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Cefiderocol treatment in polymicrobial infections: subgroup analysis of the real-world PROVE observational study

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BACKGROUND

- Despite the approval of several treatments for carbapenem-resistant (CR) Gram-negative bacterial infections, outcomes often remain poor with high rates of morbidity and mortality [1].
  - For patients infected with two or more CR Gram-negative pathogens, significantly higher 30-day mortality has been observed, with polymicrobial infections proposed as a risk factor for 30-day mortality [2,3].
  - Moreover, when compared with monomicrobial infections, empirical therapy of polymicrobial infections is often suboptimal [4].
- Cefiderocol, a siderophore cephalosporin antibiotic, has demonstrated potent activity against a broad range of Gram-negative bacteria, including CR strains.
  - Cefiderocol is approved in Europe for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options [5].
  - In addition, cefiderocol is approved in the United States for the treatment of complicated urinary tract infections (including pyelonephritis) and hospital-acquired and ventilator-associated bacterial pneumonia [6].
- This subgroup analysis of the PROVE study [7] assessed real-world outcomes and infection characteristics of patients with polymicrobial infections who were treated with cefiderocol.

METHODS

Design

- International
- Observational cohort
- Real-world cefiderocol use

Inclusion criteria

- Adults hospitalised between Nov 2020 and Jul 2024
- Confirmed Gram-negative bacterial infection
- Cefiderocol treatment for ≥72 hours

Descriptive data

- Baseline demographics
- Clinical characteristics
- Cefiderocol use
- Clinical cure[a]
- Clinical response[b]
- All-cause mortality[c]

In this analysis, data were collected from patients hospitalised due to polymicrobial infections.
Presented data have been revised since abstract submission.

Use QR code to access manuscript [7]

[a]Resolution or improvement of infection signs or symptoms without evidence of later relapse or death.
[b]Resolution or improvement of signs or symptoms at end of treatment as judged by the physician, excluding patients who died during therapy.
[c]Including patients who died during their hospitalisation.

RESULTS

Baseline characteristics

- A total of 306 patients, with a median (interquartile range) age of 58 (44.0–69.0) years, had polymicrobial infections (**Table 1**).
- Country of enrolment for patients with polymicrobial infections is shown in **Figure 1A**.
  - The incidence of polymicrobial infections ranged from 17.9% in Germany to 34.7% in Italy (**Figure 1B**).
- Respiratory tract infections and skin and skin structure infections were the most common infection types (**Figure 2**).
- Key pathogens were Enterobacterales, *Pseudomonas* spp., and *Acinetobacter* spp. (**Figure 3**).
  - Overall, 25 (8.2%) and 52 (17.0%) patients were previously colonised or infected by the same pathogen.
- Cefiderocol was primarily used in documented infections, with smaller proportions of patients receiving empirical or salvage treatment (**Table 1**).

Clinical outcomes and all-cause mortality

- Overall, 65.0% of patients had clinical cure, and 72.9% clinical response at end of treatment (**Table 2**).
  - Clinical cure was 59.6–75.0% and clinical response was 67.2–83.3% for key pathogens (**Table 2**).
  - Overall, 22.5% of patients died by Day 30.
  - By infection site, clinical cure rates ranged from 47.4% in bloodstream infections to 95.5% in urinary tract infections, with numerical differences in all-cause mortality rates at Day 30 (**Table 2**).
- Clinical cure and clinical response were higher in patients who received cefiderocol for documented infection compared with those who received empirical or salvage treatment (**Figure 4**).

Table 1. Patient demographics, baseline clinical characteristics, and cefiderocol use

Characteristic	Polymicrobial infections (N=306)
Median (IQR) age, years	58.0 (44.0–69.0)
Age ≥65 years, n (%)	107 (35.0)
Sex, male, n (%)	201 (65.7)
Any pre-existing medical condition, n (%)	281 (91.8)
Diabetes	68 (22.2)
Diabetes with end organ damage	39 (12.7)
Chronic pulmonary disease	66 (21.6)
Moderate-to-severe CKD	62 (20.3)
Any medical condition at admission, n (%)	
COVID-19	47 (15.4)
Sepsis	47 (15.4)
Septic shock	14 (4.6)
Secondary BSI, n (%)	34 (11.1)
Previous colonisation by the same pathogen	25 (8.2)
Previous infection by the same pathogen	52 (17.0)
CR infection, n (%)[a]	266 (86.9)
ICU stay at time of cefiderocol initiation, n (%)	179 (58.5)
Any organ support at time of cefiderocol initiation, n (%)	141 (46.1)
Type of organ support, n (%)	
Mechanical ventilation	141 (46.1)
Vasopressor use	105 (34.3)
Renal replacement therapy	45 (14.7)
ECMO	15 (4.9)
Reason for cefiderocol use, n (%)	
Documented infection	222 (72.5)
Empirical use	37 (12.1)
Salvage therapy	39 (12.7)
Unsure empirical or documented	1 (0.3)
Other/unknown	7 (2.3)
Median (IQR) time from culture to first cefiderocol dose, days	4.0 (2.0–7.0)
Median (IQR) duration of cefiderocol use, days	11.0 (7.0–15.0)
Gram-negative combination therapy (any), n (%)	80 (26.1)

[a]CR infection: presence of any CR pathogen in the index culture reported in the medical charts.
BSI, bloodstream infection; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CR, carbapenem-resistant; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.

CONCLUSIONS

- Cefiderocol, predominantly administered as monotherapy, demonstrated benefits in this difficult-to-treat population of patients with polymicrobial infections.
- Benefits were observed across infection sites and for infections caused by various Gram-negative pathogens, including Enterobacterales, *Pseudomonas* spp. *Acinetobacter* spp. and *Stenotrophomonas* spp.
- Mortality risk was highest in those with respiratory infections, while patients with polymicrobial urinary tract infections demonstrated a high rate of clinical cure.
- Clinical cure and clinical response rates with therapy for documented infections and empirical use were high, however, poorer outcomes were observed for patients who received cefiderocol as salvage therapy.

Table 2. Clinical outcomes and all-cause mortality at days 14 and 30 overall, by key pathogen, and by infection site

	n/N, % [95% confidence interval]			
	Clinical cure[a]	Clinical response at EOT[b]	Day 14 ACM	Day 30 ACM
All polymicrobial infections	199/306 **65.0** [59.4; 70.4]	223/306 **72.9** [67.5; 77.8]	36/306 **11.8** [8.4; 15.9]	69/306 **22.5** [18.0; 27.7]
Key pathogen[c]				
Enterobacterales	146/221 **66.1** [59.4; 72.3]	163/221 **73.8** [67.4; 79.4]	22/221 **10.0** [6.3; 14.7]	45/221 **20.4** [15.3; 26.3]
Pseudomonas spp.	125/188 **66.5** [59.3; 73.2]	140/188 **74.5** [67.6; 80.5]	17/188 **9.0** [5.4; 14.1]	34/188 **18.1** [12.9; 24.3]
Acinetobacter spp.	81/136 **59.6** [50.8; 67.9]	92/136 **67.6** [59.1; 75.4]	21/136 **15.4** [9.8; 22.6]	40/136 **29.4** [21.9; 37.8]
Stenotrophomonas spp.	35/58 **60.3** [46.6; 73.0]	39/58 **67.2** [53.7; 79.0]	9/58 **15.5** [7.4; 27.4]	14/58 **24.1** [13.9; 37.2]
Other NF-GN	18/24 **75.0** [53.3; 90.2]	20/24 **83.3** [62.6; 95.3]	1/24 **4.2** [0.1; 21.1]	3/24 **12.5** [2.7; 32.4]
Infection site				
Respiratory	100/163 **61.3** [53.4; 68.9]	116/163 **71.2** [63.6; 78.0]	25/163 **15.3** [10.2; 21.8]	47/163 **28.8** [22.0; 36.4]
Skin and skin structure	33/52 **63.5** [49.0, 76.4)	37/52 **71.2** [56.9; 82.9)	4/52 **7.7** [2.1; 18.5]	8/52 **15.4** [6.9; 28.1]
Urinary tract	21/22 **95.5** [77.2; 99.9]	21/22 **95.5** [77.2; 99.9]	1/22 **4.5** [0.1; 22.8]	1/22 **4.5** [0.1; 22.8]
Intra-abdominal	16/22 **72.7** [49.8; 89.3]	16/22 **72.7** [49.8; 89.3]	2/22 **9.1** [1.1; 29.2]	3/22 **13.6** [2.9; 34.9]
Bone and joint	14/19 **73.7** [48.8; 90.9]	15/19 **78.9** [54.4; 94.0]	1/19 **5.3** [0.1; 26.0]	5/19 **26.3** [9.2; 51.2]
Bloodstream	9/19 **47.4** [24.5; 71.1]	12/19 **63.2** [38.4; 83.7]	3/19 **15.8** [3.4; 39.6]	4/19 **21.1** [6.1; 45.6]
Other	6/9 **66.7** [29.9; 92.5]	6/9 **66.7** [29.9; 92.5]	0/9 **0** [0; 33.6]	1/9 **11.1** [0.3; 48.3]

Data are expressed as n/N (%; 95% confidence interval). [a]Patients were considered as clinically cured if the Principal Investigator reported the case to be resolved or improved, excluding those who relapsed. [b]Patients were considered as having clinical response if the Principal Investigator reported the case to be resolved or improved at EOT. [c]These infections are not mutually exclusive. ACM, all-cause mortality; EOT, end of treatment; NF-GN, non-fermenting Gram-negative.

Figure 1A. Country of enrolment among patients with polymicrobial infections in the PROVE study (2020–2024; N=306)

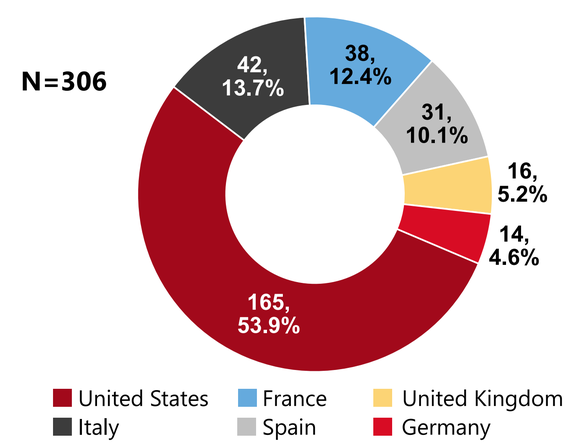
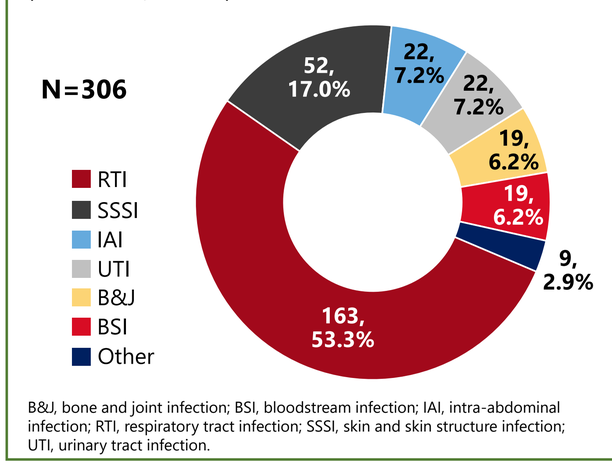


Figure 2. Primary site of infection among patients with polymicrobial infections in the PROVE study (2020–2024; N=306)



B&J, bone and joint infection; BSI, bloodstream infection; IAI, intra-abdominal infection; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Figure 1B. Proportion of polymicrobial infections by country

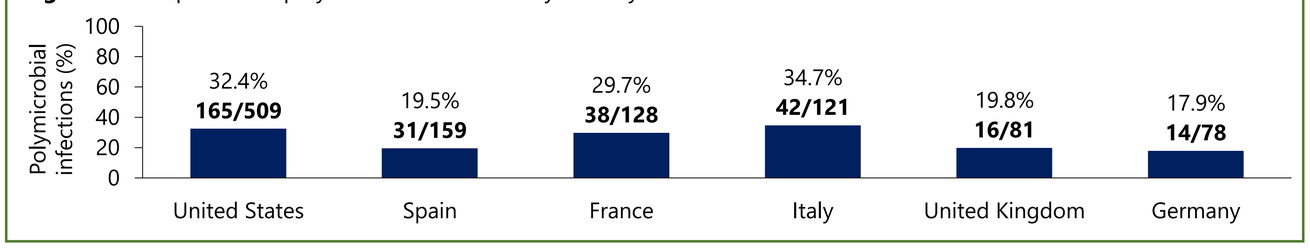


Figure 3. Key causative pathogens among patients with polymicrobial infections in the PROVE study (2020–2024; N=306)

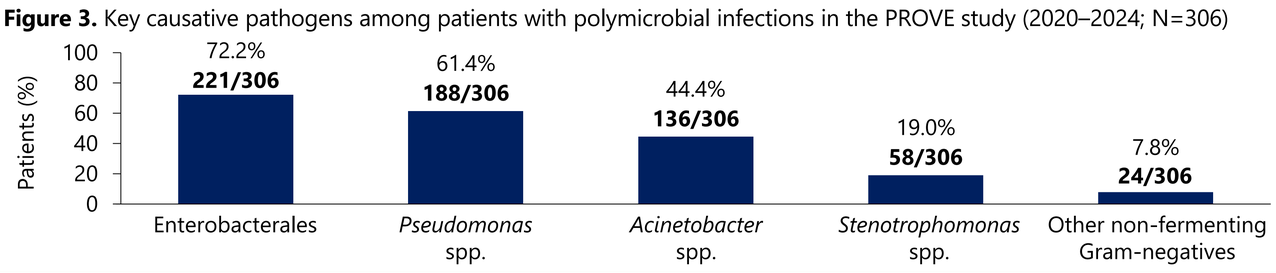
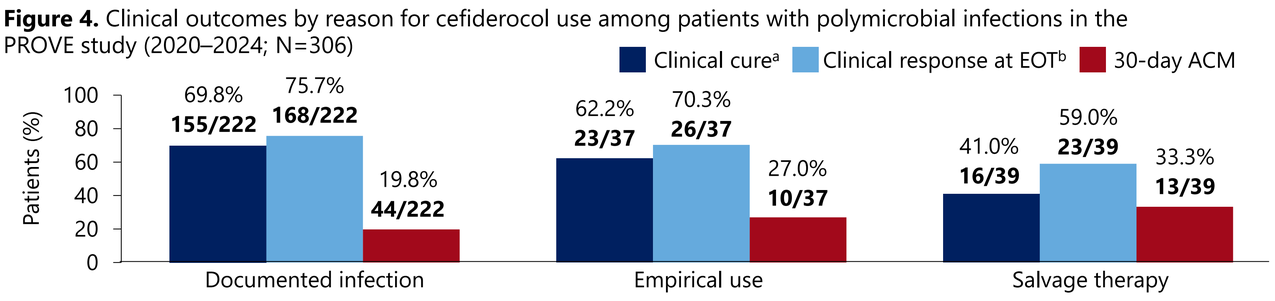


Figure 4. Clinical outcomes by reason for cefiderocol use among patients with polymicrobial infections in the PROVE study (2020–2024; N=306)



[a]Patients were considered as clinically cured if the Principal Investigator reported the case to be resolved or improved, excluding those who relapsed. [b]Patients were considered as having clinical response if the Principal Investigator reported the case to be resolved or improved at EOT. ACM, all-cause mortality; EOT, end of treatment.

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Conflict of interest
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