Fetroja® – Activity Against Resistant *Acinetobacter* spp.

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Summary

Phase 3 Clinical Studies

APEKS-NP, a Phase 3, multicenter, randomized, double-blind, noninferiority trial evaluated the efficacy and safety of cefiderocol vs meropenem in patients with nosocomial pneumonia caused by Gram-negative bacteria[1,2]

- ACM at Day 14 was 19% in the cefiderocol arm and 22% in the meropenem arm for patients with *Acinetobacter* spp. infections[1,2]
- ACM rates for infections caused by *Acinetobacter* spp. with meropenem MIC >8 µg/mL were similar at Day 14 (cefiderocol arm: 28%; meropenem arm: 28%)[2]

CREDIBLE-CR, a Phase 3, multicenter, randomized, prospective, open-label, parallel-group, descriptive study evaluated the efficacy and safety of cefiderocol or BAT in adult patients with serious infections caused by CR Gram-negative bacteria[3,4]

- Clinical cure rate at TOC was 41% in the cefiderocol arm and 53% in the BAT arm for patients with CR *Acinetobacter* spp. infections[3]
- ACM was higher for patients with *Acinetobacter* spp. infections in the cefiderocol arm than in the BAT arm through EOS (cefiderocol: 50%; BAT: 18%)
  - Increased mortality may have been impacted by the higher proportion of patients in the cefiderocol group compared to the BAT group at baseline with CrCl <50 mL/min (cefiderocol: 33%; BAT: 18%), ongoing shock (cefiderocol: 19%; BAT: 6%) or shock within 31 days prior to randomization (cefiderocol: 26%; BAT: 6%), or ICU at randomization (cefiderocol: 81%; BAT: 47%)

Real-World Evidence

Giannella et al (2023) conducted a retrospective, observational, descriptive cohort study (**ARES**) in 147 patients treated with cefiderocol for CR *Acinetobacter* spp. across 4 European countries[5]

- The overall clinical success rate was 53.1%, with a survival rate at Day 28 of 44.9%

PROVE was a multicenter retrospective chart review study describing the clinical and microbiological characteristics and outcomes in patients receiving cefiderocol for the first time treatment of serious Gram-negative bacterial infections, including those caused by *Acinetobacter baumannii*, in a real-world setting[6,7]

- Interim global analysis: Clinical cure rate for *A. baumannii* infections (n=96) was 60.4% and 30-day ACM rate was 24%[6]
- Final global analysis (1075 total hospitalizations): Clinical cure rate for *A. baumannii* infections (n=195) was 60.5%, and the 30-day ACM was 28.2%[7]

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Summary

Real-World Evidence (Cont.)

In observational studies, treatment with cefiderocol was associated with significantly lower 28- and 30-day ACM compared to non-cefiderocol treatment[8,9]

Outcomes in patients with CRAB infections among several observational, retrospective studies have been reported[10,11]

- The 30-day ACM was 34% and 55.8% in the cefiderocol and colistin-based regimen arms, respectively (*P*=0.018)[10]
- Patients treated with cefiderocol-containing regimens had significantly lower 14- and 30-day mortality rates compared to patients treated with colistin[11]

In a study of patients with CRAB infections, patients that received cefiderocol-based treatment (n=60) were compared to a historical control group that previously received colistin-based therapy (n=51)[12]

- The 30-day mortality rate was 51% and 37% for the cefiderocol and colistin groups, respectively (*P*=0.13)
- Clinical cure was achieved by 73% and 67% of patients in the cefiderocol and colistin-groups, respectively (*P*=0.440)
- The study did not identify any independent predictors of mortality or clinical cure

A retrospective study compared outcomes in patients with COVID-19 and CRAB co infections who were receiving cefiderocol or colistin[13]

- ACM at Day 28 was 55% and 58% in patients treated with cefiderocol and colistin, respectively (*P*=0.706)

Surveillance Studies

The *in vitro* activity of cefiderocol against resistant *Acinetobacter* spp. has been demonstrated in several multinational surveillance studies (eg, **SENTRY**)[14–19]

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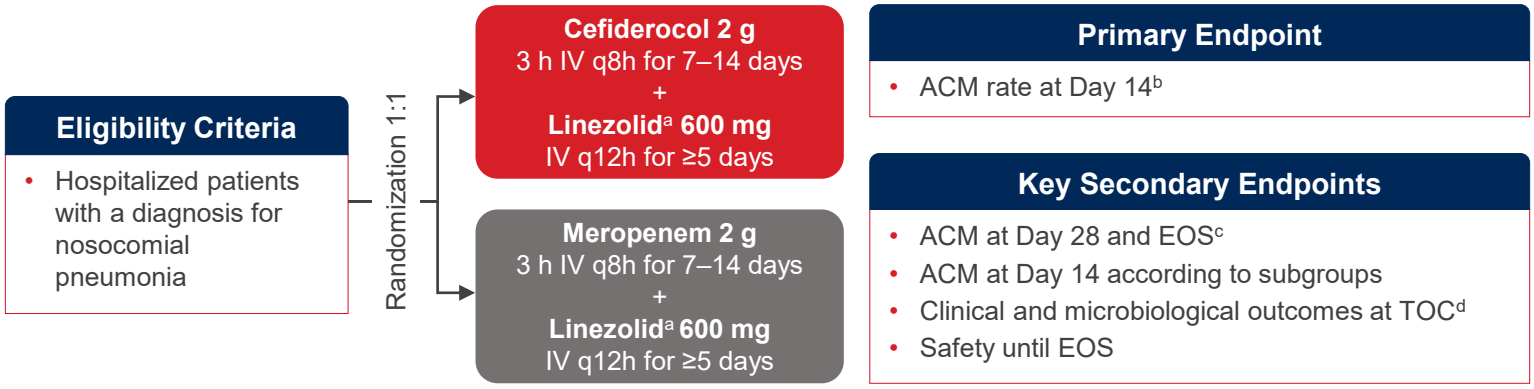
Phase 3 Clinical Studies

APEKS-NP

Methods

- APEKS-NP (**NCT03032380**) was a Phase 3, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in patients with VABP, HABP, or HCABP caused by suspected Gram-negative pathogens (**Figure 1**)[1]

Figure 1. APEKS-NP Study Design[1]



Abbreviations: ACM, all-cause mortality; EOS, end of study; EOT, end of treatment; h, hours; IV, intravenous; mITT, modified intention-to-treat; q12h, once every 12 hours; q8h, once every 8 hours; RTI, respiratory tract infection; TOC, test of cure.

[a]Administered to cover Gram-positive bacteria.

[b]In the mITT population (noninferiority margin, -12.5%), defined as all randomized patients who received ≥1 dose of a study drug and had evidence of a Gram-negative lower RTI.

[c]EOT + 28 days (±3 days).

[d]EOT + 7 days (±2 days).

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Phase 3 Clinical Studies

APEKS-NP

Results

- Patients (N=300) were randomly assigned to treatment arms (cefiderocol, n=148; meropenem, n=152)[1]
- Day 14 ACM was evaluated in the mITT population (cefiderocol, n=145; meropenem, n=147), which excluded patients with only Gram-positive monomicrobial infections (3 patients in each arm)[1]
- 53 patients had *Acinetobacter* spp. infections, including:
  - *A. baumannii* (cefiderocol, n=23; meropenem, n=24)[1]
  - *Acinetobacter nosocomialis* (cefiderocol, n=2; meropenem, n=1)[1]
  - *Acinetobacter pittii* (cefiderocol, n=1; meropenem, n=0)[1]
  - *Acinetobacter junii* and *Acinetobacter nonspeciated* (cefiderocol, n=0; meropenem, n=1; each)[2]
- Results for ACM at Day 14, Day 28, and EOS, and clinical and microbiological outcomes are summarized in **Table 1** and **Table 2**, respectively

Table 1. ACM in the mITT Population[1,2]

Population	Cefiderocol, n/N (%)	Meropenem, n/N (%)	Treatment Difference (95% CI)
Day 14			
Overall mITT	18/145 (12)	17/146 (12)	0.8 (–6.7 to 8.2)
mITT with *Acinetobacter* spp. infection	5/26 (19)	6/27 (22)	–3 (–24.8 to 18.8)
Meropenem MIC >8 µg/mL[a,b]			
Yes	5/18 (28)	5/18 (28)	0 (–29.3 to 29.3)
No	0/7 (0)	1/9 (11)	–11.1 (NA)
Day 28			
Overall mITT	30/143 (21)	30/146 (21)	0.5 (–8.7 to 9.8)
mITT with *Acinetobacter* spp. infection	8/25 (32)	8/27 (30)	2.4 (–22.7 to 27.5)
Meropenem MIC >8 µg/mL[a,b]			
Yes	6/18 (33)	7/18 (39)	–5.6 (–36.9 to 25.8)
No	1/6 (17)	1/9 (11)	5.6 (NA)
EOS			
mITT with *Acinetobacter* spp. infection	9/25 (36)	9/27 (33)	2.7 (–23.2 to 28.6)
Meropenem MIC >8 µg/mL[a,b]			
Yes	7/18 (39)	8/18 (44)	–5.6 (–37.7 to 26.6)
No	1/6 (17)	1/9 (11)	5.6 (NA)

Table 2. Outcomes at TOC Based on Meropenem MIC >8 µg/mL for *Acinetobacter* spp. (mITT Population)[2]

n (%)	Overall		Meropenem MIC >8 µg/mL[a]		Meropenem MIC ≤8 µg/mL	
	Cefiderocol (n=26)	Meropenem (n=27)	Cefiderocol (n=18)	Meropenem (n=18)	Cefiderocol (n=7)	Meropenem (n=9)
Clinical outcomes						
Clinical cure	14 (54)	15 (56)	8 (44)	9 (50)	6 (86)	6 (67)
Clinical failure	6 (23)	8 (30)	4 (22)	5 (28)	1 (14)	3 (33)
Indeterminate	6 (23)	4 (15)	6 (33)	4 (22)	0	0
Microbiological outcomes						
Eradication	11 (42)	9 (33)	6 (33)	4 (22)	5 (71)	5 (56)
Persistence	5 (19)	8 (30)	3 (17)	6 (33)	1 (14)	2 (22)
Indeterminate	10 (39)	10 (37)	9 (50)	8 (44)	1 (14)	2 (22)

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Phase 3 Clinical Studies

Table 1. ACM in the mITT Population[1,2]

Population	Cefiderocol, n/N (%)	Meropenem, n/N (%)	Treatment Difference (95% CI)
Day 14			
Overall mITT	18/145 (12)	17/146 (12)	0.8 (–6.7 to 8.2)
mITT with *Acinetobacter* spp. infection	5/26 (19)	6/27 (22)	–3 (–24.8 to 18.8)
Meropenem MIC >8 µg/mL[a,b]			
Yes	5/18 (28)	5/18 (28)	0 (–29.3 to 29.3)
No	0/7 (0)	1/9 (11)	–11.1 (NA)
Day 28			
Overall mITT	30/143 (21)	30/146 (21)	0.5 (–8.7 to 9.8)
mITT with *Acinetobacter* spp. infection	8/25 (32)	8/27 (30)	2.4 (–22.7 to 27.5)
Meropenem MIC >8 µg/mL[a,b]			
Yes	6/18 (33)	7/18 (39)	–5.6 (–36.9 to 25.8)
No	1/6 (17)	1/9 (11)	5.6 (NA)
EOS			
mITT with *Acinetobacter* spp. infection	9/25 (36)	9/27 (33)	2.7 (–23.2 to 28.6)
Meropenem MIC >8 µg/mL[a,b]			
Yes	7/18 (39)	8/18 (44)	–5.6 (–37.7 to 26.6)
No	1/6 (17)	1/9 (11)	5.6 (NA)

Percentages for overall mITT were calculated as the number of patients who died from any cause at or before Day 14 or Day 28 divided by the total number of patients in the analysis populations or within subgroups with known survival status at Day 14 or Day 28.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; EOS, end of study; MIC, minimum inhibitory concentration; mITT, modified intention-to-treat; NA, not applicable; spp., species.
[a]Percentages are calculated using the number of patients with nonmissing baseline *Acinetobacter* spp. infections (ie, *A. baumannii*, *A. nonspeciated* in the meropenem MIC >8 µg/mL category) with known survival status as the denominator (1 patient withdrew from the study).
[b]Post hoc analysis.
Table adapted from Wunderink et al. *Lancet Infect Dis*. 2021 (plus Supplementary Material).

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Phase 3 Clinical Studies

Table 2. Outcomes at TOC Based on Meropenem MIC >8 µg/mL for *Acinetobacter* spp. (mITT Population)[2]

n (%)	Overall		Meropenem MIC >8 µg/mL[a]		Meropenem MIC ≤8 µg/mL	
	Cefiderocol (n=26)	Meropenem (n=27)	Cefiderocol (n=18)	Meropenem (n=18)	Cefiderocol (n=7)	Meropenem (n=9)
Clinical outcomes						
Clinical cure	14 (54)	15 (56)	8 (44)	9 (50)	6 (86)	6 (67)
Clinical failure	6 (23)	8 (30)	4 (22)	5 (28)	1 (14)	3 (33)
Indeterminate	6 (23)	4 (15)	6 (33)	4 (22)	0	0
Microbiological outcomes						
Eradication	11 (42)	9 (33)	6 (33)	4 (22)	5 (71)	5 (56)
Persistence	5 (19)	8 (30)	3 (17)	6 (33)	1 (14)	2 (22)
Indeterminate	10 (39)	10 (37)	9 (50)	8 (44)	1 (14)	2 (22)

Abbreviations: mITT, modified intention-to-treat; MIC, minimum inhibitory concentration; spp., species; TOC, test of cure.
[a]Post hoc analysis.
Table adapted from Wunderink et al. *Lancet Infect Dis*. 2021.

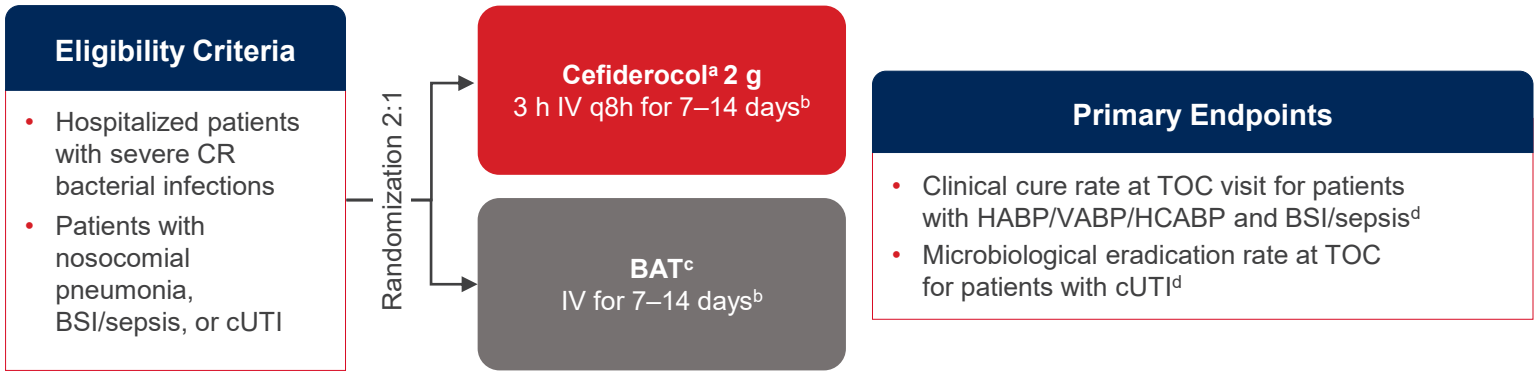
Phase 3 Clinical Studies

CREDIBLE-CR

Methods

- CREDIBLE-CR (NCT02714595) was a prospective, randomized, open-label, multicenter, parallel-group, descriptive, Phase 3 study that assessed the efficacy and safety of cefiderocol and BAT in hospitalized patients with severe CR bacterial infections (Figure 2)[3]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[3]

Figure 2. CREDIBLE-CR Study Design[3]



Abbreviations: BAT, best-available therapy; BSI, bloodstream infection; CR, carbapenem-resistant; cUTI, complicated urinary tract infection; h, hours; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; IV, intravenous; q8h, once every 8 hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.

[a]Could be complemented with 1 adjunctive antibiotic therapy, excluding polymyxins, cephalosporins, and carbapenems and combinations with a β-lactamase inhibitor.

[b]Could be extended up to 21 days at the discretion of the investigator.

[c]Selected before randomization and could consist of up to 3 systemic antibiotics.

[d]Defined as all patients with a confirmed CR Gram-negative pathogen who received ≥1 dose of study drug.

Phase 3 Clinical Studies

CREDIBLE-CR (Cont.)

Clinical & Microbiological Outcomes

- Patients (N=152) were randomly assigned to treatment arms (**Table 3**)[3]

Table 3. Population Randomization in Analyses Sets[3]

n	Cefiderocol	BAT
ITT and safety population (n=150)[a]	101	49
CR-Micro-ITT population (n=118)[b]	80	38

Abbreviations: BAT, best-available therapy; CR-Micro-ITT, carbapenem-resistant microbiological ITT; ITT, intention-to-treat.
[a]Received treatment.
[b]Patient's baseline Gram-negative pathogen was CR as confirmed by central laboratory testing.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021.

- Clinical and microbiological outcomes in patients with *A. baumannii* and *A. nosocomialis* are shown in **Table 4**[4]

Table 4. Summary of Outcomes at TOC in the CR-Micro-ITT Population[4]

n (%)	Patients with *A. baumannii* Infection		Patients with *A. nosocomialis* Infection	
	Cefiderocol (n=37)	BAT (n=17)	Cefiderocol (n=2)	BAT (n=0)
Clinical outcomes				
Clinical cure	16 (43)	9 (53)	0	NA
Clinical failure	17 (46)	6 (35)	1 (50)	NA
Indeterminate	4 (11)	2 (12)	1 (50)	NA
Microbiological outcomes				
Eradication	10 (27)	5 (29)	0	NA
Persistence	5 (14)	4 (24)	0	NA
Indeterminate	22 (60)	8 (47)	2 (100)	NA

Abbreviations: BAT, best-available therapy; CR-Micro-ITT, carbapenem-resistant microbiological intention-to-treat; NA, not applicable; TOC, test of cure.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021 (Supplementary Appendix).

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Phase 3 Clinical Studies

CREDIBLE-CR (Cont.)

Mortality

- Higher ACM through EOS was observed in the cefiderocol arm vs BAT arm (34% [34/101] vs 18% [9/49], respectively)[4]
- No deaths were considered to be related to cefiderocol (eg, drug toxicity)[3]
- ACM was higher in the cefiderocol arm than in the BAT arm for patients with polymicrobial *Pseudomonas aeruginosa* and *Acinetobacter* spp. infections but identical for patients with only *P. aeruginosa* infections (Table 5)[3]
- Outcomes suggest that the difference in ACM between the cefiderocol and BAT arms may have been impacted by the difference in ACM in the subset of patients with *Acinetobacter* spp. infections[3]
- Among patients with *Acinetobacter* spp. infections at baseline, the following parameters were higher in the cefiderocol arm vs BAT arm, respectively:[3,4]
  - Incidence of CrCl <50 mL/min: 33% vs 18%
  - Ongoing shock: 19% vs 6%
  - Shock within 31 days before randomization: 26% vs 6%
  - ICU admission at randomization: 81% vs 47%
- Mortality rates at Day 14, Day 28, and EOS in patients with and without *Acinetobacter* spp. infections are shown in Table 6[4]
  - An additional study compared the ACM rates with *Acinetobacter* spp. infections in CREDIBLE-CR with those in other pathogen-focused studies[20]
  - ACM rates with *Acinetobacter* spp. infections in CREDIBLE-CR were found to be comparable to those reported in other pathogen-focused studies (Figure 3)[20]

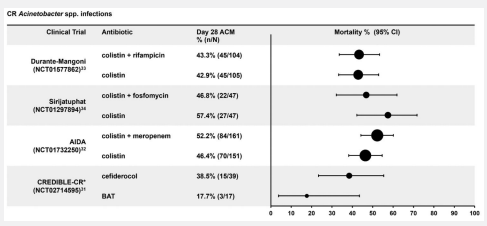
Table 5. ACM Rates Through EOS by Pathogen (Safety Population)[3]

n/N (%)	Cefiderocol (n=101)	BAT (n =49)
Acinetobacter spp.[a]	21/42 (50)	3/17 (18)
A. 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 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
Stenotrophomonas maltophilia	4/5 (80)	NA
without *Acinetobacter* spp.	2/3 (67)	NA

Table 6. Mortality at Day 14, Day 28, and EOS in Patients in the Safety Population[4]

Mortality, n (%)	Patients with *Acinetobacter* spp. Infection[a]		Patients without *Acinetobacter* spp. Infection	
	Cefiderocol (n=42)	BAT (n=17)	Cefiderocol (n=59)	BAT (n=32)
Day 14	12 (29)	3 (18)	7 (12)	3 (9)
Day 28	16 (38)	3 (18)	9 (15)	6 (19)
EOS	21 (50)	3 (18)	13 (22)	6 (19)

Figure 3. Day 28 ACM Rates in CR-*Acinetobacter*–Focused Studies[20]



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Table 5. ACM Rates Through EOS by Pathogen (Safety Population)[3]

n/N (%)	Cefiderocol (n=101)	BAT (n=49)
Acinetobacter spp.[a]	21/42 (50)	3/17 (18)
A. baumannii	19/39 (49)	3/17 (18)
Klebsiella 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)
Escherichia coli	1/6 (17)	0/3 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
Stenotrophomonas maltophilia	4/5 (80)	NA
without *Acinetobacter* spp.	2/3 (67)	NA

Data are n/N (%); n, number of cases; N, total number of patients within the category.
Abbreviations: ACM, all-cause mortality; BAT, best-available therapy; EOS, end of study; NA, not available; spp., species.
[a]Includes *A. baumannii* (cefiderocol, n=39; BAT, n=17), *A. nosocomialis* (cefiderocol, n=2; BAT, n=0), and *A. radioresistens* (cefiderocol, n=1; BAT, n=0).
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021.

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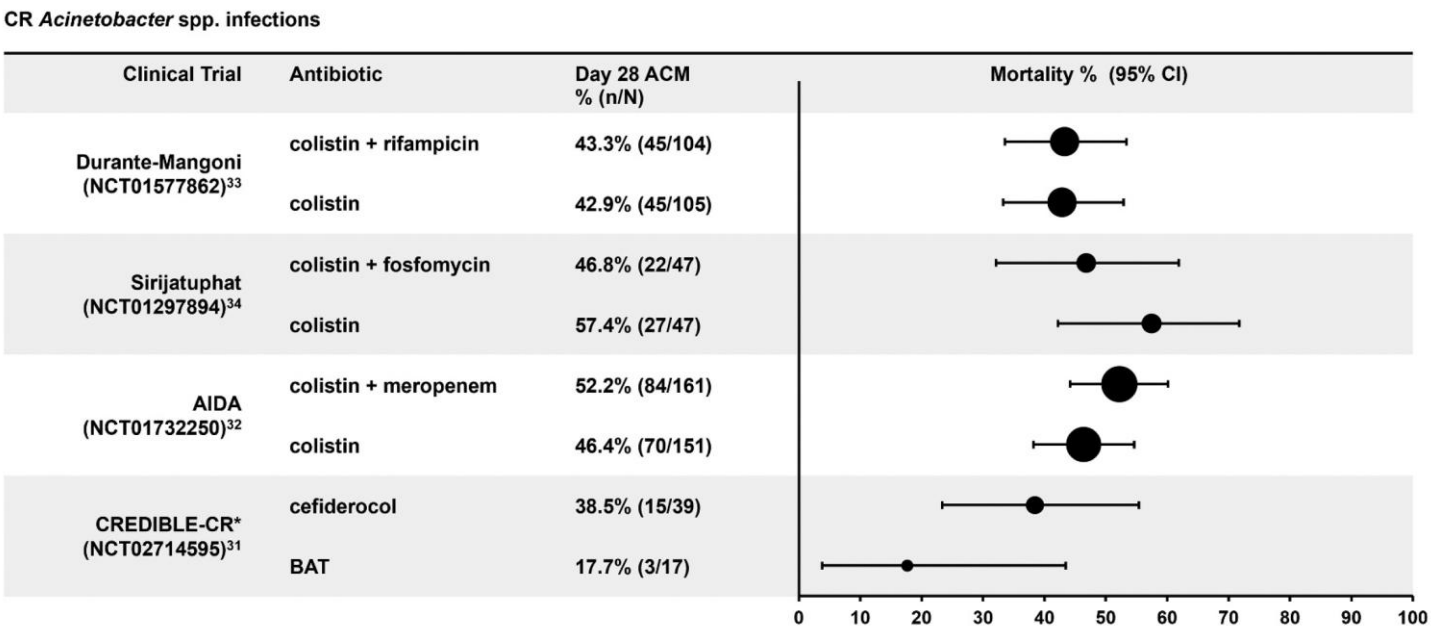
Table 6. Mortality at Day 14, Day 28, and EOS in Patients in the Safety Population[4]

Mortality, n (%)	Patients with *Acinetobacter* spp. Infection[a]		Patients without *Acinetobacter* spp. Infection	
	Cefiderocol (n=42)	BAT (n=17)	Cefiderocol (n=59)	BAT (n=32)
Day 14	12 (29)	3 (18)	7 (12)	3 (9)
Day 28	16 (38)	3 (18)	9 (15)	6 (19)
EOS	21 (50)	3 (18)	13 (22)	6 (19)

Abbreviations: BAT, best-available therapy; EOS, end of study; spp., species.
[a]Includes *A. baumannii* (cefiderocol, n=39; BAT, n=17), *A. nosocomialis* (cefiderocol, n=2; BAT, n=0), and *A. radioresistens* (cefiderocol, n=1; BAT, n=0).
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021 (Supplementary Appendix).

Phase 3 Clinical Studies

Figure 3. Day 28 ACM Rates in CR-*Acinetobacter*–Focused Studies[20]



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Abbreviations: ACM, all-cause mortality; BAT, best-available therapy; CI, confidence interval; CR, carbapenem-resistant; CR-micro-ITT population, CR microbiological ITT; ITT, intention-to-treat.
Figure adapted from Lodise et al. *Expert Rev Anti Infect Ther*. 2022.

Real-World Evidence

Giannella et al (2023) conducted a retrospective, observational, descriptive cohort study (**ARES**) in 147 adult patients with CR *Acinetobacter* spp. infections between April 2020 and April 2021 across 4 European countries. Cefiderocol was obtained through the EAP in Europe, and initiated for ≥72 h in patients receiving cefiderocol for the first time. Clinical success, defined as a composite of clinical resolution of signs and symptoms of infection at Day 14, or survival at Day 28 following the initial dose of cefiderocol, was the primary outcome.[5]

- Secondary outcomes included clinical outcomes (resolution of signs and symptoms of infection and treatment failure at Day 7 and Day 14 and relapse of primary infection), survival at Day 14 and Day 28, and safety

Results[5]

- Overall, 78/147 (53.1%) patients achieved clinical success, with 58 (39.5%) patients achieving resolution of infection at Day 14 and 66 (44.9%) patients surviving through Day 28
  - In total, 46 (31.3%) patients had both resolution of infection at Day 14 and survived through Day 28
- Similar clinical success was observed between patients with monomicrobial compared to polymicrobial infections (58/111 patients [52.3%] vs 20/36 patients [55.6%])
  - 44/96 (45.8%) patients with RTIs as the primary site of infection achieved clinical success, while the clinical success rate for BSI with unknown source and catheter-related BSI was achieved in 12/23 (52.2%) and 12/16 (75%) patients, respectively
- The clinical success rates for patients with and without septic shock was 26/70 (37.1%) vs 35/56 (62.5%); with and without COVID-19 was 57/120 (47.5%) vs 21/27 (77.8%) respectively
  - Where both COVID-19 and septic shock were present, the clinical success rate was 18/58 (31%)
- When cefiderocol was used as a first-line therapy, the clinical success rate was 15/22 (68.2%), while the rate was higher in those given monotherapy compared to combination therapies (30/49 [61.2%] vs 48/98 [49%])

Safety[5]

- ADRs occurred in 7 (4.8%) patients with 2 (1.4%) patients experiencing 3 severe/serious ADRs (cardiac arrest, renal tubular necrosis, and tubulointerstitial nephritis)

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Real-World Evidence

PROVE (Retrospective Cefiderocol Chart Review Study)[6,7]

- PROVE was an international, multicenter, retrospective chart review study investigating clinical and microbiological characteristics and outcomes following cefiderocol treatment
- This real-world study included patients with documented Gram-negative bacterial infections, including *A. baumannii*, treated with cefiderocol for ≥72 h, along with information on doses, type of infection, and clinical outcomes
- Patients receiving cefiderocol before local commercial availability are excluded from the study

Methods[6]

- Antibiotic susceptibility testing, by zone size or MIC according to laboratory preference, was conducted locally on index culture samples taken before cefiderocol initiation
- Susceptibility is defined according to the breakpoints recommended by CLSI M100 31st and 32nd editions (MIC≤4 µg/mL; zone size ≥15 mm) and FDA 2022 recommendations (MIC≤1 µg/mL; zone size ≥19 mm)
- In the less common event of cefiderocol being used empirically, cultures were collected after antibiotic initiation[5]
- Outcomes were clinical resolution defined as evidence of resolution/improvement without relapse of *A. baumannii* infection at end of cefiderocol treatment, 30-day ACM from first cefiderocol dose, and AEs

Interim Results[6]

Baseline Characteristics[6]

- At interim analysis, 98 patients with *A. baumannii* infection were treated with cefiderocol (71 from the US, 27 from Europe)
- Median age on admission was 57 years
- Overall, 92.9% of patients had comorbid conditions at baseline; the most frequent were hypertension (29.6%), hemiplegia, paraplegia, or quadriplegia (16.3%), uncomplicated diabetes mellitus (15.3%), and moderate or severe renal disease (15.3%)

Infection Sites, Pathogens, and Antimicrobial Susceptibility[6]

- Monomicrobial infections accounted for 61 (63.5%) of the primary infections presented by patients
- The most frequent infections were respiratory infections and bacteremia, accounting for 36% and 26.2% of monomicrobial infections, and 57.1% and 8.6% of polymicrobial infections, respectively
- Of 90 *A. baumannii* isolates with susceptibility results, 83 (92.2%) were CR
- *A. baumannii* susceptibility to cefiderocol was assessed in 44 patients, of which 37 (84%) and 33 (75%) were susceptible based on CLSI and FDA breakpoints, respectively

Real-World Evidence

PROVE (Retrospective Cefiderocol Chart Review Study) (Cont.)

Interim Results (Cont.)

Cefiderocol Utilization[6]

- Documented infection was the most frequent reason for starting cefiderocol (78.6%) (**Table 7**)
- Treatment in 8.2% of patients was as empiric therapy for suspected CR GNBI
- Cefiderocol was used as monotherapy in 40.8% of cases
- Median duration of cefiderocol treatment was 11.5 days

Table 7. Characteristics of Cefiderocol Utilization[6]

Characteristic	n	%
Reason for starting cefiderocol (n=98)		
Documented infection	77	78.6
Salvage treatment, prior antibiotics failed	12	12.2
Empiric for suspected CR GNBI	8	8.2
Other	1	1
Any GNA used with cefiderocol[a] (n=58)		
Aminoglycosides	2	2
Carbapenems	4	4.1
Polymyxins	17	17.3
Tetracyclines and tigecycline	26	26.5
Others	29	29.6

Abbreviations: CR, carbapenem-resistant; GNA, Gram-negative antibiotic; GNBI, Gram-negative bacterial infection.
[a]GNA used for at least 2 days with start date on or after cefiderocol initiation date but not after last cefiderocol dose.
Table adapted from Timsit et al. ECCMID. 2023.

Infection Severity[6]

- Vasopressor support was received by 30.2% of patients and was associated with ~3× the risk of mortality
- During cefiderocol treatment, 44.8% received mechanical ventilation and 57.3% were in an ICU setting

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Real-World Evidence

PROVE (Retrospective Cefiderocol Chart Review Study) (Cont.)

Results[6]

- Overall, 60.4% of patients achieved clinical cure and the mortality rate 30 days after starting cefiderocol was 24%
- Clinical cure rates and 30-day ACM for monomicrobial and polymicrobial infections varied by site (**Table 8**)
  - Monomicrobial infections (n=61): clinical cure rate=36 (59%), 30-day ACM=14 (23%)
  - Polymicrobial infections (n=35): clinical cure rate=22 (62.9%), 30-day ACM=9 (26%)
  - Documented infections classified as salvage (n=12): clinical cure rate=7 (58.3%), 30-day ACM=2 (16.7%)
  - Empirically treated patients (n=6): clinical cure rate=5 (83.3%); mortality=0

Table 8. Clinical Outcomes[6]

	Overall		Clinical Cure[b]		30-Day Post-Cefiderocol Mortality	
	n	%	n	%	n	%
Number of patients[a]	96		58	60.4	23	24
Index Infection Type						
Monomicrobial – primary infection site	**61**	**63.5**	**36**	**59**	**14**	**23**
Blood only	7	7.3	3	42.9	3	42.9
Blood & other (same pathogen)[c]	9	9.4	3	33.3	4	44.4
Respiratory only	22	22.9	14	63.6	3	13.6
Other sites[d]	23	24	16	69.6	4	17
Polymicrobial – primary infection site	**35**	**36.5**	**22**	**62.9**	**9**	**26**
Blood only	1	1	1	100	–	–
Blood & other (same pathogen)[c]	2	2.1	1	50	1	50
Respiratory only	20	20.8	12	60	5	25
Other sites[d]	12	13	8	67	3	25
Other primary infection site pathogens (≥10%)						
K. pneumoniae	11	11.5	7	63.6	4	36.4
P. aeruginosa	15	15.6	6	40	5	33.3
Cefiderocol Utilization						
Cefiderocol as monotherapy[e]						
Yes	39	40.6	27	69.2	6	15.4
No	57	59.4	31	54.4	17	29.8
Carbapenem resistant (n=90)						
Yes	83	92.2	50	60.2	23	27.7
No	7	7.3	5	71.4	–	–

Safety[6]

- Among patients with primary *A. baumannii* infections (n=96), 2 (2%) patients had adverse drug reactions, including 1 case of interstitial nephritis which resulted in drug withdrawal

Clancy et al (2024) reported the final global results of the PROVE study for patients from the US and Europe.[7]

Final Global Results[7]

- Of the total 1075 hospitalizations, *A. baumannii* infection was the primary pathogen in 195 cases
- The clinical cure rate for patients with infections due to *A. baumannii* treated with cefiderocol was 60.5%, while the ACM at Day 30 was 28.2%

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Real-World Evidence

Table 8. Clinical Outcomes[6]

	Overall		Clinical Cure[b]		30-Day Post-Cefiderocol Mortality	
	n	%	n	%	n	%
Number of patients[a]	96		58	60.4	23	24
Index Infection Type						
Monomicrobial – primary infection site	**61**	**63.5**	**36**	**59**	**14**	**23**
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Blood & other (same pathogen)[c]	9	9.4	3	33.3	4	44.4
Respiratory only	22	22.9	14	63.6	3	13.6
Other sites[d]	23	24	16	69.6	4	17
Polymicrobial – primary infection site	**35**	**36.5**	**22**	**62.9**	**9**	**26**
Blood only	1	1	1	100	–	–
Blood & other (same pathogen)[c]	2	2.1	1	50	1	50
Respiratory only	20	20.8	12	60	5	25
Other sites[d]	12	13	8	67	3	25
Other primary infection site pathogens (≥10%)						
K. pneumoniae	11	11.5	7	63.6	4	36.4
P. aeruginosa	15	15.6	6	40	5	33.3
Cefiderocol Utilization						
Cefiderocol as monotherapy[e]						
Yes	39	40.6	27	69.2	6	15.4
No	57	59.4	31	54.4	17	29.8
Carbapenem resistant (n=90)						
Yes	83	92.2	50	60.2	23	27.7
No	7	7.3	5	71.4	–	–

[a]Number of patients includes only those with a primary site culture of *A. baumannii*; two co-infections unrelated to the primary infection that prompted cefiderocol use were excluded.
[b]Clinical cure based on answer to the Clinical Assessment question: resolved, improved = cured; resolved then relapse, failure, or unknown = Not cured.
[c]Same *A. baumannii* pathogen at both sites.
[d]Other sites include bone/joint, skin/wound, urine, intra-abdominal, other.
[e]Monotherapy defined as cefiderocol only without overlap of other Gram-negative antibiotics.
Table adapted from Timsit et al. ECCMID. 2023.

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Real-World Evidence

Observational Studies[8–11]

Cohort Study[8]

- An observational cohort study examined the association between cefiderocol-containing treatment regimens and 28-day mortality in ICU patients (N=121) with VAP due to CRAB, as well as COVID-19
- Effect of cefiderocol was assessed as both monotherapy and in combination (within 72 h of treatment initiation) with other agents for the treatment of CRAB

Methods[8]

- The study population included patients ≥18 years of age
- Cefiderocol was administered as 2 g q8h (3 h infusion), adjusted for renal function
- All patients also received high-dose nebulized colistimethate
- Propensity scores were calculated to balance the patients that received either cefiderocol or non-cefiderocol regimens

Outcome Measures[8]

- Primary outcome was 28-day ACM
- Secondary outcomes:
  - Need for IMV 28 days following CRAB-VAP diagnosis
  - Cefiderocol resistance development (based on EUCAST clinical breakpoints)
  - VAP relapse
  - Microbiological failure

Results[8]

Patient Characteristics[8]

- 28 (23%) patients were female
- Median age (IQR) was 66 (59–72) years
- Median (IQR) CCI was 4 (3–6)
- Median (IQR) SOFA score was 8 (5–10)

Treatment Regimens[8]

- 55 patients received a cefiderocol-containing treatment regimen; 66 received a non-cefiderocol containing regimen
- Patients received cefiderocol as monotherapy or in combination with other antibiotics for CRAB. The most frequent were:
  - Cefiderocol monotherapy: 12 (21.8%)
  - Cefiderocol + colistin: 18 (29%)
  - Cefiderocol + colistin + tigecycline: 11 (20%)
- Non-cefiderocol treatment regimens most frequently included:
  - Colistin + tigecycline + fosfomycin: 48 (72.7%)

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Real-World Evidence

Observational Studies (Cont.)

Cohort Study (Cont.)

Results (Cont.)

Study Outcomes[8]

- Patients receiving a cefiderocol treatment regimen had significantly lower 28-day mortality (44%) compared to non-cefiderocol regimens (67%) (*P*=0.011)
- Microbiological failure occurred more frequently with cefiderocol regimens compared to non-cefiderocol containing regimens (53% vs 31%, respectively) (*P*=0.038)
- Relapse of VAP occurred in 16% and 13% of patients that received cefiderocol regimens and cefiderocol non-containing regimens, respectively (*P*=0.73)
- The need for mechanical ventilation within 28 days of VAP diagnosis occurred in 35% and 4.5% of patients that received cefiderocol regimens and non-cefiderocol containing regimens, respectively (*P*=0.008)
- The propensity-adjusted multiple logistic regression model showed cefiderocol treatment was predictive of 28-day survival (OR, 0.35; 95% CI, 0.14 to 0.83)
- Multiple variables were significantly associated with greater risk of 28-day mortality:
  - CCI (OR, 1.36; 95% CI, 1.16 to 1.78)
  - SOFA score (OR, 1.24; 95% CI, 1.09 to 1.57)
  - Septic shock (OR, 3.71; 95% CI, 1.44 to 12.73)
- Of 20 (10%) patients with follow-up susceptibility results that received cefiderocol, 2 developed resistance

Safety[8]

- Incidence of AEs was not significantly different between the treatment groups
- AKI was reported in 5 (9.1%) patients in the cefiderocol group and in 11 (17%) patients in the non-cefiderocol treatment group (*P*=0.22)
  - LFTs >2× ULN occurred in 1 patient in each group

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Real-World Evidence

Observational Studies (Cont.)

Comparative Study[9]

- A comparative, retrospective, observational, study was conducted to evaluate the safety and efficacy of cefiderocol vs colistin treatment in patients with BSI due to monomicrobial CRAB (N=118)

Methods[9]

- The study population included patients ≥18 years of age
- Patients had to receive ≥48 h of cefiderocol treatment
- 43 patients were treated with cefiderocol-based regimens; 75 patients received colistin-based regimens

Outcome Measures[9]

- Primary endpoint was 30-day ACM
- Key secondary endpoints included:
  - Incidence of 30-day infection-related mortality
  - Incidence of severe AEs to antibiotic treatment
  - 90-day recurrence of BSI due to CRAB
  - Resistance development to cefiderocol or colistin during treatment
  - Predictors of 30-day ACM were assessed by using multivariate Cox regression as well as an adjustment analysis based on IPTW methodology

Results[9]

Demographic and Clinical Characteristics[9]

- 59% of patients were male
- Median (IQR) age was 70 (62–79) years
- Median (IQR) CCI was 6 (4–8)
- Common comorbidities included renal failure (42%), type 2 diabetes (36%), and chronic heart disease (25%)
- Differences in baseline clinical characteristics among cefiderocol-treated and colistin-treated patients included:
  - More frequent use of cefiderocol (37%) compared to colistin monotherapy (4%) (P<0.001)
  - More patients in the colistin group vs the cefiderocol group had BSI that needed surgical source control (31% vs 7%) (P=0.003)
  - More patients in the cefiderocol-based regimen group received targeted therapy within 24 h of infection onset (37%) compared to the colistin-based regimen group (21%) (P=0.036)

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Real-World Evidence

Observational Studies (Cont.)

Comparative Study (Cont.)

Results (Cont.)

Outcome Measures[9]

- 30-day ACM occurred in 17 (40%) patients in the cefiderocol group vs 44 (59%) patients in the colistin group (*P*=0.045)
- 30-day infection-related mortality occurred in 13 (30%) cefiderocol-treated patients and in 42 (56%) colistin-treated patients (*P*=0.007)
- 90-day BSI recurrence/relapse occurred in 4 (9%) and 4 (5%) patients in the cefiderocol and colistin group, respectively (*P*=0.409)
- The development of cefiderocol resistance occurred in 2 (5%) patients following treatment, while development of resistance was not detected in the colistin-treated group
- Multivariate analyses identified independent risk factors for 30-day ACM:
  - Cefiderocol-based treatment regimen (aHR, 0.49; 95% CI, 0.25 to 0.93; *P*=0.029)
  - Increased age (aHR, 1.03; 95% CI, 1.00 to 1.05; *P*=0.035)
  - Septic shock (aHR, 1.93; 95% CI, 1.05 to 3.53; *P*=0.033)
  - Receipt of appropriate antibiotic therapy beyond 72 h of BSI onset (aHR, 2.42; 95% CI, 1.11 to 5.25; *P*=0.025)
  - An IPTW-adjustment analysis confirmed that cefiderocol was independently associated with lower 30-day mortality rate (aHR, 0.53; 95% CI, 0.27 to 0.98; *P*=0.047) while septic shock was associated with mortality (aHR, 2.81; 95% CI, 1.35 to 5.84; *P*=0.005)

Safety[9]

- Incidence of AEs associated with antibiotic treatment was higher in the colistin group compared to the cefiderocol group (*P*=0.022)
  - 1 (2%) cefiderocol-treated patient experienced an allergic skin rash
  - 12 (16%) colistin-treated patients experienced a Grade 3–4 AE, including AKI (n=10) and PN (n=2)

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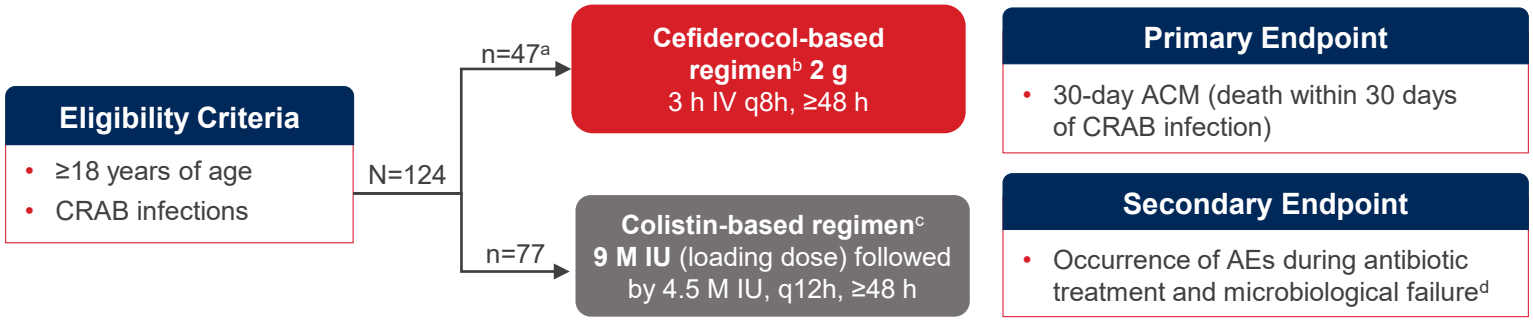
Real-World Evidence

Observational Studies (Cont.)

Retrospective Cohort Study[10]

- A retrospective observational cohort study was conducted in patients with CRAB infections who were consecutively hospitalized at the University Hospital of Pisa in Italy between June 2019 and August 2021 (**Figure 4**)

Figure 4. Study Design[10]



Abbreviations: ACM, all-cause mortality; AE, adverse event; CRAB, carbapenem-resistant *A. baumannii*; EOT, end of treatment; h, hours; IU, international unit; IV, intravenous; M, million; q12h, once every 12 hours; q8h, once every 8 hours.
[a]Monotherapy (n=15) or in combination with other antibiotics (n=32) based on clinical judgment.
[b]Adjusted for renal dosing if needed.
[c]Administered with other antibiotics based on clinical judgment.
[d]Defined as CRAB from the same infection site, isolated ≥7 days after EOT.

Methods[10]

- Infections were classified according to CDC/NHSN criteria as BSI (n=79), VAP (n=35), and others (n=10)
- Clinical data were collected from Day 1 of CRAB isolation through Day 30
- Multivariable analysis using Cox proportional hazards regression was conducted to identify the independent factors that were associated with 30-day ACM

Real-World Evidence

Observational Studies (Cont.)

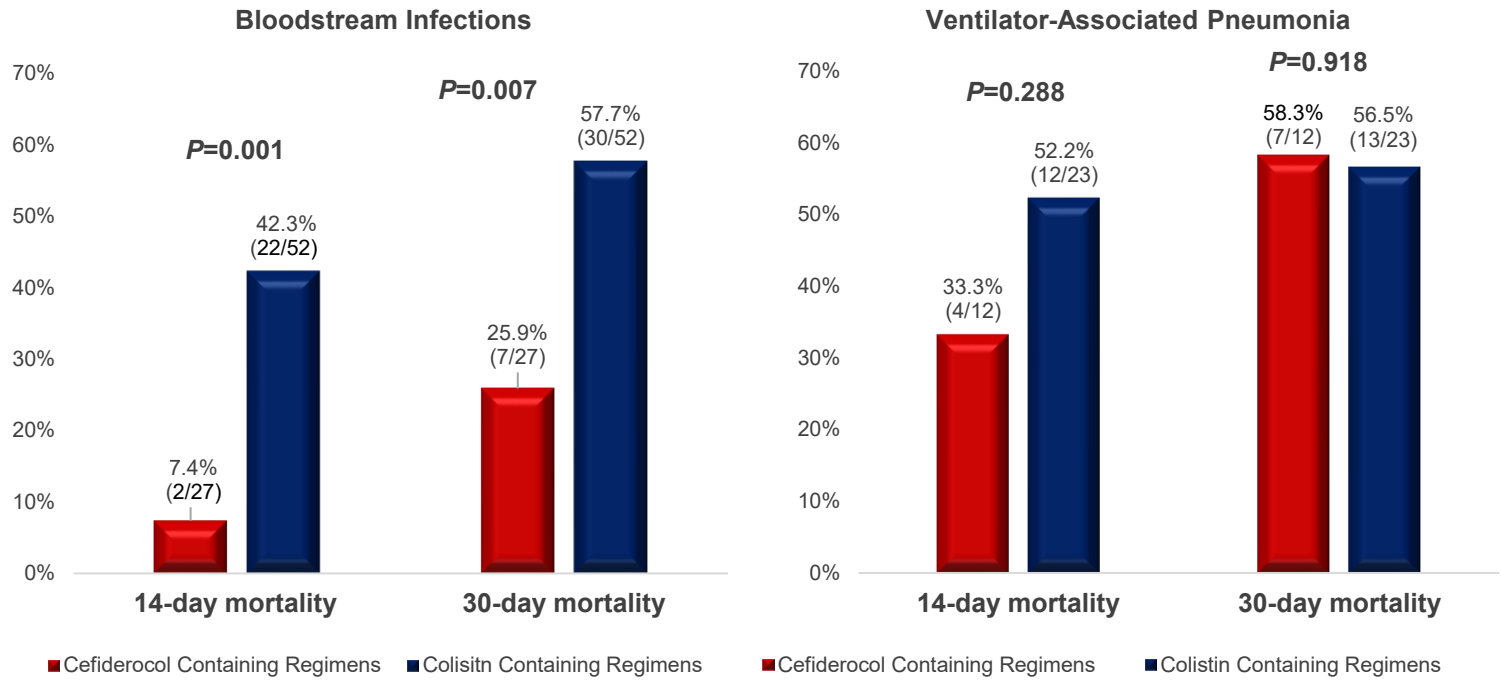
Retrospective Cohort Study (Cont.)

Results[10]

30-Day Mortality[10]

- 30-day ACM for the cefiderocol group was 34% and 55.8% in the colistin arm (*P*=0.018)
- A subgroup analysis in patients with BSI and VAP was conducted for mortality at Days 14 and 30 (**Figure 5**)
  - 30-day ACM in BSI for cefiderocol and colistin groups was 7 (25.9%) and 30 (57.7%), respectively (*P*=0.007)
  - In patients with VAP, 30-day ACM was 7 (58.3%) in the cefiderocol arm and 13 (56.5%) in the colistin arm (no statistically significant difference; *P*=0.918)

Figure 5. 14- and 30-Day Mortality in Patients with BSI and VAP[10]



Abbreviations: BSI, bloodstream infection; VAP, ventilator-associated pneumonia.
Figure adapted from Falcone et al. *Antimicrob Agents Chemother*. 2022.

Real-World Evidence

Observational Studies (Cont.)

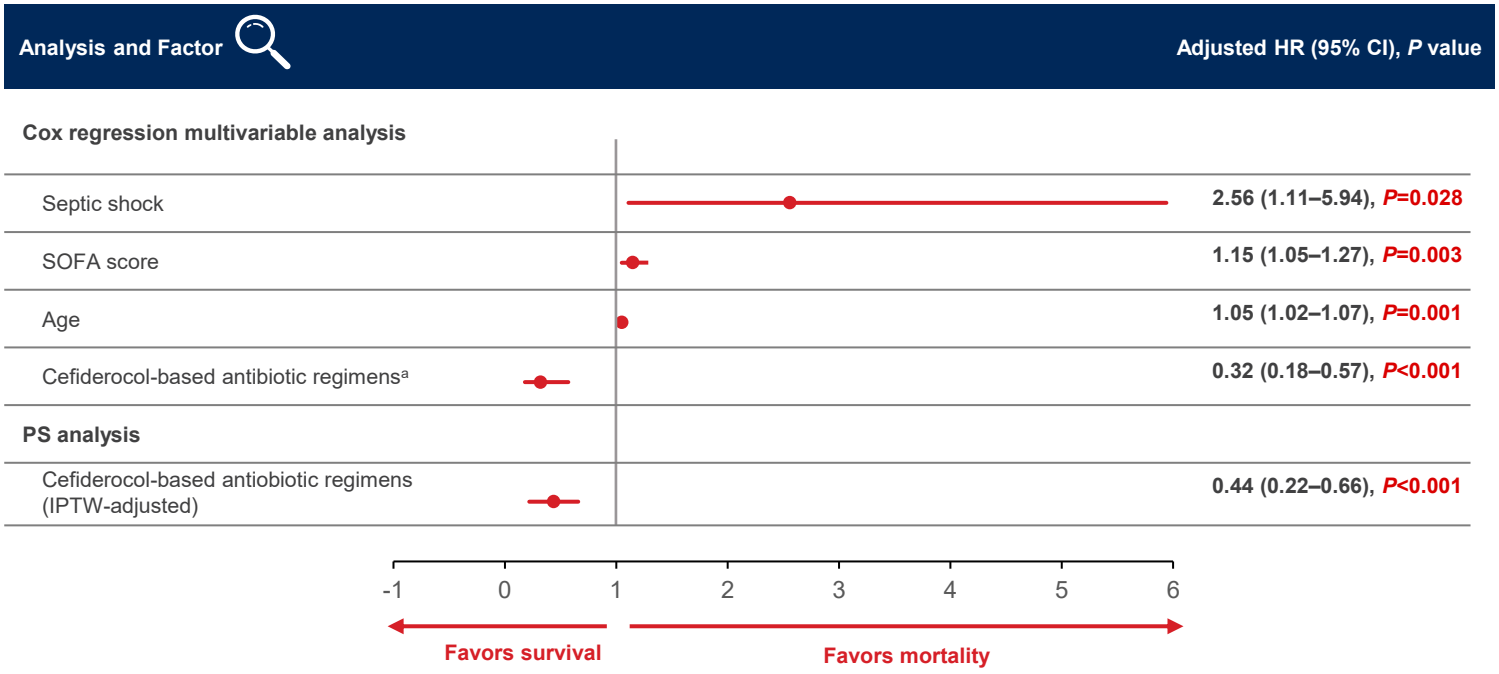
Retrospective Cohort Study (Cont.)

Results (Cont.)

30-Day Mortality (Cont.)[10]

- Results from multivariable analysis showed that cefiderocol was seen as a protective factor for 30-day mortality compared with colistin-based regimens (HR, 0.32; 95% CI, 0.18 to 0.57; *P*<0.001) (**Figure 6**)

Figure 6. Cox Regression Multivariable Analysis of Factors Independently Associated with 30-Day Mortality[10]



Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse-probability treatment weighted; PS, propensity score; SOFA, sequential organ failure assessment.
[a]Compared with colistin-based regimens.
Figure adapted from Falcone et al. *Antimicrob Agents Chemother*. 2022.

Real-World Evidence

Observational Studies (Cont.)

Retrospective Cohort Study (Cont.)

Results (Cont.)

Microbiological Failure and Resistance[10]

- Microbiological failure rate was calculated for 120 patients with follow-up culture and were not statistically significant between treatment groups (**Table 9**)
- Cefiderocol patients experienced microbiological failure (n=8), which included 7 patients with burns and 4 isolates (50%) with resistant MICs (based on EUCAST breakpoints of 4 to ≥32 µg/mL)
- Of the 4 cases with resistant MICs, 2 developed during treatment and 2 emerged after cefiderocol discontinuation
- All patients in the cefiderocol group experiencing failure had BSI; of these, 6 patients received cefiderocol monotherapy
- Microbiological failure was significantly higher in the cefiderocol patients treated with monotherapy vs combination therapy (42.9% vs 6.3%) (*P*=0.006)

Table 9. Microbiological Failure Rates in Patients[10]

	Cefiderocol Arm, n/N (%)	Colistin Arm, n/N (%)	*P* Value
Microbiological failure rates	8/46 (17.4)	5/74 (6.8)	0.079

Table adapted from Falcone et al. *Antimicrob Agents Chemother*. 2022.

Safety[10]

- An AE occurred in 1 (2.1%) patient treated with cefiderocol and 16 (21.1%) patients treated with colistin-based regimens (*P*=0.003)
- All AEs in the colistin-based group were AKI during treatment, and in the cefiderocol group were skin rash

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Real-World Evidence

Observational Studies (Cont.)

Retrospective Comparative Study[11]

- A retrospective observational study (N=73) was conducted to evaluate the impact of cefiderocol compared to colistin in patients with VAP and concomitant BSI due to CRAB and COVID-19
- The primary goal was to identify and assess risk factors associated with survival or death 30 days after VAP onset

Methods[11]

- This was a single-center study of patients that were admitted between March 2020 to August 2022 to the COVID-ICU of a tertiary care hospital
- Susceptibility was established according to EUCAST interpretive criteria
  - For cefiderocol, disc diffusion was utilized
- Data were analyzed via multivariate analysis, including Cox regression model and a proportional hazards model analysis
  - A PS was included in the model to address the nonrandomized treatment groups

Results[11]

- Demographic data and clinical characteristics are presented in **Table 10**

Table 10. Comparisons Between Cefiderocol and Colistin Regimens in Targeted Therapy[11]

Variables	Cefiderocol Regimen n=19	Colistin Regimen n=54	*P* Value
Patient history factors and comorbidities			
Male sex, n (%)	5 (26.3)	13 (24)	0.879
Age, median (IQR), years	61 (52.5–70.5)	60 (52.5–65)	0.755
Previous hospitalization (90 days), n (%)	0	3 (5.5)	0.083
Previous ICU (90 days), n (%)	0	1 (1.8)	0.322
>2 comorbidities, n (%)	13 (68.4)	28 (51.8)	0.391
Cardiovascular disease, n (%)	15 (78.9)	28 (51.8)	0.060
Heart failure, n (%)	2 (10.5)	7 (12.9)	0.765
CCI, median (IQR), points	2.6 (1.25–3.75)	2.9 (1–4)	0.216
Diabetes, n (%)	6 (31.5)	15 (27.7)	0.771
Previous and targeted antibiotic therapy during hospitalization			
Duration of previous therapy, median (IQR), days	9 (5.5–12)	9 (5–13)	0.912
Duration of targeted therapy, median (IQR), days	12 (9–14)	11 (6–15)	0.566

- 67 (91.7%) patients developed septic shock, and 42 (57.5%) and 59 (80.8%) of patients died at 14 days and 30 days, respectively
- All *A. baumannii* isolates were classified as XDR or PDR
- 54 (74%) patients received a colistin-containing treatment regimen:
  - 12 (22.2%) colistin monotherapy
  - 12 (22.2%) colistin + meropenem + tigecycline
  - 9 (16.6%) colistin + meropenem
  - As targeted therapy, median (IQR) treatment duration for colistin was 11 (6–15) days
- 33 (45.2%) out of all study patients received aerosolized colistin as adjunctive therapy
- 19 (26%) patients received a cefiderocol-containing treatment regimen (all were combination treatment):
  - 6 (31.5%) cefiderocol + fosfomycin
  - 3 (15.8%) cefiderocol + fosfomycin + tigecycline
  - 3 (15.8%) cefiderocol + meropenem + fosfomycin + tigecycline
  - As targeted therapy, median (IQR) treatment duration for cefiderocol was 12 (9–14) days

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Real-World Evidence

Table 10. Comparisons Between Cefiderocol and Colistin Regimens in Targeted Therapy[11]

Variables	Cefiderocol Regimen n=19	Colistin Regimen n=54	*P* Value
Patient history factors and comorbidities			
Male sex, n (%)	5 (26.3)	13 (24)	0.879
Age, median (IQR), years	61 (52.5–70.5)	60 (52.5–65)	0.755
Previous hospitalization (90 days), n (%)	0	3 (5.5)	0.083
Previous ICU (90 days), n (%)	0	1 (1.8)	0.322
>2 comorbidities, n (%)	13 (68.4)	28 (51.8)	0.391
Cardiovascular disease, n (%)	15 (78.9)	28 (51.8)	0.060
Heart failure, n (%)	2 (10.5)	7 (12.9)	0.765
CCI, median (IQR), points	2.6 (1.25–3.75)	2.9 (1–4)	0.216
Diabetes, n (%)	6 (31.5)	15 (27.7)	0.771
Previous and targeted antibiotic therapy during hospitalization			
Duration of previous therapy, median (IQR), days	9 (5.5–12)	9 (5–13)	0.912
Duration of targeted therapy, median (IQR), days	12 (9–14)	11 (6–15)	0.566

Abbreviations: CCI, Charlson Comorbidity Index; ICU, intensive care unit; IQR, interquartile range.
Table adapted from Russo et al. *Int J Antimicrob Agents*. 2023.

- Sixty-seven (91.7%) patients developed septic shock, and 42 (57.5%) and 59 (80.8%) of patients died at 14 days and 30 days, respectively[7]
- All *A. baumannii* isolates were classified as extensively drug resistant (XDR) or pandrug resistant (PDR)[7]
- Fifty-four (74%) patients received a colistin-containing treatment regimen[7]:
  - Twelve (22.2%) colistin monotherapy
  - Twelve (22.2%) colistin + meropenem + tigecycline
  - Nine (16.6%) colistin + meropenem
  - As targeted therapy, median (IQR) treatment duration for colistin was 11 (6-15) days
- Thirty-three (45.2%) out of all study patients received aerosolized colistin as adjunctive therapy[7]
- Nineteen (26%) patients received a cefiderocol-containing treatment regimen (all were combition treatment)[7]:
  - Six (31.5%) cefiderocol + fosfomycin
  - Three (15.8%) cefiderocol + fosfomycin + tigecycline
  - Three (15.8%) cefiderocol + meropenem + fosfomycin + tigecycline
  - As targeted therapy, median (IQR) treatment duration for cefiderocol was 12 (9-14) days

Real-World Evidence

Observational Studies (Cont.)

Retrospective Comparative Study (Cont.)

Results (Cont.)

Outcome Measures[11]

- Age (HR, 1.12; 95% CI, 1.01 to 1.1; *P*=0.001) and COPD (HR, 1.4; 95% CI, 1.3 to 12.2; *P*=0.022) were independently associated with 30-day mortality
- Cefiderocol treatment regimens (HR, 0.34; 95% CI, 0.1 to 0.56; *P*<0.001) and cefiderocol combined with fosfomycin (HR, 0.22; 95% CI, 0.1 to 0.55; *P*<0.001) were independent factors associated with survival at Day 30. These results were also confirmed by PS analysis
- Survivors and nonsurvivors, respectively, significantly differed on multiple characteristics, including the following:
  - Median age (60 vs 64 years; *P*=0.031)
  - CKD (0% vs 10.1%; *P*=0.013)
  - COPD (7.1% vs 25.4%; *P*=0.026)
  - Time to negativization of blood cultures (2 vs 4 days; *P*=0.002)
- Patients treated with cefiderocol-containing regimens had significantly lower mortality rates compared to patients treated with colistin at both Day 14 (5.2% vs 75.9%; *P*<0.001) and Day 30 (31.5% vs 98.1%; *P*<0.001) (**Figure 7**)
- The development of cefiderocol resistance was observed in 2 patients

Figure 7. 14- and 30-Day Mortality Rates in Cefiderocol vs Colistin Treatment Groups[11]

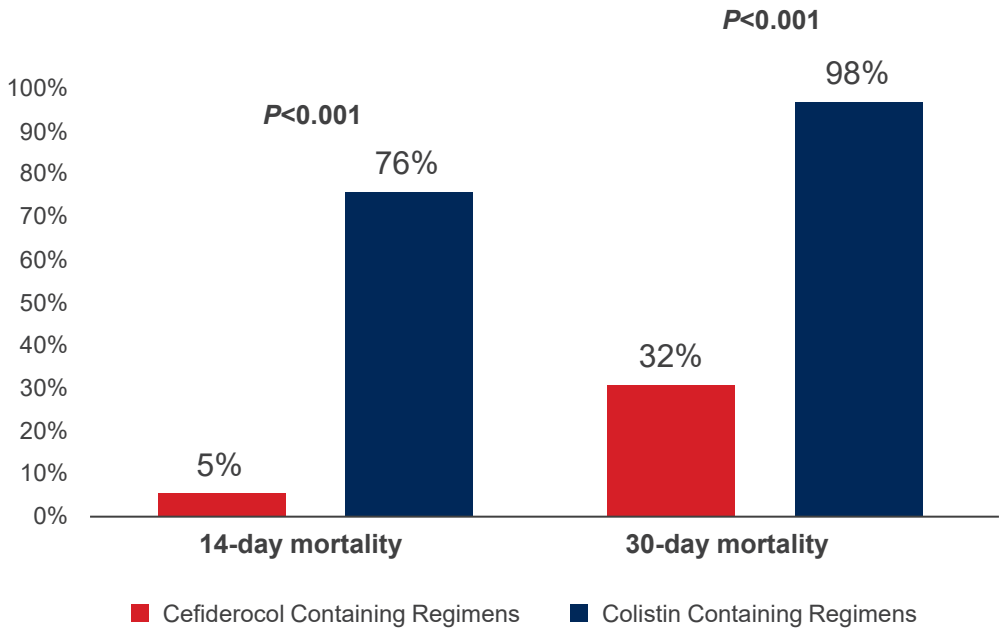


Figure adapted from Russo et al. *Int J Antimicrob Agents*. 2023.

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Real-World Evidence

Additional Retrospective Studies[12,13]

Retrospective Cohort Study[12]

- A retrospective cohort study was conducted in adult inpatients from a single university hospital with documented infection by CRAB receiving cefiderocol-based treatment
- Patients with documented CRAB infections who were treated the previous year with colistin-based therapy served as the control group
- 111 patients with BSI or pneumonia were enrolled; 60 (54.1%) received cefiderocol-based treatment and 51 (45.9%) received colistin-based therapy

Methods[12]

- MICs were classified per breakpoints established by EUCAST
- Primary outcomes:
  - Clinical cure, defined as resolution of signs/symptoms of infection 14 days following the initiation of treatment
  - 30-day ACM
- Secondary outcomes:
  - Microbiological cure, defined as no further isolation of *A. baumannii* from the primary infection site after 7 to 14 days of treatment
  - Identification of clinical and laboratory predictors as significant risk factors in study outcomes
- Differences in clinical outcomes between patients treated with cefiderocol either as monotherapy or as combination therapy were also assessed

Results[12]

- Select demographic data and clinical characteristics are presented in **Table 11**
- 60 patients were treated with cefiderocol:
  - 30 (50%) received monotherapy
  - 30 (50%) also received fosfomycin (13.3% of cases), tigecycline (30% of cases), and meropenem (18.3% of cases)
- 51 patients were treated with colistin-based therapy the previous year:
  - No patients received monotherapy
  - Colistin was combined with tigecycline (96.1% of cases), meropenem (80.4% of cases), and fosfomycin (5.8% of cases)

Table 11. Select Demographic and Clinical Characteristics of Study Population[12]

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
Diabetes, n (%)	27 (24)	10 (17)	17 (33)	0.041
Obesity, n (%)	41 (37)	16 (27)	25 (49)	0.015
BSI, n (%)	53 (47.7)	34 (56.6)	19 (37.2)	0.003
Pneumonia, n (%)	58 (52.3)	26 (43.4)	32 (62.8)	0.003
Length of stay, days, median (IQR)	45 (24–70)	52 (32–73)	34 (20–72)	0.023

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Obesity, n (%)	41 (37)	16 (27)	25 (49)	0.015
BSI, n (%)	53 (47.7)	34 (56.6)	19 (37.2)	0.003
Pneumonia, n (%)	58 (52.3)	26 (43.4)	32 (62.8)	0.003
Length of stay, days, median (IQR)	45 (24–70)	52 (32–73)	34 (20–72)	0.023

Abbreviations: BSI, bloodstream infection; IQR, interquartile.
Table adapted from Mazzitelli et al. *Microorganisms*. 2023.

Real-World Evidence

Additional Retrospective Studies (Cont.)

Retrospective Cohort Study (Cont.)

Results (Cont.)[12]

- Total mortality rate was 43% (n=48) and was higher in patients treated with cefiderocol (51%) vs patients receiving colistin (37%) (*P*=0.13)[11]
- Clinical cure and microbiological cure did not significantly differ between treatment groups[11]
  - Clinical cure: 44 (73%) for cefiderocol and 34 (67%) for colistin-based regiments (*P*=0.44)
  - Microbiological cure: 26 (43%) for cefiderocol and 21 (41%) for colistin (*P*=0.82)
- No significant differences in outcome were observed between cefiderocol monotherapy and combination treatment groups[11]
  - Mortality: 10 (33.3%) for monotherapy and 16 (53.3%) for combination therapy (*P*=0.81)
  - Clinical cure: 23 (76.7%) for monotherapy and 21 (70%) for combination therapy (*P*=0.55)
  - Microbiological cure: 15 (50%) for monotherapy and 11 (36.7%) for combination therapy (*P*=0.29)
- Overall analysis using a PS weighting approach found no significant differences in clinical outcomes comparing cefiderocol-based and colistin-based treatment regimens, and no independent predictors of clinical cure or mortality were identified[11]

Safety[12]

- Significantly more patients taking colistin developed AKI (13; 25.5%) vs those receiving cefiderocol (6; 10%) (*P*=0.031)
- No adverse reactions or notable laboratory value changes occurred in patients that received cefiderocol

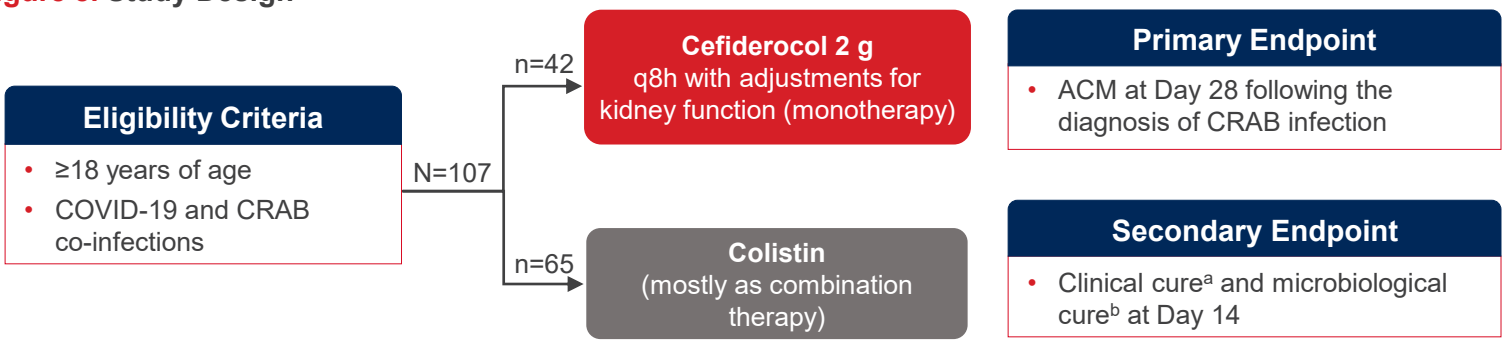
Real-World Evidence

Additional Retrospective Studies (Cont.)

Retrospective Multicenter Study[13]

A retrospective, multicenter, blinded, cohort study was conducted in Italy for adult ICU patients with COVID-19 and CRAB co-infections between January 2020 to April 2021 (**Figure 8**)

Figure 8. Study Design[13]



Abbreviations: ACM, all-cause mortality; COVID-19, Coronavirus disease 2019; CRAB, carbapenem-resistant *A. baumannii*; q8h, once every 8 hours.
[a]Resolution of fever and hypotension.
[b]Clearance of bacteria from follow-up blood samples or respiratory samples.

Results[13]

- Patient clinical characteristics are presented in **Table 12**, and outcome measures assessed at Day 14 and Day 28 are presented in **Table 13**

Table 12. Clinical Characteristics[13]

n (%)	Overall (N=107)	Cefiderocol (n=42)	Colistin (n=65)
Lower RTI	44 (41)	–	–
BSI	62 (58)	–	–
Septic shock	43 (41)	18 (46)	25 (38)
Appropriate antibiotic treatment	41 (38)	20 (47)	21 (32)

Abbreviations: BSI, bloodstream infection; RTI, respiratory tract infection.
Table adapted from Pascale et al. *JAC Antimicrob Resist*. 2021.

Table 13. Clinical and Microbiological Outcomes at Day 14 and Day 28[13]

Outcome, n (%)	Cefiderocol (n=42)	Colistin (n=65)	*P* Value
Clinical cure (Day 14)	17 (40)	24 (36)	0.453
Microbiological cure (Day 14)	12 (28)	14 (21)	0.246
Death (Day 14)	17 (40)	33 (51)	0.147
Death (Day 28)	23 (55)	38 (58)	0.706

Table adapted from Pascale et al. *JAC Antimicrob Resist*. 2021.

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Surveillance Studies

- Several studies that evaluated the *in vitro* susceptibility of resistant *Acinetobacter* spp. to cefiderocol are summarized in **Table 14**[14–19]
- ID-CAMHB was used in the MIC determination for cefiderocol and CAMHB for other antibiotics unless specified otherwise

Table 14. List of Surveillance Studies[14–19]

Study	Collection Years and Countries	Number of Isolates	Susceptibility Testing and Interpretive Criteria	Results
SENTRY Antimicrobial Surveillance Program (Yamano et al 2025)[14]	US and Europe 2020–2024	4808 ABC isolates	• Broth microdilution • CLSI breakpoints	• **Figure 9** shows the trend in the number of (A) ABC isolates and (B) CRAB isolates over the 5-year study period • Consistently high activity was observed for cefiderocol against ABC over the 5-year period studied – see **Figure 10** and **Figure 11** – Susceptibility to cefiderocol was 93.2–98.9% for all ABC isolates, and 87–97.7% for the CRAB subset • Susceptibilities of 89.4% and 87% were observed for CRAB isolates in the US and Europe in 2024, respectively
SENTRY Antimicrobial Surveillance Program (Mendes et al 2025)[15]	US 2020–2024	1999 ABC isolates	• Broth microdilution • CLSI/FDA breakpoints	• 587 isolates (29.4%) were identified as CRAB. The distribution of infection types caused by CRAB isolates is shown in **Figure 12**, and the distribution of CRAB among the 9 US Census Regions is shown in **Figure 13** • 507 (86.4%) of the 587 CRAB isolates were shown to carry carbapenemase genes, with bla_{NDM-25} being the most common – see **Table 15** • Cefiderocol was determined to have the lowest $MIC_{50/90}$ (0.12/1 mg/L; 92.9–97.7% susceptible) against all ABC isolates, while retaining 81.8–94.4% susceptibility against overall CRAB ($MIC_{50/90}$ 2 mg/L) – see **Table 15** • In the subset of 80 CRAB isolates (13.6%) that did not carry acquired carbapenemases, cefiderocol inhibited 91.2% and 78.8% of isolates based on CLSI and FDA breakpoints, respectively
SENTRY Antimicrobial Surveillance Program (Dubrovskaya et al 2025)[16]	US and Europe 2001–2022	29 ABC isolates carrying MBLs	• Broth microdilution • CLSI/FDA/EUCAST breakpoints	• MIC values for cefiderocol ranged from 0.06–16 µg/mL, with IMP-carrying isolates showing lower values compared with NDM-carrying isolates – see **Figure 14** • According to CLSI, EUCAST, and FDA breakpoints, respectively, 82.8%, 69%, and 44.8% of the ABC isolates showed susceptibility to cefiderocol – see **Table 16** – Most comparator antimicrobial agents showed lower susceptibilities (<30%), with minocycline and colistin being the only other active agents – see **Table 16** • Additional β-lactamases were commonly detected in NDM-carrying ABC isolates, but no correlation between this and cefiderocol MIC value could be determined

Figure 9. Trends in the Number (US and Global) of (A) ABC Isolates (n=4806) and (B) CRAB Isolates from Over 5 Years of the SENTRY Surveillance Program (2020–2024)[14]

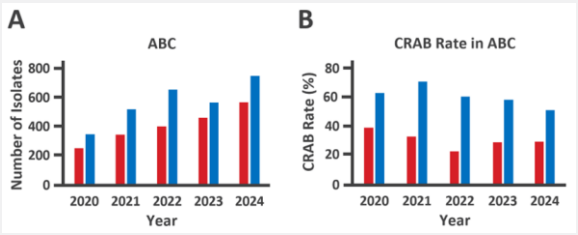


Figure 10. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from US Hospitals during the SENTRY Surveillance Program (2020–2024)[14]

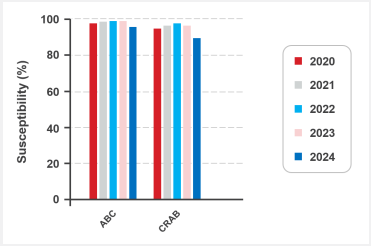


Figure 11. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from European Hospitals during the SENTRY Surveillance Program (2020–2024)[14]

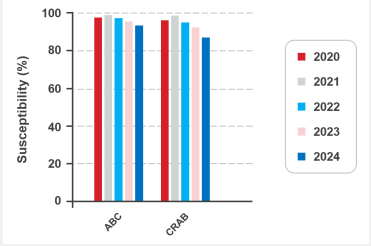


Figure 12. Distribution of Infection Types caused by CRAB (US Isolates)[15]

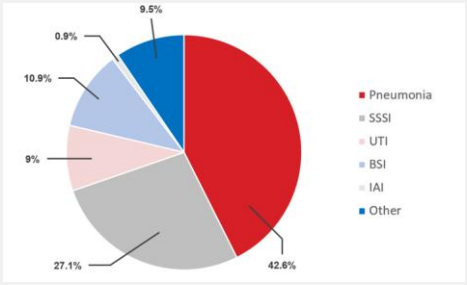
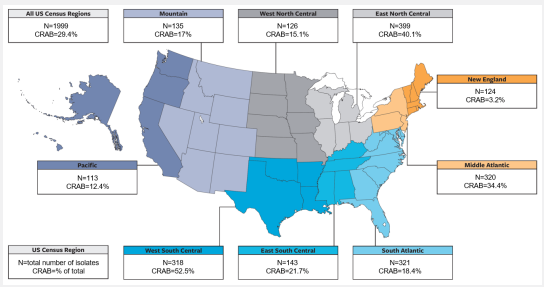


Figure 13. Distribution of CRAB (n=587) among US Census Regions[15]



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Surveillance Studies

Table 15. Activity of Cefiderocol and BL–BLI Combinations against ABC and Resistant Subsets from the US[15]

Phenotype/Genotype[a] (Number Tested)	$MIC_{50/90}$ in mg/L (% Susceptible by CLSI/FDA Criteria)[b]					
	Cefiderocol	Imipenem–Relebactam	Meropenem	Ampicillin–Sulbactam	Ceftazidime	Colistin
All (1999)	0.12/1 (97.7/92.9)	0.25/>8 (72)	0.5/>32 (70.7)	4/64 (67.6)	8/>32 (66.8)	0.5/1 (96.5)
Carb-NS (587)	0.25/2 (94.4/81.8)	>8/>8 (4.8)	>32/>32 (0.2)	32/>64 (12.1)	>32/>32 (16.5)	0.5/1 (95.1)
Carbapenemase-positive (507)	0.25/2 (94.9/82.2)	>8/>8 (0.8)	>32/>32 (0)	32/>64 (4.3)	>32/>32 (18.3)	0.5/1 (95.1)
OXA-23 (301)	0.5/2 (95.3/81.4)	>8/>8 (0)	>32/>32 (0)	32/>64 (1)	>32/>32 (13.6)	0.5/1 (93.7)
OXA-24 (178)	0.25/2 (97.8/88.2)	>8/>8 (2.2)	>32/>32 (0)	32/>64 (9.6)	32/>32 (27)	0.5/0.5 (97.7)
Other[c] (28)	0.5/64 (71.4/53.6)	>8/>8 (0)	>32/>32 (0)	64/>64 (7.1)	>32/>32 (14.3)	0.5/1 (92.9)
Carbapenemase-negative[d] (80)	0.25/4 (91.2/78.8)	8/>8 (30)	16/32 (1.2)	8/64 (61.2)	>32/>32 (5)	0.5/1 (95)

Figure 14. Cefiderocol MIC Distribution of MBL-producing ABC US and Global Isolates (n=29)[16]

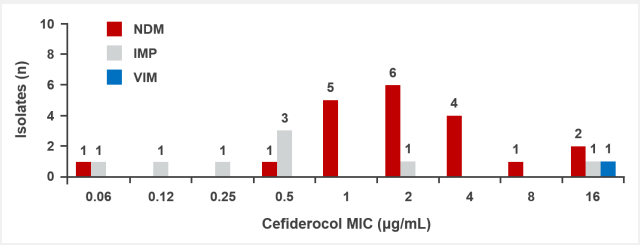


Table 16. Antimicrobial Activity of Cefiderocol and Comparator Agents Tested against MBL-producing ABC US and Global Isolates Collected during the SENTRY Antimicrobial Surveillance Program (n=29)[16]

Antimicrobial Agent	MIC (g/mL)			CLSI[b]			EUCAST[b]			FDA[b]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R	%S	%I	%R
Cefiderocol	2	16	0.06 to 16	82.8	3.4	13.8	69[e]		31[e]	44.8	24.1	31
Sulbactam–durlobactam	>32	>32	2 to >32	27.6	0	72.4				27.6	0	72.4
Ampicillin–sulbactam	>64	>64	4 to >64	10.3	0	89.7				10.3	0	89.7
Imipenem–relebactam	>16	>16	1 to >16							3.4	0	96.6
Meropenem	>32	>32	4 to >32	0	3.4	96.6	0	3.4	96.6	0	3.4	96.6
Imipenem	>8	>8	>8	0	0	100	0	0	100	0	0	100
Ceftazidime	>32	>32	>32	0	0	100				0	0	100
Minocycline	2	32	0.12 to 32	82.8	0	17.2				82.8	0	17.2
Colistin	0.25	0.5	0.12 to 8		96.6	3.4	96.6		3.4			

Table 17. Cefiderocol MIC Distribution for the 95 CRAB Isolates[18]

	Number	MIC_{50}	MIC_{90}	Cefiderocol MIC (µg/mL)					
				0.125	0.25	0.5	1	2	4
CRAB	95	1	2	4	7	19	43	21	1
FDA criteria				S	S	S	S	I	R
CLSI criteria				S	S	S	S	S	S

Table 18. MIC Values for Cefiderocol and Comparator Agents Tested against a Collection of 113 *A. baumannii* Clinical Isolates[19]

Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	%S	%I	%R
	µg/mL			n (%)		
Cefiderocol	0.5	>64	≤0.03 to >64	90 (79.6)	1 (0.88)	23 (20.35)
Cefepime	>16	>16	≤0.125 to >16	15 (13.27)	4 (3.54)	94 (83.18)
Ceftazidime–avibactam[a]	>16	>16	≤0.125 to >16	NA	NA	NA
Meropenem	>16	>16	0.125 to >16	22 (19.47)	2 (1.77)	89 (78.76)
Meropenem–vaborbactam[a]	>16	>16	0.125 to >16	NA	NA	NA
Imipenem–relebactam[a]	>16	>16	0.125 to >16	NA	NA	NA
Ampicillin–sulbactam	32	64	≤2 to >64	24 (21.24)	20 (17.7)	69 (61.06)
Ciprofloxacin	>8	>8	≤0.125 to >8	12 (10.62)	0 (0)	101 (89.38)
Minocycline	4	>8	≤0.25 to >8	65 (57.52)	21 (18.58)	27 (23.89)
Tigecycline[a]	2	4	≤0.125 to >4	NA	NA	NA
Trimethoprim–sulfamethoxazole	>8	>8	≤0.25 to >8	19 (16.81)	NA	94 (83.18)
Colistin[b]	0.5	8	≤0.25 to >8	NA	99 (87.61)	14 (12.39)

Surveillance Studies

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SENTRY Antimicrobial Surveillance Program (Mendes et al 2025)[15]	US 2020–2024	1999 ABC isolates	• Broth microdilution • CLSI/FDA breakpoints	• 587 isolates (29.4%) were identified as CRAB. The distribution of infection types caused by CRAB isolates is shown in Figure 12, and the distribution of CRAB among the 9 US Census Regions is shown in Figure 13 • 507 (86.4%) of the 587 CRAB isolates were shown to carry carbapenemase genes, with *bla*$_{OXA-23}$ being the most common – see Table 15 • Cefiderocol was determined to have the lowest MIC$_{50/90}$ (0.12/1 mg/L; 92.9–97.7% susceptible) against all ABC isolates, while retaining 81.8–94.4% susceptibility against overall CRAB (MIC$_{90}$=2 mg/L) – see Table 15 • In the subset of 80 CRAB isolates (13.6%) that did not carry acquired carbapenemases, cefiderocol inhibited 91.2% and 78.8% of isolates based on CLSI and FDA breakpoints, respectively
SENTRY Antimicrobial Surveillance Program (DeJonge et al 2025)[16]	US and Europe 2001–2022	29 ABC isolates carrying MBLs	• Broth microdilution • CLSI/FDA/EUCAST breakpoints	• MIC values for cefiderocol ranged from 0.06–16 µg/mL, with IMP-carrying isolates showing lower values compared with NDM-carrying isolates – see Figure 14 • According to CLSI, EUCAST, and FDA breakpoints, respectively, 82.8%, 69%, and 44.8% of the ABC isolates showed susceptibility to cefiderocol – see Table 16 – Most comparator antimicrobial agents showed lower susceptibilities (<30%), with minocycline and colistin being the only other active agents – see Table 16 • Additional β-lactamases were commonly detected in NDM-carrying ABC isolates, but no correlation between this and cefiderocol MIC value could be determined

Abbreviations: ABC, *A. baumannii* complex; CLSI, Clinical and Laboratory Standards Institute; CR, carbapenem-resistant; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; IMP, imipenemase β-lactamase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; US, United States.

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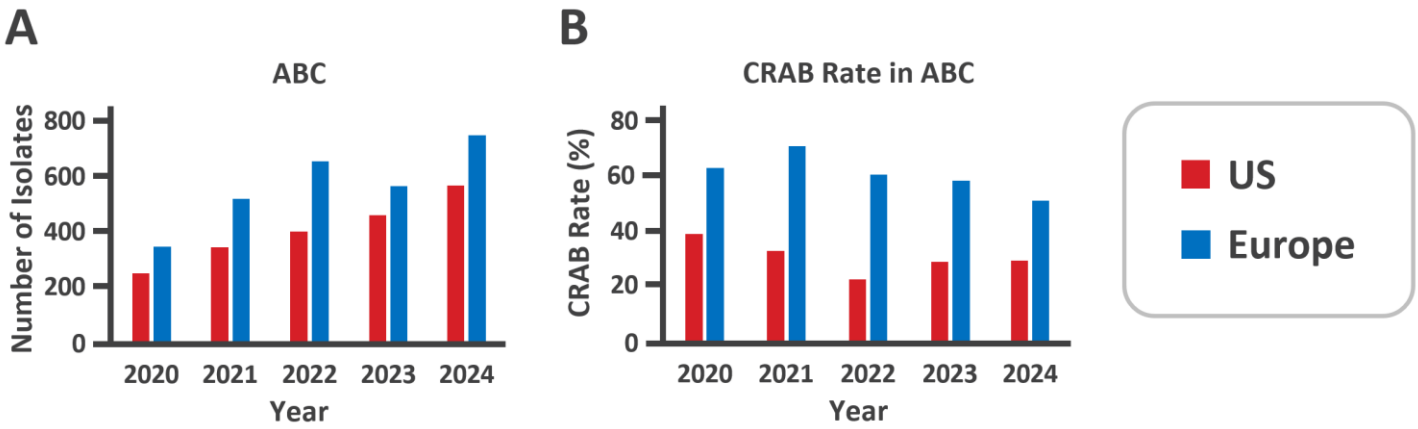
Table 14. List of Surveillance Studies (Cont.)[14–19]

Study	Collection Years and Countries	Number of Isolates	Susceptibility Testing and Interpretive Criteria	Results
Palavecino et al 2025[17]	US 2019–2024	159 CRAB isolates	• Broth microdilution • CLSI breakpoints	• 146 (91.8%) CRAB isolates were demonstrated to be susceptible to cefiderocol (with $MIC_{50/90}$ values of 0.5 and 2 mg/L) – $MIC_{50/90}$ values were also 0.5 and 2 mg/L among isolates positive for the bla_{OXA-23} gene (n=116), while $MIC_{50/90}$ values were 0.25 and 1 mg/L for isolates carrying the $bla_{OXA-24/40}$ gene (n=17)
Ymaña et al 2025[18]	Peru	95 CRAB isolates	• CLSI and FDA breakpoints	• Cefiderocol MICs ranged from 0.125–4 µg/mL ($MIC_{50/90}$ was 1/2 µg/mL) • A single CRAB isolate was defined as susceptible to cefiderocol as per CLSI criteria, but resistant by FDA criteria (MIC=4 µg/mL) • Using FDA criteria, a total of 21 CRAB isolates (22.1%) were defined as intermediate – see Table 17
Ballesté-Delpierre et al 2022[19]	Argentina, Azerbaijan, Croatia, Greece, Italy, Morocco, Mozambique, Peru, and Spain (collection year was not specified)	113 CR or MDR *A. baumannii* isolates	• Broth microdilution • CLSI breakpoints	• Susceptibility rates to cefiderocol and comparator antibiotics are shown in Table 18. The cefiderocol $MIC_{50/90}$ values were 0.5/>64 µg/mL, with an overall susceptibility rate of 79.6% • 67 (75.3%) of 89 meropenem-resistant *A. baumannii* isolates were susceptible to cefiderocol • 76 (76.8%) of 99 MDR *A. baumannii* isolates were susceptible to cefiderocol

Abbreviations: ABC, *A. baumannii* complex; CLSI, Clinical and Laboratory Standards Institute; CR, carbapenem-resistant; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; IMP, imipenemase β-lactamase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; US, United States.

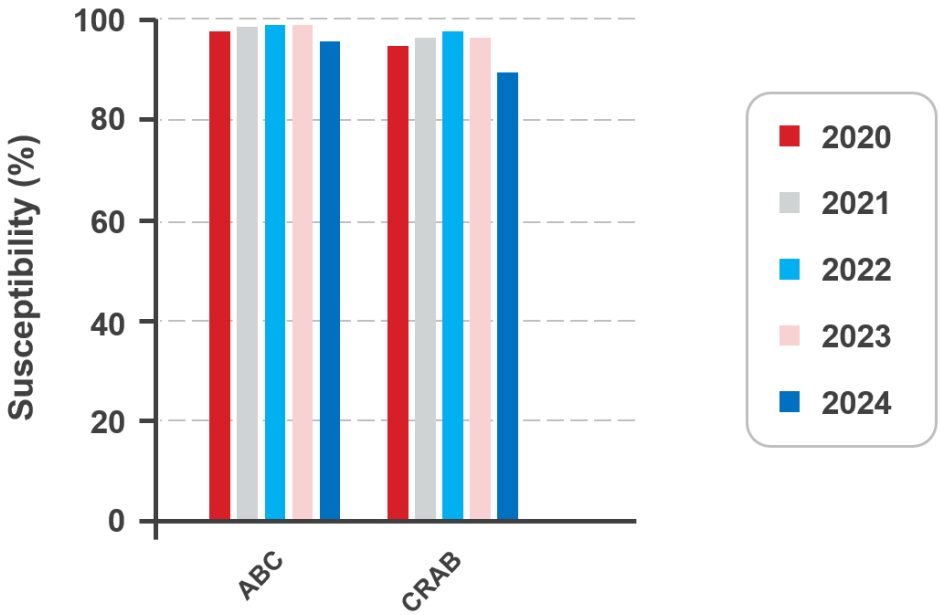
Surveillance Studies

Figure 9. Trends in the Number (US and Global) of (A) ABC Isolates (n=4806) and (B) CRAB Isolates from Over 5 Years of the SENTRY Surveillance Program (2020–2024)[14]



Abbreviations: ABC, *A. baumannii* complex; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; US, United States.
Figure adapted from Yamano et al. IDWeek. 2025.

Figure 10. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from US Hospitals during the SENTRY Surveillance Program (2020–2024)[14]

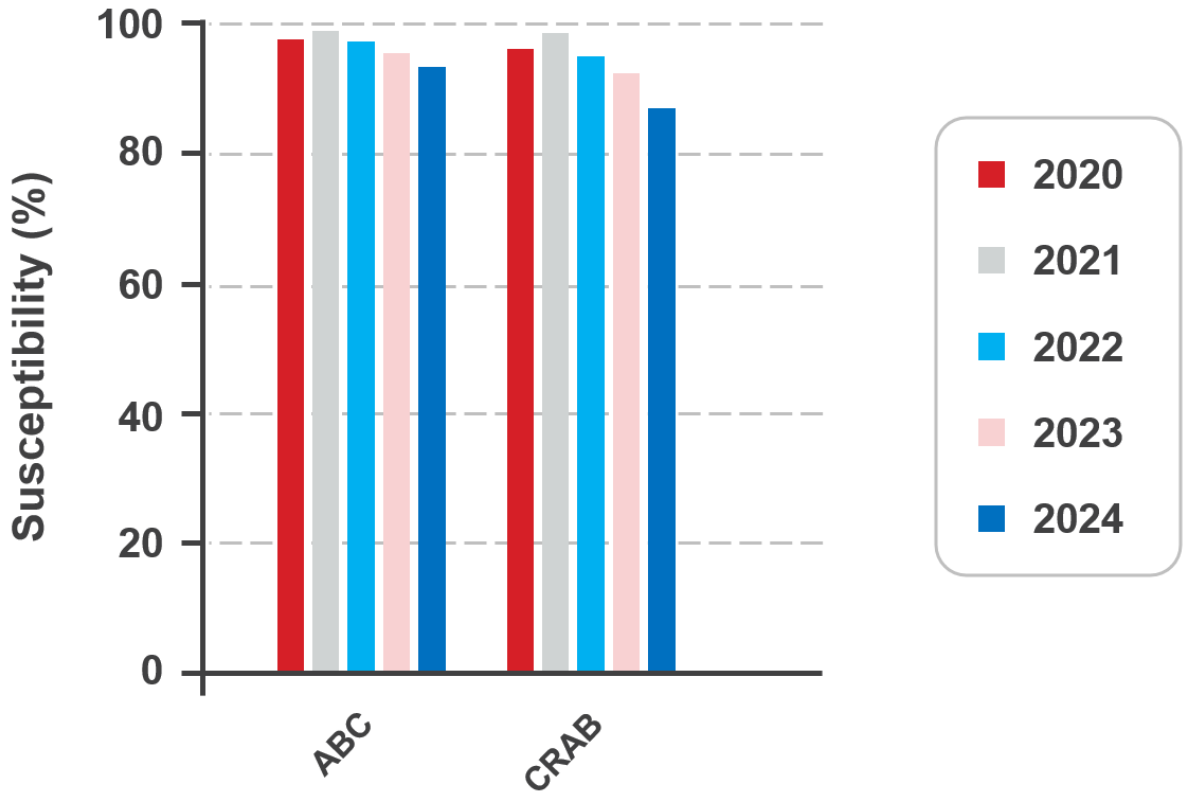


Abbreviations: ABC, *A. baumannii* complex; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; US, United States.
Figure adapted from Yamano et al. IDWeek. 2025.

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Surveillance Studies

Figure 11. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from European Hospitals during the SENTRY Surveillance Program (2020–2024)[14]



Abbreviations: ABC, *A. baumannii* complex; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex.
Figure adapted from Yamano et al. IDWeek. 2025.

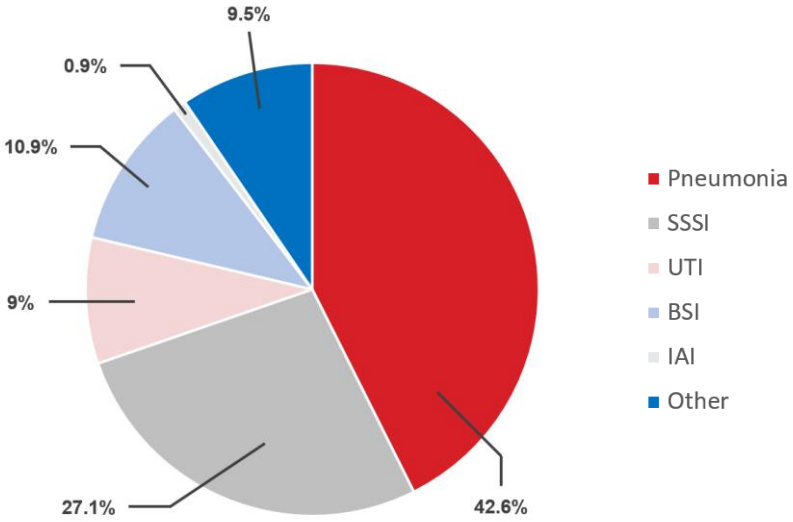
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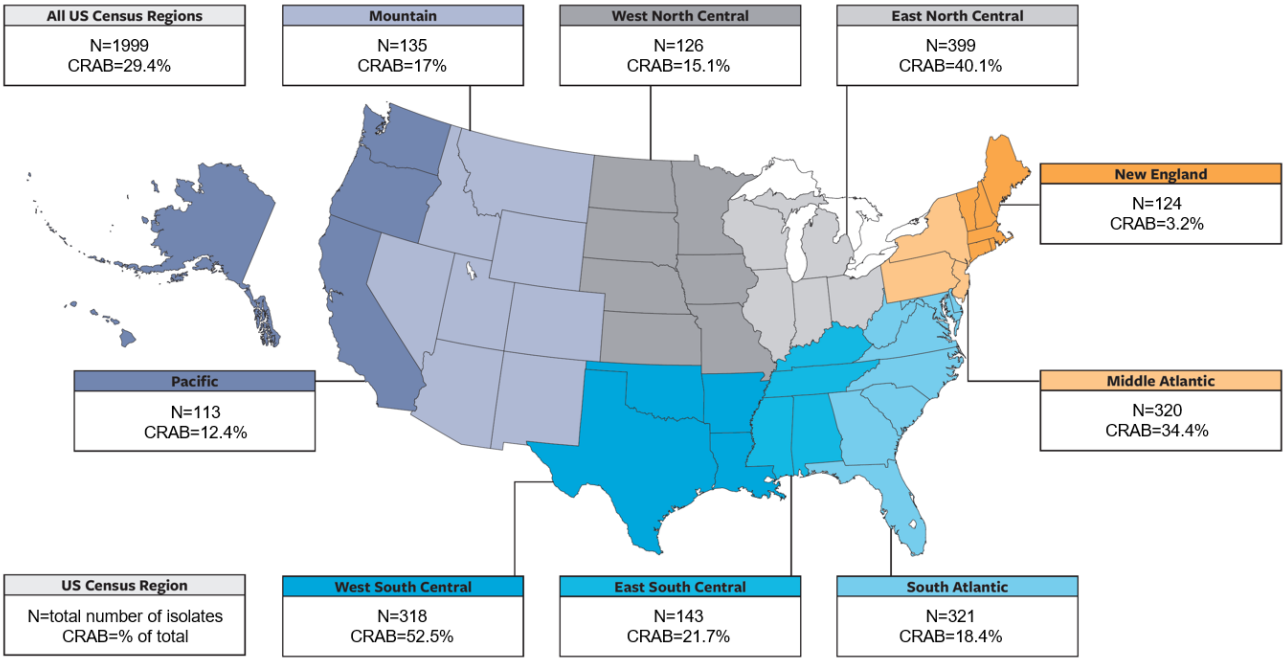
Surveillance Studies

Figure 12. Distribution of Infection Types caused by CRAB (US Isolates)[15]



Abbreviations: BSI, bloodstream infections; CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; IAI, intra-abdominal infections; SSSI, skin and skin structure infections; UTI, urinary tract infections.
Figure adapted from Mendes et al. IDWeek. 2025.

Figure 13. Distribution of CRAB (n=587) among US Census Regions[15]



Abbreviations: CRAB, carbapenem-resistant *A. baumannii*-calcoaceticus species complex; US, United States.
Figure adapted from Mendes et al. IDWeek. 2025.

Fetroja® – Activity Against Resistant *Acinetobacter* spp.

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Surveillance Studies

Table 15. Activity of Cefiderocol and BL–BLI Combinations against ABC and Resistant Subsets from the US[15]

Phenotype/Genotype[a] (Number Tested)	$MIC_{50/90}$ in mg/L (% Susceptible by CLSI/FDA Criteria)[b]					
	Cefiderocol	Imipenem–Relebactam	Meropenem	Ampicillin–Sulbactam	Ceftazidime	Colistin
All (1999)	0.12/1 (97.7/92.9)	0.25/>8 (72)	0.5/>32 (70.7)	4/64 (67.6)	8/>32 (66.8)	0.5/1 (96.5)
Carb-NS (587)	0.25/2 (94.4/81.8)	>8/>8 (4.8)	>32/>32 (0.2)	32/>64 (12.1)	>32/>32 (16.5)	0.5/1 (95.1)
Carbapenemase-positive (507)	0.25/2 (94.9/82.2)	>8/>8 (0.8)	>32/>32 (0)	32/>64 (4.3)	>32/>32 (18.3)	0.5/1 (95.1)
OXA-23 (301)	0.5/2 (95.3/81.4)	>8/>8 (0)	>32/>32 (0)	32/>64 (1)	>32/>32 (13.6)	0.5/1 (93.7)
OXA-24 (178)	0.25/2 (97.8/88.2)	>8/>8 (2.2)	>32/>32 (0)	32/>64 (9.6)	32/>32 (27)	0.5/0.5 (97.7)
Other[c] (28)	0.5/64 (71.4/53.6)	>8/>8 (0)	>32/>32 (0)	64/>64 (7.1)	>32/>32 (14.3)	0.5/1 (92.9)
Carbapenemase-negative[d] (80)	0.25/4 (91.2/78.8)	8/>8 (30)	16/32 (1.2)	8/64 (61.2)	>32/>32 (5)	0.5/1 (95)

Abbreviations: ABC, *A. baumannii* complex; BL–BLI, β-lactam–β-lactamase inhibitor; Carb-NS, carbapenem-nonsusceptible; CLSI, Clinical and Laboratory Standards Institute; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; OXA, oxacillinase; US, United States.

[a]Carb-NS defined as isolates NS to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L).

[b]Cefiderocol MIC results were interpreted according to the CLSI/FDA breakpoints, whereas comparator agent MIC results were interpreted based on the FDA susceptible breakpoint for imipenem–relebactam, and CLSI criteria for other agents, including intermediate results provided by the respective colistin breakpoint.

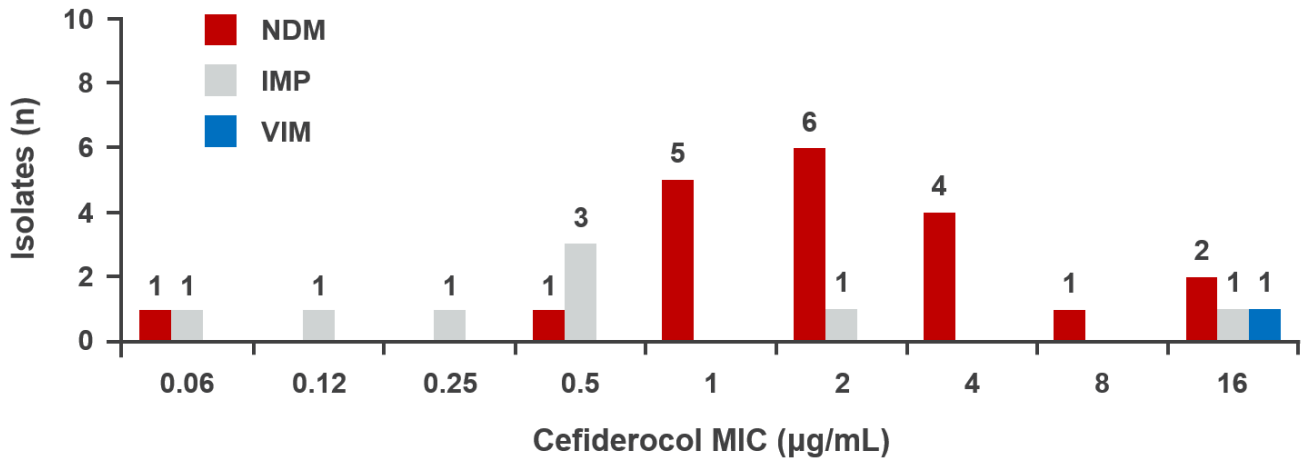
[c]Includes bla_{NDM-1} (1), bla_{NDM-1} + bla_{OXA-23} (8), bla_{NDM-1} + bla_{OXA-58} (1), bla_{NDM-5} + bla_{OXA-23} (1), $bla_{OXA-134-like}$ (5), bla_{OXA-23} + bla_{OXA-24} (12).

[d]Acquired carbapenemase genes not detected.

Table adapted from Mendes et al. IDWeek. 2025.

Surveillance Studies

Figure 14. Cefiderocol MIC Distribution of MBL-producing ABC US and Global Isolates (n=29)[16]



Abbreviations: ABC, *A. baumannii* complex; IMP, imipenemase metallo-β-lactamase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.
Table adapted from DeJonge et al. IDWeek. 2025.

Surveillance Studies

Table 16. Antimicrobial Activity of Cefiderocol and Comparator Agents Tested against MBL-producing ABC US and Global Isolates Collected during the SENTRY Antimicrobial Surveillance Program (n=29)[16]

Antimicrobial Agent	MIC (g/mL)			CLSI[a]			EUCAST[a]			FDA[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R	%S	%I	%R
Cefiderocol	2	16	0.06 to 16	82.8	3.4	13.8	69[b]		31[b]	44.8	24.1	31
Sulbactam–durlobactam	>32	>32	2 to >32	27.6	0	72.4				27.6	0	72.4
Ampicillin–sulbactam	>64	>64	4 to >64	10.3	0	89.7				10.3	0	89.7
Imipenem–relebactam	>16	>16	1 to >16							3.4	0	96.6
Meropenem	>32	>32	4 to >32	0	3.4	96.6	0	3.4	96.6	0	3.4	96.6
Imipenem	>8	>8	>8	0	0	100	0	0	100	0	0	100
Ceftazidime	>32	>32	>32	0	0	100				0	0	100
Minocycline	2	32	0.12 to 32	82.8	0	17.2				82.8	0	17.2
Colistin	0.25	0.5	0.12 to 8		96.6	3.4	96.6		3.4			

Abbreviations: ABC, *A. baumannii* complex; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; I, intermediate; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; R, resistant; S, susceptible; US, United States.

[a]Criteria as published by CLSI (2024), EUCAST (2024), and FDA (2024).

[b]There are insufficient clinical data to determine a clinical breakpoint, but isolates with MIC values >2 µg/mL will likely be resistant.

Table adapted from DeJonge et al. IDWeek. 2025.

Surveillance Studies

Table 17. Cefiderocol MIC Distribution for the 95 CRAB Isolates[18]

	Number	MIC_{50}	MIC_{90}	Cefiderocol MIC (µg/mL)					
				0.125	0.25	0.5	1	2	4
CRAB	95	1	2	4	7	19	43	21	1
FDA criteria				S	S	S	S	I	R
CLSI criteria				S	S	S	S	S	S

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; CRAB, carbapenem-resistant *A. baumannii*; FDA, US Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; MIC_{50}, minimum concentration that inhibits 50% of isolates; MIC_{90}, minimum concentration that inhibits 90% of isolates; R, resistant; S, susceptible; US, United States.
Table adapted from Ymaña et al. *Microbiol Spectr*. 2025.

Figure 10. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from US Hospitals during the SENTRY Surveillance Program (2020–2024)[14]

Figure 11. Susceptibility to Cefiderocol by Year of ABC vs CRAB Isolates Collected from European Hospitals during the SENTRY Surveillance Program (2020–2024)[14]

Figure 12. Distribution of Infection Types caused by CRAB (US Isolates)[15]

Figure 13. Distribution of CRAB (n=587) among US Census Regions[15]

Surveillance Studies

Table 18. MIC Values for Cefiderocol and Comparator Agents Tested against a Collection of 113 *A. baumannii* Clinical Isolates[19]

Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	%S	%I	%R
	µg/mL			n (%)		
Cefiderocol	0.5	>64	≤0.03 to >64	90 (79.6)	1 (0.88)	23 (20.35)
Cefepime	>16	>16	≤0.125 to >16	15 (13.27)	4 (3.54)	94 (83.18)
Ceftazidime–avibactam[a]	>16	>16	≤0.125 to >16	NA	NA	NA
Meropenem	>16	>16	0.125 to >16	22 (19.47)	2 (1.77)	89 (78.76)
Meropenem–vaborbactam[a]	>16	>16	0.125 to >16	NA	NA	NA
Imipenem–relebactam[a]	>16	>16	0.125 to >16	NA	NA	NA
Ampicillin–sulbactam	32	64	≤2 to >64	24 (21.24)	20 (17.7)	69 (61.06)
Ciprofloxacin	>8	>8	≤0.125 to >8	12 (10.62)	0 (0)	101 (89.38)
Minocycline	4	>8	≤0.25 to >8	65 (57.52)	21 (18.58)	27 (23.89)
Tigecycline[a]	2	4	≤0.125 to >4	NA	NA	NA
Trimethoprim–sulfamethoxazole	>8	>8	≤0.25 to >8	19 (16.81)	NA	94 (83.18)
Colistin[b]	0.5	8	≤0.25 to >8	NA	99 (87.61)	14 (12.39)

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; I, intermediate; $MIC_{50/90}$, minimum concentration that inhibits 50%/90% of the isolates; NA, not available; R, resistant; S, susceptible.
[a]No breakpoints available at CLSI.
[b]CLSI update released in April 2021 removed the susceptible breakpoint for colistin; only intermediate (≤2 µg/mL) and resistant (≥4 µg/mL) breakpoints for colistin are available.
Table adapted from Ballesté-Delpierre et al. *Antibiotics (Basel)*. 2022

Figure 12. Distribution of Infection Types caused by CRAB (US Isolates)[15]

Figure 13. Distribution of CRAB (n=587) among US Census Regions[15]

Relevant Prescribing Information

Fetroja is indicated in patients ≥18 years for the treatment of:[21]

- Complicated UTI, including pyelonephritis caused by the following susceptible Gram-negative microorganisms:
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
  - *Pseudomonas aeruginosa*
  - *Enterobacter cloacae* complex

- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms:
  - *Acinetobacter baumannii* complex
  - *Escherichia coli*
  - *Enterobacter cloacae* complex
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*

Fetroja is contraindicated in:[21]

- Patients with a known history of severe hypersensitivity to cefiderocol or other β-lactam antibacterial drugs, or any other component of Fetroja.

Please read the attached Fetroja **Full Prescribing Information**.

Literature Search

As of June 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) has identified additional relevant references regarding the use of cefiderocol in treating resistant *Acinetobacter* spp. For your review, these references are listed in the bibliography that follows:

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Literature Search (Cont.)

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Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from them should not be considered all-inclusive.

Abbreviations

ABC	*A. baumannii* complex	CR-Micro-ITT	CR microbiological ITT
ACM	all-cause mortality	cUTI	complicated urinary tract infection
ADC	*Acinetobacter*-derived cephalosporinase	CZ	Czechia
ADR	adverse drug reaction	DE	Germany
AE	adverse event	DTR	difficult-to-treat resistant
aHR	adjusted hazard ratio	EAP	Early Access Program
AKI	acute kidney injury	EOS	end of study
AmpC	chromosomal cephalosporinase	EOT	end of treatment
AR	Argentina	EUCAST	European Committee on Antimicrobial Susceptibility Testing
BAT	best-available therapy	FDA	US Food and Drug Administration
BE	Belgium	g	grams
BL	β-lactamase	GNA	Gram-negative antibiotic
BL–BLI	β-lactam–β-lactamase inhibitor	GNBI	Gram-negative bacterial infection
BR	Brazil	GR	Greece
BSI	bloodstream infection	h	hours
CAMHB	cation-adjusted Mueller–Hinton broth	HABP	hospital-acquired bacterial pneumonia
Carb-NS	carbapenem-nonsusceptible	HCABP	healthcare-associated bacterial pneumonia
CCI	Charlson comorbidity index	HR	hazard ratio
CDC	Centers for Disease Control and Prevention	I	intermediate
CI	confidence interval	IAI	intra-abdominal infection
CKD	chronic kidney disease	ICU	intensive care unit
CLSI	Clinical and Laboratory Standards Institute	ID-CAMHB	iron-depleted cation-adjusted Mueller-Hinton broth
COPD	chronic obstructive pulmonary disease	IL	Israel
COVID-19	coronavirus disease 2019	IMP	imipenemase metallo-β-lactamase
CR	carbapenem-resistant	IMV	invasive mechanical ventilation
CRAB	carbapenem-resistant *A. baumannii*	IN	India
CrCl	creatinine clearance	IPTW	inverse-probability treatment weighted

Abbreviations (Cont.)

IQR	interquartile range	PS	propensity score
IU	international unit	q8h	every 8 hours
IV	intravenous	q12h	every 12 hours
LFT	liver function test	R	resistant
M	million	RO	Romania
MBL	metallo-β-lactamase	RTI	respiratory tract infection
MDR	multidrug-resistant	S	susceptible
MIC	minimum inhibitory concentration	SOFA	sequential organ failure assessment
$MIC_{50/90}$	minimum concentration that inhibits 50%/90% of the isolates	spp.	species
mITT	modified intention-to-treat	SSSI	skin and skin structure infection
NA	not applicable	TEM	Temoneira
NDM	New Delhi metallo-β-lactamase	TOC	test of cure
NGS	next-generation sequencing	TR	Turkey
NHSN	National Healthcare Safety Network	ULN	upper limit of normal
NR	not reported	US	United States
NS	nonsusceptible	UTI	urinary tract infection
OR	odds ratio	VABP	ventilator-associated bacterial pneumonia
OXA	oxacillinase	VAP	ventilator-associated pneumonia
PCR	polymerase chain reaction	VIM	Verona integron-encoded metallo-β-lactamase
PDR	pandrug resistant	WGS	whole genome sequencing
PIHP	pneumonia in hospitalized patients	XDR	extensively drug resistant
PN	peripheral neuropathy		

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ENCLOSURE

Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.