# Cefiderocol

Matteo Bassetti
Infectious Diseases Clinic
University of Genoa and San Martino-IST University Hospital
Genova, Italy

UNIVERSITÀ DEGLI STUDI
DI GENOVA

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

# Disclosures (past 5 years)

- Advisor/consultant/speaker bureau/research grants
  - Angelini, Bayer, Biomerieux, Cidara, Dompè, Gilead, Menarini, Mundipharma, MSD, Pfizer, Roche, Shionogi

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Activity of new agents against Gram-negative pathogens.

Grey shading: variable activity; red shading: non-activity; green shading: activity. KPC: Klebsiella pneumoniae carbapenemases; OXA: OXA-β-lactamases; NDM: New Delhi metallo-β-lactamase.

| | *Enterobacterales* | | | | | |
|---|---|---|---|---|---|---|
| | Class A Carbapenemase (*e.g.* KPC) | Class B Carbapenemase (*e.g.* NDM) | Class D Carbapenemase (*e.g.* OXA-48) | *Pseudomonas aeruginosa* | *Acinetobacter baumannii* | *Stenotrophomonas maltophilia* |
| Ceftobiprole | | | | | | |
| Ceftolozane-tazobactam | | | | | | |
| Ceftazidime-avibactam | | | | | | |
| Cefiderecol | | | | | | |
| Meropenem-vaborbactam | | | | | | |
| Imipenem-relebactam | | | | | | |
| Aztreonam-avibactam | | | | | | |
| Plazomicin | | | | | | |
| Eravacycline | | | | | | |

Bassetti M et al. Eur Respir Rev. 2022 Dec 31; 31(166): 220119

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# Activity of cefiderocol

- Efflux pumps ✓
- Porin mutations ✓
- Carbapenemases (all classes) ✓

Some cases of GNB isolates resistant to cefiderocol have been described (possibly reduced production of iron transport system components or mutations in the binding site for the iron transport system on the outer membrane of GNB, deficiency of the iron transporter PiuA in *P. aeruginosa*)

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Genoa, Italy

Ito et al. Antimicrob Agents Chemother 2016
Hackel et al. Antimicrob Agents Chemother 2017
Hsueh et al. J Antimicrob Chemother 2019

# Cefiderocol demonstrated activity against Enterobacterales and non-fermenter GN isolates (EU)

## Comparison of susceptibilities to cefiderocol and comparators from collected GN isolates

| Pathogen | Antimicrobial | MIC$_{50}$ (mg/L) | MIC$_{90}$ (mg/L) | % Susceptible[a] |
|---|---|---|---|---|
| **Enterobacterales** (n=3,994) | **Cefiderocol** | **0.12** | **0.50** | **98.9** |
| | Imipenem/relebactam | 0.12 | 1 | 98.2 |
| | Meropenem/vaborbactam | <0.06 | 0.06 | 99.0 |
| | Ceftazidime/avibactam | 0.12 | 0.5 | 99.1 |
| | Piperacillin/tazobactam | 2.00 | 64 | 81.8 |
| | Meropenem | <0.06 | 0.06 | 96.9[b] |
| | Colistin | 0.25 | >8 | 83.9[c] |
| ***P. aeruginosa*** (n=1,213) | **Cefiderocol** | **0.12** | **0.50** | **99.4** |
| | Imipenem/relebactam | 0.25 | 1 | 95.5 |
| | Ceftazidime/avibactam | 2 | 4 | 96.4 |
| | Ceftolozane/tazobactam | 0.50 | 2 | 94.6 |
| | Piperacillin/tazobactam | 4 | 128 | 76.9[b] |
| | Meropenem | 0.50 | 8 | 77.3 |
| | Colistin | 1 | 1 | 99.7[c] |
| ***A. baumannii calcoacetius* complex** (n=340) | **Cefiderocol** | **0.25** | **1.00** | **94.4** |
| | Imipenem/relebactam | >8 | >8 | 37.6 |
| | Ceftazidime | >32 | >32 | N/A |
| | Piperacillin/tazobactam | >128 | >128 | N/A |
| | Meropenem | >32 | >32 | 37.6 |
| | Ciprofloxacin | >4 | >4 | 37.1[b] |
| | Colistin | 0.50 | >8 | 80.9[c] |

*Shortridge D et al. Microbiol Spectr 2022;10:e0271221*

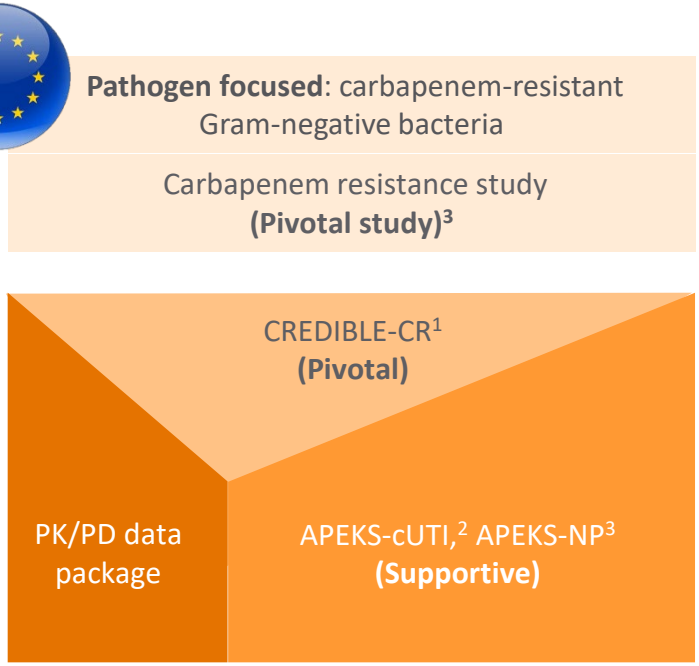
# Developement of cefiderocol resistance

- Klebsiella pnuemoniae
  - Moon SH et al.  Microbiol Spectr. 2023 Jun 15;11(3):e0349622
- P. aeruginosa
  - Brakert L et al. J Glob Antimicrob Resist 2023 Jun 26;S2213-7165(23)00097-8
- A. Baumannii
  - Liu X et al. mSystems. 2023 Jun 22:e0129122
- Burkholderia pseudomallei
  - Hall CM et al.  Antimicrob Agents Chemother. 2023 Jun 15;67(6):e001712

# Approval process for cefiderocol: different approaches – pathogen focused in Europe and infection site/organism led in the USA

**Pathogen focused**: carbapenem-resistant Gram-negative bacteria

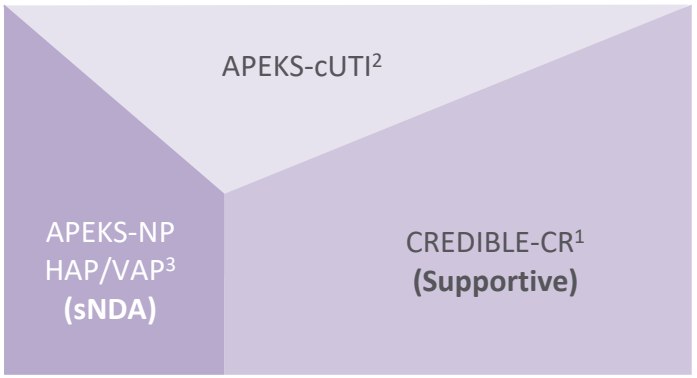
Carbapenem resistance study
**(Pivotal study)[3]**




**Aerobic Gram-negative organisms with limited treatment options[4]**

**Infection site specific**: carbapenem-susceptible cUTI, HAP/VAP Gram-negative infection

**Establish clinical efficacy and safety profile of cefiderocol 2000 mg q8h[3]**

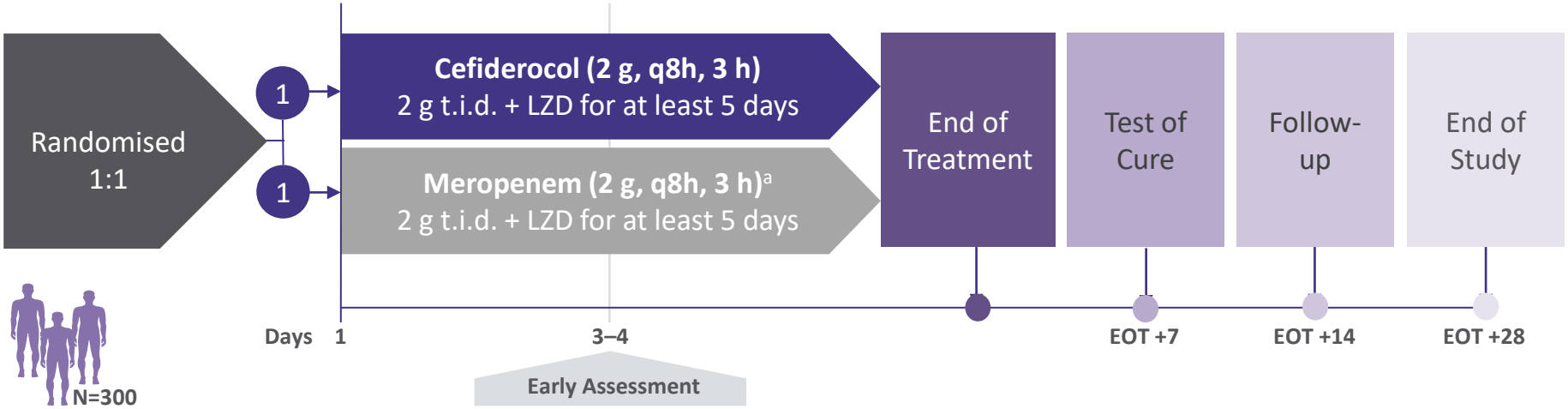



**cUTI, HAP/VAP[5]**

CR, carbapenem resistant; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MAA, marketing authorisation application; NDA, new drug application; NP, nosocomial pneumonia; PD, pharmacodynamic; PK, pharmacokinetic; sNDA, supplemental NDA; q8h, every 8 hours; VAP, ventilator-associated pneumonia.

1. Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9; 2. .Portsmouth S, et al. *Lancet Infect Dis* 2018;18:1319-28; 3. Wunderink RG, et al. Lancet Infect Dis 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731-3; 4. Fetcroja (cefiderocol). Summary of Product Characteristics. Shionogi BV. https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf [Accessed Jan 2021]; 5. Fetroja (cefiderocol). Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf [Accessed Jan 2021]

# APEKS-NP: a double-blind, clinical trial to compare cefiderocol vs high-dose extended-infusion meropenem in nosocomial pneumonia




## Objectives

- **Primary endpoint:** Day 14 ACM with a 12.5% non-inferiority margin
- **Secondary endpoint:** clinical and microbiological outcomes at TOC, and Day 14 ACM tested for superiority after non-inferiority was demonstrated

ACM, all-cause mortality; EOT, end of treatment; LZD, linezolid; NP, nosocomial pneumonia; PD, pharmacodynamic; PK, pharmacokinetic; TOC, test of cure.

[a]Prolonged-infusion meropenem regimen (2 g infused over 3 hours, q8h) is preferred to the approved regimen (1 g infused over 30 minutes, q8h) to achieve higher exposure.

Wunderink RG, et al. *Lancet Infect Dis* 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731–3

# APEKS-NP: all-cause mortality was similar in both treatment groups at all timepoints – cefiderocol non-inferior to high-dose, extended-infusion meropenem[a]

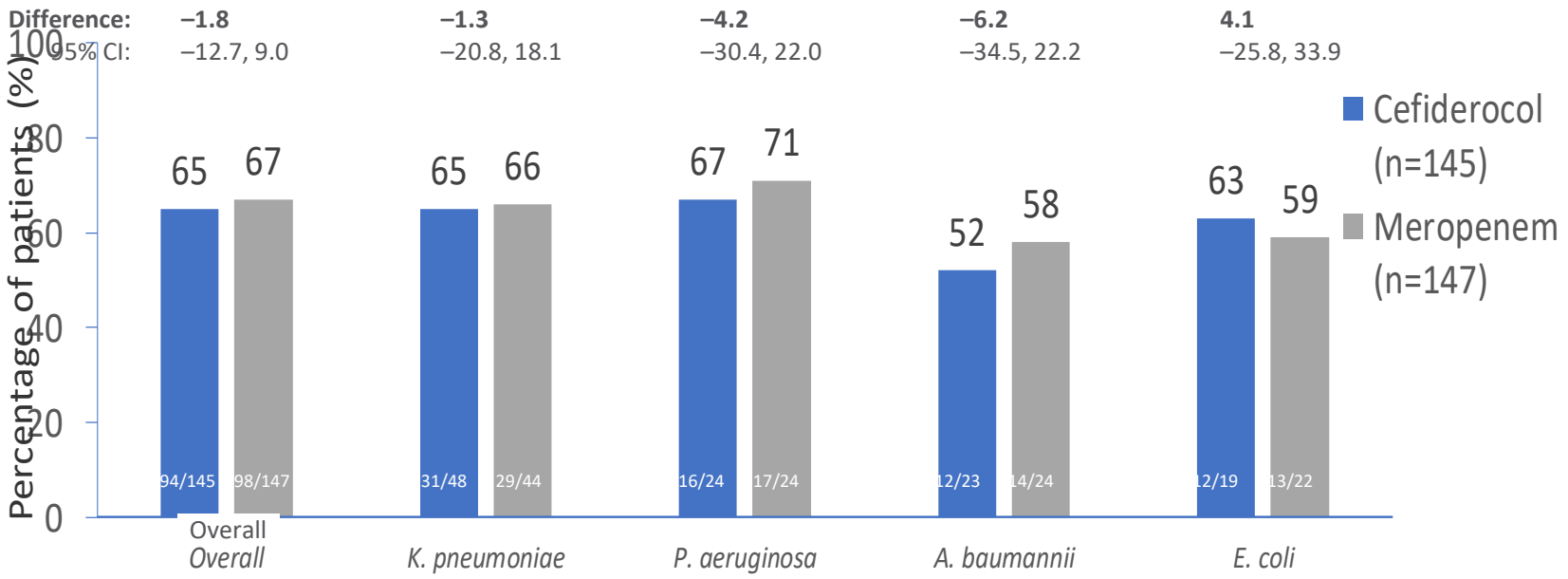
| Timepoint | Cefiderocol % (n/N) | Meropenem % (n/N) | Treatment Difference % (95% CI) |
|---|---|---|---|
| Day 14 (Primary endpoint) | 12.4 (18/145) | 11.6 (17/146) | 0.8 (–6.6, 8.2) |
| Day 28 | 20.9 (30/143) | 20.5 (30/146) | 0.4 (–8.9, 9.8) |

[a]micro-ITT population

Micro-ITT, microbiological intention to treat population; CI, confidence interval.

Wunderink RG, et al. *Lancet Infect Dis* 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731–3

# APEKS-NP: clinical cure rates, by key pathogen, were similar in both treatment groups[a]

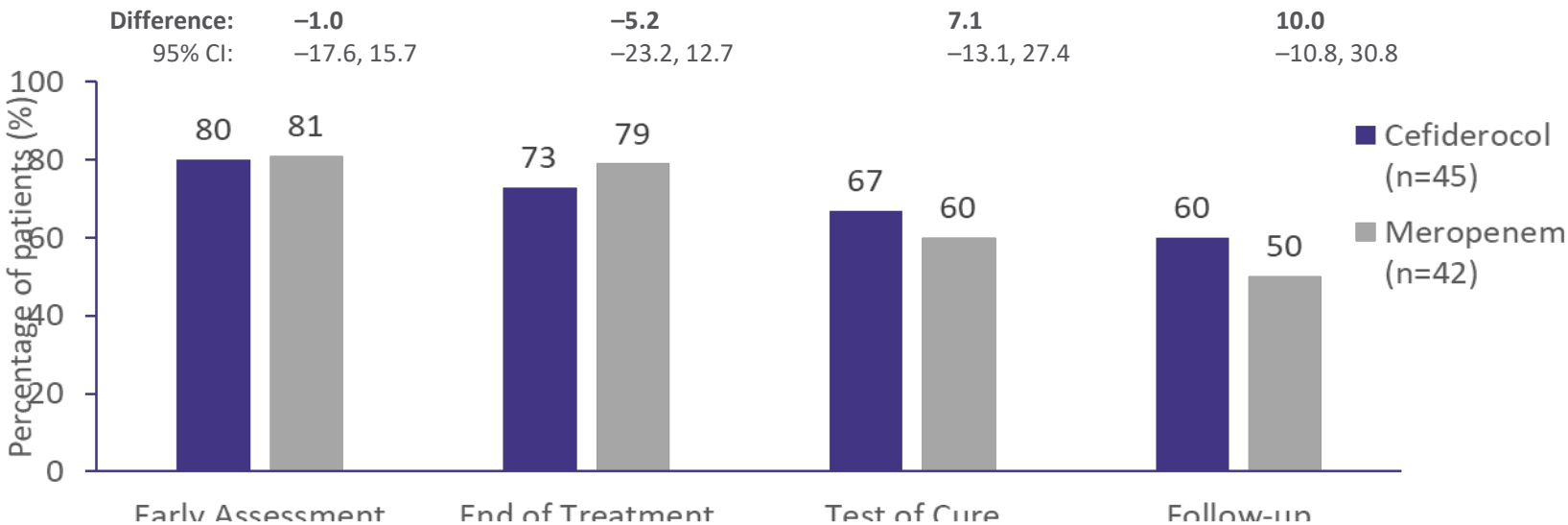



[a]micro-ITT population

CI, confidence interval; micro-ITT, microbiological intent to treat.

Wunderink RG, et al. *Lancet Infect Dis* 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731–3

# APEKS-NP: similar clinical cure rates in patients with ESBL-producing bacteria at each timepoint and in line with the overall population[a]




[a]micro-ITT population

CI, confidence interval; ESBL, extended-spectrum beta-lactamase; micro-ITT, microbiological intent to treat.

Wunderink RG, et al. *Lancet Infect Dis* 2020; published online Oct 12. http://dx.doi.org/10.1016/S1473-3099(20)30731–3

# CREDIBLE-CR: pathogen-focused Phase 3 study

## Population

**High-risk, severely ill patients;** infections include non-fermenter species such as *Acinetobacter* spp.

**Patients were enrolled irrespective of infection type**, comorbidities, pathogen species, or CR mechanism

## Study drug

**Cefiderocol (2 g)** (n=101) (mostly monotherapy) or **best available therapy (BAT)** (n=49) that could include up to three antibiotics, dosed according to country's label

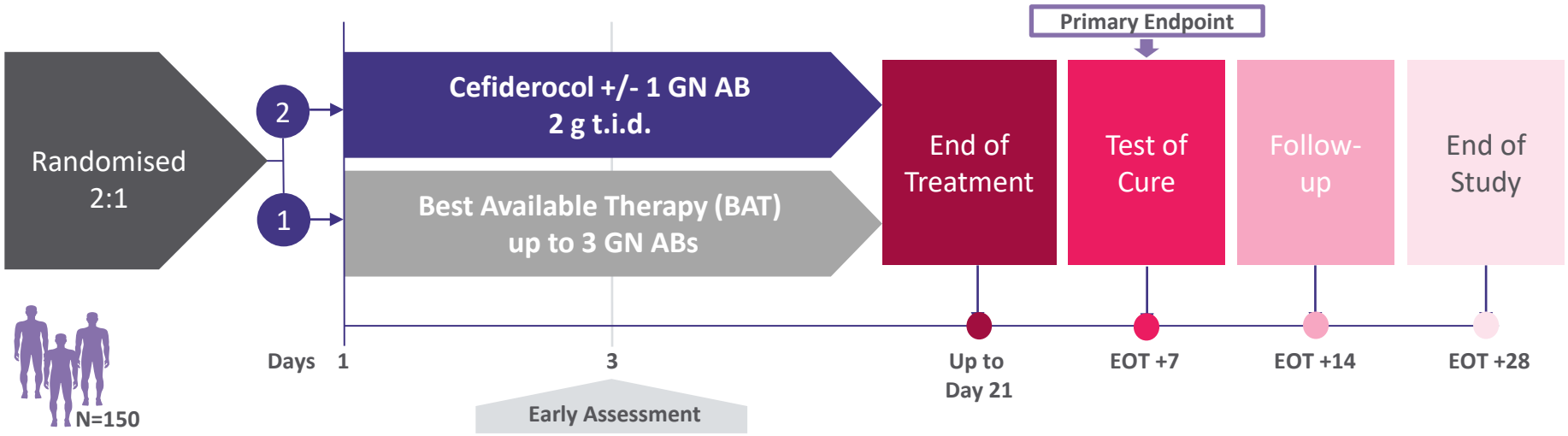
## Open-label design

Randomised, pathogen-focused, **open-label, non-inferential, descriptive trial** to assess the efficacy and safety of cefiderocol or BAT.

BAT, best available therapy; CR, carbapenem resistant.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

# CREDIBLE-CR: a novel, pathogen-focused, open-label study to explore cefiderocol therapy and BAT in CR GN infections




## Objectives

- **Primary endpoint at TOC:** HAP/VAP/HCAP and bloodstream infections/sepsis – clinical outcome; cUTI – microbiological outcome
- **Secondary endpoint:** clinical and microbiological outcomes at TOC, EOT and FU, and Day 14 and 28 ACM

ACM, all-cause mortality; AB, antibiotic; BAT, best available therapy; CR, carbapenem resistant; cUTI, complicated urinary tract infection; EOT, end of treatment; FU, follow-up; GN, Gram negative; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; t.i.d., three times daily dosing; TOC, test of cure; VAP, ventilator-associated pneumonia.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

# CREDIBLE-CR: baseline CR Gram-negative pathogens – *A. baumannii* the most commonly identified resistant pathogen[a,b]

| | Cefiderocol (n=80) n (%) | BAT (n=38) n (%) |
|---|---|---|
| CR *A. baumannii* | 37 (46) | 17 (45) |
| CR *K. pneumoniae* | 27 (34) | 12 (32) |
| CR *P. aeruginosa* | 12 (15) | 10 (26) |
| *S. maltophilia* | 5 (6) | 0 |

[a]CR micro-ITT population

[b]Data reflects isolated resistant pathogens; patients may have had mixed infections and infections with >1 CR pathogen

BAT, best available therapy; CR, carbapenem resistant; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
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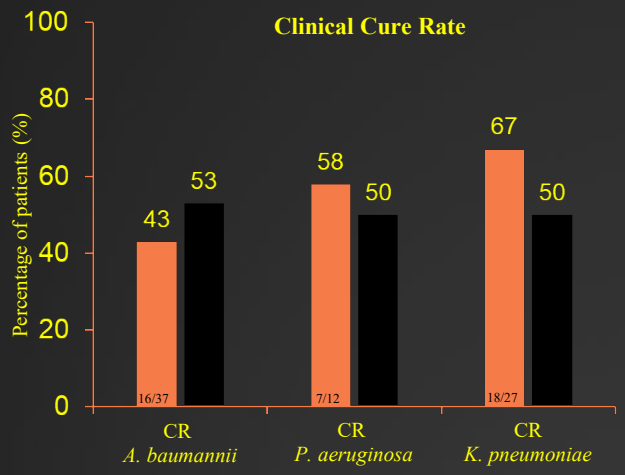
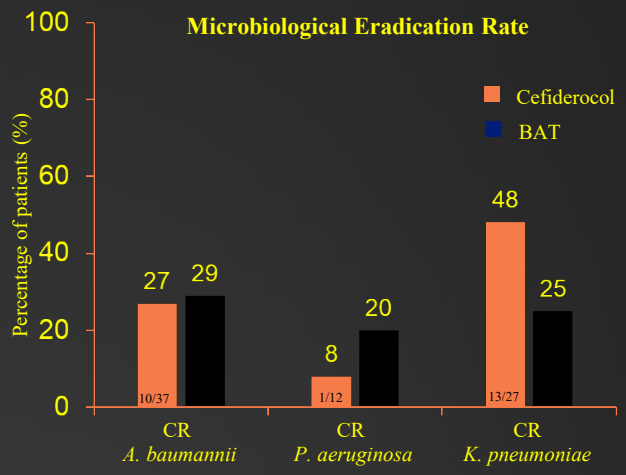
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# CREDIBLE-CR: similar rates at TOC by baseline pathogen, but higher for cefiderocol in Enterobacterales infection[a]




[a]CR micro-ITT population

BAT, best available therapy; CR, carbapenem resistant; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; TOC, test of cure.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

# High rates of clinical cure and microbiological eradication with cefiderocol in CRE infections

## Clinical cure

| | Cefiderocol % (n/N) | BAT % (n/N) |
|---|---|---|
| CRE | 66% (19/29) | 45% (5/11) |
| CR non-fermenters | 45% (22/49) | 52% (13/25) |
| Mixed | 50% (1/2) | 50% (1/2) |

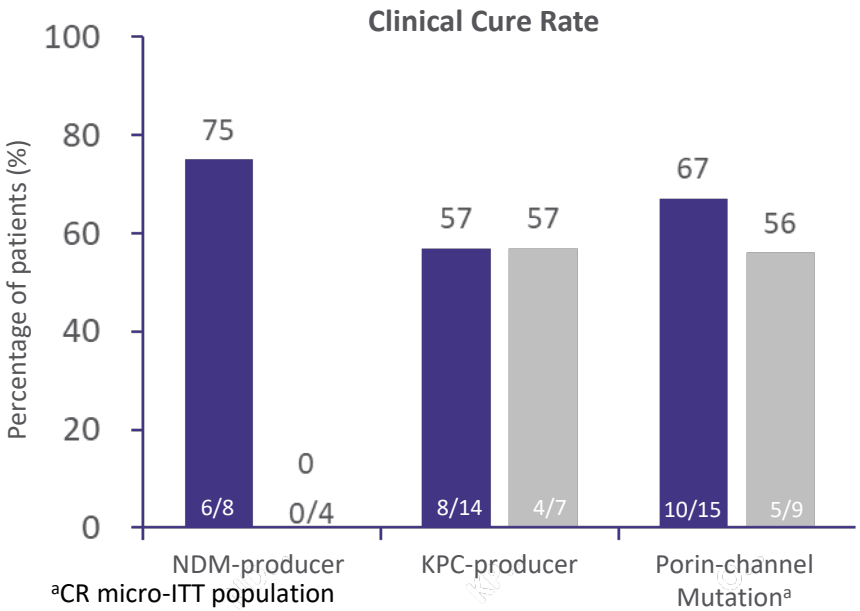
## Microbiological eradication

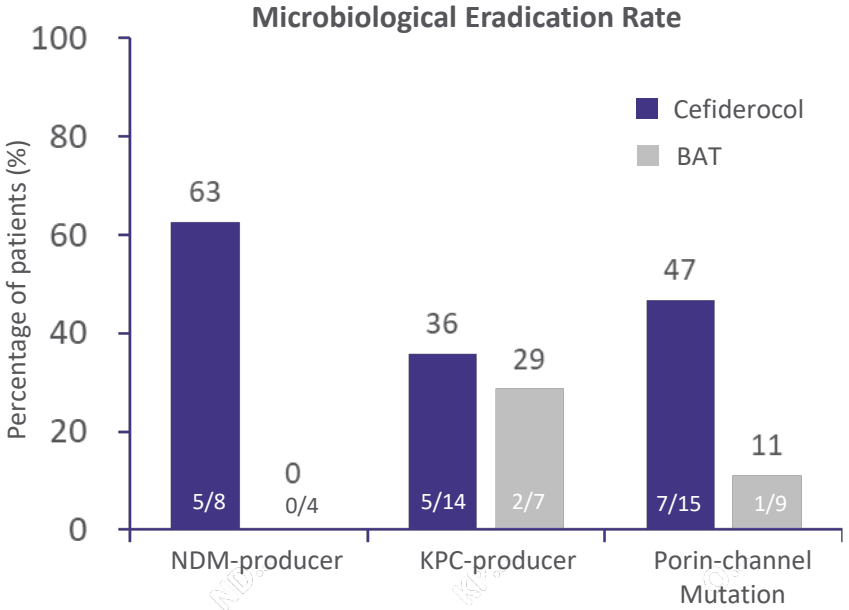
| | Cefiderocol % (n/N) | BAT % (n/N) |
|---|---|---|
| CRE | 48% (14/29) | 18% (2/11) |
| CR non-fermenters | 22% (11/49) | 24% (6/25) |
| Mixed | 0% (0/2) | 50% (1/2) |

BAT, best available therapy; CRE, carbapenem resistant Enterobacteriaceae; CR, carbapenem resistant

Bassetti M, et al. Lancet Infect Dis 2020 Oct 12:S1473-3099(20)30796-9. doi: 10.1016/S1473-3099(20)30796–9

# CREDIBLE-CR: cefiderocol effective at TOC in resistant Enterobacterales due to carbapenemase producers and porin-channel mutations[a]



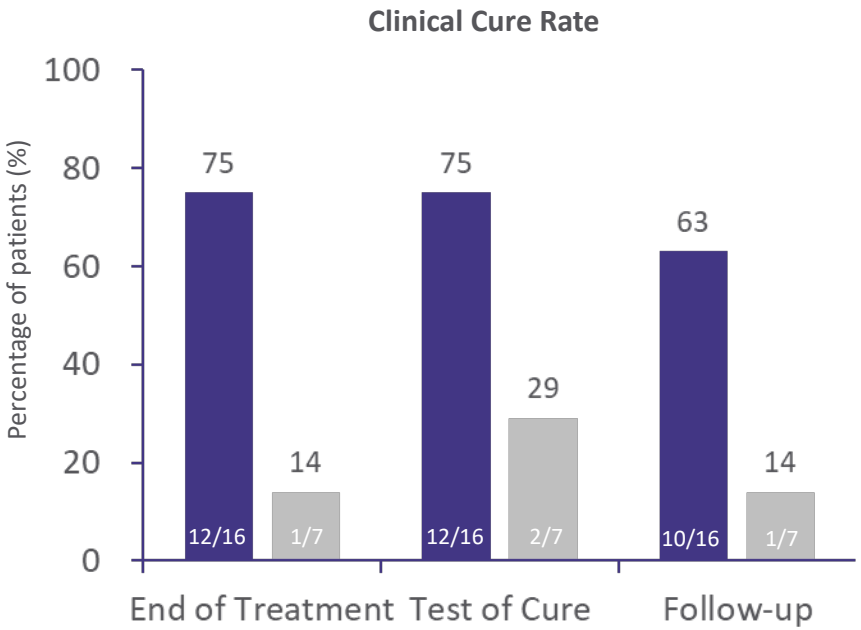

[a]CR micro-ITT population

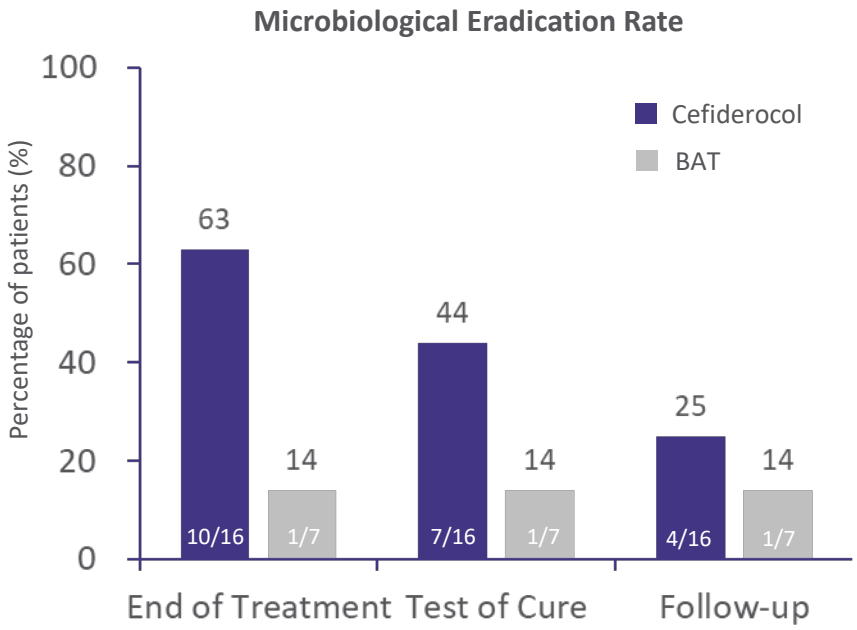
BAT, best available therapy; CR, carbapenem resistant; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-beta-lactamases; NDM, New Delhi metallo-beta-lactamase; TOC, test of cure.

[a]OMPK35/36-deficient; only patients with molecular data are included.

Matsunaga Y, et al. Presented at IDWeek, October 2-6, 2020 (virtual) Abstract 904840, Oral Presentation O165

# CREDIBLE-CR: cefiderocol rates at TOC were higher with cefiderocol than BAT treatment in MBL producing GN pathogens[a]




[a]CR micro-ITT population

BAT, best available therapy; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; GN, Gram negative; MBL, metallo-beta-lactamases; TOC, test of cure.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

# CREDIBLE-CR: all-cause mortality, Day 28 and End of Study[a]

| Timing of death | Cefiderocol (n=101) n (%) | BAT (n=49) n (%) |
|---|---|---|
| Up to Day 28 | 25 (25) | 9 (18) |
| Late: Day 29 to end of study | 9 (9) | 0 (0) |
| Overall mortality: end of study | 34 (34) | 9 (18) |

[a]Safety population

BAT, best available therapy.

Bassetti M, et al. *Lancet Infect Dis* 2020; Published online October 12, 2020 https://doi.org/10.1016/S1473-3099(20)30796–9

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Dipartimento di Scienze della Salute (DISSAL)
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Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Mortality in CREDIBLE-CR was associated with *A. baumannii* infection, but characteristics of shock and infection severity may also contribute

The underlying reasons for the mortality imbalance in CREDIBLE may never be known, but mortality appears to be associated with *A. baumannii*

Patients infected with *A. baumannii* and treated with cefiderocol had a higher unadjusted mortality rates than patients without *A. baumannii* or treated with BAT; numbers were small

**Characteristics of *A. baumannii* patients treated with cefiderocol**

- Older (>65 years)
- More severely ill (APACHE II ≥16)
- Progressed to shock
- Resident in the ICU

**But patient numbers were small**

APACHE, Acute Physiology and Chronic Health Evaluation; BAT, BAT, best available therapy; ICU, intensive care unit.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

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Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# CREDIBLE-CR: 49-day mortality rates, by most frequent baseline pathogen, appear to be associated with *Acinetobacter* spp infections[a]

| | Cefiderocol (n=101) n (%) | BAT (n=49) n (%) |
|---|---|---|
| ***Acinetobacter* spp.**[a] | 21/42 (50) | 3/17 (18) |
| ***A. baumannii*** | 19/39 (49) | 3/17 (18) |
| ***K. pneumoniae*** | 8/34 (24) | 4/16 (25) |
| without *Acinetobacter* spp. | 6/28 (21) | 4/15 (27) |
| ***P. aeruginosa*** | 6/17 (35) | 2/12 (17) |
| without *Acinetobacter* spp. | 2/11 (18) | 2/11 (18) |
| ***E. coli*** | 1/6 (17) | 0/3 (0) |
| without *Acinetobacter* spp. | 0/3 (0) | 0/1 (0) |
| ***S. maltophilia*** | 4/5 (80) | – |
| without *Acinetobacter* spp. | 2/3 (67) | – |

[a]Safety population

**Due to the small numbers, no conclusions can be drawn**

BAT, best available therapy.

[a]*Acinetobacter* spp. includes *A. baumannii*, *A. nosocomialis* and *A. radioresistens*.

Bassetti M, et al. *Lancet Infect Dis* 2020; Published online October 12, 2020 https://doi.org/10.1016/S1473-3099(20)30796–9

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Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
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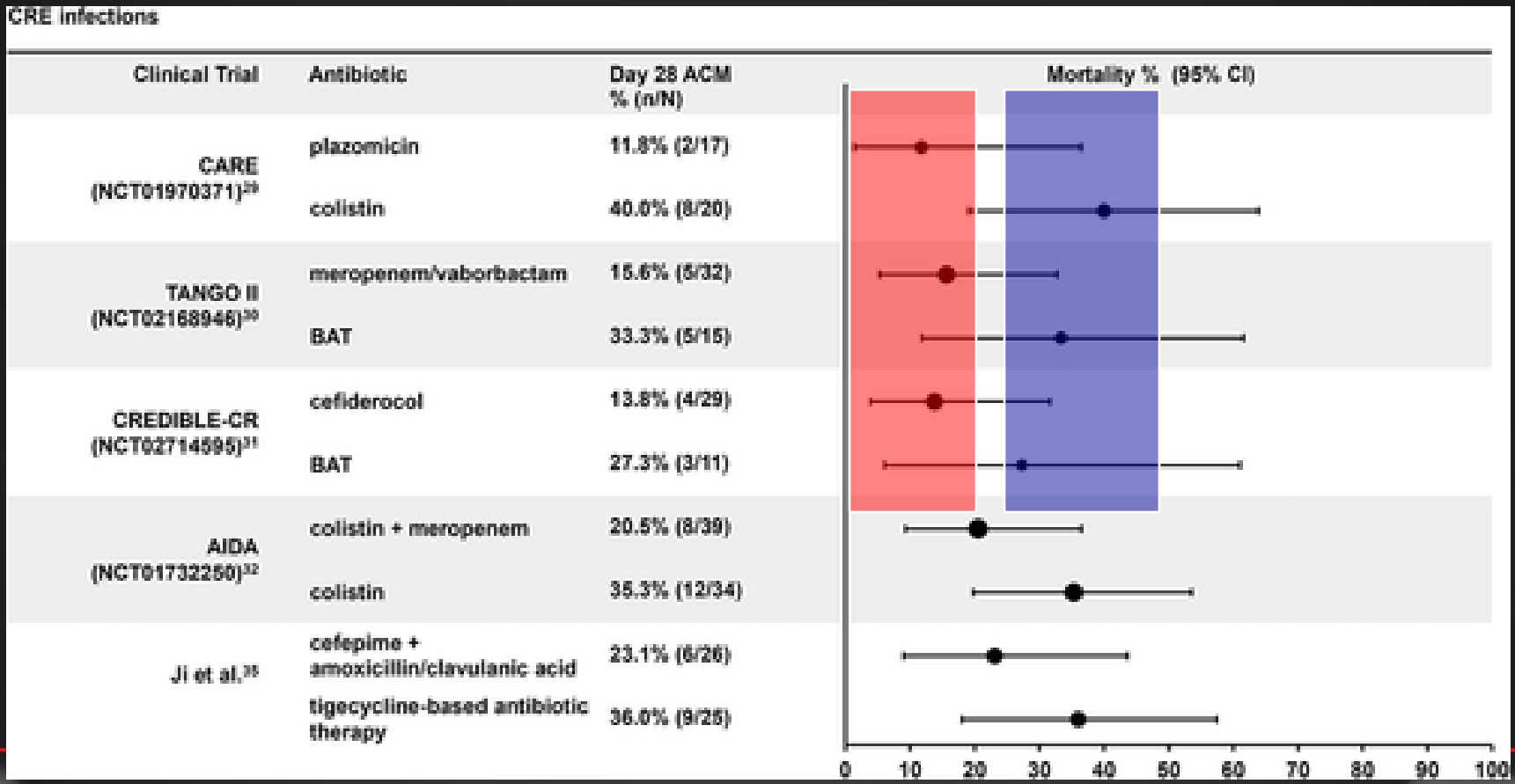
# Day 28 all-cause mortality rates in carbapenem-resistant Enterobacterales infections.



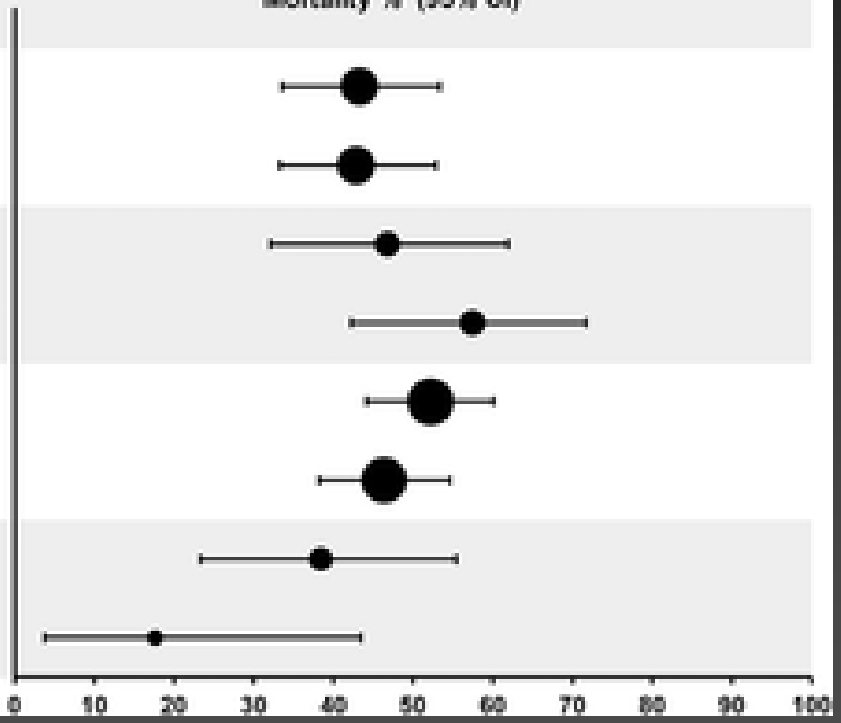



Lodise TP et al. *Expert Rev Anti Infect Ther* 2022 Jan 12;1-13

# Day 28 all-cause mortality rates in carbapenem-resistant Acinetobacter spp. infections

CR *Acinetobacter* spp. infections

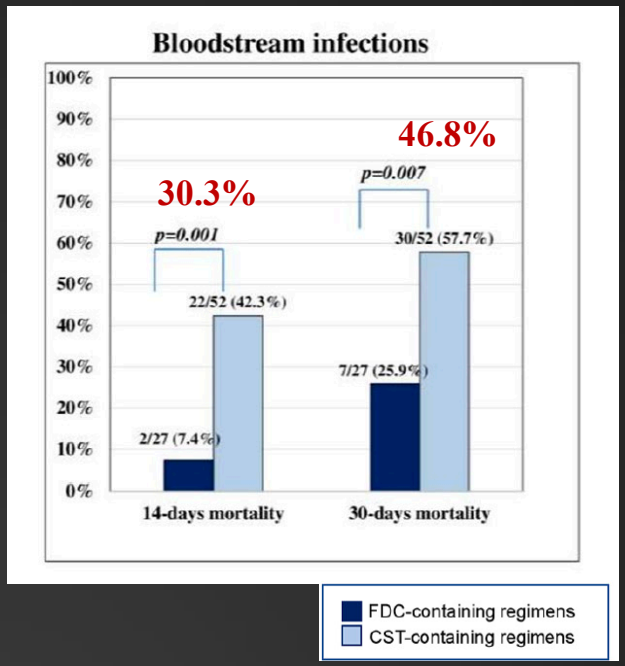
| Clinical Trial | Antibiotic | Day 28 ACM % (n/N) |
|---|---|---|
| Durante-Mangoni (NCT01577862)[33] | colistin + rifampicin | 43.3% (45/104) |
| | colistin | 42.9% (45/105) |
| Sirijatuphat (NCT01297894)[34] | colistin + fosfomycin | 46.8% (22/47) |
| | colistin | 57.4% (27/47) |
| AIDA (NCT01732250)[32] | colistin + meropenem | 52.2% (84/161) |
| | colistin | 46.4% (70/151) |
| CREDIBLE-CR* (NCT02714595)[31] | cefiderocol | 38.5% (15/39) |
| | BAT | 17.7% (3/17) |




Lodise TP et al. *Expert Rev Anti Infect Ther* 2022 Jan 12;1-13

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

- **Study population**
  - 124 patients with *A. baumannii* infections
  - 47 (37.9%) FDC vs 77 (62.1%) CST-containing regimens
- **Risk factors for 30-day mortality**
  - Septic shock
  - SOFA score
  - Age were
  - Cefiderocol therapy (HR 0.44)
- **AEs:** 21.1% COL Vs 2.1%, FDC p<0.01.




Falcone M et al AAC. 2022

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Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

*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]

# Characteristics and outcome of study patients according to clinical failure or resolution upon first-line CRAB active therapy.

| | 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 | 1 | 3 (23) |
| Sepsis | 1 | 9 (34) |
| Septic shock | 2 | 5 (45) |
| **Bacteraemic VAP** | 15 | (26.8) |
| **Augmented renal clearance** | 1 | (18) |
| **CRRT** | 8 (24) | 8 (14) |
| **vv-ECMO** | 1 (3) | 3 (5) |
| **Known respiratory CRAB colonization** | 18 (53) | 34 (61) |
| **Fast molecular diagnostics at VAP onset** | 3 (8.8) * | 17 (30.3) |
| **Timely (≤24 h) targeted therapy** | 22 (65) * | 50 (89) |
| **Cefiderocol-based regimens** | 10 (29) * | 30 (54) |
| Cefiderocol–inhaled colistin | 9 (26.5) | 10 (17.8) |
| Cefiderocol–fosfomycin–inhaled colistin | 1 (3) * | 20 (35.7) |
| **Colistin-based regimens** | 24 (71) * | 26 (46) |
| Colistin–tigecycline–inhaled colistin | 16 (47) * | 11 (20) |
| Colistin–ampicillin/sulbactam–inhaled colistin | 7 (21) | 8 (14) |
| Colistin–meropenem–inhaled colistin | 1 (3) | 7 (13) |
| **14-day mortality** | 14 (41) * | 0 (0) |
| **28-day mortality** | 24 (71) * | 12 (21) |
| **ICU length of stay (days)** | 21 (17–25) * | 24 (21–28) |

Data are presented as No. (%) of included patients or as median (interquartile range), unless otherwise indicated. * $p < 0.05$ vs. clinical resolution group. APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; BMI: Body Mass Index; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRRT: Continuous Renal Replacement Therapy; SOFA: Sequential Organ Failure Assessment; VAP: Ventilator Associated Pneumonia; vv-ECMO: veno-venous Extra-Corporeal Membrane Oxygenation.

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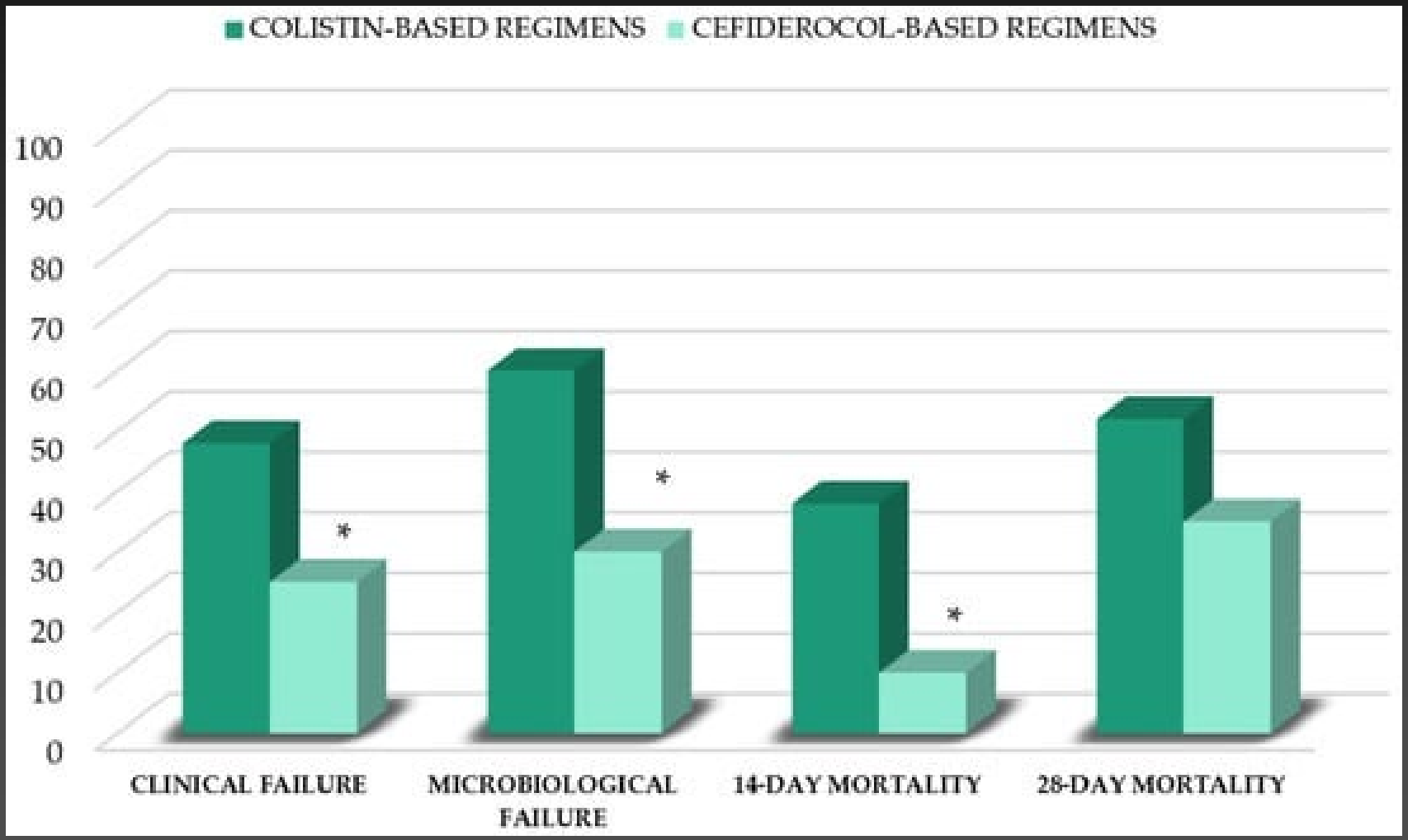
# Outcomes of patients stratified by first-line therapy

*** p < 0.05 vs. colistin group.**

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ical failure with first-line antimicrobial therapy.
lure assessment; VAP: ventilator-associated pneumonia.

# 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 |

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# Real- World use of cefiderocol in the EU and US for *P. Aeruginosa*: interim data from the PROVE study – poster 2274

**Baseline characteristics of patients**

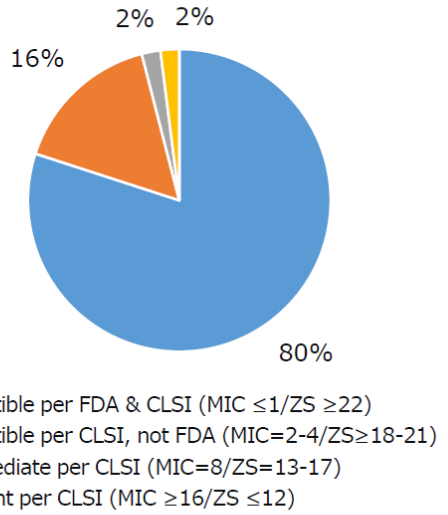
- 194 patients in PROVE were identified with PA as of November 1, 2022, the first having been sampled May 1, 2021. 191 were primary site pathogens for which cefiderocol was prescribed.

**Infection sites, pathogens, and antimicrobial susceptibility**

- Monomicrobial infections accounted for most (67.5%) of the primary infections (N=191; **Figure 1**). Respiratory and bloodstream infections (BSIs) accounted for 76.4% (146/191) of all primary infections.
- MIC or zone size was available for 107 primary PA infections. EUCAST breakpoints for cefiderocol susceptibility (MIC ≤2 µg/mL or zone size ≥22 mm) classified 91.6% (98/107) as susceptible. Applying FDA and CLSI breakpoints, 96.3% (CLSI) and 80% (FDA) were susceptible **(Figure 2)**.

**Figure 1.** Primary sites of infection

**Figure 2.** PA susceptibility (FDA and CLSI) to cefiderocol (n=107)[a]




[a]Also includes the non-primary PA cultures (N=4).
ZS, zone size

*Refers to secondary bacteremia with another primary site of infection.

# PROVE study: clinical outcomes

**Table 3**. Outcomes by key characteristics (n=191)

| | Overall | | Clinical cure[b] | | 30-day post-CFDC mortality | |
|---|---|---|---|---|---|---|
| | n | % | n | Row% | n | Row% |
| Number of patients[a] | 191 | 100% | 124 | 64.9% | 37 | 19.4% |

**Clinical outcomes**

- Overall, 64.9% of patients achieved clinical cure without relapse and 30-day ACM was 19.4% (**Table 3**). Similar cure rates were observed in patients with monomicrobial and polymicrobial infections.
- Respiratory site accounted for the majority of infections, with cure rates of 60.8% and 71.0%, respectively for monomicrobial and polymicrobial infections.
- Patients with monomicrobial BSI (alone or as secondary bacteremia) (n=31) had a combined cure rate of 67.7% and a 30-day ACM of 22.6%.
  - **Clinical cure was greatest for empiric treatment and documented infections:** 73.3% (95% CI, 44.9%–92.2%) and 68.0% (95% CI, 59.8%–75.5%), respectively.
  - **Clinical cure was lowest for salvage treatment after failure of a prior Gram-negative antibiotic:** 42.3% (95%CI, 23.4%–63.1%).
  - **Clinical cure was greater for monotherapy than for combination therapy:** 74.3% (95% CI, 65.1%–82.2%) vs. 52.4% (95% CI, 41.1%–63.6%).
  - **30-day ACM was lower for empiric therapy than for documented pathogen therapy:** 6.7% (95% CI, 0.17%–31.9%) vs. 19.7% (95% CI, 13.6–27.1).
  - **30-day ACM was lower for monotherapy than for combination therapy:** 12.8% (95% CI, 7.2%–20.6%) vs. 28.1% (95% CI, 18.7%–39.1%).

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# PROVE study: clinical severity of patients during treatments

Table 3. Outcomes by key characteristics (n=191)

| | Overall | | Clinical cure[b] | | 30-day post-CFDC mortality | |
|---|---|---|---|---|---|---|
| | n | % | n | Row% | n | Row% |
| Number of patients[a] | 191 | 100% | 124 | 64.9% | 37 | 19.4% |
| **Severity upon starting CFDC** | | | | | | |
| **Patient in ICU** | | | | | | |
| Yes | 143 | 74.9% | 87 | 60.8% | 34 | 23.8% |
| No | 48 | 25.1% | 37 | 77.1% | 3 | 6.3% |
| **Mechanical ventilation** | | | | | | |
| Yes | 92 | 48.2% | 53 | 57.6% | 26 | 28.3% |
| No | 99 | 51.8% | 71 | 71.7% | 11 | 11.1% |
| **Vasopressor support** | | | | | | |
| Yes | 70 | 36.6% | 36 | 51.4% | 24 | 34.3% |
| No | 121 | 63.4% | 88 | 72.7% | 13 | 10.7% |

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# PROVE study: Cefiderocol utilization

Cefiderocol was initiated for a documented pathogen in the majority of cases (77.3%; **Table 2**). It was used empirically in 7.7%. Monotherapy was more common (56.7%) than combination therapy.

**Table 3**. Outcomes by key characteristics (n=191)

| | Overall | | Clinical cure[b] | | 30-day post-CFDC mortality | |
|---|---|---|---|---|---|---|
| | n | % | n | Row% | n | Row% |
| **Number of patients[a]** | **191** | **100%** | **124** | **64.9%** | **37** | **19.4%** |
| **CFDC utilization** | | | | | | |
| **Reason for starting CFDC** | | | | | | |
| Documented infection | 147 | 77.0% | 100 | 68.0% | 29 | 19.7% |
| Salvage treatment (failure of prior GNA) | 26 | 13.6% | 11 | 42.3% | 7 | 26.9% |
| Empiric for suspected CR GNBI | 15 | 7.9% | 11 | 73.3% | 1 | 6.7% |
| Other | 3 | 1.6% | 2 | 66.7% | 0 | – |
| **CFDC as monotherapy[e]** | | | | | | |
| Yes | 109 | 57.1% | 81 | 74.3% | 14 | 12.8% |
| No | 82 | 42.9% | 43 | 52.4% | 23 | 28.1% |
| **Local S,I,R classification[f]** | | | | | | |
| Susceptible | 124 | 64.9% | 87 | 70.2% | 26 | 21.0% |
| Intermediate | 7 | 3.7% | 4 | 57.1% | 0 | – |
| Resistant | 7 | 3.7% | 3 | 42.9% | 2 | 28.6% |
| Not tested or not available | 53 | 27.7% | 30 | 56.6% | 9 | 17.0% |
| **Carbapenem susceptibility** | | | | | | |
| Resistant | 159 | 83.2% | 106 | 66.7% | 31 | 19.5% |
| Susceptible | 18 | 9.4% | 10 | 55.6% | 5 | 27.8% |

[a]Number of patients includes only those with a primary site culture of PA; co-infections unrelated to the primary infection that prompted CFDC use were excluded from outcomes. [b]Clinical cure based on answer to the Clinical Assessment question: resolved, improved = cured; resolved then relapse, failure, or unknown = Not cured. [c]Same PA pathogen cultured in the blood associated with another site. [d]Other sites include bone/joint, skin/wound, urine, intra-abdominal, other. [e]Monotherapy defined as receiving only CFDC without overlap of other GNAs. [f]Local susceptibility results were reported for 138 isolates, exceeding the number of available MIC or zone size results (n=107). CFDC, cefiderocol; CR, carbapenem resistant; GNA, Gram-negative antibiotic; ICU, intensive care unit.

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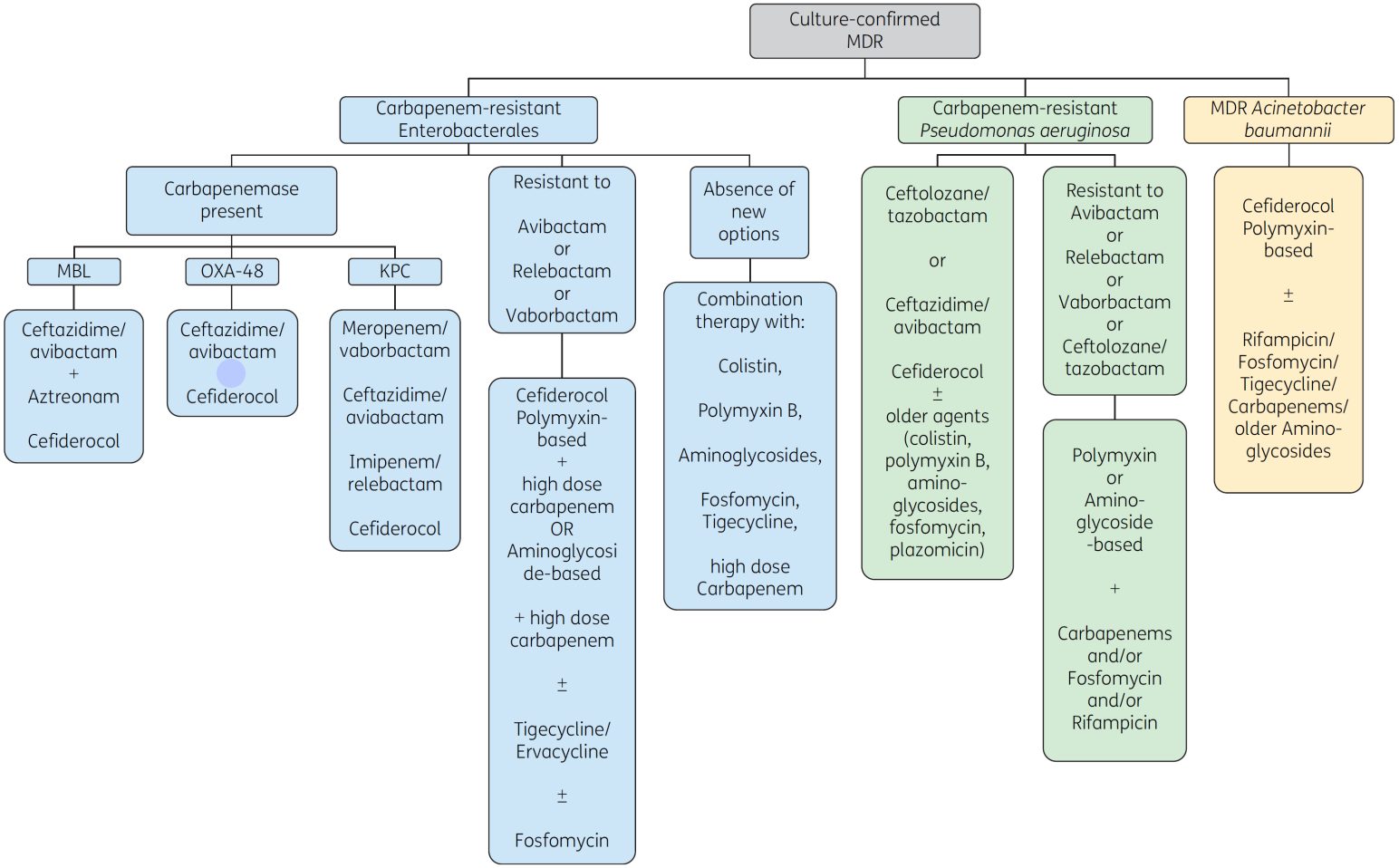
# Suggested treatments for carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa, and multidrug-resistant Acinetobacter baumannii






Genoa, Italy

Bassetti M, Garau X. . *J Antimicrob Chemother* 2021; **76** : iv23–iv37

# Marzo 2023

- L'Agenzia Italiana del Farmaco (AIFA) ha riconosciuto al farmaco lo status di farmaco "innovativo", seppur condizionato, e ha stilato un apposito piano terapeutico che ne limita il campo d'impiego ai pazienti affetti da MDRO con documentata resistenza ai carbapenemi (terapia mirata) o con infezioni invasive ad eziologia fortemente sospetta da batteri gram-negativi resistenti ai carbapenemi (terapia empirica).
- Si informano gli utenti dei Registri dei Farmaci sottoposti a Monitoraggio che, a seguito della pubblicazione della Determina AIFA nella GU n. 67 del 20/03/2023, a partire dal 21/03/2023 è possibile utilizzare, in regime di rimborsabilità SSN, il medicinale FETCROJA per il trattamento di pazienti adulti ricoverati con infezioni gravi sostenute da:

  - Enterobacterales carbapenem resistant (CR) che produconometallo-beta-lattamasi (MBL)
  - Pseudomonas aeruginosa che produce metallo-beta-lattamasi (MBL) e
  - patogeni Gram-Negativi (GN) non fermentanti Difficult to Treat(DTR): Pseudomonas aeruginosa carbapenem resistant (CRPA), Acinetobacter baumannii carbapenem resistant (CRAB) e Stenotrophomonas maltophilia, in assenza di altre opzioni terapeutiche e secondo i principi di ottimizzazione dell'uso degli antibiotici.

# RACCOMANDAZIONI PER UNA STRATEGIA EFFICACE CONTRO LA RESISTENZA ANTIMICROBICA

FARMINDUSTRIA

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

1. **Metodologia di valutazione dei nuovi antibiotici contro i ceppi batterici resistenti**

   Adattare le attuali metodologie per la determinazione del valore degli antibiotici alle caratteristiche di questi farmaci, considerando il loro ruolo salvavita, tenendo presente che questo richiederà una prospettiva più ampia e l'analisi di scenari ed evidenze oltre a quelle necessarie per le attuali richieste di registrazione.

2. **Criteri per il conferimento dello status di farmaco "innovativo" ai nuovi antibiotici contro i ceppi batterici resistenti**

   Utilizzare indicatori specifici capaci di misurare efficacemente il grado di innovatività dei nuovi antibiotici, adattando, se necessario, gli attuali elementi di valutazione a supporto della richiesta

3. **Modelli di rimborso ad hoc per i nuovi antibiotici attivi per le resistenze batteriche**

   Visto che la stewardship antimicrobica fornisce indicazioni restrittive sull'uso dei nuovi antibiotici nel trattamento delle infezioni causate dai ceppi resistenti per ridurre la probabilità che si sviluppino nuove forme di resistenza, è necessario identificare delle modalità di rimborso[9] che garantiscano agli sviluppatori un ritorno economico tale da aumentare e mantenere nel tempo gli investimenti in ricerca e sviluppo in quest'area.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy