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Summary

- **CREDIBLE-CR**, a prospective, randomized, open-label, multicenter, parallel-group, Phase 3 trial assessed the efficacy and safety of cefiderocol to BAT in patients with HABP, VABP, HCABP, BSI, sepsis, or cUTIs caused by CR Gram-negative pathogens, with no pre-specified statistical hypothesis. Cefiderocol 2 g q8h over a 3 h IV infusion or IV BAT was administered for 7–14 days, which could be extended up to 21 days at the discretion of the investigator[1]
- In the CR-Micro-ITT population, clinical cure at TOC was achieved by 20 (50%) and 10 (53%) patients with HABP/VABP/HCABP, and by 10 (43%) and 6 (43%) patients with BSI/sepsis in the cefiderocol and BAT groups, respectively[1]
- In the CR-Micro-ITT population, microbiological eradication at TOC was achieved by 9 (53%) and 1 (20%) patients with cUTI in the cefiderocol and BAT groups, respectively[1]
- In the cefiderocol arm, a total of 12 isolates from 12 patients experienced a ≥4-fold increase in MIC from baseline. Of these 12 isolates, there were 3 that had a MIC that exceeded 4 µg/mL (2 *Acinetobacter baumannii*, 1 *Pseudomonas aeruginosa*). In the BAT group, there were 6 isolates from 5 patients with a ≥4-fold increase in baseline MIC to the active agents, all of which met the criteria for resistance[1–3]
- TEAEs were reported in a total of 92 of 101 patients (91%) in the cefiderocol group and 47 of 49 patients (96%) in the BAT group[1]
- ACM through EOS was higher in the cefiderocol group compared to BAT (34 [34%] vs 9 [18%], respectively)[1]
  - An evaluation of the study deaths by an external, independent, masked adjudication committee found that approximately 50% of deaths were attributable to causes other than the underlying Gram-negative infection in both treatment groups. In addition, none of the deaths in the cefiderocol group were considered drug-related (eg, drug toxicity)[1]
  - Logistic regression analysis for Day 28 ACM did not identify a baseline parameter that explained the mortality difference[1]
  - *Acinetobacter* spp. infections may have impacted the ACM difference. The ACM was higher in the cefiderocol group than the BAT group for patients with polymicrobial *P. aeruginosa* and *Acinetobacter* spp. infections, but was identical in patients with only *P. aeruginosa* infections[1]
  - Of the patients with *Acinetobacter* spp. infections, the incidence of moderate-severe renal impairment, ongoing shock or shock within 31 days prior to randomization, or ICU at randomization was higher at baseline in the cefiderocol group than the BAT group[1]

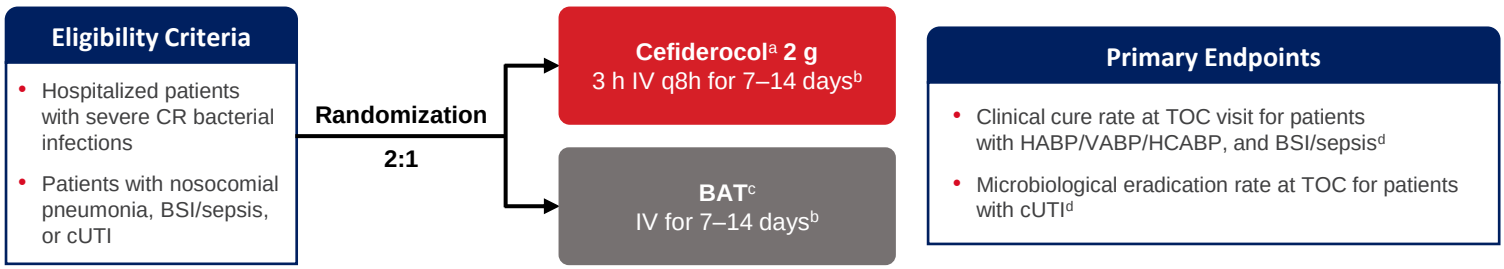
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CREDIBLE-CR: Methods

CREDIBLE-CR (NCT02714595) was a Phase 3, prospective, open-label, multicenter, randomized, parallel-group, descriptive study that assessed the efficacy and safety of cefiderocol and BAT in hospitalized patients with severe CR bacterial infections.[1]

- CREDIBLE-CR was designed as a descriptive study with no hypothesis testing or formal inferential analyses
- The CREDIBLE-CR study design is shown below (**Figure 1**)

Figure 1. CREDIBLE-CR Study Design[1]



Abbreviations: BAT, best available therapy; BSI, bloodstream infection; CR, carbapenem-resistant; cUTI, complicated urinary tract infection; IV, intravenous; g, grams; h, hours; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; q8h, 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.

- A total of 152 patients were randomly assigned to cefiderocol or BAT, of whom 150 patients (n=101 cefiderocol; n=49 BAT) received treatment (ITT and safety population)

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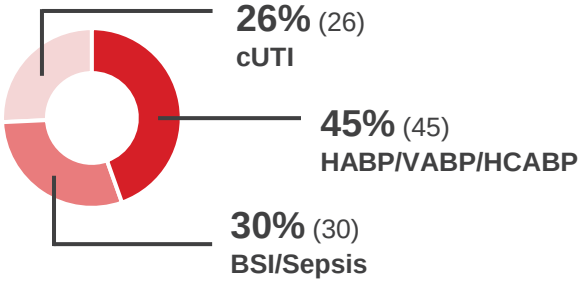
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CREDIBLE-CR: Results

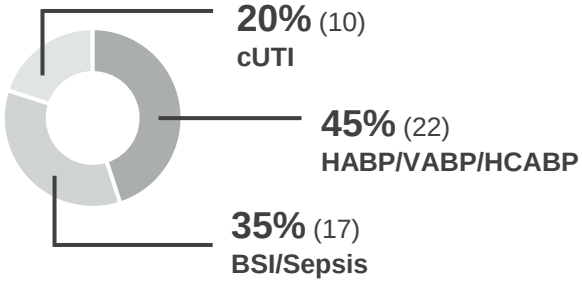
RESULTS[1]

In the ITT population, in the cefiderocol and BAT groups, the proportion of patients had the following infections:

Proportion of Infection Sites in the Cefiderocol Group (n=101)



Proportion of Infection Sites in the BAT Group (n=49)



- A numerically higher proportion of patients in the cefiderocol group compared with the BAT group were aged ≥65 years (63% vs 45%)
- Moderate renal impairment (CrCl 30–50 mL/min) was seen in 23% vs 16% of patients in the cefiderocol and BAT groups, respectively, while severe renal impairment (CrCl <30 mL/min) was seen in 20% vs 14% of patients in the cefiderocol and BAT groups, respectively
- The percentage of patients who were in the ICU at randomization (56% vs 43%) was numerically higher in the cefiderocol group compared with the BAT group
- The full baseline demographics and clinical characteristics of patients treated with cefiderocol and BAT in the ITT/safety population are shown in **Appendix Table 1**
- In the primary efficacy population (CR-Micro-ITT), 66 of 80 patients (83%) received cefiderocol monotherapy, and 25 of 38 patients (66%) in the BAT group received a colistin-based regimen at Days 1 and 2

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CREDIBLE-CR: Results (Cont.)

EFFICACY[1]

- Overall, clinical cure at TOC was achieved by 42 (53%) patients and 19 (50%) patients in the cefiderocol and BAT groups, respectively (**Table 1**)
- Clinical cure at TOC was achieved by 20 (50%) and 10 (53%) patients with HABP/VABP/HCABP, and 10 (43%) and 6 (43%) patients with BSI/sepsis in the cefiderocol and BAT groups, respectively
- Microbiological eradication was achieved by 9 (53%) and 1 (20%) patients with cUTI in the cefiderocol and BAT groups, respectively
- The most frequently isolated CR pathogens were *A. baumannii*, *P. aeruginosa*, and *Klebsiella pneumoniae* in both treatment groups
- The clinical and microbiological outcomes by pathogen at TOC overall are shown in **Table 2**
- The entire distribution of Gram-negative pathogens isolated at baseline in the CR-Micro-ITT population is included in **Appendix Table 2**

Table 1. Clinical and Microbiological Outcomes by Infection Site and by Visit (CR-Micro-ITT Population)[1]

	Overall		HABP/VABP/HCABP		BSI/Sepsis		cUTI	
	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)
EOT[a]								
Clinical cure	66	58	60	63	70	50	77	60
Clinical failure	25	40	33		26	50	6	20
Eradication	48	26				29	71	20
Persistence	20	26				7	0	0
TOC[b]								
Clinical cure	53	50				43	71	60
Clinical failure	34	37				50	12	20
Eradication	31	24				29	53	20
Persistence	20	26				14	29	20
FU[c]								
Clinical cure	48	34	50		39	29	53	60
Clinical failure	34	37	40	32	39	50	12	20
Eradication	26	18	20	16	26	21	41	20
Persistence	20	26	20	37	13	14	29	20

Table 2. Overall Clinical and Microbiological Outcomes by Key Baseline CR Pathogen at TOC Visit (CR-Micro-ITT Population)[2]

	Cefiderocol (n=80) n/N (%)	BAT (n=38) n/N (%)
Clinical cure		
A. baumannii	16/37 (43)	9/17 (53)
P. aeruginosa	7/12 (58)	5/10 (50)
K. pneumoniae		6/12 (50)
S. maltophilia		Not applicable
Clinical failure		
A. baumannii		6/17 (35)
P. aeruginosa		4/10 (40)
K. pneumoniae		4/12 (33)
S. maltophilia		Not applicable
Eradication		
A. baumannii		5/17 (29)
P. aeruginosa		2/10 (20)
K. pneumoniae		3/12 (25)
S. maltophilia		Not applicable
Persistence		
A. baumannii	5/37 (14)	4/17 (24)
P. aeruginosa	4/12 (33)	2/10 (20)
K. pneumoniae	4/27 (15)	4/12 (33)
S. maltophilia	5/5 isolates were indeterminate	Not applicable

CREDIBLE-CR: Results (Cont.)

Table 1. Clinical and Microbiological Outcomes by Infection Site and by Visit (CR-Micro-ITT Population)[1]

	Overall		HABP/VABP/HCABP		BSI/Sepsis		cUTI	
	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)	Cefiderocol (%)	BAT (%)
EOT[a]								
Clinical cure	66	58	60	63	70	50	77	60
Clinical failure	25	40	33	37	26	50	6	20
Eradication	48	26	30	26	61	29	71	20
Persistence	20	26	38	47	4	7	0	0
TOC[b]								
Clinical cure	53	50	50	53	43	43	71	60
Clinical failure	34	37	40	32	39	50	12	20
Eradication	31	24	23	21	30	29	53	20
Persistence	20	26	20	37	13	14	29	20
FU[c]								
Clinical cure	48	34	50	32	39	29	53	60
Clinical failure	34	37	40	32	39	50	12	20
Eradication	26	18	20	16	26	21	41	20
Persistence	20	26	20	37	13	14	29	20

Abbreviations: BAT, best available therapy; BSI, bloodstream infection; CR-Micro-ITT, carbapenem-resistant microbiological intent-to-treat; cUTI, complicated urinary tract infection; EOT, end of treatment; FU, follow-up; HABP, hospital acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.

[a]EOT defined as last day of study treatment.

[b]TOC defined as EOT + 7 days (±2 days).

[c]FU defined as EOT + 14 days (±3 days).

Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021.

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CREDIBLE-CR: Results (Cont.)

Table 2. Overall Clinical and Microbiological Outcomes by Key Baseline CR Pathogen at TOC Visit (CR-Micro-ITT Population)[2]

	Cefiderocol (n=80) n/N (%)	BAT (n=38) n/N (%)
Clinical cure		
A. baumannii	16/37 (43)	9/17 (53)
P. aeruginosa	7/12 (58)	5/10 (50)
K. pneumoniae	18/27 (67)	6/12 (50)
S. maltophilia	0/5 (0%)	Not applicable
Clinical failure		
A. baumannii	17/37 (46)	6/17 (35)
P. aeruginosa	3/12 (25)	4/10 (40)
K. pneumoniae	5/27 (19)	4/12 (33)
S. maltophilia	3/5 (60%)	Not applicable
Eradication		
A. baumannii	10/37 (27)	5/17 (29)
P. aeruginosa	1/12 (8)	2/10 (20)
K. pneumoniae	13/27 (48)	3/12 (25)
S. maltophilia	5/5 isolates were indeterminate	Not applicable
Persistence		
A. baumannii	5/37 (14)	4/17 (24)
P. aeruginosa	4/12 (33)	2/10 (20)
K. pneumoniae	4/27 (15)	4/12 (33)
S. maltophilia	5/5 isolates were indeterminate	Not applicable

Abbreviations: BAT, best available therapy; CR, carbapenem-resistant; Micro-ITT, microbiological intent-to-treat; TOC, test of cure.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021 (Supplementary Appendix).

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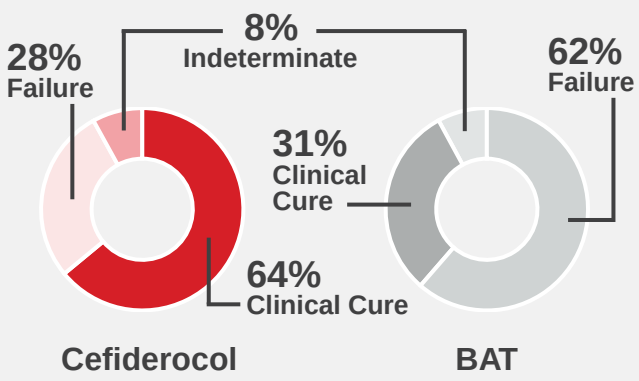
CREDIBLE-CR: Results (Cont.)

OUTCOMES BASED ON BACTEREMIA STATUS AT BASELINE[4]

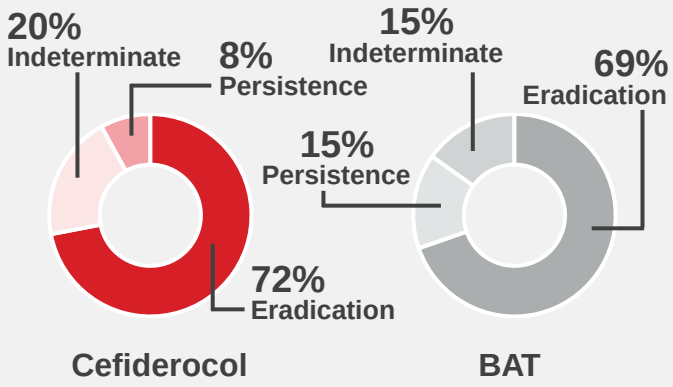
- In a post hoc analysis of a subset of patients with Gram-negative bacteremia (cefiderocol [n=25] and BAT [n=13]), the following were seen at EA and TOC:

Early Assessment

Clinical Outcomes

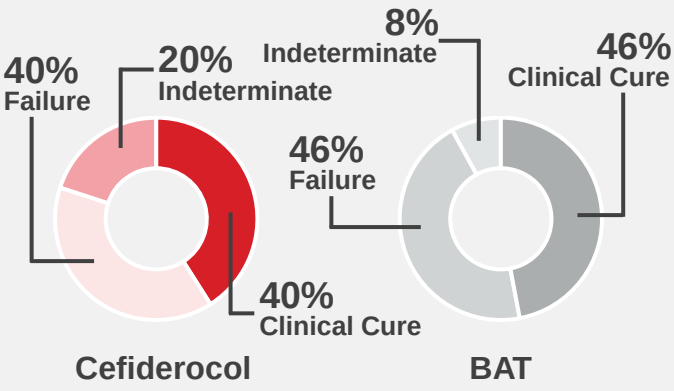


Bacteremia Outcomes

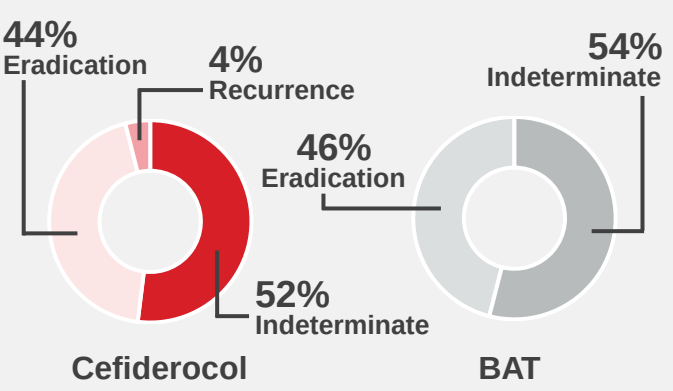


Test of Cure

Clinical Outcomes



Bacteremia Outcomes



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CREDIBLE-CR: Results (Cont.)

MOLECULAR CHARACTERIZATION

Pathogens with available molecular characterization from patients treated with cefiderocol were as follows:



Among 42 Enterobacterales[5–7]

- 10 isolates expressed MBLs (NDM, VIM, IMP)
- 14 isolates were KPC producers
- 7 isolates were OXA-48 producing *K. pneumoniae*[6]
- 14 isolates did not possess carbapenemase genes
- 15 isolates were porin channel OmpK35/36 deficient[7]



Among 17 *P. aeruginosa* isolates[5]

- 4 isolates expressed MBLs (NDM, VIM, IMP)
- 13 isolates did not possess carbapenemase genes
- 10 isolates were porin channel oprD deficient



Among 39 *A. baumannii* isolates[5]

- 2 isolates expressed MBLs (NDM)
- 36 isolates were OXA-23/24 or OXA-40 producers
- 2 isolates did not possess carbapenemase genes

- The clinical and microbiological outcomes at the TOC for cefiderocol and BAT in Gram-negative pathogens based on molecular characterization are shown in Appendix Table 3 and Appendix Table 4[5,8]

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CREDIBLE-CR: Results (Cont.)

MONITORING FOR THE DEVELOPMENT OF NON-SUSCEPTIBILITY[2,9]

- There were 9 isolates that showed an increase in cefiderocol MIC ≥4-fold from baseline, comprising (**Appendix Table 5**):
  - *A. baumannii* (n=3)
  - *P. aeruginosa* (n=3)
  - *K. pneumoniae* (n=2)
  - *S. maltophilia* (n=1)
- In the BAT arm, 6 isolates had an increase in MIC ≥4-fold to the antibiotics used for BAT, all of which met criteria for resistance
- The increase in median MIC from baseline ranged from 4- to 128-fold (**Appendix Table 6**)

CREDIBLE-CR: Results (Cont.)

SAFETY[1,2]

- The most common AEs (≥10%) reported for either cefiderocol or BAT were diarrhea, pyrexia, septic shock, vomiting, decubitus ulcer, and hypokalemia
- The AEs reported more frequently (≥5% difference between the treatment groups) in the cefiderocol group compared to the BAT group were diarrhea, AST increases, pleural effusion, pneumonia, ALT increases, and chest pain (majority of cases were considered non-cardiovascular in nature and not related to cefiderocol)
- The AEs reported more frequently (≥5% difference between the treatment groups) in the BAT group compared to the cefiderocol group were hypokalemia, hyperkalemia, rash and depression
- Liver-related TEAEs including liver enzyme increases or clotting abnormalities occurred more frequently in the cefiderocol group (30 [30%]) than in the BAT group (7 [14%]); however, none of the cases met the clinical and biochemical criteria for Hy's law or drug-induced liver injury
- The overall safety of cefiderocol and BAT is shown in **Table 3**

Table 3. Safety Summary in CREDIBLE-CR Study (Safety Population)[1]

	Cefiderocol (N=101)	BAT (N=49)
Patients with TEAEs	92 (91%)	47 (96%)
Patients with treatment-related AEs	15%)	11 (22%)
Patients discontinuing due to TEAEs	0%)	3 (6%)
Patients discontinuing due to treatment-related AE	3%)	2 (4%)
Patients with treatment-emergent SAEs	0 (50%)	23 (47%)
Patients with treatment-related SAEs	1 (1%)	5 (10%)
TEAEs leading to death[a]	34 (34%)	9 (18%)

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CREDIBLE-CR: Results (Cont.)

Table 3. Safety Summary in CREDIBLE-CR Study (Safety Population)[1]

	Cefiderocol (N=101)	BAT (N=49)
Patients with TEAEs	92 (91%)	47 (96%)
Patients with treatment-related AEs	15 (15%)	11 (22%)
Patients discontinuing due to TEAEs	10 (10%)	3 (6%)
Patients discontinuing due to treatment-related AEs	3 (3%)	2 (4%)
Patients with treatment-emergent SAEs	50 (50%)	23 (47%)
Patients with treatment-related SAEs	1 (1%)	5 (10%)
TEAEs leading to death[a]	34 (34%)	9 (18%)

Abbreviations: AE, adverse event; BAT, best available therapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Patients could have experienced ≥1 SAE that led to death.
Data expressed as n (%).
AEs that started after the first dose of the study drug and up to end of study visit were defined as treatment emergent.
A patient could have ≥2 AEs but would be counted only once within a System Organ Class category.
1 patient who received cefiderocol after completion of BAT is included in BAT arm in this table.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021.

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CREDIBLE-CR: Results (Cont.)

MORTALITY[1,2,7]

- ACM through EOS was higher in the cefiderocol group compared to BAT (34 [34%] vs 9 [18%], respectively) (**Table 4**, **Figure 2**). None of the deaths were considered to be related to cefiderocol (eg, drug toxicity)
- When comparing the individual clinical diagnoses at 3 timepoints throughout the study, mortality was higher in patients treated with cefiderocol compared to BAT for HABP/VABP/HCABP and BSI/sepsis, while mortality was lower for cUTI (**Figure 3**)
- Post hoc analyses of the mortality difference as requested for regulatory review (including mortality at Day 49 (21 days of treatment plus 28 days of follow up) is described in **Table 5**
- A post hoc logistic regression analysis for Day 28 ACM did not identify a baseline parameter that explained the mortality difference
- *Acinetobacter* spp. infections may have impacted the ACM difference. The ACM was higher in the cefiderocol group than the BAT group for patients with polymicrobial *P. aeruginosa* and *Acinetobacter* spp. infections but was identical in patients with only *P. aeruginosa* infections (**Table 6**)
- Of the patients with *Acinetobacter* spp. infections, the incidence of CrCl <50 mL/min (33% vs 18%), ongoing shock (19% vs 6%), shock within 31 days prior to randomization (26% vs 6%), or ICU at randomization (81% vs 47%) was higher at baseline in the cefiderocol group than the BAT group, respectively

CREDIBLE-CR: Results (Cont.)

Table 4. ACM in the CREDIBLE-CR Study (Safety Population)[1]

	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
14-day mortality	19 (19%)	6 (12%)
28-day mortality	25 (25%)	9 (18%)
EOS[a]	34 (34%)	9 (18%)

Abbreviations: ACM, all-cause mortality; BAT, best available therapy; EOS, end of study; EOT, end of treatment.
[a]The additional deaths reported spontaneously after the study ended (2 patients in the cefiderocol group and 5 patients in the BAT group) were not included in this table.
ACM through EOS was defined as deaths that occurred through the EOS visit (EOT + 28 [±3] days) and fatal outcomes of SAEs with an onset before or on the EOS visit (followed until resolution, stabilization, the subject was lost to follow-up, or the outcome was fatal).
Percentage was calculated using N as the denominator, where n is the number of patients who had the specified clinical diagnosis and known vital status at each time point.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021.

Table 5. ACM (Safety Population) with Treatment Difference and 95% CI in Post Hoc Analyses[2]

	Cefiderocol (N=101)	BAT (N=49)	Treatment Difference	95% CI
Day 28[a,b]	25 (25%)	9 (18%)	6.4%	–8.6 to 19.2
EOS[b]	34 (34%)	9 (18%)	15.3%	–0.2 to 28.6
Day 49[a]	34 (34%)	10 (20%)	13.3%	–2.5 to 26.9

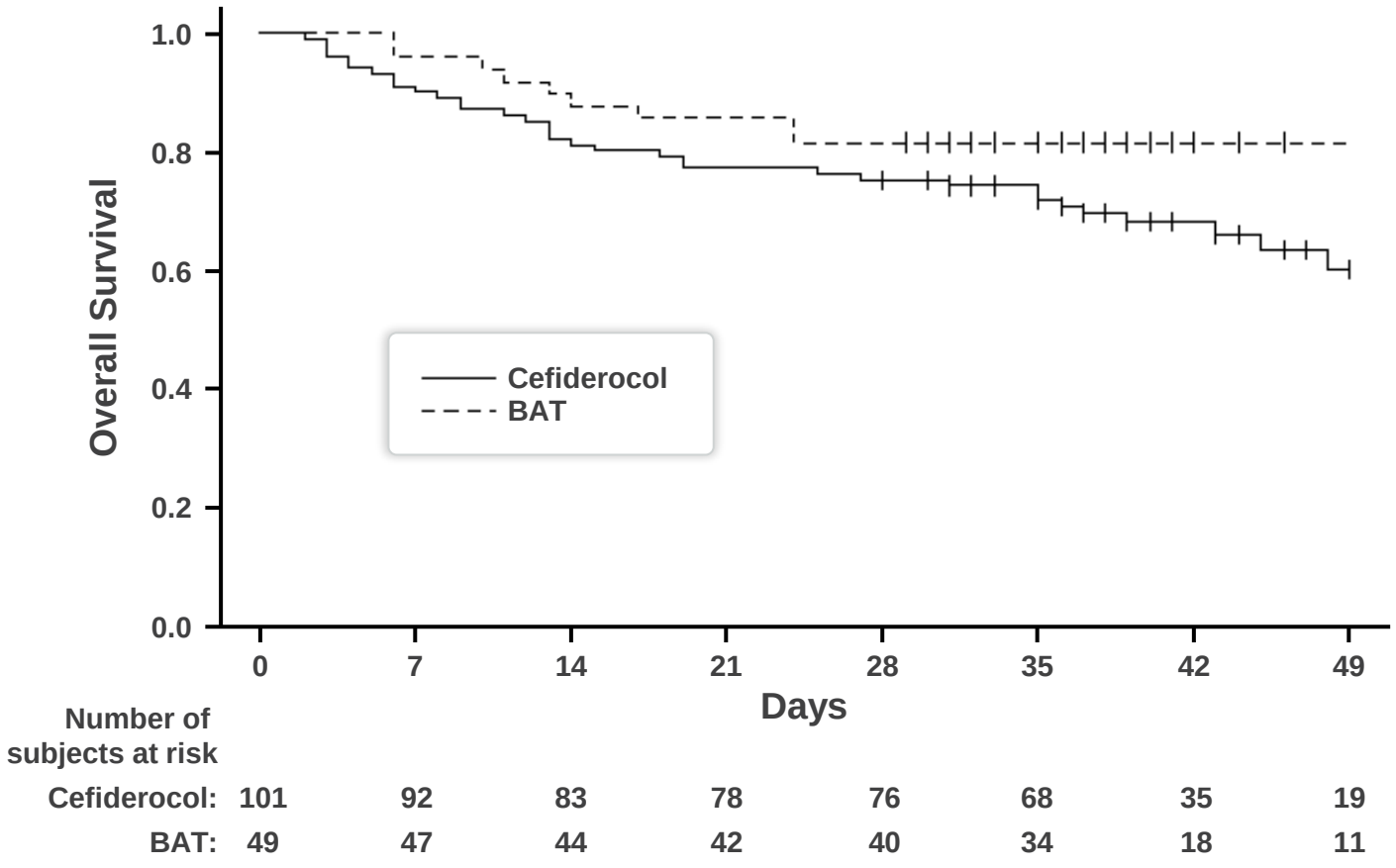
Abbreviations: ACM, all-cause mortality; BAT, best available treatment; CI, confidence interval; EOS, end of study (end of treatment +28 [±3] days); FDA, US Food and Drug Administration; EMA, European Medicines Agency.
[a]FDA-requested post hoc statistical testing.
[b]EMA-requested post hoc statistical testing.
Table adapted from Bassetti et al. *Lancet Infect Dis*. 2021 (Supplementary Appendix).

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CREDIBLE-CR: Results (Cont.)

Figure 2. Kaplan-Meier Curve of Likelihood of Survival in the CREDIBLE-CR Study (Safety Population)[2]

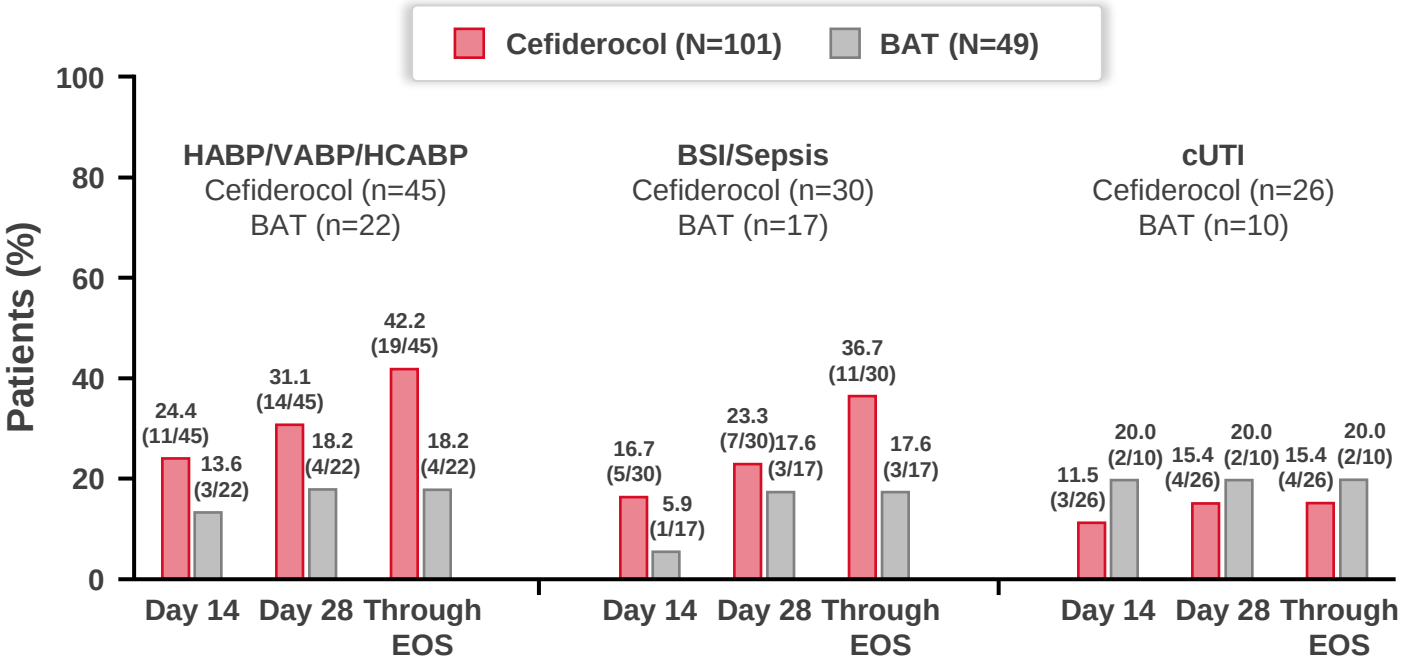


Abbreviation: BAT, best available therapy.
Figure adapted from Bassetti et al. *Lancet Infect Dis*. 2021 (Supplementary Appendix).

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CREDIBLE-CR: Results (Cont.)

Figure 3. ACM by Infection Site in the CREDIBLE-CR Study (Safety Population)[1,7]



Abbreviations: ACM, all-cause mortality; BAT, best available therapy; BSI, bloodstream infection; cUTI, complicated urinary tract infection; EOS, end of study; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

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CREDIBLE-CR: Results (Cont.)

Table 6. **ACM Rates Through EOS by Pathogen (Safety Population)**[1]

Pathogen(s)	Cefiderocol (N=101) n/N (%)	BAT (N=49) n/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)
Escherichia coli	1/6 (17)	0/3 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
S. maltophilia	4/5 (80)	NA
without *Acinetobacter* spp.	2/3 (67)	NA

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

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CREDIBLE-CR: Adjudication Committee

EXTERNAL ADJUDICATION COMMITTEE:[1,7]

- An external, independent, blinded adjudication committee determined attributable mortality
- The members of the adjudication committee were blinded to the treatment and results of the trial
- Each member independently assessed whether the cause of death was unrelated to the original Gram-negative infection, marked under Category 1, or if the death was directly related to the original Gram-negative infection, recorded under Category 2
- All deaths listed under Category 1 were further characterized as being due to an underlying comorbidity, a different infection, a drug-related AE, or an iatrogenic cause
- Deaths in Category 2 were further assessed for study regimen treatment failure

CATEGORIZATION OF DEATHS:

- The categorization of deaths is shown in **Table 7**
- None of the deaths were categorized as a drug-related AE[1]
- Approximately 50% of deaths were attributable causes other than the original Gram-negative infection in both treatment groups (cefiderocol: 16/34 and BAT: 4/9, respectively)[1]
- The difference in mortality between the cefiderocol group and the BAT group was similar for deaths in Category 1 and in Category 2[7]

Table 7. Categorization of Deaths by the Adjudication Committee (Safety Population)[7]

Category and Subcategory	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Overall mortality	34 (33.7)	9 (18.4)
1. Death not directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	16 (15.8)	4 (8.2)
1A. Likely due to the patient's underlying comorbidity	10 (9.9)	2 (4.1)
1B. Related to infection other than original Gr	4 (4.0)	2 (4.1)
1C. Due to drug-related AE	0 (0.0)	0 (0.0)
1D. Due to iatrogenic cause	0 (0.0)	0 (0.0)
Cases that did not have a unanimous subcate	2 (2.0)	0 (0.0)
2. Death directly related to the Gram-negative i the patient was randomized into the CREDIBLE	18 (17.8)	5 (10.2)
Yes. Infection-related death represents a failure of antibiotic treatment	16 (15.8)	4 (8.2)
No. Infection-related death does not represent a failure of antibiotic treatment	1 (1.0)	1 (2.0)
Cases that did not have a unanimous subcategory vote in category 2	1 (1.0)	0 (0.0)

CREDIBLE-CR: Adjudication Committee

Table 7. Categorization of Deaths by the Adjudication Committee (Safety Population)[7]

Category and Subcategory	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Overall mortality	34 (33.7)	9 (18.4)
1. Death not directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	16 (15.8)	4 (8.2)
1A. Likely due to the patient's underlying comorbidity	10 (9.9)	2 (4.1)
1B. Related to infection other than original Gram-negative infection	4 (4)	2 (4.1)
1C. Due to drug-related AE	0 (0)	0 (0)
1D. Due to iatrogenic cause	0 (0)	0 (0)
Cases that did not have a unanimous subcategory vote in category 1	2 (2)	0 (0)
2. Death directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	18 (17.8)	5 (10.2)
Yes. Infection-related death represents a failure of antibiotic treatment	16 (15.8)	4 (8.2)
No. Infection-related death does not represent a failure of antibiotic treatment	1 (1)	1 (2)
Cases that did not have a unanimous subcategory vote in category 2	1 (1)	0 (0)

Abbreviations: AE, adverse events; BAT, best available therapy.

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PK/PD Analysis

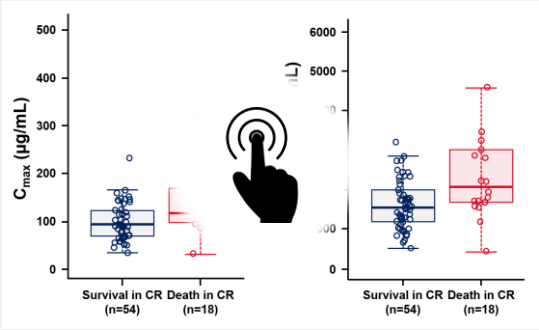
A population PK model was developed using plasma concentration data of cefiderocol from various studies, including the Phase 2 (APEKS-cUTI) and Phase 3 (APEKS-NP, CREDIBLE-CR) clinical trials. Post hoc estimates of Cmax and daily AUC for patients in CREDIBLE-CR were calculated using the final population PK model.[10–12]

- In CREDIBLE-CR, the geometric mean for cefiderocol C_{max} and daily AUC in death cases was 1.4-fold higher than survival cases (**Table 8** and **Figure 4**)[10]

Table 8. Post Hoc Estimates of Cefiderocol Exposure for Death Cases and Survival Cases in CREDIBLE-CR[10]

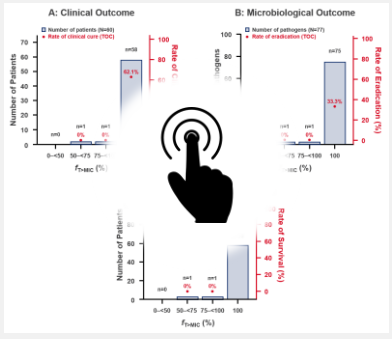
Vital Status	N	[illegible] (μg/mL)[a]	Daily AUC (μg*hr/mL)[a]
Survival	54	(39.4)	1495 (42.5)
Death	18	5 (52.2)	2130 (63.3)

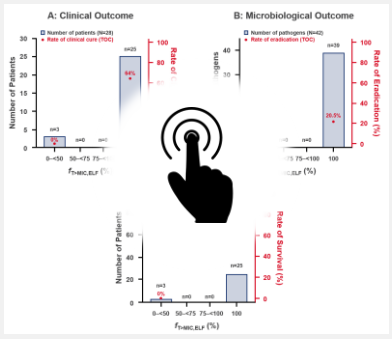
Figure 4. Box Plots of Post Hoc Estimates for Cefiderocol Exposure in Death Cases and Survival Cases in the CREDIBLE-CR Study[10]



- In addition, a population PK analysis evaluated the relationship of the percentage of time for which free drug concentration exceeded the MIC over the dosing interval (%$f_{T>MIC}$) as well as %$f_{T>MIC}$ in ELF (%$f_{T>MIC,ELF}$) with the clinical outcome, microbiological outcome, and survival rate at Day 28 in CREDIBLE-CR (**Figure 5** and **Figure 6**)[10]
- In CREDIBLE-CR, there was no clear PK/PD relationship identified for any of the outcomes[7]
- In the cefiderocol group, the %$f_{T>MIC}$ was 100% in ≥95% of the patients, and the %$f_{T>MIC,ELF}$ was 100% in 89.3% of the patients[10]

Figure 5. Relationship of %$f_{T>MIC}$ and Figure 6. Relationship of %$f_{T>MIC,ELF}$ with Clinical Outcome, Microbiological Outcome, and Survival Rate in the CREDIBLE-CR Study[10–12]





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PK/PD Analysis

Table 8. Post Hoc Estimates of Cefiderocol Exposure for Death Cases and Survival Cases in CREDIBLE-CR[10]

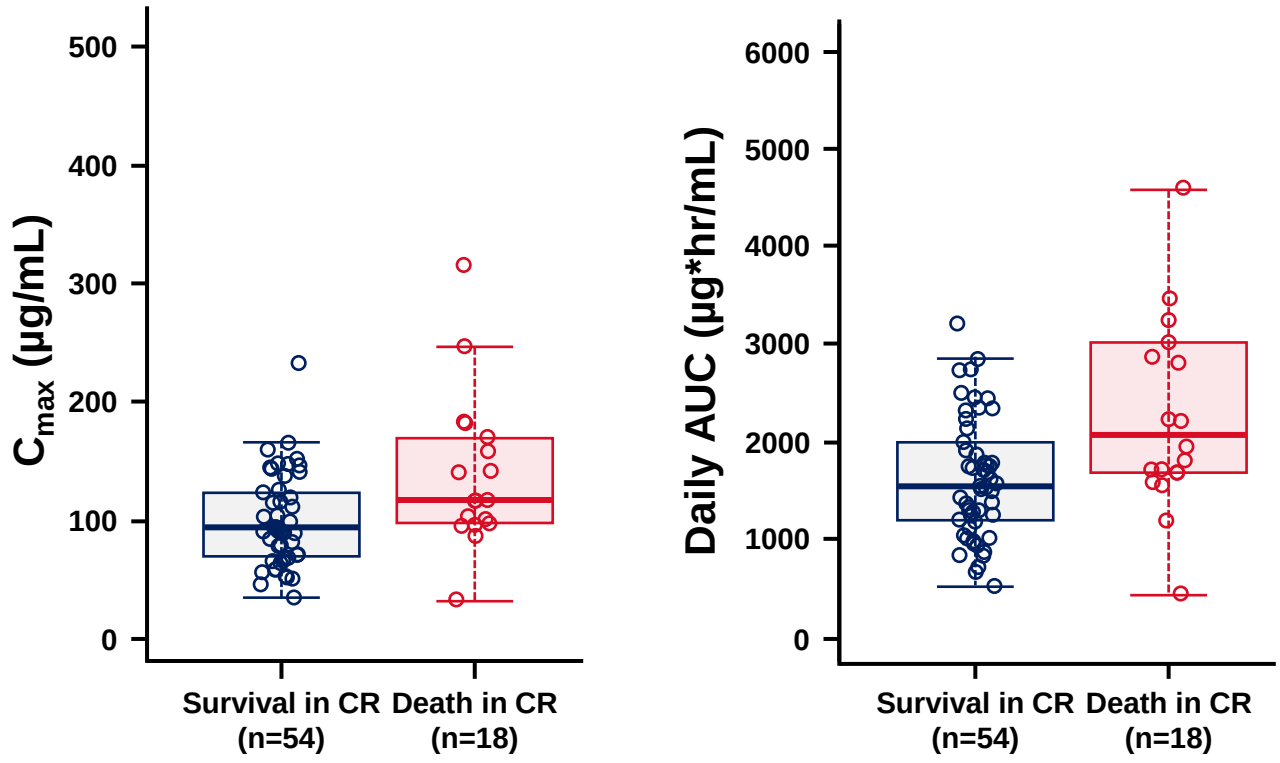
Vital Status	N	C_{max} (µg/mL)[a]	Daily AUC (µg*hr/mL)[a]
Survival	54	92.5 (39.4)	1495 (42.5)
Death	18	125 (52.2)	2130 (63.3)

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration.
[a]Geometric mean (CV%) of parameters estimated using the final model.

- In addition, a population PK analysis evaluated the relationship of the percentage of time for which free drug concentration exceeded the MIC over the dosing interval (%$f_{T>MIC}$) as well as %$f_{T>MIC}$ in ELF (%$f_{T>MIC,ELF}$) with the clinical outcome, microbiological outcome, and survival rate at Day 28 in **CREDIBLE-CR** (**Figure 4** and **Figure 5**)[10]
- In **CREDIBLE-CR**, there was no clear PK/PD relationship identified for any of the outcomes[7]
- In the cefiderocol group, the %$f_{T>MIC}$ was 100% in ≥95% of the patients, and the %$f_{T>MIC,ELF}$ was 100% in 89.3% of the patients[10]

Figure 4. Relationship of %$f_{T>MIC}$ and Figure 5. Relationship of %$f_{T>MIC,ELF}$ with Clinical Outcome, Microbiological Outcome, and Survival Rate in the CREDIBLE-CR Study[10–12]

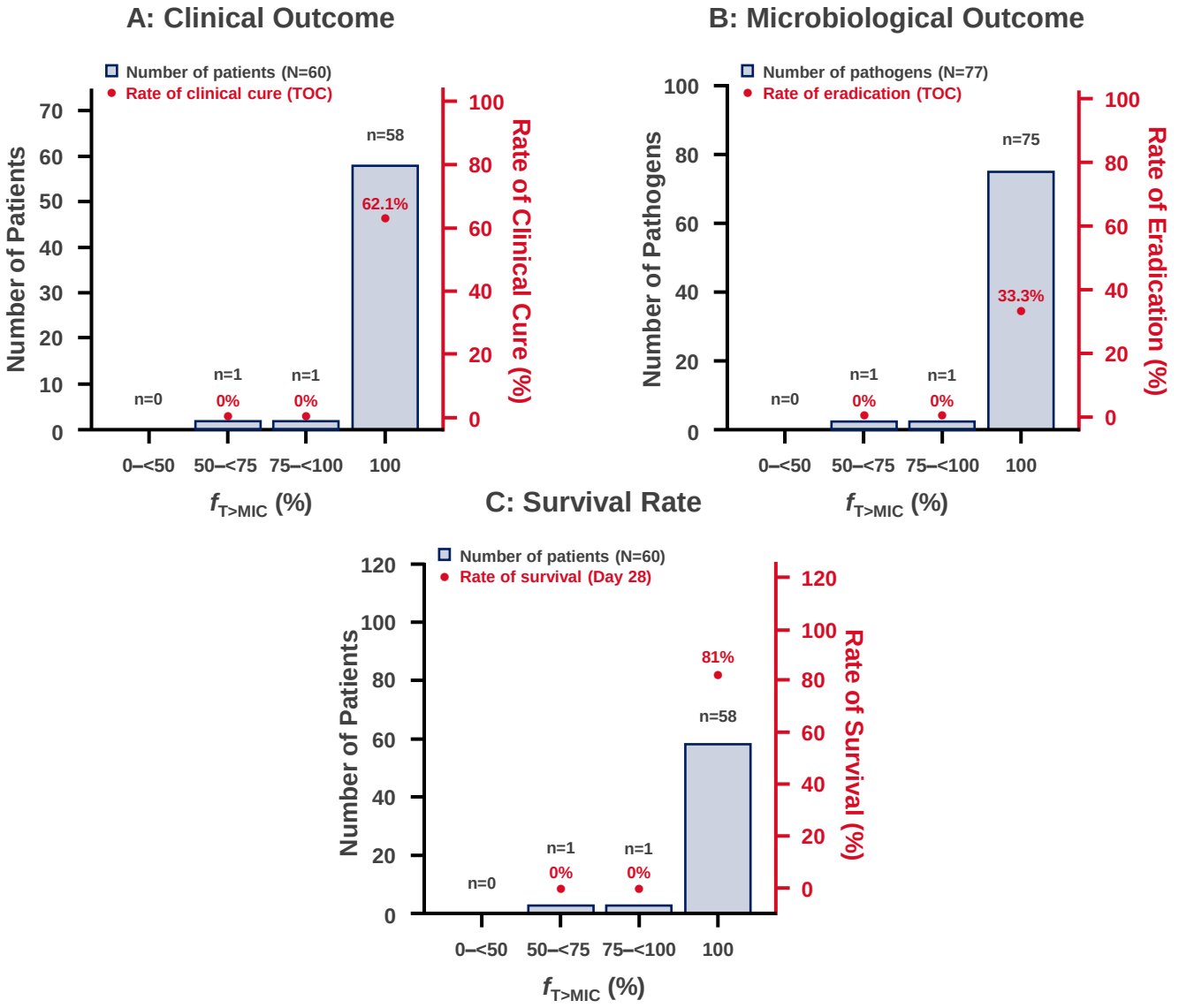
Figure 4. Box Plots of Post Hoc Estimates for Cefiderocol Exposure in Death Cases and Survival Cases in the CREDIBLE-CR Study[10]



Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration.

PK/PD Analysis

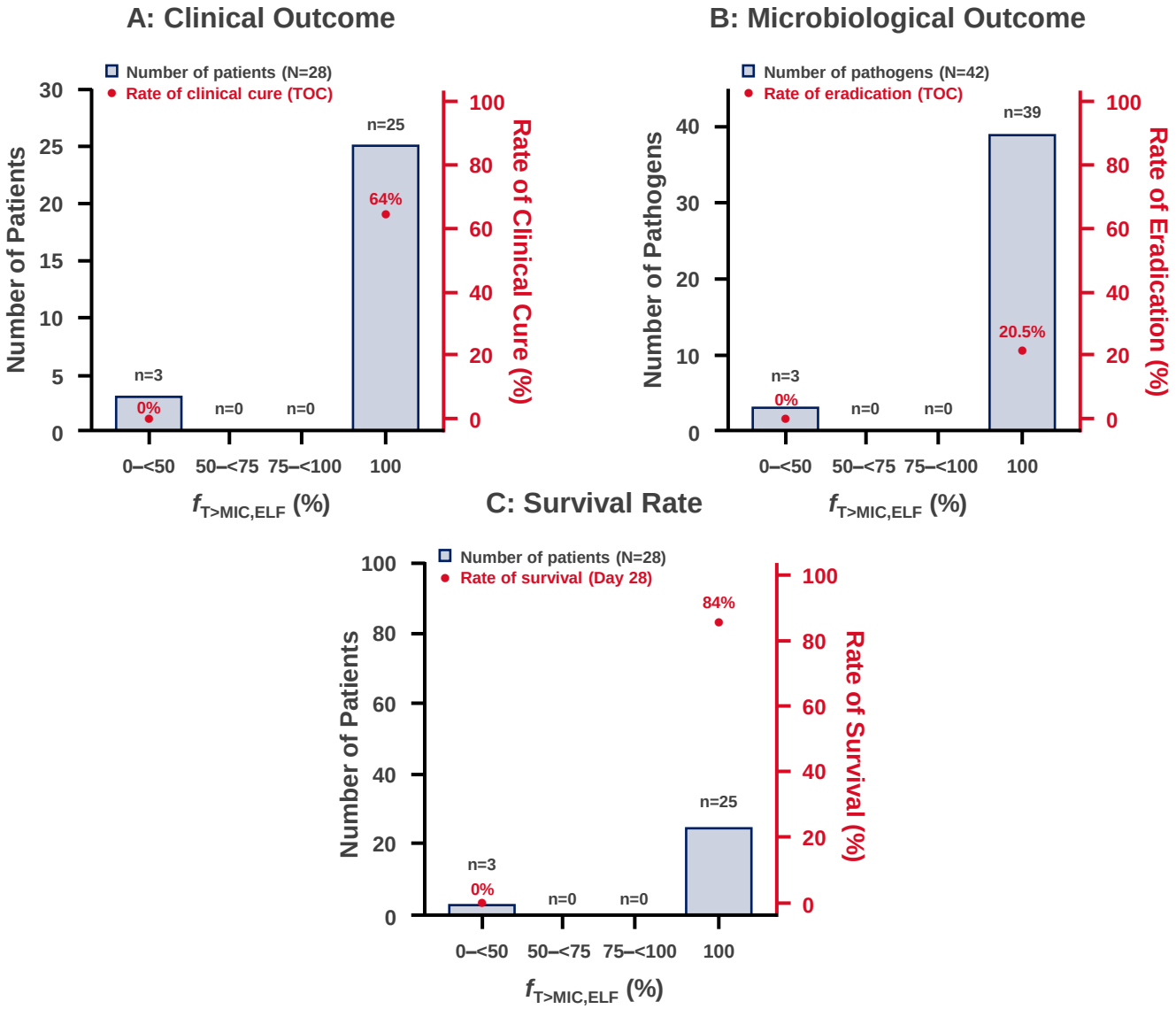
Figure 5. Relationship of %$f_{T>MIC}$ with Clinical Outcome, Microbiological Outcome, and Survival Rate in the CREDIBLE-CR Study (All Patients with Infection)[10,11]



Abbreviations: MIC, minimum inhibitory concentration; TOC, test of cure.
Figures 5A and 5B adapted from Katsube et al. IDWeek. 2020.

PK/PD Analysis

Figure 6. Relationship of %$f_{T>MIC,ELF}$ with Clinical Outcome, Microbiological Outcome, and Survival Rate in the CREDIBLE-CR Study (Patients with HABP, VABP, HCABP)[10,12]



Abbreviations: ELF, epithelial lining fluid; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; MIC, minimum inhibitory concentration; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.
Figures 6A and 6B adapted from Kawaguchi et al. *J Clin Pharmacol*. 2022.

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Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[13]

- Complicated urinary tract infections (cUTIs), 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:[13]

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

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Relevant Prescribing Information (Cont.)

Section 5 Warnings and Precautions of the **Fetroja Full Prescribing Information** states the following:[13]

5.1 Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

- An increase in all-cause mortality was observed in patients treated with FETROJA as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.
- The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with FETROJA than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.
- Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

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

Abbreviations

ACM	all-cause mortality	EA	early assessment
AE	adverse event	ELF	epithelial lining fluid
ALT	alanine aminotransferase	EMA	European Medicines Agency
AST	aspartate aminotransferase	ENT	Enterobacterales
AUC	area under the curve	EOS	end of study
BAT	best available therapy	EOT	end of treatment
BSI	bloodstream infection	EUCAST	European Committee on Antimicrobial Susceptibility Testing
CCI	Charlson Comorbidity Index	FDA	US Food and Drug Administration
CDS	coding sequences	FU	follow-up
CI	confidence interval	g	grams
cIAI	complicated intra-abdominal infection	h	hours
CLSI	Clinical and Laboratory Standards Institute	HABP	hospital-acquired bacterial pneumonia
C_{max}	maximum plasma concentration	HCABP	healthcare-associated bacterial pneumonia
CPIS	Clinical Pulmonary Infection Score	I	intermediate
CR	carbapenem-resistant	ICU	intensive care unit
CrCl	creatinine clearance	IMP	imipenemase
cUTI	complicated urinary tract infection	ITT	intent-to-treat

Abbreviations (Cont.)

IV	intravenous	R	resistant
KPC	*K. pneumoniae* carbapenemase	S	susceptible
MBL	metallo-β-lactamases	SAE	serious adverse event
MIC	minimum inhibitory concentration	SD	standard deviation
Micro-ITT	microbiological intent-to-treat	SIRS	Systemic Inflammatory Response Syndrome
NA	not available	SOFA	Sequential Organ Failure Assessment
NDM	New Delhi MBL	spp.	species
NF	non-fermenter	SSSI	skin and soft skin structure infection
NT	not tested	TEAE	treatment-emergent adverse event
OXA	oxacillinase	TOC	test of cure
PD	pharmacodynamics	VABP	ventilator-associated bacterial pneumonia
PK	pharmacokinetics	VIM	Verona integron-encoded MBL
q8h	every 8 hours	WGS	whole-genome sequencing

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2. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(Suppl):S1-S124.
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13. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

Enclosure

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

Appendices

Appendix Table 1. Baseline Demographics and Clinical Characteristics in the ITT/Safety Population[1]

	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Sex		
Male	66 (65)	35 (71)
Female	35 (35)	14 (29)
Age, years		
Mean (SD)	63.1 (19)	63 (16.7)
Median (range)	69 (19–92)	62 (19–92)
(IQR)	(52–77)	(51–76)
<65	37 (37)	27 (55)
≥65	64 (63)	22 (45)
<75	72 (71)	35 (71)
≥75	29 (29)	14 (29)
BMI, kg/m^2[2,a]		
Median (range)	25 (12–52.4)	23.5 (14.3–48.9)
(IQR)	(21.3–27.8)	(20.3–29.2)
Region		
Europe	57 (56)	28 (57)
Asia-Pacific	29 (29)	14 (29)
North America	6 (6)	3 (6)
South America	9 (9)	4 (8)
Race		
White	63 (62)	32 (65)
Asian	29 (29)	14 (29)
Black or African American	0 (0)	0 (0)
Other	9 (9)	3 (6)
Clinical Diagnosis		
HABP/VABP/HCABP	45 (45)	22 (45)
HABP	20 (20)	7 (14)
VABP	24 (24)	13 (27)
HCABP	1 (1)	2 (4)
BSI/Sepsis[b]	30 (30)	17 (35)
BSI	22 (22)	9 (18)
cIAI	3 (3)	2 (4)
SSSI	1 (1)	0 (0)
IV line	4 (4)	2 (4)
Other[c]	5 (5)	1 (2)
Unknown	9 (9)	4 (8)
Sepsis	8 (8)	8 (16)
cIAI	2 (2)	1 (2)

Appendices (Cont.)

Appendix Table 1 (Cont.). Baseline Demographics and Clinical Characteristics in the ITT/Safety Population[1]

	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
SSSI	4 (4)	3 (6)
IV line	0 (0)	3 (6)
Other[c]	2 (2)	1 (2)
cUTI	26 (26)	10 (20)
Ventilation at randomization	50 (50)	26 (53)
CrCl, mL/min		
Mean (SD)	85.8 (79.3)	88.9 (64.2)
Median (range) (IQR)	59.2 (9.4–539.26) (33.9–107.9)	69.4 (4.6–270.8) (47.6–119.8)
≥120	20 (20)	12 (24)
>80–<120	18 (18)	10 (20)
>50–≤80	20 (20)	12 (24)
≥30–≤50	23 (23)	8 (16)
<30	20 (20)	7 (14)
Empirical treatment failure	58 (57)	27 (55)
Previous therapy[d]		
Antibiotics[e]	93 (92)	49 (100)
Carbapenems	60 (59)	26 (53)
Systemic corticosteroids	44 (44)	17 (35)
ICU at randomization	57 (56)	21 (43)
Shock	19 (19)	6 (12)
Immunocompromised	27 (27)	10 (20)
Positive blood culture	25 (25)	13 (27)
APACHE II score		
Mean (SD)	15.3 (6.5)	15.4 (6.2)
Median (range) (IQR)	15 (2–29) (11–20)	14 (2–28) (11–20)
≤15	55 (54)	27 (55)
16–19	17 (17)	9 (18)
≥20	29 (29)	13 (27)
CPIS score[f]		
Mean (SD)	4.9 (1.7)	4.6 (1.5)
Median (range) (IQR)	5 (2–9) (4–6)	5 (0–7) (4–5)
≤5	30/45 (67)	16/22 (73)
≥6	14/45 (31)	5/22 (23)
Missing	1/45 (2)	1/22 (5)

Appendices (Cont.)

Appendix Table 1 (Cont.). Baseline Demographics and Clinical Characteristics in the ITT/Safety Population[1]

	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
SOFA score[g]		
Mean (SD)	5.1 (4)	5.1 (3.8)
Median (range)	4 (0–17)	4 (0–16)
(IQR)	(2–8)	(2–8)
≤6	67 (66)	32 (65)
≥7	33 (33)	17 (35)
≤9	84 (83)	43 (88)
≥10	16 (16)	6 (12)
Missing	1 (1)	0
CCI score		
Mean (SD)	5.5 (3.1)	5.4 (3.1)
Median (range)	5 (0–12)	6 (0–13)
(IQR)	(3–8)	(3–7)
Medical history based on CCI components	101 (100)	49 (100)
Renal disease	40 (40)	20 (41)
Chronic pulmonary disease	40 (40)	16 (33)
Diabetes	35 (35)	17 (35)
Cancer	24 (24)	13 (27)
Congestive heart failure	12 (12)	10 (20)
Peripheral vascular disease	11 (11)	5 (10)
Moderate/severe liver disease	11 (11)	4 (8)
Hepatitis	12 (12)	2 (4)
Severity of infection[h]		
Mild	5 (5)	4 (8)
Moderate	41 (41)	22 (45)
Severe	55 (55)	23 (47)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BAT, best available therapy; BMI, body mass index; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; cIAI, complicated intra-abdominal infection; CPIS, Clinical Pulmonary Infection Score; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; ITT, intent-to-treat; SD, standard deviation; SIRS, Systemic Inflammatory Response syndrome; SOFA, Sequential Organ Failure Assessment; SSSI, skin and soft skin structure infection; VABP, ventilator-associated bacterial pneumonia.

[a]Data available for 99 patients assigned cefiderocol and 49 assigned BAT.

[b]The BSI/sepsis category included bacteremia or sepsis caused by infections other than HABP/VABP/HCABP or cUTI. Sepsis diagnoses were based on SIRS criteria that were valid at the time of study design.

[c]Including biliary tract infection, pelvic infection, respiratory tract infections other than infection sites identified as HABP, VABP, HCABP (eg, community-acquired pneumonia, lung abscess, pleural space, or empyema).

[d]A patient taking 2 or more medications was counted only once within a treatment classification; however, the same patient might have contributed to 2 or more Preferred Terms in the same classification, according to the Medical Dictionary for Regulatory Activities (version 18.1).

[e]Previous antimicrobial therapy taken within 2 weeks before randomization.

[f]Shown only for patients with nosocomial pneumonia; data available for 44 patients assigned to cefiderocol and 21 assigned best available therapy.

[g]Data available for 100 patients assigned cefiderocol and 49 assigned BAT.

[h]Based on the investigators' clinical judgement (ie, there were no pre-defined criteria for infection severity).

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Appendices (Cont.)

Appendix Table 2. Distribution of Gram-negative Pathogens Isolated at Baseline in the CR-Micro-ITT Population[1]

Pathogen[a]	Cefiderocol (n=87)[a] n (%)	BAT (n=40)[b] n (%)
A. baumannii	37 (46)	17 (45)
K. pneumoniae	27 (34)	12 (32)
P. aeruginosa	12 (15)	10 (26)
S. maltophilia	5 (6)	0 (0)
A. nosocomialis	2 (3)	0 (0)
E. cloacae	2 (3)	0 (0)
E. coli	2 (3)	1 (3)

Abbreviations: BAT, best available therapy; CR, carbapenem-resistant; CR-Micro-ITT, carbapenem-resistant microbiological intent-to-treat.
[a]Total number of baseline CR Gram-negative pathogens in the cefiderocol group.
[b]Total number of baseline CR Gram-negative pathogens in the BAT group.

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Appendices (Cont.)

Appendix Table 3. Clinical and Microbiological Outcomes at TOC in the CR-Micro-ITT Population[5,7]

KPC-producing Enterobacterales		
Outcome, n (%)	**Cefiderocol (n=14)**	**BAT (n=7)**
Clinical cure	8 (57.1)	4 (57.1)
Microbiological eradication	5 (35.7)	2 (28.6)
NDM-producing Enterobacterales		
Outcome, n (%)	**Cefiderocol (n=8)**	**BAT (n=4)**
Clinical cure	6 (75)	0 (0)
Microbiological eradication	5 (62.5)	0 (0)
OmpK35/36-deficient Enterobacterales		
Outcome, n (%)	**Cefiderocol (n=15)**	**BAT (n=9)**
Clinical cure	10 (66.7)	5 (55.6)
Microbiological eradication	7 (46.7)	1 (11.1)
MBL*-producing *P. aeruginosa*		
Outcome, n (%)	**Cefiderocol (n=4)**	**BAT (n=3)**
Clinical cure	4 (100)	2 (66.7)
OprD-deficient *P. aeruginosa*		
Outcome, n (%)	**Cefiderocol (n=10)**	**BAT (n=10)**
Clinical cure	7 (70)	5 (50)
OXA-producing *Acinetobacter* spp.		
Outcome, n (%)	**Cefiderocol (n=36)**	**BAT (n=17)**
Clinical cure	15 (41.7)	9 (52.9)

Abbreviations: BAT, best available therapy; CR-Micro-ITT, carbapenem-resistant microbiological intent-to-treat; KPC, *K. pneumoniae* carbapenemase; MBL, metallo-β-lactamases; NDM, New Delhi metallo-β-lactamases; OXA, oxacillinase; TOC, test of cure.
*Includes VIM, IMP, NDM.

Appendices (Cont.)

Appendix Table 4. Clinical Cure, Microbiological Eradication, and Day 28 ACM in Infections Caused by MBL-producing Bacteria[8]

	Clinical Cure at TOC, % (n/N)		Microbiological Eradication at EOT, % (n/N)		ACM Day 28, % (n/N)	
	Cefiderocol (n=16)	BAT (n=7[a])	Cefiderocol (n=16)	BAT (n=7[a])	Cefiderocol (n=16)	BAT (n=7[a])
Overall	75 (12/16)	28.6 (2/7)	62.5 (10/16)	14.3 (1/7)	6.3 (1/16)	57.1 (4/7)
MBL Type[b]						
NDM	60 (6/10)	20 (1/5[a])	70 (7/10)	0 (1/5[a])	10 (1/10)	60 (3/5[a])
Non-NDM	100 (6.6)	33.3 (1/3[a])	50 (3/6)	33.3 (1.3[a])	0 (0/6)	33.3 (1/3[a])
Pathogen Type[b]						
Enterobacterales	60 (3/5)	100 (1/1)	60 (3/5)	100 (1/1)	20 (1/5)	0 (0/1)
Non-fermenters[c]	66.7 (2/3)	50 (1/2)	33.3 (1/3)	50 (1/2)	33.3 (1/3)	50 (1/2)

Abbreviations: ACM, all-cause mortality; BAT, best available therapy; EOT, end of treatment; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; TOC, test of cure.
[a]One (1) isolate expressed an NDM and an IMP-62 MBL.
[b]n/N', where N' is the number of patients within the category.
[c]Cefiderocol: *P. aeruginosa* (n=4), *A. baumannii* (n=2); BAT: *P. aeruginosa* (n=3).

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Appendices (Cont.)

Appendix Table 5. Pre- and Post-MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment WGS-Identified Mutations in Multilocus Sequence Typing-Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from CREDIBLE-CR (Micro-ITT Population)[9]

Species and Site of Infection	Timepoint for MIC Increase	Original MIC (µg/mL)	Fold of Baseline MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#2 (µg/mL)	MIC#3 (µg/mL)	Median MIC (µg/mL)	Fold of Median Baseline MIC	CLSI S/I/R ≤4/8/≥16	FDA S/I/R ≤4/8/≥16 ENT & ≤1/2/≥4 NF	EUCAST S/R ≤2/≥2 (ENT, PA)		
A. baumannii	Baseline	0.25		1	1	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-66[d]; TEM-1D	
	Day 14	4	16x	2	4	4	4×	S	R	R	ADC-25-like[d]; OXA-23; OXA-66[d]; TEM-1D	PBP3 (H370Y)
A. baumannii	Baseline	1		1	2	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-69[d]	
	EOT	8	8x	64	64	64	64x	R	R	R	ADC-25-like[d]; OXA-23-like; OXA-69[d]	OXA-23 (N85I and P225S)
A. baumannii[a]	Baseline	1		0.25	1	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-71[d]	
	Unscheduled (Day 10)	8	8x	8	8	8	8x	I	R	R	ADC-25-like[d]; OXA-23; OXA-71[d]	Not identified
K. pneumoniae	Baseline	0.06		≤0.03	0.06	0.06		S	S	S	SHV-61-like[e]	
	Unscheduled (Day 8)	0.5	8x	1	1	1	16x	S	S	S	SHV-61-like[e] partial CDS; TEM-18	Not identified
K. pneumoniae[b]	Baseline	0.25		0.12	0.25	0.25		S	S	S	KPC-2; SHV-1	
	Day 14	2	8x	4	2	2	8x	S	S	S	KPC-2; SHV-1	Not identified

Appendices (Cont.)

Appendix Table 5 (Cont.). Pre- and Post-MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment WGS-Identified Mutations in Multilocus Sequence Typing-Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from CREDIBLE-CR (Micro-ITT Population)[9]

Species and Site of Infection	Timepoint for MIC Increase	Original MIC (µg/mL)	Fold of Baseline MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#2 (µg/mL)	MIC#3 (µg/mL)	Median MIC (µg/mL)	Fold of Median Baseline MIC	CLSI S/I/R ≤4/8/≥16	FDA S/I/R ≤4/8/≥16 ENT & ≤1/2/≥4 NF	EUCAST S/R ≤2/≥2 (ENT, PA)		
P. aeruginosa	Baseline	0.12		0.12	0.12	0.12		S	S	S	OXA-847[f]; PDC-11; VIM-2	
	EA	16	128x	16	16	16	128x	R	R	R	OXA-847[f]; PDC-11; VIM-2	Not identified
P. aeruginosa	Baseline	0.25		0.12	0.12	0.12		S	S	S	OXA-488[f]; PDC-30	
	EOT	2	8x	2	2	2	16x	S	I	S	OXA-488[f]; PDC-30-like	PDC30 (4 AA deletion "TPMA" position 316-319)
P. aeruginosa	Baseline	0.5		1	0.25	0.5		S	S	S	Oxa-50-like[g]; PDC-11	
	EOT	2	4x	4	2	2	4x	S	I	S	Oxa-50-like[g]; PDC-11	Not identified
S. maltophilia[c]	Baseline	0.06		0.06	0.12	0.06		NA	NA	NA	L1, L2[h]	
	EOT	0.25	4x	0.12	0.25	0.25	4x	NA	NA	NA	L1, L2[h]	Not identified

Abbreviations: CDS, coding sequences; CLSI, Clinical and Laboratory Standards Institute; EA, Early Assessment; ENT, Enterobacterales; EOT, end of treatment; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; Micro-ITT, microbiological intent-to-treat; NF, non-fermenters; NT, not tested; R, resistant; S, susceptible; TOC, test of cure; WGS, whole-genome sequencing.
[a]Treatment with combination of cefiderocol+ampicillin–sulbactam; [b]Treatment with combination of cefiderocol+tigecycline; [c]Treatment with combination of cefiderocol+levofloxacin; [d]In *A. baumannii*, OXA-66, OXA-69, OXA-71, and ADC-25 are naturally occurring and weakly expressed; [e]In *K. pneumoniae*, SHV-61 is naturally occurring; [f]In *P. aeruginosa*, OXA-847 and OXA-488 are naturally occurring and weakly expressed, and do not interfere with common resistance patterns. They belong to OXA-50-like group of β-lactamases. [g]OXA-50-like groups of β-lactamases are naturally occurring enzymes and weakly expressed; [h]L1 and L2 are naturally occurring β-lactamases; L1: a MBL and L2: an extended-spectrum β-lactamase, respectively. L1 was not available in the ResFinder database but was detected by manual analysis of the assembled sequence.

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Appendices (Cont.)

Appendix Table 6. Pre- and Post-MICs and the Mechanisms of Resistance in Pathogens with ≥4-Fold MIC Increases in the BAT[a] Arm from CREDIBLE-CR (Micro-ITT Population)[1,2]

Isolate	MIC (µg/mL)		Fold Change in MIC	Day of Isolation	Mutation Identified in Post-Treatment Isolates
	Pre-Treatment[b]	Post-Treatment			
Ceftazidime/avibactam					
K. pneumoniae	0.25	16	64	20	Not evaluated
Tigecycline					
K. pneumoniae[c]	1	>4	>4	13	Not evaluated
A. baumannii[d]	2	>4	>4	11	Not evaluated
Colistin					
K. pneumoniae	≤0.5	>8	>16	13	Not evaluated
K. pneumoniae[c]	≤0.5	8	>16	13	Not evaluated
A. baumannii[d]	≤0.5	>8	>16	4	Not evaluated
A. baumannii[e]	1	>8	>8	14	Not evaluated
E. coli[e]	2	8	>4	14	Not evaluated

Abbreviations: BAT, best available therapy; CR, carbapenem-resistant; MIC, minimum inhibitory concentration; Micro-ITT, microbiological intent-to-treat.
[a]BAT agents were selected based on local standard of care for CR infections, and MICs were confirmed by the central laboratory.
[b]Latest isolate before study drug initiation.
[c]The patient had *K. pneumoniae* infection and was treated with tigecycline and colistin; MIC increased to both agents.
[d]The patient had *A. baumannii* infection and was treated with tigecycline and colistin; MIC increased to both agents.
[e]Polymicrobial infection treated with colistin; increase in MIC for both pathogens.

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