ESCMID Global

Abstract Book 2026

36th Congress of the European Society of Clinical Microbiology and Infectious Diseases

2026

P1891 | 05213

Cefiderocol therapy in multidrug-resistant Gram-negative infections: analysis from the SUSANA cohort

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Background

The spread of multi-drug-resistant (MDR) Gram-negative bacteria (GNB) represents a major clinical challenge and necessitates the use of novel agents such as cefiderocol (FDC). Its use in randomized clinical trials[1,2] and real-world settings raises questions regarding optimal clinical use.

Methods

We conducted a retrospective analysis of adult patients who received cefiderocol either as monotherapy or in combination therapy for ≥72 hours. Data were obtained from SUSANA (Surveillance of Safety and Outcome of New Antibiotics), a multicentre retrospective cohort study collecting demographic, clinical and microbiological variables for patients treated with novel antibiotics since November 2019. Univariate and multivariate regression analyses were performed to identify factors associated with 28-day recurrence.

Results

A total of 131 patients treated with FDC were included; 95 (73%) were male, with a median age of 65 years (IQR 52–74). The most frequent site of infection was the lower respiratory tract (58,44%). 71 (54%) patients developed bacteraemia, 86 (70%) had sepsis, and 21 (16%) experienced septic shock. The most frequent pathogens were carbapenem-resistant *Acinetobacter* spp. (67, 51%), carbapenem-resistant *Klebsiella pneumoniae* (37, 28%), difficult-to-treat-resistant *Pseudomonas aeruginosa* (18, 14%), and *Stenotrophomonas maltophilia* (16, 12%). The median duration of therapy was 12 days (IQR 9–15). Monotherapy was administered in 65 patients (49.6%). Clinical cure was achieved in 85 patients (65%), while recurrence occurred in 17 (13%). No difference in 28-day survival was observed between monotherapy and combination therapy (16 vs.13 deaths). Recurrence occurred in 11(17%) patients receiving monotherapy and 6(9%) receiving combination therapy. In regression analysis restricted to survivors who received ≥72 hours of each antibiotic at the start of follow-up, no independent predictors of 28-day recurrence were identified after adjusting for demographics, comorbidities, and combination therapy.

Conclusions

These findings may guide the use of FDC for infections caused by MDR-GNB; however, its use should remain conditional and individualized, given the current evidence. No significant differences in 28-day mortality or recurrence were observed between monotherapy and combination therapy, nor across different pathogen groups. Larger, prospective studies are essential to define the optimal clinical scenarios for FDC use and to guide evidence-based treatment strategies.

Figure 1. Baselines characteristics and outcomes of patients treated with cefiderocol either in monotherapy or combination therapy. Legend ICU= Intensive care unit ; Immunocompromised state= active hematologic malignancy, solid organ or stem cell transplantation, ongoing chemotherapy, neutropenia (absolute neutrophil count < 500/mm^3), HIV infection with CD4 < 200 cell/mm^3, chronic corticosteroid therapy equivalent to =20 mg/day of prednisone for =14 days, other immunsuppresive treatment

Baseline characteristics and outcomes of patients treated with cefiderocol in monotherapy or combination therapy

	Monotherapy (n = 65)	Combination therapy (n = 66)
Demographics		
Age (years, median [IQR])	67 [58-75]	64 [47-73]
Male sex, n (%)	49 (75.4)	46 (69.7)
Charlson comorbidity index [IQR]	5 [2 – 7]	3 [1– 6]
Nursing home resident, n (%)	5 (7.7)	1 (1.5)
Immunocompromised status	16 (24.6)	10 (15.2)
Hospitalization in the past 12 months	27 (41.5)	25 (37.9)
Major surgery in past 90 days	14 (21.5)	20 (30.3)
Clinical characteristics		
Sepsis, n (%)	45 (69.2)	41 (62.1)
Septic shock, n (%)	15 (23.1)	6 (9.1)
ICU admission, n (%)	30 (46.2)	34 (51.5)
Dialysis, n (%)	8 (12.3)	5 (7.6)
Source of infection		
Primary/CVC-related, n (%)	14 (21.5)	13 (19.7)
Respiratory tract, n (%)	26 (40.0)	32 (48.5)
Abdominal, n (%)	6 (9.2)	4 (6.1)
Genitourinary, n (%)	10 (15.4)	9 (13.6)
Osteoarticular, n (%)	1 (1.5)	4 (6.1)
Other sites, n (%)	10 (15.4)	14 (21.2)
With bacteremia, n (%)	36 (55.4)	35 (53.0)
Type of isolate		
Klebsiella pneumoniae, n (%)	16 (24.6)	21 (31.8)
Pseudomonas Aeruginosa, n (%)	9 (13.8)	9 (13.6)
Acinetobacter spp., n (%)	30 (46.2)	37 (56.1)
Stenotrophomonas maltophilia, n (%)	11 (16.9)	5 (7.6)
Other, n (%)	5 (7.7)	2 (3.0)
Treatment characteristics		
Days of therapy, n [IQR]	12 [9-16]	13 [8-15]
Outcome (28 days)		
Clinical cure, n (%)	38 (58.5)	47 (71.2)
Death, n (%)	16 (24.6)	13 (19.7)
Recurrence, n (%)	11 (16.9)	6 (9.1)

Figure 2. Univariate and multivariate regression analysis for risk factors associated with 28-day recurrence. Legend: ICU= Intensive care unit.

Regression analysis for 28-day recurrence		
	Univariate analysis (OR–CI 95%)	Multivariate analysis (OR–CI 95%)
Age	1.00 (0.97–1.03)	1.01 (0.97-1.04)
Major surgery in past 90 days	0.23 (0.05–1.08)	0.34 (0.06-1.86)
Respiratory tract infection	**3.11 (1.01–9.61)**	2.27 (0.61-8.39)
ICU	2.34 (0.76–7.23)	1.23 (0.28-5.47)
Septic shock	**6.00 (1.36–26.45)**	2.91 (0.48-17.63)
Sepsis	1.24 (0.34–4.61)	0.73 (0.16-3.34)
Dialysis	**6.67 (1.68–26.51)**	3.80 (0.80-18.03)
Combination therapy	0.46 (0.14–1.54)	0.57 (0.14-2.32)

References
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P1892 | 05224

Antibiotic strategies in difficult-to-treat *Pseudomonas aeruginosa* infections: monotherapy vs combination therapy in the italian SUSANA multi-centre study

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Background
Evidence comparing monotherapy versus combination strategies with novel beta-lactam/beta-lactamase inhibitors (BL/BLI) for difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa* infections is limited. Combination therapy is widely used, but factors guiding its use and its impact on outcomes remain unclear. We aimed to identify predictors of monotherapy versus combination therapy and variables associated with 28-day mortality.

Methods
We performed a retrospective analysis of patients with pneumonia or bloodstream infection caused by DTR *P. aeruginosa* treated with a novel BL/BLI [ceftolozane/tazobactam (C/T), ceftazidime/avibactam (C/A), cefiderocol, imipenem/relebactam, or meropenem/vaborbactam], either as monotherapy or combination therapy (BL/BLI plus aminoglycoside, fluoroquinolone, colistin, or fosfomycin). Data were obtained from the multicenter SUSANA cohort, which collects demographic, clinical, and microbiological information. Outcomes were assessed up to 28 days after therapy initiation. Kaplan–Meier curves evaluated crude survival; uni- and multivariable regression analyses identified factors associated with 28-day mortality.

Results
A total of 172 patients were included in the study (123 monotherapy, 49 combination therapy). Demographic and clinical characteristics are summarized in Table 1. Patients on combination therapy were younger, with fewer comorbidities and less chronic kidney disease (CKD). C/A was more frequent in combination regimens, whereas C/T and cefiderocol were primarily prescribed as monotherapy. Overall, 28-day mortality was 23.8%. In multivariable Cox regression adjusted for age, sex, CVD, CKD and treatment strategy, the presence of sepsis or septic shock was independently associated with mortality [adjusted hazard ratio (aHR) 4.30, 95% confidence interval (CI) 1.30–14.21]. Treatment strategy did not significantly affect survival (aHR for combination vs monotherapy 0.74, 95% CI 0.31–1.74). Prescribing decisions appeared driven by baseline patient characteristics rather than infection severity.

Conclusions
In this multicentre cohort, the choice of novel BL/BLI agents was primarily driven by patient-related factors, such as age, comorbidity burden and renal function. Sepsis or septic shock emerged as the strongest predictor of 28-day mortality, with monotherapy and combination therapy yielding comparable adjusted outcomes. Controlled studies are needed to determine the most effective treatment strategies for DTR *P. aeruginosa* infections and to improve patient stratification in comparative effectiveness research.