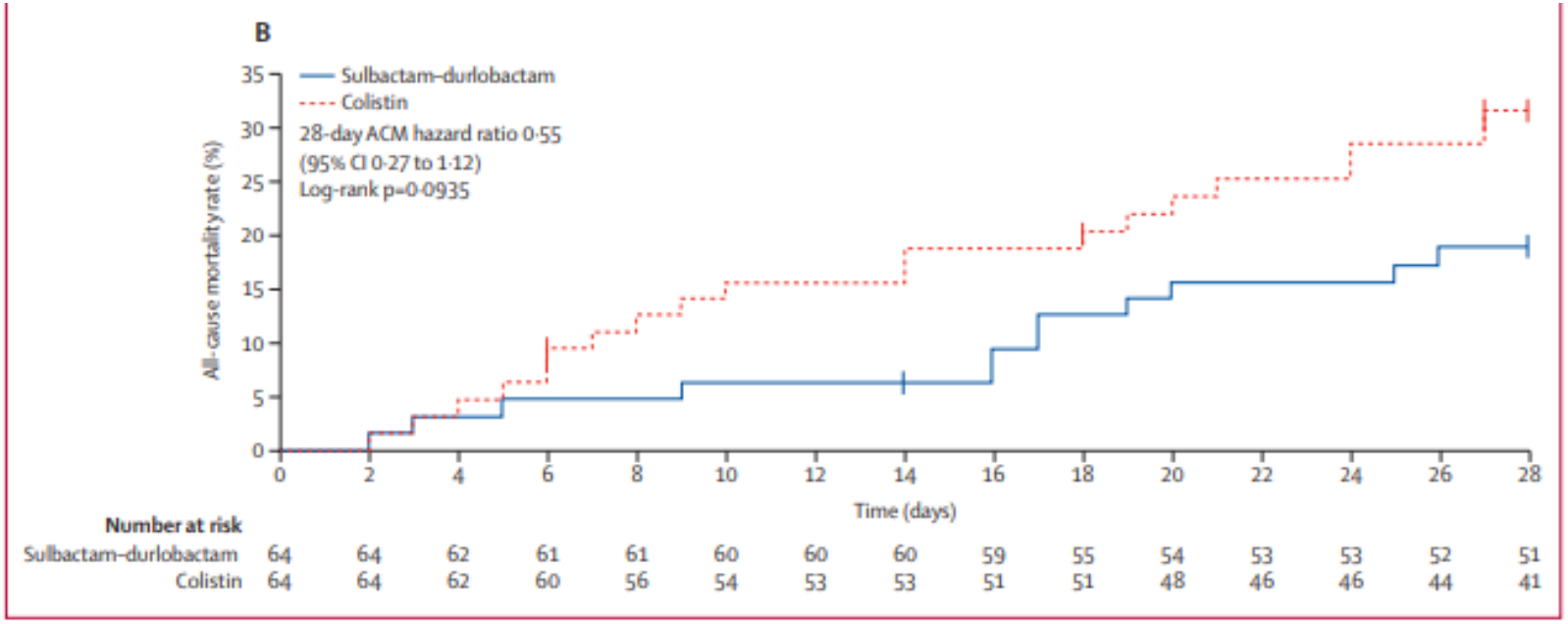

Figure 2: **All-cause mortality**

(A) Primary and secondary efficacy analyses of 28-day all-cause mortality and 14-day all-cause mortality. These analyses exclude patients who transferred from part A to part B (one in each treatment group) and patients who withdrew consent before having survival status assessed at day 14 or day 28. The non-inferiority hypothesis test for the primary endpoint (28-day ACM in the carbapenem-resistant ABC microbiologically modified ITT) was concluded if the upper limit of the two-sided 95% CI was less than +20%. There were no patients with missing mortality data. (B) Kaplan-Meier analysis of time to death by day 28 (carbapenem-resistant ABC microbiologically modified ITT population). Hazard ratio and 95% CIs were obtained from a Cox proportional hazards model with treatment as a factor. The p value was calculated from a log-rank test. ACM=all-cause mortality. ABC=*Acinetobacter baumannii-calcoaceticus* complex. ITT=intention to treat.

Entrambi i farmaci vengono utilizzati in associazione a Imipenem-cilastatina come terapia di background

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

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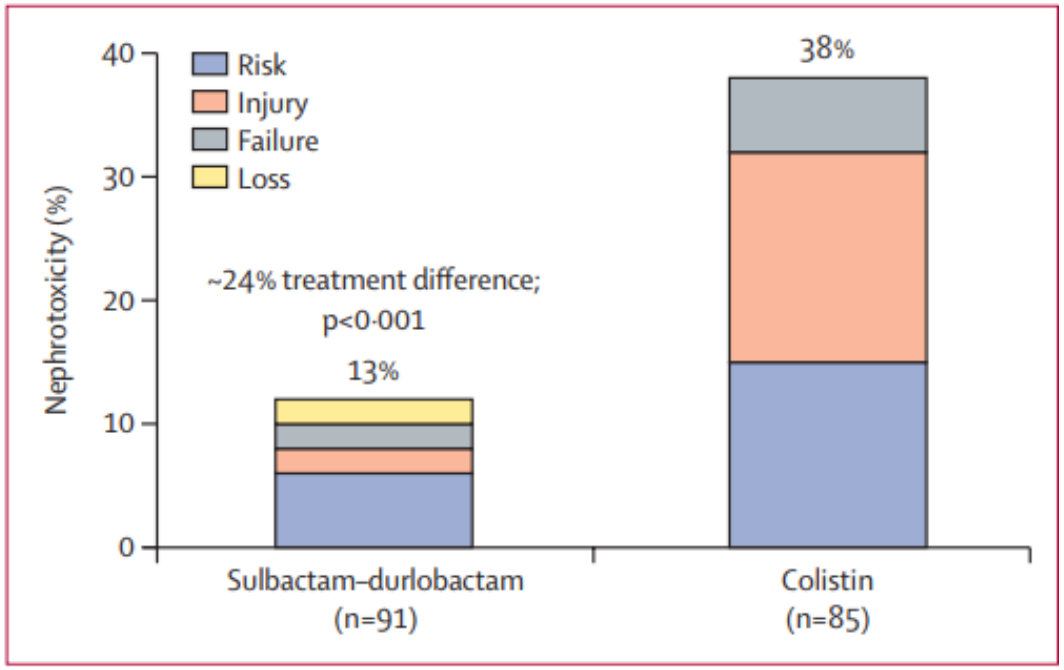

***Figure 3*: Incidence of nephrotoxicity (at any visit after baseline), as measured by modified RIFLE criteria (part A, safety population)**

Nephrotoxicity analysis for the safety population excluded one patient in the colistin group with chronic haemodialysis at baseline. Nephrotoxicity was assessed using modified RIFLE criteria measured by creatinine level or glomerular filtration rate, but not urinary volume, as described previously.[20] If patients had multiple RIFLE events, the patient was counted only once at the highest severity. Although two patients in the sulbactam–durlobactam group were assigned loss by the investigators, neither patient satisfied the criteria of persistent acute renal failure or complete loss of function for more than 4 weeks after study drug day 1. No patients in either treatment group had end-stage renal disease. RIFLE criteria: risk is defined as an increased creatinine level (×1·5) or GFR decrease of more than 25%; injury is defined as an increased creatinine level (×2) or GFR decrease of more than 50%; failure is defined as an increased creatinine level (×3), GFR decrease of more than 75%, or creatinine level of 4 mg/dL or more; loss is defined as persistent acute renal failure or complete loss of function for more than 4 weeks; and end-stage kidney disease is defined by the disease persisting for 3 months or longer. RIFLE=Risk, Injury, Failure, Loss, End-stage renal disease. GFR=glomerular filtration rate.

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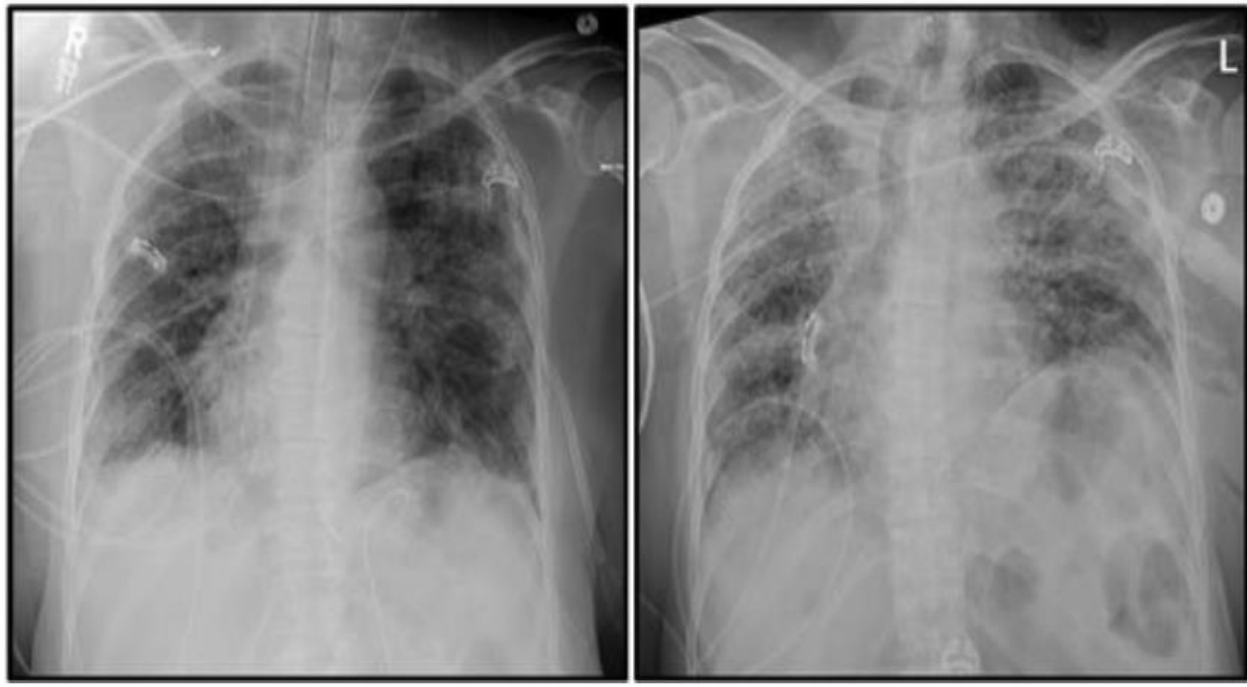
CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Check for updates

Extensively Drug-Resistant *Acinetobacter baumannii* Nosocomial Pneumonia Successfully Treated with a Novel Antibiotic Combination

Noor Zaidan,[a] J. Patrik Hornak,[b] David Reynoso[b]



Due to the concomitant dosing of cefiderocol, it is impossible to know which agent was the primary driver of microbial eradication; however, it is possible that durlobactam, in addition to providing protection to sulbactam, was also able to enhance the activity of cefiderocol

Successful Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Meningitis With Sulbactam-Durlobactam

Pranita D. Tamma,[1] Shanan Immel,[2] Sara M. Karaba,[3] Caitlin L. Soto,[4] Rick Conzemius,[5] Emily Gisriel,[6] Tsigereda Tekle,[6] Haley Stambaugh,[6] Emily Johnson,[7] Jeffrey A. Tornheim,[3] and Patricia J. Simner[3,6]

We report the case of a 42-year-old woman with CRAB meningitis who experienced persistently positive cerebrospinal fluid (CSF) cultures for 13 days despite treatment with high-dose ampicillin-sulbactam and cefiderocol.

On day 13, she was transitioned to sulbactam-durlobactam and meropenem; 4 subsequent CSF cultures remained negative. After 14 days of sulbactam-durlobactam, she was cured of infection.

This case describes successful treatment of refractory CRAB meningitis with the administration of sulbactam-durlobactam and meropenem and highlights the need to be cognizant of the paradoxical effect that can be observed with broth microdilution testing of CRAB isolates with cefiderocol.

International Journal of *Molecular Sciences*

MDPI

Review

Unveiling the Secrets of *Acinetobacter baumannii*: Resistance, Current Treatments, and Future Innovations

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MECHANISMS OF ACTION: PHYSIOLOGICAL EFFECTS

Intrinsic Antibacterial Activity of Xeruborbactam *In Vitro*: Assessing Spectrum and Mode of Action

Dongxu Sun,[a] Ruslan Tsivkovski,[a] Joe Pogliano,[b,c] Hannah Tsunemoto,[b] Kirk Nelson,[a] Debora Rubio-Aparicio,[a] Olga Lomovskaya[a]

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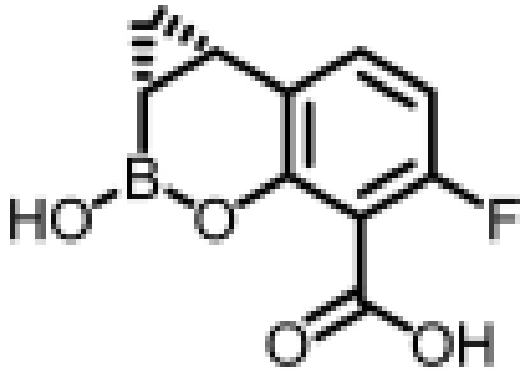
| Antimicrobial Chemotherapy | Full-Length Text



QPX7728

In vitro potency of xeruborbactam in combination with multiple β-lactam antibiotics in comparison with other β-lactam/β-lactamase inhibitor (BLI) combinations against carbapenem-resistant and extended-spectrum β-lactamase-producing *Enterobacterales*

Brief Report

Antimicrobial Therapy Duration for Bloodstream Infections Caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii-calcoaceticus complex*: A Retrospective Cohort Study

Rodrigo Douglas Rodrigues [1], Rebeca Carvalho Lacerda Garcia [1], Gabriel Almeida Bittencourt [2], Vicente Bouchet Waichel [2], Ester Carvalho Lacerda Garcia [3] and Maria Helena Rigatto [1,4,5,*]

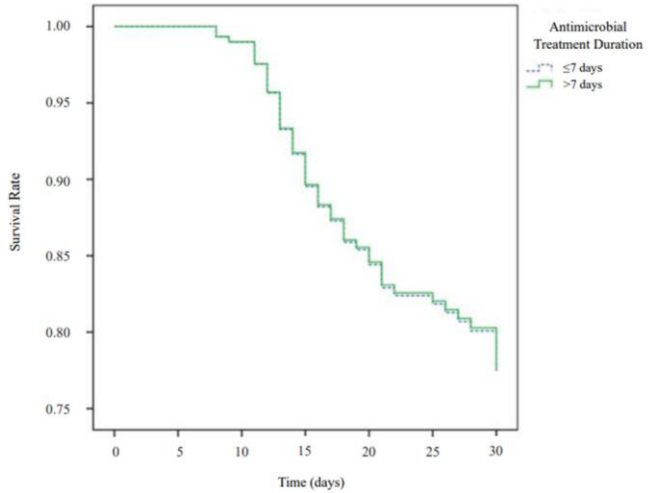


Table 2. Multivariate analysis for 30-day and in-hospital mortality in patients with Pseudomonas aeruginosa or Acinetobacter baumannii-calcoaceticus complex bloodstream infections.

Variables	30-Day Mortality			In-Hospital Mortality		
	aHR	95% CI	*p*	aHR	95% CI	*p* Value
Short-term therapy (vs. long-term) **	1.01	0.47–2.20	0.98	0.70	0.37–1.34	0.70
Pitt bacteraemia score	1.10	1.02–1.19	0.02	1.08	1.01–1.15	0.03
Charlson Comorbidity Index	1.18	1.07–1.30	<0.01	1.13	1.04–1.22	<0.01
Carbapenem resistance	2.65	1.28–5.48	<0.01	1.91	1.09–3.36	0.02

aHR, adjusted hazard ratio; CI, confidence interval. ** Short term therapy ≤ 7 days, long-term therapy > 7 days.