

Cefiderocol: Rationale for EUCAST Clinical Breakpoints

Current version	2.0	April 2023
Previous versions	1.1	March 2022

Introduction

Cefiderocol is an injectable siderophore cephalosporin. As with other β -lactam antibiotics, the principal antibacterial/bactericidal activity of cefiderocol occurs by inhibition of Gram-negative bacterial cell wall synthesis by binding to penicillin binding proteins. Cefiderocol has highest affinity for PBP3, with lesser affinity for PBP2 and PBP1a/1b.

Cefiderocol is relatively stable to hydrolysis by both serine- and metallo- β -lactamases from all four Ambler classes. In addition to entering the bacterial cell passively through outer membrane porin channels, cefiderocol also binds to free ferric iron (Fe-III) via a catechol group and is actively taken up via iron transport proteins. As a result, cefiderocol is less affected by non-specific resistance mechanisms such as porin loss or over-expression of efflux pumps which contribute to resistance to many β -lactams including carbapenems.

Cefiderocol shows antibacterial activity against a wide spectrum of aerobic Gram-negative bacteria including members of *Enterobacterales* (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and *Proteus* spp.) as well as glucose non-fermentative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex, *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia*. Cefiderocol does not have useful activity against Gram-positive or anaerobic Gram-negative bacteria.

Cefiderocol is indicated for the treatment of infections due to aerobic gram-negative bacteria in adult patients with limited treatment options.

This version is extracted from version 1.1, and will be format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 2 g x 3 iv over 3 hours
High dosage: None

MIC distributions and epidemiological cut-off (ECOFF) values

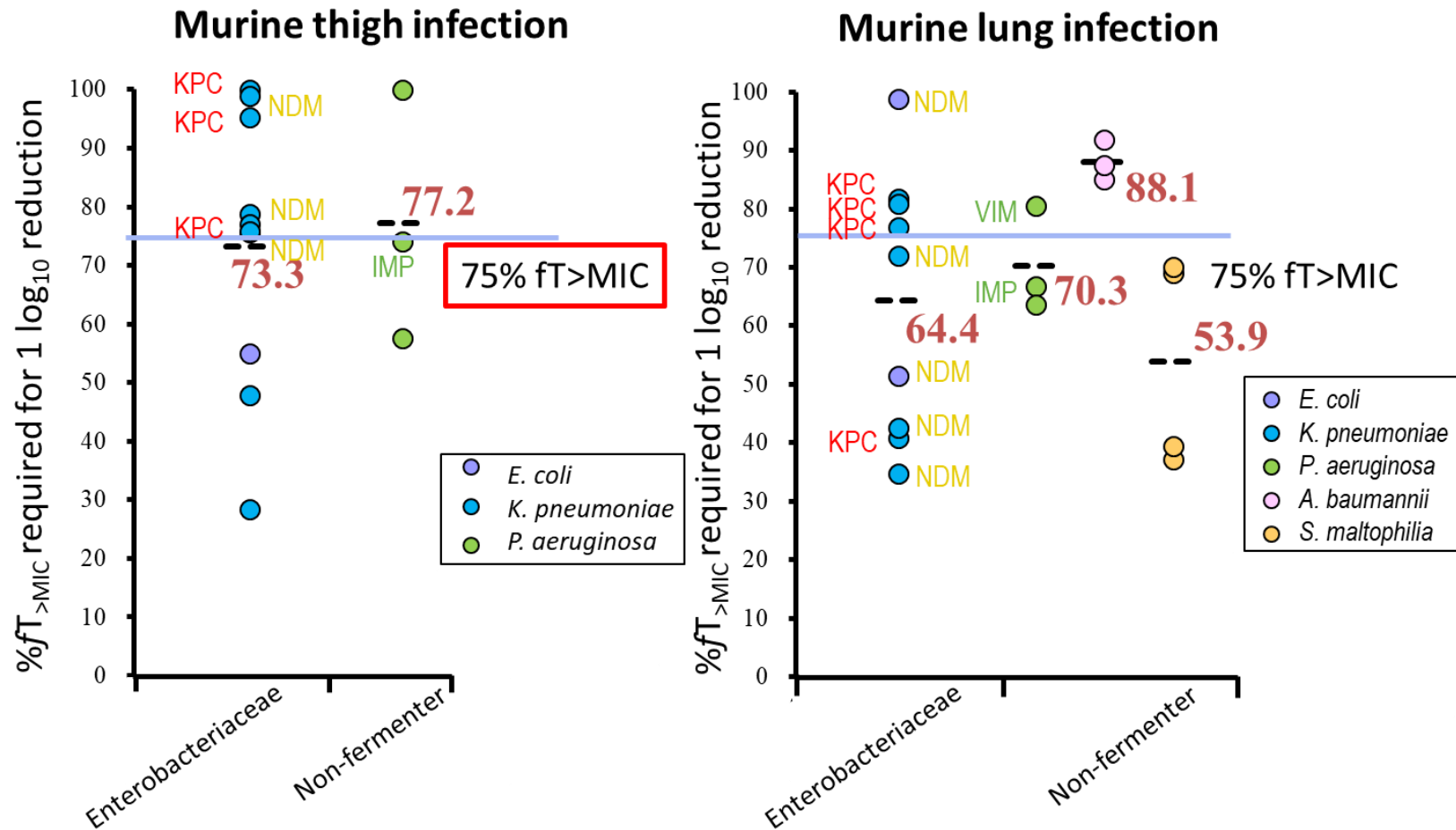
MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

Pharmacokinetics

PK parameter	Pharmacological studies		
	Single dose, 2 g iv over 1 hour Geometric mean (CV%), N = 6	Multiple doses (Day 10) 2 g x 3 (iv over 1 hour) Geometric mean (CV%), N = 8	Single dose, 2 g iv over 3 hours Geometric mean (CV%), N = 43
C _{max} (mg/L)	156 (7.9)	153 (12.9)	89.7 (20.5)
C _{min} (mg/L)	7.72 (15.6)	7.30 (36.7)	11.5 (30.0)
Total body clearance (L/h)	5.13 (9.0)	5.46 (14.0)	5.18 (17.2)
T _{1/2} (h), mean (range)	2.74 (10.2)	2.72 (21.6)	2.41 (14.0)
AUC _{0-8h,ss} (mg.h/L)		366.5 (14.0)	
AUC _{0-∞} (mg.h/L)	389.7 (9.0)		386.1 (172)
Fraction unbound (%)	42.2	42.2	42.2
Volume of distribution _{ss} (L)	20.3 (11.1)		18.0 (18.1)

Pharmacodynamics

Index*	Neutropenic mouse thigh				
	<i>E. coli</i> (N=1)	<i>K. pneumoniae</i> (N=9)	<i>P. aeruginosa</i> (N=3)		
	Mean (SD range)	Mean (SD range)	Mean (SD range)		
f%T>MIC for bacteriostasis	40 (-)	65 (37-93)	63 (48-79)		
f%T>MIC for 1-log ₁₀ kill	55 (-)	75 (52-99)	77 (56-99)		
Index*	Neutropenic mouse lung				
	<i>E. coli</i> (N=2)	<i>K. pneumoniae</i> (N=7)	<i>P. aeruginosa</i> (N=3)	<i>A. baumannii</i> (N=3)	<i>S. maltophilia</i> (N=4)
	Mean (SD range)	Mean (SD range)	Mean (SD range)	Mean (SD range)	Mean (SD range)
f%T>MIC for bacteriostasis	67 (22-111)	51 (32-71)	57 (47-68)	82 (77-87)	46 (27-65)
f%T>MIC for 1-log ₁₀ kill	75 (42-109)	61 (40-82)	70 (61-79)	88 (85-92)	54 (36-72)

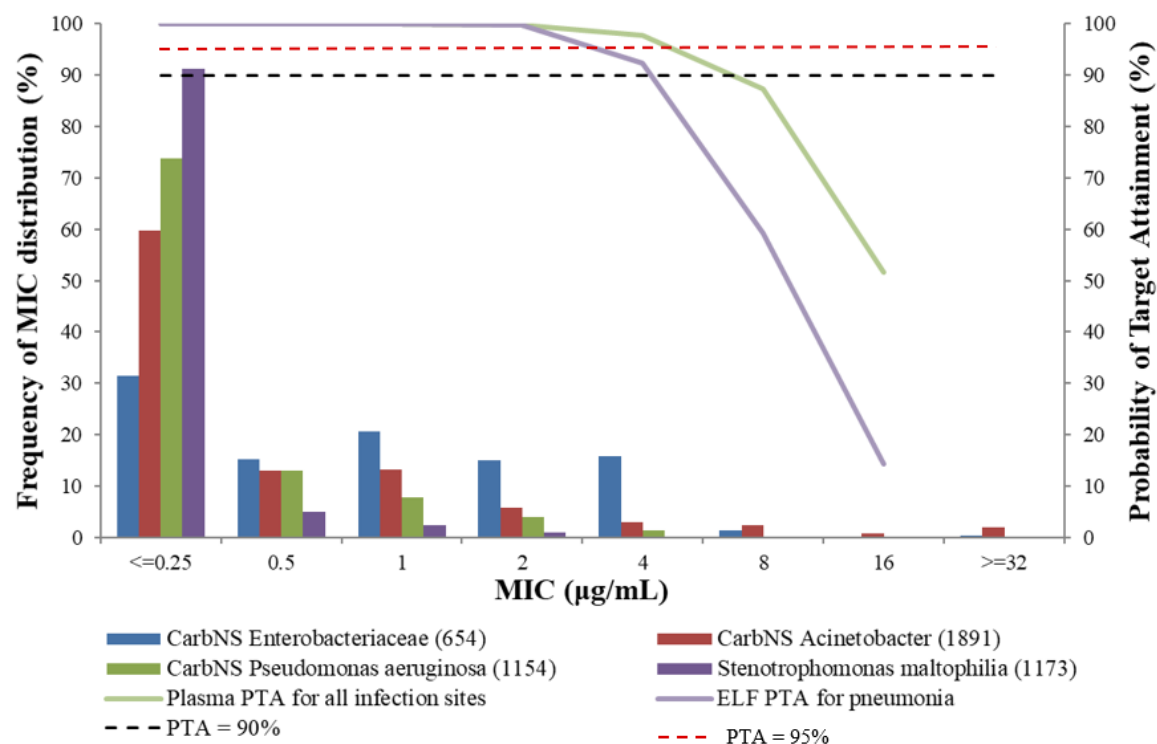


fT_{>MIC} in ID-CAMHB Required for Efficacy in Neutropenic Murine Thigh and Lung Infection Models for Each Strain

Monte Carlo simulations

The population PK model developed is a 3-compartment model using CrCl as a significant covariate, parameter estimation for the model was done using plasma concentration from healthy volunteers, but also from patients in the cUTI Study, CREDIBLE-CR Study, and APEKS-NP Study (see Section 8) and epithelial lining fluid (ELF) PK from pneumonia patients in a separate ELF PK study. Probabilities of target attainment (PTA) for 75%, 90% and 100% $fT > MIC$ in plasma were calculated by infection site and renal function in patients caused by carbapenem-resistant pathogens when cefiderocol is dosed at 2 g iv over 3 hours. Overall PTA was calculated by weighting for the distributions of CrCL based on the information in the phase 3 studies.

The ELF concentrations of cefiderocol in patients with pneumonia were predicted using a developed ELF model based on the ELF concentrations in 20 healthy subjects and 7 ventilated patients with pneumonia. The penetration ratios of AUC_{ELF} to $fAUC_{plasma}$ were 0.34 in pneumonia patients and 0.263 in healthy subjects.



Probability of PK-PD Target Attainment in plasma and ELF for all infection sites and renal function groups, based on PK-PD targets of 100% $fT > MIC$ for 1 log₁₀ kill overlaid on distribution of cefiderocol MIC for 4872 carbapenem non-susceptible Gram-negative bacteria.

Clinical studies

Complicated UTI

Study 1409R2121 compared cefiderocol 2 g iv over 3 hours x 3 (n=300) with 1 g dose of imipenem/cilastatin 1 g iv over 1 hour x 3 (n=148) and showed non-inferiority for a composite clinical and microbiological endpoint. Outcomes versus MICs of the infecting *Enterobacterales* are shown below. Cefiderocol clinical response and microbiological eradication were seen in 80% and 47% respectively of *P. aeruginosa* infections.

Species/group	Outcome	MIC (mg/L)											
		≤ 0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8
<i>Enterobacterales</i>	No. of isolates	24	13	19	26	32	40	29	16	13	9	4	1
	Clinical	92%	92%	100%	89%	94%	88%	76%	94%	100%	8	4	0
	Microbiological	79%	77%	100%	81%	75%	78%	62%	69%	85%	5/9	3/4	0/1

APEKS-NP

The APEKS-NP study compared cefiderocol 2 g iv over 3 hours x 3 (n=150) with 1 g dose of meropenem 2 g iv over 3 hours x 3 (n=150) for nosocomial pneumonia. The most frequently occurring gram-negative pathogens in both treatment groups at baseline were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Noninferiority of cefiderocol to meropenem was met for the primary efficacy endpoint of Day 14 all-cause mortality. Outcomes versus MICs of the infecting *Enterobacterales* are shown below: Cefiderocol clinical response and microbiological eradication were seen in 67% and 38% respectively of *P. aeruginosa* infections.

Species/group	Outcome	MIC (mg/L)											
		≤ 0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	> 32
<i>Enterobacterales</i>	No. of isolates	17	14	5	13	19	16	11	2	0	0	0	0
	Clinical	59%	71%	36%	60%	54%	47%	64%	1				
	Microbiological	53%	29%	60%	46%	42%	63%	36%	0/2				

CREDIBLE-CR

CREDIBLE-CR was an open label study of cefiderocol in infections, regardless of site, caused by carbapenem-resistant gram-negative pathogens (n=101), compared to best available therapy (n=49). *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were the most frequently occurring baseline pathogens in both groups. Clinical cure rates were 53% in the cefiderocol group and 50% in the best available therapy group. The microbiological eradication rates were 31% and 24% respectively. Outcomes versus MICs of the infecting *Enterobacterales* are shown below: Cefiderocol clinical response and microbiological eradication were seen in 56% and 12% respectively of *P. aeruginosa* infections. The rates for *Acinetobacter baumannii* were 41% and 26% respectively.

Species/group	Outcome	MIC (mg/L)											
		≤ 0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	> 32
<i>Enterobacterales</i>	No. of isolates	3	5	3	7	4	6	6	4	0	2	0	0
	Clinical	1	3	3	5	4	4	2	3		1		
	Microbiological	2	1	1	2	4	4	2	3		0		

There were too few isolates of *S. maltophilia* in any of the studies to provide breakpoint assessment.

Clinical breakpoints

The clinical breakpoints for cefiderocol can be found in the most recent version of the Breakpoint tables: https://www.eucast.org/clinical_breakpoints

All breakpoints are based on the specialised broth required to test cefiderocol, Guidance can be found on the EUCAST website:

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefiderocol_MIC_testing_EUCAST_guidance_document_201217.pdf

A warning pertaining to media and methods is posted on the EUCAST website: <https://www.eucast.org/ast-of-bacteria/warnings> (items 10 and 12)

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