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Abstract e poster highlights dal congresso **ESCMID Global 2024**
(European Society of Clinical Microbiology and Infectious Diseases)

Focus su:

Cefiderocol nelle infezioni causate da batteri antibiotico-resistenti: novità da studi *in vitro* e da real-world evidence

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Nelle nozioni esposte in questo volume si riflette lo "stato dell'arte", come poteva essere delineato al momento della stesura in base ai dati desumibili dalla letteratura internazionale più autorevole.
È soprattutto in materia di terapia che si determinano i mutamenti più rapidi: sia per l'avvento di farmaci e di procedimenti nuovi, sia per il modificarsi, in rapporto alle esperienze maturate degli orientamenti sulle circostanze e sulle modalità d'impiego di quelli già in uso da tempo. Gli Autori, l'Editore e quanti altri hanno avuto una qualche parte nella stesura o nella pubblicazione del volume non possono essere ritenuti in ogni caso responsabili degli errori concettuali dipendenti dall'evolversi del pensiero clinico; e neppure di quelli materiali di stampa in cui possano essere incorsi, nonostante tutto l'impegno dedicato a evitarli. Il lettore che si appresti ad applicare qualcuna delle nozioni terapeutiche riportate deve dunque verificarne sempre l'attualità e l'esattezza, ricorrendo a fonti competenti e controllando direttamente sul riassunto delle caratteristiche del prodotto allegato ai singoli farmaci tutte le informazioni relative alle indicazioni cliniche, alle controindicazioni, agli effetti collaterali e specialmente alla posologia.

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(European Society of Clinical Microbiology and Infectious Diseases)

Focus su:

Cefiderocol nelle infezioni causate da batteri antibiotico-resistenti: novità da studi *in vitro* e da *real-world* evidence

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Indice

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Introduzione con commento generale

La resistenza agli antimicrobici (AMR) è un problema di salute pubblica che deve essere affrontato con urgenza. A livello globale, nel 2019 sono stati registrati 1,27 milioni di decessi attribuibili alla AMR e, in mancanza di alternative terapeutiche, si prevede che questo fenomeno causerà 10 milioni di morti all'anno entro il 2050, con un elevatissimo costo per l'economia globale. Negli ultimi anni, la Food and Drug Administration (FDA) e l'Agenzia Europea per i Medicinali (EMA) hanno approvato la commercializzazione di diversi nuovi antimicrobici, tra cui cefiderocol, una nuova cefalosporina dotata di un meccanismo d'azione completamente innovativo. La peculiarità di questa molecola è costituita dalla presenza nella sua struttura di un gruppo catecolico che, competendo con il trasporto del ferro, ne facilita la penetrazione attraverso la membrana batterica e gli permette di aggirare i principali meccanismi di resistenza: giunta a questo livello, la molecola inibisce la produzione della parete batterica legandosi alle *penicillin-binding protein* (PBP), in analogia alle altre cefalosporine.

In occasione della 34ª edizione di ESCMID Global tenutasi a Barcellona dal 27 al 30 aprile 2024, sono stati presentati i risultati di molteplici studi di interesse infettivologico e microbiologico, fra cui alcuni interessanti lavori inerenti all'uso nella pratica clinica di cefiderocol. Innanzitutto, sono stati **presentati i dati *real world evidence* (RWE) dello studio PERSEUS, il più grande a livello europeo, riguardante il trattamento con cefiderocol di 261 pazienti adulti in condizioni critiche con infezioni da batteri Gram-negativi resistenti ai carbapenemi (64,8%), con un precedente fallimento ad altri trattamenti antimicrobici (44,4%).** Il trattamento con cefiderocol (di una durata <28 giorni) dei pazienti ospedalizzati infettati da *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* e *Stenotrophomonas maltophilia* ha permesso di raggiungere un tasso di successo clinico dell'84,7% e di guarigione clinica dell'80,5%. In particolare, **tra i pazienti con infezioni da *P. aeruginosa*, il tasso di guarigione clinica e il tasso di mortalità al giorno 28 sono stati rispettivamente dell'84,5% e del 17,2%.** Dei 261 pazienti totali, il 30,3% presentava immunosoppressione associata a un elevato tasso di comorbilità (89,9%) e un'infezione prevalentemente da *P. aeruginosa* (51,9%), *S. maltophilia* (13,9%), *Pseudomonas* spp. (11,4%) e altri batteri non fermentatori (11,4%). In questo sottogruppo di pazienti, il tasso di successo clinico complessivo è stato dell'81,0%, il tasso di guarigione clinica del 77,2% e il tasso di mortalità al giorno 28 del 24,1%. Nei pazienti con infezioni intraddominali complicate (14,6%) da *P. aeruginosa* (60,5%), *K. pneumoniae* (18,4%) e *Pseudomonas* spp. (7,9%), il 76,3% ha raggiunto il successo clinico, il 68,4% una guarigione clinica, mentre il 23,7% è deceduto entro il giorno 28. Infine, **il trattamento a lungo termine (>28 giorni) con cefiderocol di pazienti con infezioni causate da *P. aeruginosa* (84,6%), *S. maltophilia* (7,7%) ed *Elizabethkingia miricola* (7,7%) ha portato a un tasso di guarigione clinica dell'84,6% e a un tasso di mortalità al giorno 90 del 23,1%.**

Parallelamente, sono stati presentati i risultati dello studio prospettico internazionale PROVE (RetrosPective Cefiderocol Chart Review) – condotto in Europa e negli USA – e relativi al trattamento con cefiderocol in 42 pazienti ospedalizzati con infezioni ossee e articolari causate da batteri Gram-negativi come *Acinetobacter baumannii* (30,2%), Enterobacterales (18,6%) e *P. aeruginosa* (14,0%). **In questi pazienti sono state riscontrate una guarigione clinica complessiva al termine del trattamento nell'81,4% dei casi e una mortalità al giorno 30 del 9,3%.**

Osservando le novità in ambito di studi microbiologici, fra cui, in particolare, il **programma di sorveglianza antimicrobica SENTRY 2020-2022**, è stata determinata la suscettibilità *in vitro* di cefiderocol e di altre molecole antibiotiche considerate di elezione per il trattamento delle infezioni da ceppi multiresistenti di *P. aeruginosa* e *Acinetobacter calcoaceticus-baumannii* complex (ACB), raccolti in Europa e negli Stati Uniti. Questi microrganismi vengono classificati dalla Organizzazione Mondiale della Sanità (OMS) come una priorità critica poiché presentano molteplici meccanismi di resistenza intrinseca e contemporanea capacità di acquisirne altri, che risulta in una estesa resistenza fenotipica, che comprende anche la resistenza ai carbapenemi. Le analisi condotte su un totale di 3926 isolati di *P. aeruginosa* provenienti da 16 Paesi europei, Israele e Turchia hanno evidenziato che il 25,4% di essi non era sensibile ai carbapenemi e che l'11,6% esprimeva carbapenemasi. Al contrario, **cefiderocol ha mostrato una suscettibilità del 98,2-99,2% contro gli isolati non sensibili ai carbapenemi, compreso il sottogruppo di ceppi che non producevano carbapenemasi, mentre la sensibilità degli inibitori beta-lattamici/beta-lattamasi (BL-BLI) era pari al 62,9-84,2%.** Inoltre, cefiderocol è risultato egualmente attivo contro gli isolati produttori di carbapenemasi (suscettibilità del 95,8-100%). Nel caso, invece, di ACB, il 66,2% non era suscettibile ai

carbapenemi e, tra questi, quasi tutti (992/996) erano produttori di carbapenemasi. Cefiderocol ha mostrato un'attività *in vitro* del 94,4-97,6% contro tutti gli isolati, incluso il sottogruppo non sensibile ai carbapenemi, superando in modo significativo la sensibilità <85,5% ottenuta dai comparatori.

L'attività *in vitro* di cefiderocol è stata inoltre testata su campioni clinici di Enterobacterales, *P. aeruginosa*, ACB e *Stenotrophomonas maltophilia* provenienti dal Nord America e dall'Europa. Anche in questo caso, è risultato l'antimicrobico più attivo contro tutti gli isolati che causano batteriemie, compresi i sottogruppi di ceppi isolati non suscettibili ai carbapenemi per i quali le opzioni di trattamento sono limitate. Per quel che riguarda i risultati dell'analisi delle proprietà antimicrobiche di cefiderocol contro isolati Gram-negativi non comuni, ovvero che rappresentano meno del 5% di tutti i Gram-negativi negli isolamenti clinicamente significativi, cefiderocol ha dimostrato una potente attività verso gli *Enterobacterales* (*Proteus* spp., *Serratia* spp. e *Citrobacter* spp.) e i batteri non fermentanti.

Infine, l'attività di cefiderocol è stata testata in un campione di circa 400 isolati clinici di *Stenotrophomonas* raccolti in un grande ospedale universitario in Italia. I farmaci di riferimento sono stati saggiati per sensibilità attraverso la disco-diffusione mentre cefiderocol attraverso la disco-diffusione e microdiluizione in brodo (BMD). I ceppi resistenti a trimetroprim-sulfametossazolo sono stati successivamente caratterizzati genotipicamente per la presenza di integroni IntI1 e geni gen1 e gen2, noti determinanti la resistenza per il sulfamidico. Complessivamente la MIC per cefiderocol variava da 0,032 µg a 1 µg, con una MIC50 di 0,25 µg e una MIC90 di 0,5 µg. **Nei ceppi resistenti a trimetroprim-sulfametossazolo ed esprimenti i genotipi di resistenza citati, cefiderocol manteneva il profilo di sensibilità.**

Abstract 1

Real-world effectiveness and safety of cefiderocol in patients with Gram-negative bacterial infections in the early access programme in Spain: results of the PERSEUS study

Paula Ramirez[1], *Esperanza Merino*[2], *Jessica Sarda*[3], *A. Javier Gonzalez*[3], *Stefano Verardi*[4], *Jesus Fortun*[5]

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Background

Cefiderocol was utilised for the treatment of life-threatening Gram-negative bacterial infections (GNBIs) through the Shionogi early access programme (EAP) in Spain. In the PERSEUS study, the effectiveness and safety of cefiderocol in patients with GNBIs were evaluated in real-world settings in Spain.

Methods

PERSEUS was a retrospective, multicentre, observational, medical chart review study (2018–2022). Hospitalised patients with confirmed GNBIs in the EAP were treated with cefiderocol for the first time for ≥72 hours. Patient characteristics, clinical success, clinical cure, all-cause mortality rates at Day 28, and safety were evaluated. The primary endpoint population included patients with a treatment duration of ≤28 days. Patients with *Acinetobacter baumannii* were not enrolled by design. Only descriptive statistics were used.

Results

Of 261 patients, 77.4% were male, and the median age was 61 years (range: 49–68) (**Table 1**). Patients most frequently had respiratory tract infection (RTI; 47.9%), intra-abdominal infection (14.6%) and urinary tract infection (UTI; 14.6%) (**Table 2**). Most frequent pathogens were *Pseudomonas aeruginosa* (66.7%), *Klebsiella pneumoniae* (10.0%) and *Stenotrophomonas maltophilia* (7.7%). The median treatment duration was 10.0 days (range: 7.0–14.0). At baseline, 63.2% of patients were in the intensive care unit (ICU) and 28.0% had septic shock. Overall, the clinical success rate was 84.7% (221/261), clinical cure rate was 80.5% (210/261) and 21.5% (56/261) of patients died by Day 28. Clinical success was achieved in 80.8% (101/125) of patients with RTI, 83.3% (20/24) of patients with bloodstream infection and 94.7% (36/38) of patients with UTI. Among patients with *P. aeruginosa* infections, the clinical cure rate and mortality rate at Day 28 were 84.5% and 17.2%, respectively (**Table 2**). Six patients experienced adverse drug reactions (mild/moderate/severe: 4/1/1); cefiderocol was withdrawn for three patients. The outcome was recovery for five patients, and one case was fatal (patient experienced toxic epidermal necrolysis).

Conclusions

In patients with a range of GNBIs in the EAP who were predominantly infected by *P. aeruginosa* and/or treated in the ICU, cefiderocol treatment was effective and well tolerated, with high clinical success and low mortality rates.

Table 1. Baseline characteristics and rationale for administration of cefiderocol

	Overall (N=261)
Age, years, median (range)	61 (49–68)
Sex, male, n (%)	202 (77.4)
Comorbidities, n (%)	199 (76.2)
Charlson Comorbidity Index, median (range)	3.0 (2.0–4.0)
Symptomatic COVID-19, n (%)	63 (24.1)
ICU at the time of initiation of cefiderocol, n (%)	165 (63.2)
Septic shock at the time of initiation of cefiderocol, n (%)	73 (28.0)
Mechanical ventilation at the time of initiation of cefiderocol[a]	95 (36.4)
Renal replacement therapy at baseline, n (%)[b]	74 (28.4)
Rationale for administering cefiderocol	
Resistance to all tested antibiotics	169 (64.8)
Treatment failure with prior antibiotics	116 (44.4)
Adverse events to other susceptible antibiotics	21 (8.0)
Other	26 (10.0)
Cefiderocol treatment duration, days, median (range)	10.0 (7.0–14.0)
Secondary bacteraemia, n (%)[c]	45 (17.2)
Polymicrobial infection, n (%)	51 (19.5)
Previous colonisation, n (%)[d]	135 (51.7)

[a]Unknown for 136 patients; [b]Unknown for 7 patients; [c]Unknown for 28 patients; [d]Unknown for 6 patients.
COVID-19, coronavirus disease-2019; ICU, intensive care unit.

Table 2. Clinical success, clinical cure and all-cause mortality at Day 28; overall, by infection site and by pathogen in the primary population

	Baseline	Clinical success[a]	Clinical cure[b]	All-cause mortality at Day 28
Overall, n (%)	261 (100)	221 (84.7)	210 (80.5)	56 (21.5)
By infection site, n (%)				
Respiratory tract	125 (47.9)	101/125 (80.8)	95/125 (76.0)	33/125 (26.4)
Urinary tract	38 (14.6)	36/38 (94.7)	36/38 (94.7)	6/38 (15.8)
Intra-abdominal	38 (14.6)	29/38 (76.3)	26/38 (68.4)	9/38 (23.7)
Skin and soft tissue	26 (10.0)	25/26 (96.2)	24/26 (92.3)	2/26 (7.7)
Bloodstream	24 (9.2)	20/24 (83.3)	19/24 (79.2)	6/24 (25.0)
Other[c]	10 (3.8)	10/10 (100)	10/10 (100)	0/10 (0)
ICU, n (%)	165 (63.2)	128/165 (77.6)	122/165 (73.9)	49/165 (29.7)
Septic shock, n (%)	73 (28.0)	55/73 (75.3)	50/73 (68.5)	25/73 (34.2)
By pathogen, n (%)				
Pseudomonas aeruginosa	174 (66.7)	156/174 (89.7)	147/174 (84.5)	30/174 (17.2)
Klebsiella pneumoniae	26 (10.0)	18/26 (69.2)	18/26 (69.2)	10/26 (38.5)
Stenotrophomonas maltophilia	20 (7.7)	14/20 (70.0)	14/20 (70.0)	6/20 (30.0)
Pseudomonas spp.	15 (5.7)	13/15 (86.7)	12/15 (80.0)	2/15 (13.3)
Other non-fermenters[d]	14 (5.4)	10/14 (71.4)	10/14 (71.4)	5/14 (35.7)
Other Enterobacterales[e]	12 (4.6)	10/12 (83.3)	9/12 (75.0)	3/12 (25.0)
Polymicrobial infection, n (%)	51 (19.5)	42/51 (82.4)	39/51 (76.5)	12/51 (23.5)

[a]Clinical success (primary endpoint for patients with treatment duration up to 28 days): cessation of antibiotic treatment due to clinical resolution of signs and symptoms of the infection for which cefiderocol was started, as assessed by the investigator at end of treatment, or survival at Day 28 following first dose of treatment. [b]Clinical cure: cessation of antibiotic treatment due to improvement of signs and symptoms. [c]Includes osteoarticular (6), other (4; central nervous system [2]; mediastinitis [2]). [d]*Burkholderia cepacia* complex (8); *Achromobacter* spp. (5); *Ralstonia mannitolilytica* (1). [e]*Serratia marcescens* (5); *Enterobacter cloacae* (3); *Klebsiella oxytoca* (2); *Citrobacter freundii* (1); other *Serratia* sp. (1). ICU, intensive care unit.

Poster 2523

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Real-world effectiveness and safety of cefiderocol in patients with Gram-negative bacterial infections in the early access programme in Spain: results of the PERSEUS study

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SHIONOGI

Revised abstract

Background: Cefiderocol was utilised for the treatment of life-threatening Gram-negative bacterial infections (GNBIs) through the Shionogi early access programme (EAP) in Spain. In the PERSEUS study, the effectiveness and safety of cefiderocol in patients with GNBIs were evaluated in real-world settings in Spain.

Methods: PERSEUS was a retrospective, multicentre, observational, medical chart review study (2018–2022). Hospitalised patients with confirmed GNBIs in the EAP were treated with cefiderocol for the first time for ≥72 hours. Patient characteristics, clinical success, clinical cure, all-cause mortality rates at Day 28 and safety were evaluated. The primary endpoint population included patients with a treatment duration of ≤28 days. Patients with *Acinetobacter baumannii* were not enrolled by design. Only descriptive statistics were used.

Results: Of 261 patients, 77.4% were male, and the median age was 61 years (range: 49–68). Patients most frequently had respiratory tract infection (RTI; 47.9%), intra-abdominal infection (14.6%) and urinary tract infection (UTI; 14.6%). The most frequent pathogens were *Pseudomonas aeruginosa* (66.7%), *Klebsiella pneumoniae* (10.0%) and *Stenotrophomonas maltophilia* (7.7%). The median treatment duration was 10.0 days (range: 7.0–14.0). At baseline, 63.2% of patients were in the intensive care unit (ICU) and 28.0% had septic shock. Overall, the clinical success rate was 84.3% (220/261), clinical cure rate was 80.5% (210/261) and 21.5% (56/261) of patients died by Day 28. Clinical success was achieved in 80.0% (100/125) of patients with RTI, 83.3% (20/24) of patients with bloodstream infection and 94.7% (36/38) of patients with UTI. Among patients with *P. aeruginosa* infections, the clinical cure rate and mortality rate at Day 28 were 84.5% and 17.2%, respectively. Six patients out of 261 experienced adverse drug reactions (mild/moderate/severe: 4/1/1); cefiderocol was withdrawn for three patients. The outcome was recovery for five patients, and one case was fatal (patient experienced toxic epidermal necrolysis).

Conclusions: In patients with a range of GNBIs in the EAP who were predominantly infected by *P. aeruginosa* and/or treated in the ICU, cefiderocol treatment was effective and well tolerated, with high clinical success and low mortality rates.

OBJECTIVES

In the PERSEUS retrospective study, patients were treated with cefiderocol through the early access programme (EAP) in Spain [1]. The key objectives of this study were to assess the baseline characteristics and the clinical outcomes in patients who were treated with cefiderocol for up to 28 days in the PERSEUS study.

METHODS

Study design: a retrospective, multicentre, observational study in patients receiving cefiderocol for the first time in the EAP in Spain.

Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours for a confirmed Gram-negative bacterial infection.

Exclusion criteria: confirmed *Acinetobacter* spp. at baseline; confirmed cefiderocol-resistant Gram-negative pathogen at baseline; incomplete medical records; enrolled into other clinical studies of investigational products.

Endpoints: baseline patient characteristics, Gram-negative bacterial pathogens, cefiderocol use pattern, clinical success (composite of clinical cure and/or survival at Day 28), clinical cure (cessation of antibiotic treatment due to improvement of signs and symptoms) at end of treatment and all-cause mortality at Day 28.

RESULTS

Patient characteristics	(N=261)	Main comorbidities	
Sex, male	202 (77.4%)	Immunosuppression	79 (30.3%)
Age, median (Q1–Q3), years	61 (49–68)	Tumour (solid/haematological)	62 (23.8%)
CCI score, median (Q1–Q3)	3 (2–4)	Diabetes	58 (22.2%)
APACHE II score, median (Q1–Q3)	15.0 (10.5–22)	Transplant recipient	54 (20.7%)
Symptomatic COVID-19	63 (24.1%)	Chronic renal disease	34 (13.0%)
ECMO	12 (4.6%)	COPD	27 (10.3%)

63.2% (n=165) — **ICU at the time of cefiderocol**

47.1% (n=123) — **Mechanical ventilation**

28.0% (n=73) — **Septic shock**

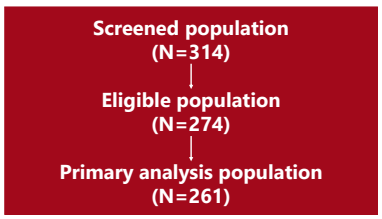
27.2% (n=71) — **Renal replacement therapy**

Baseline Gram-negative pathogens and rationale for cefiderocol administration	Overall (N=261)
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	174 (66.7)
Stenotrophomonas maltophilia	20 (7.7)
Pseudomonas spp.	15 (5.7)
Other non-fermenters[a]	14 (5.4)
Klebsiella pneumoniae	26 (10.0)
Other Enterobacterales[b]	12 (4.6)
Secondary bacteraemia, n (%)[c]	45 (18.9)
Polymicrobial infection, n (%)	51 (19.5)
Previous colonisation, n (%)[d]	135 (52.9)
Previous treatment with antibiotics, n (%)	219 (83.9)
Rationale for administering cefiderocol[e]	
Resistance to all tested antibiotics	169 (64.8)
Treatment failure with prior antibiotics	116 (44.4)
Adverse events to other susceptible antibiotics	21 (8.0)
Other	26 (10.0)
Cefiderocol treatment duration, median (range), days	10.0 (7.0–14.0)
Cefiderocol combination therapy, n (%)	91 (34.9)
Adverse drug reactions, n (%)	6 (2.3)
Serious adverse drug reactions, n (%)	3 (1.1)
Serious adverse drug reactions leading to death, n (%)	1 (0.4)

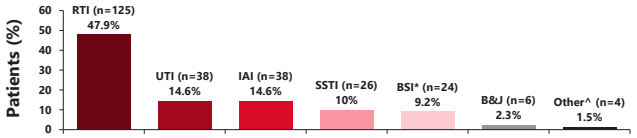
[a]*Burkholderia cepacia* complex (8); *Achromobacter* spp. (5); *Ralstonia mannitolilytica* (1); [b]*Serratia marcescens* (5); *Enterobacter cloacae* (3); *Klebsiella oxytoca* (2); *Citrobacter freundii* (1); other *Serratia* sp. (1); [c]Missing (23); [d]Missing (6); [e]Not mutually exclusive.

RESULTS CONT'D

Patient attrition

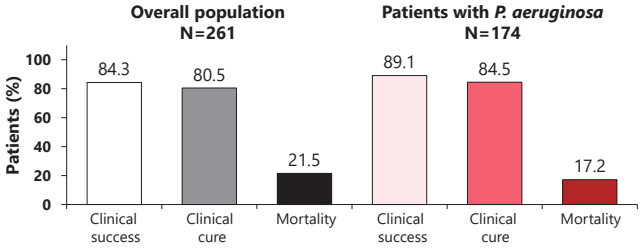


Site of infection

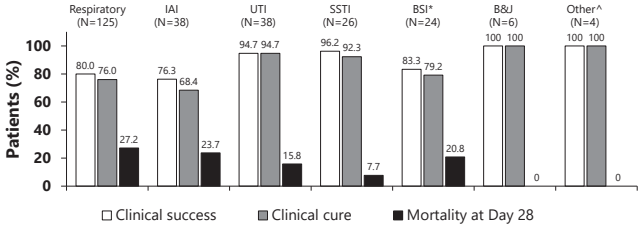


*Includes catheter-related (15), unknown source (9). ^Central nervous system infection (2); mediastinitis (2).

Clinical outcomes



Clinical outcomes by infection site



*Includes catheter-related (15), unknown source (9); ^Central nervous system infection (n=2), mediastinitis (n=2).

Clinical outcomes by antibiotic use

Number of days with prior antibiotics	Overall n (%) N=212	Clinical success n (%)	Clinical cure n (%)	Mortality Day 28 n (%)
≤3	55 (25.9)	49 (89.1)	49 (89.1)	9 (16.4)
4–7	70 (33.0)	62 (88.6)	59 (84.3)	13 (18.6)
>7	87 (41.0)	67 (77.0)	60 (69.0)	25 (28.7)
Cefiderocol as first line	**N=261**			
No	219 (83.9)	182 (83.1)	172 (78.5)	50 (22.8)
Yes	42 (16.1)	38 (90.5)	38 (90.5)	6 (14.3)
Combination treatment	**N=261**			
No	170 (65.1)	150 (88.2)	143 (84.1)	30 (17.6)
Yes	91 (34.9)	70 (76.9)	67 (73.6)	26 (28.6)

Clinical outcomes by resistance to BL–BLIs

Overall	Resistance phenotype	Clinical success	Clinical cure	Mortality Day 28
C/T-R, n/N' (%)	99/130* (76.2)	85/99 (85.9)	82/99 (82.8)	17/99 (17.2)
CZA-R, n/N' (%)	134/160* (83.8)	111/134 (82.8)	107/134 (79.9)	31/134 (23.1)
Patients with *P. aeruginosa*, n (%)				
C/T-R, n/N' (%)	75/105* (71.4)	67/75 (89.3)	65/75 (86.7)	10/75 (13.3)
CZA-R, n/N' (%)	96/112* (85.7)	83/96 (86.5)	80/96 (83.3)	18/96 (18.8)

*Number of patients with known susceptibility results.

CONCLUSIONS

- Cefiderocol treatment was effective with high clinical success and clinical cure rates in patients with serious Gram-negative bacterial infections, including patients with MDR and BL–BLI-resistant *P. aeruginosa* and other non-fermenters.
- Early administration of cefiderocol showed a numerical trend towards higher clinical cure and lower mortality rates.

Acknowledgements

The PERSEUS study was funded by Shionogi. Sarda J, Verardi S, Gonzalez AJ are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK and this support was funded by Shionogi.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; BL–BLIs, beta-lactam–beta-lactamase inhibitors; BSI, bloodstream infection; B&J, bone and joint; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; C/T-R, ceftolozane-tazobactam resistant; CZA-R, ceftazidime-avibactam resistant; ECMO, extracorporeal membrane oxygenation; IAI, intra-abdominal infection; LOS, length of stay; MDR, multidrug resistant; Q, quartile; RTI, respiratory tract infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

Reference

1. ClinicalTrials.gov: NCT05789199.

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Abstract 2

Effectiveness of cefiderocol in immunosuppressed patients with serious Gram-negative bacterial infections in the PERSEUS study in Spain

*Maria Rosa Oltra[1], **Jessica Sarda**[2], A. Javier Gonzalez[2], Stefano Verardi[3], Belen Loeches[4]*

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Background
Cefiderocol has demonstrated potent *in vitro* activity against carbapenem-resistant and multidrug-resistant Gram-negative bacteria, including Enterobacterales, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and other non-fermenting species. Cefiderocol was accessible in the Shionogi early access programme (EAP) for the treatment of patients with serious infections with no alternative treatment options in Spain (2018–2022). In this analysis, the real-world effectiveness of cefiderocol treatment in immunosuppressed patients was evaluated.

Methods
PERSEUS was a retrospective, multicentre, observational, medical chart review study enrolling hospitalised patients in the EAP with confirmed Gram-negative bacterial infections, who received first-time cefiderocol treatment for ≥72 hours. Patients with *Acinetobacter baumannii* infections were not enrolled in this study by design. Data included patient baseline characteristics, clinical success, clinical cure, all-cause mortality rates at Day 28 and adverse drug reactions. Only descriptive statistics were used.

Results
Of 261 eligible patients in the PERSEUS study, 79 (30.3%) had immunosuppression. Immunosuppressed patients had a median age of 59 years (range: 46–66) and 70.9% (n=56) were male (**Table 1**). Comorbid conditions were present in 89.9% of patients, most commonly solid/haematological cancer (44.3%), chronic renal disease (19.0%) and diabetes mellitus (16.5%). At baseline, 49.4% of patients were in the intensive care unit, 24.1% had septic shock, 26.6% had renal replacement therapy and 7.6% had secondary bacteraemia. Immunosuppressed patients most frequently had respiratory tract infection (35.4%), urinary tract infection (20.3%) and intra-abdominal infection (19.0%). The most frequent pathogens were *P. aeruginosa* (51.9%), *S. maltophilia* (13.9%), *Pseudomonas* spp. (11.4%) and other non-fermenters (11.4%). Polymicrobial infections were present in 11.4% of patients. The median duration of treatment was 10.0 days (range: 6.5–14.0). In this subgroup of patients, the overall clinical success rate was 81.0% (64/79), clinical cure rate was 77.2% (61/79) and mortality rate at Day 28 was 24.1% (19/79) (**Table 1**). Two patients (2.5%) reported adverse drug reactions; both events were mild and both patients recovered.

Conclusions
Cefiderocol was effective, with a high clinical cure rate and rare adverse drug reactions, in immunosuppressed patients with serious infections caused mainly by *P. aeruginosa* and other non-fermenters.

Table 1. Baseline characteristics, rationale for cefiderocol administration and outcomes in patients with immunosuppression[a] in the PERSEUS study

	Overall (N=79)
Age, years, median (range)	59 (46–66)
Sex, male, n (%)	56 (70.9)
Comorbidities, n (%)	71 (89.9)
Charlson Comorbidity Index, median (range)	4.0 (2.0-4.0)
Symptomatic COVID-19, n (%)	15 (19.0)
ICU at the time of initiation of cefiderocol, n (%)	39 (49.4)
Septic shock at the time of initiation of cefiderocol, n (%)	19 (24.1)
Renal replacement therapy at the time of initiation of cefiderocol, n (%)[b]	21 (26.6)
ECMO, n (%)	3 (3.8)
Infection site, n (%)	
Respiratory tract	28 (35.4)
Urinary tract	16 (20.3)
Intra-abdominal	15 (19.0)
Skin and soft tissue	6 (7.6)
Bloodstream	13 (16.5)
Other	1 (1.3)
Secondary bacteraemia, n (%)	6 (7.6)
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	41 (51.9)
Stenotrophomonas maltophilia	11 (13.9)
Pseudomonas spp.	9 (11.4)
Other non-fermenters[c]	9 (11.4)
Klebsiella pneumoniae	5 (6.3)
Other Enterobacterales[d]	4 (5.0)
Polymicrobial infection, n (%)	9 (11.4)
Treatment with previous antibiotics, n (%)	68 (86.1)
Rationale for administering cefiderocol, n (%)[e]	
Resistance to all tested antibiotics	53 (67.1)
Treatment failure with prior antibiotics	35 (44.3)
Adverse events to other susceptible antibiotics	8 (10.1)
Other	5 (6.3)
Cefiderocol treatment duration, days, median (range)	10.0 (6.5–14.0)
Cefiderocol combination therapy, n (%)	27 (34.2%)
Outcomes	
Clinical success, n (%)[f]	64 (81.0)
Clinical cure, n (%)[g]	61 (77.2)
All-cause mortality at Day 28, n (%)	19 (24.1)

[a]Transplant recipient, immunosuppressive treatment (e.g. high-dose corticosteroids, calcineurin inhibitors, anti-CD20, IL-1 inhibitors, and IL-6 inhibitors). [b]Unknown for 4 patients. [c]*Burkholderia cepacia* complex (5), *Achromobacter* spp. (3), *Ralstonia mannitolilytica* (1). [d]*Klebsiella oxytoca* (2), *Citrobacter freundii* (1), *Enterobacter cloacae* (1). [e]Not mutually exclusive. [f]Clinical success (primary endpoint for patients with treatment duration up to 28 days): cessation of antibiotic treatment due to clinical resolution of signs and symptoms of the infection for which cefiderocol was started, as assessed by the investigator at end of treatment or survival at Day 28 following first dose of treatment. [g]Clinical cure: cessation of antibiotic treatment due to improvement of signs and symptoms.
COVID-19, coronavirus disease-2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Poster 3734

34th ECCMID 2024
Barcelona, Spain
27–30 April, 2024

Effectiveness of cefiderocol in immunosuppressed patients with serious Gram-negative bacterial infections in the PERSEUS study in Spain

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SHIONOGI

Revised abstract

Background: Cefiderocol has demonstrated potent *in vitro* activity against carbapenem-resistant and multidrug-resistant Gram-negative bacteria, including Enterobacterales, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and other non-fermenting species. Cefiderocol was accessible in the Shionogi early access programme (EAP) for the treatment of patients with serious infections with no alternative treatment options in Spain (2018–2022). In this analysis, the real-world effectiveness of cefiderocol treatment in immunosuppressed patients was evaluated.

Methods: PERSEUS was a retrospective, multicentre, observational, medical chart review study enrolling hospitalised patients in the EAP with confirmed Gram-negative bacterial infections, who received first-time cefiderocol treatment for ≥72 hours. Patients with *Acinetobacter baumannii* infections were not enrolled in this study by design. Data included patient baseline characteristics, clinical success, clinical cure, all-cause mortality rates at Day 28 and adverse drug reactions. Only descriptive statistics were used.

Results: Of 261 eligible patients in the PERSEUS study, 79 (30.3%) had immunosuppression. Immunosuppressed patients had a median age of 59 years (range: 45–66) and 70.9% (n=56) were male. Comorbid conditions were present in 89.9% of patients, most commonly solid/haematological cancer (44.3%), chronic renal disease (19.0%) and diabetes mellitus (16.5%). At baseline, 49.4% of patients were in the intensive care unit, 24.1% had septic shock, 25.3% received renal replacement therapy and 7.6% had secondary bacteraemia. Immunosuppressed patients most frequently had respiratory tract infection (35.4%), urinary tract infection (20.3%) and intra-abdominal infection (19.0%). The most frequent pathogens were *P. aeruginosa* (51.9%), *S. maltophilia* (13.9%), *Pseudomonas* spp. (11.4%) and other non-fermenters (11.4%). Polymicrobial infections were present in 11.4% of patients. The median duration of treatment was 10.0 days (range: 6.0–14.0). In this subgroup of patients, the overall clinical success rate was 81.0% (64/79), clinical cure rate was 77.2% (61/79) and mortality rate at Day 28 was 22.8% (18/79). Two patients (2.5%) reported adverse drug reactions; both events were mild, and both patients recovered.

Conclusions: Cefiderocol was effective, with a high clinical cure rate and rare adverse drug reactions, in immunosuppressed patients with serious infections caused mainly by *P. aeruginosa* and other non-fermenters.

OBJECTIVES

In the PERSEUS study, patients were treated with cefiderocol for ≥72 hours for a confirmed Gram-negative bacterial infection and were mainly infected by *Pseudomonas aeruginosa* [1]. Of 261 eligible patients, 80.5% (210/261) achieved clinical cure and 21.5% (56/261) died by Day 28 [1]. The objective of this subgroup analysis of the PERSEUS study was to describe the baseline characteristics and the clinical outcomes in patients with immunosuppression at baseline, who were treated with cefiderocol for up to 28 days.

METHODS

Study design: a retrospective, multicentre, observational study in patients receiving cefiderocol for the first time in the early access programme in Spain.

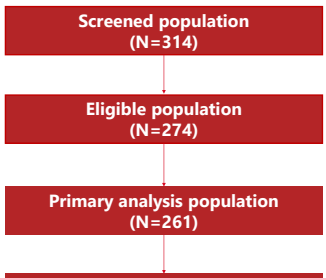
Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours for a confirmed Gram-negative bacterial infection, with tested sensitivity to cefiderocol.

Exclusion criteria: confirmed *Acinetobacter* spp. at baseline; confirmed cefiderocol-resistant Gram-negative pathogen at baseline; incomplete medical records; enrolled into other clinical studies of investigational products.

Endpoints: baseline patient characteristics, Gram-negative bacterial pathogens, clinical success (composite of clinical cure and/or survival at Day 28), clinical cure (cessation of antibiotic treatment due to clinical resolution of signs and symptoms) at end of treatment and all-cause mortality at Day 28.

RESULTS

Patient attrition



*Transplant recipient, immunosuppressive treatment (e.g. high-dose corticosteroids, calcineurin inhibitors, anti-CD20, IL-1 inhibitors, and IL-6 inhibitors).

Patient characteristics (N=79)		Main comorbidities	
Sex, male	56 (70.9%)	Transplant recipient	53 (67.1%)
Age, median (Q1–Q3), years	59 (45–66)	Tumor (solid/haematological)	35 (44.3%)
CCI score, median (Q1–Q3)	4 (2–5)	Chronic renal disease	15 (19.0%)
Symptomatic COVID-19	15 (19.0%)	Diabetes	13 (16.5%)

49.4% (n=39) — **ICU at the time of cefiderocol**

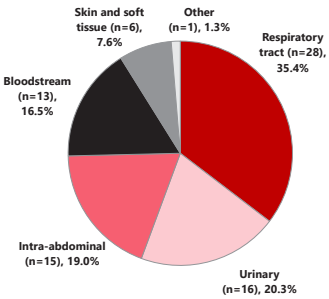
41.8% (n=33) — **Mechanical ventilation**

25.3% (n=20) — **Renal replacement therapy**

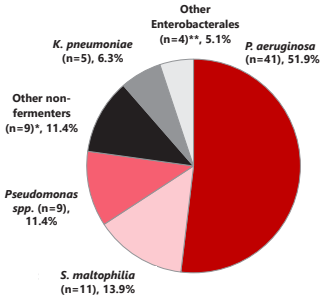
24.1% (n=19) — **Septic shock**

RESULTS CONT'D

Site of infection



Distribution of pathogens

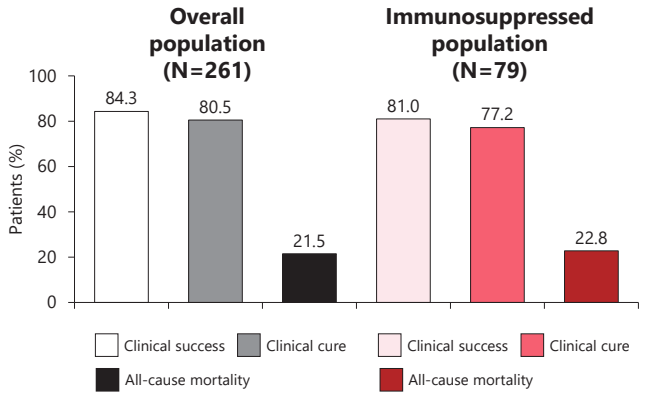


*Burkholderia cepacia complex (5), Achromobacter spp. (3), Ralstonia mannitolilytica (1); **Klebsiella oxytoca (2), Citrobacter freundii (1), Enterobacter cloacae (1);

Baseline infection characteristics and rationale for cefiderocol administration in patients with immunosuppression[a] (N=79)	
Secondary bacteraemia, n (%)	6 (7.6)
Polymicrobial infection, n (%)	9 (11.4)
Previous colonisation with the same pathogen, n (%)	41 (51.9)
Previous treatment with antibiotics, n (%)	66 (83.5)
Rationale for administering cefiderocol[b]	
Resistance to all tested antibiotics	53 (67.1)
Treatment failure with prior antibiotics	35 (44.3)
Adverse events to other susceptible antibiotics	8 (10.1)
Other	5 (6.3)
Cefiderocol treatment duration, median (range), days	10.0 (6.0–14.0)
Cefiderocol combination therapy, n (%)	35 (44.3)
Adverse drug reactions, n (%)	2 (2.5)

[a]Transplant recipient, immunosuppressive treatment (e.g. high-dose corticosteroids, calcineurin inhibitors, anti-CD20, IL-1 inhibitors, and IL-6 inhibitors); [b]Not mutually exclusive.

Clinical outcomes



CONCLUSIONS

Cefiderocol was effective with a high clinical cure rate in immunosuppressed patients with serious infections caused mainly by *P. aeruginosa* and other non-fermenters. Adverse drug reactions were rare.

Reference

1. Ramirez P, et al. Real-world effectiveness and safety of cefiderocol in patients with Gram-negative bacterial infections in the early access programme in Spain: results of the PERSEUS study. Presented at 34th ECCMID, Barcelona, Spain; 27–30 April 2024. Poster 2523.

Acknowledgements

The PERSEUS study was funded by Shionogi. Sarda J, Verardi S, Gonzalez AJ are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK and this support was funded by Shionogi.

Abbreviations

CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IL, interleukin; Q, quartile.

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Abstract 3

Effectiveness of cefiderocol in patients with intra-abdominal infections caused by Gram-negative bacteria in the PERSEUS study in Spain

*Carmen Maria Saez[1], Fernando Mateos[2], **Jessica Sarda**[3], A. Javier Gonzalez[3], Stefano Verardi[4], Joaquin Lobo Palanco[5]*

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Background

Cefiderocol has potent *in vitro* activity against multidrug-resistant strains of Enterobacterales and non-fermenting Gram-negative bacteria, including *Pseudomonas aeruginosa*. Data on its effectiveness in patients with complicated intra-abdominal infections (cIAIs) are limited. This subgroup analysis of the PERSEUS study aimed to evaluate the effectiveness of cefiderocol in patients with cIAIs in the Shionogi early access programme in Spain.

Methods

PERSEUS was a retrospective, multicentre, observational, medical chart review study (2018–2022) enrolling hospitalised patients with confirmed Gram-negative bacterial infections, excluding *Acinetobacter baumannii* infections, and for whom other treatment options failed or were not available. Patients were treated with cefiderocol for the first time for ≥72 hours. Patient demographics, baseline clinical characteristics, rates of clinical success, clinical cure and Day 28 all-cause mortality, and safety were evaluated. Only descriptive statistics were used.

Results

Among 261 eligible patients, 14.6% (n=38) had cIAIs. The median age of this subgroup was 62 years (range: 51–70) and 81.6% (31/38) were male. Comorbidities were present in 86.8% (33/38) of patients (**Table 1**). At baseline, up to 44.7% of patients were in the intensive care unit (ICU), 26.3% had septic shock and 26.3% received renal replacement therapy while in the ICU. Secondary bacteraemia was reported for 18.4% of patients with cIAIs. The most frequent Gram-negative pathogens were *P. aeruginosa* (60.5%, 23/38), *Klebsiella pneumoniae* (18.4%, 7/38) and *Pseudomonas* spp. (7.9%, 3/38). Polymicrobial infections were detected in 21.1% (8/38) of patients, and >50% of patients were previously colonised. The median cefiderocol treatment duration was 10.0 days (range: 7.0–16.5). The frequent reasons for starting cefiderocol treatment included resistance to all tested antibiotics (63.2%), treatment failure with prior antibiotics (50.0%) and adverse events (10.5%). Overall, 76.3% (29/38) of patients achieved clinical success, 68.4% (26/38) had clinical cure and 23.7% (9/38) died by Day 28 (**Table 1**). No adverse drug reactions related to cefiderocol were reported for these patients.

Conclusions

Cefiderocol was effective and well tolerated in patients with cIAIs caused by Gram-negative bacteria in a complex, ICU, real-world population with no alternative treatment option in Spain.

Table 1. Baseline characteristics, rationale for administering cefiderocol and outcomes in patients with intra-abdominal infections in the PERSEUS study

	Overall (N=38)
Age, years, median (range)	62 (51–70)
Sex, male, n (%)	31 (81.6)
Comorbidities, n (%)	33 (86.8)
Solid/haematological cancer	18 (47.4)
Immunosuppression	15 (39.5)
Chronic kidney disease	6 (15.8)
Chronic liver disease	6 (15.8)
Charlson Comorbidity Index, median (range)	4.0 (3.0–5.0)
Symptomatic COVID-19, n (%)	3 (7.9)
ICU at the time of initiation of cefiderocol, n (%)	17 (44.7)
Septic shock at the time of initiation of cefiderocol, n (%)	10 (26.3)
Renal replacement therapy at the time of initiation of cefiderocol, n (%)[a]	10 (26.3)
Secondary bacteraemia, n (%)	7 (18.4)
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	23 (60.5)
Klebsiella pneumoniae	7 (18.4)
Stenotrophomonas maltophilia	2 (5.3)
Pseudomonas spp.	3 (7.9)
Other non-fermenters[b]	1 (2.6)
Other Enterobacterales[c]	2 (5.3)
Polymicrobial infection, n (%)	8 (21.1)
Previous colonisation, n (%)	20 (52.6)
Treatment with previous antibiotics, n (%)	35 (92.1)
Rationale for administering cefiderocol[d]	
Resistance to all tested antibiotics	24 (63.2)
Treatment failure with prior antibiotics	19 (50.0)
Adverse events to other susceptible antibiotics	4 (10.5)
Other	2 (5.3)
Cefiderocol treatment duration, days, median (range)	10.0 (7.0–16.5)
Cefiderocol in combination therapy, n (%)	8 (21.1)
Outcomes	
Clinical success, n (%)[e]	29 (76.3)
Clinical cure, n (%)[f]	26 (68.4)
All-cause mortality at Day 28, n (%)	9 (23.7)

[a]Unknown for 2 patients. [b]*Burkholderia cepacia* complex (1). [c]*Klebsiella oxytoca* (1), *Citrobacter freundii* (1). [d]Not mutually exclusive. [e]Clinical success (primary endpoint for patients with treatment duration up to 28 days): cessation of antibiotic treatment due to clinical resolution of signs and symptoms of the infection for which cefiderocol was started, as assessed by the investigator at end of treatment, or survival at Day 28 following first dose of treatment. [f]Clinical cure: cessation of antibiotic treatment due to improvement of signs and symptoms.
COVID-19, coronavirus disease-2019; ICU, intensive care unit.

Poster 2525

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Barcelona, Spain
27–30 April, 2024

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Effectiveness of cefiderocol in patients with intra-abdominal infections caused by Gram-negative bacteria in the PERSEUS study in Spain

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SHIONOGI

Revised abstract

Background: Cefiderocol has potent *in vitro* activity against multidrug-resistant strains of Enterobacterales and non-fermenting Gram-negative bacteria, including *Pseudomonas aeruginosa*. Data on its effectiveness in patients with complicated intra-abdominal infections (cIAIs) are limited. This subgroup analysis of the PERSEUS study aimed to evaluate the effectiveness of cefiderocol in patients with cIAIs in the Shionogi early access programme in Spain.

Methods: PERSEUS was a retrospective, multicentre, observational, medical chart review study (2018–2022) enrolling hospitalised patients with confirmed Gram-negative bacterial infections, excluding *Acinetobacter baumannii* infections, and for whom other treatment options had failed or were not available. Patients were treated with cefiderocol for the first time for ≥72 hours. Patient demographics, baseline clinical characteristics, rates of clinical success, clinical cure and Day 28 all-cause mortality, and safety were evaluated. Only descriptive statistics were used.

Results: Among 261 eligible patients, 14.6% (n=38) had cIAIs. The median age of this subgroup was 62 years (range: 51–71) and 81.6% (31/38) were male. Comorbidities were present in 86.8% (33/38) of patients. At baseline, up to 44.7% of patients were in the intensive care unit (ICU), 26.3% had septic shock and 23.7% received renal replacement therapy while in the ICU. Secondary bacteraemia was reported for 18.4% of patients with cIAIs. The most frequent Gram-negative pathogens were *P. aeruginosa* (60.5%, 23/38), *Klebsiella pneumoniae* (18.4%, 7/38) and *Pseudomonas* spp. (7.9%, 3/38). Polymicrobial infections were detected in 21.1% (8/38) of patients, and >50% of patients were previously colonised. The median cefiderocol treatment duration was 10.0 days (range: 7.0–17.0). The frequent reasons for starting cefiderocol treatment included resistance to all tested antibiotics (63.2%), treatment failure with prior antibiotics (50.0%) and adverse events (10.5%). Of patients with cIAIs, 76.3% (29/38) of patients achieved clinical success, 68.4% (26/38) had clinical cure and 23.7% (9/38) died by Day 28. No adverse drug reactions related to cefiderocol were reported for these patients.

Conclusions: Cefiderocol was effective and well tolerated in patients with cIAIs caused by Gram-negative bacteria in a complex, ICU, real-world population with no alternative treatment option in Spain.

OBJECTIVES

The PERSEUS retrospective study enrolled hospitalised patients with Gram-negative bacterial infections, who were treated with cefiderocol through the early access programme (EAP) in Spain [1]. Of 261 eligible patients, 80.5% (210/261) achieved clinical cure and 21.5% (56/261) died by Day 28 [1]. Clinical data in patients with complicated intra-abdominal infections (cIAIs) treated with cefiderocol are limited. The objective of this subgroup analysis was to describe the baseline characteristics and the clinical outcomes in patients with cIAIs treated with cefiderocol for up to 28 days in the PERSEUS study.

METHODS

Study design: a retrospective, multicentre, observational study in patients receiving cefiderocol for the first time in the EAP in Spain.

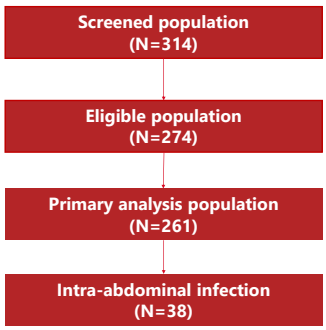
Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours for a confirmed Gram-negative bacterial infection.

Exclusion criteria: confirmed *Acinetobacter* spp. at baseline; confirmed cefiderocol-resistant Gram-negative pathogen at baseline; incomplete medical records; enrolled into other clinical studies of investigational product.

Endpoints: baseline patient characteristics, Gram-negative bacterial pathogens, clinical success (composite of clinical cure and/or survival at Day 28), clinical cure (cessation of antibiotic treatment due to clinical resolution of signs and symptoms) at end of treatment and all-cause mortality at Day 28.

RESULTS

Patient attrition



Patient characteristics (N=38)		Main comorbidities	
Sex, male	31 (81.6%)	Solid/haematological cancer	18 (47.4%)
Age, median (Q1–Q3), years	62 (51–71)	Immunosuppression	15 (39.5%)
CCI score, median (Q1–Q3)	4 (2–5)	Transplant	12 (31.6%)
APACHE II score, median (Q1–Q3)	12.5 (8.5–17.5)	Chronic kidney disease	6 (15.8%)
LOS, median (Q1–Q3), days	59.5 (38–94)	Chronic liver disease	6 (15.8%)
ICU LOS, median (Q1–Q3), days	50.0 (33–64)	Symptomatic COVID-19	3 (7.9%)

44.7% (n=17) — **ICU at the time of cefiderocol**

31.6% (n=12) — **Mechanical ventilation**

26.3% (n=10) — **Septic shock**

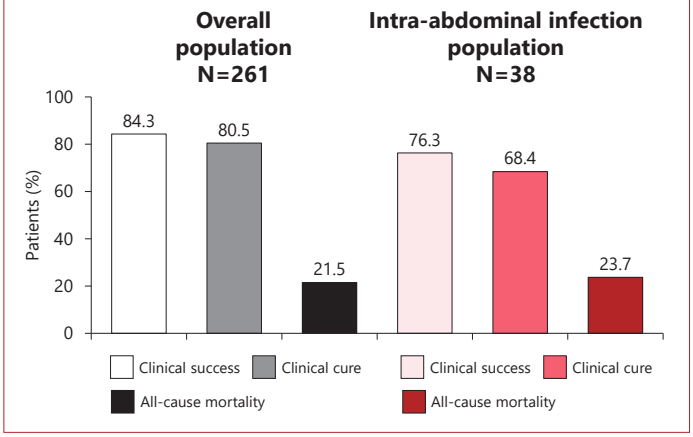
23.7% (n=9) — **Renal replacement therapy**

RESULTS CONT'D

Baseline Gram-negative pathogens and rationale for cefiderocol administration in patients with intra-abdominal infections (N=38)	
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	23 (60.5)
Klebsiella pneumoniae	7 (18.4)
Stenotrophomonas maltophilia	2 (5.3)
***Pseudomonas* spp.**	3 (7.9)
***Burkholderia cepacia* complex**	1 (2.6)
Other Enterobacterales[a]	2 (5.3)
Secondary bacteraemia, n (%)	7 (18.4)
Polymicrobial infection, n (%)	8 (21.1)
Previous colonisation, n (%)	20 (52.6)
Previous treatment with antibiotics, n (%)	35 (92.1)
Rationale for administering cefiderocol[b]	
Resistance to all tested antibiotics	24 (63.2)
Treatment failure with prior antibiotics	19 (50.0)
Adverse events to other susceptible antibiotics	4 (10.5)
Other	2 (5.3)
Cefiderocol treatment duration, median (range), days	10.0 (7.0–17.0)
Cefiderocol combination therapy, n (%)	14 (36.8)
Adverse drug reactions, n (%)	0 (0)

[a]*Klebsiella oxytoca* (1), *Citrobacter freundii* (1); [b]Not mutually exclusive.

Clinical outcomes



CONCLUSIONS

- Cefiderocol was effective and well tolerated in patients with cIAIs caused by Gram-negative bacteria in a complex, ICU, frequently colonised, real-world population with limited treatment options in Spain.
- Cefiderocol may be an appropriate antibiotic option for the treatment of patients with Gram-negative bacterial cIAIs.

Reference

1. Ramirez P, et al. Real-world effectiveness and safety of cefiderocol in patients with Gram-negative bacterial infections in the early access programme in Spain: results of the PERSEUS study. Presented at 34th ECCMID, Barcelona, Spain; 27–30 April 2024. Poster 2523.

Acknowledgements

The PERSEUS study was funded by Shionogi. Sarda J, Verardi S, Gonzalez AJ are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK and this support was funded by Shionogi.

Abbreviations

CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LOS, length of stay; Q, quartile.

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Abstract 4

Real-world effectiveness and safety of long-term (>28 days) cefiderocol treatment in patients with Gram-negative bacterial infections in the PERSEUS study in Spain

*Maria Jose Perez-Pedrero[1], Jorge Calderón Parra[2], **Jessica Sarda**[3], A. Javier Gonzalez[3], Stefano Verardi[4]*

[1]Department of Critical Care Medicine, Complejo Hospitalario de Toledo, Toledo, Spain, [2]Internal Medicine Department, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain, [3]Shionogi S.L.U., Madrid, Spain, [4]Shionogi B.V., London, UK

Background

Cefiderocol was utilised through the Shionogi early access programme (EAP) for the treatment of patients with serious Gram-negative bacterial infections (GNBIs), who had no alternative treatment options, in Spain between 2018 and 2022. In the PERSEUS study, the effectiveness of cefiderocol in patients with GNBIs, excluding *Acinetobacter baumannii*, was evaluated in real-world settings in Spain. The current subgroup analysis assessed the long-term effectiveness and safety of cefiderocol administered for longer than 28 days.

Methods

PERSEUS was an observational, multicentre, retrospective, medical chart review study of hospitalised patients with confirmed GNBIs who participated in the Shionogi EAP and were treated with cefiderocol for the first time for ≥72 hours. Patients with documented *A. baumannii* infections were excluded by design. In this analysis, patients with a treatment duration of >28 days were included. Patient demographics, baseline clinical characteristics, clinical cure, all-cause mortality at Day 90 and safety were evaluated. Only descriptive statistics were used.

Results

A total of 13 patients received cefiderocol for >28 days. All patients were male, and the median age was 54 years (range: 40–65) (**Table 1**). In this subgroup, patients most frequently had intra-abdominal infection (30.8%, 4/13), osteoarticular infection (30.8%, 4/13) and respiratory tract infection (23.1%, 3/13). Bloodstream infection and vascular prosthesis infection were each found in one patient (7.7%). The causative pathogens were *Pseudomonas aeruginosa* (84.6%, 11/13), *Stenotrophomonas maltophilia* (7.7%, 1/13) and *Elizabethkingia miricola* (7.7%, 1/13). At baseline, the proportion of patients in the intensive care unit was 46.2% (6/13), and one patient (7.7%) had septic shock, five (38.5%) received renal replacement therapy and three (23.1%) had secondary bacteraemia. The median treatment duration was 40.0 days (range: 34–46). Overall, the clinical cure rate was 84.6% (11/13), and mortality rate at Day 90 was 23.1% (3/13) (**Table 1**). Cefiderocol was well tolerated without any adverse drug reaction in these patients.

Conclusions

Cefiderocol treatment administered for > 28 days resulted in a high clinical cure rate and was well tolerated in patients with serious infections and no alternative treatment options.

Table 1. Baseline characteristics, rationale for cefiderocol administration and outcomes in patients with cefiderocol treatment for >28 days in the PERSEUS study

	Overall (N=13)
Age, years, median (range)	54 (40–65)
Sex, male, n (%)	13 (100)
Comorbidities, n (%)	10 (76.9)
Solid/haematological cancer	5 (38.5)
Chronic renal disease	4 (30.8)
Peripheral vascular disease	3 (23.1)
Myocardial infarction	3 (23.1)
Charlson Comorbidity Index, median (range)	2.0 (2–7)
ICU at the time of initiation of cefiderocol, n (%)	6 (46.2)
Septic shock at the time of initiation of cefiderocol, n (%)	1 (7.7)
Renal replacement therapy at the time of initiation of cefiderocol, n (%)[a]	5 (38.5)
Secondary bacteraemia, n (%)	3 (23.1)
Site of infection, n (%)	
Intra-abdominal	4 (30.8)
Osteoarticular	4 (30.8)
Respiratory tract	3 (23.1)
Bloodstream	1 (7.7)
Vascular prosthesis	1 (7.7)
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	11 (84.6)
Stenotrophomonas maltophilia	1 (7.7)
Elizabethkingia miricola	1 (7.7)
Treatment with previous antibiotics, n (%)	11 (84.6)
Rationale for administering cefiderocol[b]	
Resistance to all tested antibiotics	7 (53.8)
Treatment failure with prior antibiotics	5 (38.5)
Adverse events to other susceptible antibiotics	2 (15.4)
Other	3 (23.1)
Cefiderocol treatment duration, days, median (range)	40 (34–46)
Outcomes	
Clinical cure, n (%)[c]	11 (84.6)
All-cause mortality at Day 90, n (%)	3 (23.1)

[a]Unknown for 1 patient. [b]Not mutually exclusive. [c]Clinical cure: cessation of antibiotic treatment due to improvement of signs and symptoms.
ICU, intensive care unit.

Poster 2524

34th ECCMID 2024
Barcelona, Spain
27–30 April, 2024

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Real-world effectiveness and safety of long-term (>28 days) cefiderocol treatment in patients with Gram-negative bacterial infections in the PERSEUS study in Spain

Maria Jose Perez-Pedrero,[1] Jorge Calderón Parra,[2] **Jessica Sarda**,[3] A. Javier Gonzalez,[3] Stefano Verardi,[4]

1. Department of Critical Care Medicine, Complejo Hospitalario de Toledo, Toledo, Spain; 2. Internal Medicine Department, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; 3. Shionogi S.L.U., Madrid, Spain; 4. Shionogi B.V., London, UK

SHIONOGI

Abstract

Background: Cefiderocol was utilised through the Shionogi early access programme (EAP) for the treatment of patients with serious Gram-negative bacterial infections (GNBIs), who had no alternative treatment options, in Spain between 2018 and 2022. In the PERSEUS study, the effectiveness of cefiderocol in patients with GNBIs, excluding *Acinetobacter baumannii*, was evaluated in real-world settings in Spain. The current subgroup analysis assessed the long-term effectiveness and safety of cefiderocol administered for longer than 28 days.

Methods: PERSEUS was an observational, multicentre, retrospective, medical chart review study of hospitalised patients with confirmed GNBIs who participated in the Shionogi EAP and were treated with cefiderocol for the first time for ≥72 hours. Patients with documented *A. baumannii* infections were excluded by design. In this analysis, patients with a treatment duration of >28 days were included. Patient demographics, baseline clinical characteristics, clinical cure, all-cause mortality at Day 90 and safety were evaluated. Only descriptive statistics were used.

Results: A total of 13 patients received cefiderocol for >28 days. All patients were male, and the median age was 54 years (range: 40–65). In this subgroup, patients most frequently had intra-abdominal infection (30.8%, 4/13), osteoarticular infection (30.8%, 4/13) and respiratory tract infection (23.1%, 3/13). Bloodstream infection and vascular prosthesis infection were each found in one patient (7.7%). The causative pathogens were *Pseudomonas aeruginosa* (84.6%, 11/13), *Stenotrophomonas maltophilia* (7.7%, 1/13) and *Elizabethkingia miricola* (7.7%, 1/13). At baseline, the proportion of patients in the intensive care unit was 46.2% (6/13), and one patient (7.7%) had septic shock, five (38.5%) received renal replacement therapy and three (23.1%) had secondary bacteraemia. The median treatment duration was 40.0 days (range: 34–46). Overall, the clinical cure rate was 84.6% (11/13) and mortality rate at Day 90 was 23.1% (3/13). Cefiderocol was well tolerated without any adverse drug reaction in these patients.

Conclusions: Cefiderocol treatment administered for >28 days resulted in a high clinical cure rate and was well tolerated in patients with serious infections and no alternative treatment options.

OBJECTIVES

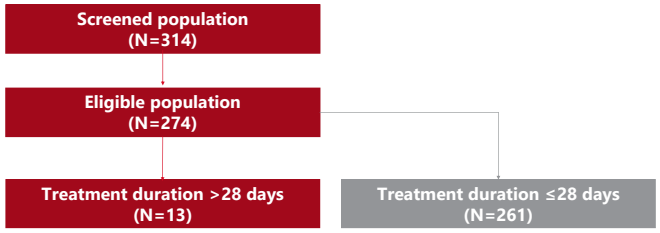
In the PERSEUS retrospective study, of the overall eligible population, who were treated with cefiderocol for ≥72 hours for a confirmed Gram-negative bacterial infection and primarily infected by *Pseudomonas aeruginosa*, 80.5% (210/261) achieved clinical cure and 21.5% (56/261) died by Day 28 [1]. The objective of this subgroup analysis was to describe the baseline characteristics and the clinical outcomes following cefiderocol treatment administered for >28 days in patients with Gram-negative bacterial infections enrolled into the PERSEUS study in Spain.

METHODS

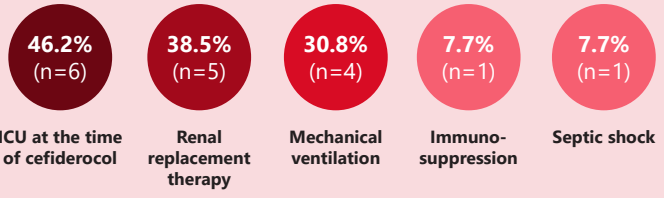
Study design: a retrospective, observational study in patients receiving cefiderocol for the first time in the early access programme (EAP) in Spain.
Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours for a confirmed Gram-negative bacterial infection.
Exclusion criteria: confirmed *Acinetobacter* spp. at baseline; confirmed cefiderocol-resistant Gram-negative pathogen at baseline; incomplete medical records; enrolled into other clinical studies of investigational products.
Endpoints: baseline patient characteristics, Gram-negative species, clinical cure (cessation of antibiotic treatment due to clinical resolution of signs and symptoms) at end of treatment and all-cause mortality at Day 90.

RESULTS

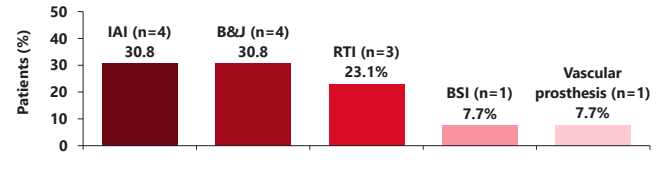
Patient attrition



Patient characteristics (N=13)		Main comorbidities	
Sex, male	13 (100%)	Tumour (solid/haematological)	5 (38.5%)
Age, median (Q1–Q3), years	54 (40–65)	Chronic renal disease	4 (30.8%)
CCI score, median (Q1–Q3)	2 (2–7)	Peripheral vascular disease	3 (23.1%)
APACHE II score, median (Q1–Q3)	16 (14–20)	Myocardial infarction	3 (23.1%)



Site of infection

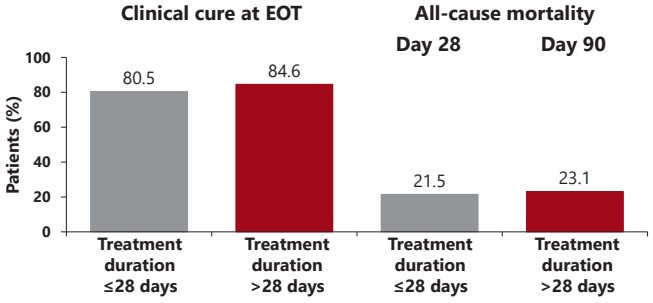


RESULTS CONT'D

Baseline Gram-negative pathogens and rationale for cefiderocol administration in patients with treatment duration of >28 days (N=13)	
Gram-negative pathogen, n (%)	
Pseudomonas aeruginosa	11 (84.6)
Stenotrophomonas maltophilia	1 (7.7)
Elizabethkingia miricola	1 (7.7)
Secondary bacteraemia, n (%)	**3 (23.1)**
Polymicrobial infection, n (%)	**2 (15.4)**
Previously colonised with the same pathogen, n (%)	**8 (61.5)**
Other pathogens isolated, n (%)	**6 (46.2)**
Gram-positive pathogen, n (%)	**5 (83.3)**
Fungi, n (%)	**3 (50.0)**
Anaerobes, n (%)	**1 (16.7)**
Previous treatment with antibiotics, n (%)	**11 (84.6)**
Rationale for administering cefiderocol[a]	
Resistance to all tested antibiotics	**7 (53.8)**
Treatment failure with prior antibiotics	**5 (38.5)**
Adverse events to other susceptible antibiotics	**2 (15.4)**
Other	**3 (23.1)**
Cefiderocol treatment duration, median (range), days	**40 (34–46)**
Cefiderocol combination therapy, n (%)	**7 (53.8)**
Adverse drug reactions, n (%)	**0 (0)**

[a]Not mutually exclusive.

Clinical outcomes



CONCLUSIONS

- Where cefiderocol treatment was administered for long term (i.e., >28 days), it was driven by deep seated infections, such as IAI and B&J infections. In these patients, clinical cure rate was high and mortality rate at day 90 was <25% in this subgroup of the PERSEUS study.
- Cefiderocol was well tolerated in patients with serious infections and limited treatment options that required prolonged treatment.

Reference

1. Ramirez P, et al. Real-world effectiveness and safety of cefiderocol in patients with Gram-negative bacterial infections in the early access programme in Spain: results of the PERSEUS study. Presented at 34th ECCMID, Barcelona, Spain; 27–30 April 2024. Poster 2523.

Acknowledgements

The PERSEUS study was funded by Shionogi. Sarda J, Verardi S, Gonzalez AJ are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK and this support was funded by Shionogi.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; B&J, bone and joint infection; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; EOT, end of treatment; IAI, intra-abdominal infection; ICU, intensive care unit; LOS, length of stay; Q, quartile; RTI, respiratory tract infection.

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Highlights

- Lo studio retrospettivo, multicentrico e osservazionale PERSEUS ha analizzato l'efficacia e la sicurezza di cefiderocol in diverse popolazioni di pazienti con infezioni da batteri Gram-negativi (GNBI) in un setting *real-world* in Spagna.
- Lo studio ha incluso i pazienti che hanno ricevuto un trattamento con cefiderocol per ≥72 ore ospedalizzati con GNBI confermata: i risultati hanno mostrato un tasso di successo clinico dell'84,7%, un tasso di guarigione clinica dell'80,5% e una mortalità del 21,5% entro il 28° giorno.
- Nei pazienti immunosoppressi con infezioni delle vie respiratorie, urinarie o intraddominali *da P. aeruginosa*, *S. maltophilia*, *Pseudomonas* spp. o altri Gram-negativi non fermentanti, il tasso di successo clinico complessivo è stato dell'81,0%, il tasso di guarigione clinica del 77,2% e il tasso di mortalità al giorno 28 del 24,1%.
- Nei pazienti con infezioni intraddominali complicate (cIAIs) il trattamento con cefiderocol ha portato a un successo clinico nel 76,3% e a una guarigione clinica nel 68,4% dei pazienti. Il tasso di mortalità entro il 28° giorno è stato del 23,7%.

Abstract 5

Real-World Experience of Cefiderocol in Bone and Joint infections from the PROVE (Retrospective Cefiderocol Chart Review) Study

Aurelien Dinh[1], Stefano Verardi[2] , Stephen Marcella[3], Anne Santerre Henriksen[2]

[1]Raymond Poincare Hospital, APHP, Garches, FR, [2]Shionogi B.V., London, UK, [3]Shionogi Inc, Florham Park, USA

Background

Cefiderocol (CFDC) is a siderophore cephalosporin approved in Europe for the treatment of Gram-negative infections in adults with limited treatment options. PROVE is an ongoing international, retrospective study. This analysis describes infection characteristics, and outcomes of CFDC treatment in bone and joint infections (BJI).

Methods

Patients were eligible if they have BJI and received ≥ 72 hours of CFDC. Patient and pathogen characteristics, hospital course, and antibiotic treatment patterns were described. All-cause mortality (ACM) at 14 and 30 days and clinical cure (defined as improvement or resolution of the signs and symptoms of the indicated GNBI within the current hospitalization) were examined as outcomes, overall, and by key characteristics such as patient demographics or infection site. Adverse drug reactions (ADR) were recorded.

Results

To date 43 patients were treated with CFDC for BJI in US or Europe (29 in USA, 10 in France, 3 in Italy and 1 in Germany). Median age was 60 years and majority of patients were male (67.4%). Mean treatment duration was 26.6 days. *Acinetobacter baumannii* as a single pathogen represented 30.2% of the infections followed by Enterobacterales (18.6%) and *Pseudomonas aeruginosa* (14.0%). Overall clinical cure at the end of cefiderocol treatment was achieved in 81.4% of the patients and 30-day ACM was 9.3%. Results were largely similar in the different patient populations looking at monomicrobial, polymicrobial infection or by pathogens. Only 1 patient reported 2 ADRs, an urticarial rash and an interstitial nephritis leading to drug discontinuation.

Conclusion

In this large cohort of patients treated for BJI, clinical outcomes suggest that cefiderocol is a promising alternative treatment for these patients.

Table 1: Patient and clinical characteristics at inclusion (N=43)

Patient information	
Age, years, median (range)	60 (20-90)
Sex, n (%)	
Female	14 (32.6)
Male	29 (67.4)
Hospital admission, n (%)	
Emergency	23 (53.5)
Transfer from Another Medical Care Facility	9 (20.9)
Scheduled	10 (23.3)
Other	1 (2.3)
Risks Factors for CR-GNBI (not mutually exclusive)	
Admitted to Hospital in the Past 6 Months, n (%)	34
History of CR-GNBI, n (%)	11
Received a carbapenemin prior 30 days, n (%)	12
Pathogens	
Monomicrobial infection, n (%)	**28 (65.1)**
Acinetobacter spp, n (%)	13 (30.2)
Enterobacterales, n (%)	8 (18.6)
Pseudomonas spp, n (%)	6 (14.0)
Polymicrobial infection, n (%)	**15 (34.9)**
Carbapenem resistance, n (%)	**32 (74.4)**
Cefiderocol monotherapy, n (%)	**25 (58.1)**

Table 2: Outcomes by patient population

	Clinical cure n (%)	**14 Days mortality n (%)**	**30 Days mortality n (%)**
Overall, N=43	**35 (81.4)**	**1 (2.3)**	**4 (9.3)**
Monomicrobial infection, N=28	**24 (85.7)**	**1 (3.6)**	**1 (3.6)**
Acinetobacter spp, N=13	10 (76.9)	1 (7.7)	1 (7.7)
Enterobacterales, N=8	8 (100)	-	-
Pseudomonas spp, N=6	5 (83.3)	0	0
Polymicrobial infection, N=15	**11 (73.3)**	**0**	**3 (20.0)**
Carbapenem resistance, N=32	**26 (81.3)**	**1 (3.1)**	**3 (9.4)**

Poster 3185

34th ECCMID 2024
Barcelona, Spain
27–30 April, 2024

Real-world experience of cefiderocol in bone and joint infections from the PROVE (retrospective cefiderocol chart review) study

Aurelien Dinh,[1] Stefano Verardi,[2] Stephen Marcella,[3] Anne Santerre Henriksen[2]
[1]Raymond Poincare Hospital, APHP, Garches, France; [2]Shionogi B.V., London, UK;
[3]Shionogi Inc., Florham Park, NJ, USA

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SHIONOGI

OBJECTIVES

We aimed to describe the characteristics and the outcomes of cefiderocol treatment in bone and joint infections caused by Gram-negative bacterial species among patients included in the ongoing observational PROVE study.

METHODS

Design: retrospective, observational, international study.

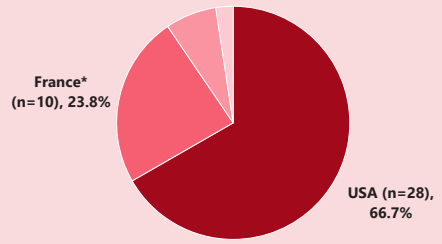
Inclusion criteria: adult hospitalised patients with bone and joint infections caused by Gram-negative pathogens, treated with cefiderocol consecutively for ≥72 hours (November 2020–March 2023).

Endpoints: patient and pathogen characteristics, hospitalisation course, antibiotic treatment patterns, clinical cure (clinical cure is defined as improvement or resolution of signs/symptoms without evidence of relapse or death at end of hospitalisation), and 14-day and 30-day all-cause mortality (ACM). Only descriptive statistics are used.

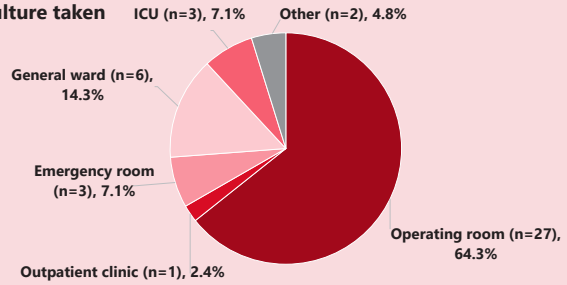
RESULTS

Patient characteristics (N=42)		Main comorbidities	
Age, median (Q1–Q3), years	59.5 (45–69)	Diabetes with end-organ damage	11 (26.2%)
Sex, male	28 (66.7%)	Peripheral vascular disease	10 (23.8%)
CCI score, median (Q1–Q3)	2 (1–5)	Hemiplegia	9 (21.4%)
ICU at time of cefiderocol	5 (11.9%)	Musculoskeletal abnormality/ degenerative disease	9 (21.4%)
		Renal disease	7 (16.7%)

Country



Index culture taken



CCI, Charlson Comorbidity Index; ICU, intensive care unit; Q, quartile. *One patient, who received cefiderocol in compassionate use/early access programme, was a protocol violation; data will be excluded from further analyses.

Admission type (N=42)	n (%)
Emergency or urgent admission	23 (54.8)
Direct transfer from another medical care facility	7 (16.7)
Scheduled admission	11 (26.2)
Other	1 (2.4)
Hospitalisation course and cefiderocol use	**Median (Q1–Q3)**
Days from admission to index culture	3.0 (1–11)
Days from index culture to starting cefiderocol	5.0 (3–8)
Days in hospital	36.5 (22–64)
Days on cefiderocol	22.5 (14–39)
>21 days on cefiderocol, n (%)	22 (52.4%)
Adverse drug reactions, n (%)*	1 (2.4)
Serious adverse drug reactions, n(%)^	1 (2.4)

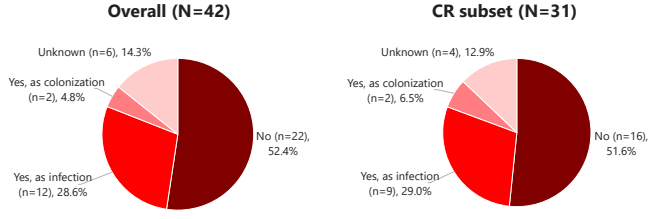
*Urticarial rash; ^Interstitial nephritis.

CONCLUSIONS

In this large cohort of patients, clinical outcomes suggest that cefiderocol is an effective treatment for bone and joint infections in patients with limited treatment options.

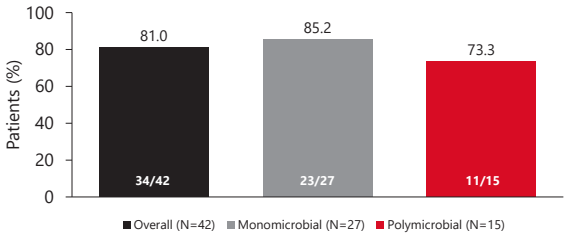
RESULTS CONT'D

Patients had the same pathogen as index culture pathogen prior to the current hospitalisation

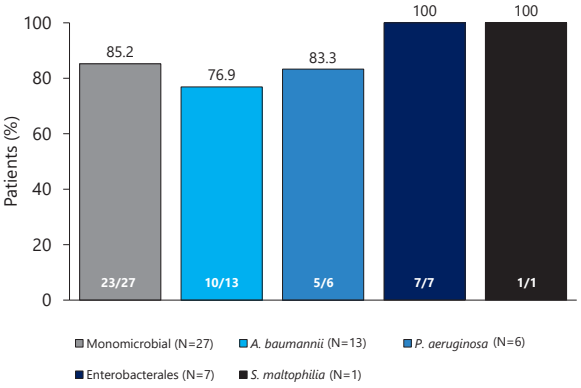


CR, carbapenem resistant.; carbapenem susceptible: 1; missing susceptibility: 10.

Clinical cure overall and by infection type



Clinical cure by primary pathogen in monomicrobial infections



Clinical cure is defined as improvement or resolution of signs/symptoms without evidence of relapse or death at end of hospitalization.

Index culture pathogen	N or N' (%)	30-day ACM n (%)
Overall	**42 (100)**	**4 (9.5)**
Monomicrobial	**27 (64.3)**	**1 (3.7)**
A. baumannii	13 (31.0)	1 (7.7)
P. aeruginosa	6 (14.3)	0
Enterobacterales	7 (16.7)	0
S. maltophilia	1 (2.4)	0
Polymicrobial*	**15 (35.7)**	**3 (20.0)**
A. baumannii/*P. aeruginosa*	2 (4.8)	1 (50.0)
A. baumannii/Enterobacterales	2 (4.8)	1 (50.0)
P. aeruginosa/Enterobacterales	2 (4.8)	0
Another other 2 pathogens*	5 (11.9)	1 (20.0)
Another other ≥3 pathogens*	4 (9.5)	0

N, total number of patients; N', number of patients in the category; *only Gram-negative species.
Owing to differential consent requirements between alive and deceased patients in certain sites, mortality may be overestimated in this dataset.

Acknowledgements
The study was funded by Shionogi. SV, SM, ASH are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK, and this support was funded by Shionogi.
Shionogi thanks all investigators and their institutions for their participation in the PROVE study.

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Poster 3228

34th ECCMID 2024
Barcelona, Spain
27–30 April, 2024

Real-world experience of cefiderocol in France from the PROVE (retrospective cefiderocol chart review) study

Alexandre Bleibtreu,[1] Romaric Larcher,[2] Jean-Francois Timsit,[3] Marc Olivier Vareil,[4] Lelia Escaut,[5] Francois Parquin,[6] Sarah Soueges,[7] Karim Jaffal,[8] Stephen Marcella,[9] Stefano Verardi,[10] Anne Santerre Henriksen[10]

[1]Pitie Salpetriere Hospital, APHP, Paris, France; [2]CHU Nimes, Nimes, France; [3]Bichat Hospital, APHP, Paris, France; [4]CH Cote Basque, Bayonne, France; [5]Bicetre Hospital, APHP, Kremlin Bicetre, France; [6]Foch Hospital, Suresnes, France; [7]Hospices Civils de Lyon, Lyon, France; [8]Hospital Raymond Poincare, APHP, Garches, France; [9]Shionogi Inc., Florham Park, NJ, USA; [10]Shionogi B.V., London, UK

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OBJECTIVES

We aimed to describe usage of cefiderocol, post commercialisation, for the treatment of patients with Gram-negative bacterial infections from 10 French centres, who were included in the ongoing PROVE study.

METHODS

Design: ongoing, international, retrospective, medical chart review study.

Inclusion criteria: adult hospitalised patients treated with cefiderocol consecutively for ≥72 hours (November 2020–June 2023).

Endpoints: patient and pathogen characteristics, hospitalisation course, antibiotic treatment patterns, clinical cure, and 14-day 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.

RESULTS

Patient characteristics (N=129)*		Main comorbidities	
Age, median (Q1–Q3), years	57 (45–69)	Diabetes (uncomplicated)	28 (21.7%)
Sex, male	95 (73.6%)	Chronic pulmonary disease	24 (18.6%)
CCI score, median (Q1–Q3)	1 (0–3)	Peripheral vascular disease	15 (11.6%)
		Congestive heart failure	14 (10.9%)

58.9% (n=76)	38.0% (n=49)	31.8% (n=41)	20.9% (n=27)
ICU stay	Organ support^	Mechanical ventilation	Vasopressor use

Hospitalisation course	
➢ Hospital stay, median (Q1–Q3), days	60.0 (33–100)
➢ Infection-associated ICU stay, median (Q1–Q3), days	48.5 (23–87)

Cefiderocol use	
➢ Cefiderocol treatment, median (Q1–Q3), days	13 (8–16)
➢ Time from index culture to cefiderocol start, median (Q1–Q3), days	4.0 (3–6)

CCI, Charlson Comorbidity Index; COVID-19; coronavirus disease 2019; ICU, intensive care unit; Q, quartile.
*One patient, who received cefiderocol in compassionate use/early access programme, was a protocol violation; data will be excluded from further analyses.
^Organ support was present at the time when cefiderocol was initiated or within two days of cefiderocol initiation.

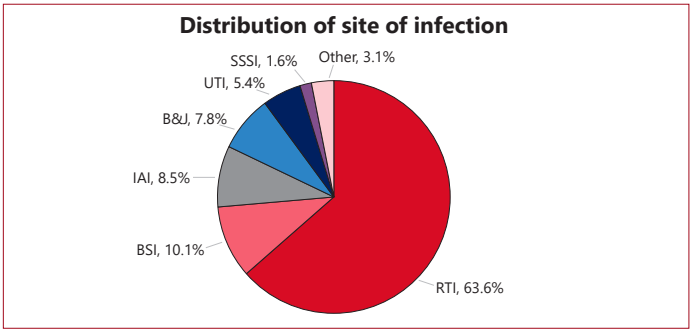
Index culture pathogen	n (%)	14-day ACM n (%)	30-day ACM n (%)
Monomicrobial Gram-negative infection	94 (72.9)	14 (14.9)	18 (19.1)
P. aeruginosa	59 (45.7)	6 (10.2)	8 (13.6)
Enterobacterales	13 (10.1)	1 (7.7)	2 (15.4)
A. baumannii	13 (10.1)	3 (23.1)	3 (23.1)
S. maltophilia	6 (4.7)	3 (–§)	4 (–§)
Other*	3 (2.3)	1 (–§)	1 (–§)
Polymicrobial Gram-negative infection	35 (27.1)	3 (8.6)	7 (20.0)

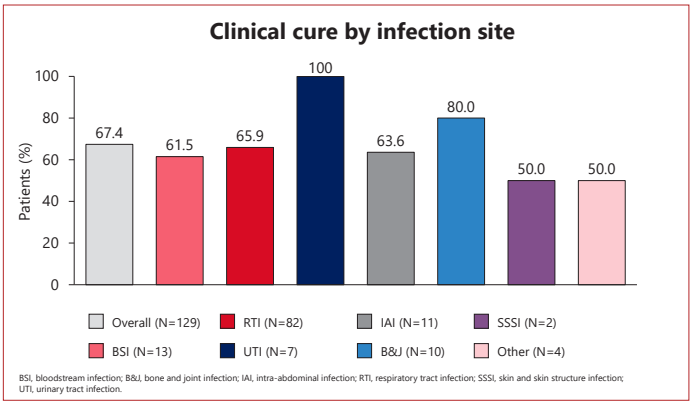
*_Burkholderia cepacia_ complex (2), _Achromobacter_ spp. (1).
§% is not calculated with patient numbers <10.

CONCLUSIONS

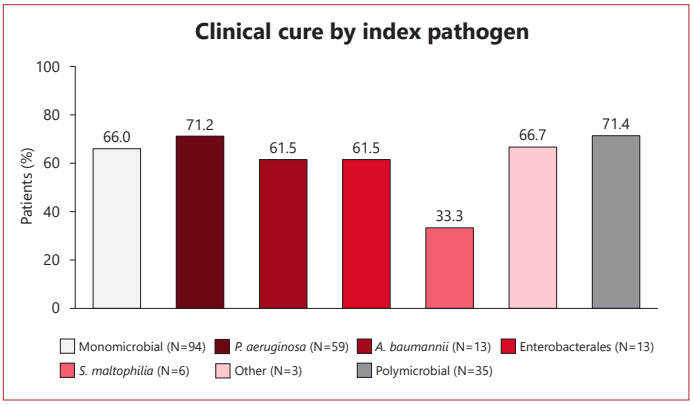
- This large cohort of real-world evidence post commercialisation of cefiderocol in France showed that cefiderocol was used primarily to treat respiratory infections and non-fermenter pathogens, including mainly *Pseudomonas* spp.
- A large proportion of patients responded to cefiderocol treatment and mortality rates overall were approximately 15% and 20% at days 14 and 30.

RESULTS CONT'D





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



Primary infection site*	14-day ACM n (%)	30-day ACM n (%)
Overall (N=129)	17 (13.2)	25 (19.4)
BSI (N=13)†	2 (15.4)	3 (23.1)
RTI (N=82)	13 (15.9)	18 (22.0)
UTI (N=7)	0 (0)	0 (0)
IAI (N=11)	2 (18.2)	4 (36.4)
B&J (N=10)	0 (0)	0 (0)
SSSI (N=2)	0 (0)	0 (0)
Other (N=4)†	0 (0)	0 (0)

*Driving the use of cefiderocol (includes monomicrobial and polymicrobial infections).
†There were no BSI or 'Other' polymicrobial infections.
BSI, bloodstream infection; B&J, bone and joint infection; IAI, intra-abdominal infection; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.
Owing to differential consent requirements between alive and deceased patients, mortality may be overestimated in this dataset by as much as 2.3%.

Acknowledgements

Shionogi thanks to all investigators and their institutions for participation in the PROVE study.
SV, SM, ASH are employees of Shionogi.
Editorial support was provided by Highfield, Oxford, UK; this support was funded by Shionogi & Co., Ltd., Osaka, Japan.

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Highlights

- Gli outcome clinici dello studio internazionale retrospettivo PROVE suggeriscono che cefiderocol è un trattamento antibiotico promettente nei pazienti adulti con infezioni ossee e articolari causate da germi resistenti alle molecole considerate di prima linea per queste infezioni.
- Complessivamente, al termine del trattamento, l'81,4% dei pazienti ha raggiunto la guarigione clinica.
- Allo stesso modo, i dati *real world* di un'ampia coorte di pazienti in Francia rivelano che il trattamento delle infezioni respiratorie (principalmente da *Pseudomonas* spp.) con cefiderocol è efficace, con bassi tassi di mortalità a 14 e 30 giorni (15% e 20%, rispettivamente).

Abstract 7

Activity of cefiderocol against carbapenem non-susceptible *Pseudomonas aeruginosa*, including molecularly characterised clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2022)

R. Mendes[1], J. Maher[1], J. Kimbrough[1], C. Hubler[1], D. Beekman[1], H. Sader[1], M. Castanheira[1]

[1]JMI Laboratories - North Liberty (United States)

Background

Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant organisms. Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and by the US FDA for complicated urinary tract infection, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia. The activity of cefiderocol and comparator agents was investigated against *Pseudomonas aeruginosa* collected from hospitals in European countries and adjacent regions during 2020–2022.

Methods

A total of 3,926 P. *aeruginosa* isolates were consecutively collected from 40 hospitals in 16 European countries, Israel and Turkey. Susceptibility testing was performed using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparators and iron-depleted CAMHB for cefiderocol. EUCAST and CLSI breakpoints were applied. Isolates with imipenem and/or meropenem MIC³4 mg/L (non-susceptible based on CLSI criteria) were subjected to screening of b-lactamase genes.

Results

A total of 25.4% (996/3,926) P. aeruginosa isolates were non-S to carbapenems, and 11.6% (116/996) carried carbapenemases. The latter was mostly represented by class B (81.9%) alleles compared to class A (17.2%), and blaVIM (88.4%) prevailed among class Balleles. Cefiderocol and b-lactam/b-lactamase inhibitor (BL/BLI) agents had susceptibilities of >90% against all P. aeruginosa (Table). Cefiderocol had MIC50 and MIC90 of 0.12 mg/L and 0.5 mg/L, respectively, and susceptibilities of 98.2–99.2% against carbapenem-non-susceptible isolates and the carbapenemase-negative subset, whereas BL-BLI had susceptibilities of 62.9–84.2%. In addition, cefiderocol remained active against isolates carrying carbapenemases (95.8–100% susceptible). Other comparator agents showed susceptibilities of <20% against those isolates, except for ceftazidime-avibactam against isolates carrying class A carbapenemases (90.0% susceptible).

Conclusions

Cefiderocol had consistent in vitro activity against P. aeruginosa isolates causing infections in hospitals located in European countries and adjacent regions. Cefiderocol remained active against carbapenemase-producing subsets, where newer BL/BLI agents showed limited activity. These in vitro data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens.

Abstract 8

Activity of Cefiderecol and Comparator Agents Against Difficult-to-Treat Resistant (DTR) *Pseudomonas aeruginosa* Collected During 2020-2022 as Part of the SENTRY Antimicrobal Surveillance Program

Boudewijn Dejonge[1], Sean Nguyen[2], Jason Bryowsky[2], Christopher Longshaw[3], Joshua Maher[4], Rodrigo Mendes[4], Miiki Takemura[5], Yoshinori Yamano[5]

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Background

Difficult-to-Treat Resistant (DTR) P. aeruginosa are non-susceptible to generic β-lactams and fluoroquinolones, for which alternative treatments are needed. Cefiderocol is a siderophore conjugated cephalosporin that shows a unique mode of entry into Gram-negative bacteria, resulting in potent in vitro activity. Here, susceptibility of cefiderocol and comparator agents was determined against DTR isolates of *P. aeruginosa*, collected in 2020–2022 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.

Methods

Minimum inhibitory concentrations were determined according to CLSI guidelines against 7,310 *P. aeruginosa*, collected in 2020–2022 in Europe (*n*=3,926) and the USA (*n*=3,384), using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol. Susceptibility was assessed according to CLSI, FDA, and EUCAST breakpoints. DTR was defined as being non susceptible according to CLSI breakpoints to aztreonam, ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin.

Results

4.1% (*n*=299) of *P. aeruginosa* showed the DTR phenotype, of which 97.7%, 98.3%, and 89.6% were susceptible to cefiderocol, according to EUCAST, CLSI, and FDA, breakpoints, respectively (Table 1). Colistin was also active (99.7% susceptibility, EUCAST breakpoints) but other agents, including new β-lactam/β-lactamase inhibitor combinations, showed limited activity (<63% susceptibility; Table 1). The percentage of DTR isolates amongst *P. aeruginosa* was similar in Europe (4.2%; *n*=163) and the USA (4.0%; *n*=136), but metallo-β- lactamases were more frequently encountered amongst DTR isolates from Europe (29.4%; *n*=48; VIM (*n*=41), IMP (*n*=6), NDM (*n*=1)) than the USA (2.9%; *n*=4; VIM (*n*=1), IMP (*n*=1), NDM (*n*=2)), which can account for the reduced activity observed for novel β-lactam/β-lactamase inhibitor combinations against DTR isolates collected in Europe (**Table 1**). Cefiderocol on the other hand, showed equal good activity against DTR *P. aeruginosa* isolates collected in Europe and the USA (**Table 1**).

Conclusions

Recent clinical DTR *P. aeruginosa* isolates remain highly susceptible to cefiderocol, whilst novel β-lactam/β-lactamase inhibitor combinations exhibited reduced activity against this phenotype. Cefiderocol should be considered as a treatment option for infections caused by DTR *P. aeruginosa*.

Table 1. Susceptibility of cefiderocol and comparator agents against DTR P. Aeruginosa; i.e., isolates non-susceptible to aztreonam, ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin according to CLSI breakpoints

Region (n)	EUCAST[a]			CLSI[a]			FDA[a]		
Antimicrobial agent	**%S**	**%I**	**%R**	**%S**	**%I**	**%R**	**%S**	**%I**	**%R**
Europe and USA (n=299)									
Cefiderocol	97.7		2.3	98.3	1.0	0.7	89.6	8.0	2.3
IMI-REL	54.8		45.2	54.8	16.4	28.8	54.8	16.4	28.8
MER-VAB	25.8		74.2						
CAZ-AVI	54.5		45.5	54.5		45.5	54.5		45.5
CEF-TAZ	53.5		46.5	53.5	13.4	33.1	53.5	13.4	33.1
PIP-TAZ		3.7	96.3[b]	3.7	11.7	84.6	3.7	11.7	84.6
Amikacin	62.9[c]		37.1	[d]	72.6	27.4	62.9[d]	9.7	27.4
Colistin	99.7[e]		0.3		99.7	0.3			
Europe (n=163)									
Cefiderocol	96.9		3.1	98.2	0.6	1.2	89.6	7.4	3.1
IMI-REL	48.5		51.5	48.5	11.0	40.5	48.5	11.0	40.5
MER-VAB	22.7		77.3						
CAZ-AVI	46.8		53.4	46.6		53.4	46.6		53.4
CEF-TAZ	39.9		60.1	39.9	13.5	69.3	39.9	13.5	46.6
PIP-TAZ		1.8	98.2[b]	1.8	14.7	83.4	1.8	14.7	83.4
Amikacin	50.3[c]		49.7	[d]	62.6	37.4	50.3[d]	12.3	37.4
Colistin	100[e]		0.0		100	0.0			
USA (n=136)									
Cefiderocol	98.5		1.5	98.5	1.5	0.0	89.7	8.8	1.5
IMI-REL	62.5		37.5	62.5	22.8	14.7	62.5	22.8	14.7
MER-VAB	29.4		70.6						
CAZ-AVI	64.0		36.0	64.0		36.0	64.0		36.0
CEF-TAZ	69.9		30.1	69.9	13.2	16.9	5.9	8.1	86.0
PIP-TAZ		5.9	94.1[b]	5.9	8.1	86.0	5.9	8.1	86.0
Amikacin	77.9[c]		22.1	[d]	84.6	15.4	77.9d	6.6	86.0
Colistin	99.3[e]		0.7		99.3	0.7			

n, number of isolates; S, susceptible; I, intermiedate; R, resistant; IMI-REL, imipenem-relebactam; MER-VAB, meropenem-vaborbactam; CAZ-AVI, ceftazidime-avibactam; CEF-TAZ, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobcatam; [a]Criteria as published by EUCAST (2023), CLSI (2023), and US FDA (2023); [b]An arbitrary suceptible breakpoint of ≤ 0.001 mg/L has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible-increased exposure; [c]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy. [D]Using UTI only breakpoints. [e]Colistin should not be used in monotherapy, unless used in infections where high exposure can be achieved at the site of infection (Infections emanating from the urinary tract). For systemic infections, colistin must be used in combination with other active therapy.

Poster 1360

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Activity of Cefiderocol and Comparator Agents Against Difficult-to-Treat Resistant *Pseudomonas aeruginosa* Collected During 2020–2022 as Part of the SENTRY Antimicrobial Surveillance Program

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BACKGROUND

- Difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa* shows treatment-limiting resistance to all first-line agents (i.e. β-lactams and fluoroquinolones).
- Cefiderocol is a siderophore-conjugated cephalosporin with a unique mode of entry and excellent activity against resistant *P. aeruginosa*.

OBJECTIVE

We aimed to determine the activity of cefiderocol and comparator agents against DTR *P. aeruginosa.*

METHODS

- Minimum inhibitory concentrations were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines against 7,310 *P. aeruginosa* isolates, collected in 2020–2022 in Europe (n=3,926) and the USA (n=3,384) as part of the SENTRY program, using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Susceptibility was assessed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST), CLSI, and US Food and Drug Administration (FDA) breakpoints.
- DTR *P. aeruginosa* was defined as being non-susceptible, according to CLSI breakpoints, to the β-lactams aztreonam, ceftazidime, cefepime, meropenem, imipenem, and the fluoroquinolones ciprofloxacin and levofloxacin.

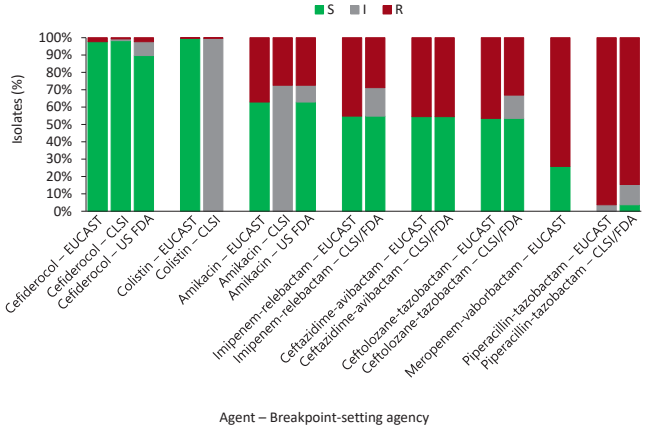
RESULTS

- 4.1% (n=299) of *P. aeruginosa* isolates showed the DTR phenotype, with similar percentages for isolates from Europe (4.2%; n=163) and the USA (4.0%; n=136).
- Cefiderocol and colistin were the most active agents against DTR *P. aeruginosa*, while other agents, including novel β-lactam–β-lactamase inhibitor (BL–BLI) combinations, showed much lower activity (Figure 1).
- Metallo-β-lactamases were more frequently encountered among DTR *P. aeruginosa* isolates from Europe than from the USA (Figure 2). This may explain, in part, why DTR *P. aeruginosa* isolates from Europe were more resistant to novel BL–BLI combinations compared with isolates from the USA (Figure 3). In contrast, cefiderocol maintained activity against isolates from both continents.

CONCLUSIONS

- Contemporary DTR *P. aeruginosa* isolates remained highly susceptible to cefiderocol, while novel BL–BLI combinations exhibited reduced activity against this phenotype.
- Cefiderocol should be considered as an early treatment option for infections known or suspected to be caused by DTR *P. aeruginosa*.

Figure 1: Susceptibility of cefiderocol and comparator agents against difficult-to-treat resistant *P. aeruginosa* (n=299)

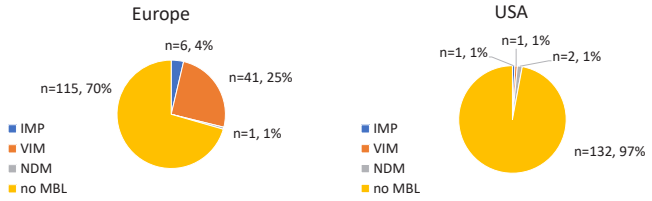


Agent – Breakpoint-setting agency

- Cefiderocol and colistin showed >90% susceptibility, while much lower percentages were obtained for other agents, including novel BL–BLI combinations.

S, susceptible; I, intermediate; R, resistant; criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); for amikacin, only urinary tract infection breakpoints were used.
For systemic infections, aminoglycosides must be used in combination with other active therapy.

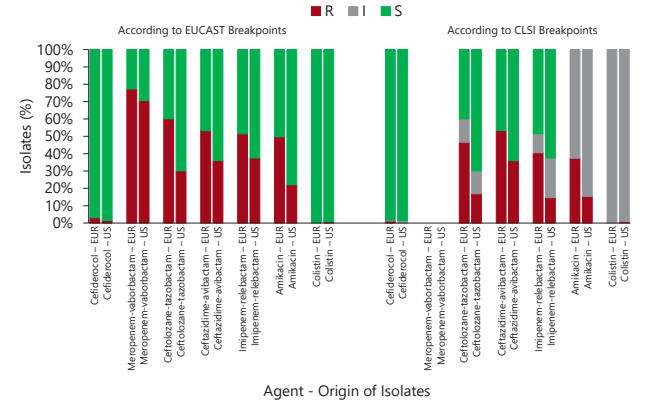
Figure 2: Prevalence of metallo-β-lactamases in difficult-to-treat resistant *P. aeruginosa* from Europe (n=163) and the USA (n=136)



- Metallo-β-lactamases were more frequently encountered in isolates from Europe (29.4%) than in those from the USA (2.9%).

IMP, imipenemase metallo-β-lactamase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

Figure 3: Susceptibility of cefiderocol and comparator agents against difficult-to-treat resistant *P. aeruginosa* from Europe (n=163) and USA (n=136) using EUCAST (left) or CLSI (right) breakpoints



Agent - Origin of Isolates

- Isolates from Europe were significantly more resistant to all agents compared with isolates from the USA, regardless of which breakpoints were used.
- Resistance for cefiderocol was low for isolates from both continents.

S, susceptible; I, intermediate; R, resistant; criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); for amikacin, only urinary tract infection breakpoints were used.
For systemic infections, aminoglycosides must be used in combination with other active therapy.

Acknowledgments

The study was funded by Shionogi. BD, STN, JJB, CL, MT, YY are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK; this support was funded by Shionogi & Co., Ltd., Osaka, Japan.

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Abstract 9

Multivariable evaluation of in-vitro performance of ceftolozane-tazobactam, ceftazidime/avibactam, imipenem/relebactam and cefiderocol on difficult-to-treat *Pseudomonas aeruginosa* isolated from clinical samples

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Background
Pseudomonas aeruginosa is a challenging organism classified by the CDC as a Serious Threat and by the WHO as a Critical Priority. Therapeutic challenges of *P. aeruginosa* are based on its multiple intrinsic resistance mechanisms and capability for acquiring others, including beta-lactamases such as blcKPC and blcVIM. The IDSA 2023 Guidance on the Treatment of AMN GN Infections, classifies *P. aeruginosa* as Difficult-toTreat (DTR), based on non-susceptible to all the following antimicrobials: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropoenem, imipenem, ciprofloxacin, and levofloxacin. In this abstract we evaluated the potency of ceftolozone/tazobactam (C/T), ceftazidime/avibactam (C/A), imipenem/relebcatam (I/R) and cefiderocol (CFD) against non-carbapemase producing *P. aeruginosa* DTR.

Methods
Susceptibility MIC dara for *P. aeruginosa* DTR isolates from multiple clinical samples across AdventHealth Orlando from January to August 2023, was mined from our laboratory system. The criteria included all non-carbapemase producing *P. aeruginosa* DTR from any clinical source with broth microdilution for C/T (bioMérieux Vitek® GN801), C/A, I/R (Thermo Fisher Sensititre®) and CFD (Liofilchem ComASP®). Multivariable analysis was used applying 2023 CLSI breakpoints.

Results
A total of 155 DTR ere initially teste for C/T with 80% (n=124) susceptible. Withinthe 31 isolates resistant to C/T, 30 (97%) isolates were susceptible to CFD, 8 (26%) susceptible to I/R and 5 (16%) susceptible to C/A. 4 isolates resistant to C/T and C/A were susceptible to I/R, and 1 isolate resistant to C/T and I/R was susceptible to C/A. 21 out of 22 isolates resistant to C/T, C/A and I/R were susceptible to CFD. The only isolate resistant to CFD was also resistant to other agents.

Conclusion
C/T is our main anti-*P. aeruginosa* DTR agent with 80% susceptibility. It is routinely tested on all DTR isolates. ON C/T resistant isolates, additional reflex testing is performed following our internal lab protocol, including C/A, I/R and CFD. This study demonstrated that C/T is our most potent 1st line agent against *P. aeruginosa* DTR and CFD demonstrated the best potency against C/T resistant strains with 97% susceptibility. CFD potency is preserved even on C/T, C/A, and I/R resistant strains

Highlights

- L'attività di cefiderocol è stata testata su 3926 isolati di *P. aeruginosa* provenienti da 16 Paesi europei, Israele e Turchia, e confrontata con le altre molecole considerate di elezione per il trattamento dei ceppi multiresistenti (imipenem/relebactam, meropenem/vaborbactam, meropenem, veftazidime/avibactam, ceftolozane/tazobactam).
- Cefiderocol e gli inibitori β-lattamici/β-lattamasi (BL/BLI) hanno dimostrato una suscettibilità >90% contro tutti gli isolati di *P. aeruginosa*; tuttavia, **cefiderocol ha evidenziato un'attività maggiore nei confronti degli isolati produttori di carbapenemasi, mentre i nuovi agenti BL/BLI hanno mostrato un'attività significativamente più ridotta verso questi ceppi**.
- Nell'ambito del programma di sorveglianza antimicrobica SENTRY, è stata testata la sensibilità di cefiderocol e dei nuovi BL/BLI nei confronti di isolati "difficult-to-treat" (DTR) di *P. aeruginosa*, provenienti da Europa e Stati Uniti.
- Il 97,7%, il 98,3% e l'89,6% dei ceppi di *P. aeruginosa* DTR sono risultati sensibili a cefiderocol secondo i breakpoint EUCAST, CLSI ed FDA, rispettivamente.

Abstract 10

Activity of cefiderocol against carbapenem-resistant *Actinobacter baummannii-calcoaceicus* complex, including molecularly characterised clinical isolates, causing infections in hospitals in European and adjacent regions (2020-2022)

R. Mendes[1], J. Kimbrough[1], D. Beekman[1], C. Hubler[1], J. Maher[1], H. Sader[1], M. Castahneira[1]

[1]JMI Laboratories – North Liberty (United States)

Background

Cefiderocol is a siderophore-conjugated cephalosporine with broad activity against Gram-negative bacteria, including multidrug-resistant organisms. Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and by the US FDA for compicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia. The activity of cefiderocol and comparators was investigated against *A. baumannii-calcoaceticus* complex (ACB) collected from hospitals in European countries and adjacent regions during 2020-2022.

Methods

1,504 ACB isolates were consecutively collected from 39 hospitals in 16 European countries, Israel and Turkey. Susceptibility testing was performed using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparators and iron-depleted CAMHB for cefiderocol. EUCAST and CLSI breakpoints were applied. Isolates with imipenem and/or meropenem MIC ³4 mg/L (non-susceptible based on CLSI criteria) were subjected to screening of b-lactamase genes.

Results

A total of 66.2% (995/1,504) ACB isolates were non-susceptible to carbapenems, and among those virtually all (992/996) carried carbapenemases. Cefiderocol (99.4-97.6% susceptible) had MIC50 of o.25 mg/L and MIC90 of 1 mg/L against all isolates and the carbapenem non-susceptible subset, whereas comparators had susceptibilities of <85.5% (**Table**). Cefiderocol 95.5-96.6% susceptible) had MIC50 of 0.12 mg/L and MIC90 of 1 mg/L against ACB carrying carbapenemases. Comparator agents had limited activity against these isolates (<79% susceptible). Cefiderocol also retained activity against isolates showing different resistanze genotypes (MIC90, 0.5-2 mg/L; 95.5-100.0% susceptible), except against those ACB carrying blaOXA-23 and blaOXA-72 or blaNDM-1 (MIC90, 8-16 mg/L) with susceptibilities of 38.5-81.0%).

Conclusions

Cefiderocol demonstrated in vitro activity against ACB causing infections in hospitals located in European countries and adjacent regions. This study demonstrated cefiderocol as the most active agent against carbapenem-non-susceptible ACB, with activity across many different resistance genotypes where other agents had limited activity. These in vitro data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens.

Abstract 11

Activity of Cefiderocol and Comparator Agents Against Difficult-to-Treat Resistant (DTR) *Acinetobacter baumannii calcoaceticus* Species Complex Isolates Collected During 2020-2022 Part of the SENTRY Antimicrobial Surveillance Program

Boudewijn Dejonge[1], Sean Nguyen[1], Jason Bryowsky[1], Christopher Longshaw[2], Joshua Maher[3], Rodrigo Mendes[3], Miki Takemura[4], Yoshinori Yamano[4]

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Background

Difficult-to-Treat Resistant (DTR) *Acinetobacter baumannii calcoaceticus* species complex show treatment-limiting resistance to b-lactams and fluoroquinolones, for wich alternative treatment options are needed. Cefiderocol is a siderophore-conjugate cephalosporin with good activity against Gram-negative bacteria, that uses the bacterium's iron-uptake systems to reach its targets, the penicillin-binding proteins. Susceptibility of cefiderocol and comparator agents was determined against DTR isolates of *Acinetobacter baumannii calcoaceticus* species complex, collected in 2020-2022 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.

Methods

Minimum inhibitory concentrations were determined according to CLSI guidelines using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for 2,485 *Acinetobacter baumannii calcoaceticus* species complex collected in 2020-2022 in Europe (n=1,504) and the USA (n=981). Susceptibility was assessed according to CLSI, EUCAST and FDA breakpoints. DTR was defined as being non-susceptible to ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin, using CLSI breakpoints.

Results

The percentage of DTR isolates was 47.0% (n=1169) and was higher in Europe (63.2%; n=951) compared to the USA (22.2%; n=218). Metallo-b-lactamases did not contribute to this, as those were not frequently encountered in either Europe (1.3%; n=12, all NDM) or the USA (0.9%; n=2, both NDM). 93.8%, 96.2%, and 89.1% of DTR *Acinetobacter baumannii calcoaceticus* species complex isolates were susceptible to cefiderocol according to EUCAST., CLSI and FDA breakpoints, respectively (**Table**). Colistin was the second most active agent with 81.2% of the isolates being susceptible (EUCAST breakpoints), but other agents, including b-lactam/b-lactamase inhibitor combinations, showed much less activity (<37% susceptibility; **Table**). DTR *Acinetobacter baumannii calcoaceticus* species complex isolates collected in Europe were in general less susceptible to comparator agents, compared to isolates collected in the USA, bu cefiderocol showed equal good activity against both sets of isolates (**Table**).

Conclusions

Recent clinical DTR *Acinetobacter baumannii calcoaceticus* species complex isolates remain highly susceptible to cefiderocol, but not against approved b-lactam/b-lactamase inhibitor combinations or other comparator agents. Cefiderocol should be considered as a treatment option for infections caused by DTR *Acinetobacter baumannii calcoaceticus* species complex.

Region (n)	**EUCAST**[a]			**CLSI**[a]			**FDA**[a]		
Antimicrobial agent	**%S**	**%I**	**%R**	**%S**	**%I**	**%R**	**%S**	**%I**	**%R**
Europe and USA (n=1,169)									
Cefiderocol	93.8		6.2	96.2	1.6	2.1	89.1	4.8	6.2
IMI-REL	0.1		99.9.				0.1	0.4	99.5
PIP-TAZ				0.1	0.7	99.2	0.1	0.7	99.2
Amikacin[b]	14.4[c]		85.6	18.0	6.9	75.1	18.0	6.9	75.1
Gentamicin	13.9[c]		86.1	13.9	6.3	79.7			
AMP-SUL				2.5	6.0	91.5	2.5	6.0	91.5
TMS	14.5	1.1	84.3	14.5		85.5			
Minocycline				36.4	20.3	43.4	36.4	20.3	43.4
Colistin	81.2[d]		18.8		81.2	18.8			
Europe (n=951)									
Cefiderocol	94.3		5.7	96.4	1.6	2.0	90.6	3.7	5.7
IMI-REL	0.1		99.9				0.1	0.1	99.8
PIP-TAZ				0.0	0.0	100.0	0.0	0.0	100.0
Amikacin	8.0[c]		92.0	11.4	7.6	81.1	11.4	7.6	81.1
Gentamicin	9.7[c]		90.3	9.7	5.7	84.6			
AMP-SUL				0.8	4.6	94.5	0.8	4.6	94.5
TMS	11.8	1.2	87.1	11.8		88.2			
Minocycline				32.2	21.2	46.6	32.2	21.2	46.6
Colistin	78.1[d]		21.9		78.1	21.9			
USA (n=218)									
Cefiderocol	91.7		8.3	95.4	1.8	2.8	82.1	9.67	8.3
IMI-REL	0.0		100				0.0	1.8	98.2
PIP-TAZ				0.5	3.7	95.9	0.5	3.7	95.9
Amikacin[f]	42.4[c]		57.6	47.0	4.1	48.8	47.0	4.1	48.8
Gentamicin	32.6[c]		67.4	32.6	9.2	58.3			
AMP-SUL				9.6	11.9	78.4	9.6	11.9	78.4
TMS	26.6	0.9	72.5.	26.7		73.3			
Minocycline				54.6	16.1	29.4	54.6	16.1	29.4
Colistin	95.0[d]		5.0		95.0	5.0			

n, number of isolates; S, susceptible; I, intermiedate; R, resistant; IMI-REL, imipenem-relebactam; PIP-TAZ, piperacillin-tazobcatam; AMP-SUL, ampicillin-sulbactam; TMS, trimethoprim-sulphamethoxazole. [a]Criteria as published by EUCAST (2023), CLSI (2023), and US FDA (2023). [b]Only 1,168 isolates were tested. [c]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapyr. [d]Colistin should not be used in monotherapy, unless used in infections where high exposure can be achieved at the site of infection (Infections emanating from the urinary tract). For systemic infections, colistin must be used in combination with other active therapy. [e]Only 950 isolates were tested. [f]Only 217 isolates were tested.

Poster 1361

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Activity of Cefiderocol and Comparator Agents Against Difficult-to-Treat Resistant *Acinetobacter baumannii-calcoaceticus* Complex Isolates Collected During 2020–2022 as Part of the SENTRY Antimicrobial Surveillance Program

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BACKGROUND

- Difficult-to-treat resistant (DTR) *Acinetobacter baumannii-calcoaceticus* complex shows treatment-limiting resistance to β-lactams and fluoroquinolones, and alternative treatment options are needed.
- Cefiderocol is a siderophore-conjugated cephalosporin that uses iron-uptake systems to enter the bacterium's periplasmic space.

OBJECTIVE

We aimed to determine susceptibility of cefiderocol and comparator agents against DTR *A. baumannii-calcoaceticus* complex isolates, collected in 2020–2022 in Europe and the USA as part of the SENTRY Antimicrobial Surveillance Program.

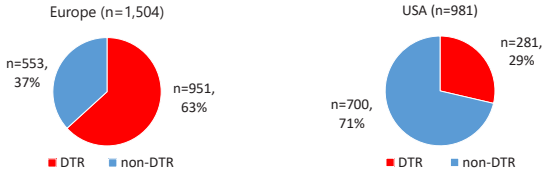
METHODS

- Minimum inhibitory concentrations 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 against 2,485 *A. baumannii-calcoaceticus* complex isolates collected in 2020–2022 in Europe (n=1,504) and the USA (n=981).
- Susceptibility was assessed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) pharmacokinetic/pharmacodynamic, CLSI, and US Food and Drug Administration (FDA) breakpoints.
- DTR was defined as being non-susceptible according to CLSI breakpoints to the β-lactams ceftazidime, cefepime, meropenem, imipenem, and fluoroquinolones ciprofloxacin and levofloxacin.

RESULTS

- The fraction of DTR isolates among *A. baumannii-calcoaceticus* complex was 47.0% (n=1,169) and was higher in Europe compared with the USA (Figure 1).
- Cefiderocol showed the highest susceptibility against DTR *A. baumannii-calcoaceticus* complex, with 93.8%, 96.2%, and 89.1% of the isolates susceptible according to EUCAST, CLSI, and FDA breakpoints, respectively (Figure 2).
- DTR *A. baumannii-calcoaceticus* complex isolates collected in Europe were generally less susceptible to comparator agents, compared with isolates collected in the USA, but cefiderocol showed equally good activity against both sets of isolates (Figure 3).

Figure 1: Prevalence of difficult-to-treat resistant *A. baumannii-calcoaceticus* complex in Europe (n=1,504) and the USA (n=981)



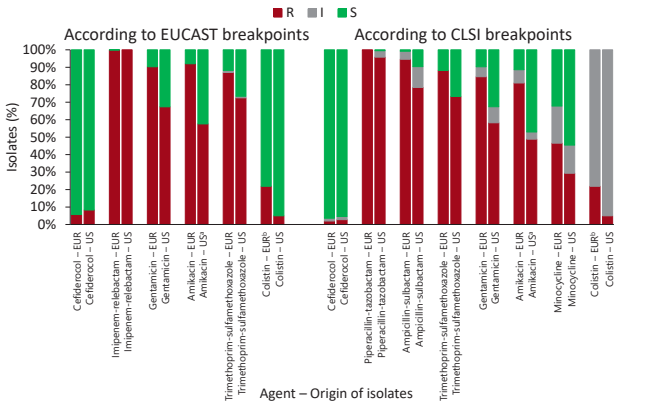
- DTR phenotype was more frequently encountered in Europe (63.2%) than in the USA (28.6%).

Figure 2: Susceptibility of cefiderocol and comparator agents against difficult-to-treat resistant *A. baumannii-calcoaceticus* complex (n=1,169)

- Cefiderocol showed >90% susceptibility, followed by colistin (~80%), while other agents showed much lower degrees of susceptibility (<37%).

S, susceptible; I, intermediate; R, resistant; criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); for amikacin, only urinary tract infection breakpoints were used.
[a]One isolate was not tested (n=1168).
For systemic infections, aminoglycosides must be used in combination with other active therapy.
Colistin should not be used in monotherapy, unless used in infections where high exposure can be achieved at the site of infection (infections emanating from the urinary tract).

Figure 3: Susceptibility of cefiderocol and comparator agents against difficult-to-treat resistant *A. baumannii-calcoaceticus* complex from Europe (n=951) and the USA (n=218) using EUCAST (left) or CLSI (right) breakpoints



- Isolates from Europe were significantly more resistant to all agents compared with isolates from the USA, regardless of which breakpoints were used.
- Resistance for cefiderocol was low for isolates from both continents.

S, susceptible; I, intermediate; R, resistant; criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); for amikacin, only urinary tract infection breakpoints were used.
[a]One isolate was not tested (n=217). [b]One isolate was not tested (n=950).
For systemic infections, aminoglycosides must be used in combination with other active therapy.
Colistin should not be used in monotherapy, unless used in infections where high exposure can be achieved at the site of infection (infections emanating from the urinary tract).

CONCLUSIONS

- DTR *A. baumannii-calcoaceticus* complex isolates from Europe were more resistant to comparator agents compared with isolates from the USA, but resistance to cefiderocol remained low for isolates from both continents.
- DTR *A. baumannii-calcoaceticus* complex isolates remained highly susceptible to cefiderocol, and cefiderocol should be considered as an early treatment option for known or suspected infections caused by these isolates.

Acknowledgments

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Highlights

- Nell'ambito del programma di sorveglianza antimicrobica SENTRY 2020-2022 è stata determinata la sensibilità di cefiderocol e degli agenti di confronto verso 1169 isolati di *A. baumannii-calcoaceticus* complex (ABC) difficili da trattare (DTR), raccolti n Europa (951) e negli Stati Uniti (218).
- **Cefiderocol è risultato l'agente con più alta percentuale di sensibilità contro gli ABC non sensibili ai carbapenemi, con un'attività che interessa diversi genotipi di resistenza.**
- **Cefiderocol deve essere considerato un'opzione di trattamento valida per le infezioni causate da *Acinetobacter baumannii-calcoaceticus* complex DTR.**

P1641

In vitro susceptibility test to cefiderocol of NDM-producing *K. pneumoniae* from bloodstream isolates: a comparison of commercial methods and the reference method.

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Introduction:

In vitro cefiderocol susceptibility testing is actually considered a challenge because of insufficient reproducibility and accuracy of the commercial methods (EUCAST warnings August 2022, September 2023). Moreover, cefiderocol often represents one of few therapeutic options to treat infections caused by MDR Gram-negative bacteria. In our study, we compared the reference method and commercial ones to determine cefiderocol susceptibility of bloodstream isolates of NDM-*Kp*.

Methods:

We considered 30 NDM-*Kp* isolates from consecutive bloodstream infections in distinct patients, from November 2022 to July 2023. Species identification were achieved by MALDI ToF MS (Bruker) and molecular carbapenemase typing by GeneXpert (Cepheid).
The broth microdilution (BMD) reference method was compared with UMIC (Bruker) and ComASP (Liofilchem). We also performed disc diffusion tests by cefiderocol 30 µg discs (Liofilchem) on Mueller-Hinton agar plates (Biolife). All methods were carried out starting from the same 0.5 Mc Farland *inoculum* for each bacterial isolate. Quality control strains *E. coli* ATCC 25922 and *K. pneumoniae* ATCC BAA-2146 (NDM1) were included. Cefiderocol MIC results were interpreted according to EUCAST (v.13.1).

Results:

Reference method results ranged between 1-32 µg/mL, whereas UMIC and ComASP MIC values ranged between 0,5-16 µg/mL. Disc diffusion inhibition's halo range was 6-24 mm. All methods were concordant to detect the 4 resistant isolates (strains 1, 8, 11, 29). The commercial BMD methods were fully concordant with the reference one also to identify the susceptible isolates (strains 2-7, 9, 10, 12-28, 30). Among the susceptible isolates, disc diffusion results were concordant with the BMD methods only for 4 strains (number 2, 3, 9, 25) as the remaining ones ranged in the "Area of Technical Uncertainty", ATU, interval (18-22 mm) (**Table 1** and **2**).

	BROTH MICRODILUTION METHODS			DISC DIFFUSION (mm)
	REFERENCE (µg/mL)	ComASP (µg/mL)	UMIC (µg/mL)	
1	8	4	8	6
2	1	1	0,5	24
3	1	1	0,5	23
4	2	2	1	21
5	1	0,5	0,25	21
6	1	0,5	0,5	21
7	1	0,5	1	20
8	32	8	8	9
9	1	0,5	0,5	24
10	1	0,5	1	21
11	8	16	16	6
12	2	0,5	1	21
13	1	0,5	0,5	21
14	1	1	1	20
15	1	0,5	0,5	21
16	1	1	1	21
17	1	0,5	0,5	21
18	1	1	1	22
19	2	2	1	22
20	1	1	1	21
21	1	0,5	1	20
22	1	0,5	0,5	21
23	1	1	1	22
24	1	1	1	22
25	2	1	1	23
26	1	1	2	20
27	1	1	2	21
28	1	0,5	1	21
29	16	8	16	6
30	2	1	1	20

S ATU R

Table 1. *In vitro* susceptibility testing values to cefiderocol of NDM-*Kp* by commercial methods and the reference one.

	SUSCEPTIBLE STRAINS	"ATU" STRAINS	RESISTANT STRAINS
REFERENCE BMD METHOD	26 (87%)	/	4 (13%)
UMIC BMD METHOD	26 (87%)	/	4 (13%)
ComASP BMD METHOD	26 (87%)	/	4 (13%)
DISC DIFFUSION METHOD	4 (13%)	22 (74%)	4 (13%)

Table 2.Interpretation of cefiderocol susceptibility for 30 NDM-Kp strains by reference and commercial methods.

Conclusions:

This study demonstrated a 100% of Essential Agreement (EA) between the reference method and the commercial BMD tests UMIC and ComASP to detect cefiderocol susceptibility for 30 NDM-*Kp* strains. In our experience, all the ATU phenotypes recorded by disc diffusion coincided with full susceptibility to cefiderocol according to the BMD methods, the reference and the commercial ones.

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34th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Barcelona, Spain
27 – 30 April 2024

Highlights

- Lo scopo dello studio è stato eseguire un confronto tra i metodi attualmente disponibili in commercio e il metodo di riferimento per testare la sensibilità *in vitro* a cefiderocol di 30 isolati di *K. pneumoniae* produttrice di NDM, provenienti da campioni di sangue di pazienti con batteriemia.
- I risultati hanno evidenziato una corrispondenza del 100% tra il test della microdiluizione in brodo (BMD) di riferimento e quelli commerciali UMIC® e ComASP®.
- **L'analisi ha evidenziato che tutti i fenotipi definibili nell'"area di incertezza tecnica" (ATU) registrati mediante il test di diffusione su disco (*disk diffusion*) dimostravano invece una piena sensibilità a cefiderocol usando i metodi di BMD.**

Poster 1367

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In vitro Activity of Cefiderocol in Bloodstream Infection Isolates from North American and European Hospitals: SENTRY 2020–2022

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BACKGROUND

Cefiderocol is approved in the United States[1] for the treatment of patients with complicated urinary tract infections and hospital-acquired/ventilator-associated bacterial pneumonia caused by susceptible Gram-negative pathogens and in Europe[2] for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Treatment of bloodstream infections (BSIs) in hospitalized patients can be challenging due to antibiotic resistance, which limits the therapeutic options.

OBJECTIVE

We aimed to evaluate the *in vitro* activity of cefiderocol and comparator agents against Gram-negative isolates causing BSI in hospitalized patients from North American and European hospitals from the SENTRY Antimicrobial Surveillance Program in 2020–2022.

METHODS

- A total of 9,655 Gram-negative BSI isolates were collected from 43 North American (N=3,985) and 39 European (N=5,670) medical centers as part of the SENTRY Antimicrobial Surveillance Program (from 2020 to 2022).
- Clinical isolates included 7,863 Enterobacterales, 1,051 *Pseudomonas aeruginosa*, 422 *Acinetobacter baumannii-calcoaceticus* complex (ABC) and 154 *Stenotrophomonas maltophilia*.
- Minimum inhibitory concentrations (MICs) were determined according to CLSI guidelines using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Susceptibility was assessed according to 2023 CLSI, FDA, and EUCAST breakpoints (Table 1):

Table 1. Susceptibility breakpoints by CLSI, FDA, and EUCAST

Organism	Breakpoint (µg/mL) by organization Susceptible/Intermediate/Resistant		
	CLSI	FDA	EUCAST
Enterobacterales	≤4/8/≥16	≤4/8/≥16	≤2/–/>2
Pseudomonas aeruginosa	≤4/8/≥16	≤1/2/≥4	≤2/–/>2
Acinetobacter spp.	≤4/8/≥16	≤1/2/≥4	≤2/–/>2[†]
Stenotrophomonas maltophilia	≤1/–/–	NA	≤2/–/>2[†]

[†]EUCAST non-species-specific pharmacokinetic/pharmacodynamic breakpoints used

- Carbapenem-nonsusceptible subsets were defined as non-susceptibility to meropenem and imipenem (excluded for *Proteus mirabilis, P. penneri*, and indole-positive Proteeae).

RESULTS

- Among BSI isolates, the most common Gram-negative organism was *Escherichia coli* (n = 3,983) followed by *Klebsiella pneumoniae* (n = 1,577) and *P. aeruginosa* (n = 1,051).
- 2.2% of Enterobacterales, 14.4% of *P. aeruginosa*, 60.4% of *A. baumannii-calcoaceticus* complex, and 100% of *S. maltophilia* tested as carbapenem non-susceptible (Table 2).
- All tested Enterobacterales isolates tested were highly susceptible to cefiderocol (>98%), while 94.3%, 94.3%, and 80.5% of carbapenem-nonsusceptible Enterobacterales isolates were susceptible to cefiderocol using the CLSI, FDA, and EUCAST breakpoints, respectively (Figure 1).
- Cefiderocol was the most active antimicrobial against all *P. aeruginosa* and carbapenem-nonsusceptible *P. aeruginosa* isolates, with $MIC_{50/90}$ values of 0.12/0.25 µg/mL and 0.12/0.5 µg/mL, respectively (Figure 2).
  - *P. aeruginosa* susceptibility to cefiderocol was 99.3%, 98.7%, and 97.4% per CLSI, EUCAST and FDA breakpoints, respectively, while only <76% were susceptible to beta-lactam/beta-lactamase inhibitor combinations for carbapenem-nonsusceptible *P. aeruginosa* isolates.
- Susceptibility of *Acinetobacter baumannii-calcoaceticus* complex isolates to cefiderocol was 97.2%, 95.5%, and 91.7% per CLSI, EUCAST, and FDA breakpoints, respectively (Figure 3).
  - Among carbapenem-nonsusceptible *Acinetobacter baumannii-calcoaceticus* complex BSI isolates, cefiderocol was the most active ($MIC_{50/90}$ 0.25/2 µg/mL) compared with comparator agents including ampicillin/sulbactam ($MIC_{50/90}$ 64/>64 µg/mL) and imipenem/relebactam ($MIC_{50/90}$ >8/>8 µg/mL).
- All *S. maltophilia* isolates were susceptible to cefiderocol per CLSI and EUCAST breakpoints and cefiderocol was the most potent agent with $MIC_{50/90}$ of 0.06/0.25 µg/mL (Figure 4).

Table 2. Activity of cefiderocol and selected comparator agents tested against 9,655 isolates of Enterobacterales, *P. aeruginosa, A. baumannii-calcoaceticus* species complex, and *S. maltophilia* isolates collected from 2020–2022 in US and European hospitals

Organism group / Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	%S[a] CLSI	%S[a] FDA	%S[a] EUCAST
Enterobacterales (n=7,863)						
Cefiderocol	0.06	0.5	≤0.004 to >64	99.8	99.8	98.8
Meropenem	0.03	0.06	≤0.015 to >32	97.6	97.6	97.8
Imipenem-relebactam	0.12	0.5	≤0.03 to >8	95.0	95.0	98.4
Meropenem-vaborbactam	0.03	0.06	≤0.015 to >8	99.1	99.1	99.2
Ceftazidime-avibactam	0.12	0.25	≤0.015 to >32	99.4	99.4	99.4
Ceftolozane-tazobactam	0.25	1	≤0.12 to >16	93.4	93.4	93.4
Carbapenem nonsusceptible - Enterobacterales (n=174)						
Cefiderocol	1	4	0.015 to >64	94.3	94.3	80.5
Imipenem-relebactam	0.5	>8	0.06 to >8	59.2	59.2	66.1
Meropenem-vaborbactam	2	>8	≤0.015 to >8	62.1	62.1	66.7
Ceftazidime-avibactam	2	>32	≤0.015 to >32	77.6	77.6	77.6
Ceftolozane-tazobactam	>16	>16	2 to >16	0.6	0.6	0.6
***Pseudomonas aeruginosa* (n=1,051)**						
Cefiderocol	0.12	0.25	≤0.004 to 16	99.9	99.1	99.8
Meropenem	0.5	8	≤0.015 to >32	84.0	84.0	84.0
Imipenem-relebactam	0.25	1	≤0.03 to >8	95.7	95.7	95.7
Meropenem-vaborbactam	0.5	8	≤0.015 to >8	N/A	N/A	92.2
Ceftazidime-avibactam	2	4	0.12 to >32	95.7	95.7	95.7
Ceftolozane-tazobactam	0.5	2	≤0.12 to >16	95.1	95.1	95.1
Carbapenem nonsusceptible - *Pseudomonas aeruginosa* (n=151)						
Cefiderocol	0.12	0.5	≤0.004 to 16	99.3	97.4	98.7
Imipenem-relebactam	2	>8	0.5 to >8	72.2	72.2	72.2
Meropenem-vaborbactam	>8	>8	2 to >8	N/A	N/A	47.0
Ceftazidime-avibactam	4	32	1 to >32	76.2	76.2	76.2
Ceftolozane-tazobactam	2	>16	0.5 to >16	71.5	71.5	71.5
***Acinetobacter baumannii-calcoaceticus* complex (n=422)**						
Cefiderocol	0.25	1	0.015 to >64	97.2	91.7	95.5
Meropenem	32	>32	0.03 to >32	39.6	39.6	39.6
Imipenem-relebactam	>8	>8	≤0.03 to >8	N/A	39.6	39.6
Ampicillin-sulbactam	32	>64	≤0.5 to >64	38.2	38.2	N/A
Colistin	0.5	2	≤0.06 to >8	N/A	N/A	91.7
Carbapenem nonsusceptible - *Acinetobacter baumannii-calcoaceticus* complex (n=255)						
Cefiderocol	0.25	2	0.03 to >64	96.1	88.6	93.7
Imipenem-relebactam	>8	>8	4 to >8	NA	0.0	0.0
Ampicillin-sulbactam	64	>64	8 to >64	2.7	2.7	N/A
Colistin	0.5	4	0.12 to >8	N/A	N/A	89.0
***Stenotrophomonas maltophilia* (n=154)**						
Cefiderocol	0.06	0.25	0.008 to 1	100	N/A	100
Levofloxacin	1	4	0.12 to 32	85.1	N/A	N/A
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >4	96.8	N/A	98.1

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50%/90% of organisms; n, number of isolates; N/A, not applicable; S, susceptible. [a]According to 2023 CLSI, FDA and EUCAST breakpoints

Figure 1. Cefiderocol MIC distributions against Enterobacterales in SENTRY 2020–2022*

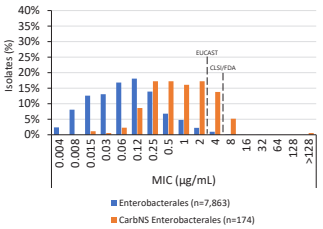


Figure 2. Cefiderocol MIC distributions against *P. aeruginosa* in SENTRY 2020–2022

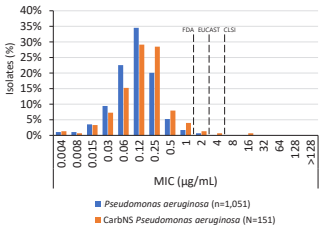


Figure 3. Cefiderocol MIC distributions against *A. baumannii-calcoaceticus* complex in SENTRY 2020–2022

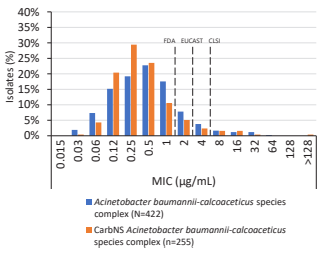
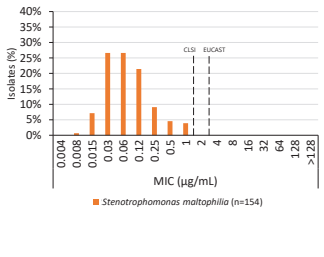


Figure 4. Cefiderocol MIC distributions against *S. maltophilia* in SENTRY 2020–2022



Criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023). MIC, minimum inhibitory concentration.

*Enterobacterales included: *Citrobacter amalonaticus / farmeri* (6), *C. braakii* (1), *C. freundii* (2), *C. freundii* species complex (134), *C. koseri* (96), *C. sedlakii* (1), *Enterobacter asburiae* (2), *E. cloacae* (234), *E. cloacae* species complex (310), *E. hormaechei* (5), *E. kobei* (1), *Escherichia coli* (3,983), *E. fergusonii* (1), *E. hermannii* (1), *E. marmotae* (1), *E. vulneris* (2), Gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (10), *Klebsiella aerogenes* (172), *K. oxytoca* (274), *K. pneumoniae* (1,577), *K. variicola* (82), *Kluyvera ascorbata* (2), *K. georgiana* (1), *Leclercia adecarboxylata* (2), *Morganella morganii* (84), *Pantoea agglomerans* (15), *P. ananatis* (2), *P. anthophila* (1), *P. dispersa* (1), *Phytobacter diazotrophicus* (1), *Plurallibacter gergoviae* (1), *Proteus hauseri* (2), *P. mirabilis* (392), *P. penneri* (5), *P. vulgaris* (25), *P. vulgaris* group (10), *Providencia rettgeri* (18), *P. stuartii* (25), *Raoultella ornithinolytica* (13), *R. planticola* (2), *Serratia liquefaciens* (5), *S. liquefaciens* complex (3), *S. marcescens* (331), *S. rubidaea* (1), unspeciated *Citrobacter* (2), unspeciated *Erwinia* (1), unspeciated *Klebsiella* (1), unspeciated *Pantoea* (5), unspeciated *Raoultella* (14), *Yersinia enterocolitica* (2).

CONCLUSIONS

- Contemporary Enterobacterales, *P. aeruginosa, A. baumannii-calcoaceticus* complex, and *S. maltophilia* causing BSIs, including carbapenem-nonsusceptible subsets for which treatment options are limited, were highly susceptible to cefiderocol.
- These data suggest that cefiderocol may be a valuable empiric and guided treatment option for BSI caused by Gram-negative pathogens in patients with risk factors for carbapenem resistance.

References

1. Fetroja (Cefiderocol). Prescribing Information. Shionogi Inc., Florham Park, NJ, USA. 2020.
2. Fetcroja (Cefiderocol). Summary of Product Characteristics. Shionogi BV, Amsterdam, The Netherlands. 2020.

Acknowledgments

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Highlights

- Nell'ambito del programma di sorveglianza antimicrobica SENTRY è stata analizzata l'attività *in vitro* di cefiderocol e di numerosi agenti antimicrobici considerati di prima linea in 9655 isolati di Enterobacterales, *P. aeruginosa*, *A. baumannii-calcoaceticus* complex e *S. maltophilia*, in Europa e Nord America.
- **Tutti gli isolati analizzati sono risultati altamente sensibili a cefiderocol, comprese le sottopopolazioni non sensibili ai carbapenemi per le quali le opzioni terapeutiche sono oggi limitate.**

Abstract 14

Activity of Cefiderocol and Comparator Agents Against Uncommon Gram-negative Isolates Collected During 2020-2022 as Part of SENTRY Antimicrobial Surveillance Program

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Background

The majority of hospital-acquired infections involving Gram-negative bacteria are caused by four groups: *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Acinetobacter baumannii* complex. Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria. In this study, the activity of cefiderocol and comparator agents were determined against less commonly represented genera collected in 2020-2022 in Europe and USA.

Methods

A total of 35,837 Gram-negative isolates were collected from clinical labs in Europe (n, 18,409) and North America (n, 17,428) between 2020-2022 as part of the SENTRY antimicrobial surveillance programme. Uncommon pathogens were defined as isolates from genera representing <5% of the total Gram-negative population. Minimum inhibitory concentrations (MIC) were determined according to CLSI guidelines against 6,461 isolates using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol. Comparator agents included b-lactam/b-lactamase inhibitor combinations ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, aztreonam-avibactam, piperacillin-tazobactam, as well as meropenem, imipenem, ceftazidime, colistin, levofloxacin, amikacin, trimethoprim-sulfamethoxazole, and minocycline. For Enterobacterales, susceptibility was interpreted by both EUCAST and CLSI breakpoints. For glucose non-fermenters, activity was interpreted against EUCAST non-species related PK-PD breakpoints.

Results

A total of 6,461 isolates were analysed of which 4,893 were Enterobacterales (20 genera) and 1,568 non-fermenters (4 genera). The most common Enterobacterales were *Proteus* spp. (32%), *Serratia* spp. (28%) and Citrobacter spp. (22%), with *Stenotrophomonas maltophilia* representing >75% of non-enterics. Enterobacterales remained susceptible to most antibiotics tested including cefiderocol (99.8% susceptible). The exception was colistin with only 27.7% susceptibility due to high number of *Proteus* spp., *Serratia* spp., *Morganella* spp., *Providencia* spp. and *Hafnia* spp. which are intrinsically resistant. Amongst non-fermenters, resistance was >50% for most antibiotic tested. Cefiderocol retained highest susceptibility (98.7%) while aztreonam-avibactam was active against *S. maltophilia* but had 16% resistance to *Burkholderia* spp. and no activity against *Achromobacter* spp. or *Chryseobacterium* spp.

Conclusions

Cefiderocol showed potent activity against a set of 6,461 contemporary uncommon Gram-negative clinical isolates. These in vitro data suggest cefiderocol could be an important treatment option for infections caused by these infrequently isolated pathogens.

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Activity of Cefiderocol and Comparator Agents Against Uncommon Gram-negative Isolates Collected During 2020–2022 as Part of the SENTRY Antimicrobial Surveillance Program

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SHIONOGI

BACKGROUND

The majority of hospital-acquired infections involving Gram-negative bacteria are caused by four pathogens: *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex. Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria.[1]

OBJECTIVE

In this study, the activity of cefiderocol and comparator agents was determined against less commonly represented genera collected during the period 2020–2022 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.

METHODS

- A total of 35,837 Gram-negative isolates were collected from clinical labs in Europe (n=18,409) and USA (n=17,428) during 2020–2022 as part of the SENTRY surveillance programme.
- Uncommon pathogens were defined as isolates from genera representing <5% of the total Gram-negative bacteria.
- Minimum inhibitory concentrations (MICs) were determined according to CLSI guidelines against 6,461 isolates using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Comparator agents included β-lactam/β-lactamase inhibitor combinations ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, aztreonam-avibactam, and piperacillin-tazobactam, as well as meropenem, imipenem, ceftazidime, colistin, levofloxacin, amikacin, trimethoprim-sulfamethoxazole, and minocycline.
- For Enterobacterales, susceptibility was interpreted by both EUCAST (i.e., ≤2 µg/mL) and CLSI (i.e., ≤4 µg/mL) breakpoints. For glucose non-fermenters, activity was interpreted against EUCAST non-species related PK/PD breakpoints (i.e., ≤2 µg/mL).

RESULTS

- A total of 6,461 isolates were analysed of which 4,893 were Enterobacterales (20 genera) and 1,568 were glucose-non-fermenters (4 genera).
- As shown in Figure 1 and Figure 2, the most common Enterobacterales were *Proteus* spp. (32%), *Serratia* spp. (28%) and *Citrobacter* spp. (22%), with *Stenotrophomonas maltophilia* representing >75% of non-enterics.
- Enterobacterales remained susceptible to most antibiotics tested (Table 1) including cefiderocol (99.8% susceptible).
  - The exception was colistin with only 27.7 % susceptibility due to high numbers of *Proteus* spp., *Serratia* spp., *Morganella* spp., *Providencia* spp. and *Hafnia* spp. which are intrinsically resistant.
  - Among glucose non-fermenters, resistance was >50% for most antibiotics tested. Cefiderocol retained highest susceptibility (98.7%), while aztreonam-avibactam was active against *S. maltophilia* but had 16% resistance in *Burkholderia* spp. and no activity against *Achromobacter* spp. or *Chryseobacterium* spp.

Figure 1: Relative frequency of uncommon (<5% total) Gram-negative pathogens collected during 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program A. Enterobacterales (N=4,893) and B. Glucose non-fermenters (N=1,568)

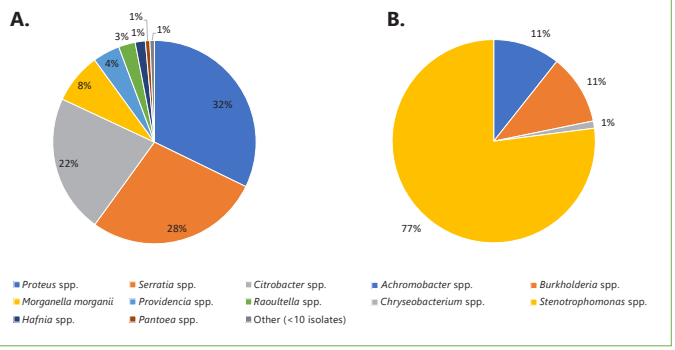

Table 1: Susceptibility of cefiderocol and comparator agents against uncommon (<5% total) Gram-negative pathogens collected during 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program

Organism group / Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	EUCAST %S	EUCAST %R	CLSI %S	CLSI %I	CLSI %R
Uncommon Enterobacterales (N=4,893)[a]								
Cefiderocol	0.06	0.25	0.04–8	99.8	0.2	99.9	0.1	0
Imipenem-relebactam	0.5	2	0.03–>8	95.2	4.8	75.5	19.7	4.8
Meropenem-vaborbactam	0.06	0.12	0.015–>8	99.9	0.1	99.9	0	0.1
Ceftazidime-avibactam	0.12	0.25	0.015–>32	99.7	0.3	99.7	0	0.3
Ceftolozane-tazobactam	0.5	1	0.12–>16	95	5	95	1	4
Aztreonam-avibactam[b]	≤0.03	0.12	0.03–8	99.8	0.02	99.9	0.1	0
Ceftazidime	0.12	2	0.015–>32	88.1	9.5	91.7	1	7.3
Piperacillin-tazobactam	1	8	0.06–>128	90.6	9.4	90.6	3.2	6.2
Meropenem	0.06	0.12	0.015–>32	99.5	0.5	99.4	0.1	0.5
Imipenem	1	2	0.12–>8	94.1	0.8	70.1	24	5.9
Levofloxacin	0.06	2	0.015–>32	84.8	11	84.8	4.1	11.1
Amikacin	2	4	0.25–>32	(98.3)	1.7	93.2	5.1	1.7
Trimethoprim-sulfamethoxazole	≤0.12	>4	0.12–>4	86.3	13	86.3	–	13.7
Minocycline	4	16	0.06–>32	N/A	N/A	61.8	12.1	26.1
Colistin	>8	>8	0.06–>8	(27.7)	72.3	–	27.7	72.3
Organism group / Agent	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC range (µg/mL)**	**EUCAST[c] %S**	**EUCAST[c] %R**			
Uncommon glucose-non-fermenters (N=1,568)[d]								
Cefiderocol	0.06	0.5	0.004–>64	98.7	1.3			
Imipenem-relebactam	>8	>8	0.03–>8	21.1	78.9			
Meropenem-vaborbactam	>8	>8	0.015–>8	23.2	76.8			
Ceftazidime-avibactam	16	>32	0.03–>32	45.1	54.9			
Ceftolozane-tazobactam	>16	>16	0.12–>16	25.1	74.9			
Aztreonam-avibactam[b]	4	>16	0.03–>16	79.9	14.4			
Ceftazidime	32	>32	0.06–>32	24.9	66.2			
Piperacillin-tazobactam	>128	>128	0.06–>128	16.5	81			
Meropenem	>32	>32	0.015–>32	14.9	77.9			
Imipenem	>8	>8	0.12–>8	9.9	86.5			
Levofloxacin	1	8	0.015–>32	23.4	44.4			
Amikacin	>32	>32	0.25–>32	0.3	99.7			
Trimethoprim-sulfamethoxazole	≤0.12	1	0.12–>4	N/A	N/A			
Minocycline	0.5	2	0.06–>32	N/A	N/A			
Colistin	8	>8	0.06–>8	N/A	N/A			

[a]Organisms included: *Citrobacter amalonaticus / farmeri* (30), *C. braakii* (2), *C. freundii* (19), *C. freundii* species complex (512), *C. koseri* (503), *C. sedlakii* (1), *C. youngae* (1), *Cronobacter sakazakii* (4), *Hafnia alvei* (77), *H. alvei/ Hafnia paralvei* (2), *Kluyvera ascorbata* (4), *K. cryocrescens* (1), *K. georgiana* (1), *Kosakonia cowanii* (1), *Leclercia adecarboxylata* (2), *Lelliottia amnigena* (2), *Morganella morganii* (393), *Pantoea agglomerans* (21), *P. ananatis* (2), *P. anthophila* (1), *P. calida* (1), *P. dispersa* (2), *P. piersonii* (1), *Phytobacter diazotrophicus* (3), *Plautia/Rahnella georgiae* (8), *Proteus hauseri* (6), *P. mirabilis* (1,377), *P. penneri* (23), *P. vulgaris* (97), *P. vulgaris* group (88), *Providencia alcalifaciens* (7), *P. rettgeri* (103), *P. stuartii* (102), *Pseudocitrobacter faecalis* (1), *Rahnella aquatilis* (3), *Raoultella ornithinolytica* (64), *R. planticola* (13), *Serratia fonticola* (5), *S. liquefaciens* (54), *S. liquefaciens complex* (11), *S. marcescens* (1,299), *S. odorifera* (5), *S. rubidaea* (4), unspecified *Citrobacter* (8), unspecified *Enterobacter* (1), unspecified *Pantoea* (7), unspecified *Providencia* (5), unspecified *Raoultella* (53), Unspecified *Yersinia* (not *Yersinia pestis*) (1), *Yersinia enterocolitica* (2), *Yokenella regensburgei* (1). [b]Aztreonam-avibactam was used in the absence of approved breakpoint for aztreonam-avibactam; [c]Susceptibility was interpreted according to EUCAST PK/PD non-species related breakpoints only; [d]Organisms included: *Achromobacter denitrificans* (1), *A. insolitus* (3), *A. marplatensis* (1), *A. xylosoxidans* (30), *Burkholderia cepacia* complex (162), *B. gladioli* (10), *B. multivorans* (3), *Chryseobacterium anthropharense* (3), *C. gleum* (1), *C. indologenes* (12), *Stenotrophomonas maltophilia* (1,208), unspecified *Achromobacter* (132), unspecified *Chryseobacterium* (2); N/A, not applicable; S, susceptible; I, intermediate; MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50%/90% of organisms; R, resistant.

Figure 2: MIC distributions of cefiderocol against uncommon Gram-negative bacteria collected during 2022–2022 as part of the SENTRY Antimicrobial Surveillance Program A) Enterobacterales and B) Glucose non-fermenters

MIC, minimum inhibitory concentration

CONCLUSIONS

- Cefiderocol showed potent activity against a set of 6,461 contemporary uncommon Gram-negative clinical isolates. These *in vitro* data suggest that cefiderocol could be an important treatment option for infections caused by these infrequently isolated pathogens.

References

1. Shortridge D, et al. Microbiol Spectr. 2022;10(2):e0271221.

Acknowledgments

The study was funded by Shionogi. CL, STN, BD, JJB, MT, YY are employees of Shionogi. Editorial support was provided by Highfield, Oxford, UK; this support was funded by Shionogi & Co., Ltd., Osaka, Japan.

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UNIVERSITÀ di VERONA
Dipartimento di DIAGNOSTICA E SANITÀ PUBBLICA

E0454

Evaluation of Cefiderocol activity against 400 *Stenotrophomonas maltophilia* clinical isolates

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Introduction

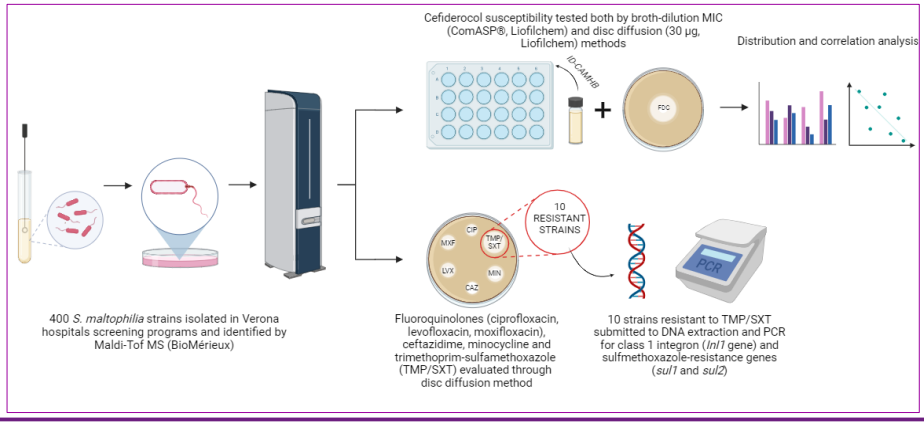
Stenotrophomonas maltophilia is a **multidrug-resistant (MDR) Gram-negative** bacterium commonly associated with difficult-to-treat nosocomial infections.

This **resistance pattern** is due to intrinsic and acquired resistance mechanisms such as its low membrane permeability, the presence of chromosomally encoded efflux pumps, antibiotic-modifying enzymes, and the acquisition of genetic mobile elements (integrons, transposons, plasmids).

S. maltophilia exhibits its resistance to numerous antimicrobial agents, such as trimethoprim-sulfamethoxazole (TMP/SMX), ß-lactams, fluoroquinolones, and carbapenems.

This study aims to evaluate the activity of **cefiderocol**, a siderophore cephalosporin, against 400 clinical *S. maltophilia* strains.

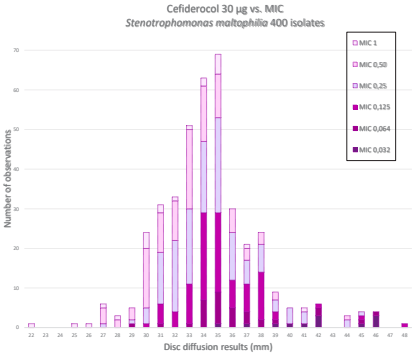
Methods



General workflow and methods are summarized in *Figure 1 (left):*

- Samples collected between 2003 and 2023.
- *ID-CAMHB* indicates iron-depleted Mueller-Hinton Broth

Cefiderocol results



Graphic 1: cefiderocol DD and MICs distributions divided by the number of observations.

Correlation analysis

Graphic 2 and Graphic 3: the continuous line represents our results, and the dotted line represents the linear prediction.

Graphic 2: The obtained determination coefficient R^2 is 0.152; about 15% of the variation in the variable "DD" can be explained by the variation in the variable "MIC".

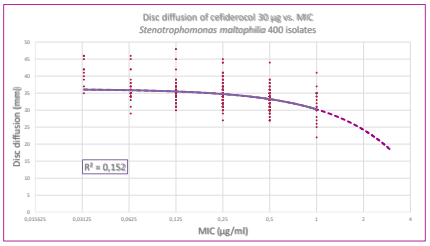
Graphic 3: The determination coefficient R^2 is 0.5651; about 56.50% of the variation in the variable "DD" can be explained by the variation in the variable "MIC".

This correlation result suggests a better predictive ability of the linear model.

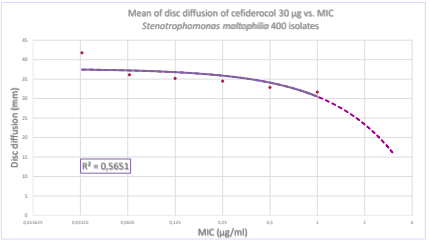
Cefiderocol distribution results

Graphic 1: distribution of the obtained MIC values based on the number of observations of the DD values.

Peak in the 30mm – 40mm range, mostly 0,125 µg – 0,5 µg MIC range. All MICs range from 0.032 µg to 1 µg, MIC_{50} **is 0.25 µg**, and MIC_{90} **is 0.5 µg**. All diameters range from 21 mm to 48 mm.



Graphic 2: the regression statistical approach represents the disc diffusion of cefiderocol DD vs MICs.



Graphic 3: the correlation approach represents the mean DD values obtained for every MIC value of cefiderocol.

Other antibiotics results

DD RANGES ⇒ ANTIBIOTICS ⇩	0-5 mm	6-10 mm	11-15 mm	16-20 mm	21-25 mm	26-30 mm	31-35 mm	36-40 mm	41-45 mm	46-50 mm
LEVOFLOXACIN	1	2	15	15	55	181	99	30	2	-
CIPROFLOXACIN	2	2	15	17	59	182	102	17	4	-
MOXIFLOXACIN	-	-	2	10	10	69	112	157	32	8
CEFTAZIDIME	68	31	56	68	86	63	16	12	-	-
MINOCYCLINE	-	-	-	4	39	195	120	36	5	1
TMP/SXT	6	2	2	57	153	133	31	15	1	-

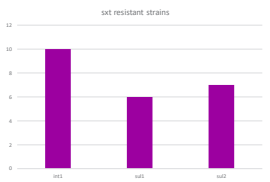
Table 1: other antibiotics DD results (fluoroquinolones, minocycline, ceftazidime, TMP/SXT). For TMP/SXT, breakpoints are available and 10 strains tested resistant.

Disc diffusion results

Table 1: fluoroquinolones (especially moxifloxacin) and minocycline showed an elevated activity towards *S. maltophilia* strains.

Ceftazidime: the 11 mm – 30 mm range is the most represented, but the 0 -10 mm range represents a quarter of the tested strains, leading to an extended lack of activity.

TMP/SXT: **10 strains tested resistant** (R ≤ 15 mm), and 390 strains tested susceptible at increased exposure to the drug (16-50 mm).



Graphic 4: 10 strains resistant to TMP/SXT molecular evaluation results.

TMP/SXT-resistant molecular analysis

Graphic 4: the 10 resistant strains harboured the ***intI1* gene** and were analysed for *sul* genes.

Six strains harbour ***sul1* and *sul2* genes in the same class 1 integron**, and only 1 strain harbours only the *sul2* gene.

Conclusions

Cefiderocol is a new antibiotic compound with **high antibacterial activity** against *S. maltophilia* strains.

Strains resistant to **TMP/SXT** harbour **class 1 integron** (*IntI1* gene), and 6 strains harbour both *sul1* and *sul2* gene.

Cefiderocol is active against these strains.

Our results suggest exploiting **moxifloxacin and minocycline** against *S. maltophilia* clinical infections instead of ceftazidime.

EUCAST document: zone diameters of ≥20 mm correspond to MIC values below the PK-PD breakpoint of S ≤ 2 µg/ml.

Our linear predictions **confirm** this assessment.

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Highlights

- Nell'ambito del programma di sorveglianza antimicrobica SENTRY è stata testata la sensibilità a cefiderocol e a numerosi antibiotici *comparatori* su 35.837 isolati Gram-negativi definiti "non comuni", ovvero che rappresentano meno del 5% della popolazione totale dei Gram-negativi ottenuti da isolamenti clinicamente significativi.
- Gli Enterobacterales sono risultati sensibili alla maggior parte degli antibiotici testati, compreso cefiderocol (che ha raggiunto il 99,8% di sensibilità), mentre tra i Gram-negativi non fermentanti la resistenza era >50% verso la maggior parte degli antibiotici testati.
- **Cefiderocol ha mantenuto una sensibilità pressoché totale (98,7%).**

Fetcroja 1 g polvere per concentrato per soluzione per infusione
▼ Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 per informazioni sulle modalità di segnalazione delle reazioni avverse[1].

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Regime di fornitura: medicinale soggetto a prescrizione medica limitativa, utilizzabile esclusivamente in ambiente ospedaliero o in struttura ad esso assimilabile (OSP).

La versione sempre aggiornata del RCP è disponibile al link **20230322-Fetcroja-RCP (shionogi.com)**

1. Fetcroja. Riassunto delle caratteristiche del prodotto.

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