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Outcomes of Patients Treated With Cefiderocol For Infections Caused by β-Lactam–β-Lactamase Inhibitor Non-Susceptible Bacteria: Subgroup Analysis of the PROVE Study

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BACKGROUND

- Infections due to antimicrobial-resistant pathogens have been identified by the World Health Organization as one of the top global public health threats.[1]
- Guidance on the treatment of antimicrobial-resistant Gram-negative infections issued by the Infectious Diseases Society of America in 2024 recommend agents such as newly developed β-lactam–β-lactamase inhibitors (BL–BLIs) and cefiderocol for the treatment of infections caused by carbapenem-resistant (CR) pathogens.[2]
- *In vitro* surveillance data suggest low cross-resistance between cefiderocol and newly developed BL–BLIs.[3,4]
- The real-world PROVE study analyzed data from patients with serious Gram-negative bacterial infections treated with cefiderocol.[5]
- In this analysis, we compared patient characteristics, pathogens, and clinical outcomes by susceptibility status to BL–BLIs.

METHODS

- The international PROVE study was an observational medical chart review study conducted between November 2020 and July 2024.[5]
- Data were collated from hospitalized patients with confirmed Gram-negative bacterial infections caused by Enterobacterales or *Pseudomonas aeruginosa* (infections due to *Stenotrophomonas maltophilia* and *Acinetobacter* spp. were excluded from this analysis) and known BL–BLI susceptibility who received treatment with cefiderocol for ≥72 hours.
- BL–BLIs tested included ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam, with susceptibility data reported in medical charts and interpreted based on locally applicable breakpoints.
  - Susceptible (S) bacteria were susceptible to all BL–BLIs tested.
  - Non-susceptible (NS) bacteria were resistant or intermediate to at least one BL–BLIs tested.
- Baseline demographics, clinical characteristics, and clinical outcomes (in terms of clinical cure, clinical response and 30-day all-cause mortality [ACM]) were assessed.
  - Clinical cure was defined as the resolution or improvement of signs and symptoms of infection at end of treatment (EOT), without evidence of a later relapse or death.
  - Clinical response was defined as the resolution or improvement of signs/symptoms of infection at EOT, as judged by the physician, excluding those patients who died during therapy.
  - All-cause mortality included patients who died during their hospitalization.
    - Data are expressed as % [95% confidence interval] and n/N. 95% confidence intervals were collected by Clopper-Pearson test.
- Data collected were descriptive, and further data analyses are ongoing.

RESULTS

- Among a total population of 504 patients, ceftazidime-avibactam susceptibility information was available for 464 patients; ceftolozane-tazobactam susceptibility information for 368 patients, and imipenem-relebactam susceptibility information for 104 patients.
- Patients infected by NS (N=382) as compared with S (N=122) bacteria were noted to be older (median age 62.0 vs 56.0 years, respectively) (**Table 1**). In all enrolling countries, both BL-BLI S and NS pathogens were identified; although proportionally BL-BLI NS isolates were approximately 10x more frequent than S isolates in patients from Germany and Spain (**Table 1**).
- Occurrence of concomitant conditions was similar between patients with NS and S bacteria, with the exception of chronic pulmonary disease, which was more frequent in patients with S bacteria (**Table 1**).
- Patients with S compared with NS pathogens more frequently had respiratory tract infections (71.3% vs 49.2%), while urinary tract infections (4.9% vs 12.3%) and skin and skin structure infections (4.1% vs 12.3%) were less frequent among patients with S vs NS bacteria, respectively (**Table 1**).
- Proportionally, fewer patients with NS bacteria than S bacteria had indicators of more severe disease at cefiderocol initiation (intensive care unit stay: 52.6% vs 67.2%; organ support: 39.8% vs 51.6%) (**Table 1**).
- Distribution of Gram-negative pathogens is shown in **Figure 1**. Polymicrobial infections were more common in patients with S than NS bacteria (45.1% vs 25.1%, respectively) (**Figure 1**).
- Patients with S bacteria compared with NS bacteria were more likely to have ≥2 risk factors for acquired CR Gram-negative bacteria (66.4% vs 58.9%) and nearly all NS bacteria were CR pathogens (**Table 2**). Among isolates with known cefiderocol susceptibility status, 94.9% (75/79) of BL-BLI S and 90.6% (281/310) of BL-BLI NS isolates were susceptible to cefiderocol suggesting lack of cross-resistance; 4 and 17 isolates were resistant to cefiderocol in these two subgroups, respectively (**Figure 2**).
- Clinical cure rates were similar in patients with S and NS bacteria (70.5% vs 70.2%, respectively). 30-day ACM was numerically lower for patients with S than NS bacteria (18.9% vs 23.6%, respectively) (**Figure 3**).
- Regardless of BL-BLI susceptibility status, lower clinical cure rates were found among patients who received cefiderocol salvage treatment compared with those with documented infection or empiric cefiderocol treatment (**Figure 4**).
- Among patients infected by NS bacteria, numerically lower clinical cure rates were observed when cefiderocol was initiated 5–7 days or >7 days after culture collection compared with earlier initiation of treatment (**Figure 5**).

Table 1. Demographics and clinical characteristics of patients with pathogens tested for BL–BLI susceptibility in the PROVE study (2020–2024)

	BL–BLI S (N=122)	BL–BLI NS (N=382)
Demographics		
Age (years), median (IQR)	56.0 (42.0-65.0)	62.0 (47.0–70.0)
≥65 years old, n (%)	33 (27.0)	160 (41.9)
Sex, male, n (%)	80 (65.6)	252 (66.0)
Country of enrollment, n (%)		
USA	67 (54.9)	156 (40.8)
France	23 (18.9)	53 (13.9)
Germany	4 (3.3)	45 (11.8)
Italy	16 (13.1)	40 (10.5)
Spain	6 (4.9)	64 (16.8)
UK	6 (4.9)	24 (6.3)
Concomitant medical conditions, n (%)		
Diabetes mellitus	40 (32.8)	116 (30.4)
Chronic pulmonary disease	30 (24.6)	69 (18.1)
Moderate-to-severe CKD	21 (17.2)	71 (18.6)
Congestive heart failure	16 (13.1)	60 (15.7)
Sepsis or septic shock	17 (13.9)	56 (14.7)
Infection site, n (%)		
Respiratory	87 (71.3)	188 (49.2)
Bloodstream	10 (8.2)	40 (10.5)
Intra-abdominal	8 (6.6)	29 (7.6)
Urinary	6 (4.9)	47 (12.3)
Bone & joint	6 (4.9)	14 (3.7)
Skin and skin structure	5 (4.1)	47 (12.3)
Other	0 (0)	17 (4.5)
Treatment pattern		
Duration of cefiderocol use (days), median (IQR)	11.0 (8.0–15.0)	11.0 (8.0–16.0)
Combination therapy, n (%)	44 (36.1)	123 (32.2)
Time from culture to cefiderocol initiation (days), median (IQR)	5.0 (3–7.0)	5.0 (3–7.0)
Cefiderocol given prior to index culture sample, n (%)	0 (0)	0 (0)
0–≤2 days, n (%)	20 (16.4)	60 (15.7)
3–4 days, n (%)	42 (34.4)	104 (27.2)
5–7 days, n (%)	34 (27.9)	123 (32.2)
>7 days, n (%)	25 (20.5)	92 (24.1)
Severity of illness, n (%)		
ICU stay at initiation of cefiderocol	82 (67.2)	201 (52.6)
Receipt of any organ support at time of cefiderocol initiation	63 (51.6)	152 (39.8)
Mechanical ventilation	58 (47.5)	131 (34.3)
Vasopressor medications	35 (28.7)	83 (21.7)
Renal replacement therapy	14 (11.5)	39 (10.2)
ECMO	7 (5.7)	8 (2.1)

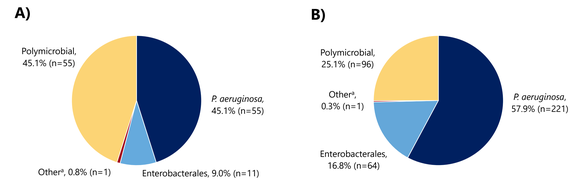
CKD, chronic kidney disease; ECMO, extra-corporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.

Table 2. Number of risk factors and carbapenem susceptibility status for patients with pathogens tested for BL–BLI susceptibility in the PROVE study

	BL–BLI S (N=122)	BL–BLI NS (N=382)
Number of risk factors[a] for CR-GNBI, n (%)		
0	10 (8.2)	34 (8.9)
1	31 (25.4)	123 (32.2)
2	42 (34.4)	114 (29.8)
3	28 (23.0)	80 (20.9)
≥4	11 (9.0)	31 (8.1)
Carbapenem susceptibility status[b], n (%)		
Resistant	96 (78.7)	357 (93.5)
Intermediate	12 (9.8)	12 (3.1)
Susceptible	10 (8.2)	6 (1.6)
Unknown	4 (3.3)	7 (1.8)

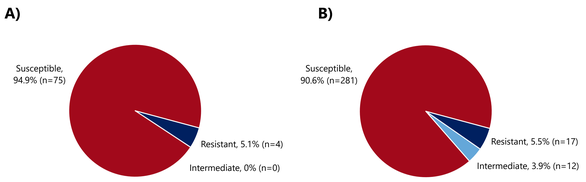
CR-GNBI, carbapenem-resistant Gram-negative bacterial infection.
[a]History of CR Gram-negative bacterial infection or colonization within last 6 months; immunocompromised patients; admitted to hospital in past 6 months; trauma, major surgery within 1 month before initiation of cefiderocol treatment; recent travel history to a foreign country; received carbapenem or non-response to carbapenem in the prior 30 days; were on ventilator at any point before taking the index culture sample; other. [b]Carbapenem susceptibility status was confirmed from the medical charts.

Figure 1. Distribution of Gram-negative pathogens among patients with A) BL–BLI S (N=122) and B) BL–BLI NS (N=382) pathogens in the PROVE study



[a]*Burkholderia* spp. n=1 in both subgroups.

Figure 2. Cefiderocol susceptibility status[a,b] among patients with A) BL–BLI S (N=122) and B) NS (N=382) pathogens in the PROVE study



[a]Unknown susceptibility: S isolates: n=43; NS isolates: n=72.
[b]Susceptibility status was reported; all cefiderocol susceptibilities were obtained from each site's local microbiology laboratory. The test result may have been collected in the local laboratory or in a reference laboratory. Susceptibility was interpreted according to local criteria in each country.

Figure 3. Clinical cure, clinical response rates and 30-day ACM overall in patients with BL–BLI S and NS pathogens in the PROVE study

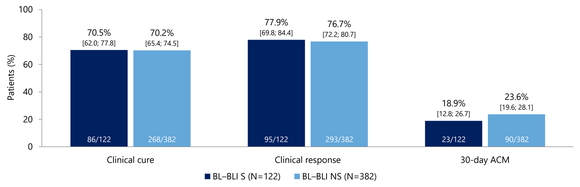
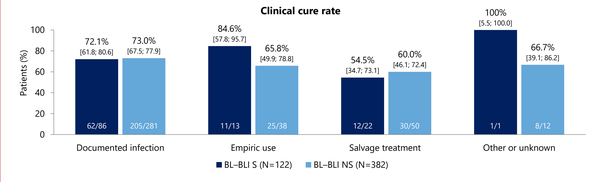
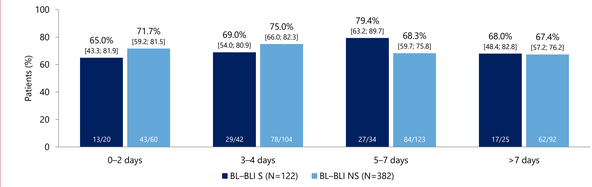


Figure 4. Clinical cure rates by reason for cefiderocol use[a] in patients with BL–BLI S and NS pathogens in the PROVE study



[a]Reported by the investigator. Documented infection: the pathogen and susceptibilities were known, and cefiderocol use was not due to failure of a prior antibiotic regimen. Empiric use: cefiderocol use started before the pathogen and/or susceptibilities were available to help guide the choice. Salvage therapy: cefiderocol was used after a prior antibiotic regimen had failed; patients usually received at least 3 days of prior antibiotic therapy to see whether there was an adequate response before the next course of antibiotic would be considered salvage. Other, including unknown: any other reason provided by the physician.

Figure 5. Clinical cure rates by time from culture collection to cefiderocol initiation in patients with BL–BLI S and NS pathogens in the PROVE study



CONCLUSIONS

- Clinical cure rates were similar in patients with BL–BLI S and NS pathogens, but observed differences in baseline severity limit the comparability of these data.
- High rates of cefiderocol susceptibility were observed among BL-BLI NS isolates, suggesting a lack of cross-resistance.

References

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Conflict of interest
SV, KG, and STN are employees of Shionogi. ASH is a contractor for Shionogi.
RKS has served as a paid consultant for Shionogi, AbbVie, Melinta, GlaxoSmithKline, and Merck, and has received investigator-initiated research funding from Shionogi, AbbVie, Melinta, Merck, and Roche.
MP has received lecture fees from and participated in an advisory board for Shionogi.
MCS-C has received honoraria for educational lectures, congress attendance, and advisory roles from Pfizer, MSD, Gilead, Shionogi, Viatris, and Mundipharma.

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