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ABSTRACT E POSTER HIGHLIGHTS DAL 35° ESCMID GLOBAL 2025

(European Congress of Clinical Microbiology and Infectious Diseases)

Focus su:

Cefiderocol nelle infezioni causate da batteri multiresistenti: ultimi dati sull'efficacia *in vitro* e negli studi *real-life*

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Cefiderocol nelle infezioni causate da batteri multiresistenti: ultimi dati sull'efficacia *in vitro* e negli studi *real-life*

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INDICE

INTRODUZIONE E COMMENTO GENERALE

La resistenza antibiotica (AMR) rappresenta una delle più gravi minacce alla sanità globale, provocando infezioni associate a mortalità più elevate, ospedalizzazioni più lunghe e costi maggiori. Infatti, è stato stimato che l'AMR nel 2021 sia stata direttamente responsabile di 1.14 milioni di morti e che abbia contribuito alla morte di 4.71 milioni di persone. Secondo le ultime stime si prevede che i patogeni multiresistenti causeranno più di 39 milioni di morti entro il 2050.

Considerando i patogeni gram-negativi resistenti ai carbapenemi, sono state stimate 1 milione di morti associate e 216000 morti direttamente attribuibili a tale resistenza nel 2021.

Per limitare la diffusione e il peggioramento dei tassi di antibiotico resistenza risulta fondamentale trovare un **equilibrio tra l'uso precoce e ottimale di antibiotici selezionati sul paziente critico** e una visione più ampia orientata a livello nazionale e globale per limitare la pressione ambientale selettiva dell'antibiotico (**antibiotic stewardship**).

Nelle terapie intensive i fattori di rischio associati alla presenza di patogeni multiresistenti (MDR, Multi-Drug Resistant) dipendono prevalentemente dall'epidemiologia locale, dall'uso precedente di antibiotici o ospedalizzazioni pregresse e da eventuali colonizzazioni note del paziente.

Tuttavia, tramite la somministrazione precoce di una terapia antibiotica adeguata con i nuovi farmaci è stato dimostrato che la mortalità non risulta incrementata anche in presenza di patogeni MDR.

Cefiderocol è una nuova cefalosporina siderofora che oltre ad entrare nella cellula batterica attraverso i canali delle porine utilizza i canali di trasporto del ferro con un meccanismo definito "a cavallo di Troia". Si lega alle proteine leganti le penicilline e risulta più stabile contro la degradazione da parte delle beta-lattamasi e risulta meno influenzato dalla up-regolazione di pompe di efflusso.

È attualmente approvato per le infezioni delle vie urinarie, per le polmoniti e infezioni causate da Gram-negativi in adulti con opzioni terapeutiche limitate grazie agli studi registrativi "APEKS-cUTI", "APEKS-NP" e "CREDIBLE-CR". **I regimi contenenti cefiderocol rispetto a quelli contenenti colistina hanno dimostrato di ridurre fallimento clinico, microbiologico e la mortalità nella polmonite associata al ventilatore (VAP) da *A. baumannii* in uno studio prospettico osservazionale.**

Specialmente nei pazienti ad alto rischio di contrarre infezioni da patogeni con **diversi meccanismi di resistenza [*Enterobacterales* Carbapeneme-Resistenti (CRE), *Acinetobacter baumannii* Carbapeneme-Resistenti (CRAB), e *Pseudomonas aeruginosa* Carbapene-**

me-Resistenti (CRPA)], cefiderocol (in monoterapia o in combinazione) **viene suggerito come terapia empirica in attesa dell'identificazione e suscettibilità definitiva di tali patogeni** (*Cortegiani 2022, Tamma IDSA Guidelines AMR 2024*).

Recentemente, nello studio "SENTRY" è stata dimostrata una suscettibilità nei confronti del farmaco maggiore del 94% in *Acinetobacter baumannii* MDR, maggiore del 96% in *Pseudomonas aeruginosa* DTR e maggiore dell'85% nei CRE.

Negli studi *real-life* cefiderocol ha dimostrato un successo clinico/clinical cure uno dei due tra il 53 e l'85% a seconda degli studi (PERSEUS, PROVE, ARES e altri) con la maggior parte dei pazienti inclusi ricoverati in terapia intensiva (ICU) con ventilazione meccanica invasiva (MV).

Lo studio "PERSEUS" ha incluso 261 pazienti (174 *P. aeruginosa*), mentre nello studio "ARES" sono stati considerati solo pazienti con infezione da *Acinetobacter baumannii* (147).

Anche nei confronti di *Stenotrophomonas maltophilia* cefiderocol ha dimostrato di avere un successo clinico del 70% (*Torre-Cisneiros J 2025*) e del 53% nei pazienti immunocompromessi (CEFI-ID).

Rispetto a specifici meccanismi di resistenza, l'attività del farmaco nei confronti dei Gram-negativi (GN) produttori di Metallo-beta-lattamasi (MBL) ha dimostrato di essere maggiore dell'86% (*Dobias J 2017, Simmer PJ 2022*).

Inoltre, la mortalità e il tasso di ricorrenza di malattia non sono risultati differenti in adulti immunocompetenti o immunodepressi quando cefiderocol veniva usato in monoterapia rispetto a regimi di combinazione (CEFI-ID).

Di seguito presentiamo una rapida rassegna di alcuni dei più interessanti dati su cefiderocol riportati nella sessione **Abstract e Poster del 35° ESCMID Global 2025.**

In questi lavori, viene ampiamente confermata **l'efficacia** di cefiderocol nelle infezioni da **Gram-negativi *(studio PROVE- P2542)* anche multiresistenti *(Studio SUSANA – E0718).*** Il trattamento con cefiderocol **migliora la sopravvivenza nei pazienti con batteriemia da *A. baumannii (studio ITACA – P0847).***

Anche gli **studi *in vitro*** presentati **confermano l'elevata attività di cefiderocol nei confronti dei ceppi di *P. Aeruginosa* ed *Enterobacterales* e di Gram-negativi** in generale, anche resistenti alla combinazione β lattamico + inibitore delle β -lattamasi e ai carbapenemi (*studio SENTRY – E0723; E0721; P1310; P1313; P1350; P1351; P1349; E0721*).

Poster 2542

35th ESCMID Global 2025
Vienna, Austria
11–15 April, 2025

Cefiderocol Treatment in Patients With Gram-Negative Bacterial Infections: European Results of the Global Retrospective Observational PROVE Study

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SHIONOGI

KEY POINTS

- Patient and disease characteristics, as well as pathogens, greatly varied across countries in the European cohort of the PROVE study.
- Patients who received cefiderocol earlier for a documented infection or empirically had numerically higher clinical cure rates than those who received cefiderocol salvage therapy.
- Outcomes were similar between monomicrobial and polymicrobial infections.

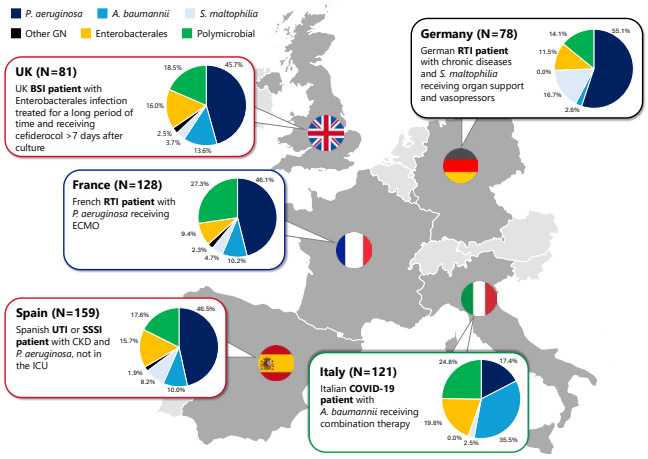
OBJECTIVE

We aimed to elucidate the clinical outcomes of cefiderocol treatment in patients with serious Gram-negative bacterial infections in real-world settings in 42 European centres across 5 countries in the PROVE study.

METHODS

Design: international, retrospective, medical chart review study.
Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours (November 2020–July 2024).
Endpoints: patient and pathogen characteristics, hospitalisation course, antibiotic treatment patterns, clinical cure, and 30-day all-cause mortality (ACM). Clinical cure was defined as resolution or improvement of signs/symptoms at the end of treatment (EOT), as judged by the physician; patients who died during therapy or had a relapse or reinfection due to the same pathogen after EOT during current hospitalisation were considered as clinical failure. ACM included patients who died during their hospitalisation. Only descriptive statistics are provided.

Figure 1: Distribution of baseline Gram-negative pathogens and description of a typical patient in each country



BSI, bloodstream infection; CKD, chronic kidney disease; COVID-19; coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; GN, Gram-negative; ICU, intensive care unit; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

RESULTS

Figure 2: Clinical cure and 30-day ACM rates by index pathogen

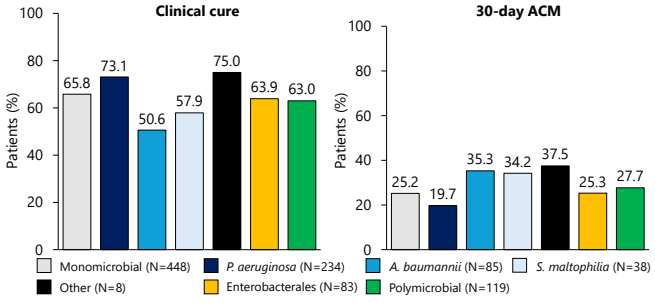
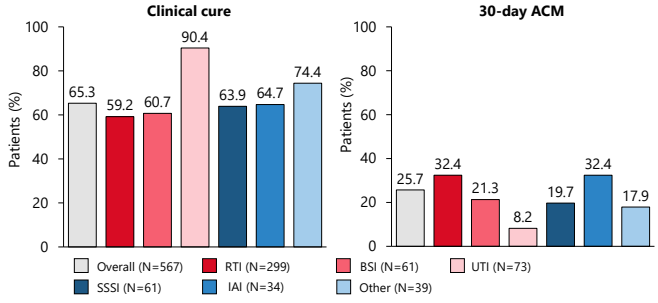


Figure 3: Clinical cure and 30-day ACM rates by infection site



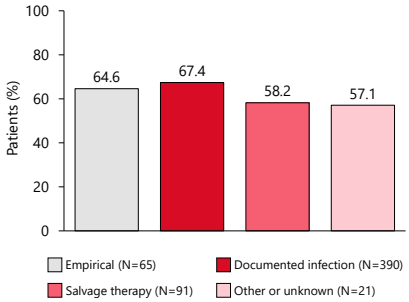
BSI, bloodstream infection; IAI, intra-abdominal infection; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Table 1: Demographics and baseline characteristics of European patients in the PROVE study

Demographics	Europe (N=567)	Spain (N=159)	France (N=128)	Italy (N=121)	Germany (N=78)	UK (N=81)
Age (years), median (IQR)	62.0 (48.0–71.0)	62.0 (50.0–70.0)	57.0 (45.0–69.0)	66.0 (52.0–74.0)	64.0 (52.0–72.0)	61.0 (42.0–69.0)
≥65 years old, n (%)	238 (42.0)	61 (38.4)	42 (32.8)	66 (54.5)	36 (46.2)	33 (40.7)
Sex, male, n (%)	394 (69.5)	113 (71.1)	94 (73.4)	81 (66.9)	51 (65.4)	55 (67.9)
Most frequent concomitant medical conditions (not mutually exclusive), n (%)						
Diabetes mellitus	140 (24.7)	34 (21.4)	34 (26.6)	31 (25.6)	21 (26.9)	20 (24.7)
COVID-19	115 (20.3)	9 (5.7)	37 (28.9)	41 (33.9)	15 (19.2)	13 (16.0)
Chronic pulmonary disease	92 (16.2)	16 (10.1)	24 (18.8)	25 (20.7)	16 (20.5)	11 (13.6)
Moderate-to-severe CKD	86 (15.2)	28 (17.6)	14 (10.9)	11 (9.1)	17 (21.8)	16 (19.8)
Congestive heart failure	67 (11.8)	21 (13.2)	14 (10.9)	11 (9.1)	14 (17.9)	7 (8.6)
Infection sites, n (%)						
RTI	299 (52.7)	69 (43.4)	82 (64.1)	72 (59.5)	34 (43.6)	42 (51.9)
BSI	61 (10.8)	13 (8.2)	13 (10.2)	16 (13.2)	8 (10.3)	11 (13.6)
UTI	73 (12.9)	34 (21.4)	7 (5.5)	11 (9.1)	11 (14.1)	10 (12.3)
SSSI	61 (10.8)	30 (18.9)	2 (1.6)	11 (9.1)	10 (12.8)	8 (9.9)
IAI	34 (6.0)	5 (3.1)	11 (8.6)	4 (3.3)	9 (11.5)	5 (6.2)
Other	39 (6.9)	8 (5.0)	13 (10.2)	7 (5.8)	6 (7.7)	5 (6.2)
Treatment characteristics						
Duration of cefiderocol use (days), median (IQR)	11.0 (8.0–16.0)	11.0 (8.0–16.0)	12.5 (8.0–16.0)	11.0 (8.0–16.0)	11.0 (8.0–15.0)	12.0 (7.0–17.0)
Combination therapy, n (%)	196 (34.6)	31 (19.5)	40 (31.3)	69 (57.0)	26 (33.3)	30 (37.0)
Severity of illness, n (%)						
ICU stay at initiation of cefiderocol	317 (55.9)	80 (50.3)	76 (59.4)	71 (58.7)	48 (61.5)	42 (51.9)
Receipt of any organ support at time of cefiderocol initiation	234 (41.3)	60 (37.7)	47 (36.7)	50 (41.3)	42 (53.8)	35 (43.2)
Mechanical ventilation	204 (36.0)	49 (30.8)	40 (31.3)	47 (38.8)	38 (48.7)	30 (37.0)
Use of vasopressor medication	149 (26.3)	39 (24.5)	25 (19.5)	32 (26.4)	36 (46.2)	17 (21.0)
ECMO	20 (3.5)	2 (1.3)	13 (10.2)	2 (1.7)	1 (1.3)	2 (2.5)
Renal replacement therapy	54 (9.5)	8 (5.0)	9 (7.0)	4 (3.3)	19 (24.4)	14 (17.3)

BSI, bloodstream infection; CKD, chronic kidney disease; COVID-19; coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Figure 4: Clinical cure rates by reason for cefiderocol administration



Clinical cure rates were numerically higher among patients who received cefiderocol as initial **empirical (64.6%)** or **targeted (67.4%) treatment** compared with patients who received it as **salvage therapy (58.2%)**.

Acknowledgements

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STUDI *REAL-WORLD*

Asensio Martin MJ et al. Cefiderocol treatment in patients with Gram-negative bacterial infections: European results of the global retrospective observational PROVE study.

Highlights

- Lo studio retrospettivo osservazionale PROVE ha esaminato gli *outcome* del trattamento con cefiderocol in 567 pazienti con infezioni batteriche serie da Gram-negativi (principalmente *Pseudomonas aeruginosa*) nel contesto *real-world* di 5 Paesi Europei, tra cui l'Italia.
- Il tasso globale di guarigione clinica è risultato pari al 65,3% e la mortalità per ogni causa a 30 giorni pari al 25,7%.
- Nei pazienti con infezione da *Pseudomonas aeruginosa* il tasso di guarigione clinica è stato del 73,1%, con una mortalità a 30 giorni del 19,7%.

I **tassi di guarigione clinica** sono stati numericamente **più elevati tra i pazienti che hanno ricevuto cefiderocol come trattamento iniziale empirico (64,6%) o mirato (67,4%)** rispetto ai pazienti che lo hanno ricevuto come terapia di salvataggio (58,2%).

Predictive factors of early and late mortality and evaluation of therapeutic efficacy in patients with bacteremia associated with MDR *Acinetobacter baumannii*: the ITACA (ITalian Advances on Carbapenem-resistant *Acinetobacter*) study

Alessandro Russo[1-2], **Sara Palma Gullì**[1], Antonio Vena[3], Silvia Corcione[4], Riccardo Serraino[1], Francesca Serapide[1], Matteo Bassetti[3], Carlo Torti[5-6], Enrico Maria Trecarichi[7]

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Introduction: Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection, especially bacteremia, represents a major challenge for clinicians due to high morbidity and mortality rates.
However, predictors of early and late mortality and the therapeutic choices associated with a higher survival rate should be definitively assessed.

Materials and Methods: This is an observational, prospective, multicenter study conducted in 52 Italian centers. The study was conducted for 18 months and hospitalized patients who developed clinically significant infection and concomitant bacteremia by CRAB were enrolled. The primary objective of the study was the analysis of clinical and therapeutic factors that could predict mortality at 14 and 30 days after the development of infection.

Results: During study period, 398 patients were enrolled. Out of these, 140 (35.2%) were male, the mean age was 67 years, and the mean Charlson Comorbidity Index was 5 points. The source of bacteremia was primary in 26.8% of patients, CVC-related in 28.6%, secondary to hospital-acquired pneumonia in 17% and ventilator-associated pneumonia in 22.6%. Other sources were intra-abdominal, urinary or skin and soft tissue infection. Overall, 89/398 (22.3%) died at 14 days and 107/398 (26.8%) at 30 days. At univariate analysis, follow-up blood cultures were more frequently negative in survivors (75.3%) compared to non survivors (48%) at 14 days (p=0.008); cefiderocol containing-regimen was associated with survival at 14 days (p<0.001). At logistic regression analysis, therapeutic failure (OR 4.03, CI 95% 2.16-7.5, p<0.001, primary bacteremia (OR 2.1, CI 95% 1.1-3.7, p=0.01), and previous colonization by *Acinetobacter baumannii* (OR 3.5, CI 95% 1.7-7.3, p<0.001) were independently associated with 30-day mortality, while respiratory improvement after 72 hours from targeted therapy (OR 0.25, CI 95% 0.13-0.49, p<0.001) with 30-day survival.

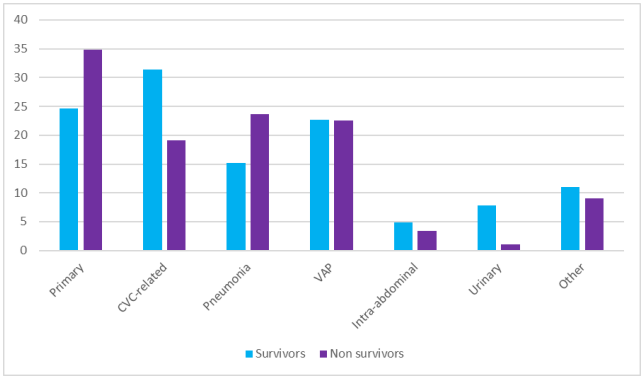

Figure 1: survivors vs non survivors at 14 days, source of bacteremia.

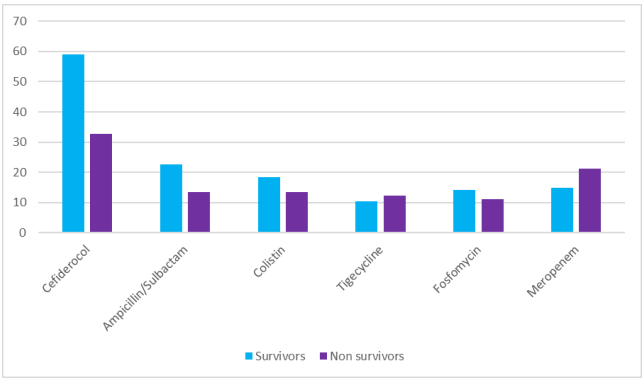

Figure 2: survivors vs non survivors at 14 days, therapeutic regimens.

VARIABLES	HR	95%CI Lower	95%CI Upper	*p*-value
Primary bacteremia	2.114	1.193	3.746	0.010
Therapeutic failure	4.033	2.167	7.505	<0.001
Respiratory improvement at 72 h	0.255	0.130	0.499	<0.001
Previous *A. baumannii* colonization	3.556	1.726	7.326	<0.001

Table 1. Logistic regression analysis about risk factors associated with 30-day mortality.

Conclusions: Data highlighted important factors associated with dead or survival in bacteremic CRAB infections. These observations represent an important advance in the management of this difficult-to-treat infection.

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Russo A et al. Predictive factors of early and late mortality and evaluation of therapeutic efficacy in patients with bacteremia associated with MDR *Acinetobacter baumannii*: the ITACA (ITalian Advances on Carbapenem-resistant *Acinetobacter*) study.

Highlights

- Studio italiano multicentrico, osservazionale, prospettico, condotto in 398 pazienti ricoverati che hanno sviluppato un'infezione significativa e batteriemia concomitante da *Acinetobacter baumannii* resistente ai carbapenemi.
- Obiettivo dello studio era quello di esaminare i fattori clinici e terapeutici predittivi di mortalità a 14 e 30 giorni.
- Il fallimento terapeutico, la batteriemia primaria e la pregressa colonizzazione da *Acinetobacter baumannii* sono risultati significativamente associati in maniera indipendente alla mortalità a 30 giorni (rispettivamente $p<0,001$; $p=0,01$; $p=0,001$), mentre il miglioramento respiratorio dopo 72 h dalla terapia mirata ha mostrato di associarsi significativamente alla sopravvivenza a 30 giorni ($p<0,001$).

Lo **studio ITACA** dimostra che i regimi contenenti **cefiderocol** sono significativamente associati ad una **sopravvivenza a 14 giorni (p<0,001) nei pazienti con batteriemia associata a MDR *Acinetobacter baumannii*.**

Impact of cefiderocol therapy on patient survival across different multi drug-resistant Gram-negative bacilli infections: insights from the SUSANA cohort

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BACKGROUND

- The spread of multi-drug resistant (MDR) Gram-negative bacteria (GNB) poses a significant challenge, often managed with novel antibiotics like cefiderocol (FDC).
- Because of its unique mechanism of action and extensive spectrum, FDC is considered a last-resort option.
- Real-world data are essential to clarify its role in combination therapy regimens and stewardship programs.

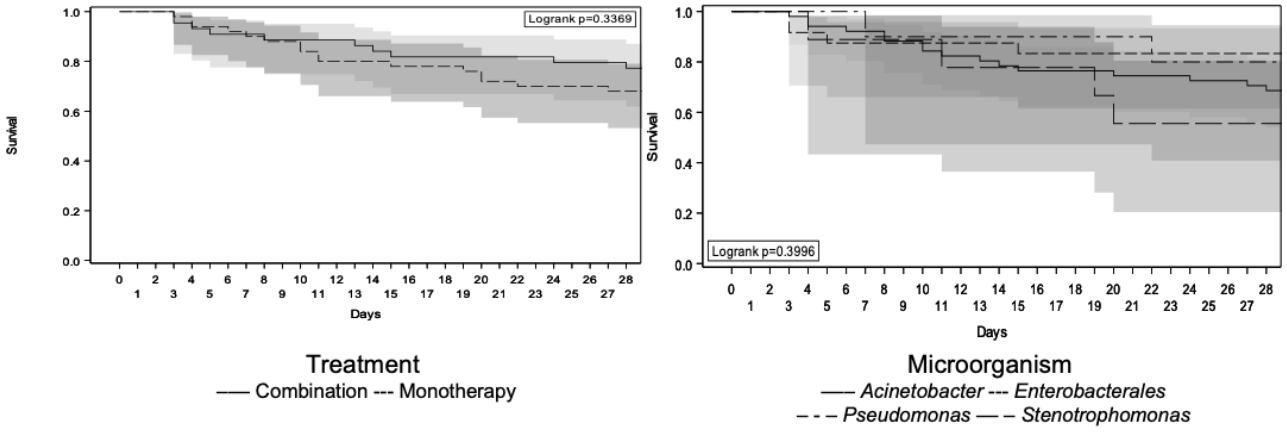
METHODS

- Data were extracted from the SUSANA (Surveillance of Safety and outcome of New Antibiotics) database, a retrospective, multicentric cohort study started in November 2019 on the use of new antibiotics for patients with suspected or microbiologically documented MDR infections.
- The dataset includes patient demographics, underlying comorbidities, treatment regimens, type and site of infection, pathogen characteristics and end-of-treatment outcomes.
- Continuous variables were analysed using the Mann-Whitney U test, while categorical variables were assessed with either the χ^2 or Fisher's exact test. Kaplan-Meier survival curves, along with log-rank tests were applied to examine 28-day survival.

RESULTS

- Ninety-four patients treated with FDC were included; 69 patients (73%) were men, with a median age of 68 years (IQR 57-75). The most common site of infection was the lower respiratory tract (41, 44%). Forty-two patients (45%) developed bacteraemia, 66 (70%) sepsis and 13 (14%) septic shock.
- The main isolated microorganisms were carbapenem-resistant *Acinetobacter baumannii* (CRAB; 51, 54%), carbapenem-resistant *Enterobacterales* (CRE; 24, 25%), difficult-to-treat resistant *Pseudomonas aeruginosa* (DTRPA; 10, 11%) and *Stenotrophomonas maltophilia* (9, 10%).
- The median duration of therapy was 11 days (IQR 8-14). Monotherapy was used for 50 (53%) patients.
- The overall clinical cure rate was 65% (61/94) but only 51% (39/51) in patients with CRAB infections.
- As shown in Figure 1, no significant differences in 28-day survival were found between monotherapy and combination therapy (χ^2 0.9, *p* 0.33) or across different MDR infections (χ^2 2.9, *p* 0.39). However, monotherapy carried a significantly higher risk of infection recurrence compared to combination therapy (χ^2 3.87, *p* 0.04).

Figure 1. Kaplan-Meier curves illustrating 28-day survival between treatment different treatment options and across different microorganisms.



No significant 28-day survival differences between monotherapy and combination therapy or among different pathogens were observed, but a higher risk of infection recurrence was associated with monotherapy.

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Highlights

- In questo studio sono stati utilizzati i dati di 94 pazienti (età mediana: 68 anni) della coorte del trial multicentrico, retrospettivo SUSANA (*Surveillance of Safety and outcome of New Antibiotics*), il cui obiettivo era quello di indagare l'impiego di nuovi antibiotici, come cefiderocol, nelle infezioni multi-resistenti (MDR) sospette o microbiologicamente documentate.

- Con **cefiderocol**, la guarigione clinica è stata ottenuta in 61 casi (65%); il tasso di guarigione clinica nelle infezioni da *Acinetobacter baumannii* resistente a carbapenemi è risultato pari al 51% (39 pazienti).

- Nessuna differenza nei tassi di sopravvivenza a 28 giorni è stata rilevata tra la monoterapia o la terapia di combinazione o tra i patogeni (rispettivamente p=0,33 e p=0,39).

Lo studio dimostra che **cefiderocol** è efficace nel trattamento dei batteri Gram-negativi multi-resistenti.

Ceftazidime-avibactam plus aztreonam *versus* cefiderocol in the treatment of infections caused by Metallo-β-lactamase-Producing Microorganisms: real-word data from the Italian cohort SUSANA

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Background

- Metallo-β-lactamase (MBL)-producing *Enterobacterales* are increasingly prevalent in Europe, including Italy[1,2], posing a major therapeutic challenge due to limited treatment options.
- Previous studies have reported 30-day mortality rates of up to 35%, significantly higher than those associated with infections caused by carbapenem-susceptible gram-negative bacilli[3].
- Current guidelines recommend ceftazidime-avibactam plus aztreonam (CAZ/AVI+ATM) or cefiderocol (FDC) as preferred treatment options[4], yet comparative clinical data remain scarce.

Methods

- A multicenter, retrospective, real-world cohort study was conducted on patients treated with CAZ/AVI+ATM or FDC for microbiologically documented MBL infections between 2021 and 2024, as part of the ongoing SUSANA cohort (Surveillance of Safety and Outcome of New Antibiotics).
- Collected data included demographics, comorbidities, treatment regimens, infection sites, pathogen profiles, and end-of-treatment clinical outcomes.
- Continuous variables were compared using the Mann-Whitney U test, while categorical variables were analyzed with the chi-square or Fisher's exact test. Kaplan-Meier curves with log-rank tests were used to evaluate 28-day survival.

Results

- Forty-one patients were analysed (20 treated with CAZ/AVI+ATM, 21 with FDC). Most patients were male (65% vs. 91%), with a median age of 69 and 64 years, respectively. The Charlson Comorbidity Index was comparable between groups (5 vs. 4, p=0.529). These and other characteristics are detailed in Table 1.
- As shown in Table 2, urinary tract infections were more frequent in the CAZ/AVI+ATM group (39.1% vs. 20%), while lower respiratory tract infections were more common in the FDC group (28% vs. 4.3%). Bloodstream infections occurred in 60% of CAZ/AVI+ATM patients and 61.9% of FDC patients.
- The median treatment duration was 13 days for CAZ/AVI+ATM and 10 days for FDC.
- *Klebsiella* species was the most common isolated pathogen (90% vs. 61.9%). New Delhi Metallo-β-lactamase (NDM) was the prevalent type of MBL (80% vs. 71.4%).

	CAZ/AVI+ATM(N=20)	FDC (N=21)	p-value
Male sex, n (%)	13 (65%)	19 (90.5%)	0.067
Median age, years (IQR)	69 (51-75)	64 (53-79)	0.948
Comorbidities, n (%)			
Diabetes	3 (15%)	5 (23.8%)	0.697
Localized or metastatic solid cancer	5 (25%)	5 (23.8%)	0.433
Peripheral Vascular Disease	3 (15%)	3 (14.3%)	1.000
Moderate to Severe Chronic Kidney Disease	4 (20%)	4 (19.1%)	1.000
History of Stroke	4 (20%)	2 (9.5%)	0.410
History of Myocardial Infarction	4 (20%)	3 (14.3%)	0.689
COPD	3 (15%)	4 (19.1%)	1.000
Congestive Heart Failure	4 (20%)	2 (9.5%)	0.661
Liver Disease	2 (10%)	1 (4.8%)	0.606
Haematological malignancy	2 (10%)	0	0.299
Median CCI, (IQR)	5 (3-7)	4 (2-6)	0.529
Hospitalization in the previous 12 months, n (%)	14 (70%)	10 (47.6%)	0.197
Immunosuppressed state, n (%)	5 (25%)	8 (38.1%)	0.511
Septic shock at treatment start, n (%)	5 (25%)	1 (4.8%)	0.093
ICU admitteted at treatment start, n (%)	3 (15%)	7 (33.3%)	0.277

Table 1. Baseline Patient Characteristics.
IQR: Interquartile Range; CCI: Charlson Comorbidity Index; COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit.

	CAZ/AVI+ATM(N=20)	FDC (N=21)	p-value
Source of infection, n (%)			
Genitourinary tract	9 (39.1%)	5 (20%)	0.506
Abdominal	5 (21.7%)	4 (16%)	1.000
Lower respiratory tract	1 (4.3%)	7 (28%)	0.045
Central venous catheter-related	3 (13%)	5 (20%)	0.698
Skin and soft tissue	2 (8.7%)	1 (4%)	0.606
Osteoarticular	1 (4.3%)	0	0.488
Cardiovascular	0	1 (4%)	1.000
Other	2 (8.9%)	2 (8%)	
Positive blood cultures, n (%)	12 (60%)	13 (61.9%)	0.675
Isolated microrganism, n (%)			0.222
Klebsiella species	18 (90%)	13 (61.9%)	
Pseudomonas species	1 (5%)	3 (14.3%)	
Others	1 (5%)	5 (23.8%)	
Type of Metallo-β-lactamase, n (%)			0.261
NDM	16 (80%)	15 (71.4%)	
VIM	4 (20%)	6 (28.6)	
Median treatment duration, days (IQR)	13 (10-16)	10 (7-14)	0.089

Table 2. Infection Types and Treatment Characteristics.
NDM: New Delhi Metallo-β-lactamase; VIM: Verona Integron-encoded Metallo-β-lactamase.

- Clinical success was achieved in 85% of CAZ/AVI+ATM patients vs. 71.4% of FDC patients, while mortality at 28-day occurred in 10% and 23.8% of patients, respectively (p=0.499).
- As shown in Fig 1, Kaplan-Meier analysis showed no significant difference in 28-day survival between treatment groups (log-rank p=0.207).

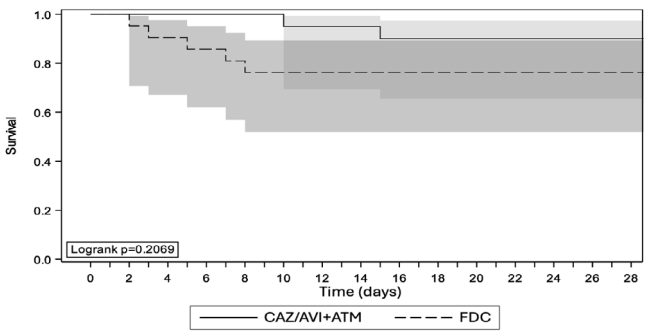

Figure 1 Kaplan-Meier curve illustrating 28-day survival between treatment groups.

CAZ/AVI+ATM and FDC showed comparable effectiveness in the treatment of infections caused by Metallo-β-lactamase-producing microorganisms.

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Mezzadri L et al. Ceftazidime-avibactam plus aztreonam *versus* cefiderocol in the treatment of infections caused by Metallo-β-lactamase-Producing Microorganisms: real-word data from the Italian cohort SUSANA.

Highlights

- Studio multicentrico retrospettivo, di coorte, in *real-world*, su pazienti trattati con l'associazione ceftazidime-avibactam plus aztreonam (CAZ/AVI+ATM) o con cefiderocol (FDC) per infezioni da *Enterobacterales* produttori di Metallo ß-lattamasi, microbiologicamente documentate, tra 2021 e 2024, nell'ambito della coorte SUSUNA (*Surveillance of Safety and Outcome of New Antibiotics*).

- È stato riportato il successo clinico nell'85% dei pazienti CAZ/AVI+ATM *vs.* 71,4% dei pazienti FDC, mentre la mortalità al 28° giorno è stata del 10% e del 23,8% dei pazienti CAZ/AVI+ATM e FDC rispettivamente (p=0,499). La sopravvivenza al 28° giorno non è risultata significativamente differente tra i due gruppi di trattamento (log-rank p=0,207).

Il trattamento con l'associazione CAZ/AVI+ATM e quello con **cefiderocol** hanno mostrato **efficacia sovrapponibile nella terapia delle infezioni causate da *Enterobacterales* produttori di Metallo-ß-lattamasi.**

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Activity of cefiderocol against carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2023)

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Introduction

- Cefiderocol is approved in Europe for the treatment of infections in adult patients due to aerobic Gram-negative organisms, where limited treatment options are available.
  - Cefiderocol is also approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms like carbapenem-resistant *Acinetobacter baumannii*.
- The activity of this molecule is due to its ability to achieve high periplasmic concentrations by hijacking the bacterial iron transport machinery, which increases cell entry.
  - In addition, cefiderocol remains stable to hydrolysis by serine β-lactamases (ESBLs, KPCs, and OXA-type carbapenemases) and metallo-β-lactamases.
- This study evaluated the activity of cefiderocol and comparator agents against *A. baumannii-calcoaceticus* complex collected from hospitals in European countries, Israel, and Turkey during 2020–2023.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 2,067 *A. baumannii-calcoaceticus* complex collected from various clinical specimens in patients hospitalized in 42 medical centers in 17 European countries, Israel, and Turkey during 2020–2023.
- Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local institutional criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2024) guidelines.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories; North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted CAMHB per CLSI guidelines.
- Quality assurance was performed by sterility checks, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- MIC results for cefiderocol and comparator agents were interpreted according to the FDA/EUCAST (PK/PD)/CLSI criteria.
- Isolates with imipenem and/or meropenem MIC ≥8 mg/L (resistant based on CLSI criteria) were subjected to genome sequencing and screening of β-lactamase genes.

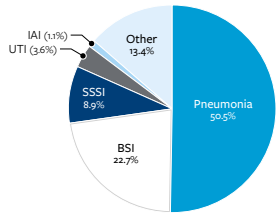
Table 1. Distribution of carbapenem-resistant *A. baumannii-calcoaceticus* complex in European countries, Israel, and Turkey

Region Country (Number included)	Number of carbapenem-resistant (%)
Eastern (1291)	1009 (78.2)
Czech Republic (23)	8 (34.8)
Greece (161)	158 (98.1)
Hungary (61)	44 (72.1)
Israel (441)	304 (69.0)
Poland (135)	125 (92.6)
Romania (70)	63 (90.0)
Slovakia (11)	8 (72.7)
Slovenia (54)	12 (22.2)
Turkey (335)	287 (85.7)
Western (776)	279 (36.0)
Belgium (25)	2 (8.0)
France (75)	5 (6.7)
Germany (202)	20 (9.9)
Ireland (13)	1 (7.7)
Italy (269)	206 (76.6)
Portugal (27)	12 (44.4)
Spain (53)	22 (41.5)
Sweden (17)	2 (11.8)
Switzerland (64)	9 (14.1)
UK (31)	0 (0.0)
Total (2067)	1288 (62.3)

Results

- A total of 62.3% (1288/2067) *A. baumannii-calcoaceticus* species complex isolates were classified as carbapenem-resistant (Table 1).
  - Most carbapenem-resistant isolates originated from pneumonia patients (50%), whereas smaller percentages originated from bloodstream infections (23%), skin and skin structure infections (9%), and urinary tract infections (4%) (Figure 1).
- A carbapenem resistance phenotype amongst *A. baumannii-calcoaceticus* species complex was observed in 78.2% and 36.0% of isolates originating from Eastern (including Israel and Turkey) and Western European countries, respectively (Table 1).
  - Isolates originating from most Eastern European regions showed high carbapenem resistance (≥69%), except for Czech Republic (35%) and Slovenia (22%).
  - Most countries in Western Europe had carbapenem resistance at <15%, except for Italy (77%), Portugal (44%), and Spain (42%).
- Among carbapenem-resistant *A. baumannii-calcoaceticus* species complex, all but 9 (99.3%; 1279/1288) carried carbapenemase genes (Table 2).
  - bla_{OXA-23}-like (73.5%; 940/1279) was among the most common carbapenemase gene detected, followed by bla_{OXA-24}-like (16.3%; 209/1279) (Table 2).
  - A smaller subset (9.8%; 125/1279) carried bla_{NDM-1}, dual carbapenemases or bla_{OXA} carbapenemases in combination with Class A extended-spectrum β-lactamases (bla_{GES-22} or bla_{PER-1} or bla_{PER-7}).
- In general, cefiderocol ($MIC_{50/90}$, 0.25/1 mg/L; 92.7–97.0% susceptible) had the lowest $MIC_{50/90}$ against all *A. baumannii-calcoaceticus* species complex (Table 2).
  - Comparators had limited activity (34.6–37.7% susceptible), except for colistin (87.9% susceptible).
- Cefiderocol (89.4–95.4% susceptible) had $MIC_{50/90}$ values of 0.25/2 mg/L against the carbapenem-resistant and carbapenemase-positive subsets, whereas comparator agents shown in Table 2 were not active (0.0–1.2% susceptible), except for colistin, which was active against 81.1% of these isolates (Table 2).
- Cefiderocol (89.0–98.3% susceptible) showed $MIC_{50/90}$ of 0.25/1-2 mg/L against isolates carrying bla_{OXA-23}-like and bla_{OXA-24}-like
  - All isolates carrying bla_{OXA-58}-like were inhibited by cefiderocol at MIC of ≤0.25 mg/L, as well as those with no acquired carbapenemases and carrying only the intrinsic bla_{OXA-51}-like and $bla_{OXA-213}$-like genes (n=9), except for 1 *A. baumannii-calcoaceticus* species complex isolate with a cefiderocol MIC of 2 mg/L.
- Cefiderocol (62.4–68.8% susceptible) had $MIC_{50/90}$ of 0.5/64 mg/L against a small subset of isolates carrying bla_{NDM-1}, dual carbapenemases or bla_{OXA} carbapenemases in combination with bla_{GES-22} or bla_{PER-1} or bla_{PER-7}.

Figure 1. Distribution of infection types[a] caused by carbapenem-resistant *A. baumannii-calcoaceticus* complex in European countries, Israel, and Turkey



[a] BSI, bloodstream infections; IAI, intra-abdominal infections; SSSI, skin and skin-structure infections; UTI, urinary tract infections.

Conclusions

- Cefiderocol had the highest *in vitro* activity against all and each resistant subset of *A. baumannii-calcoaceticus* species complex causing infections in hospitals in European countries, Israel, and Turkey.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens, as comparator and recommended agents are not active.

Acknowledgments

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Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and other comparator agents against *A. baumannii-calcoaceticus* complex and carbapenem-resistant subsets

Phenotype[a]/genotype (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by FDA/EUCAST/CLSI criteria)[b]					
	FDC	IMR	MER	A/S	CAZ	COL
All (2,067)	0.25/1 (92.7/95.5/97.0)	>8/>8 (37.7)	>32/>32 (37.5)	32/>64 (36.3)	>32/>32 (34.6)	0.5/8 (87.9)
Carbapenem-susceptible (774)	0.06/0.25 (98.4/99.4/99.6)	0.25/0.25 (100)	0.25/1 (100)	2/8 (94.3)	4/8 (91.2)	0.25/1 (99.0)
Carbapenem-resistant (1288)	0.25/2 (89.4/93.2/95.4)	>8/>8 (0.2)	>32/>32 (0.0)	64/>64 (1.3)	>32/>32 (0.7)	0.5/>8 (81.1)
Carbapenemase-positive (1,279)	0.25/2 (89.4/93.1/95.4)	>8/>8 (0.1)	>32/>32 (0.0)	64/>64 (1.2)	>32/>32 (0.7)	0.5/>8 (81.1)
OXA-23-like (940)	0.25/1 (93.0/96.4/98.3)	>8/>8 (0.0)	>32/>32 (0.0)	64/>64 (0.4)	>32/>32 (0.6)	0.5/>8 (77.8)
OXA-24-like (209)	0.25/2 (89.0/95.2/98.1)	>8/>8 (0.0)	>32/>32 (0.0)	64/>64 (4.3)	>32/>32 (1.4)	0.5/8 (87.1)
OXA-58-like (5)	0.12/- (100/100/100)	16/- (2.4)	16/- (0.0)	64/- (0.0)	>32/- (0.0)	0.25/- (100)
Other[c] (125)	0.5/64 (62.4/64.8/68.8)	>8/>8 (0.8)	>32/>32 (0.0)	>64/>64 (0.0)	>32/>32 (0.0)	0.5/1 (95.2)
Carbapenemase-negative[d] (9)	0.25/- (88.9/100/100)	>8/- (11.1)	>32/- (0.0)	16/- (22.2)	>32/- (0.0)	0.25/- (77.8)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MER, meropenem; A/S, ampicillin-sulbactam; CAZ, ceftazidime; COL, colistin.
[a] Carbapenem-susceptible, isolates susceptible to imipenem and meropenem based on EUCAST/CLSI criteria (MIC values ≤2 mg/L); carbapenem-resistant, isolates resistant to imipenem and/or meropenem based on CLSI criteria (MIC values ≥8 mg/L).
[b] Cefiderocol MIC results were interpreted according to the FDA/EUCAST (PK/PD)/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria, except for imipenem-relebactam that used FDA, and ampicillin-sulbactam and ceftazidime that used CLSI criteria.
[c] Includes bla_{NDM-1} (4), bla_{NDM-1} + bla_{OXA-23} (21), bla_{NDM-1} + bla_{OXA-72} (54), bla_{OXA-23} + bla_{OXA-58} (25), bla_{OXA-23} + bla_{OXA-72} + bla_{PER-7} (6), bla_{OXA-23} + bla_{PER-1} (4), bla_{OXA-23} + bla_{PER-7} (8), bla_{OXA-72} + bla_{PER-7} (1), bla_{OXA-72} + bla_{GES-22} (2).
[d] Includes *A. pittii* (5) and *A. baumannii* (4), where $bla_{OXA-213}$- and bla_{OXA-51}-variants are intrinsic, respectively. Acquired carbapenemases were not detected in these isolates.

STUDI *IN VITRO*

Mendes RE et al. Activity of cefiderocol against carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2023).

Highlights

- Studio che ha valutato l'attività di cefiderocol e comparatori contro *Acinetobacter* spp e sottogruppi di *A. baumannii-calcoaceticus* complex (ACB) caratterizzati molecolarmente in 2.067 ACB e in 300 non-ACB isolati provenienti da 42 ospedali di 17 Paesi Europei, Israele e Turchia.

- **Cefiderocol** ha mostrato i valori di $MIC_{50/90}$ più bassi nei confronti di *Acinetobacter* spp ($MIC_{50/90}$=0,12/1 mg/l; 92,9-97,3% sensibili), mentre i comparatori hanno manifestato un'attività limitata (39,8-45,4% sensibili), ad eccezione di colistina.

- **Cefiderocol** ha mostrato valori di $MIC_{50/90}$ pari a 0,25/1-2 mg/l contro isolati portatori dei geni bla_{OXA-23} e bla_{OXA-24} (89-98,3% sensibili) e valori di $MIC_{50/90}$ pari a 0,5/64 mg/l contro i sottogruppi di isolati portatori dei geni bla_{NDM-1} o esprimenti multiple carbapenemasi (62,4-68,8% sensibili).

Cefiderocol ha mostrato l'attività *in vitro* più elevata contro *Acinetobacter* spp e ciascun sottogruppo di ACB.

I risultati di tale studio indicano che **cefiderocol** è un'importante opzione per il trattamento di infezioni sostenute da tali patogeni.

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Activity of cefiderocol against clinical isolates of *Pseudomonas aeruginosa* collected from five European countries as part of the SENTRY antimicrobial surveillance programme 2020–2023

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SHIONOGI

BACKGROUND

Pseudomonas aeruginosa (PA) is an important pathogen that is resistant to many first-line antibiotics and associated with high mortality. Cefiderocol (FDC) is a siderophore-conjugated cephalosporin with activity against *P. aeruginosa* including difficult-to-treat resistant isolates and is approved for treatment of aerobic Gram-negative bacterial infections with limited options.

In this study, the activity of cefiderocol against contemporary isolates of *P. aeruginosa* from patients in Europe was evaluated.

METHODS

- Isolates were collected between 2020–2023 as part of the SENTRY surveillance programme[1].
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines using broth microdilution with iron-depleted cation-adjusted Mueller-Hinton broth for cefiderocol and cation-adjusted Mueller–Hinton broth for comparator agents.
- Comparator agents included the β-lactam/β-lactamase inhibitor combinations ceftolozane-tazobactam (TOL-TAZ), ceftazidime-avibactam (CZA), imipenem-relebactam (IMI-REL) and aztreonam-avibactam (ATM-AVI).
- Susceptibility was interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) v14 breakpoints where available. Since aztreonam-avibactam has no EUCAST breakpoints for pathogens other than Enterobacterales, the percentage of isolates with MIC ≤4 mg/L is reported. Carbapenem resistance (CR) was defined as MIC ≥4 mg/L to meropenem or imipenem.

RESULTS

- 4,497 clinical isolates of PA were collected from Europe with 66% (n=2,945) from France, Germany, Italy, Spain or UK, of which 495 were carbapenem-resistant (17%).
- Of 47 carbapenemase-producing isolates, 74% contained metallo-β-lactamases, with VIM-2 the most frequent, while GES-5 was present in 26% **(Figure 1)**.
- Carbapenem susceptibility **(Figure 2)** varied from 10.4% in UK to 22.5% in Germany.
- Overall, 99.1% PA were susceptible to cefiderocol at the breakpoint of 2 mg/L (96% of CRPA isolates), including all GES-5 and 95% of metallo-β-lactamase producers.
- Cefiderocol MIC distributions for CRPA were similar between countries with a modal MIC of 0.12–0.25 mg/L **(Figure 3).**
- Overall isolates from all countries showed high susceptibility to comparators except aztreonam-avibactam, which was poorly active against *P. aeruginosa* **(Table 1).**
- 104 isolates (17% of CRPA) were resistant to TOL-TAZ. Of these, 76% were cross-resistant to ATM-AVI, 58% to CZA , 52% to IMI-REL but only 8% to FDC.

Table 1: Susceptibility rates of cefiderocol and comparator antibiotics against 2,945 *P. aeruginosa* isolates from 5 European countries: SENTRY 2020–2023

Country (n) Agent	France	Germany	Italy	Spain	UK
All *P. aeruginosa* (n=2,945)	**532**	**654**	**790**	**700**	**269**
Cefiderocol	99%	99%	99%	99%	100%
Ceftolozane-tazobactam	96%	98%	95%	96%	99%
Ceftazidime-avibactam	97%	97%	96%	97%	98%
Imipenem-relebactam	97%	98%	97%	96%	99%
Aztreonam-avibactam	62%	47%	52%	55%	48%
Carbapenem resistant (n=495)	**80**	**147**	**114**	**126**	**28**
Cefiderocol	96%	97%	98%	100%	100%
Ceftolozane-tazobactam	80%	93%	74%	79%	93%
Ceftazidime-avibactam	84%	91%	83%	87%	86%
Imipenem-relebactam	81%	92%	77%	79%	96%
Aztreonam-avibactam	48%	34%	24%	35%	11%
TOL-TAZ resistant (n=104)	**21**	**14**	**39**	**27**	**3**
Cefiderocol	81%	86%	95%	100%	3/3
Ceftazidime-avibactam	38%	36%	36%	63%	0/3
Imipenem-relebactam	48%	64%	49%	30%	2/3
Aztreonam-avibactam	19%	14%	13%	52%	0/3

n, number of isolates. Interpretations according to EUCAST breakpoint table v14 and Guidance on what to do when no breakpoints. Cefiderocol, breakpoint of ≤2 mg/L for *Pseudomonas* and other non-fermenters; Aztreonam-avibactam is reported at percentage with MIC ≤4 mg/L. **Key:** Green, >90%; Amber, 50-90%; Red <50% susceptible.

Figure 1: Summary of carbapenemases from 47/495 CR *P. aeruginosa*

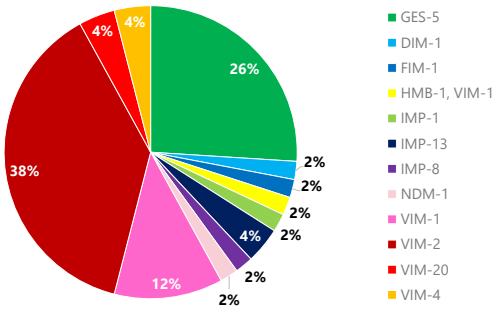


Figure 2: Carbapenem resistance in 2,945 isolates of *P. aeruginosa* from 5 European countries: SENTRY 2020–2023

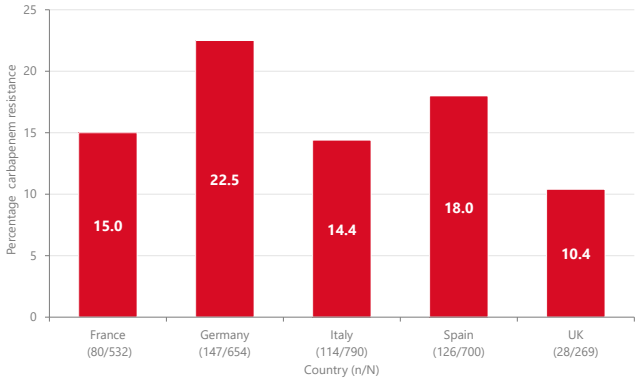
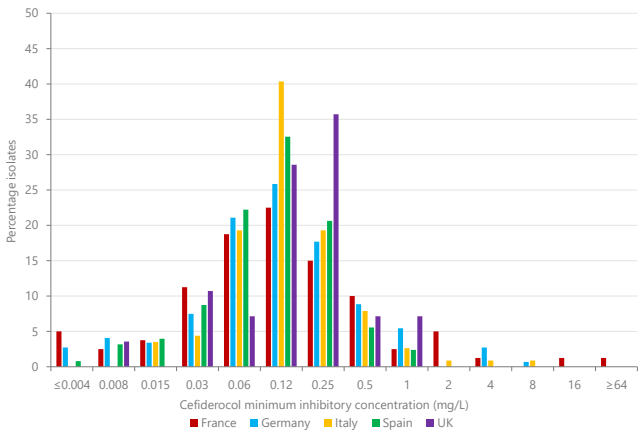


Figure 3: Cefiderocol MIC distributions for 495 CR *P. aeruginosa* isolates from 5 European countries: SENTRY 2020–2023



CONCLUSIONS

Cefiderocol showed the highest susceptibility rates against contemporary isolates of *P. aeruginosa*, including isolates resistant to carbapenems. High levels of cross-resistance between β-lactam/β-lactamase inhibitor combinations was observed, most of which remained susceptible to cefiderocol. Cefiderocol should be considered as a treatment for patients infected by *P. aeruginosa* with limited treatment options.

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Acknowledgments

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Longshaw C et al. Activity of cefiderocol against clinical isolates of *Pseudomonas aeruginosa* collected from five European countries as part of the SENTRY antimicrobial surveillance programme 2020–2023.

Highlights

- Studio che ha valutato l'attività di **cefiderocol** nei confronti di *Pseudomonas aeruginosa*; a tal fine sono stati raccolti 9.572 isolati di derivazione da Paesi Europei (tra cui l'Italia) come parte del programma di sorveglianza SENTRY (2020-2023).
- La resistenza ai carbapenemi è risultata simile tra i Paesi (Francia, Germania, Italia e Gran Bretagna), variando dal 10,4% in Gran Bretagna al 22,5% in Germania.
- Complessivamente, il 99,1% degli isolati risultava sensibile a **cefiderocol** al breakpoint di 2 mg/l (96% di isolati resistenti ai carbapenemi), incluse tutte le varianti GES-5 e i produttori di ß-lattamasi.

Cefiderocol ha mostrato la sensibilità più elevata contro gli isolati contemporanei. Sono stati riportati elevati livelli di resistenza crociata alla combinazione ß-lattamico/inibitore delle ß-lattamasi.

La maggior parte dei ceppi resistenti a questa combinazione rimane sensibile a cefiderocol.

ESCMID 2025 | Poster #P1349

Activity of cefiderocol against carbapenem-resistant *Pseudomonas aeruginosa*, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2023)

RE Mendes, JM Maher, HS Sader, M Castanheira
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Introduction

- *Pseudomonas aeruginosa* possess various intrinsic treatment-limiting resistance mechanisms, leading to decreased antibiotic permeability.
  - Isolates may acquire β-lactamase genes, such as those encoding class A carbapenemases and especially class B metallo-β-lactamases further decreasing susceptibility to numerous β-lactam agents.
- Cefiderocol is approved in Europe for the treatment of infections in adult patients due to aerobic Gram-negative organisms, where limited treatment options are available.
  - Cefiderocol is also approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms, carbapenem-resistant and difficult-to-treat *P. aeruginosa*.
- In this study, the activity of cefiderocol and comparator agents was investigated against *P. aeruginosa* collected from hospitals in European countries, Israel and Turkey during 2020–2023, as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 5,172 *P. aeruginosa* collected from various clinical specimens in patients hospitalized in 43 centers in 17 European countries, Israel, and Turkey during 2020–2023. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local institutional criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2024) guidelines.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories; North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted CAMHB per CLSI guidelines.
- Quality assurance was performed by sterility checks, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- Cefiderocol MIC results were interpreted according to the FDA/EUCAST/CLSI criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- Isolates with imipenem and/or meropenem MIC ≥8 mg/L (resistant based on CLSI criteria) were subjected to genome sequencing and screening of β-lactamase genes.

Table 1. Distribution of carbapenem-resistant *P. aeruginosa* in European countries, Israel, and Turkey

Region Country (Number)	Number (%)
Eastern (1571)	455 (29.0)
Czech Republic (93)	22 (23.7)
Greece (173)	57 (32.9)
Hungary (155)	42 (27.1)
Israel (367)	71 (19.3)
Poland (179)	91 (50.8)
Romania (111)	32 (28.8)
Slovakia (19)	9 (47.4)
Slovenia (166)	27 (16.3)
Turkey (308)	104 (33.8)
Western (3601)	600 (16.6)
Belgium (99)	24 (24.2)
France (532)	80 (15.0)
Germany (654)	147 (22.5)
Ireland (120)	27 (22.5)
Italy (790)	114 (14.4)
Portugal (150)	20 (13.3)
Spain (700)	126 (18.0)
Sweden (133)	18 (13.5)
Switzerland (154)	16 (10.4)
UK (269)	28 (10.4)
Total (5172)	1055 (20.4)

Results

- A total of 20.4% (1,055/5,172) *P. aeruginosa* isolates were classified as carbapenem-resistant (Figure 1 and Table 1).
  - Most carbapenem-resistant *P. aeruginosa* originated from pneumonia patients (60%), whereas smaller percentages originated from bloodstream infections (14%), skin and skin structure infections (13%), and urinary tract infections (8%).
- A carbapenem resistance phenotype was observed in 29.0% and 16.6% of isolates originating from Eastern (includes Israel and Turkey) and Western European countries, respectively (Table 1).
  - Poland (51%), Slovakia (47%), Turkey (34%), and Greece (33%) showed highest percentages of carbapenem resistance among isolates from the Eastern European region.
  - Belgium (24%), Germany (23%), and Ireland (23%) showed highest percentages of carbapenem resistance among isolates from the Western region.
- Among carbapenem-resistant isolates, 21.1% (146/1,055) carried carbapenemases (Figure 1 and Table 2).
  - Carbapenemse genes were mostly represented by class B (85.5%; 125/146), where bla_{VIM} consisted of 79.2% (99/125) of alleles.
  - Class A genes were detected in 14.5% (21/146) carbapenemase-positive isolates.
- Cefiderocol had MIC_{50} and MIC_{90} values of 0.12 mg/L and 0.5 mg/L, respectively, and susceptibilities of 95.3–98.9% against carbapenem-resistant *P. aeruginosa*, whereas β-lactam-β-lactamase inhibitor (BL-BLI) combinations had susceptibilities of 54.2–80.6% (Table 2).
- Cefiderocol had $MIC_{50/90}$ values of 0.12/0.25 mg/L against isolates carrying class A (100% susceptible) and $MIC_{50/90}$ of 0.25/2 mg/L against isolates with class B (83.2–94.4% susceptible) carbapenemases (Table 2).
  - Other comparators showed susceptibilities of <15% against both subsets, except for ceftazidime-avibactam against isolates carrying class A carbapenemases (90.5% susceptible).
- Cefiderocol (96.8–99.4% susceptible), imipenem-relebactam (90.5% susceptible), and ceftazidime-avibactam (91.0% susceptible) showed high susceptibilities against carbapenem-resistant, carbapenemase-negative isolates (Table 2).

Conclusions

- Cefiderocol was the most active agent tested *in vitro* against *P. aeruginosa* isolates causing infections in hospitals located in European countries, Israel and Turkey.
- Cefiderocol remained active against carbapenemase-producing subsets, where BL-BLI combinations and other agents were not active.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens, for which antibiotic treatment options are limited.

Acknowledgments

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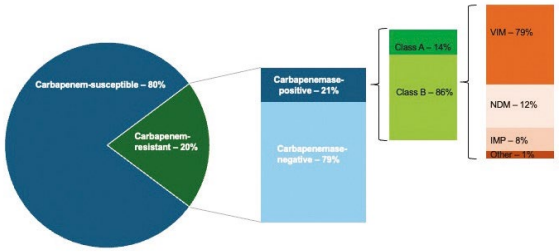
Figure 1. Distribution of phenotypes and genotypes[a] observed among *P. aeruginosa*



[a] Additional information related to the carbapenemase genes detected is described in the footnotes of Table 2.

Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and meropenem against *P. aeruginosa* and carbapenem-resistant subsets from European countries, Israel, and Turkey

Phenotype/genotype[a] (No. tested)	MIC_{50}/MIC_{90} in mg/L (% susceptible by FDA/EUCAST/CLSI criteria)[b]					
	FDC	IMR	MEV	CZA	C/T	MER
All (5,172)	0.12/0.5 (98.6/99.4/99.7)	0.25/1 (95.5)	0.5/8 (90.7)	2/4 (95.6)	0.5/2 (94.7)	0.5/8 (79.6)
Carbapenem-resistant (1,055)	0.12/0.5 (95.3/97.8/98.9)	1/>8 (78.0)	8/>8 (54.2)	4/32 (80.6)	1/>16 (77.2)	8/>32 (9.7)
Carbapenemase-positive[c] (146)	0.25/2 (85.6/93.2/95.2)	>8/>8 (0.0)	>8/>8 (12.3)	32/>32 (16.4)	>16/>16 (0.0)	>32/>32 (5.5)
Class A[d] (21)	0.12/0.25 (100/100/100)	>8/>8 (0.0)	>8/>8 (0.0)	4/4 (90.5)	8/>16 (0.0)	>32/>32 (0.0)
Class B[e] (125)	0.25/2 (83.2/92.0/94.4)	>8/>8 (0.0)	>8/>8 (14.4)	>32/>32 (4.0)	>16/>16 (0.0)	>32/>32 (6.4)
Carbapenemase-negative (909)	0.12/0.5 (96.8/98.6/99.4)	1/2 (90.5)	8/>8 (60.9)	4/8 (91.0)	1/8 (89.6)	8/32 (10.3)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; MER, meropenem.
[a] Carbapenem-resistant, isolates resistant to imipenem and/or meropenem based on CLSI criteria (MIC values ≥8 mg/L).
[b] Cefiderocol MIC results were interpreted according to the FDA/EUCAST/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria.
[c] Includes bla_{GES-5} (17), bla_{GES-6} (4), bla_{IMI-1} (1), bla_{KPC-3} (1), bla_{KPC-7} (5), bla_{KPC-8} (1), bla_{KPC-10} (1), bla_{KPC-13} (2), bla_{NDM-1} (15), bla_{VIM-1} (9), bla_{VIM-2} (77), bla_{VIM-4} (8), bla_{VIM-5} (1), bla_{VIM-20} (2), bla_{VIM-43} (1), bla_{VIM-2} + bla_{GES-5} (1).
[d] Includes bla_{GES-5} (17) and bla_{GES-6} (4).
[e] Includes bla_{IMI-1} (1), bla_{KPC-3} (1), bla_{KPC-7} (5), bla_{KPC-8} (1), bla_{KPC-10} (1), bla_{KPC-13} (2), bla_{NDM-1} (15), bla_{VIM-1} (9), bla_{VIM-2} (77), bla_{VIM-4} (8), bla_{VIM-5} (1), bla_{VIM-20} (2), bla_{VIM-43} (1), bla_{VIM-2} + bla_{GES-5} (1).

Mendes RE et al. Activity of cefiderocol against carbapenem-resistant *Pseudomonas aeruginosa*, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020-2023).

Highlights

- Studio che ha valutato le attività di cefiderocol e comparatori nei confronti di *Pseudomonas aeruginosa* in 5.172 isolati provenienti da 43 ospedali di 17 Paesi Europei, Israele e Turchia.
- **Cefiderocol** e le principali combinazioni ß-lattamici/inibitori della ß-lattamasi (BL/BLi) hanno mostrato valori di sensibilità >90% contro *P. aeruginosa*.
- **Cefiderocol** ha mostrato valori di $MIC_{50/90}$ rispettivamente pari a 0,12 mg/l e 0,5 mg/l, con valori di sensibilità del 95,3-98,9% contro *P. aeruginosa* resistente a carbapenemi, a differenza di BL/BLi che mostravano valori di sensibilità del 54,2-80,6%.
- **Cefiderocol** ha mostrato valori di $MIC_{50/90}$ pari a 0,12/0,25 mg/l nei confronti di isolati portatori dei geni carbapenemasi di classe A (100% sensibili) e di $MIC_{50/90}$ pari a 0,25/2 mg/l nei confronti di quelli portatori dei geni di classe B (83,2-94,4% sensibili), mentre gli altri comparatori hanno manifestato sensibilità <15% contro entrambi i subset di isolati (ad eccezione di ceftazidima-avibactam).

Cefiderocol è risultato l'agente più attivo *in vitro* in isolati di ***Pseudomonas aeruginosa***.

Cefiderocol ha mostrato di mantenere la sua attività nei confronti dei produttori di carbapenemasi, **verso i quali i nuovi agenti BL/BLi hanno mostrato un'attività limitata.**

I risultati di tale studio indicano che **cefiderocol** è un'importante opzione per il trattamento di infezioni da tali patogeni resistenti.

Activity of cefiderocol against carbapenem-resistant and molecularly characterized Enterobacterales isolates causing infections in hospitals in Europe and adjacent regions (2020–2023)

RE Mendes, A Scullin, D. Beekman, Z Kockler, JM Maher, HS Sader, M Castanheira

[1] Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA

Introduction

- Cefiderocol is approved in Europe for the treatment of infections in adult patients due to aerobic Gram-negative organisms, where limited treatment options are available.
  - Cefiderocol is also approved by the US Food and Drug Administration (FDA) in 2019 for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant organisms like carbapenem-resistant Enterobacterales (CRE).
- The activity of cefiderocol is due to its ability to achieve high periplasmic concentrations by hijacking the bacterial iron transport machinery, which increases cell entry.
  - In addition, cefiderocol remains stable to hydrolysis by serine β-lactamases (ESBLs, KPCs, and OXA-type carbapenemases) and metallo-β-lactamases.
- The activities of cefiderocol and comparator agents were evaluated against CRE characterized for β-lactamase content and collected from hospitals in European countries and adjacent regions during 2020–2023.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 16,904 Enterobacterales collected from various clinical specimens from patients hospitalized in 42 centers in 17 European countries, Israel, and Turkey during 2020–2023. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local institutional criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories; North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted CAMHB per CLSI guidelines.
- Quality assurance was performed by sterility checks, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- Cefiderocol MIC results were interpreted according to the EUCAST/FDA (FDA breakpoints are the same as CLSI) criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- Enterobacterales with MIC ≥4 mg/L (resistant by CLSI/EUCAST criteria) for imipenem (excluded for *P. mirabilis*, *P. penneri*, and indole-positive Proteeae) or meropenem were screened for β-lactamase genes by genome sequencing and *in silico* analysis.

Results

- A total of 3.7% (623/16,904) CRE isolates were detected among all participating medical sites (Table 1).
  - CRE isolates were observed in 9.3% and 1.6% of isolates originating from Eastern (including Israel and Turkey) and Western European countries, respectively (Table 1).
  - The highest rates of CRE were observed in Poland (20.5%), Greece (19.3%), and Slovakia (18.3%).
  - Countries in Western Europe had low prevalence of CRE (<2%), except for Italy (5.5%).
- Among CRE isolates, 89.7% (559/623) carried carbapenemase genes (Figure 1 and Table 2).
  - Class A genes (bla_{KPC}; 40.6%) prevailed, followed by class B (25.9%) and class D (bla_{OXA}; 20.2%) carbapenemases.
  - In addition, 13.2% of CRE had multiple carbapenemases.
- Cefiderocol (80.3/94.5% susceptible) had MIC_{50} of 1 mg/L and MIC_{90} of 4 mg/L against CRE, and carbapenemase-positive CRE isolates (Table 2).
  - Other agents had susceptibilities of <69% against these two resistant subsets.
- Cefiderocol (92.5/99.1% susceptible; EUCAST/FDA criteria) and β-lactam-β-lactamase inhibitor combinations (98.2–99.6% susceptible) were active against CRE carrying class A carbapenemases.
- Cefiderocol had the lowest MIC_{50} against isolates carrying class B genes ($MIC_{50/90}$, 2/4 mg/L; 63.4/90.0% susceptible)
  - MIC_{90} of >8 mg/L were obtained for comparators.
- Cefiderocol (90.3/99.1% susceptible) and ceftazidime-avibactam (100% susceptible) were active against CRE carrying class D genes.
- Cefiderocol ($MIC_{50/90}$, 2/8 mg/L; 60.8/81.1% susceptible) showed the lowest MIC_{50} value against isolates carrying multiple carbapenemases.
  - Other agents had limited activity (MIC_{50}, >8 mg/L).

Conclusions

- Cefiderocol showed consistent *in vitro* activity against CRE isolates carrying different carbapenemase genes causing infections in hospitals in European countries and adjacent regions.
- Notably, this consistent activity was most pronounced against CRE carrying class B and multiple carbapenemases, which comprised 39.2% of carbapenemase-carrying CRE.
- These *in vitro* data position cefiderocol as a critical option for the treatment of infections caused by these resistant pathogens.

Acknowledgments

This research and poster presentation were sponsored by Shionogi & Co., LTD.

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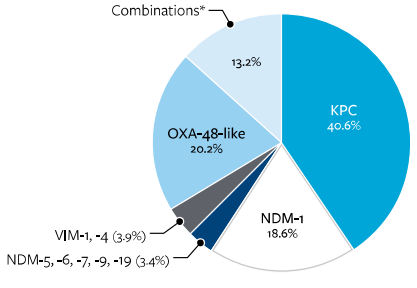
Table 1. Distribution of CRE in European countries, Israel, and Turkey

Region Country (Number included)	Number (%) of CRE
Eastern (4533)	423 (9.3)
Czech Republic (346)	4 (1.2)
Greece (590)	114 (19.3)
Hungary (470)	0 (0.0)
Israel (649)	20 (3.1)
Poland (396)	81 (20.5)
Romania (269)	21 (7.8)
Slovakia (109)	20 (18.3)
Slovenia (691)	1 (0.1)
Turkey (1013)	162 (16.0)
Western (12371)	200 (1.6)
Belgium (535)	3 (0.6)
France (1690)	9 (0.5)
Germany (2738)	22 (0.8)
Ireland (597)	3 (0.5)
Italy (2212)	122 (5.5)
Portugal (535)	7 (1.3)
Spain (1665)	31 (1.9)
Sweden (657)	0 (0.0)
Switzerland (575)	0 (0.0)
UK (1167)	3 (0.3)
Total (16904)	623 (3.7)

Figure 1. Distribution of carbapenemase genes detected in CRE isolates included in this study



* Combination of 2 carbapenemase genes, as follows: bla_{KPC-2} + $bla_{OXA-232}$ (4), bla_{KPC-2} + bla_{OXA-48} (6), bla_{KPC-2} + bla_{NDM-1} (3), bla_{KPC-3} + $bla_{OXA-181}$ (4), bla_{KPC-3} + bla_{OXA-48} (32), bla_{KPC-31} + $bla_{OXA-232}$ (4), bla_{KPC-31} + bla_{OXA-48} (7), bla_{KPC-31} + $bla_{OXA-181}$ (1), bla_{KPC-3} + bla_{VIM-1} (6), bla_{KPC-3} + bla_{VIM-4} (4), bla_{KPC-3} + bla_{OXA-1} (1), and bla_{KPC-3} + bla_{OXA-48} (2)

Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and other comparator agents against CRE and molecular characterized subsets

Phenotype/genotype[a] (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/FDA criteria)[b]					
	FDC	IMR	MEV	CZA	MER	COL
All (16,904)	0.06/0.5 (98.7/99.7)	0.12/1 (97.3)	0.03/0.06 (98.3)	0.12/0.5 (98.6)	0.03/0.06 (96.5)	0.25/>8 (83.1)
CRE (623)	1/4 (81.1/94.5)	2/>8 (53.5)	4/>8 (55.2)	2/>32 (65.3)	32/>32 (5.3)	0.25/>8 (68.6)
Carbapenemase-positive[c] (559)	1/4 (80.3/94.3)	4/>8 (48.3)	8/>8 (50.3)	2/>32 (61.7)	>32/>32 (5.2)	0.25/>8 (67.6)
Class A (227)	0.5/2 (92.5/99.1)	0.12/0.5 (99.6)	0.25/2 (98.2)	1/4 (99.1)	>32/>32 (2.6)	0.25/>8 (76.7)
Class B (145)	2/4 (63.4/90.0)	>8/>8 (2.1)	>8/>8 (18.6)	>32/>32 (1.4)	32/>32 (6.9)	0.25/>8 (70.3)
Class D (113)	1/2 (90.3/99.1)	4/>8 (31.9)	>8/>8 (19.5)	1/2 (100)	32/>32 (10.6)	2/>8 (50.4)
Multiple (74)	2/8 (60.8/81.1)	>8/>8 (6.8)	>8/>8 (12.2)	>32/>32 (6.8)	>32/>32 (1.4)	0.25/>8 (60.8)
Carbapenemase-negative[d] (64)	1/4 (87.5/96.9)	0.25/2 (98.4)	2/8 (98.4)	2/4 (96.9)	8/16 (6.2)	0.25/>8 (77.8)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; MER, meropenem; COL, colistin.
[a] CRE, isolates resistant to imipenem (excluded for *P. mirabilis*, *P. penneri*, and indole-positive Proteeae) and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L) or nonsusceptible based on EUCAST criteria.
[b] Cefiderocol MIC results were interpreted according to the EUCAST/FDA criteria (FDA are the same as CLSI criteria), whereas MIC for comparator agents were interpreted based on EUCAST criteria.
[c] Includes the class A bla_{KPC-2} (87), bla_{KPC-3} (139) and bla_{KPC-31} (1) genes; the class B bla_{NDM-1} (104), bla_{NDM-5} (1), bla_{NDM-6} (13), bla_{NDM-7} (1), bla_{NDM-9} (2), bla_{NDM-19} (2), bla_{VIM-1} (21), and bla_{VIM-4} (1) genes; the class D bla_{OXA-48} (50), $bla_{OXA-181}$ (5), $bla_{OXA-232}$ (55), and $bla_{OXA-244}$ (3) genes; and the combinations bla_{KPC-2} + bla_{OXA-48} (4), bla_{KPC-2} + bla_{NDM-1} (6), bla_{KPC-2} + bla_{VIM-4} (3), bla_{KPC-3} + $bla_{OXA-181}$ (4), bla_{KPC-3} + bla_{OXA-48} (32), bla_{KPC-3} + $bla_{OXA-232}$ (4), bla_{KPC-3} + bla_{NDM-1} (7), bla_{KPC-3} + bla_{OXA-48} (1), bla_{KPC-3} + bla_{VIM-1} (6), bla_{KPC-3} + bla_{VIM-4} (4), bla_{KPC-3} + bla_{OXA-1} (1), and bla_{KPC-3} + bla_{OXA-48} (2).
[d] Carbapenemase genes were not detected in the following species: *Enterobacter cloacae* species complex (6), *Klebsiella aerogenes* (5), and *K. pneumoniae* (53).

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Mendes RE et al. Activity of cefiderocol against carbapenem-resistant and molecularly characterized Enterobacterales clinical isolates causing infection in hospitals in Europe and adjacent regions (2022-2023).

Highlights

- Studio che ha valutato le attività di **cefiderocol** e comparatori nei confronti di *Enterobacterales* resistenti a carbapenemi (CRE), caratterizzate in base al contenuto di ß-lattamasi; a tal fine sono stati raccolti 16.904 isolati di *Enterobacterales* provenienti da 42 ospedali di 17 Paesi Europei, Israele e Turchia.

- **Cefiderocol**, le combinazioni ß-lattamici/inibitori di ß-lattamasi (BL/BLi) e meropenem hanno mostrato valori di sensibilità ≥96% contro le *Enterobacterales*; in particolare per **cefiderocol**, la cui sensibilità era dell'80-94,5%, la MIC_{50} risultava pari a 1 mg/l e la MIC_{90} a 4 mg/l nei confronti degli isolati CRE e degli isolati CRE carbapenemasi-positivi, contro i quali altri agenti mostravano sensibilità <69%.

- **Cefiderocol** ha mostrato il valore più basso di MIC contro gli isolati portatori dei geni di classe B ($MIC_{50/90}$=2/4 mg/l; 63,4/90%sensibili).

- **Cefiderocol** ($MIC_{50/90}$=2/8 mg/l; 60,8/81,1% sensibili) ha mostrato i valori più bassi di MIC_{90} contro isolati portatori di carbapenemasi multiple, mentre altri agenti hanno manifestato attività limitate (MIC_{90} >8 mg/l).

Cefiderocol ha mostrato un'attività *in vitro* più marcata contro gli isolati CRE portatori di differenti geni di carbapenemasi;
la rilevante attività di cefiderocol è risultata particolarmente evidente nei confronti degli isolati CRE portatori dei geni di classe B e di carbapenemasi multiple.

I risultati di tale studio indicano che **cefiderocol** è **un'importante opzione per il trattamento di infezioni da *Enterobacterales resistenti*.**

Poster 1350

35th ESCMID Global 2025
Vienna, Austria
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Activity of Cefiderocol Against Enterobacterales Carrying Multiple Carbapenemases, Collected as Part of the SENTRY Antimicrobial Surveillance Program

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SHIONOGI

BACKGROUND

- Carbapenemases are major determinants of resistance to carbapenems and other β-lactam antibiotics in Enterobacterales.
- They can be categorized as metallo-β-lactamases (MBLs; NDM, IMP, and VIM enzymes) or serine-based β-lactamases (KPC, OXA-48-like, and certain GES enzymes).
- Cefiderocol is a siderophore-conjugated cephalosporin with remarkable stability against β-lactamases, including all classes of carbapenemases, and it leverages the iron-uptake systems of bacteria to facilitate transportation into the cell.

OBJECTIVE

- The objective of this study was to elucidate the *in vitro* activity of cefiderocol and comparator agents against contemporary Enterobacterales isolates carrying multiple carbapenemases.

METHODS

- Isolates were collected from 2020 to 2023 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) methods using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Isolates non-susceptible to meropenem or imipenem (excluding *Proteus mirabilis, P. penneri*, and indole-positive Proteaea) or extended-spectrum β-lactamase phenotypes were subject to whole-genome sequencing to determine β-lactamase content.
- Susceptibility was assessed according to 2024 European Committee on Antimicrobial Susceptibility Testing (EUCAST), CLSI, and US Food and Drug Administration (FDA) breakpoints.

RESULTS

- Of the 32,053 Enterobacterales collected, 82 (0.3%) carried multiple carbapenemase genes, the majority of which were found in *Klebsiella pneumoniae* (**Figure 1**).
- All isolates carried two carbapenemases, except for one *K. pneumoniae* isolate, which carried two MBLs (NDM-1, NDM-4) and an OXA-48-like enzyme.
  - The combination of MBL and OXA-48-like enzymes was the most frequently encountered, followed by combinations of MBL and KPC enzymes (**Table 1**).
- Cefiderocol showed good activity against isolates expressing multiple carbapenemases, with 63.4% and 81.7% of the isolates being susceptible according to EUCAST and CLSI/FDA breakpoints, respectively (**Table 2**).
  - Among MBL-producing isolates (n=78), cefiderocol displayed highest activity against VIM-producing isolates (n=18), with 88.9% and 94.4% of the isolates being susceptible according to EUCAST and CLSI/FDA breakpoints, respectively (**Table 1**).
- β-lactam–β-lactamase inhibitor combinations showed low susceptibility against isolates expressing multiple carbapenemases, suggesting a lack of cross resistance with cefiderocol (**Table 2**).
- Other comparator agents, with the exception of tigecycline (92.7% at the FDA breakpoint), also demonstrated limited activity for these resistant isolates (**Table 2**).

Figure 1: Isolates carrying multiple carbapenemase genes (n=82)

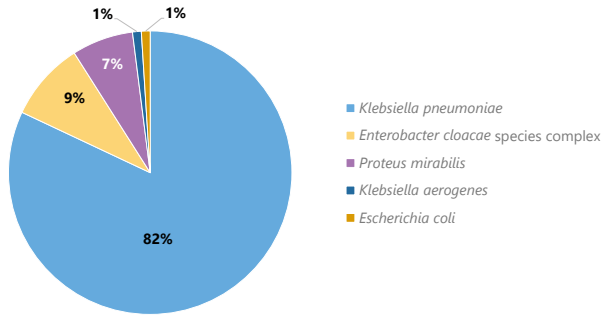

Table 1: Cefiderocol MIC frequency distribution for isolates with multiple carbapenemases (n=82)

Carbapenemase combinations	MIC (µg/mL)											Total
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	
MBL + OXA-48-like	**0**	**0**	**1**	**2**	**0**	**2**	**22**	**13**	**9**	**2**	**1**	**52**
NDM-1, OXA-48						2	11	11	5	2	1	32
NDM-5, OXA-48				1			6					7
NDM-1, OXA-181				1			1		3			5
NDM-1, OXA-232			1				1	1	1			4
VIM-1, OXA-48							2					2
NDM-5, OXA-181								1				1
NDM-1, NDM-4, OXA-232 KPN							1					1
MBL + KPC	**0**	**0**	**1**	**0**	**6**	**0**	**8**	**2**	**2**	**1**	**0**	**20**
NDM-1, KPC-2							5	1				6
VIM-1, KPC-2			1		3		1		1			6
VIM-1, KPC-3					3			1				4
NDM-1, KPC-3							2		1			3
NDM-5, KPC-65										1		1
MBL + MBL	**1**	**2**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**4**
VIM-4, VIM-75		2		1	1							4
VIM-1, VIM-75	1											1
KPC + OXA-48-like	**0**	**1**	**1**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**
KPC-2, OXA-48		1	1	2								4
MBL + GES	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**
VIM-1, GES-6						1						1

Table 2: Activity of cefiderocol and comparator agents against Enterobacterales carrying multiple carbapenemases (n=82)

Agent*	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	% Susceptibility		
				CLSI	EUCAST	FDA
Cefiderocol	2	8	0.03 to 32	81.7	63.4	81.7
Imipenem-relebactam	>8	>8	0.5 to >8	3.7	6.1	3.7
Meropenem-vaborbactam	>8	>8	0.25 to >8	13.4	17.1	13.4
Ceftazidime-avibactam	>32	>32	0.5 to >32	6.1	6.1	6.1
Ceftolozane-tazobactam	>16	>16	8 to >16	0.0	0.0	0.0
Aztreonam	>16	>16	0.12 to >16	20.7	12.2	20.7
Ciprofloxacin	>4	>4	0.5 to >4	0.0	0.0	0.0
Levofloxacin	32	>32	0.5 to >32	1.2	1.2	1.2
Amikacin	>32	>32	2 to >32	18.3	19.5	37.8
Gentamicin	>16	>16	0.25 to >16	17.1	17.1	18.3
Trimethoprim-sulfamethoxazole	>4	>4	0.25 to >4	22.0	22.0	22.0
Tigecycline	0.5	2	0.12 to 8			92.7
Minocycline	4	32	0.5 to >32	69.5		69.5
Colistin	0.25	>8	0.12 to >8		57.3	

*Susceptibility to cephalosporins, carbapenems, and piperacillin-tazobactam were all <10%.

CONCLUSIONS

- Cefiderocol showed good *in vitro* activity against Enterobacterales carrying multiple carbapenemases that are often multidrug resistant.
- No correlation between MIC value and carbapenemase content was observed, suggesting that other additional factors play a role in cefiderocol susceptibility.
- Cefiderocol should be considered as a treatment option when Enterobacterales isolates carrying multiple carbapenemases are encountered.

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Bryowsky JJ et al. Activity of cefiderocol against Enterobacterales carrying multiple carbapenemases, collected as part of the SENTRY antimicrobial surveillance programme.

Highlights

- Studio che ha valutato l'attività di cefiderocol e di agenti comparatori contro *Enterobacterales* portatori di multipli geni delle carbapenemasi. A tal fine, tra il 2000 e il 2023 sono stati raccolti 32.053 isolati di Enterobatteri di provenienza Europea e Statunitense, nell'ambito del programma di sorveglianza antimicrobica SENTRY.

- 82 isolati (0,3%) risultavano portatori di multipli geni delle carbapenemasi e in gran parte si trattava di *Klebsiella penumoniae*.

- **Cefiderocol** ha mostrato una buona attività contro tali isolati, con valori di sensibilità pari rispettivamente all'81,7% e al 63,4% secondo i breakpoint CLSI/FDA ed EUCAST.

- Le combinazioni ß-lattamasi/inibitori della ß-lattamasi hanno invece dimostrato un'attività inferiore (sensibilità <18%), così come gli altri agenti comparatori (con l'eccezione di tigeciclina, la cui sensibilità era del 92,7%), dimostrando le poche opzioni disponibili per tali isolati.

Cefiderocol ha mostrato una buona attività *in vitro* in *Enterobacterales* portatori di multipli geni di carbapenemasi (CR), che sono spesso multi-resistenti.

Cefiderocol dovrebbe essere considerato **un'opzione terapeutica per le infezioni da *Enterobacterales* portatori di geni delle carbapenemasi.**

Poster P1313

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Activity of cefiderocol against clinical isolates of *Stenotrophomonas maltophilia* collected from five European countries as part of the SENTRY antimicrobial surveillance programme 2020–2023

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BACKGROUND

Stenotrophomonas maltophilia is an important healthcare-associated pathogen that is intrinsically resistant to many β-lactam antibiotics, including carbapenems, due to the presence of the chromosomal L1 metallo-β-lactamase. Cefiderocol is a siderophore-conjugated cephalosporin approved by European Medicines Agency for treatment of aerobic Gram-negative bacterial infections with limited treatment options and one of the few agents with activity against isolates carrying metallo-β-lactamases.

OBJECTIVE

The objective of this study was to elucidate the *in vitro* activity of cefiderocol against contemporary isolates of *S. maltophilia* collected from European patients.

METHODS

- Isolates were collected between 2020–2023 as part of the SENTRY surveillance programme[1].
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute guidelines using broth microdilution with iron-depleted cation-adjusted Mueller-Hinton broth for cefiderocol and cation-adjusted Mueller–Hinton broth for comparator agents.
- Comparator agents included trimethoprim-sulfamethoxazole, minocycline and levofloxacin as well as the β-lactam/β-lactamase inhibitor combination aztreonam-avibactam.
- Susceptibility was interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidance v14. Aztreonam-avibactam has no EUCAST breakpoints for pathogens other than Enterobacterales, so only $MIC_{50/90}$ and MIC ranges are reported.

RESULTS

- Of 1,781 *S. maltophilia* isolates collected between 2020–2023, 612 originated from Europe and 68% (n=418) were from France, Germany, Italy, Spain and the UK.
- All isolates were susceptible to cefiderocol (MIC ≤2 mg/L) and a comparison between countries showed similar MIC distributions with a combined modal MIC of 0.06 mg/L (Figure 1).
- Isolates from all five countries showed high susceptibility to comparators except levofloxacin, for which only 17–35% isolates were susceptible (Table 1).
- $MIC_{50/90}$ values for aztreonam-avibactam were 4/4 mg/L for isolates from all five countries except Italy, which showed a higher MIC_{90} value of 8 mg/L.

Figure 1: Cefiderocol MIC distributions for 418 *S. maltophilia* isolates from 5 European countries: SENTRY 2020–2023

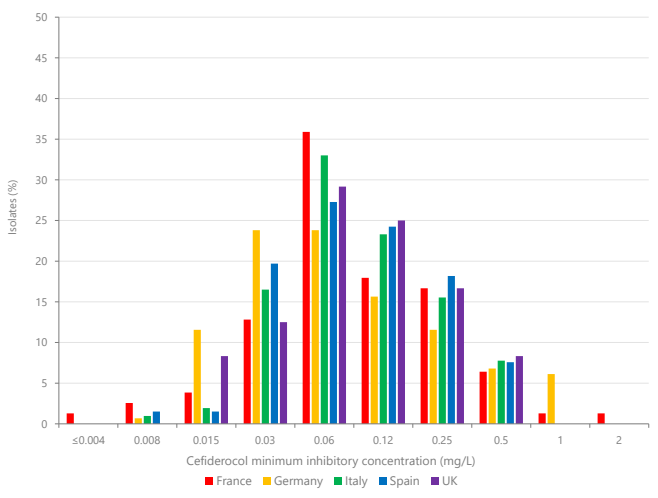

Table 1: Activity of cefiderocol and comparator antibiotics against clinical isolates of *Stenotrophomonas maltophilia* from 5 European countries (2020–2023)

Country (n) Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	EUCAST (%S)[a]
All (418)				
Cefiderocol	0.06	0.25	≤0.004–2	100
Aztreonam-avibactam	4	4	0.25–>16	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–>4	98
Minocycline	0.5	1	<0.06–8	99
Levofloxacin	1	4	0.12–16	27
France (78)				
Cefiderocol	0.06	0.25	≤0.004–2	100
Aztreonam-avibactam	2	4	1–16	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–>4	98
Minocycline	0.5	1	≤0.6–4	99
Levofloxacin	1	4	0.12–16	26
Germany (147)				
Cefiderocol	0.06	0.5	0.008–1	100
Aztreonam-avibactam	2	4	1–16	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–>4	98
Minocycline	0.5	1	0.12–8	99
Levofloxacin	1	2	0.25–8	35
Italy (103)				
Cefiderocol	0.06	0.25	0.008–2	100
Aztreonam-avibactam	4	8	0.25–>16	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–>4	97
Minocycline	0.5	1	0.12–4	99
Levofloxacin	1	4	0.25–16	17
Spain (66)				
Cefiderocol	0.06	0.25	0.008–0.5	100
Aztreonam-avibactam	2	4	2–>16	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–>4	99
Minocycline	0.5	1	≤0.06–4	97
Levofloxacin	1	8	0.25–16	24
UK (24)				
Cefiderocol	0.06	0.25	0.015–0.5	100
Aztreonam-avibactam	2	4	1–8	-
Trimethoprim-sulfamethoxazole	<0.12	0.5	≤0.12–2	100
Minocycline	0.5	1	0.12–1	100
Levofloxacin	1	4	0.25–4	25

S, susceptible or susceptible with increased exposure; n, number of isolates.
a. Interpretations according to EUCAST breakpoint table v14 and Guidance on what to do when no breakpoints. Cefiderocol, breakpoint of <4 mg/L for *Pseudomonas* and other non-fermenters; Aztreonam-avibactam, no breakpoints or guidance have been established for *S. maltophilia*; Trimethoprim-sulfamethoxazole, breakpoint of <8 mg/L; Minocycline R breakpoint of <4 mg/L; Levofloxacin breakpoint of <1 mg/L. **Key:** Green, >90%; Amber, 50-90%; Red <50% susceptible.

CONCLUSIONS

Isolates of *S. maltophilia* from 5 European countries remained largely susceptible to standard-of-care antibiotics except for levofloxacin, which had poor levels of susceptibility in all countries.

Cefiderocol showed higher potency than aztreonam-avibactam and remained active against 100% of isolates tested, including those resistant to standard-of-care antibiotics. Cefiderocol should be considered as a treatment option for patients with limited treatment options.

References

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Acknowledgments

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Longshaw C et al. Activity of cefiderocol against clinical isolates of *Stenotrophomonas maltophilia* collected from five European countries as part of the SENTRY antimicrobial surveillance programme 2020-2023.

Highlights

- Tra 1.781 isolati di *Stenotrophomonas maltophilia* raccolti nello studio, 418 provenivano da Francia, Germania, Italia, Spagna e UK.
- Tutti gli isolati sono risultati sensibili a cefiderocol con una MIC<2 (CLSI), la $MIC_{50/90}$ per aztreonam-avibactam è risultata essere di 4.
- TMP-SMX e minociclina hanno dimostrato una percentuale di sensibilità secondo EUCAST maggiore del 98% nei confronti degli isolati mentre levofloxacina è risultata essere efficace solamente nel 27% dei casi.

Cefiderocol ha mostrato una potenza maggiore rispetto ad aztreonam-avibactam ed è rimasto attivo contro il 100% degli isolati testati, compresi quelli resistenti agli antibiotici standard.

Cefiderocol dovrebbe essere considerato una scelta appropriata per i pazienti con opzioni terapeutiche limitate.

Poster 1310

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Cefiderocol Activity Against Resistant Bacteria From Patients With Ventilator-Associated Pneumonia From European and US Hospitals

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BACKGROUND

- Treatment of ventilator-associated pneumonia (VAP) caused by Gram-negative pathogens is often complicated by resistance, resulting in limited treatment options.
- Cefiderocol is a siderophore cephalosporin with activity against Gram-negative bacteria, including multidrug-resistant isolates.

OBJECTIVE

- In this study, the activity of cefiderocol and comparators was evaluated against carbapenem-non-susceptible (CarbNS) and difficult-to-treat resistant (DTR) phenotypes of Gram-negative bacteria isolated from hospitalized patients with VAP from European and US hospitals.

METHODS

- 3,475 Gram-negative isolates from patients with VAP were collected in the SENTRY Antimicrobial Surveillance Program from 2020 to 2023; Enterobacterales (n=1,877; 54%), *Pseudomonas aeruginosa* (n=1,100; 32%), *Acinetobacter baumannii-calcoaceticus* species complex (n=240; 7%), and *Stenotrophomonas maltophilia* (n=219; 6%) were the most common species collected.
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- CarbNS subsets were defined as non-susceptibility to meropenem and imipenem based on CLSI criteria.
- DTR phenotype was defined as non-susceptibility to aztreonam (except *A. baumannii*), cefepime, ceftazidime, ceftriaxone (for Enterobacterales only), imipenem, meropenem, ciprofloxacin, and levofloxacin. Susceptibility was assessed according to 2024 CLSI, US Food and Drug Administration (FDA), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

RESULTS

- 4.3% and 3.3% of Enterobacterales, 25.9% and 5.4% of *P. aeruginosa*, and 63.8% and 62.5% of *A. baumannii-calcoaceticus* species complex were CarbNS and DTR, respectively. 100% of *S. maltophilia* were CarbNS.
- CarbNS and DTR Enterobacterales isolates showed more elevated MIC values for cefiderocol compared with the overall Enterobacterales population, but this was less the case for *P. aeruginosa* and *A. baumannii-calcoaceticus* species complex (**Figure 1**).
- Nonetheless, cefiderocol showed good activity against all CarbNS and DTR isolates regardless of species, with >95% of isolates being susceptible by CLSI breakpoints, which was higher than comparator agents, including β-lactam–β-lactamase inhibitor combinations (**Table 1**).

Figure 1: Cefiderocol MIC distributions for Enterobacterales, *P. aeruginosa*, and *A. baumannii-calcoaceticus* species complex isolates collected from VAP patients, as part of SENTRY 2020–2023

*Criteria as published by CLSI (2024), EUCAST (2024), and US FDA (2024)

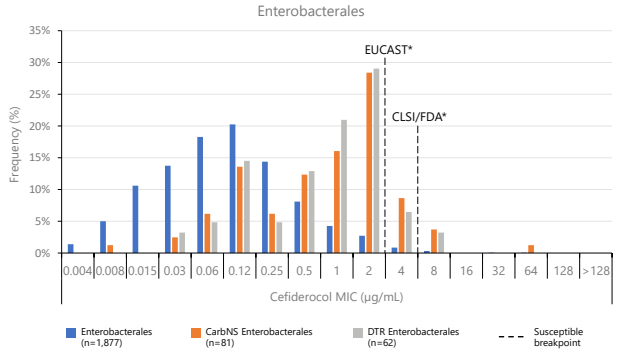

Figure 1 cont.

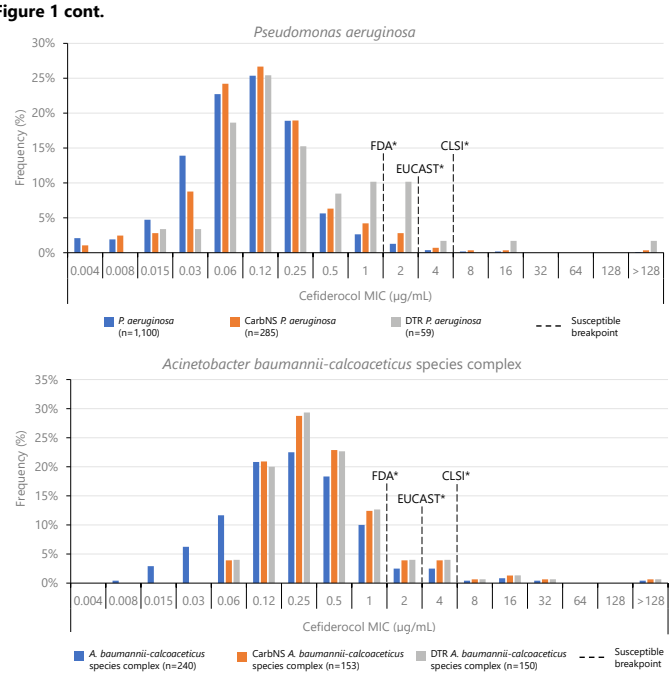

Table 1: Antibacterial activity of cefiderocol and comparators against CarbNS and DTR Gram-negative pathogens collected from patients with VAP in the SENTRY Antimicrobial Surveillance Program during 2020–2023

Organism group Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	%S[a] CLSI	%S[a] FDA	%S[a] EUCAST
CarbNS Enterobacterales (n=81)						
Cefiderocol	1	4	0.008 to 64	95.1	95.1	86.4
Imipenem-relebactam	0.5	>8	0.12 to >8	50.6	50.6	50.6
Meropenem-vaborbactam	2	>8	≤0.015 to >8	53.1	53.1	60.5
Ceftazidime-avibactam	2	>32	0.06 to >32	60.5	60.5	60.5
Ceftolozane-tazobactam	>16	>16	1 to >16	4.9	4.9	4.9
DTR Enterobacterales (n=62)						
Cefiderocol	1	2	0.03 to 8	96.8	96.8	90.3
Imipenem-relebactam	0.5	>8	0.12 to >8	53.2	53.2	53.2
Meropenem-vaborbactam	2	>8	≤0.015 to >8	54.8	54.8	61.3
Ceftazidime-avibactam	2	>32	0.12 to >32	62.9	62.9	62.9
Ceftolozane-tazobactam	>16	>16	8 to >16	0.0	0.0	0.0
CarbNS *P. aeruginosa* (n=285)						
Cefiderocol	0.12	0.5	≤0.004 to >64	98.9	95.4	98.2
Imipenem-relebactam	1	8	0.25 to >8	80.4	80.4	80.4
Meropenem-vaborbactam	8	>8	1 to >8	NA	NA	50.2
Ceftazidime-avibactam	4	16	0.5 to >32	83.1	83.1	83.1
Ceftolozane-tazobactam	1	>16	0.25 to >16	84.9	84.9	84.9
DTR *P. aeruginosa* (n=59)						
Cefiderocol	0.12	2	0.015 to >64	96.6	84.7	94.9
Imipenem-relebactam	4	>8	0.25 to >8	44.1	44.1	44.1
Meropenem-vaborbactam	>8	>8	1 to >8	NA	NA	18.4
Ceftazidime-avibactam	16	>32	2 to >32	47.5	47.5	47.5
Ceftolozane-tazobactam	8	>16	1 to >16	49.2	49.2	49.2
CarbNS *A. baumannii-calcoaceticus* species complex (n=153)						
Cefiderocol	0.25	2	0.06 to >64	96.7	88.9	92.8
Imipenem-relebactam	>8	>8	>8 to >8	NA	0	NA
Ampicillin-sulbactam	64	>64	16 to >64	0	0	NA
Colistin	0.5	>8	0.12 to >8	0	0	69.9
Minocycline	16	16	0.25 to >32	20.9	20.9	NA
DTR *A. baumannii-calcoaceticus* species complex (n=150)						
Cefiderocol	0.25	2	0.06 to >64	96.7	88.7	92.7
Imipenem-relebactam	>8	>8	>8 to >8	NA	0	NA
Ampicillin-sulbactam	64	>64	16 to >64	0	0	NA
Colistin	0.5	>8	0.12 to >8	NA	NA	69.3
Minocycline	16	16	0.25 to >32	20.7	20.7	NA
***S. maltophilia* (n=219)**						
Cefiderocol	0.06	0.25	≤0.004 to 2	99.5	NA	100.0
Levofloxacin	1	4	0.12 to 32	84.9	NA	NA
Minocycline	0.5	1	0.12 to 8	93.2	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >4	96.3	NA	NA

S, susceptible; n, number of isolates; NA, not applicable.
[a]According to 2024 CLSI, FDA, and EUCAST breakpoints.

CONCLUSIONS

- Cefiderocol demonstrated greater activity than β-lactam–β-lactamase inhibitor combinations against Gram-negative isolates from patients with VAP, including those with a CarbNS or DTR phenotype for which treatment options are limited.
- No cross-resistance between cefiderocol and β-lactam–β-lactamase inhibitor combinations was observed.
- Cefiderocol is an important treatment option for hospitalized patients on mechanical ventilation at risk for an infection caused by Gram-negative pathogens.

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Nguyen ST et al. Cefiderocol activity against resistant bacteria from patients with ventilator-associated pneumonia from European and US hospitals.

Highlights

- Tra 3.475 isolati di patogeni Gram-negativi in pazienti con VAP raccolti nello studio SENTRY 2020-2023 sono stati identificati nel 54% dei casi *Enterobacterales*, nel 32% *P. aeruginosa*, nel 7% *A. baumannii-calcoaceticus*, nel 6% *S. maltophilia*.

- L'attività di cefiderocol (suscettibilità secondo EUCAST) nei confronti di *Enterobacterales* resistenti ai carbapenemi e DTR è risultata dell'86,4% e 90% rispettivamente, del 98% e 94% nei confronti di *P. aeruginosa* carbaR e DTR, del 92% nei confronti di *A. baumannii* e del 100% nei confronti di *S. maltophilia*.

Cefiderocol ha dimostrato maggiore attività rispetto agli altri ß-lattamici nei confronti di Gram-negativi multiresistenti nelle VAP.

Con il contributo non condizionante di

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