I EDIZIONE

# USO RAZIONALE DEGLI ANTIBIOTICI NELL'ERA DELLE RESISTENZE BATTERICHE

17 MAGGIO
2024

Sala Congressi
PO "Villa Malta" di Sarno
Via Sarno Striano

Sessione Bugs
*Acinetobacter baumannii*

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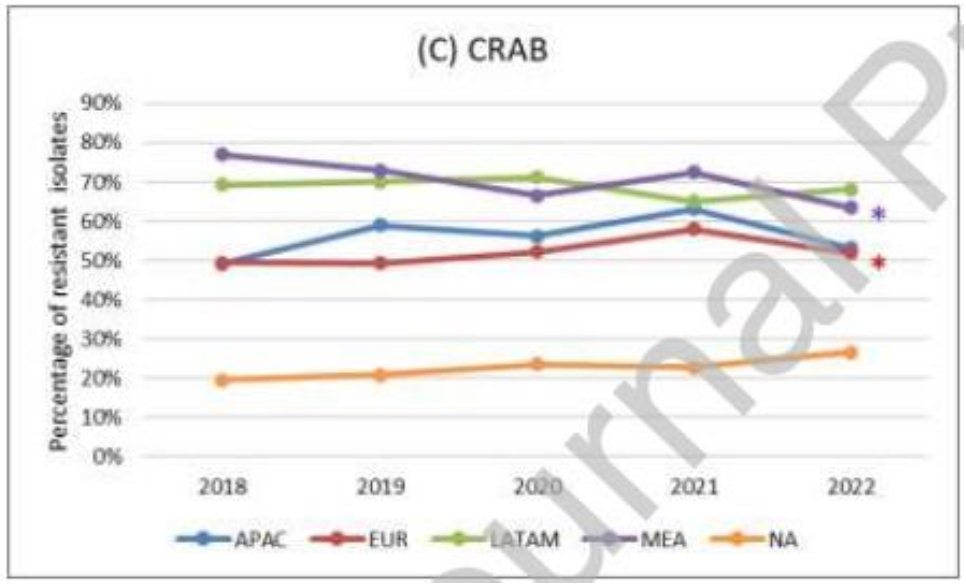




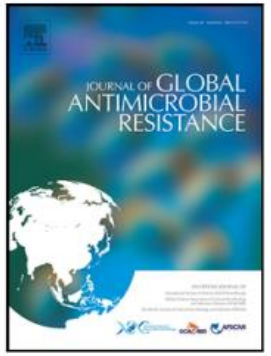


Global Trends in Carbapenem- and Difficult-to-Treat-Resistance Among World Health Organization Priority Bacterial Pathogens: ATLAS Surveillance Program 2018-2022

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PII: S2213-7165(24)00072-9
DOI: https://doi.org/10.1016/j.jgar.2024.03.020
Reference: JGAR 2312

To appear in: *Journal of Global Antimicrobial Resistance*

Received date: 28 February 2024
Accepted date: 28 March 2024

# CRAB Infections

# Mortalità

**Comparison of Septic Shock Due to Multidrug-Resistant *Acinetobacter baumannii* or *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* in Intensive Care Unit Patients**

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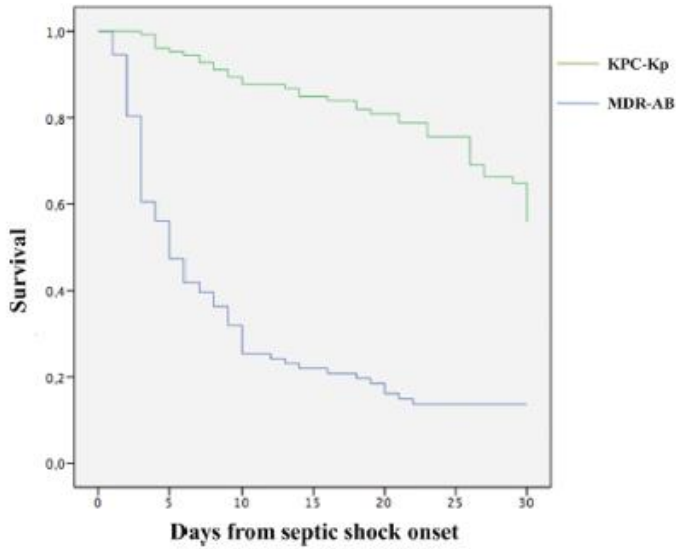



**FIG 1** Kaplan-Meier curves for 30-day survival of KPC-Kp or MDR-AB infections. *, $P < 0.001$. KPC-Kp, *Klebsiella pneumoniae* carbapenem-resistant *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.

Russo et al. AAC 2018

## Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit

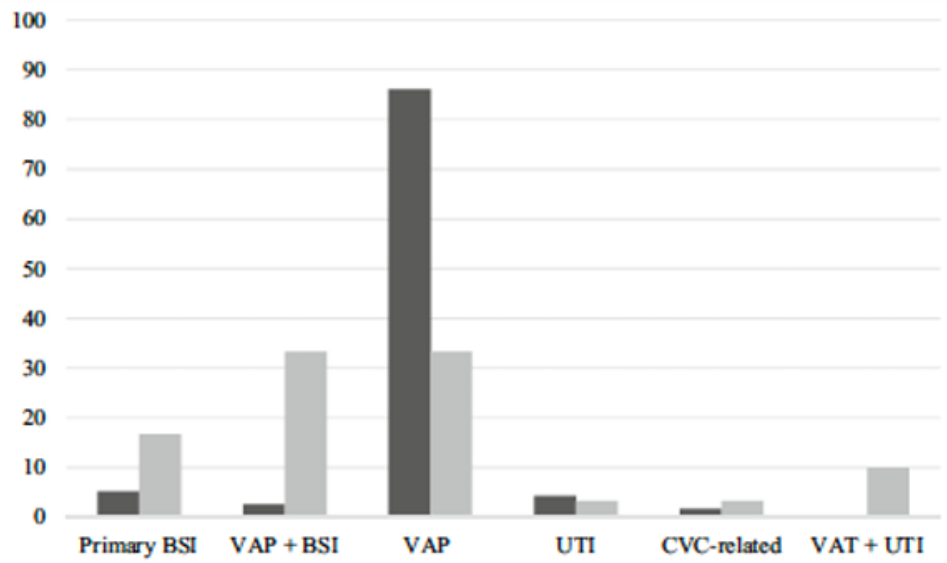



**Fig. 1** Sites of MDR-AB infection in COVID-19 (gray line) or non-COVID-19 (black line).

Russo et al, Infection 2021

# Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit

**Table 2** Relative risk* associated or not with MDR-AB infection in patients affected or not by COVID-19

| Variables | RR | CI 95% | *p* value |
|---|---|---|---|
| Previous hospitalization (90 days) | 0.4 | 0.2–0.9 | 0.031 |
| COPD | 0.3 | 0.1–0.9 | 0.029 |
| Chronic steroid therapy | 0.1 | 0.0–0.9 | 0.041 |
| Infection at time of ICU admission | 0.1 | 0.0–0.4 | 0.001 |
| Serum lactate levels > 2 mmol/l | 1.8 | 1.3–2.5 | 0.001 |
| *Acinetobacter baumannii* colonization | 7.9 | 4.0–15.7 | < 0.001 |
| Bloodstream infection | 6.5 | 3.2–13.3 | < 0.001 |
| Steroid therapy | 18.4 | 7.6–44.1 | < 0.001 |

**Table 3** Logistic regression analysis about risk factors associated with 30-days mortality

| Variables | OR | CI 95% | *p* value |
|---|---|---|---|
| Serum lactate levels > 2 mmol/l | 4.9 | 2.1–11.3 | < 0.001 |
| *Acinetobacter baumannii* colonization | 17.1 | 5.5–53.3 | < 0.001 |
| Bloodstream infection | 13.6 | 4.8–38.2 | < 0.001 |
| Steroid therapy | 46.9 | 13.9–157.5 | < 0.001 |

**Table 5** Multivariate analysis about risk factors associated with development of bloodstream infection

| Variables | OR | CI 95% | *p* value |
|---|---|---|---|
| Severe COVID-19 | 15.1 | 3.7–40.1 | < 0.001 |
| WBC > 11,000 mm$^3$ | 5.2 | 2.1–11.5 | < 0.001 |
| Serum lactate levels > 2 mmol/l | 2.7 | 1.2–6.4 | 0.022 |
| Infections at time of ICU admission | 0.4 | 0.2–1 | 0.030 |
| *Acinetobacter baumannii* colonization | 4.8 | 1.9–12.1 | < 0.001 |
| Steroid therapy | 8.8 | 3.5–22.1 | < 0.001 |

Russo et al, Infection 2021

# Guidelines comparison



**Table 4**
Summary of recommendations for the treatment of CRAB.

| Guideline, year | Recommendations | | | | | | | | | Dosage mentioned | Duration mentioned | Paediatrics dosage included |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | COS-CR | POX | SUC | TGC | CDR | MNC | APS | TRS | CT | | | |
| Chinese guideline, 2023 [11] | | | | | | | | | √[a] | NM | NM | No |
| ESCMID guideline, 2022 [12] | | | | | | | √[b] | | √[c] | NM | NM | No |
| IDSA guideline, 2022 [14] | | √[2de] | | √[2f] | | √[d] | √[1df] | | √[2g] | √ | NM | No |
| Italian guideline, 2022 [16] | | | | | √[1] | | | | √[2h] | √ | NM | No |
| Italian guideline, 2022 [17] | √ | | | | √ | | | | | NM | NM | No |
| Spanish guideline, 2022 [18] | | | | | | | | | √[i] | √ | NM | √ |
| German guideline, 2020 [23] | | | √ | | | | | √ | √[j] | NM | NM | No |
| American guideline, 2019 [24] | | | | | | √[2] | √[2k] | | √[1l] | √ | NM | No |
| British guideline, 2018 [26] | | | | | | | √ | | | NM | NM | No |
| Spanish guideline, 2018 [27] | | √[mn] | √ | √ | | | | | √[#o] | √ | NM | No |
| ESICM guideline, 2015 [28] | √[p] | | | √[#2q] | | | | | √[r] | √ | √ | No |
| European guideline, 2013 [30] | | | | | | | | | √[st] | NM | √ | No |

√indicates that these drugs are recommended. Superscript 1 indicates they are stated as the first-line therapy, and 2 indicates that they are stated as alternative therapy. # indicates MDR *A. baumannii*.

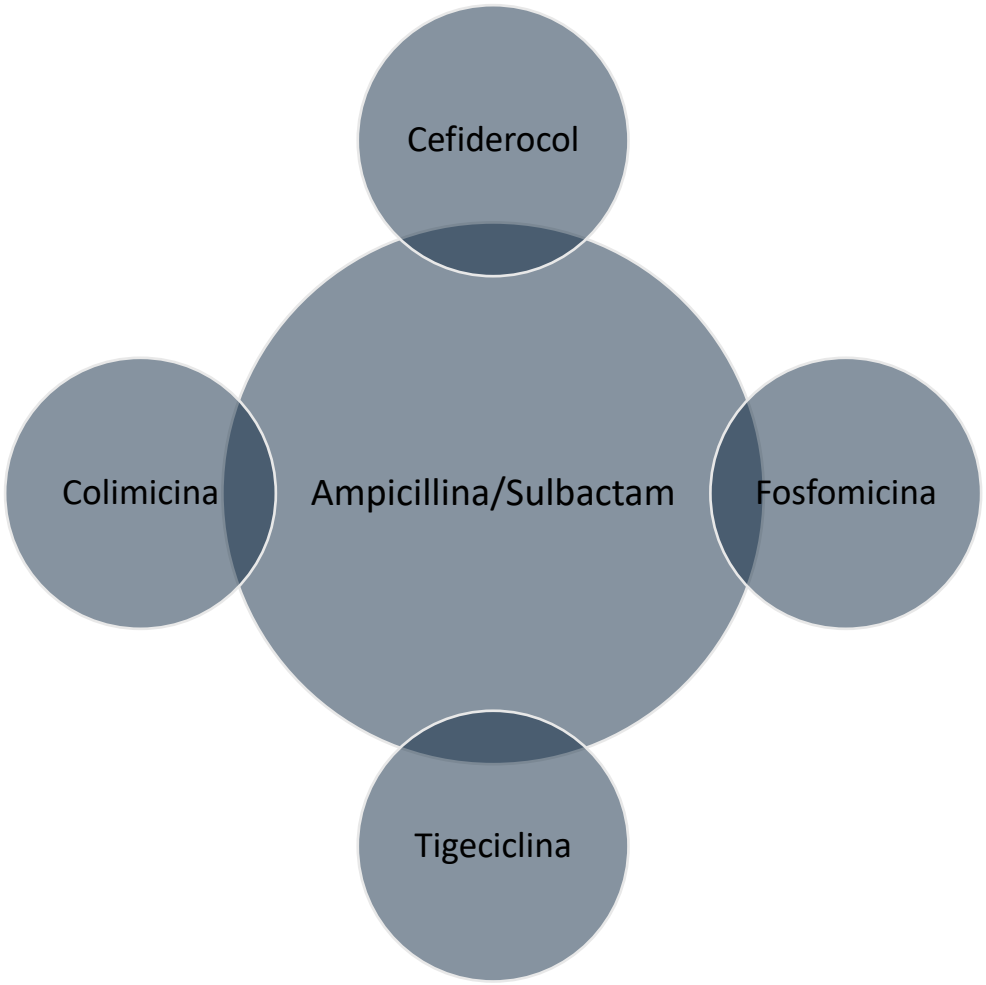
Abbreviations: COS-CR: colistin-containing regimens; POX, polymyxins; SUC, sulbactam; TGC, tigecycline; CDR, cefiderocol; MNC, minocycline; APS, ampicillin-sulbactam; TRS, cotrimoxazole (trimethoprim-sulfamethoxazole); CT, combination therapy; NM, not mentioned.

a: polymycin based; sulbactam or sulbactam-containing $\beta$-lactamase inhibitor based; b: susceptible to sulbactam and hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP); c: ① two in vitro active antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations); ② carbapenem combination therapy (meropenem MIC ≤8 mg/L, using high-dose extended-infusion carbapenem dosing); d: mild CRAB infections; e: colistin for urinary CRAB infections; f: high-dose; g: moderate to severe CRAB infections, ampicillin-sulbactam, polymyxin B, tetracycline derivatives (eg: minocycline), high-dose, extended-infusion meropenem, cefiderocol; h: fosfomycin plus ampicillin-sulbactam plus inhaled colistin; i: ① sulbactam based; ② colistin, minocycline, tigecycline, aminoglycosides, cefideroco based; j: colistin + carbapenem or sulbactam or another combination partner; k: sulbactam dose ≥9 g daily, dose adjusted for creatinine clearance; l: carbapenem plus colistin or polymyxin B; m: especially colistin; n: colistin or colistin and tigecycline (previously colonised solid organ transplant recipients or with high clinical suspicion of CRAB infection, who have risk factors for poor clinical outcome); o: colistin-carbapenem (meropenem or doripenem, both administered by extended infusion; p: or polymyxin; q: for infections of the approved indications (complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs)) caused by MDR *A. baumannii* if the MIC to this agent is ≤ 1 mg/L; r: ① tigecycline based in non-approved indications; ② high dose meropenem plus colistin or aminoglycoside (meningitis); s: colistin/polymyxin B, tigecycline, be used in combination with other in vitro active agents, addition of rifampin can be considered; t: ampicillin sulbactam resistant.

# ESCMID/IDSA

| | ESCMID guidelines | IDSA guidance |
|---|---|---|
| **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<br>(1 g sulbactam component q6h) | Back-bone treatment for all CRAB infection<br>(6-9 g sulbactam component daily) |
| **Polymyxins** | Either colistin or polymyxin B:<br>for patients with CRAB resistant to sulbactam susceptible to polymyxins;<br>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<br>(Colistin only for CRAB UTIs) |
| **Tetracycline derivatives** | High-dose tigecycline: for patients with CRAB resistant to sulbactam susceptible to tigecycline;<br>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 |
| **Aminoglycosides** | In combination with one other *in-vitro* active agent for severe, susceptible to aminoglycosides, CRAB infection | Not recommended |
| **Meropenem** | In combination with one other *in-vitro* active agent for severe CRAB infections with a meropenem MIC <8 mg/L<br>(2 g q8h over 3 hrs infusion) | Not recommended |

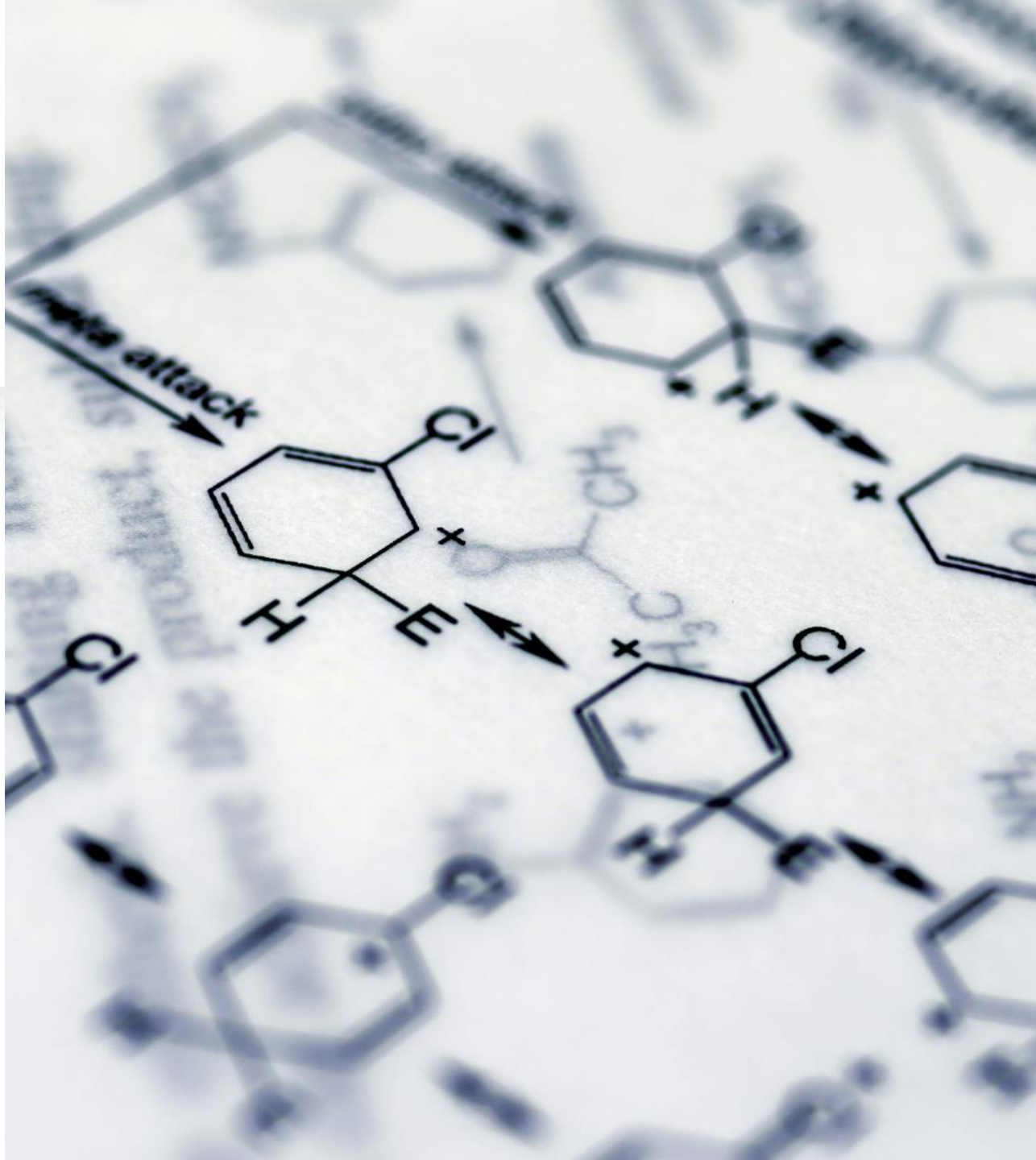
# Opzioni terapeutiche
# Linee guida



# Sulbactam backbone

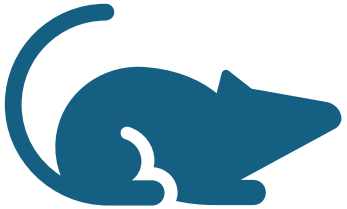
- Suggested approach: The use of high-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) in combination with at least one other agent is suggested for the treatment of CRAB infections.

*IDSA Guidelines 2022*



# Perché il Sulbactam

Sulbactam is a competitive, irreversible β-lactamase inhibitor that, in high doses, saturates PBP1a/1b and PBP3 of A. baumannii isolates.



Sulbactam’s unique activity against A. baumannii isolates has been demonstrated through in vitro studies, animal models, and clinical outcomes data

# Clinical efficacy of sulbactam

A clinical trial including 39 CRAB pneumonia patients (with clinical isolates susceptible to both colistin and sulbactam) identified clinical improvement by day 5 in 16% and 70% of patients randomized to colistin monotherapy versus colistin in combination with high-dose sulbactam (total daily dose of at least 8 grams of the sulbactam component).

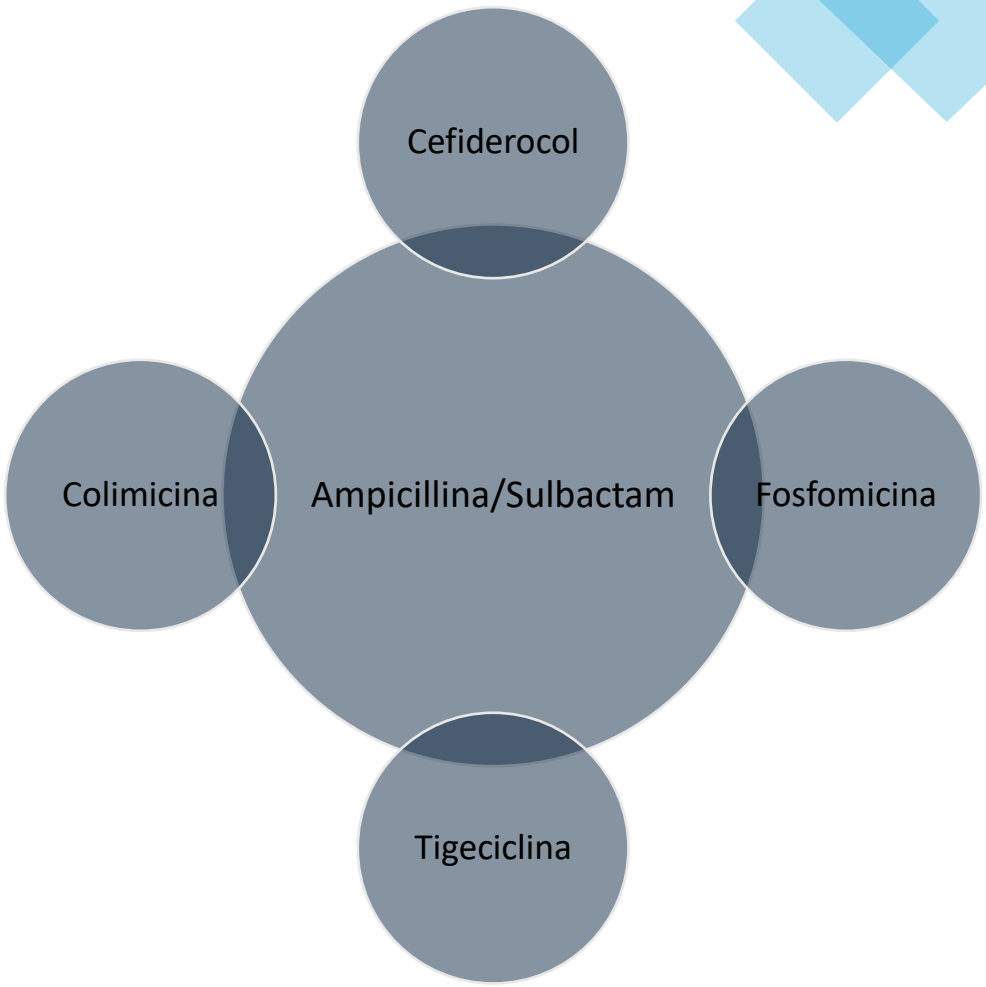
This trial had a number of limitations including the following: small sample size, the open-label design may have led to biased outcome assignment, and an appropriate evaluation of long-term outcomes could not be undertaken as patients could transition to other agents after day 5. These limitations notwithstanding, this trial identified clinical improvement with a colistin-sulbactam combination for the treatment of CRAB infections.

# Ampicillin/Sulbactam in clinical trial

Two other clinical trials have not identified a difference in clinical outcomes with the use of ampicillin-sulbactam. An open label trial comparing the outcomes of 47 patients with CRAB pneumonia randomized to meropenem/colistin and meropenem/ampicillin-sulbactam (total daily dose of 6 grams of the sulbactam component) for a 14-day course identified similar clinical responses in both groups

Another trial randomized 28 CRAB pneumonia patients to colistin monotherapy versus ampicillin-sulbactam monotherapy (total daily dose of at least 6 grams of the sulbactam component). Neither differences in 28-day mortality or clinical failure reached statistical significance (33% versus 30% and 33% versus 38%, among patients in the colistin and ampicillin-sulbactam arms, respectively). Nephrotoxicity was identified in 33% versus 15%, comparing the two groups.

# Opzioni terapeutiche
# Linee guida



# COLISTIN

**Table 2.** Cox regression analysis of outcomes for critically ill patients receiving LD colistin and LD colistin with nebulized colistin after inverse probability weighting (IPW) (n = 261).

| Variable | LD Colistin Monotherapy (n = 95) | LD Colistin with Nebulized Colistin (n = 166) | Crude HR (95% CI) | *p*-Value | Adjusted HR * (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| Efficacy<br>Primary outcomes | | | | | | |
| 30-day survival | 47 (49.7) | 69 (41.6) | 1.13 (0.78–1.64) | 0.503 | 1.17 (0.80–1.72) | 0.418 |
| Survival in SOFA score ≥ 2 | 19 (20.00) | 31 (18.67) | 1.08 (0.69–1.70) | 0.737 | 1.12 (0.71–1.78) | 0.625 |
| Secondary outcomes | | | | | | |
| Clinical response | 52 (55.2) | 90 (54.1) | 0.97 (0.69–1.36) | 0.853 | 0.93 (0.66–1.31) | 0.688 |
| Microbiological response | 63 (66.5) | 86 (52.1) | 1.22 (0.87–1.70) | 0.251 | 1.21 (0.85–1.73) | 0.279 |
| Safety | | | | | | |
| Nephrotoxicity (RIFLE criteria) | 53 (55.6) | 73 (44.1) | 1.16 (0.81–1.67) | 0.418 | 1.14 (0.79–1.64) | 0.492 |
| • Risk | 21 (39.7) | 37 (41.7) | | | | |
| • Injury | 12 (22.8) | 17 (23.6) | | | | |
| • Failure | 11 (20.6) | 11 (14.4) | | | | |
| • Loss | 9 (16.2) | 13 (17.7) | | | | |
| • ESRD | 0 (0.0) | 2 (1.3) | | | | |

LD, loading dose; CI, confidence interval; HR, hazard ratio; * Adjusted using inverse probability weighting (IPW) with the propensity score for baseline covariate adjustment.

*Katip et al.*
*Antibiotics 2024*

# COLISTIN

**Table 1**
Clinical characteristics of patients with CRAB pneumonia.

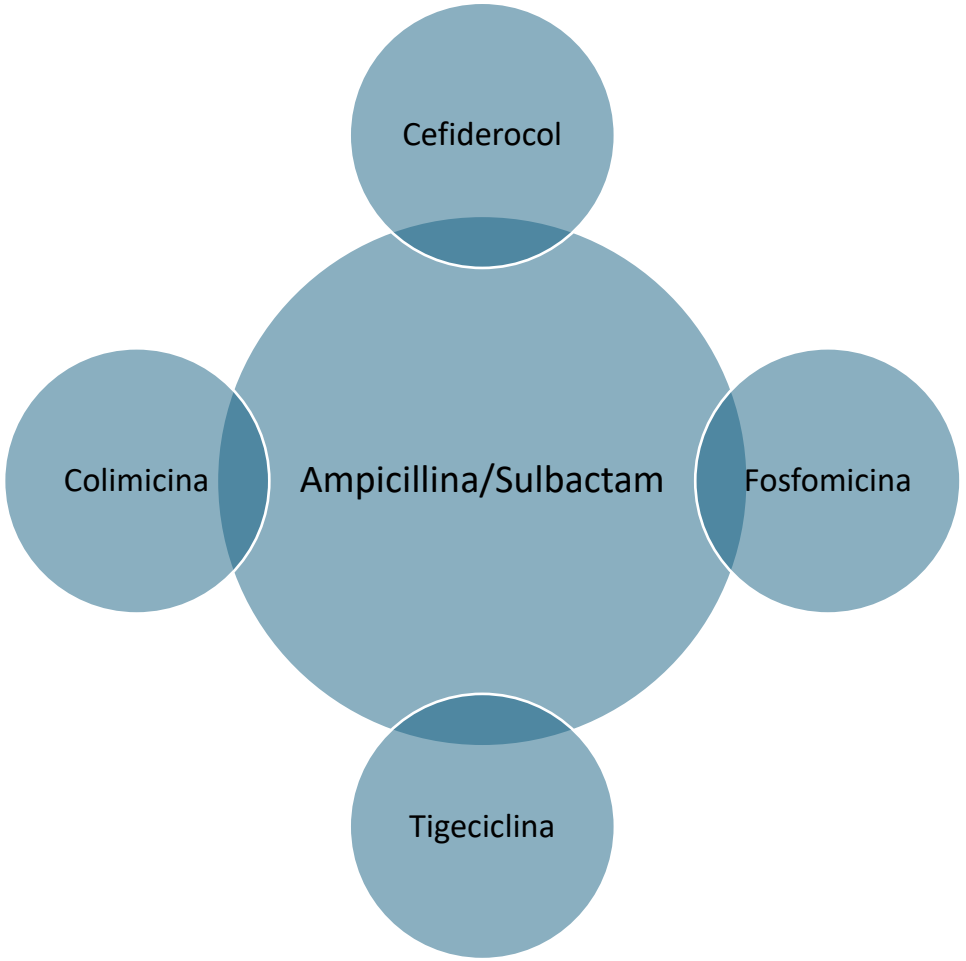
| | Overall (n = 168) | No active drug (n = 123) | Colistin (n = 45) | P-value |
|---|---|---|---|---|
| **Patient demographics** | | | | |
| Gender (male) | 118 (70.2) | 83 (67.5) | 35 (77.8) | 0.196 |
| Age | 70.5 (60.3 – 80) | 70 (62-80) | 71 (58.5-81) | 0.662 |
| **Pneumonia signs and symptoms** | | | | |
| New infiltrate on chest image | 168 (100) | 123 (100) | 45 (100) | > 0.999 |
| Hyper/hypothermia | 114 (67.9) | 83 (67.5) | 31 (68.9) | 0.862 |
| Purulent respirator | | | | |
| Leukocytosis | | | | |
| Hypoxemia | | | | |
| **Acquisition site** | | | | |
| Community acquir | | | | |
| Healthcare facility | | | | |
| Hospital acquired | | | | |
| Ventilator associat | | | | |
| **Underlying diseas** | | | | |
| Diabetes mellitus | | | | |
| Hypertension | | | | |
| Chronic heart failure | 25 (14.9) | 16 (13.0) | 9 (20.0) | 0.259 |
| Chronic renal disease | 27 (16.1) | 22 (17.9) | 11 (11.1) | 0.287 |
| Decompensated liver cirrhosis | 4 (2.4) | 2 (1.6) | 2 (4.4) | 0.291 |
| Chronic pulmonary disease | 20 (11.9) | 12 (9.8) | 8 (17.8) | 0.155 |
| Decompensated liver cirrhosis | 4 (2.4) | 2 (1.6) | 2 (4.4) | 0.291 |
| Metastatic solid cancer | 15 (8.9) | 10 (8.1) | 5 (11.1) | 0.549 |
| Updated CCI | 2 (1-3) | 2 (1-3) | 2 (1-4) | 0.601 |
| **Disease severity** | | | | |
| Bacteremia | 21 (1.5) | 13 (10.6) | 8 (17.8) | 0.211 |
| Shock at presentation | 67 (39.9) | 47 (38.2) | 20 (44.4) | 0.465 |
| Presence of bacteremia | 21 (12.5) | 13 (10.6) | 8 (17.8) | 0.211 |
| SOFA score | 8 (5-11) | 8( 5-11) | 9 (5.5-11) | 0.378 |
| **Treatment** | | | | |
| Carbapenem use | 92 (54.8) | 60 (48.8)[a] | 32 (71.1)[b] | 0.010 |

**Table 3**
Risk factors for acute kidney injury in patients with CRAB pneumonia.

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
| Colistin | 1.53 (0.87-2.68) | 0.143 | 1.26 (0.64-2.46) | 0.457 |
| Hyper/hypothermia | 0.55 (0.32-0.96) | 0.036 | 0.64 (0.36-1.13) | 0.120 |
| Hypoxemia | 7.03 (1.05-55.36) | 0.045 | 3.57 (0.47-27.3) | 0.182 |
| Ventilator-associated pneumonia | 2.34 (1.36-4.23) | 0.002 | 1.26 (0.65-2.46) | 0.500 |
| SOFA score (per 1-point) | 1.17 (1.09-1.25) | < 0.001 | 1.12 (1.04-1.23) | 0.005 |

SOFA, Sequential Organ Failure Assessment

# Opzioni terapeutiche
# Linee guida



# Fosfomicina

**Efficacy of a Fosfomycin-Containing Regimen for Treatment of Severe Pneumonia Caused by Multidrug-Resistant *Acinetobacter baumannii*: A Prospective, Observational Study**

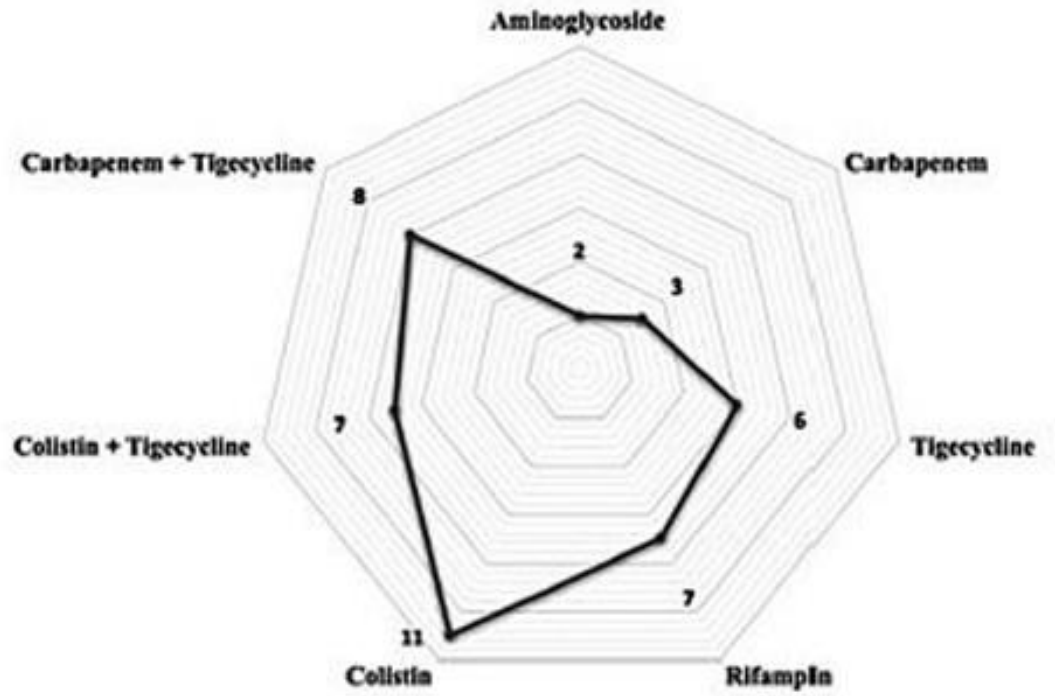
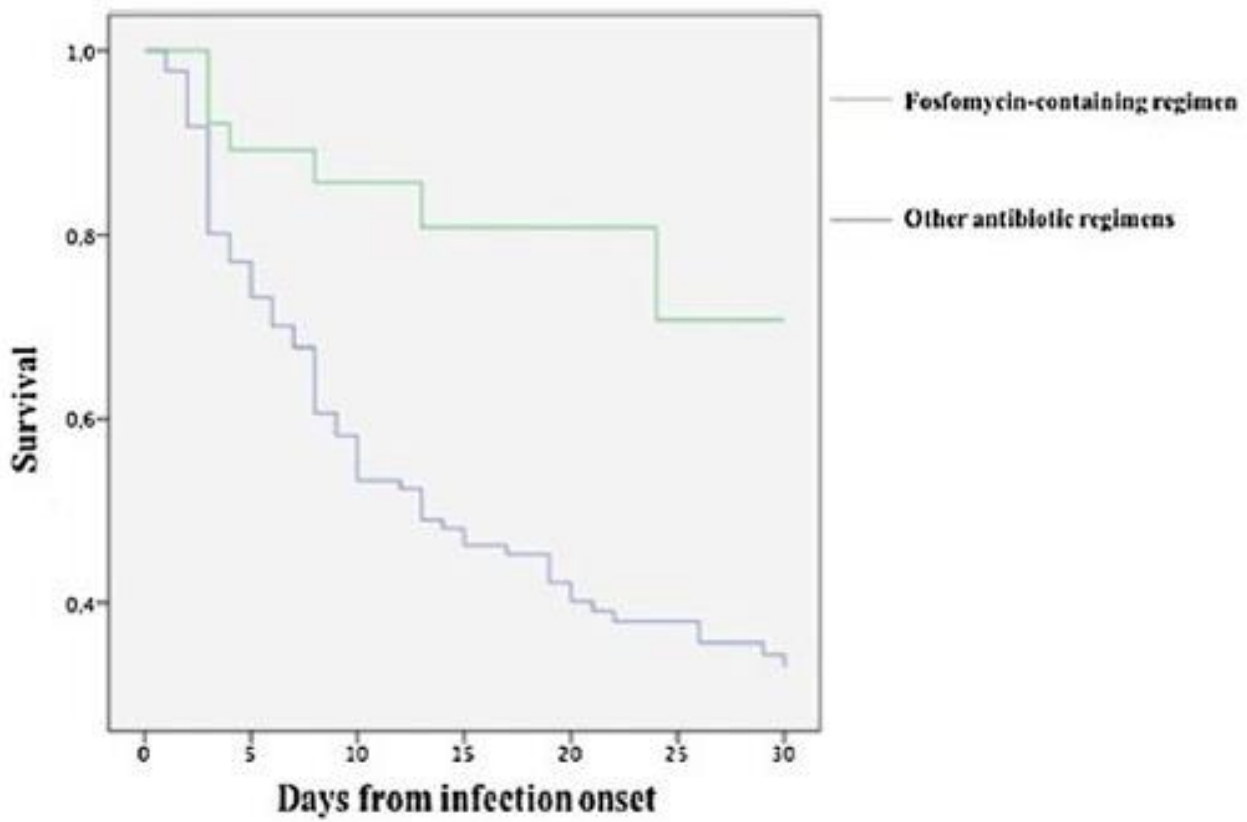



**Fig. 1** Antibiotics in combination with fosfomycin in definitive therapy (no. of patients treated)

Russo et al, IDT, 2020

# Fosfomicina

**Efficacy of a Fosfomycin-Containing Regimen for Treatment of Severe Pneumonia Caused by Multidrug-Resistant *Acinetobacter baumannii*: A Prospective, Observational Study**




Russo et al, IDT, 2020

# Fosfomicina

Fosfomycin may be an effective adjunctive therapy for pneumonia caused by MDR/XDR *A. baumannii* strains, considering the synergistic effect of colistin and fosfomycin reported in *in vitro* studies.

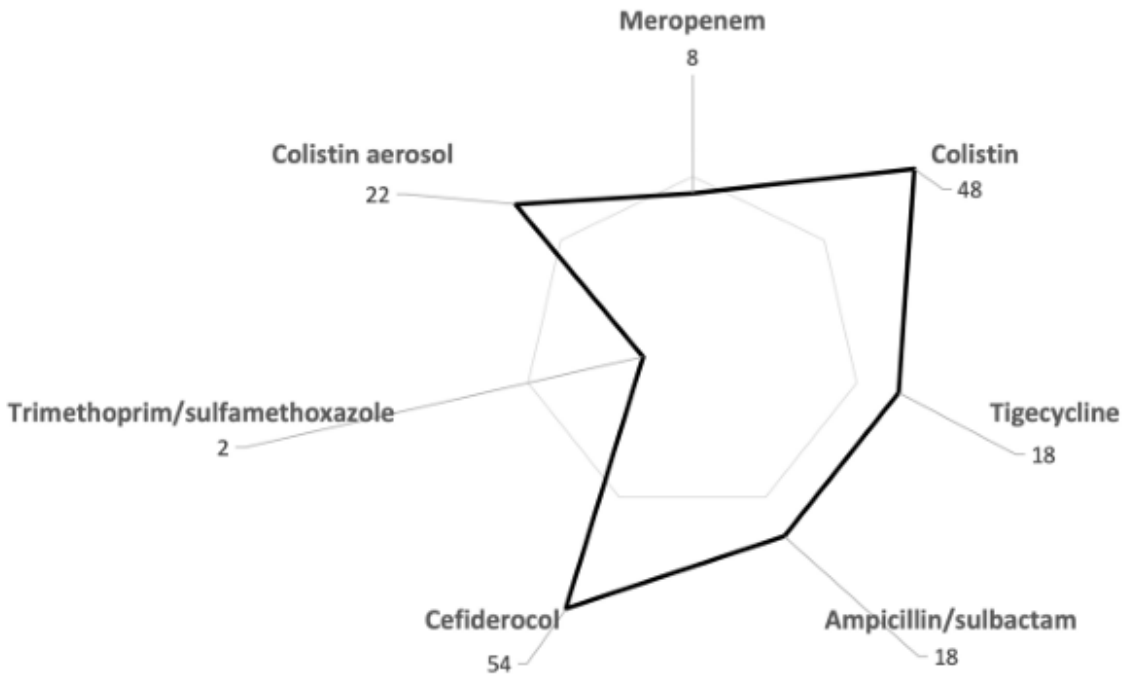
Fosfomycin achieves effective concentrations in infected lung tissue, and in association with colistin showed bactericidal and synergistic effects at 8 h, reducing the bacterial load in the lungs at 48 h as recently showed in clinical studies

A combination regimen containing fosfomycin showed significantly better microbiologic responses with trends toward more favorable treatment outcomes and lower mortality

Russo et al, IDT, 2020

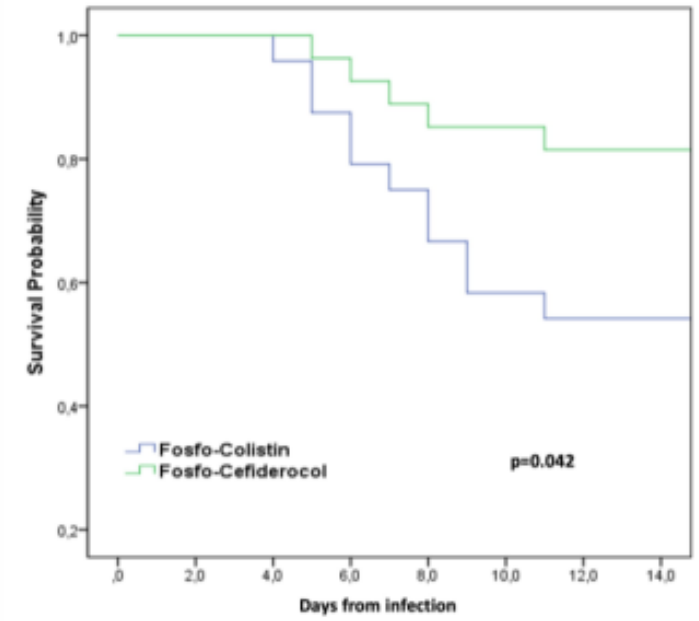
# Fosfomicina

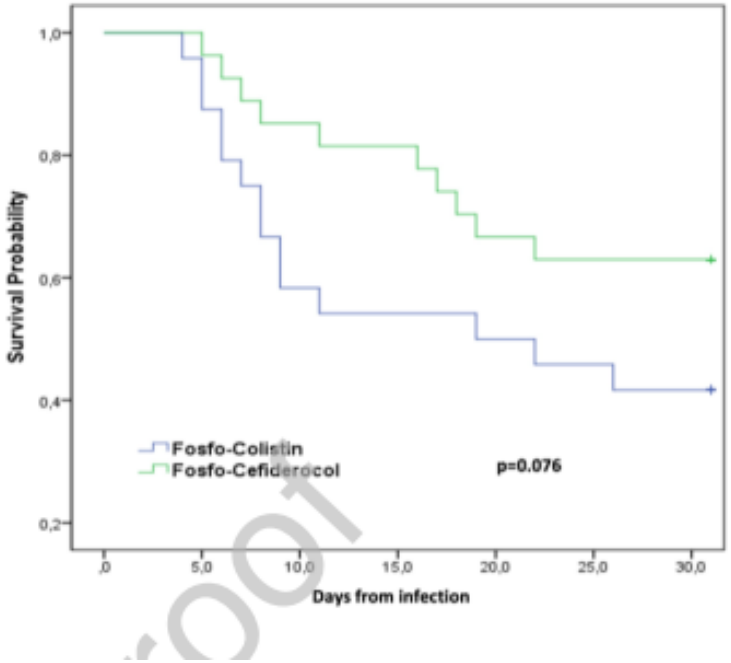
**Intravenous fosfomycin for treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*: a multicenter clinical experience**



# FOSFOMYCIN

**Figure 1**. Kaplan-Meier curves for 14- and 30-day survival in patients treated with cefiderocol or colistin in combination with fosfomycin




*Russo et al. Int Journ of Antimicrob agents 2023*

# FOSFOMYCIN

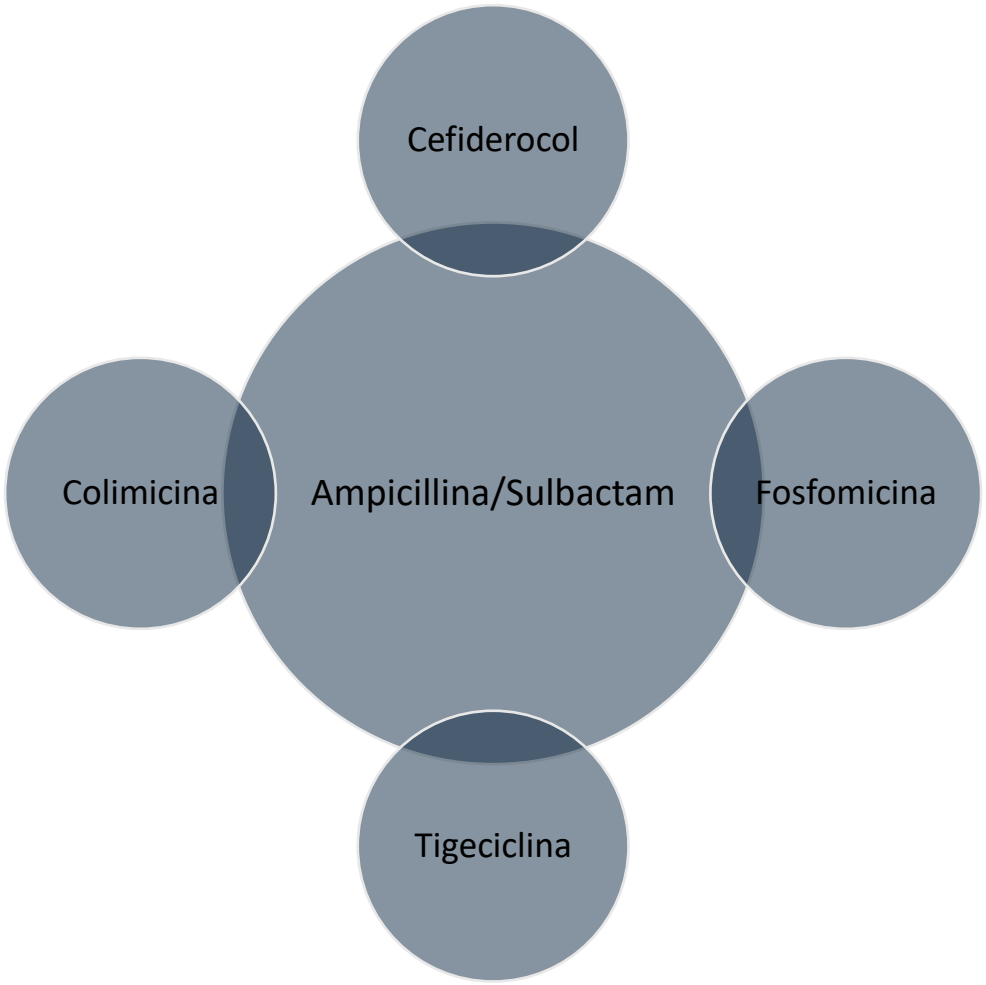
**Table 2.** COX regression analysis on risk factors associated with death at 30 days

| Variables | Adjusted-HR (95% CI) | p-value |
|---|---|---|
| Diabetes | 4.5 (2.73-7.141) | <0.001 |
| Adequate source control | 0.36 (0.226-0.566) | <0.001 |
| Primary bacteremia | 1.59 (1.12-2.26) | 0.009 |
| Early 24 h active *in vitro* therapy | 0.75 (0.60-0.94) | 0.011 |
| Colistin | 1.87 (1.21-2.9) | 0.005 |
| Cefiderocol | 0.66 (0.44-0.98) | 0.039 |
| **Propensity score analysis** | | |
| Colistin | 1.72 (1.19-3.2) | 0.003 |
| Cefiderocol | 0.54 (0.32-0.88) | 0.018 |



*Russo et al. Int Journ of Antimicrob agents 2023*

# Opzioni terapeutiche
# Linee guida



# CEFIDEROCOL

**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**

Numerically 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**

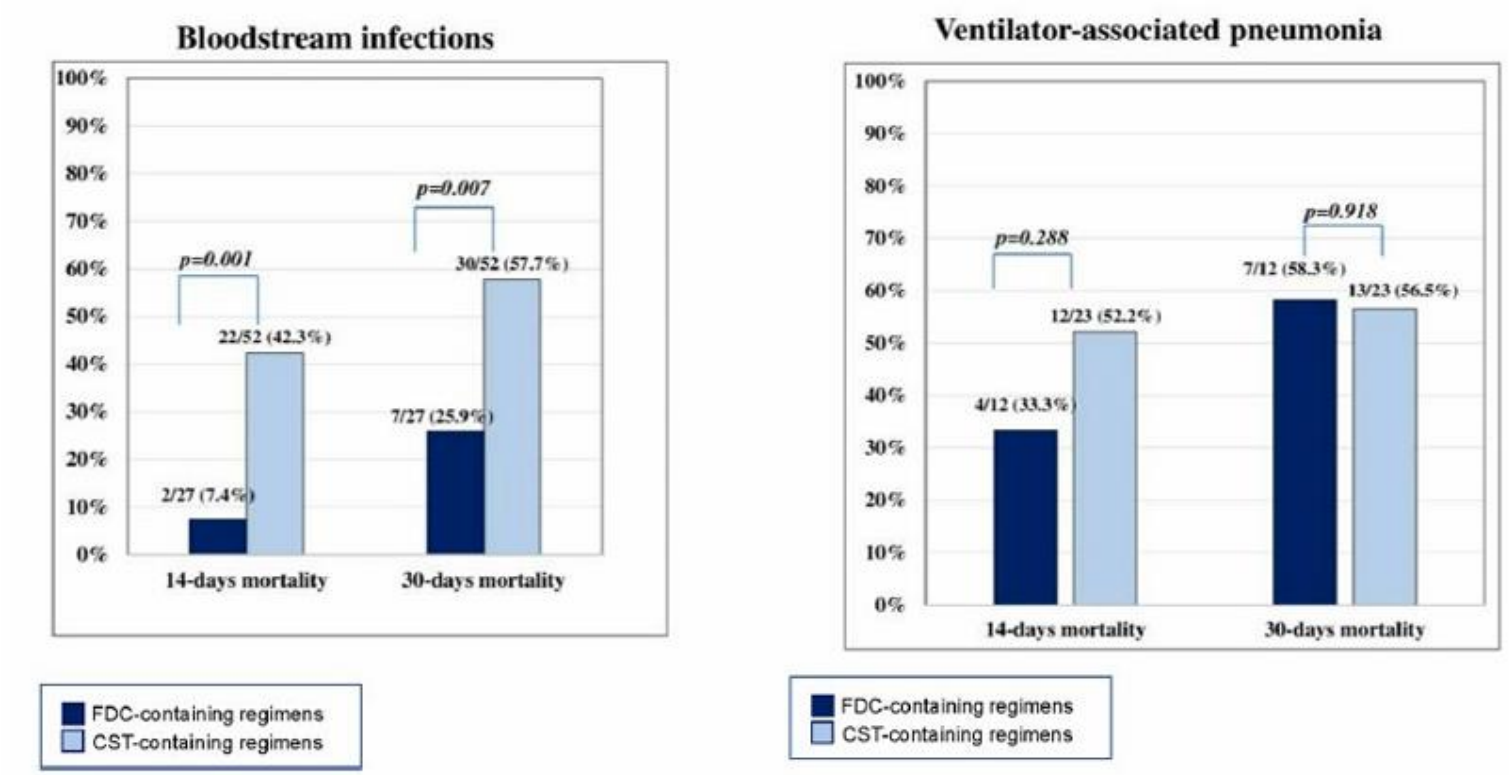
For patients with *Acinetobacter* spp infections was observed, at baseline, an increased rate of:

- moderate or severe renal dysfunction
- ICU at randomisation
- ongoing shock
- shock within 31 days before randomisation

in the cefiderocol group than in the best available therapy group

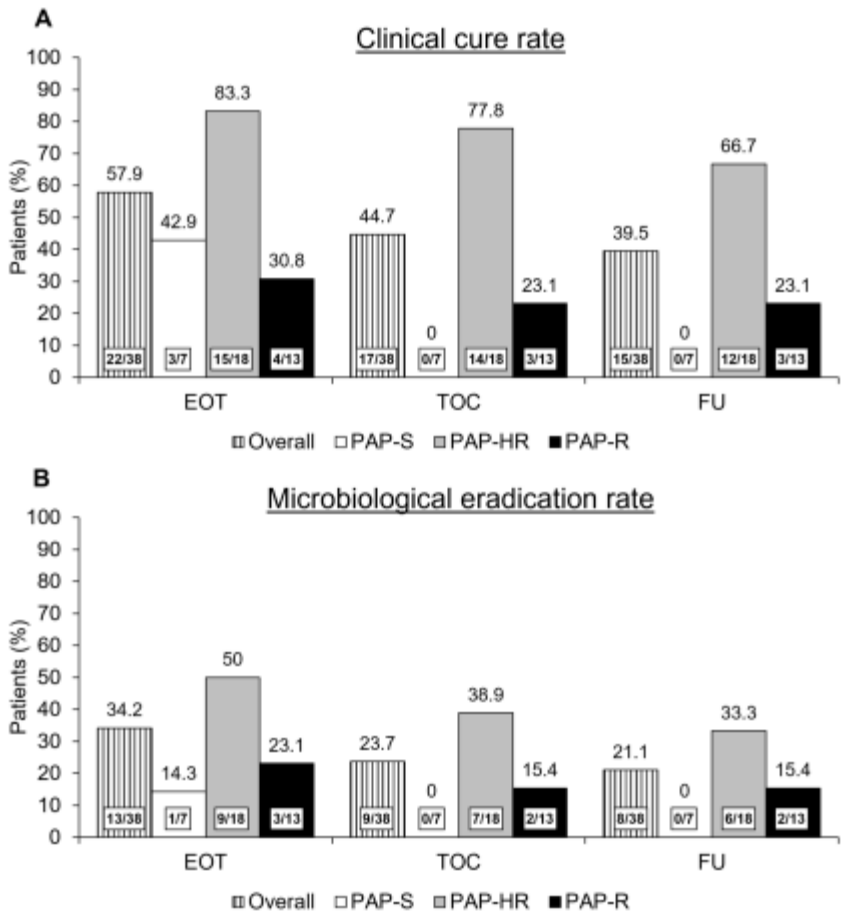
Bassetti et al, LID 2021

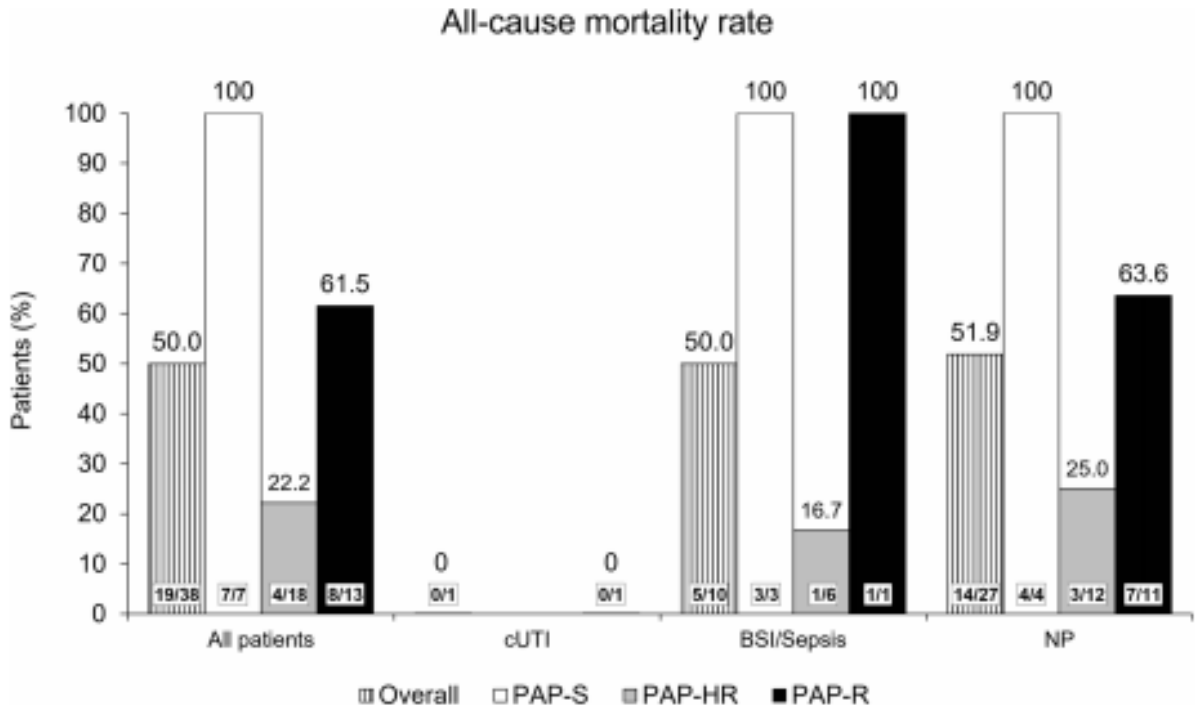
# CEFIDEROCOL




Falcone et al, AAC 2022

# CEFIDEROCOL




*Longshaw et al., Microbiology spectrum 2023*

| | | | | |
|---|---|---|---|---|
| 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** |

**Table 1** continued

| | **Overall (*n*. 118)** | **Colistin-based regimens (*n*. 75)** | **Cefiderocol-based regimens (*n*. 43)** | ***p* value** |
|---|---|---|---|---|
| Combinations of more than 2 drugs | 48 (41) | 48 (64) | 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** |

*q1–q3* first–third quartile, *BSI* bloodstream infection, *CVC* central venous catheter
Boldface means statistically significant ($p < 0.05$)

# CEFIDEROCOL

*Bavaro et al.*
*Infect Dis Ther 2023*

| Characteristics | | Overall n = 111 | Cefiderocol n = 60 | Colistin n = 51 | p-Value |
|---|---|---|---|---|---|
| Age, years, median (IQR) | | 69 (59–78) | 62 (48–75) | 72 (64–81) | <0.001 |
| Gender, male, n (%) | | 75 (68) | 38 (63) | 37 (73) | 0.300 |
| Number of comorbidities, median (IQR) | | 3 (2–4) | 2.4 (1–4) | 3 (2–4) | 0.067 |
| Coinfections, n (%) | COVID-19 | 36 (32) | 16 (27) | 20 (39) | 0.160 |
| | Gram-positive infection | 22 (19.8) | 11 (18.3) | 11 (21.6) | 0.670 |
| | Candidemia | 7 (6.3) | 5 (8.3) | 2 (3.9) | 0.340 |
| Comorbidities, n (%) | Cardiovascular disease | 73 (66) | 35 (58) | 38 (75) | 0.073 |
| | Diabetes | 27 (24) | 10 (17) | 17 (33) | 0.041 |
| | Obesity | 41 (37) | 16 (27) | 25 (49) | 0.015 |
| | Lung disease | 30 (27) | 20 (33) | 10 (20) | 0.100 |
| | Chronic kidney disease | 18 (16) | 12 (22) | 5 (10) | 0.091 |
| | Psychiatric disorders | 43 (39) | 20 (33) | 23 (45) | 0.100 |
| | Malignancy | 19 (17) | 9 (15) | 10 (20) | 0.520 |
| Type of infection, n (%) | Bloodstream infection | 53 (47.7) | 34 (56.6) | 19 (37.2) | 0.005 |
| | Pneumonia | 58 (52.3) | 26 (43.4) | 32 (62.8) | |
| Length of stay, days, median (IQR) | | 45 (24–70) | 52 (32–73) | 34 (20–72) | 0.023 |
| Ward of admission, n (%) | Medical | 51 (46) | 22 (27) | 29 (57) | 0.087 |
| | Surgery | 25 (23) | 17 (28) | 8 (16) | |
| | ICU | 35 (32) | 21 (25) | 14 (27) | |
| CVVH, n (%) | | 5 (4.5) | 4 (6.6) | 1 (1.9) | 0.23 |
| ECMO, n (%) | | 3 (2.7) | 3 (5) | 0 (0) | 0.1 |
| Mechanical ventilation, n (%) | | 22 (20) | 13 (22) | 9 (18) | 0.6 |
| SOFA score, median (IQR) | | 2.5 (1–4.2) | 3.5 (2–5) | 2 (1–4) | 0.072 |
| APACHE score, median (IQR) | | 10 (7–13) | 10 (7.8–13.2) | 10 (7–13) | 0.890 |
| C-reactive protein, mg/dl, median (IQR) | | 104 (66–160) | 97 (67–160) | 110 (61–162) | 0.880 |
| Procalcitonin, ng/mL, median (IQR) | | 0.74 (0.16–3) | 0.52 (0.13–1.65) | 1.1 (0.2–5.1) | 0.270 |
| White blood count, median (IQR) | | 11.9 (7.6–17.6) | 11.8 (7.3–17.6) | 11.9 (7.8–17.6) | 0.830 |
| Creatinine, mmol/L, median (IQR) | | 69 (44–101) | 64 (36–88) | 77 (52–118) | 0.042 |
| Acute kidney injury, n (%) | | 19 (17.1) | 6 (10) | 13 (25.5) | 0.031 |
| Study outcomes | Clinical cure, n (%) | 78 (70) | 44 (73) | 34 (67) | 0.440 |
| | Microbiological cure, n (%) | 47 (42) | 26 (43) | 21 (41) | 0.820 |
| | Deaths, n (%) | 48 (43) | 26 (51) | 22 (37) | 0.130 |

# CEFIDEROCOL

No differences in mortality and clinical cure
Higher AKI in colistin group

*Mazzitelli et al. Microganisms 2023*

# CEFIDEROCOL

Table 2. Cefiderocol- and Colistin-associated treatment.

| Regimen-Associated Antimicrobial Agents | Cefiderocol n = 60 | Colistin n = 51 | *p*-Value |
|---|---|---|---|
| Fosfomycin, n (%) * | 8 (13.3) | 3 (5.8) | 0.19 |
| Meropenem, n (%) * | 13 (21.7) | 41 (80.4) | <0.001 |
| Tigecycline, n (%) * | 18 (30) | 49 (96.1) | <0.001 |
| Monotherapy | 30 (50) | 0 (0) | - |

| Characteristics | | Overall n = 60 | Cefiderocol Monotherapy n = 30 | Cefiderocol Combination Therapy n = 30 | *p*-Value |
|---|---|---|---|---|---|
| Ward of admission, n (%) | Medical | 22 (27) | 11 (36.7) | 11 (36.7) | 1 |
| | Surgery | 17 (28) | 9 (30) | 8 (26.7) | 0.77 |
| | ICU | 21 (25) | 10 (33.3) | 11 (36.7) | 0.78 |
| CVVH, n (%) | | 4 (6.6) | 2 (6.7) | 2 (6.7) | 1 |
| ECMO, n (%) | | 3 (5) | 1 (3.3) | 2 (6.7) | 0.55 |
| Study outcomes | Clinical cure, n (%) | 44 (73) | 23 (76.7) | 21 (70) | 0.55 |
| | Microbiological cure, n (%) | 26 (43) | 15 (50) | 11 (36.7) | 0.29 |
| | Deaths, n (%) | 26 (51) | 10 (33.3) | 16 (53.3) | 0.81 |

Legend for Table 2: n = number, % = percentage, and IQR = interquartile range.

*Mazzitelli et al. Microganisms 2023*

# CEFIDEROCOL

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-024-04833-8

ORIGINAL ARTICLE

## Clinical effectiveness of cefiderocol for the treatment of bloodstream infections due to carbapenem-resistant *Acinetobacter baumannii* during the COVID-19 era: a single center, observational study

Alessandra Oliva[1] · L Liguori[1] · S Covino[1] · F Petrucci[1] · F Cogliati-Dezza[1] · A Curtolo[1] · G Savelloni[1] · M Comi[1] · F Sacco[2] · G Ceccarelli[1] · A Viscido[2] · F Alessandri[3] · G Raponi[2] · F Pugliese[3] · CM Mastroianni[1] · M Venditti[1]

Received: 8 September 2023 / Accepted: 9 April 2024

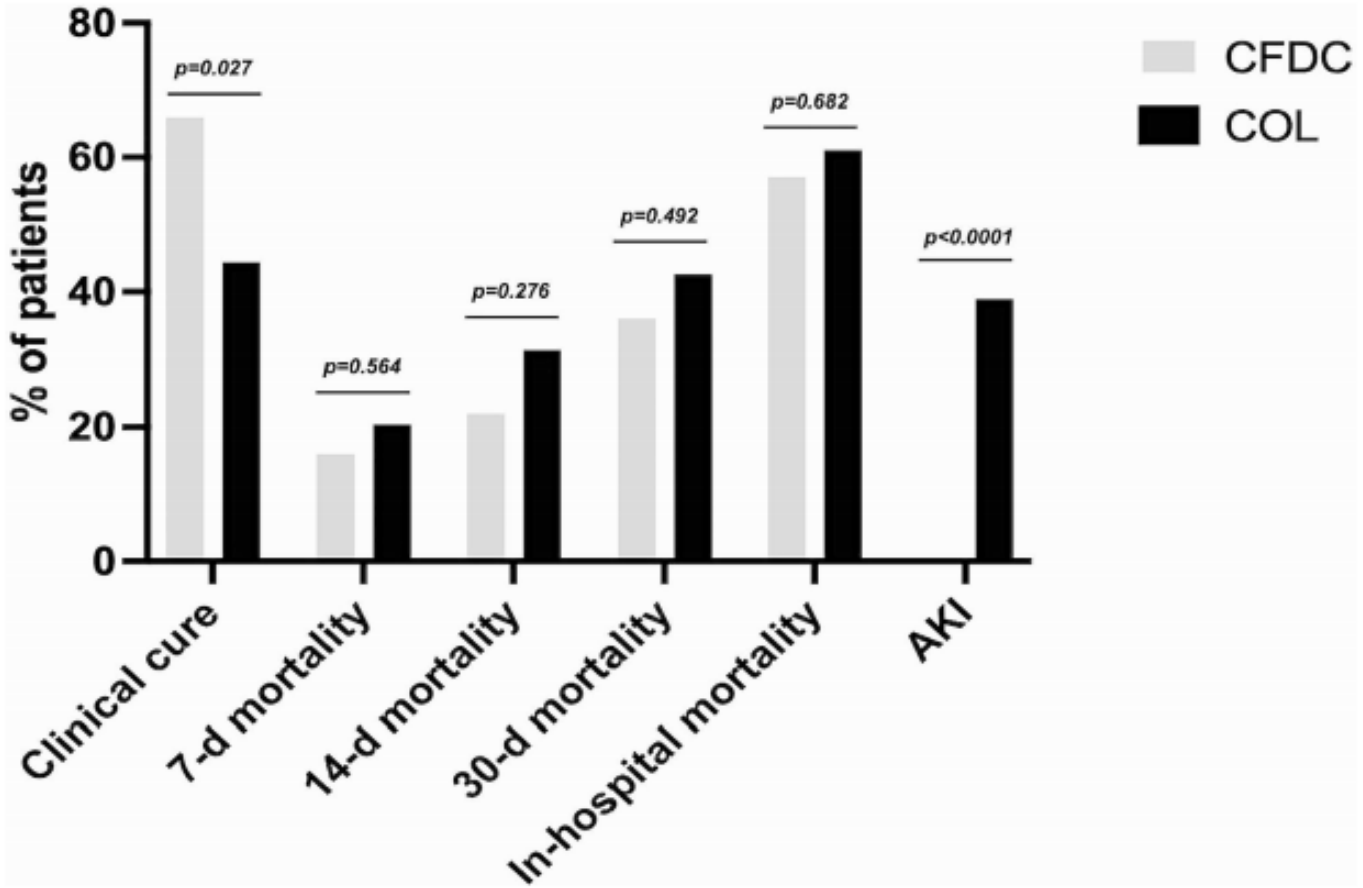
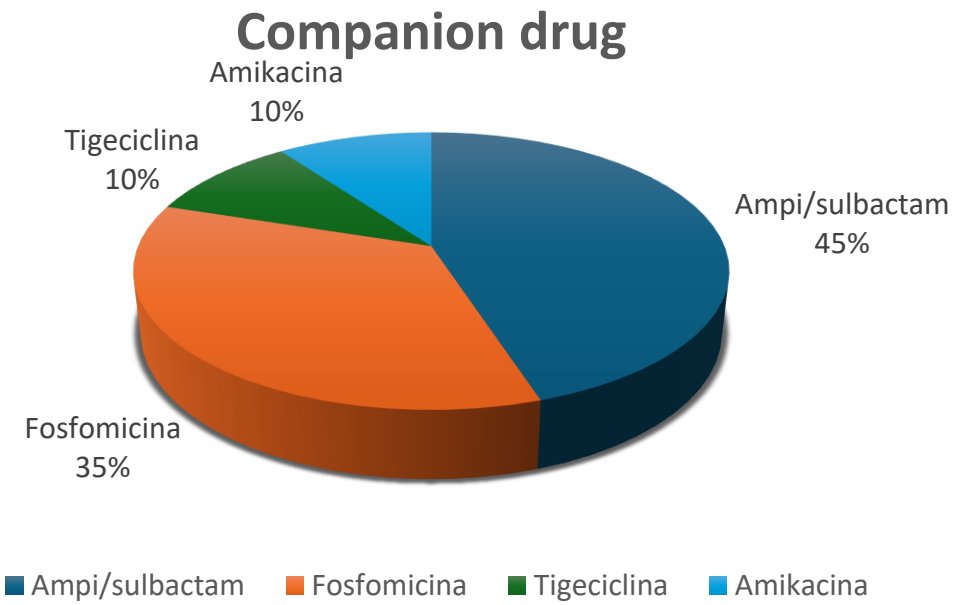




**Fig. 1** Study outcomes and adverse events according to CFDC or COL regimens. CFDC: cefiderocol; COL: colistin. AKI: Acute Kidney Injury

# CEFIDEROCOL

| | Monotherapy | Combination | |
|---|---|---|---|
| **30 days mortality, n° (%)** | 14 (48.3) | 5 (45.5) | 0.87 |
| **Clinical failure (7 days), n° (%)** | 12 (41.4) | 7 (63.7) | 0.20 |
| **Microbiological failure, (7 days) n° (%)** | 7 (24.1) | 1 (9.1) | 0.28 |
| **Clinical failure (End of treatment), n° (%)** | 8(27.6) | 5 (45.5) | 0.06 |
| **Microbiological failure (End of treatment), n° (%)** | 4 (13.8) | 0 (0) | 0.19 |




*Calò et al.*
*Journal of Infection and Public Health*
*2023*

# CEFIDEROCOL

- ✓ In un'ampia coorte di pazienti con VAP monomicrobica causata da CRAB, il fallimento clinico dopo la terapia mirata di prima linea ha coinvolto quasi il 40% dei pazienti ed è stato associato a tassi di mortalità in terapia intensiva a 14 e 28 giorni pari al 41% e al 71%. rispettivamente.
- ✓ I tassi di fallimento clinico sono stati pari al 48% nei pazienti che avevano ricevuto regimi a base di colistina e al 25% in quelli trattati con regimi a base di cefiderocol
- ✓ la terapia mirata tempestiva e i regimi di prima linea a base di cefiderocol hanno ridotto fortemente il rischio di fallimento
- ✓ quasi il 90% dei pazienti che hanno avuto una risoluzione dell'infezione hanno ricevuto agenti attivi CRAB entro 24 ore dall'insorgenza della VAP e una terapia mirata tempestiva si è rivelata in grado di ridurre in modo indipendente il rischio di fallimento clinico del 60%.
- ✓ Il 58% dei pazienti è stato colonizzato da CRAB e, di conseguenza, sono state intraprese strategie terapeutiche empiriche guidate
- ✓ I tassi rilevanti di terapia attiva tempestiva, che hanno portato alla risoluzione della VAP, sono stati raggiunti grazie al contributo significativo della diagnostica molecolare rapida eseguita in pazienti ad alto rischio. Questa scoperta conferma il valore dei pannelli respiratori multiplex RT, che includono, oltre alla sospensione degli antibiotici, l'aiuto ai medici a indirizzare tempestivamente la terapia nei pazienti con VAP grave.

Dalfino et al, Antibiotics 2023

# CEFIDEROCOL

| | Clinical Resolution ($n$ = 56) | Clinical Failure ($n$ = 34) |
|---|---|---|
| **Age (years)** | 62 (52–69) | 71 (64–78) * |
| **Male sex** | 38 (68) | 16 (47) |
| **Surgical admission** | 30 (54) | 18 (53) |
| **Immunodepression** | 12 (21) | 15 (44) * |
| **Charlson comorbidity index** | 4 (2–6) | 8 (6–8) * |
| **Main comorbidities** | | |
| Diabetes mellitus | 8 (14) | 17 (50) * |
| Cardiovascular disease | 13 (23) | 18 (53) * |
| Chronic respiratory disease | 6 (11) | 15 (44) * |
| Chronic kidney disease | 4 (7) | 6 (18) |
| Chronic liver disease | 2 (4) | 3 (9) |
| Solid cancer | 6 (11) | 5 (15) |
| Active hematologic malignancies | 2 (4) | 5 (15) |
| Solid organ transplantation | 3 (5) | 6 (18) |
| Obesity (BMI > 30 kg/m$^2$) | 5 (9) | 4 (12) |
| **APACHE II score upon ICU admission** | 22 (20–25) | 23 (20–25) |
| **VAP onset from ICU admission (days)** | 8 (6–11) | 9 (7–11) |
| **SOFA score at VAP onset** | 9 (7–11) | 10 (9–11) * |
| **Oxygenation at VAP onset** | | |
| $PaO_2$ to $FiO_2$ ratio >200 | 9 (16) | 4 (12) |
| $PaO_2$ to $FiO_2$ ratio >100 and <200 | 41 (73) | 26 (76) |
| $PaO_2$ to $FiO_2$ ratio <100 | 6 (11) | 4 (12) |
| **Infection severity at VAP onset** | | |
| Uncomplicated infection | 13 (23) | 2 (6) * |
| Sepsis | 19 (34) | 10 (29) |
| Septic shock | 25 (45) | 22 (65) |
| **Bacteraemic VAP** | 15 (26.8) | 14 (41.2) |
| **Augmented renal clearance** | 10 (18) | 5 (15) |
| **CRRT** | 8 (14) | 8 (24) |
| **vv-ECMO** | 3 (5) | 1 (3) |
| **Known respiratory CRAB colonization** | 34 (61) | 18 (53) |
| **Fast molecular diagnostics at VAP onset** | 17 (30.3) | 3 (8.8) * |
| **Timely (≤24 h) targeted therapy** | 50 (89) | 22 (65) * |
| **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) |
| **14-day mortality** | 0 (0) | 14 (41) * |
| **28-day mortality** | 12 (21) | 24 (71) * |
| **ICU length of stay (days)** | 24 (21–28) | 21 (17–25) * |

Dalfino et al, Antibiotics 2023

# CEFIDEROCOL

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

The aim of this study was to evaluate the impact of cefiderocol-containing regimens compared to colistin-containing regimens on the outcome of patients with VAP and concomitant bloodstream infection (BSI) caused by CRAB infection in COVID-19 patients

Russo et al, IJAA 2023

# CEFIDEROCOL

- During the study period, 73 patients who developed VAP and concomitant positive blood cultures caused by CRAB were enrolled in the COVID-ICU. Of these patients, 67 (91.7%) developed septic shock, 42 (57.5%) died at 14 days and 59 (80.8%) died at 30 days. All *Acinetobacter baumannii* strains were classified as XDR or PDR.

- Overall, 54 (74%) patients were treated using a colistin-containing regimen: 12 (22.2%) patients with colistin monotherapy, 12 (22.2%) with colistin plus meropenem plus tigecycline, and 9 (16.6%) with colistin plus meropenem.

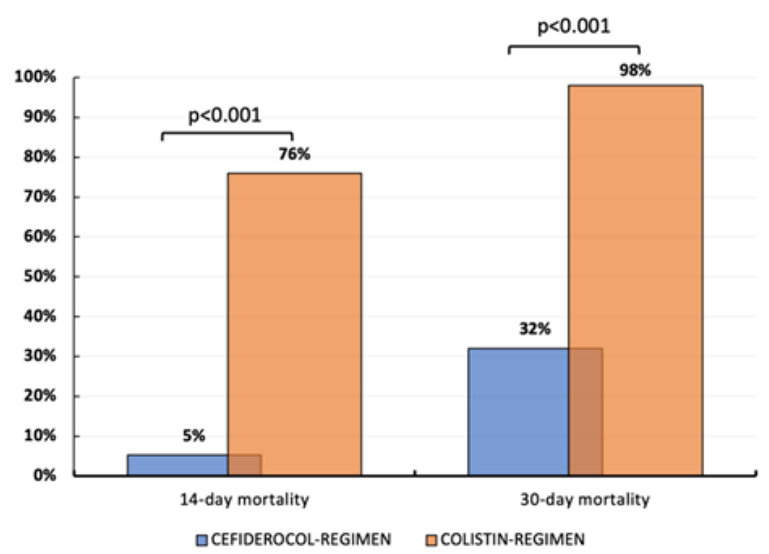
- Nineteen (26%) patients were treated with a cefiderocol-containing regimen: no patients were treated with cefiderocol as monotherapy, six (31.5%) with cefiderocol plus fosfomycin, three (15.8%) with cefiderocol plus fosfomycin plus tigecycline, and three (15.8%) with cefiderocol plus meropenem plus fosfomycin plus tigecycline.

- Finally, 33 (45.2%) were treated with colistin aerosol as adjunctive therapy.

Russo et al, IJAA 2023

# CEFIDEROCOL

No differences were observed in relation to sex, age, comorbidities, septic shock or length of ICU stay. Patients treated with colistin-containing regimens showed higher rates of 14-day (75.9% Vs 5.2%, $p < 0.001$) and 30-day mortality (98.1% Vs 31.5%, $p < 0.001$) compared to patients in the cefiderocol group




Russo et al, IJAA 2023

# CEFIDEROCOL

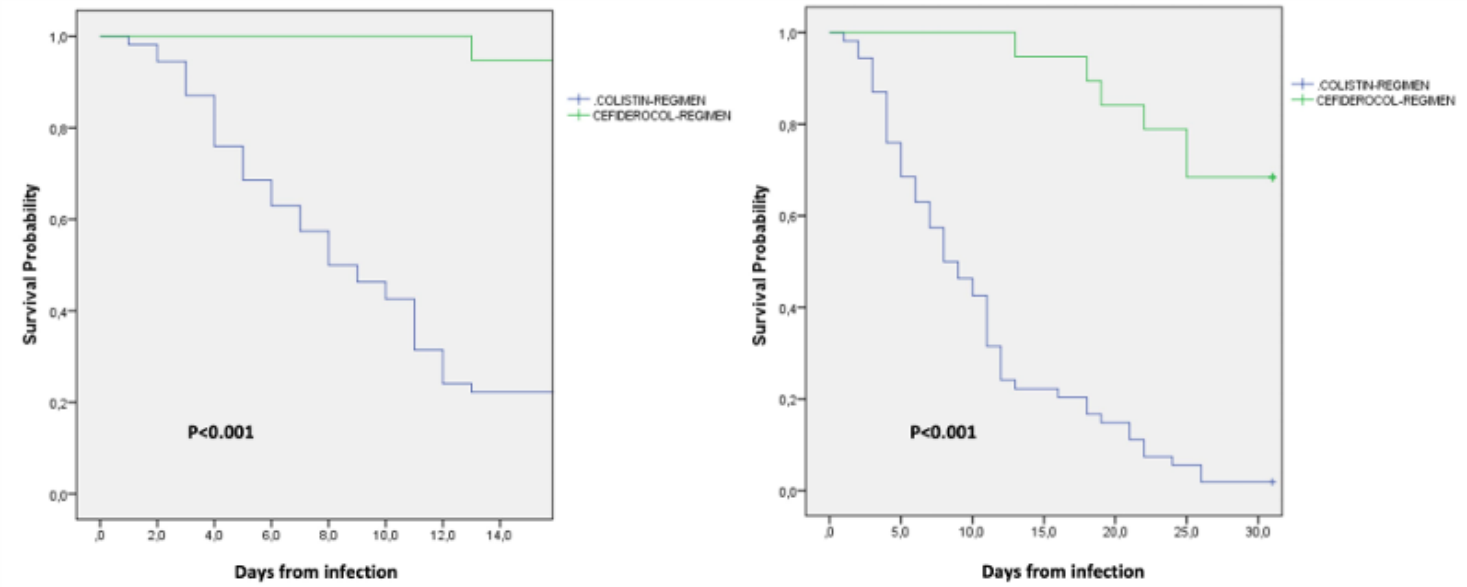
COX regression analysis on risk factors associated with death at 30 days and propensity-score analysis

| 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 – fosfomycin (IPTW-adjusted) | 0.33 (0.12-0.54) | < 0.001 |

Russo et al, IJAA 2023

# CEFIDEROCOL

Kaplan-Meier curves for 14- and 30-day survival in patients treated with cefiderocol-or colistin-containing regimens




Russo et al, IJAA 2023

# CEFIDEROCOL



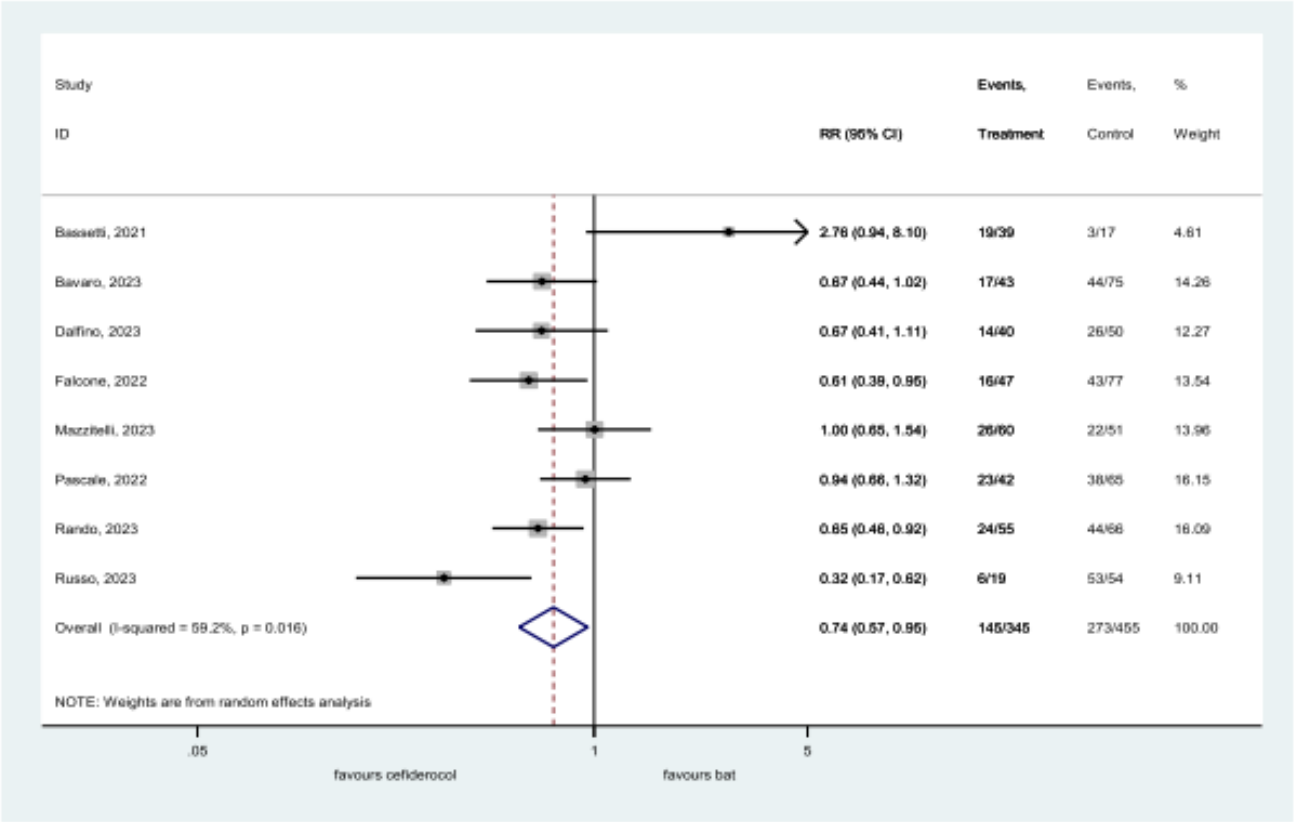



**Fig. 4.** Meta-analysis of studies comparing 30-day mortality rate in patients treated with cefiderocol or best available therapy.

# CEFIDEROCOL



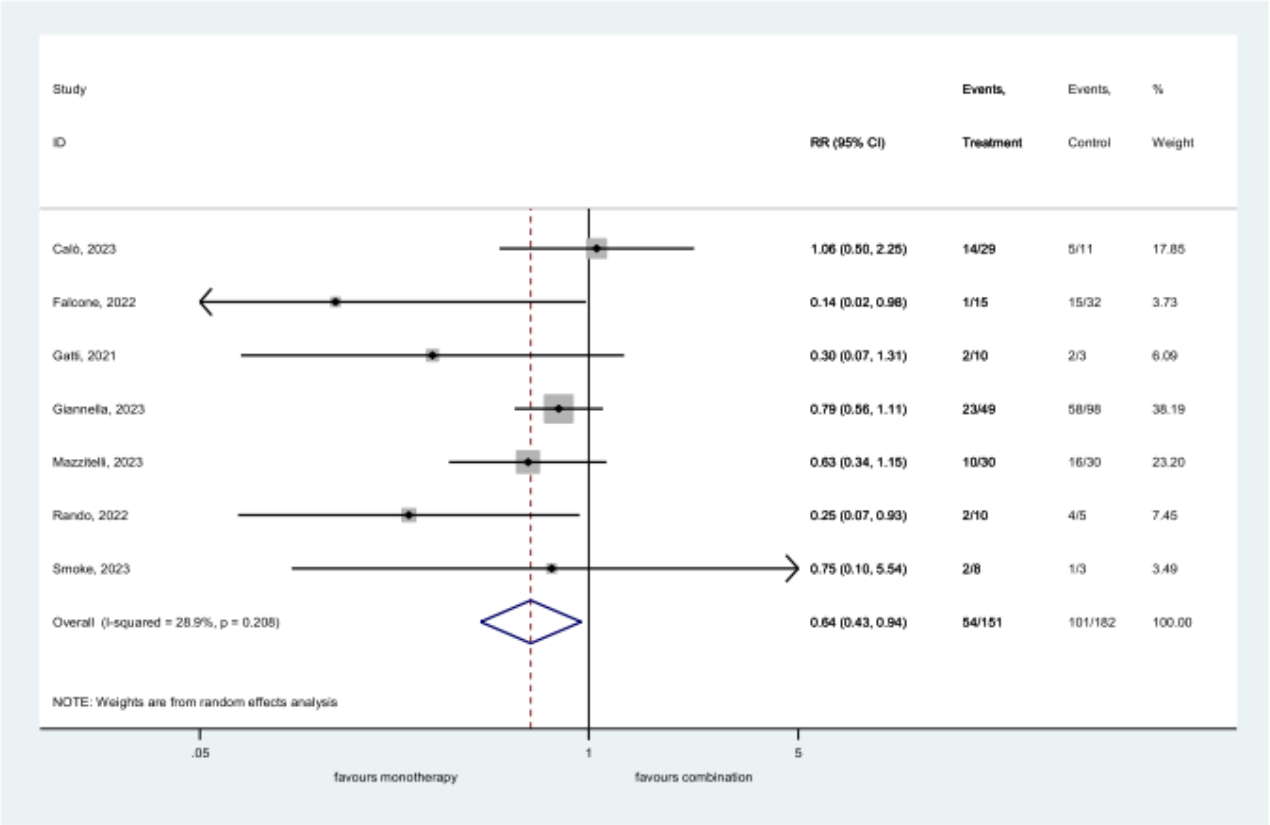



**Fig. 3.** Meta-analysis of studies comparing 30-day mortality rate in patients treated with cefiderocol monotherapy or combination therapy.

# CEFIDEROCOL

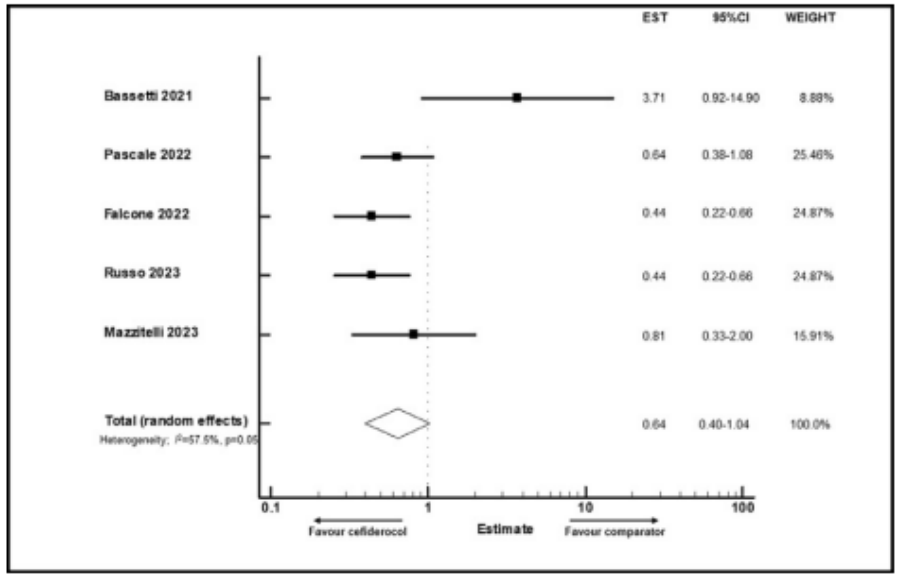



**Figure 1.** Forest plot of mortality rate in patients treated with cefiderocol-based regimens vs. non-cefiderocol-based regimens for CRAB infections.

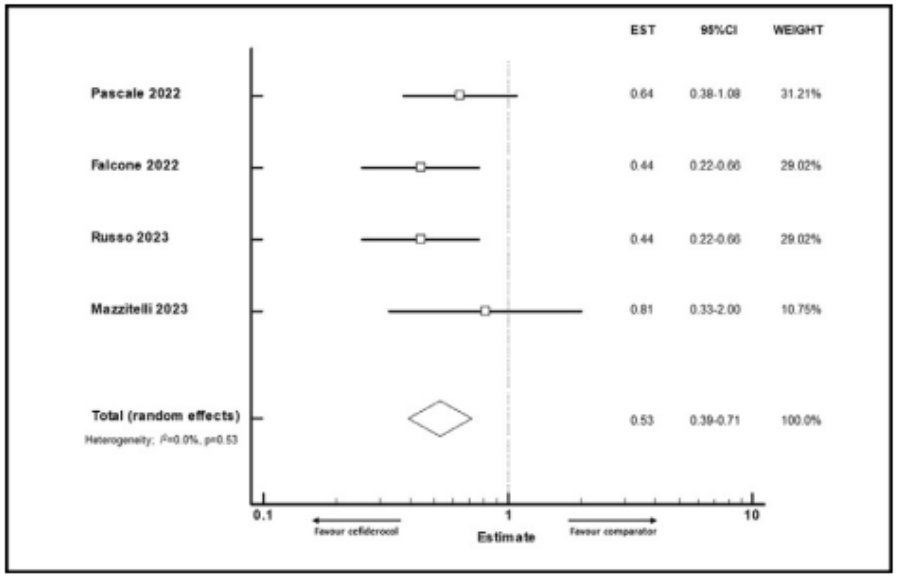



**Figure 2.** Forest plot of mortality rate in patients treated with cefiderocol-based regimens vs. non-cefiderocol-based regimens for CRAB infections, in subgroup analysis including only observational studies providing adjustment for confounders.

# Nuove opzioni terapeutiche

*Karruli et al. Antibiotics 2023*

The efficacy of SUL-DUR in treating *A. baumannii* infections was assessed in a phase III clinical trial [80]. This was a multinational, randomized, active-controlled, non-inferiority trial. A total of 125 patients were included in the efficacy analysis, of whom 63 were treated with SUL-DUR at the dose of 2 g every 6 h, and 62 with colistin, with a maintenance dose of 2.5 mg/kg after a loading dose of 5 mg/kg of colistin base activity. Imipenem/cilastatin was used as a combination agent in both groups. Infections included BSI, hospital-acquired pneumonia (HAP), and VAP. SUL–DUR was non-inferior to colistin in terms of 28-day all-cause mortality in the microbiologically (CRAB) modified ITT population.

The 28-day all-cause mortality was 19% (12 patients) in the SUL–DUR group compared with 32.3% (20 patients) in the colistin group, with an observed treatment difference of –13.2% (95% C.I. –30 to 3.5). The 14-day all-cause mortality rate in the microbiologically (CRAB) modified ITT population was 6% (4 of 64) with SUL–DUR versus 19% (12 of 63) with colistin.

The authors performed a Kaplan–Meier analysis showing patients treated with SUL-DUR had a higher survival probability compared to those treated with colistin, with the difference becoming evident after the 6th day of treatment.

As for the microbiological eradication at the test of cure, a more favorable outcome was observed in the SUL-DUR group compared to colistin (43 of 63 treated with SUL-DUR [68%] vs. 26 of 62 patients treated with colistin [42%]).

# Case reports

*JAC Antimicrob Resist*
https://doi.org/10.1093/jacamr/dlad078

JAC-Antimicrobial Resistance

## Salvage therapy with sulbactam/durlobactam against cefiderocol-resistant *Acinetobacter baumannii* in a critically ill burn patient: clinical challenges and molecular characterization

Giusy Tiseo [1], Cesira Giordano[2], Alessandro Leonildi[2], Niccolò Riccardi[1], Valentina Galfo[1], Federica Limongi[3], Manuela Nicastro[3], Simona Barnini[2] and Marco Falcone [1*]

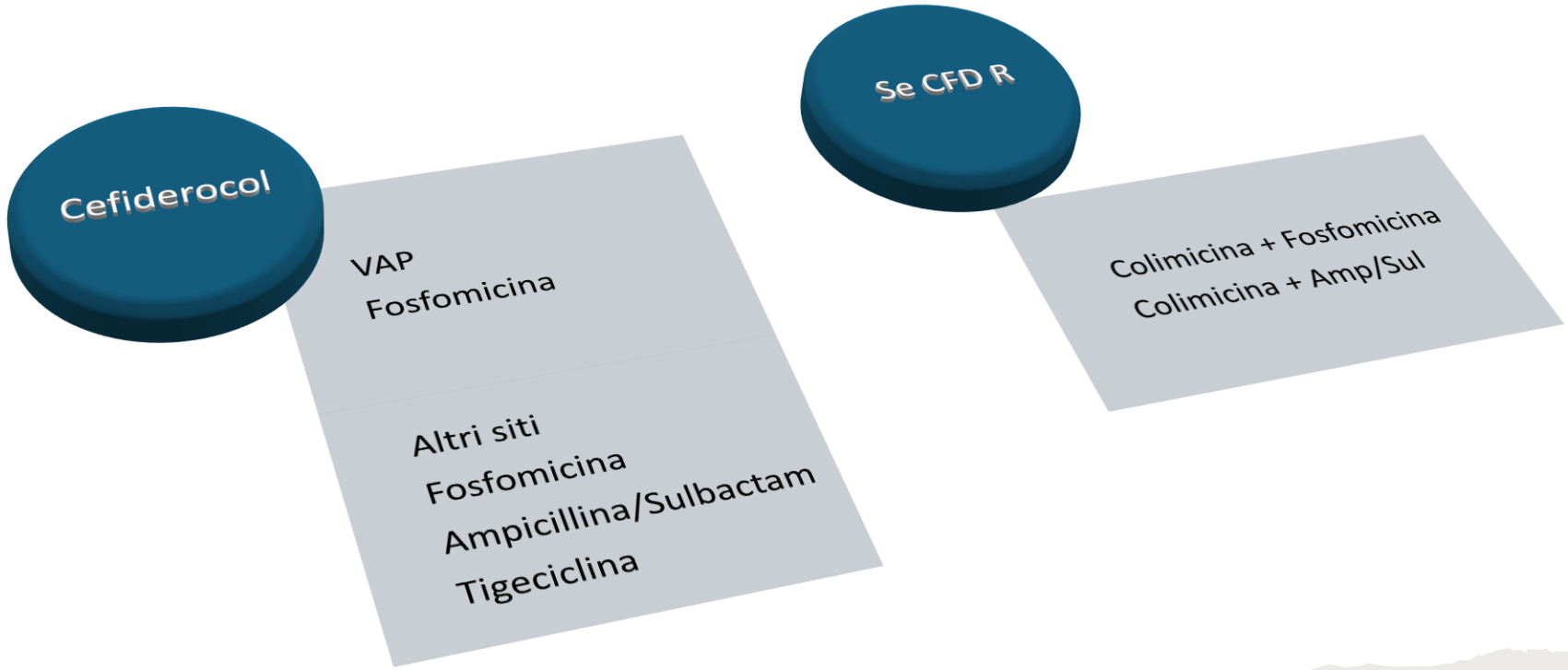
## Successful Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Meningitis with Sulbactam-Durlobactam

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], & Patricia J. Simner[3,6]

# Approccio Terapeutico ragionato

Sulbactam/Durlobactam

Che ruolo?



Grazie per l’attenzione