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# Outcomes in Patients with Gram-Negative Bacteremia from Phase 2 and Phase 3 Clinical Trials of Cefiderocol, a Novel Siderophore Cephalosporin

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## Introduction

Gram-negative bacteremia is a relatively common complication of serious infections such as nosocomial pneumonia, intra-abdominal infection, urinary tract infection, or skin and skin structure infection.[1] Routine collection of follow-up blood samples is not considered cost-effective and may lead to inappropriate antibiotic treatment.[1]

Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a broad range of Gram-negative bacteria, including Enterobacterales and glucose non-fermenting species.[2]

Under a streamlined development programme,[3] cefiderocol has been investigated in 3 clinical studies in a total of 900 patients.[4–7] The APEKS-cUTI Phase 2 pivotal study has demonstrated the non-inferiority (and superiority) of cefiderocol monotherapy to imipenem-cilastatin (IMP/CS) in the composite outcome of clinical cure and microbiological eradication in the treatment of complicated urinary tract infection (cUTI) in patients who were at risk of multidrug-resistant Gram-negative infections.[4] The APEKS-NP Phase 3 study has recently demonstrated that cefiderocol monotherapy was non-inferior to high-dose, extended-infusion meropenem (MEPM) in critically ill patients with nosocomial pneumonia caused by a broad range of Gram-negative bacteria, including the non-fermenters *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[5] The CREDIBLE-CR Phase 3 study was a pathogen-focused, open-label descriptive study (without prior hypothesis testing) in seriously ill patients with carbapenem-resistant Gram-negative infections, including non-fermenters and Enterobacterales.[6,7] Based on descriptive data, the study showed similar clinical cure and microbiological eradication rates between cefiderocol and best-available therapy (BAT) in patients with nosocomial pneumonia, bloodstream infections (BSI)/sepsis and cUTI. A difference in mortality was observed with a higher rate in the cefiderocol arm than in the BAT arm.[6,7]

Cefiderocol has been approved in the USA for the treatment of adults with cUTI and hospital-acquired and ventilator-associated bacterial pneumonia (HABP, VABP),[8] and in Europe for infections in adults caused by Gram-negative bacteria with limited treatment options.[9]

We aimed to evaluate the efficacy of cefiderocol in the clearance of bacteremia in patients with bacteremia enrolled in these 3 clinical studies.

## Methods

**Table 1**. Design and primary endpoints in APEKS-cUTI, APEKS-NP, and CREDIBLE-CR studies[4–7]

| | APEKS-cUTI[4] (NCT02321800) | | APEKS-NP[5] (NCT03032380) | | CREDIBLE-CR[6,7] (NCT02714595) | |
|---|---|---|---|---|---|---|
| Design | Multicenter, double-blind, Phase 2, non-inferiority, traditional | | Multicenter, double-blind, Phase 3, non-inferiority, traditional | | Multicenter, open-label, Phase 3, descriptive, pathogen-focused | |
| Randomization | 2:1 | | 1:1 | | 2:1 | |
| Patient population | Complicated UTI | | HAP, VAP, HCAP | | • HAP, VAP, HCAP<br>• BSI/sepsis<br>• cUTI | |
| Treatment arms | Cefiderocol, 2 g, q8h, 1-hour infusion | Imipenem/ cilastatin 1 g/ 1 g, q8h, 1-hour infusion | Cefiderocol, 2 g, q8h, 3-hour infusion | Meropenem 2 g, q8h, 3-hour infusion | Cefiderocol, 2 g, q8h, 3-hour infusion | Best available therapy |
| Adjunctive therapy | Not allowed | Not allowed | Not allowed | Not allowed | Maximum 1 agent* | Up to 3 agents in combination |
| Pathogens | Carbapenem-susceptible Gram-negative Enterobacterales and non-fermenters | | Carbapenem-susceptible Gram-negative Enterobacterales and non-fermenters | | Carbapenem-resistant Gram-negative Enterobacterales and non-fermenters | |
| Primary endpoint | Composite of clinical and microbiological outcome at test of cure | | All-cause mortality at Day 14 | | Clinical cure rate at test of cure in HAP/VAP/HCAP and BSI/Sepsis, and microbiological eradication rate at test of cure in cUTI | |

HCAP, healthcare-associated pneumonia. *Except cUTI patients.

- To confirm the presence of bacteremia in each study, 2 blood samples from separate venepunctures were collected for culture and susceptibility at randomization and were tested for the presence of bacteria. If bacteremia was identified, investigators in each study were asked to collect additional blood samples to confirm eradication of causative pathogen during treatment.
- To assess eradication rate in each study, if patients had post baseline blood culture, the blood culture was used as first criteria for eradication during treatment and at end of treatment, test of cure, or follow up. If no post-randomization blood culture was collected, the clinical response was considered: if patient was considered clinical cure, then bacteremia outcome was considered presumed eradication. Indeterminate bacteremia response occurred due to lack of blood culture, or administration of effective concomitant antibiotics.

## Results

- A total of 900 patients were randomized in the 3 clinical studies and 84 patients had microbiologically confirmed Gram-negative bacteremia (cefiderocol 52 and comparator agents 32) (**Figure 1**). Bacteremia rate by study was 6.2% (28/452) in APEKS-cUTI, 6.0% (18/298) in APEKS-NP, and 25.3% (38/150) in CREDIBLE-CR.
- The source of bacteremia is shown in **Table 2**. In APEKS-cUTI, acute pyelonephritis was the most frequent source of bacteremia, while in APEKS-NP, VAP patients developed bacteremia most frequently. In CREDIBLE-CR, patients with BSI/sepsis had confirmed bacteremia at baseline. Additionally, 4 patients with a primary diagnosis of VAP and 2 with cUTI also developed bacteremia.

## Results

**Figure 1**.

Overall: 84 out of 900 randomized patients with Gram-negative bacteremia
Cefiderocol: 52 patients [9.4%] (of 552) Comparators: 32 patients [9.2%] (of 348)

- Cefiderocol: 55 pathogens
- Comparators: 34 pathogens

APEKS-cUTI (NCT02321800; Ph2, double-blind; 2:1 randomization)
Cefiderocol: 19 patients [6.3%] (of 303) Imipenem-cilastatin: 9 patients [6.0%] (of 149)

- Cefiderocol: 19 pathogens
- Imipenem/cilastatin: 9 pathogens

APEKS-NP (NCT03032380; Ph3, double-blind; 1:1 randomization)
Cefiderocol: 8 patients [5.4%] (of 148) Meropenem: 10 patients [6.7%] (of 150)

- Cefiderocol: 9 pathogens
- Meropenem: 10 pathogens

CREDIBLE-CR (NCT02714595; Ph3, double-blind; 2:1 randomization)
Cefiderocol: 25 patients [24.8%] (101) Best-available therapy: 13 patients [26.5%] (of 49)

- Cefiderocol: 27 pathogens
- Best available therapy: 15 pathogens

**Table 2**. Source of bacteremia by patient across the 3 studies

| Original Site of Infection | APEKS-cUTI CFDC (N=19) | APEKS-cUTI IMP/CS (N=9) |
|---|---|---|
| Urinary | | |
| cUTI with pyelonephritis | 7 (37%) | 4 (44%) |
| cUTI without pyelonephritis | 4 (21%) | 1 (11%) |
| Acute uncomplicated pyelonephritis | 8 (42%) | 4 (44%) |
| **Respiratory** | **APEKS-NP CFDC (N=8)** | **APEKS-NP MEPM (N=10)** |
| VAP | 4 (50%) | 6 (60%) |
| HAP | 3 (38%) | 2 (20%) |
| *Ventilated HAP* | *0* | *1 (10%)* |
| HCAP | 1 (13%) | 2 (20%) |
| *Ventilated HCAP* | *1 (13%)* | *2 (20%)* |
| | ***CREDIBLE-CR*** | |
| | **CFDC (N=25)** | **BAT (N=13)** |
| Respiratory | | |
| VAP | 2 (8%) | 2 (15%) |
| BSI/Sepsis | | |
| cIAI | 4 (16%) | 2 (15%) |
| SSSI | 2 (8%) | 0 |
| Intravenous line | 3 (12%) | 5 (38%) |
| Other* | 4 (16%) | 1 (8% |
| Unknown | 7 (28%) | 3 (23%) |
| Urinary | 3 (12%) | 0 |

BAT, best-available therapy; CFDC, cefiderocol, cIAI, complicated intra-abdominal infection; MEPM, meropenem; SSSI, skin and skin structure infection. *Other category could include biliary tract infection, pelvic infection, respiratory tract (other than infections sites identified as HAP, VAP, HCAP) could include community-acquired pneumonia, lung abscess, pleural space, or empyema.

**Table 3**. Baseline bacteremia Gram-negative pathogens by pathogen across studies

| Pathogen type | APEKS-cUTI CFDC (N=19) | APEKS-cUTI IMP/CS (N=9) | APEKS-NP CFDC (N=9) | APEKS-NP Meropenem (N=10) | CREDIBLE-CR CFDC (N=27) | CREDIBLE-CR BAT (N=15) | Overall CFDC (N=55) | Overall Comparators (N=34) |
|---|---|---|---|---|---|---|---|---|
| Enterobacterales (N=62) | | | | | | | | |
| *K. pneumoniae (23)* | | | 3 | 4 | 11 | 5 | 14 | 9 |
| *K. oxytoca (2)* | 1 | | | | 1 | | 2 | 0 |
| *E. coli (29)* | 16 | 8 | 1 | 1 | 3 | | 20 | 9 |
| *E. aerogenes (1)* | 1 | | | | | | 1 | 0 |
| *E. cloacae (1)* | | | | 1 | | | 0 | 1 |
| *P. stuartii (2)* | | | | 1 | | 1 | 0 | 2 |
| *M. morganii (1)* | | | | | | 1 | 0 | 1 |
| *S. marcescens (3)* | | | 2 | 1 | | | 2 | 1 |
| Carbapenem resistant | NA | NA | 1 | 0 | 12 | 6 | - | - |
| Carbapenem susceptible | 16 | 7 | 5 | 8 | 3 | 1 | - | - |
| Non-fermenters (N=27) | | | | | | | | |
| *A. baumannii (19)* | | 1 | 1 | | 11 | 6 | 12 | 7 |
| *A. anitratus (1)* | | | 1 | | | | 1 | 0 |
| *A. radioresistens (1)* | | | | | 1 | | 1 | 0 |
| *P. aeruginosa (4)* | 1 | | | 1 | | 2 | 1 | 3 |
| *B. cenocepacia (2)* | | | 1 | 1 | | | 1 | 1 |
| Carbapenem resistant* | 0 | 1 | 1 | 0 | 10* | 8 | - | - |
| Carbapenem susceptible | 1 | 0 | 2 | 2 | 1 | 0 | - | - |

BAT, best-available therapy; CFDC, cefiderocol; IMP/CS, imipenem/cilastatin; MEPM, meropenem; NA, not available. *Missing: n=1.

- Severe disease was found in 15.8% and 33.3% of patients in APEKS-cUTI study in the cefiderocol arm and IMP/CS arm, while in APEKS-NP and CREDIBLE-CR studies in both arms ≥50% of patients in both arms had severe disease (APEKS-NP: cefiderocol 50%, meropenem: 60%; CREDIBLE-CR: cefiderocol: 68%, BAT: 61.5%).
- In APEKS-NP, patients in both arms had high APACHE II scores (>20). In CREDIBLE-CR, patients in both arms had high median SOFA score at baseline (7.0).
- A total of 89 pathogens were isolated from the blood of 84 patients (**Table 3**). *Escherichia coli* (n=29), *Klebsiella pneumoniae* (n=23) and *Acinetobacter* spp. (n=21) were the most frequent species.
- *E. coli* was most frequent in APEKS-cUTI, *K. pneumoniae* in APEKS-NP, and *A. baumannii* in CREDIBLE-CR study.

**Table 4**. Clinical outcome across studies

| | APEKS-cUTI CFDC (N=19) | APEKS-cUTI IMP/CS (N=9) | APEKS-NP CFDC (N=8) | APEKS-NP MEPM (N=10) | CREDIBLE-CR CFDC (N=25) | CREDIBLE-CR BAT (N=13) |
|---|---|---|---|---|---|---|
| Clinical outcome at TOC | | | | | | |
| Clinical cure | 15 (79%) | 6 (67%) | 1 (13%) | 5 (50%) | 10 (40%) | 6 (46%) |
| Clinical failure | 1 (5%) | 1 (11%) | 4 (50%) | 4 (40%) | 10 (40%) | 6 (46%) |
| Indeterminate | 3 (16%) | 2 (22%) | 3 (38%) | 1 (10%) | 5 (20%) | 1 (8%) |
| Enterobacterales | N'=18 | N'=8 | N'=6 | N'=8 | N'=15 | N'=7 |
| Clinical cure | 14 (78%) | 5 (63%) | 1 (17%) | 4 (50%) | 8 (53%) | 3 (43%) |
| Clinical failure | 1 (6%) | 2 (25%) | 3 (50%) | 3 (38%) | 4 (27%) | 3 (43%) |
| Indeterminate | 3 (17%) | 1 (13%) | 2 (33%) | 1 (13%) | 3 (20%) | 1 (14%) |
| *Acinetobacter* spp. | N'=0 | N'=1 | N'=2 | N'=0 | N'=12 | N'=6 |
| Clinical cure | 0 | 1 (100% | 0 | 0 | 4 (33%) | 3 (50%) |
| Clinical failure | 0 | 0 | 2 (100%) | 0 | 6 (50%) | 3 (50%) |
| Indeterminate | 0 | 0 | 0 | 0 | 2 (17%) | 0 |
| *P. aeruginosa* | N'=1 | N'=0 | N'=0 | N'=1 | N'=0 | N'=2 |
| Clinical cure | 1 (100%) | 0 | 0 | 1 (100%) | 0 | 1 (100%) |
| Clinical failure | 0 | 0 | 0 | 0 | 0 | 1 (100%) |
| Indeterminate | 0 | 0 | 0 | 0 | 0 | 0 |
| *B. cenocepacia* | N'=0 | N'=0 | N'=1 | N'=1 | N'=0 | N'=0 |
| Clinical cure | 0 | 0 | 0 | 0 | 0 | 0 |
| Clinical failure | 0 | 0 | 1 (100%) | 1 (100%) | 0 | 0 |
| Indeterminate | 0 | 0 | 0 | 0 | 0 | 0 |

BAT, best-available therapy; CFDC, cefiderocol; IMP/CS, imipenem/cilastatin; MEPM, meropenem.

- Clinical outcomes varied by study and infection source and were often confounded (indeterminate response) (**Table 4**).
- The highest clinical cure rates at TOC were observed in APEKS-cUTI, which included patients who were not so seriously ill[4] compared with APEKS-NP[5] and CREDIBLE-CR[6].
- Indeterminate responses in the cefiderocol arm in both APEKS-NP and CREDIBLE-CR studies could have occurred due to either additional antibiotic treatment or due to death for any reason (mainly found in CREDIBLE-CR).

**Table 5**. Bacteremia outcome across studies

| | APEKS-cUTI CFDC (N=19) | APEKS-cUTI IMP/CS (N=9) | APEKS-NP CFDC (N=8) | APEKS-NP MEPM (N=10) | CREDIBLE-CR CFDC (N=25) | CREDIBLE-CR BAT (N=13) |
|---|---|---|---|---|---|---|
| Bacteremia outcome at TOC | | | | | | |
| Eradication | 17 (89%) | 7 (78%) | 1 (13%) | 6 (60%) | 16 (64%) | 11 (85%) |
| Persistence | 0 | 1 (11%) | 0 | 0 | 2 (8%) | 1 (8%) |
| Indeterminate | 2 (11%) | 1 (11%) | 7 (88%) | 4 (40%) | 7 (28%) | 1 (8%) |
| Enterobacterales | N'=18 | N'=8 | N'=6 | N'=8 | N'=15 | N'=7 |
| Eradication | 16 (89%) | 6 (75%) | 1 (17%) | 5 (63%) | 10 (67%) | 5 (71%) |
| Persistence | 0 | 1 (13%) | 0 | 0 | 1 (7%) | 1 (14%) |
| Indeterminate | 2 (11%) | 1 (13%) | 5 (83%) | 3 (38%) | 4 (27%) | 1 (14%) |
| *Acinetobacter* spp. | N'=0 | N'=1 | N'=2 | N'=0 | N'=12 | N'=6 |
| Eradication | 0 | 1 (100%) | 0 | 0 | 8 (67%) | 6 (100%) |
| Persistence | 0 | 0 | 0 | 0 | 1 (8%) | 0 |
| Indeterminate | 0 | 0 | 2 (100%) | 0 | 3 (25%) | 0 |
| *P. aeruginosa* | N'=1 | N'=0 | N'=0 | N'=1 | N'=0 | N'=2 |
| Eradication | 1 (100%) | 0 | 0 | 1 (100%) | 0 | 2 (100%) |
| Persistence | 0 | 0 | 0 | 0 | 0 | 0 |
| Indeterminate | 0 | 0 | 0 | 0 | 0 | 0 |
| *B. cenocepacia* | N'=0 | N'=0 | N'=1 | N'=1 | N'=0 | N'=0 |
| Eradication | 0 | 0 | 0 | 0 | 0 | 0 |
| Persistence | 0 | 0 | 0 | 0 | 0 | 0 |
| Indeterminate | 0 | 0 | 1 (100%) | 1 (100%) | 0 | 0 |

BAT, best-available therapy; CFDC, cefiderocol; IMP/CS, imipenem/cilastatin; MEPM, meropenem.

## Results (continued)

- Eradication at TOC was determined for 27/39 (69%) for cefiderocol and 16/23 (70%) for controls in patients with Enterobacterales, and for 9/16 (56%) for cefiderocol and 10/11 (91%) for controls in patients with NFs, respectively.
- Rates of indeterminate response were high in APEKS-NP study due to lack of post-baseline blood cultures or indeterminate clinical outcome.
- Persistence of bacteremia (ie, repeat positive blood culture during intravenous antibiotic treatment) at TOC was seen in 2/52 (3.8%) cefiderocol and 2/32 (6.2%) control patients, usually due to lack of source control (**Table 5**). Details of persistence cases are shown in **Table 6**.

**Table 6**. Cases with persistent bacteremia

| | Treatment | Primary Diagnosis | Pathogen from blood | Clinical outcome at TOC | Micro outcome in blood | Comments |
|---|---|---|---|---|---|---|
| **APEKS-cUTI study** | | | | | | |
| Case 1 | Imipenem | cUTI with pyelonephritis | *E. coli* (CFDC MIC: 0.015; imipenem: 0.12) | Failure | Persistence at EOT (Day 2)<br>No sample after EOT | Urine sample collected only at baseline, EOT was on Day 2 due to adverse event. Ceftriaxone was administered from Day 2 to Day 14 |
| **CREDIBLE-CR** | | | | | | |
| Case 1 | CFDC monotherapy | BSI (unknown) | CR *A. baumannii* (CFDC MIC: 0.06) | Failure | Persistence at EA<br>No other samples | CR *K. pneumoniae* (CFDC MIC: 0.06) detected at EA (Day 4) and *A. baumannii*. Patient died on therapy (Day 6) |
| Case 2 | CFDC monotherapy | BSI (IAI) | CR *E. coli* (CFDC MIC: <0.03) | Failure | Eradication at EA, EOT<br>Recurrence at TOC | Clinical cure at EOT<br>Patient alive at EOS and Day 49 |
| Case 3 | Colistin<br>Fosfomycin | BSI (unknown) | CR *K. pneumoniae* (colistin MIC: <0.5) | Failure | Eradication at EA, EOT (Day 10)<br>Recurrence at Day 13 and Day 15<br>No sample at TOC | Source control questions intraabdominal<br>Clinical failure at EOT<br>Patient died on Day 17 |

EA, early assessment; EOT, end of treatment; EOS, end of study; MIC, minimum inhibitory concentration.

## Conclusions

Across the 3 cefiderocol clinical studies, methodological differences existed, which influenced outcomes overall and in each study.

- Post-treatment negative blood cultures were inconsistently collected, especially in APEKS-NP and APEKS-cUTI, however, negative blood cultures on therapy without recurrence was seen in 94% (34/36) of cefiderocol patients with sufficient information.

True documented persistence rates were low in each study. Lack of source control was a likely explanation for persistence in 3 of 4 cases, and recurrence occurred in 2 patients.

Due to the small numbers in the subgroups, conclusions about the cefiderocol eradication rate remain unclear and further studies are therefore warranted. A dedicated clinical trial in Gram-negative bacteremia (GAME CHANGER; NCT03869437) is ongoing and will better delineate microbiological outcomes following cefiderocol treatment.

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