EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale for EUCAST clinical breakpoints

Agent	**Ceftazidime-avibactam**

Current version	**1.0**	**30 July 2020**
Previous versions		

Foreword

EUCAST
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at http://www.EUCAST.org.

EUCAST rationale documents
EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents
All EUCAST documents are freely available from the EUCAST website at http://www.EUCAST.org.

Citation of EUCAST documents

This rationale document should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Ceftazidime-avibactam: Rationale for the clinical breakpoints, version 1.0 year 2020. http://www.eucast.org.

1. Introduction

Avibactam is a first-in-class diazabicyclooctane non-β-lactam β-lactamase inhibitor that protects the antimicrobial activity of ceftazidime when used in combination. Avibactam differs from other clinically used β-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam, in several key aspects, such as chemical structure, expanded spectrum of β-lactamase inhibition, and covalent reversible mechanism of inhibition. The carbamoyl link to the catalytic serine of inactivated β-lactamase is more stable to enzyme-assisted hydrolysis than the ester linkages found with β-lactam-based β-lactamase inhibitors. Avibactam inhibits both Ambler class A and class C β-lactamases, including extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemases (KPC), and AmpC enzymes. Ceftazidime-avibactam is also generally active *in vitro* against *Enterobacterales* that produce the class D carbapenemase, OXA-48.

Ceftazidime-avibactam is indicated for the treatment of the following infections in adults: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, and hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Ceftazidime-avibactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.
Metallo-β-lactamases are not inhibited by avibactam. Therefore*, Enterobacterales* or *Pseudomonas aeruginosa* that produce these enzymes are considered to be resistant to ceftazidime-avibactam.

The dose for adults with normal renal function or mild renal impairment (estimated creatinine clearance [CrCl] >50 mL/min, calculated using the Cockcroft-Gault formula) is 2000 mg ceftazidime/500 mg avibactam given as a 2-h intravenous (IV) infusion every 8 h (q8h). The dose is adjusted for patients with CrCl values ≤50 mL/min, and all doses are given as a 2-h IV infusion. It is recommended that patients with a CrCl of 31 to 50 mL/min be administered 1000 mg ceftazidime/250 mg avibactam q8h, with a CrCl of 16 to 30 mL/min be administered 750 mg ceftazidime/187.5 mg avibactam every 12 hours, with a CrCl of 6 to 15 mL/min be administered 750 mg ceftazidime/187.5 mg avibactam every 24 hours, and with a CrCl <6 mL/min be administered 750 mg ceftazidime/187.5 mg avibactam every 48 hours. For patients on haemodialysis, ceftazidime-avibactam should be administered after haemodialysis on haemodialysis day as both ceftazidime and avibactam are haemodialysable.

2. Dosage

Standard dose schedule	2000 mg ceftazidime/500 mg avibactam as a 2-h IV infusion q8h
High dose schedule	None
Available formulations	IV

3. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

Updated MIC distributions and ECOFFs for both ceftazidime and ceftazidime-avibactam can be found at https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init

ECOFFs for the combination are those of ceftazidime alone.

4. Breakpoints prior to revision (mg/L) S≤ / R>

Not applicable

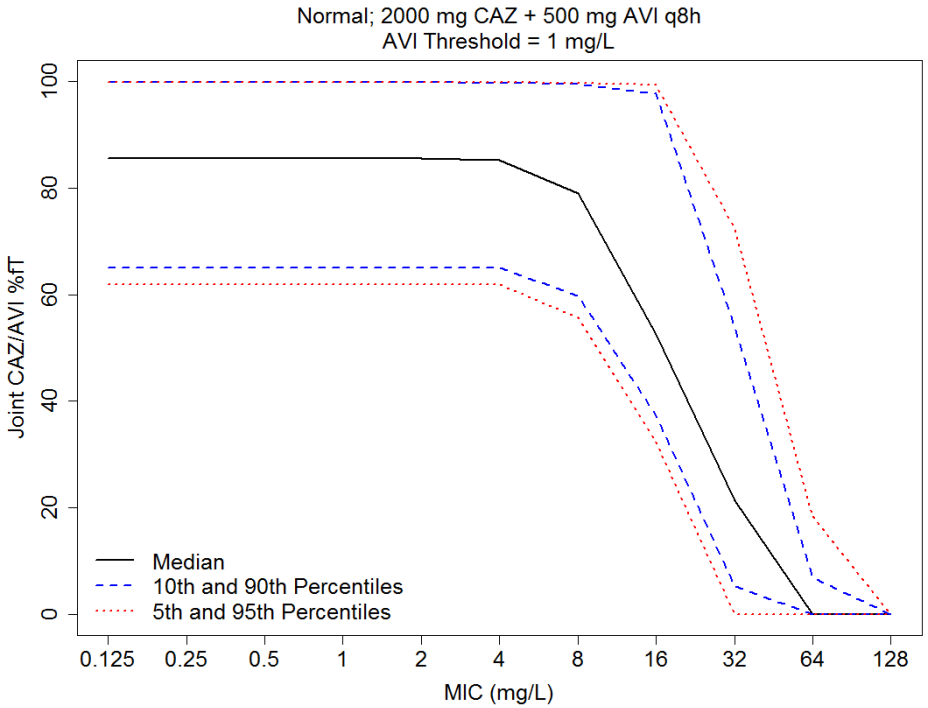
5. Pharmacokinetics (PK)

Dosage (mg)	Ceftazidime 2000 mg q8h (2-h IV infusion) in combination with 500 mg avibactam	Avibactam 500 mg q8h (2-h IV infusion) in combination with 2000 mg ceftazidime
C_{max} (mg/L) (geometric mean [%CV])	90.4 (15.7)	14.6 (17.0)
Total body clearance (L/h) (arithmetic mean [SD])	6.9 (1.0)	13.3 (2.4)
$t_{½}$ (h), mean (arithmetic mean [SD])	2.8 (0.2)	2.8 (0.6)
$AUC_{0\text{-}tau,ss}$ (mg·h/L) (geometric mean [%CV])	291.0 (15.2)	38.2 (18.9)
AUC_{∞}[a] (mg·h/L) (geometric mean [%CV])	289.1 (15.4)[b]	42.1 (16.0)[c]
Fraction unbound (%)	85 (in vitro data)	91.8 (in vitro data)
Comments	Phase 1[1] study in healthy volunteers (n=16), q8h, steady state data	Phase 1[1] study in healthy volunteers (n=16)
	[a] single dose, [b] n=15, [c] n=13 No drug-drug interaction between ceftazidime and avibactam	
Reference	[1] Das S, Li J, Armstrong J , Learoyd M, Edeki T. Randomized pharmacokinetic and drug-drug interaction studies of ceftazidime avibactam, and metronidazole in healthy subjects. *Pharmacol Res Perspec* 2015 Oct;3(5):e00172.	

6. Pharmacodynamics (PD)	
%*f*T>MIC is the dominant PD index for ceftazidime and %*f*T> C_T is the dominant PD index for avibactam	
Summary of ceftazidime PK/PD	
	Enterobacterales and *P. aeruginosa*
Animal data for ceftazidime	%*f*T>MIC: 25-40 for bacteriostasis; 45-55 for 2-log reduction[1-3]
Clinical data for ceftazidime	%*f*T>MIC: 45-53 for eradication (or presumed eradication) of Gram-negative bacteria[4,5]
Summary of avibactam PK/PD	
Hollow fibre data for avibactam	*Enterobacterales*
	Under various combinations of concentration-time profiles of ceftazidime and avibactam, avibactam C_T ≥0.5 mg/L prevented ceftazidime-resistant, class A and C β-lactamase-producing isolates from growing in the presence of ceftazidime[6]
Animal data for avibactam	*P. aeruginosa*
	When superimposed on intermittent ceftazidime dosing: In neutropenic mouse thigh infections, avibactam 40% (SD 20%) *f*T>C_T of 1 mg/L yielded bacteriostasis and 50% (SD 15%) *f*T>1 mg/L yielded 1-log reduction[7] In neutropenic mouse lung infections, avibactam 20% (SD 2.5%) *f*T>C_T 1 mg/L yielded bacteriostasis, 24% (SD 6%) *f*T>1 mg/L yielded 1-log reduction, and 30%(SD 15%) *f*T>1 mg/L yielded 2-log reduction[8]
Comments	The PTA of ceftazidime-avibactam is based on maintaining 50% *f*T>MIC for ceftazidime and 50% *f*T>C_T of 1 mg/L for avibactam simultaneously
Clinical data for avibactam	None
References	[1] Ceftazidime: Rationale for the EUCAST breakpoints, version 1.0, dated 26th September 2010. [2] Craig, Infect Dis Clin N Am 2003; 17: 479-501. [3] Bakker-Woudenberg, et al., Antimicrob Agents Chemother 2006; 50: 2919-25. [4] Muller, et al, J Antimicrob Chemother 2014; 68 :900-6. [5] MacVane, et al., Antimicrob Agents Chemother 2014; 58: 1359-64. [6] Coleman, et al., Antimicrob Agents Chemother 2014; 59: 3366-72. [7] Berkhout J et al, Antimicrob Agents Chemother. 2015;60:368-75. [8] Berkhout J et al., Antimicrob Agents Chemother. 2015;59:2299-304

7. Monte Carlo simulations and PK/PD breakpoints

Probabilities of target attainment (PTA) for 2000 mg ceftazidime/500 mg avibactam 2-h IV infusion × 3 in patients with cIAI are shown in Figure 1.



%fT = proportion of the dosing interval (time) during which the free concentration of ceftazidime-avibactam exceeds the target organism's MIC; AVI = avibactam; CAZ = ceftazidime; MIC = minimum inhibitory concentration; q8h = every 8 hours.

Figure 1. Probabilities of target attainment for 2000 mg ceftazidime/500 mg avibactam 2-h IV infusion × 3 IV.

The PTA was obtained by Monte Carlo simulations using population PK models developed for ceftazidime-avibactam and covariate distribution in patients with cIAI. The PK of ceftazidime-avibactam was described as a 2-compartment model, characterized by central clearance (CL), apparent volume of the central compartment (V_c), inter-compartmental clearance (Q), and apparent volume of the peripheral compartment (V_p) with first-order elimination from the central compartment.

The ceftazidime-avibactam PK is similar in patients with nosocomial pneumonia (NP). PTA using covariate distributions in patients with NP is comparable to Figure 1 (*ECCMD-1506: Pharmacokinetic modelling of ceftazidime and avibactam and probability of target attainment to support the dosing regimen in patients with nosocomial pneumonia including ventilator-associated pneumonia*. Paper presented at: 25th ECCMID 2015; Copenhagen, Denmark).

The following typical PK parameters and inter-subject variability (CV%) values were used to obtain the PTA:

Ceftazidime:
CL: 7.16 L/h, CV 39%
V_c: 10.6 L, CV 33%
Q: 7.01 L/h
V_p: 6.81 L

Avibactam:
CL: 10.4 L/h, CV 56%
V_c: 11.9 L, CV 32%
Q: 7.52 L/h
V_p: 7.5 L, CV 19%

A joint PK/PD target of 50% *f*T>MIC for ceftazidime and 50% *f*T>C_T of 1 mg/L MIC for avibactam and a >95% joint target attainment rate results in a susceptible breakpoint of 8 mg/L for ceftazidime-avibactam for a dosage of 2000 mg ceftazidime/500 mg avibactam 2-h IV infusion q8h. There is no higher dose, so the resistant breakpoint is >8 mg/L.

8. Clinical data

The efficacy of ceftazidime-avibactam was compared to imipenem-cilastatin in hospitalised adults with serious complicated urinary tract infections due to gram-negative pathogens [1]. Overall, 135 patients received study therapy (safety population); 62 were included in the ME population (ceftazidime–avibactam, n= 27; imipenem–cilastatin, n= 35). The predominant uropathogen was *Escherichia coli*. Favourable microbiological response was achieved in 70.4% of ME patients receiving ceftazidime–avibactam and 71.4% receiving imipenem–cilastatin at the TOC visit (observed difference -1.1% [95% CI: -27.2%, 25.0%]). Among ME patients with ceftazidime-resistant uropathogens, response was observed in 6/7 (85.7%) receiving ceftazidime–avibactam. Limitations of the study include the small number of patients in the ME population. Outcomes by pathogen are shown in Table 1.

Table 1 Favorable microbiological response rate at test-of-cure visit according to primary diagnosis and baseline uropathogens (microbiologically evaluable population).

	Ceftazidime–avibactam (*n* = 27)	Imipenem–cilastatin (*n* = 35)	Observed difference (95% CI)
Primary diagnosis, *n* (%):			
Acute pyelonephritis	13/18 (72.2)	14/19 (73.7)	−1.5 (−35.5, 32.6)
Other cUTI	6/9 (66.7)	11/16 (68.8)	−2.1 (−49.0, 44.9)
Baseline uropathogen, *n* (%)			
E. coli	19/25 (76.0)	23/33 (69.7)	6.3 (−20.1, 32.8)
P. aeruginosa	0/2 (0.0)	0/0	–
C. koseri	1/1 (100.0)	0/0	–
E. cloacae	0/0	1/1 (100.0)	–
P. mirabilis	0/0	1/1 (100.0)	–
Ceftazidime-resistant pathogens, *n* (%)			
E. coli	6/7 (85.7)	8/10 (80.0)	–
E. cloacae	0/0	1/1 (100)	–

n, number of patients; CI, confidence interval; cUTI, complicated urinary tract infection.

The efficacy and safety of ceftazidime-avibactam plus metronidazole were compared with meropenem in 1066 men and women with complicated intra-abdominal infections from 2 identical, randomized, double-blind phase 3 studies [2]. Ceftazidime-avibactam plus metronidazole was noninferior to meropenem across all primary analysis populations. Clinical cure rates with ceftazidime-avibactam plus metronidazole and meropenem, respectively, were as follows: mMITT population, 81.6% and 85.1% (between-group difference, -3.5%; 95% confidence interval -8.64 to 1.58); modified intention-to-treat, 82.5% and 84.9% (-2.4%; -6.90 to 2.10); and clinically evaluable, 91.7% and 92.5% (-0.8%; -4.61 to 2.89). The clinical cure rate with ceftazidime-avibactam plus metronidazole for ceftazidime-resistant infections was comparable to that with meropenem (mMITT population, 83.0% and 85.9%, respectively) and similar to the regimen's own efficacy against ceftazidime-susceptible infections (82.0%).

Table 2 **Clinical Response at the Test-of-Cure Visit for Patients with Ceftazidime-Resistant and Ceftazidime-Susceptible Gram-Negative Pathogens (Microbiologically Modified Intention-to-Treat Analysis Population)**

Pathogen	Ceftazidime Avibactam + Metronidazole (n = 413)		Meropenem (n = 410)		Between-Group Difference in Clinical Cure Rates, (95% CI), %[a]
	Patients, No.	Clinical Cure, No. (%)	Patients, No.	Clinical Cure, No. (%)	
All					
Ceftazidime resistant	47	39 (83.0)	64	55 (85.9)	–3.0 (–17.89 to 10.60)
Ceftazidime susceptible	289	237 (82.0)	292	256 (87.7)	–5.7 (–11.57 to 0.17)
Enterobacteriaceae					
Ceftazidime resistant	44	36 (81.8)	62	53 (85.5)	–3.7 (–19.31 to 10.44)
Ceftazidime susceptible	279	229 (82.1)	280	245 (87.5)	–5.4 (–11.45 to 0.54)
Escherichia coli					
Ceftazidime resistant	24	19 (79.2)	37	31 (83.8)	–4·6 (–26.77 to 14.86)
Ceftazidime susceptible	236	192 (81.4)	239	210 (87.9)	–6.5 (–13.09 to –0.02)
Klebsiella pneumoniae					
Ceftazidime resistant	13	10 (76.9)	13	9 (69.2)	7.7 (–27.10 to 40.96)
Ceftazidime susceptible	34	28 (82.4)	35	27 (77.1)	5.2 (–14.43 to 24.56)
Non-Enterobacteriaceae					
Ceftazidime resistant	4	4 (100.0)	4	4 (100.0)	0.0 (–52.33 to 52.33)
Ceftazidime susceptible	35	31 (88.6)	43	41 (95.3)	–6.8 (–22.10 to 5.99)
Pseudomonas aeruginosa					
Ceftazidime resistant	2	2 (100.0)	4	4 (100.0)	0.0 (–69.74 to 53.54)
Ceftazidime susceptible	30	27 (90.0)	32	30 (93.8)	–3.8 (–20.55 to 11.90)

A pivotal phase III trial (REPROVE) evaluated the efficacy of ceftazidime-avibactam versus meropenem in the treatment of patients with HAP/VAP [3]. Eight hundred seventy randomized patients received treatment and were included in the ITT population (CAZ-AVI, 870 randomized patients received treatment and were included in the ITT population (CAZ-AVI, CAZ-AVI was noninferior to meropenem for the primary end point (28-day all-cause mortality; ITT) based on the prespecified 10% noninferiority margin (CAZ-AVI, 9.6%; meropenem, 8.3%; difference, 1.5%; 95% confidence interval , –2.4% to 5.3%) and for the clinical cure end point in the ITT population based on a prespecified –10% noninferiority margin (CAZ-AVI, 67.2%; meropenem, 69.1%; difference, −1.9%; 95% CI, –8.1% to 4.3%). Clinical cure rates at TOC for patients infected with CAZ-non-susceptible pathogens were similar (CAZ-AVI, 75.5%; meropenem, 71.2%; micro-ITT). Outcomes by pathogen are shown in Table 3

Table 3. Favorable Clinical and Microbiological Response Rates at TOC by Baseline Pathogen[a] (Micro-ITT Population)

	Per-Patient Clinical Cure[b]		Per-Pathogen Microbiological Eradication[c]	
Pathogen Group/Pathogen	CAZ-AVI, n/N (%)	Meropenem, n/N (%)	CAZ-AVI, n/N (%)	Meropenem, n/N (%)
Aerobic Gram-negative	126/187 (67.4)	143/195 (73.3)	155/256 (60.5)	174/267 (65.2)
Enterobacteriaceae	92/133 (69.2)	108/147 (73.5)	111/168 (66.1)	126/182 (69.2)
Enterobacter aerogenes	5/8 (62.5)	4/9 (44.4)	5/8 (62.5)	6/9 (66.7)
Enterobacter cloacae	25/29 (86.2)	13/23 (56.5)	22/29 (75.9)	14/23 (60.9)
Escherichia coli	12/22 (54.5)	17/23 (73.9)	14/22 (63.6)	16/23 (69.6)
Klebsiella pneumoniae	44/65 (67.7)	56/75 (74.7)	39/65 (60.0)	54/75 (72.0)
Proteus mirabilis	12/14 (85.7)	9/12 (75.0)	11/14 (78.6)	8/12 (66.7)
Serratia marcescens	11/15 (73.3)	12/13 (92.3)	10/15 (66.7)	8/13 (61.5)
Gram-negative pathogens other than Enterobacteriaceae	54/85 (63.5)	61/84 (72.6)	44/88 (50.0)	48/85 (56.5)
Haemophilus influenzae	13/16 (81.3)	20/25 (80.0)	14/16 (87.5)	23/25 (92.0)
Pseudomonas aeruginosa	38/64 (59.4)	37/51 (72.5)	24/64 (37.5)	20/51 (39.2)
CAZ-NS pathogens[d]	37/49 (75.5)	42/59 (71.2)	35/52 (67.3)	33/64 (51.6)
Enterobacteriaceae	29/36 (80.6)	31/45 (68.9)	31/40 (77.5)	29/47 (61.7)
E. aerogenes	3/4 (75.0)	2/2 (100.0)	3/4 (75.0)	2/2 (100.0)
E. cloacae	6/6 (100.0)	4/6 (66.7)	5/6 (83.3)	5/6 (83.3)
E. coli	4/6 (66.7)	5/8 (62.5)	4/6 (66.7)	4/8 (50.0)
K. pneumoniae	17/22 (77.3)	22/31 (71.0)	17/22 (77.3)	18/31 (58.1)
P. aeruginosa	7/12 (58.3)	13/16 (81.3)	4/12 (33.3)	4/16 (25.0)

References

[1] Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012; 28:1921–31.

[2] Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, Llorens L, Newell P, Pachl J. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. *Clin Infect Dis*. 2016 Jun 1;62(11):1380-1389.

[3] Torres A, Rank D, Melnick D, Rekeda L, Chen X, Riccobene T, Critchley IA, Lakkis HD, Taylor D, Talley AK. Randomized trial of ceftazidime-avibactam vs meropenem for treatment of hospital-acquired and ventilator-associated bacterial pneumonia (REPROVE): analyses per US FDA-specified end points. *Open Forum Infect Dis.* 2019 Apr 25;6(4):ofz149.

9. Clinical breakpoints

PK/PD breakpoints	PK/PD breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only as a guide for organisms that do not have specific breakpoints. For ceftazidime-avibactam, the PK-PD breakpoints are S ≤ 8 mg/L, R > 8 mg/L			
Species-related breakpoints	**Organism group**	**MIC breakpoints (mg/L)**		**Notes**
		S ≤	**R >**	
	Enterobacterales	8	8	A joint PK/PD target of 50% *f*T>MIC for ceftazidime and 50% *f*T>C_T of 1 mg/L MIC for avibactam and a >95% joint target attainment rate results in a susceptible breakpoint of 8 mg/L for ceftazidime-avibactam for a dosage of 2000 mg ceftazidime/500 mg avibactam 2-h IV infusion q8h. There is no higher dose, so the resistant breakpoint is >8 mg/L.
	Pseudomonas spp.	8	8	
Clinical qualifications				
Dosage	Breakpoints apply to a daily intravenous dose of 2000 mg ceftazidime/500 mg avibactam × 3 over a 2-h infusion and to the adjusted doses as recommended for patients with a CrCl ≤50 mL/min.			
Additional comment				

10. Exceptions noted for individual national committees
