Carbapenem resistant *Acinetobacter baumannii* (CRAb)

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Ospedale Amedeo di Savoia

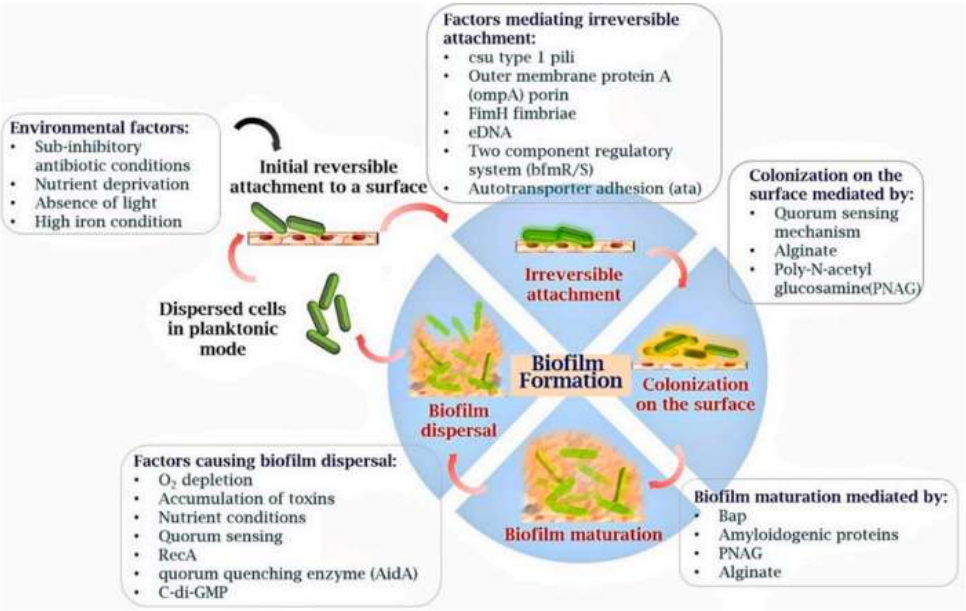
Acinetobacter baumannii complex

Aerobic, gram-negative, pleomorphic and non-fermenting bacterium

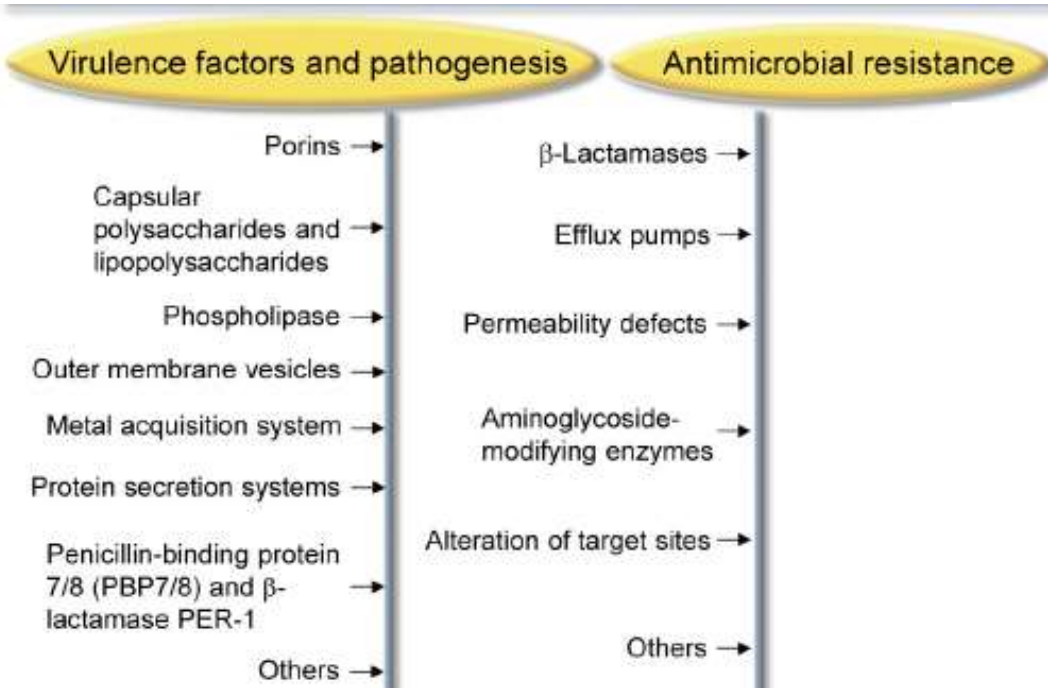
Has emerged from an organism of questionable pathogenicity to an infectious agent of importance to hospitals worldwide

A. baumannii virulence mechanism

The persist and resist strategy



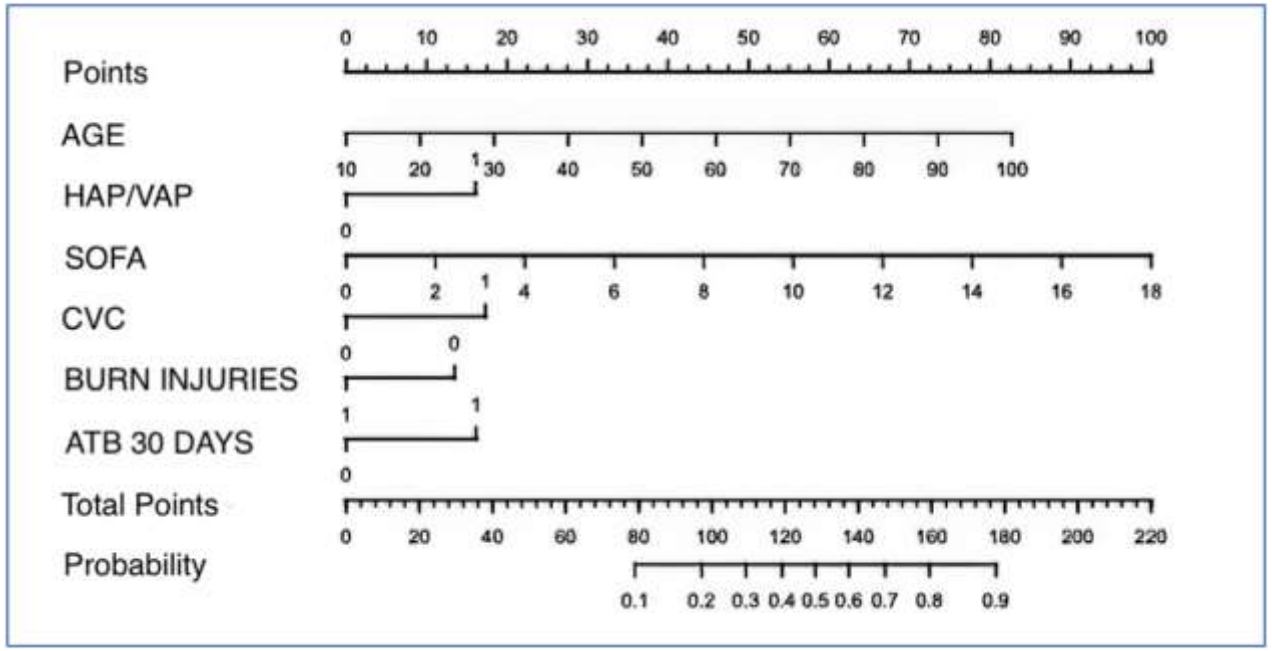
Survive environmental desiccation for weeks promoting transmission through fomite contamination in hospitals



Adapted by Lee, 2017.

CRAB Infection: mortality

Mortality rates for individuals with *A. baumannii* infections are alarmingly high, ranging from 29% to 73% and exceeding 90% in patients with septic shock.



Corcione, J *Glob Antimicrob Resist*. 2024

CRAB Infection: mortality

Table 4. Primary Outcome: Crude 30-Day Mortality and Attributable Mortality for Each Cohort of Carbapenem-Resistant Gram-Negative Bacilli

Carbapenam-resistant Gram negative bacilli	Crude 30-Day Mortality	Adjusted Odds Ratio of Death[a]	Attributable Mortality, Controls: Patients With Carbapenem-Susceptible Bloodstream Infection
Klebsiella pneumoniae carbapenemase–producing Enterobacterales[b]	26.5%	1.43 (0.92–2.22)	5%
Metallo-β-lactamase–producing Enterobacterales	36.4%	5.86 (2.72–12.76)	35%
Carbapenem-resistant *Pseudomonas aeruginosa*	32.8%	2.99 (1.48–5.95)	19%
Carbapenem-resistant *Acinetobacter baumannii*	43.2%	2.65 (1.52–4.61)	16%

Falcone M et al (ALARICO Network). *Clin Infect Dis*. 2023.

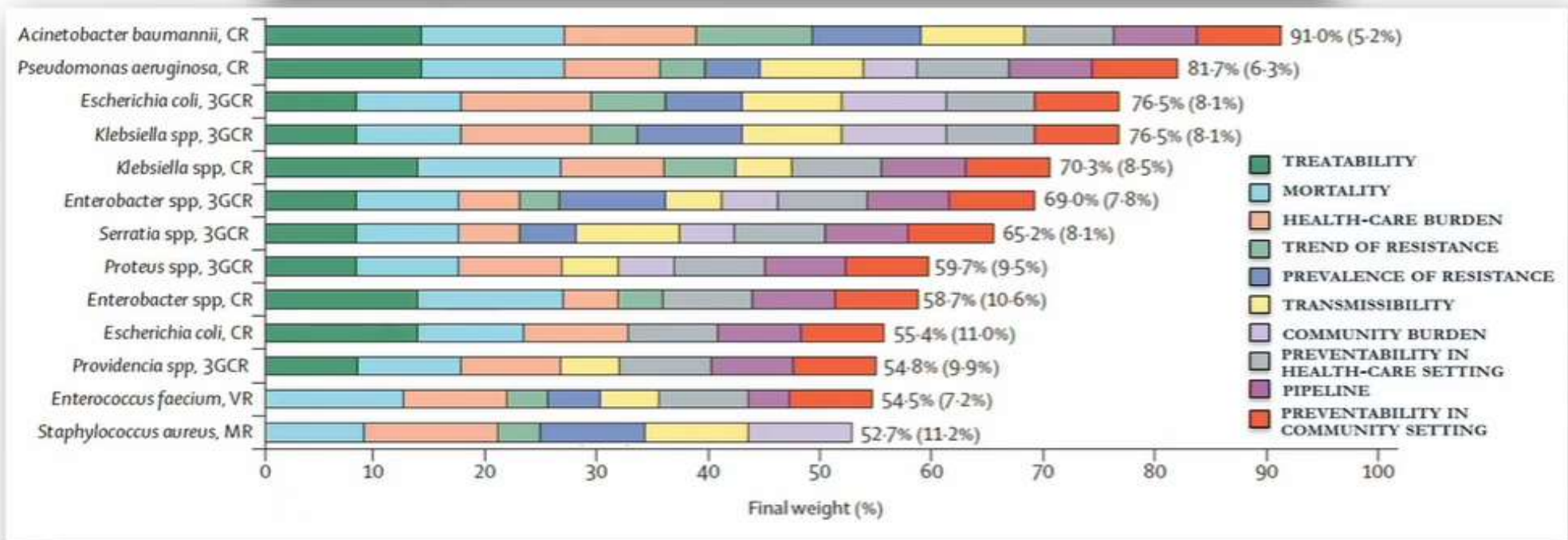
It is challenging to determine if poor clinical outcomes are attributable to suboptimal antibiotic therapy or to underlying host factors

Critical group

- Enterobacterales, carbapenem-resistant
- Enterobacterales, third-generation cephalosporin-resistant
- *Acinetobacter baumannii*, carbapenem-resistant
- *Mycobacterium tuberculosis*, rifampicin-resistant[a]

[a]RR-TB was included after an independent analysis with parallel criteria and subsequent application of an adapted MCDA matrix.

Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

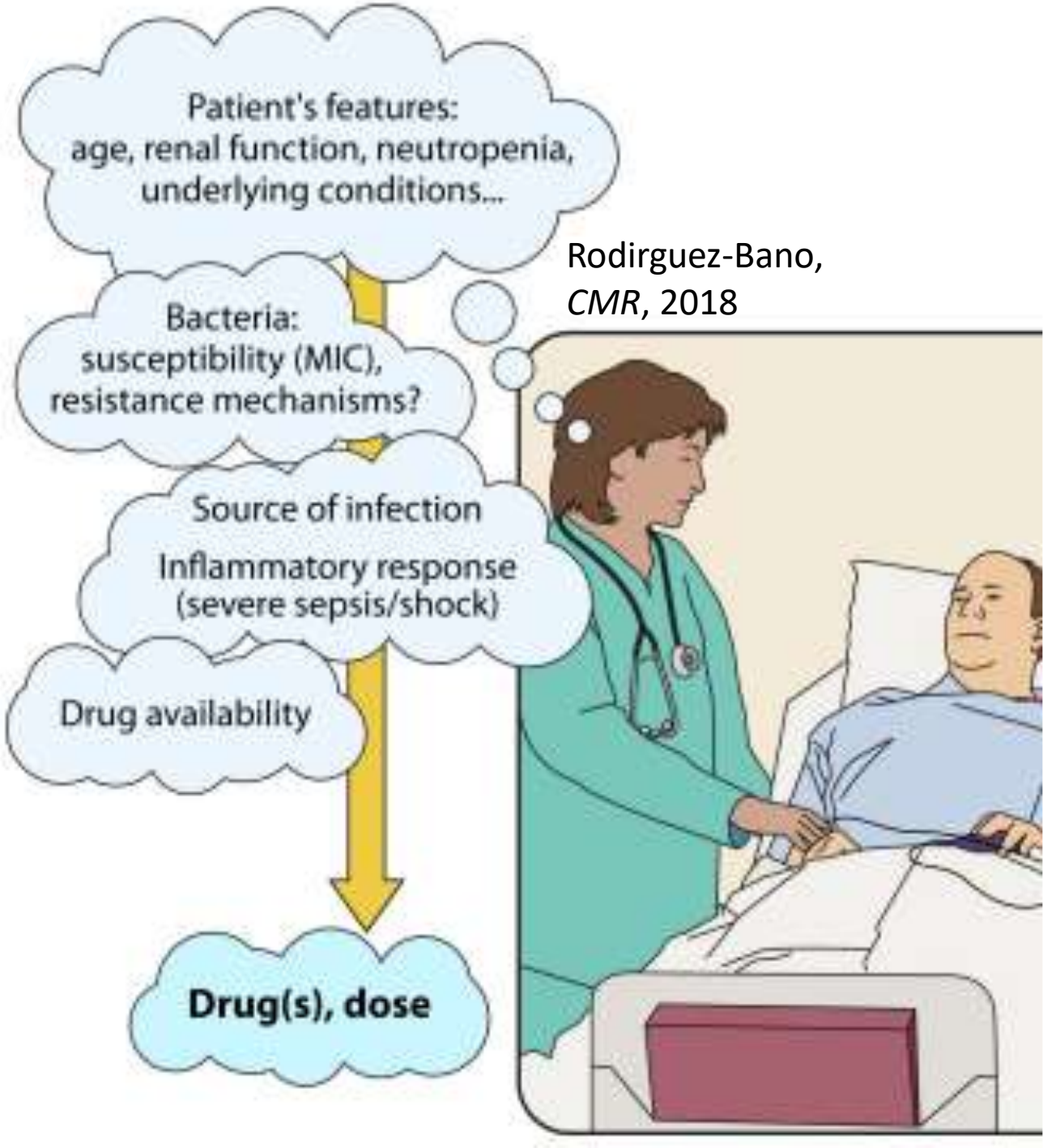


3GCR, third-generation cephalosporin-resistant; CR, carbapenem-resistant; MR, methicillin-resistant; VR, vancomycin-resistant; WHO, World Health Organization.

1. Tacconelli E, et al. *Lancet Infect Dis*. 2018;18(3):318–27. doi: 10.1016/S1473-3099(17)30753-3;
2. World Health Organization, WHO. 2024. Available at: https://www.who.int/publications/i/item/9789240093461 [Accessed April 2025].

CRAB: available treatment options

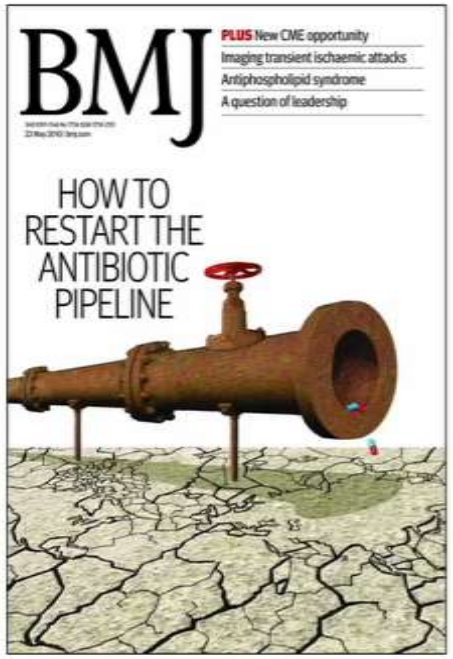
- Sulbactam
- Colistin
- Tetracyclin (minocyclin, tigecyclina)
- Aminoglycosides
- Cefiderocol



Rodirguez-Bano, *CMR*, 2018

CRAB – Guidelines indication

	ESCMID Guidelines (April 2022)	IDSA Guidance (July 2023)
Combination antibiotic regimen	For severe and high-risk CRAB infection	For moderate–severe CRAB infection
Ampicillin/sulbactam	For patients with CRAB susceptible to sulbactam and HAP/VAP (1 g sulbactam component q6h)	Back-bone treatment for all CRAB infection (6–9 g sulbactam component daily)
Polymyxins	Either colistin or polymyxin B: for patients with CRAB resistant to sulbactam susceptible to polymyxins; in combination with one other in vitro active agent for severe, susceptible to polymyxins, CRAB infection	Polymyxin B in combination with at least one other agent for the treatment of CRAB infections (Colistin only for CRAB UTIs)
Tetracycline derivatives	High-dose tigecycline: for patients with CRAB resistant to sulbactam susceptible to tigecycline; in combination with one other in vitro active agent for severe, susceptible to tigecycline, CRAB infection	High-dose minocycline (preferred option) or high-dose tigecycline in combination with at least one other agent for the treatment of CRAB infections
Cefiderocol	Not recommended	In combination with at least one other agent for the treatment of CRAB infections refractory to other antibiotics (or when the use of other antibiotics is precluded)
Aminoglycosides	In combination with one other in vitro active agent for severe, susceptible to aminoglycosides, CRAB infection	Not recommended
High-dose extended-infusion meropenem	In combination with one other in vitro active agent for severe CRAB infections with a meropenem MIC < 8 mg/L	Not recommended



Serapide et al, *Antibiotics* 2024

CRAB treatment: SULBACTAM

- **Class A beta-lactamase inhibitor**, with direct activity on A.baumannii.
- Sulbactam targets and **saturates PBP1a, PBP1b, and PBP3** in *A. baumannii-calcoaceticus* complex
- Very narrow spectrum

Bantar, *Braz J Infect Dis* 2009

Dosing:

PK/PD parameter: (*f*T > MIC). REMEMBER: drug exposures vary widely across critically ill patients

- Ampicillin-sulbactam regimen of 3 g every 4 hours when isolates test susceptible or intermediate to ampicillinsulbactam

Jaruratanasirikul, *Eur J Pharm* Sci 2019

- For isolates testing resistant (MIC ≥16 mg/L), ampicillin-sulbactam optimized regimens of 9 g every 8 hours administered as a 4-hour infusion are needed to achieve PK-PD targets

Abouelhassan, IDSA- ID Wk. 2022

CRAB treatment: SULBACTAM

Evidence available:

Systematic review and network meta-analysis

1) Jiating Liu, 2017:

- sulbactam (≥6 g/day) + levofloxacin or tigecycline VS colistin alone, colistin plus a carbapenem, or colistin with another active agent

- Clinical Improvement: RR = 2.99 [95%CI: 1.08–8.24], 3.12 [1.14–8.60], and 3.06 [1.13–8.29], respectively. No regimen was associated with significant improvements in survival

2) Jung SY, 2021:

- Sulbactam (3–8 g/day) and highdose sulbactam (≥9 g/day) as monotherapy resulted in the highest probability of reducing mortality when compared with other treatments

3) Chu 2013:

- Sulbactam-based therapies and non-sulbactam-based therapies may have similar efficacy in the treatment of A. baumannii infection.

Colistin versus Colistin Combined with Ampicillin-Sulbactam for Multiresistant *Acinetobacter baumannii* Ventilator-associated Pneumonia Treatment: An Open-label Prospective Study

Demosthenes Makris, Efi Petinaki[1], Vasssiliki Tsolaki, Efstratios Manoulakas, Konstantinos Mantzarlis, Olimpia Apostolopoulou, Dimitrios Sfyras[2], Epaminondas Zakynthinos

Departments of Critical Care and [1]Microbiology, University Hospital of Larissa, Larissa, [2]Intensive Care Unit, Lamia General Hospital, Lamia, Greece

Open-label, prospective randomized study in 2 Greek intensive care units (ICUs)

- 39 patients with CRAB pneumonia randomized to receive:

A) colistin alone

B) colistin plus high-dose ampicillin-sulbactam (6 g every 6 hours; equivalent to 8 g of sulbactam daily).

The treating clinician was allowed to change therapy if it was determined to be unsuccessful after the fourth day

Results:

- Initial clinical response was demonstrated in 16% (3/19) and 70% (14/20) of patients receiving colistin alone and colistin plus ampicillin-sulbactam, respectively (OR = 12.4; 95% CI: 2.6–59.3; *P* = .001).
- Changes: 16 patients COL arm and 3 in AS arm of the study. Among those who initially received colistin alone, a favorable clinical response was observed in 38% (6/16) when ampicillin-sulbactam was added.
- 28-day mortality rates: colistin alone (63%) VS colistin plus ampicillin-sulbactam (50%) (*P* = .52)

Given the open-label design and physician-assigned outcomes in the study, caution should be exercised in extrapolating the findings

- Conceptually speaking, the notion that an in vitro active β-lactam antibiotic like ampicillin-sulbactam would be more effective than colistin for the treatment of CRAB infections, particularly pneumonia, is somewhat intuitive given the known PK limitations and toxicity associated with colistin .

Shields, 2023

Unfortunately, such hypotheses are not supported by the available clinical data

- susceptible to cleavage by several ß-lactamases (TEM-1, (ADC)-30, OXAs (OXA-23, OXA-24/72, and OXA-58 families)
- **its clinical utility for A. baumannii infections has been compromised over time**

Coming soon: SULBACTAM-DURLOBACTAM

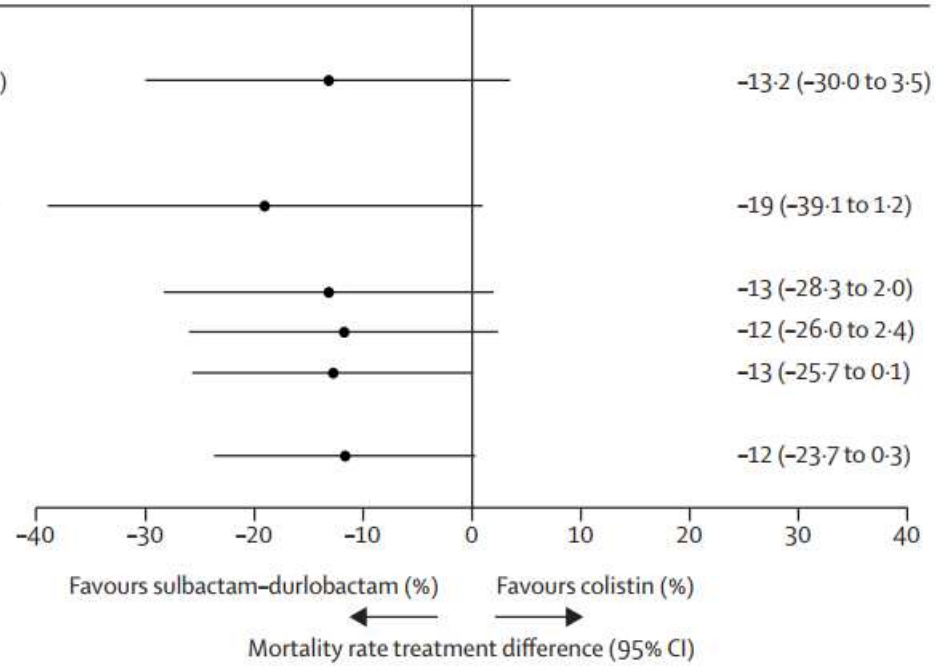
- Sulbactam/durlobactam was recently approved in the U.S. for the treatment of pneumonia due to susceptible ABC
- Durlobactam is a novel non–β-lactam diazabicyclooctane β-lactamase inhibitor, with a broad-spectrum activity against class A, C, and D β-lactamases and PBPs. Furthermore, through PBP2 inhibition, it also showed a minimal intrinsic activity against the pathogen

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

A

	Sulbactam–durlobactam, n/N (%)	Colistin, n/N (%)	Treatment difference, % (95% CI)
Primary endpoint			
28-day ACM: carbapenem-resistant ABC microbiologically modified ITT	12/63 (19·0%)	20/62 (32·3%)	−13·2 (−30·0 to 3·5)
Secondary endpoints			
28-day ACM: carbapenem-resistant ABC microbiologically evaluable	8/46 (17%)	16/44 (36%)	−19 (−39·1 to 1·2)
28-day ACM: microbiologically modified ITT	15/76 (20%)	25/76 (33%)	−13 (−28·3 to 2·0)
28-day ACM: ITT	19/90 (21%)	28/85 (33%)	−12 (−26·0 to 2·4)
14-day ACM: carbapenem-resistant ABC microbiologically modified ITT	4/64 (6%)	12/63 (19%)	−13 (−25·7 to 0·1)
14-day ACM: microbiologically modified ITT	6/77 (8%)	15/77 (20%)	−12 (−23·7 to 0·3)



CRAB treatment: COLISTIN

- the most used therapeutic options for CRAB
- binding to the anionic molecules of LPS, displacing Mg^{2+} and Ca^{2+} from the outer cell membrane of Gram-negative bacteria, causing permeability changes in the cell envelope and leakage of cell contents
- Resistance rate: 2-10% in Europe

Colistin: major concerns

TOXICITIES:
- Kidney
- CNS

Therapeutic window extremely narrow
(~2 µg/mL may be required to achieve 1-log10 reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity)

Nation RL. Antibiotic 2019

PK

The activity of IV polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs

Landersdorfer CB. J Antimicrob Chemother 2018

Cheah SE. J Antimicrob Chemother 2015

Concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity

Sandri AM. Clin Infect Dis 2013

m.i.c. (reported false susceptibility with e-test and automated system; since 2020 EUCAST suggest Broth Microdilution)

CRAB treatment: COLISTIN

- DOSING:

Dose	Dosing Suggestions[a]
Loading dose	Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later.
Daily dose[b]	Equation 2[c]: Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0048 \times CrCl + 1.825)}$ See Table 3 ("look-up" table) for the daily dose to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's creatinine clearance.

Table 3. "Look-up" Table of Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L for Narrow Windows of Creatinine Clearance

Creatinine clearance, mL/min	Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a]	
	CBA, mg/d	Million IU/d
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

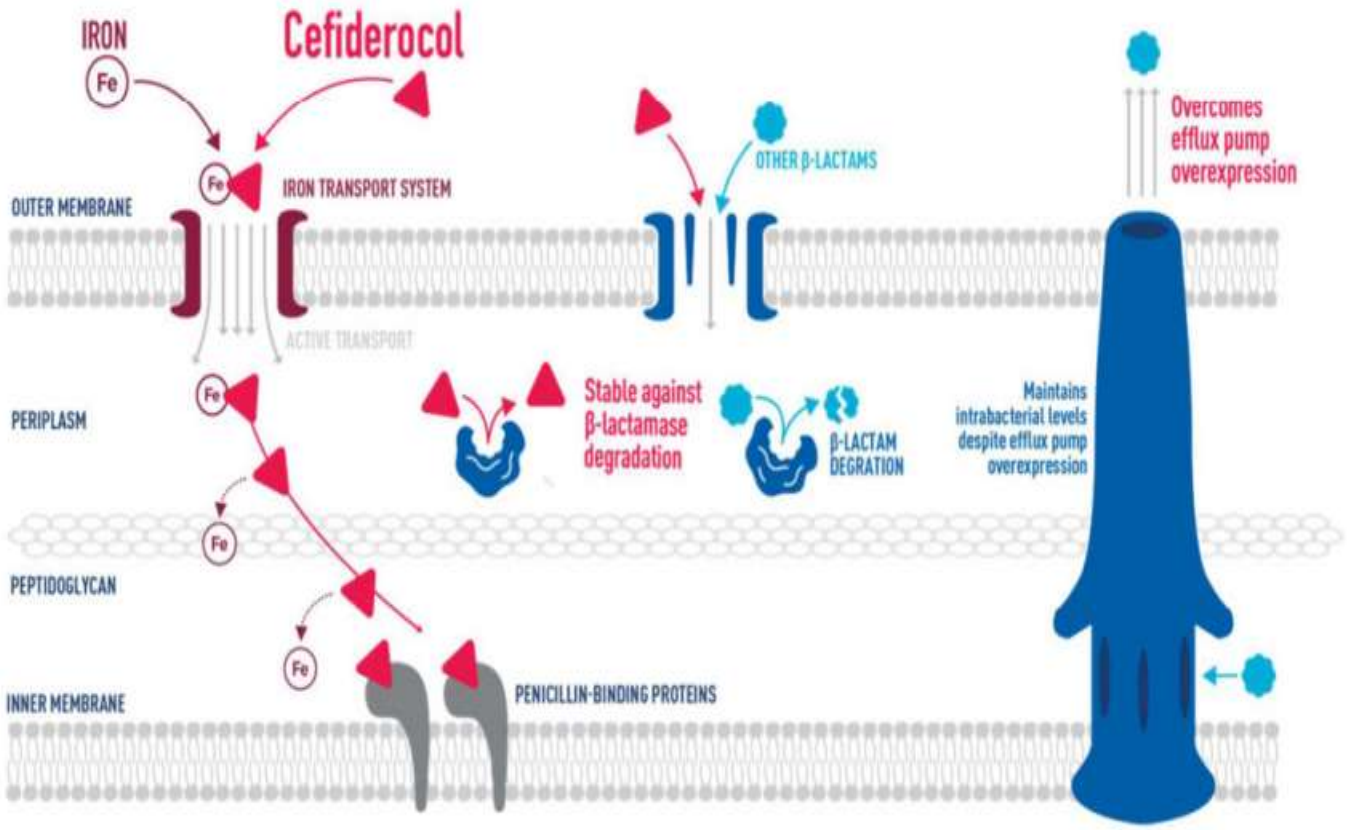
Pranita D. Tamma,[1,2] Emily L. Heil,[3] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

Question 5.10: What Is the Role of Nebulized Antibiotics for the Treatment of Respiratory Infections Caused by CRAB?

Suggested approach: Nebulized antibiotics are not suggested for the treatment of respiratory infections caused by CRAB.

Nation et al, CID, 2017

CRAB treatment: CEFIDEROCOL



- Cefiderocol is a novel catechol-substituted siderophore cephalosporin
- inhibition of PBPs (primarily PBP3)
- transported into the periplasmic space mainly through the bacterial siderophore iron uptake system

Katie A Parsels, *Journal of Antimicrobial Chemotherapy*, 2021

CRAB treatment: CEFIDEROCOL

- The cefiderocol susceptibility rate for CRAB was estimated to be between 77.9% and 97.2% across different countries.

Kollef M. Int J Antimicrob Agents.

- In the SIDERO surveillance program, 3.9% (204 out of 5225) of CRAB isolates had high (≥8 µg/mL) cefiderocol MICs without prior exposure to this antibiotic.

Karlowsky JA. Antimicrob Agents Chemother. 2022

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

More deaths occurred in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp infections, particularly in patients with nosocomial pneumonia or bloodstream infection or sepsis with *Acinetobacter* spp at baseline

	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**

		Patients with *Acinetobacter* spp. infection	
		Cefiderocol (N=42)*	BAT (N=17)^
Age	Median (Range) (Interquartile range)	68·5 (23–91) (45–77)	62 (19–83) (42–74)
	Age ≥65	26 (62%)	7 (41%)
Clinical diagnosis	HAP/VAP/HCAP	29 (69%)	10 (59%)
	BSI/Sepsis	12 (29%)	7 (41%)
	cUTI	1 (2%)	0
Severity	Mild	2 (5%)	2 (12%)
	Moderate	17 (40%)	8 (47%)
	Severe	23 (55%)	7 (41%)
Total APACHE II score	Median (Range) (Interquartile range)	17 (5–29) (13–22)	15 (5–26) (14–20)
	≥16	24 (57%)	8 (47%)
SOFA score	Median (Range) (Interquartile range)	6 (1–17) (3–9)	6 (1–11) (3–8)
CPIS score**	Median (Range) (Interquartile range)	5 (2–9) (4–6)	5 (2–7) (4–6)
CCI score	Median (Range) (Interquartile range)	5·5 (0–12) (3–8)	5·0 (0–9) (4–6)
	≥6	21 (50%)	6 (35%)
Creatinine clearance (mL/min)	Median (Range) (Interquartile range)	68·6 (17·9–539·6) (44·8–113·8)	84·6 (15·9–251·8) (59·8–105·1)
	Grading group <50 mL/min	14 (33%)	3 (18%)
Treatment failure to prior therapy		27 (64%)	13 (76%)
Shock at screening or within 31 days prior to randomisation		11 (26%)	1 (6%)
Shock (ongoing)		8 (19%)	1 (6%)
ICU at randomisation		34 (81%)	8 (47%)
Mortality	Day 14	12 (29%)	3 (18%)
	Day 28	16 (38%)	3 (18%)
	EOS	21 (50%)	3 (18%)

Bassetti, Matteo et al.The Lancet Infectious Diseases, Volume 21, Issue 2, 2020

Table 2. Retrospective observational studies comparing cefiderocol with colistin-based regimen in ICU patients with CRAB.

	Pascale et al. [32] Multicentre (January 2020–April 2021)	**Mazzitelli et al. [33] Single-Centre (August 2020–July 2022)**	**Falcone et al. [10] Single-Centre (January 2020–August 2021)**	**Russo et al. [11] Single-Centre (March 2020–August 2022)**
Population: antibiotic-based regimen groups	107 patients: 42 CFD 65 COL	111 patients: 60 CFD 51 COL	124 patients: 47 CFD 77 COL	73 patients: 19 CFD 54 COL
COVID-19 coinfection	100%	32%	38.7%	100%
Site of infection	BSI (58%) LRTI (41%) Others (1%)	BSI (47.7%) Pneumonia (52.3%)	BSI (57.4%) VAP (25.5%) Others (17%)	VAP and concomitant BSI (100%)
Patients received CFD in combination	0	30 (50%)	33 (70%)	19 (100%)
Main agents co-administered with CFD	/	TGC (18/30) MEM (13/30) FOS (8/30)	TGC (21/33) FOS (8/33)	FOS (7/19) FOS + TGC (7/19) TGC (1/19)
28–30 day all-cause mortality: CFD group vs. COL group	23 (55%) vs. 38 (58%) (p-value: 0.7)	26 (51%) vs. 22 (37%) (p-value: 0.13)	16 (34%) vs. 43 (56%) (p-value: 0.018)	6 (31.5%) vs. 53 (98%) (p-value < 0.001)

Legend. ICU: intensive care unit; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CFD: cefiderocol; COL: colistin; BSI: bloodstream infection; LRTI: low respiratory tract infection; VAP: ventilator-associated pneumonia; TGC: tigecycline; MEM: meropenem; FOS: fosfomycin.

Serapide, Antibiotics, 2024.

Table 2. Retrospective observational studies comparing cefiderocol with colistin-based regimen in ICU patients with CRAB.

	Falcone et al. [10] Single-Centre (January 2020–August 2021))21)
Population: antibiotic-based regimen groups	124 patients: 47 CFD 77 COL
COVID-19 coinfection	38.7%
Site of infection	BSI (57.4%) VAP (25.5%) Others (17%)
Patients received CFD in combination	33 (70%)
Main agents co-administered with CFD	TGC (21/33) FOS (8/33)
28–30 day all-cause mortality: CFD group vs. COL group	16 (34%) vs. 43 (56%) (*p*-value: 0.018)

Legend. ICU: intens
istin; BSI: bloodstre
TGC: tigecycline; M

Serapide, Antibiotics, 2024.

TABLE 3 Clinical characteristics and outcomes of patients with CRAB infections by treatment regimens[a]

Variable	FDC-containing regimens (*N* = 47)	Colistin-containing regimens (*N* = 77)	*p*[b]
Age, median, IQRs	63 (53.5–75)	68 (56–75)	0.414
Male sex	29 (61.7%)	63 (81.8%)	***0.013***
Comorbidities			
Diabetes mellitus	3 (6.4%)	20 (26%)	***0.006***
Cardiovascular disease	29 (61.7%)	44 (57.1%)	0.617
COPD	4 (8.5%)	13 (16.9%)	0.188
Chronic renal disease	2 (4.3%)	7 (9.1%)	0.314
Chronic liver disease	2 (4.3%)	3 (3.9%)	1.0
Solid cancer	3 (6.4%)	5 (6.5%)	0.981
Charlson Comorbidity Index, median, IQRss	3 (1–5)	3 (1–5)	0.413
SOFA score, median, IQRs	9 (6–11)	9 (4–11)	0.693
APACHE II score, median, IQRs	18 (9–25)	16 (11–22)	0.702
Invasive mechanical ventilation	25 (53.2%)	45 (55.8%)	0.459
Intravascular device	47 (100%)	77 (100%)	1.0
Septic shock	30 (63.8%)	45 (58.4%)	0.551
AKI at time of sepsis	10 (21.3%)	21 (27.3%)	0.454
Parenteral nutrition	20 (42.6%)	19 (24.7%)	***0.038***
ECMO at time of sepsis	7 (14.9%)	2 (2.6%)	***0.026***
CVVH at time of sepsis	6 (12.8%)	8 (10.5%)	0.704
Source control	18 (38.3%)	31 (40.3%)	0.828
Polymicrobial infections	8 (17%)	22 (28.6%)	0.145
Duration of targeted antibiotic therapy	12 (7–14)	10 (6.5–13)	0.089
30-day mortality	16 (34%)	43 (55.8%)	***0.018***
Microbiological failure[c]	8/46 (17.4%)	5/74 (6.8%)	0.079
Length of hospital stay after CRAB infection, median, IQRs	28 (16–34)	13 (6–23.5)	***<0.001***

Table 2. Retrospective observational studies comparing cefiderocol with colistin-based regimen in ICU patients with CRAB.

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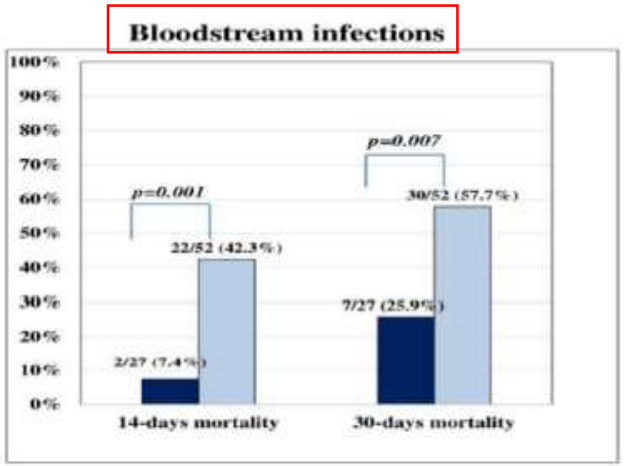
COVID-19 coinfection	38.7%
Site of infection	BSI (57.4%) VAP (25.5%) Others (17%)
Patients received CFD in combination	33 (70%)
Main agents co-administered with CFD	TGC (21/33) FOS (8/33)
28–30 day all-cause mortality: CFD group vs. COL group	16 (34%) vs. 43 (56%) (*p*-value: 0.018)



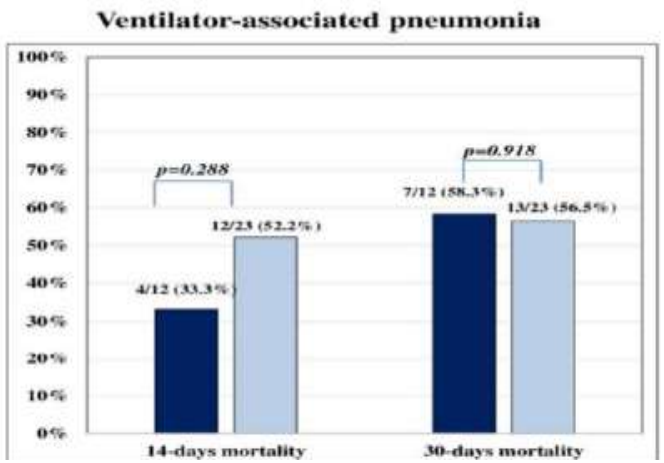


TABLE 5 Cox regression multivariable analysis of factors independently associated with 30-day mortality

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***

- increased rates of microbiological failure in patients who received cefiderocol (8/46, 17.4% versus 5/74, 6.8%, P = 0.079). Among monotherapy: 6/14, 42.9% versus 2/32, 6.3%, P = 0.006
- development of resistance to cefiderocol in the 8.5% of this group.

Serapide, Antibiotics, 2024.

Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19

A. Russo [a,†,*], A. Bruni [b,†], S. Gullì [a], C. Borrazzo [c], A. Quirino [d], R. Lionello [a], F. Serapide [a], E. Garofalo [b], R. Serraino [a], F. Romeo [a], N. Marascio [d], G. Matera [d], F. Longhini [b], E.M. Trecarichi [a,‡], C. Torti [a,‡]

	Russo et al. [11] Single-Centre March 2020–August 2022)
Population: antibiotic-based regimen groups	73 patients: 19 CFD 54 COL
COVID-19 coinfection	100%
Site of infection	VAP and concomitant BSI (100%)
Patients received CFD in combination	19 (100%)
Main agents co-administered with CFD	FOS (7/19) FOS + TGC (7/19) TGC (1/19)
28–30 day all-cause mortality: CFD group vs. COL group	6 (31.5%) vs. 53 (98%) (p-value < 0.001)

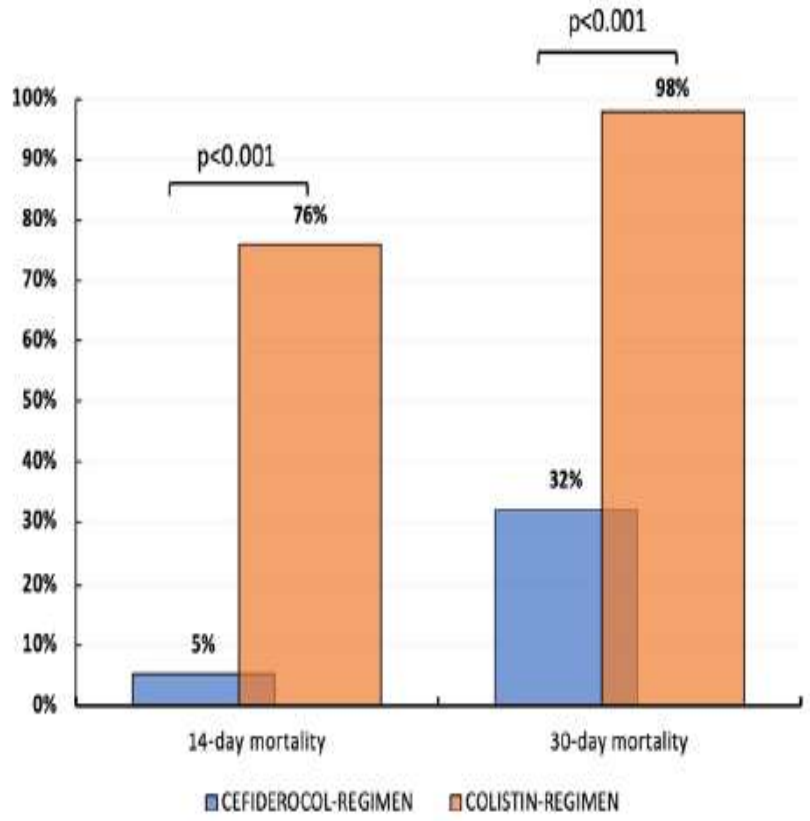


Fig. 1. Rates of 14- and 30-day mortality in patients treated with cefiderocol- or colistin-containing regimens.

Table 1
Antibiotic regimens used in targeted therapy.

Treatment regimens	n=73 patients (%)
Colistin-containing regimens	**54 (74)**
Colistin monotherapy	12 (22.2)
Colistin + meropenem + tigecycline	12 (22.2)
Colistin + meropenem	9 (16.6)
Colistin + tigecycline	6 (11.1)
Colistin + fosfomycin	3 (5.5)
Colistin + trimethoprim/sulfamethoxazole	3 (5.5)
Colistin + trimethoprim/sulfamethoxazole + meropenem + tigecycline	3 (6)
Colistin + meropenem + fosfomycin	2 (4)
Colistin + meropenem + tigecycline + ampicillin/sulbactam	2 (4)
Colistin + trimethoprim/sulfamethoxazole + tigecycline	2 (4)
Cefiderocol-containing regimens	**19 (26)**
Cefiderocol + fosfomycin	6 (31.5)
Cefiderocol + fosfomycin + tigecycline	3 (15.8)
Cefiderocol + meropenem + fosfomycin + tigecycline	3 (15.8)
Cefiderocol + trimethoprim/sulfamethoxazole	2 (10.5)
Cefiderocol + tigecycline	1 (5.2)
Cefiderocol + trimethoprim/sulfamethoxazole	1 (5.2)
Cefiderocol + ampicillin/sulbactam	1 (5.2)
Cefiderocol + fosfomycin + ampicillin/sulbactam	1 (5.2)
Cefiderocol + meropenem + fosfomycin + tigecycline + trimethoprim/sulfamethoxazole	1 (5.2)
Cefiderocol monotherapy	0
Colistin aerosol	**33 (45.2)**

	Bavaro, 2023. Single center. Obs. Retrosp. 01/20-12/22	Dalfino, 2023. Single center, Obs. Prospective. 3/21-12/22	Oliva 2023, Obs, retrosp. Single center. 6/21-4/23
Population, Antibiotic based regimen group	118, FDC:43 COL:75	90, FDC:40 COL:50	104 FDC: 50 (48.1%) COL: 54 (51.9%)
Primary Objective	Mortality (30days)	Clinical Failure	
Covid19 co-infection	0	0	42.3%
Site of Infection	BSI	VAP (+/- BSI)	BSI (BSI 44%, VAP 26%, CR.BSI 20%, HAP 10%)
Patients received FDC in combination	63%	52.5%	75%
Main Agent Co-administered	FOS 20 (47%) A/S 10 (23%)	FOS (100%)	
Mortality: FDC vs COL	FDC:17(28) COL: 44(72) p=0.045	14days FDC:10%; COL:38% p=0.003 30 days: FDC:35%; COL:52% p>0.05	FDC: 36% COL:42% P=0.42

	Bavaro, 2023. Single center. Obs. Retrosp. 01/20-12/22
Population, Antibiotic based regimen group	118, FDC:43 COL:75
Primary Objective	Mortality (30days)
Covid19 co-infection	0
Site of Infection	BSI
Patients received FDC in combination	63%
Main Agent Co-administered	FOS 20 (47%) A/S 10 (23%)
Mortality: FDC vs COL	FDC:17(28) COL: 44(72) p=0.045

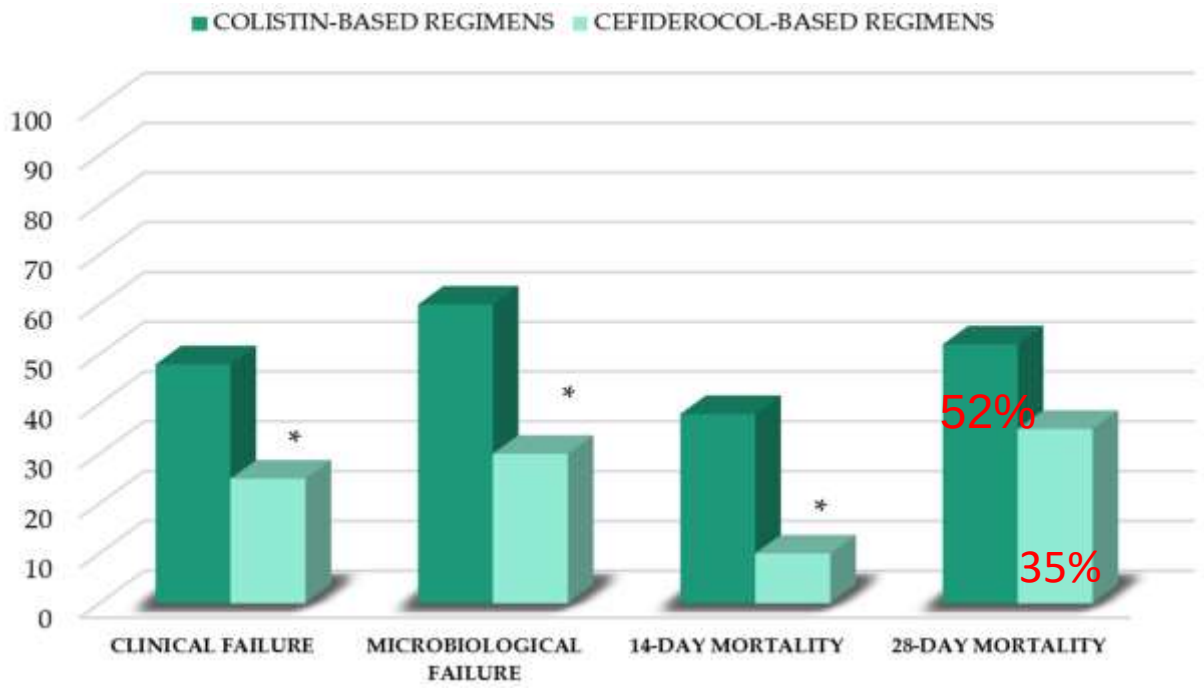
Table 1 Clinical features of patients treated with colistin- and cefiderocol-based regimens

	Overall (*n.* 118)	Colistin-based regimens (*n.* 75)	Cefiderocol-based regimens (*n.* 43)	*p* value
Median (q1–q3) age, years	70 (62–79)	71 (62–78)	69 (60–81)	0.917
Male sex, *n* (%)	70 (59)	44 (59)	26 (60)	0.848
PITT bacteriemia score > 4, *n* (%)	30 (25)	20 (27)	10 (23)	0.682
Site of infection treated with surgical source control, *n* (%)	26 (22)	23 (31)	3 (7)	**0.003**
Monotherapy, *n* (%)	19 (16)	3 (4)	16 (37)	**< 0.001**
Combination with other antibiotics, *n* (%)	99 (84)	72 (96)	27 (63)	
Ampicillin/sulbactam	35 (30)	25 (33)	10 (23)	0.249
Fosfomycin	42 (36)	22 (29)	20 (47)	0.061
Tigecycline	37 (31)	37 (49)	0	**< 0.001**
Time to targeted antibiotic therapy, *n* (%)				
Within 24 h from infection onset	32 (27)	16 (21)	16 (37)	**0.036**
From 24 to 72 h from infection onset	48 (41)	29 (39)	19 (44)	
After 72 h from infection onset	38 (32)	30 (30)	8 (19)	
Adverse events to antimicrobial therapy, *n* (%)	13 (11)	12 (16)	1 (2)	**0.022**
Median (q1–q3) duration of antibiotic therapy	11 (8–16)	13 (8–18)	10 (9–13)	**0.017**
30-day all-cause mortality, *n* (%)	61 (52)	44 (59)	17 (40)	**0.045**
30-day infection related mortality, *n* (%)	55 (47)	42 (56)	13 (30)	**0.007**
90-day infection recurrence/relapse, *n* (%)	8 (7)	4 (5)	4 (9)	0.409
90-day all-cause mortality, *n* (%)	67 (58)	48 (64)	19 (42)	**0.032**

Table 3 Univariable, multivariable, and IPTW-adjusted multivariable Cox model for 30-day all-cause mortality

	Univariable analysis			Multivariable analysis			IPTW-adjusted multivariable analysis		
	HR	95% CI	*p* value	aHR	95% CI	*p* value	aHR	95% CI	*p* value
Time to appropriate antimicrobial therapy									
Within 24 h from infection onset	1			1					
From 24 to 72 h from infection onset	1.61	0.75–3.42	0.216	1.64	0.75–3.59	0.210			
After 72 h from infection onset	2.43	1.16–5.12	**0.019**	2.42	1.11–5.25	**0.025**			
Cefiderocol-based antibiotic therapy	0.51	0.28–0.94	**0.031**	0.49	0.25–0.93	**0.029**	0.53	0.27–0.98	**0.047**
Antibiotic therapy including sulbactam	0.98	0.55–1.77	0.972	–					
Antibiotic therapy including fosfomycin	0.43	0.22–0.81	**0.010**	–					
Antibiotic therapy including tigecycline	1.65	0.95–2.85	0.070	–					
Monotherapy vs combotherapy	0.81	0.39–1.66	0.570	–					

	Dalfino, 2023. Single center, Obs. Prospective. 3/21-12/22
Population, Antibiotic based regimen group	90, FDC:40 COL:50
Covid19 co-infection	0
Site of Infection	VAP (+/- BSI)
Patients received FDC in combination	52.5%
Main Agent Co-administered	FOS (100%)
Mortality (14or30d): FDC vs COL	FDC:10% COL:38% P=0.003



(25% vs. 48%; p = 0.02) (10% vs. 38%; p = 0.03)

Table 3. Cox proportional hazard model for investigating predictors of clinical failure with first-line antimicrobial therapy.

	Univariable Analysis			Multivariable Analysis		
	aHR	95% CI	*p*-Value	aHR	95% CI	*p*-Value
Immunodepression	1.97	0.98–3.83	0.06	1.56	0.76–3.19	0.23
Charlson comorbidity index	1.28	1.12–1.47	<0.0001	1.21	1.04–1.42	0.01
SOFA score	1.15	1.02–1.30	0.02	1.07	0.92–1.25	0.35
Septic shock	1.91	0.93–3.87	0.07	1.52	0.69–3.33	0.29
Bacteremic VAP	1.46	0.74–2.90	0.28	/		
Augmented renal clearance	1.07	0.41–2.76	0.41	/		
CRRT	1.10	0.50–2.47	0.81	/		
Timely targeted therapy	0.44	0.22–0.90	0.02	0.40	0.19–0.84	0.01
Cefiderocol-based first-line regimens	0.37	0.17–0.79	0.01	0.38	0.17–0.85	0.02

CRRT: continuous renal replacement therapy; SOFA: sequential organ failure assessment; VAP: ventilator-associated pneumonia.

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]

	Clinical Resolution (n = 56)	Clinical Failure (n = 34)
Cefiderocol-based regimens	30 (54)	10 (29) *
Cefiderocol–inhaled colistin	10 (17.8)	9 (26.5)
Cefiderocol–fosfomycin–inhaled colistin	20 (35.7)	1 (3) *
Colistin-based regimens	26 (46)	24 (71) *
Colistin–tigecycline–inhaled colistin	11 (20)	16 (47) *
Colistin–ampicillin/sulbactam–inhaled colistin	8 (14)	7 (21)
Colistin–meropenem–inhaled colistin	7 (13)	1 (3)

	Oliva 2023, Obs, retrosp. Single center. 6/21-4/23
Population, Antibiotic based regimen group	104 CFD: 50 (48.1%) COL: 54 (51.9%)
Primary Objective	All causes mortality (7-14-30)
Covid19 co-infection	42.3%
Site of Infection	BSI (BSI 44%, VAP 26%, CR.BSI 20%, HAP 10%)
Patients received FDC in combination	75%
Main Agent Co-administered	
Mortality: FDC vs COL	7d: 16 vs 24% 14d: 22 vs 31% 30d: 36 vs 42% p>0.05

Table 1 General features and outcomes of study population

	Overall population n (%) = 104 (100)	CFDC n (%) = 50 (48.1)	COL n (%) = 54 (51.9)	*p*-value
Male sex, n (%)	71 (68.3)	32 (64)	39 (72.2)	*0.368*
Age, median (IQR), years	66.5 (58–78)	69 (58–77)	64 (58–78)	*0.580*
SARS-CoV-2 co-infection, n (%)	44 (42.3)	15 (30)	29 (53.7)	***0.015***
Charlson Comorbidity Index, median (IQR)	5 (2–7)	5 (3–7)	4.5 (2–6)	*0.409*
CKD, n (%)	12 (11.5)	9 (18)	3 (5.6)	***0.047***
Hemodialysis, n (%)	7 (6.7)	5 (10)	2 (3.7)	*0.200*
Liver disease, n (%)	4 (3.8)	2 (4)	2 (3.7)	*0.937*
Solid tumor, n (%)	19 (18.3)	16 (32)	3 (5.6)	***0.0001***
Hematological malignancy, n (%)	5 (4.8)	1 (2)	4 (7.4)	*0.198*
Septic shock, n (%)	35 (33.6)	12 (24)	23 (42.6)	*0.05*
Mechanical ventilation*, n (%)	51 (49.5)	22 (44)	29 (53.7)	*0.323*

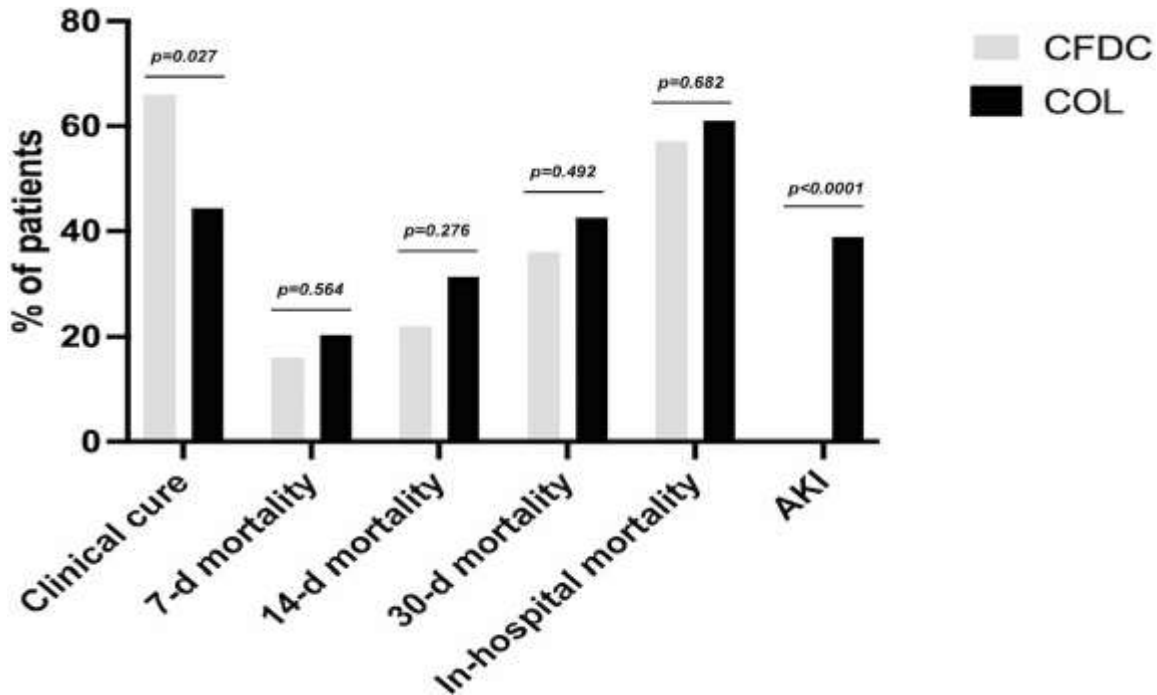
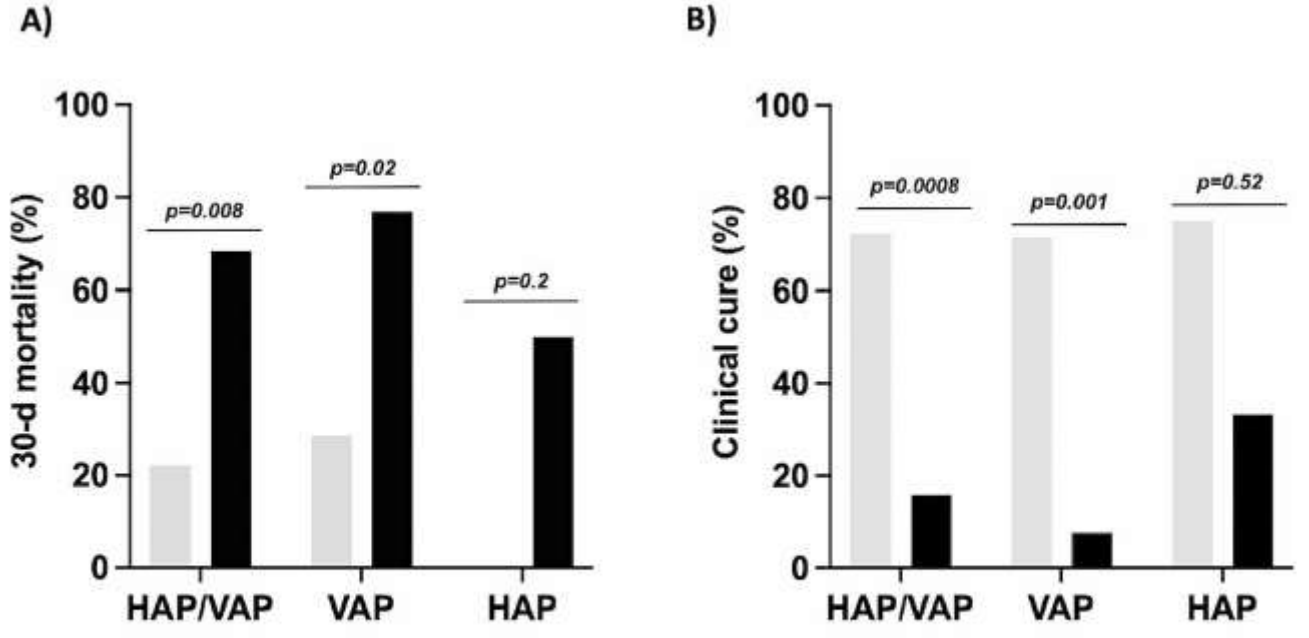


Table 1 General features and outcomes of study population

	Overall population n (%) = 104 (100)	CFDC n (%) = 50 (48.1)	COL n (%) = 54 (51.9)	*p*-value
Source of infection: skin and soft tissue, n (%)	1 (1)	1 (2)	0 (0)	*0.296*
Source of infection: LAI, n (%)	0 (0)	0 (0)	0 (0)	*NA*
Source of infection: HAP, n (%)	10 (9.6)	4 (8)	6 (11.1)	*0.591*
Source of infection: VAP, n (%)	27 (26)	14 (28)	13 (24.1)	*0.648*
Source of infection: catheter-related, n (%)	21 (20.2)	13 (26)	8 (14.8)	*0.156*
Primary BSI, n (%)	45 (43.3)	18 (36)	27 (50)	*0.150*
Polymicrobial BSI	23 (22.1)	9 (18)	14 (25.9)	*0.331*



After stratification according to the source of infection, we found that patients with HAP/VAP treated with CFDC had a statistically significant lower 30-d mortality and higher clinical cure than those treated with COL (22.2% vs. 68.4%, $p = 0.008$, and 72.2% vs. 15.8%, $p = 0.0008$, respectively), especially in patients with bacteremic VAP (28.6% vs. 76.9%, $p = 0.02$ and 71.4% vs. 7.7% $p = 0.001$, respectively)

Oliva, 2023

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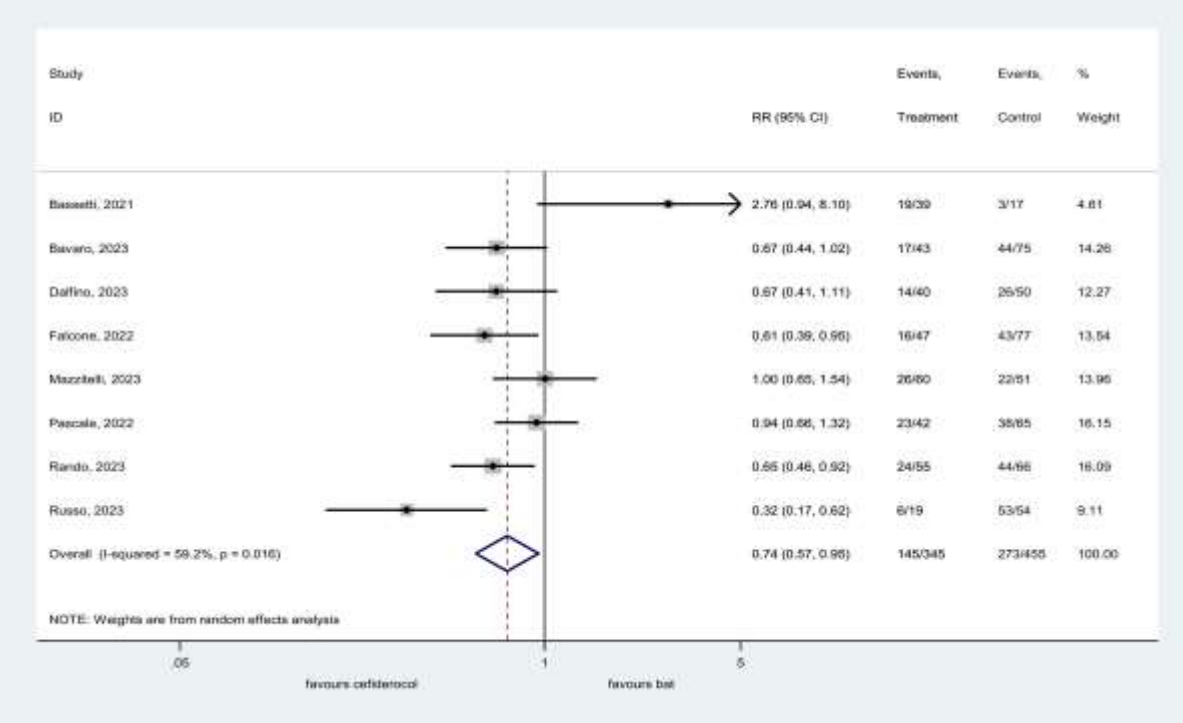
Cefiderocol either in monotherapy or combination versus best available therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections: A systematic review and meta-analysis

Lorenzo Onorato, Ilaria de Luca, Caterina Monari, Nicola Coppola *

Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania Luigi Vanvitelli, Naples, Italy



- Significantly lower mortality rate in the 345 patients treated with cefiderocol as compared to the 455 treated with BAT (RR: 0.74; 95% CI: 0.57–0.95, p = 0.02)
- BSI: lower mortality rate in the group treated with cefiderocol (RR: 0.61; 95% CI: 0.42–0.89, p = 0.01)

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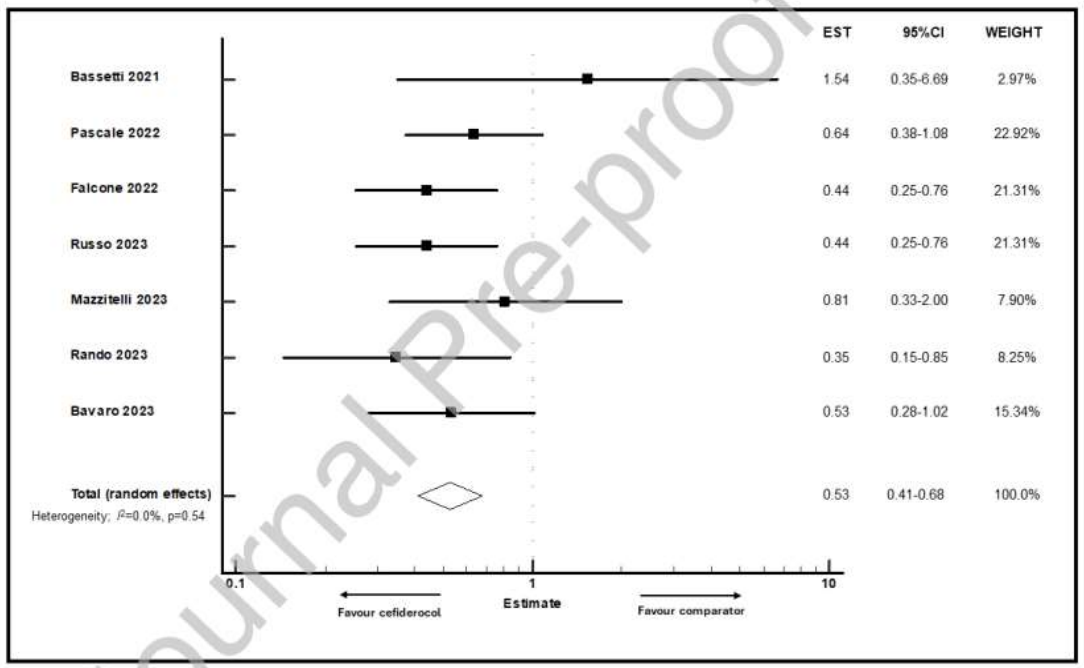
Short Communication

Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: A systematic review with meta-analysis

Milo Gatti [a,b,*], Federica Cosentino [a,c], Maddalena Giannella [a,c], Pierluigi Viale [a,c], Federico Pea [a,b]

Figure 1 – Updated forest plot of mortality rate in patients treated with cefiderocol-based regimens vs. non-cefiderocol-based regimens for CRAB infections.



(OR: 0.64; 95%CI=0.4-1.04)

A gap between results from the CREDIBLE-CR RCT and the real-world observations continues to exist and data on the efficacy of cefiderocol in patients with CRAB infections are still lacking.

Falcone M, Antimicrob Agents Chemother. 2022.

In the meantime, Cefiderocol could be considered a valuable option for the treatment of CRAB infections. Ongoing studies, such as GAME CHANGER TRIAL, the CASCADE TRIAL, and the CefiNor study, will provide additional data…

Gatti M, Int J Antimicrob Agents. 2024

CRAB: combination or monotherapy

- The general approach for the treatment of CRAB infections is to administer **combination therapy with at least 2 agents for the treatment of CRAB infections, at least until an appropriate clinical response is observed**, given the limited data supporting the effectiveness of any single antibiotic agent. It is also generally suggested that at least 1 agent in the combination is sulbactam-based.

- Although only 1 [Makris D, Indian J Crit Care Med 2018] of 7 clinical trials demonstrated any statistically significant benefit with combination therapy for CRAB infections, the panel favors the use of combination therapy for CRAB infections for the following reasons:

- (1) the vast majority of clinical trials included combinations not generally administered in clinical practice (eg, colistin and rifampin)
- (2) there is a lack of robust clinical data
- (3) high bacterial burdens are expected with CRAB infections due to almost universal delays in initiating effective therapy as common empiric antibiotic regimens are generally not active against CRAB.

When considering the high mortality associated with CRAB infections, the benefit of using 2 agents may outweigh the risks.

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1,2] Emily L. Heil,[3] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

Combination or monotherapy

Mild to moderate infections due to **ampicillin-resistant** A. baumannii

IDSA: ampicillin-sulbactam high dose in combination with a second active agent

ESCMID: polymyxins or tigecycline with high dose

SEIMC: recommend cefiderocol in combination with colistin or a triple therapy in pan-drug resistant isolates

---

Severe infections

Combination therapy with two active agents but with specific remarks

(ESCMID: conditional recommendation for use, very low certainty of evidence)

ESCMID: AVOID polymyxin-meropenem or polymyxin-rifampicin combinations (strong recommendation against use; high certainty of evidence) strong recommendation against use, moderate certainty of evidence)

IDSA: AVOID rifampicin, fosfomycin in any combination and polymyxin-meropenem without a third (active) agent

SEIMC: RECCOMEND cefiderocol (as part of combination), AVOID rifampicin

In Theory There Is No Difference Between Theory and Practice, While In Practice There Is

Combination or monotherapy: severe infection

It is generally suggested that at least 1 agent in the combination is sulbactam-based.

A) Sulbactam-durlobactam + IMP/C/MEM NOT AVAILABLE IN ITALY!!!

B) Sulbactam (A/S) + II drug.

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1,2] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

Remarks:

ESCMID 2022: AVOID polymyxin-meropenem or polymyxin-rifampicin combinations

IDSA 2022: AVOID rifampicin, fosfomycin in any combination and polymyxin-meropenem without a third (active) agent

SEIMC 2023: RACCOMAND cefiderocol (as part of combination), AVOID rifampicin

In Theory There Is No Difference Between Theory and Practice, While In Practice There Is

Cefiderocol: combination therapy

Cox regression analysis on risk factors associated with death at 30 days and propensity score analysis.

Variables	Adjusted HR (95% CI)	P-value
COPD	1.4 (1.3–12.2)	0.022
Age	1.12 (1.01–1.1)	0.001
Cefiderocol-containing regimens (colistin-containing regimens as reference variable)	0.34 (0.18–0.56)	<0.001
Cefiderocol – fosfomycin	0.22 (0.1–0.55)	<0.001
Propensity score analysis		
Cefiderocol-containing regimens (IPTW-adjusted)	0.44 (0.22–0.66)	<0.001
Cefiderocol plus fosfomycin (IPTW-adjusted)	0.33 (0.12-0.54)	<0.001

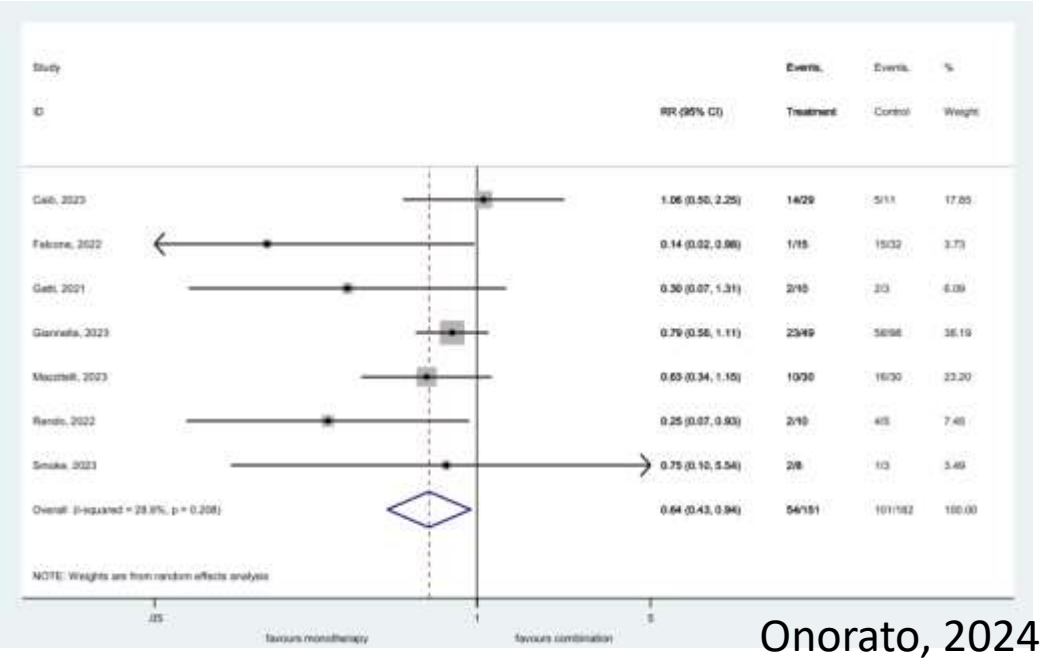
COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

Russo et Al, IJAA 2023

	Clinical Resolution (n = 56)	Clinical Failure (n = 34)
Cefiderocol-based regimens	30 (54)	10 (29) *
Cefiderocol–inhaled colistin	10 (17.8)	9 (26.5)
Cefiderocol–fosfomycin–inhaled colistin	20 (35.7)	1 (3) *
Colistin-based regimens	26 (46)	24 (71) *
Colistin–tigecycline–inhaled colistin	11 (20)	16 (47) *
Colistin–ampicillin/sulbactam–inhaled colistin	8 (14)	7 (21)
Colistin–meropenem–inhaled colistin	7 (13)	1 (3)

Dalfino et Al, Antibiotics 2023

Cefiderocol: combination therapy



Onorato, 2024

the lower mortality rate in patients treated with cefiderocol in mono therapy may be biased by:

- studies' design (mainly observational retrospective studies)
- **in the real-life practice cefiderocol in monotherapy is more often prescribed in patients with less severe infections**.

- Indeed, only 2 of the 7 studies reporting mortality data among patients treated with monotherapy or combination demonstrated a clear comparability among groups in term of clinical characteristics and severity of infections

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

CFD/FOS combination was revealed in the CR-Ab strain with OXA variants but sensitive to FOS

Palombo et Al, Antibiotics 2023

Intravenous fosfomycin for treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*: A multi-centre clinical experience

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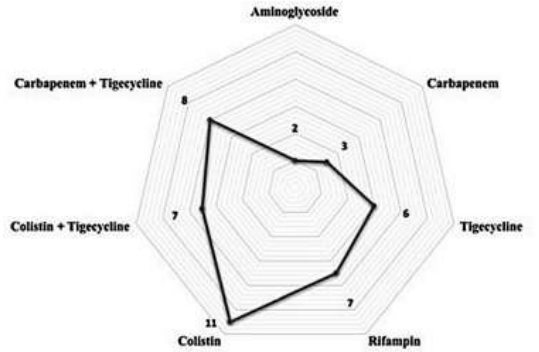

Fig. 1 Antibiotics in combination with fosfomycin in definitive therapy (no. of patients treated)

Table 4 Cox regression analysis about risk factors associated with 30-day mortality

Variables	Without propensity score adjustment			With Propensity score adjustment		
	HR	CI 95%	*p*	HR	CI 95%	*p*
Septic shock	3.5	1.32–9.58	0.012	3.1	1.45–7.88	0.001
Fosfomycin-containing regimen as definitive therapy	0.04	0.01–0.13	< 0.001	0.22	0.09–0.44	< 0.001
Secondary bacteremia	23.6	9.02–61.9	< 0.001	19.4	8.22–42.1	< 0.001

HR hazard ratio, *CI* confidence interval

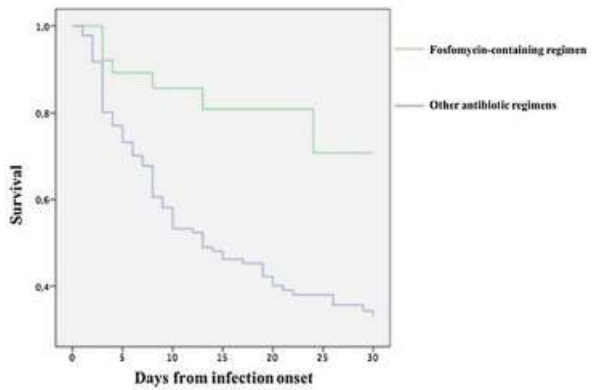

Fig. 2 Kaplan-Meier curves about 30-day survival of patients treated with fosfomycin-containing regimen or other antibiotic regimens in definitive therapy

Cox regression analysis of factors associated with 30-day mortality showed that Fosfomycin containing regimen (HR 0.04, CI 95% 0.01–0.13, p= 0.001) was associated with 30-day survival.

Grazie per l’attenzione