

Rationale for EUCAST clinical breakpoints

Agent	Ceftaroline	
Current version	1.0	10 October 2014
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

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Ceftaroline: Rationale for the clinical breakpoints, version 1.0, 2014. <http://www.eucast.org>."

1. Introduction

The cephalosporins are a large group of compounds with a 6-membered dihydrothiazine ring fused to a beta-lactam ring. They are derivatives of 7-aminocephalosporanic acid with various modifications to several ring positions resulting in differences in activity, beta-lactamase stability, and pharmacokinetic properties.

Ceftaroline is an extended spectrum cephalosporin with potent antimicrobial activity. Unlike most cephalosporins, ceftaroline has clinically useful activity against most methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is administered as the pro-drug, ceftaroline fosamil, which is rapidly converted to ceftaroline by phosphatases in blood. Ceftaroline is available only for parenteral administration.

Ceftaroline is licensed for the treatment of community-acquired pneumonia (CAP) and complicated skin and soft tissue infection (cSSTI). A dose of 600mg x 2 infused over 1 hour is used for patients with normal renal function or mild renal impairment. A dose of 400 mg x 2 infused over 1 hour is recommended for patients with moderate renal impairment (creatinine clearance 30-50 ml/min).

Ceftaroline is not considered to have useful activity against *Enterococcus* spp. or Gram-negative anaerobic bacteria.

Ceftaroline resistance in Enterobacteriaceae and *Pseudomonas* spp. may be conferred by several mechanisms alone or in combination, including the production of some beta-lactamases (ESBLs, AmpC and others), porin loss and alterations in efflux pumps. MICs of ceftaroline for *Staphylococcus* spp. with the *mecA* gene are similar to or slightly raised compared with wild type isolates, and most *mecA*-positive isolates are considered susceptible.

2. Dosage

Standard dose schedule	600 mg x 2 (60 min iv infusion)
Maximum dose schedule	600 mg x 2 (60 min iv infusion)
Available formulations	iv

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

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>512	ECOFF
<i>Citrobacter amalonaticus</i>	0	0	0	0	0	0	0	1	3	5	0	1	0	0	1	3	0	0	0	ND
<i>Citrobacter braakii</i>	0	0	0	0	0	0	11	7	0	3	0	1	0	1	6	5	0	0	0	ND
<i>Citrobacter fameri</i>	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	1	0	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	0	8	76	104	25	8	7	6	6	20	53	58	0	0	0	1
<i>Citrobacter koseri</i>	0	0	0	0	9	88	62	19	13	1	1	0	0	0	0	4	0	0	0	0.5
<i>Citrobacter sedlakii</i>	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	ND
<i>Citrobacter</i> spp.	0	0	0	0	0	4	7	13	3	1	1	3	1	2	2	3	0	0	0	ND
<i>Citrobacter youngae</i>	0	0	0	0	1	0	2	4	3	2	0	0	0	0	0	0	0	0	0	ND
<i>Edwardsiella tarda</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	1	0	8	131	121	44	15	10	6	16	19	20	71	63	2	0	0	0.5
<i>Enterobacter amnigenus</i>	0	0	0	0	0	2	3	2	0	1	0	0	0	0	2	2	0	0	0	ND
<i>Enterobacter asburiae</i>	0	0	0	0	2	3	9	2	2	0	0	0	0	0	6	0	0	0	0	ND
<i>Enterobacter cancerogenus</i>	0	0	0	0	0	0	0	1	0	0	0	0	1	0	1	1	0	0	0	ND
<i>Enterobacter cloacae</i>	0	0	1	7	26	93	392	543	223	80	37	32	51	53	263	285	41	0	0	1
<i>Enterobacter gergoviae</i>	0	0	1	0	2	3	0	1	1	0	0	0	0	0	1	2	0	0	0	ND
<i>Enterobacter hormaechei</i>	0	0	0	0	0	2	0	1	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Enterobacter intermedius</i>	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Enterobacter sakazakii</i>	0	0	0	0	0	3	5	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Enterobacter</i> spp.	0	0	0	0	2	20	38	36	6	5	4	7	2	7	14	18		0	0	ND
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	2	6	103	169	44	38	10	1	3		0	0	8
<i>Escherichia coli</i>	0	0	6	51	843	2956	2480	1161	590	333	150	83	103	91	505	998	45	0	0	0.5
<i>Escherichia vulneris</i>	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Haemophilus haemolyticus</i>	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Haemophilus influenzae</i>	0	0	2396	698	216	65	18	2	7	1	0	0	0	0	0	0	0	0	0	0.03
<i>Haemophilus parahaemolyticus</i>	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Haemophilus parainfluenzae</i>	0	0	116	38	6	8	2	2	1	0	0	0	0	0	0	0	0	0	0	0.03

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Hafnia alvei</i>	0	0	0	0	0	0	0	0	5	3	4	1	0	0	4	0	0	0	0	ND
<i>Klebsiella ornithinolytica</i>	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Klebsiella oxytoca</i>	0	0	1	3	57	206	275	263	105	27	8	10	9	10	47	110	0	0	0	0.5
<i>Klebsiella ozaenae</i>	0	0	0	0	0	2	3	2	0	0	0	0	0	1	1	1	0	0	0	ND
<i>Klebsiella pneumoniae</i>	0	0	8	19	175	1546	1269	434	232	130	83	62	72	56	450	848	39	0	0	0.5
<i>Klebsiella</i> spp.	0	0	0	0	6	21	25	6	4	4	1	0	1	0	0	0	0	0	0	ND
<i>Klebsiella terrigena</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	ND
<i>Kluyvera ascorbata</i>	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Moraxella catarrhalis</i>	0	0	75	62	287	300	228	39	7	1	0	0	0	0	0	0	0	0	0	ND
<i>Morganella morganii</i>	0	0	0	0	57	124	129	57	29	24	11	15	14	10	38	85	0	0	0	ND
<i>Morganella</i> spp.	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Pantoea agglomerans</i>	0	0	0	0	2	4	4	2	3	0	0	0	0	0	1	0	0	0	0	ND
<i>Pantoea</i> spp.	0	0	0	0	2	4	1	2	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	0	1	17	202	301	76	44	21	10	9	0	5	34	13	0	0	0	0.5
<i>Proteus penneri</i>	0	0	0	0	0	0	1	1	1	2	1	0	0	1	0	0	0	0	0	ND
<i>Proteus</i> spp.	0	0	0	0	0	1	5	0	1	2		0	0	0	0	0	0	0	0	ND
<i>Proteus vulgaris</i>	0	0	0	0	0	1	1	5	2	4	3	3	1	5	4	6	0	0	0	ND
<i>Providencia rettgeri</i>	0	0	0	0	4	3	0	1	1	0	0	1	0	0	0	0	0	0	0	ND
<i>Providencia</i> spp.	0	0	0	0	1	0	0	1	0	0	0	0	0	0	2	1	0	0	0	ND
<i>Providencia stuartii</i>	0	0	0	0	0	0	2	1	1	4	4	1	4	4	9	2	0	0	0	ND
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	0	0	1	7	13	32	92	167	301	36	0	0	0	64
<i>Raoultella planticola</i>	0	0	0	0	0	1	1		0	0	0	0	1	0	2		0	0	0	ND
<i>Salmonella brandenburg</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella enterica</i>	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella enteritidis</i>	0	0	0	0	0	0	3	4	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella heidelberg</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella panama</i>	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella paratyphi</i>	0	0	0	0	0	0	3	5	0	1	0	0	0	0	0	0	0	0	0	ND

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Salmonella schwarzengrund</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella</i> spp.	0	0	0	0	0	4	39	12	3	2	1	0	0	1	0	0	0	0	0	ND
<i>Salmonella</i> spp. Group B	0	0	0	0	0	0	7	3	0	1	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella</i> spp. Group C	0	0	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella</i> spp. Group D	0	0	0	0	0	0	1	4	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella stanley</i>	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella typhi</i>	0	0	0	0	0	6	4	3	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella typhimurium</i>	0	0	0	0	0	1	2	1	1	4	0	0	0	0	0	0	0	0	0	ND
<i>Serratia fonticola</i>	0	0	0	0	1	0	0	0	1		0	0	0	0	0	0	0	0	0	ND
<i>Serratia liquefaciens</i>	0	0	0	0	0	1	1	13	10	7	1		1		1		0	0	0	ND
<i>Serratia marcescens</i>	0	0	0	0	0	0	4	79	401	383	95	34	22	30	68	62	0	0	0	2
<i>Serratia odorifera</i>	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	ND
<i>Serratia plymuthica</i>	0	0	0	0	0	0	0	0	1	0		0	0	0	0	0	0	0	0	ND
<i>Serratia rubidaea</i>	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	ND
<i>Serratia</i> spp.	0	0	0	0	0	0	1	2	6	13	2	1	0	1	4	0	0	0	0	ND
<i>Staphylococcus aureus</i>	0	0	4	3	16	81	1604	12229	4699	4361	1277	6	2	0	0	0	0	0	0	1
<i>Staphylococcus aureus</i> MRSA	0	0	0	0	0	0	5	231	3912	4346	1276	6	2	0	0	0	0	0	0	1
<i>Staphylococcus aureus</i> MSSA	0	0	4	2	16	81	1599	11998	787	15	1	0	0	0	0	0	0	0	0	1
<i>Staphylococcus auricularis</i>	0	0	0	2	3	4	5	3	1	0	1	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus capitis</i>	0	0	1	8	26	42	12	24	21	3	4	1	0	0	0	0	1	0	0	ND
<i>Staphylococcus caprae</i>	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus carnosus</i>	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus chromogenes</i>	0	0	0	0	1	0	0	0	1	2	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus cohnii</i>	0	0	0	0	0	1	2	1	2	4	1	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus epidermidis</i>	0	0	5	6	35	288	163	590	542	92	17	3	0	0	0	0	0	0	0	ND
<i>Staphylococcus haemolyticus</i>	0	0	0	0	1	1	27	31	52	66	160	15	0	0	0	0	0	0	0	ND
<i>Staphylococcus hominis</i>	0	0	0	0	3	13	49	56	111	50	11		0	0	0	0	0	0	0	ND
<i>Staphylococcus intermedius</i>	0	0	0	0	0	2	3	1	1	0	0	0	0	0	0	0	0	0	0	ND

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Staphylococcus kloosii</i>	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus lentus</i>	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus lugdunensis</i>	0	0	1	0	1	4	24	70	5	2	1	2	0	0	0	0	0	0	ND	
<i>Staphylococcus saccharolyticus</i>	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	ND	
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	3	10	40	12	1	0	0	0	0	0	0	0	0	ND	
<i>Staphylococcus schleiferi</i>	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	ND	
<i>Staphylococcus sciuri</i>	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	ND	
<i>Staphylococcus simulans</i>	0	0	0	0	1	2	5	8	4	0	0	0	0	0	0	0	0	0	ND	
<i>Staphylococcus</i> spp. coagulase negative	0	0	5	6	26	251	212	427	417	99	63	5	0	0	0	0	0	0	ND	
<i>Staphylococcus succinus</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	ND	
<i>Staphylococcus warnerii</i>	0	0	0	1	1	26	18	13	22	5	2	0	0	0	0	0	0	0	ND	
<i>Staphylococcus xylosus</i>	0	0	0	0	1	2	3	12	4	0	2	0	0	0	0	0	0	0	ND	
<i>Streptococcus acidominimus</i>	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus agalactiae</i>	2	3	189	2099	373	4	0	0	0	0	0	0	0	0	0	0	0	0	0.06	
<i>Streptococcus alactolyticus</i>	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus anginosus</i>	0	0	50	57	111	17	0	1	2	0	0	0	0	0	0	0	0	0	0.06	
<i>Streptococcus bovis</i>	0	0	50	12	1	0	1	1	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus canis</i>	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus constellatus</i>	1	0	16	27	53	11	1	1	1	0	0	0	0	0	0	0	0	0	0.12	
<i>Streptococcus crista</i>	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus dysgalactiae</i>	0	0	140	8	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0.016	
<i>Streptococcus equi</i>	0	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus equinus</i>	0	0	2	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus equisimilis</i>	0	0	5	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus gallolyticus</i>	0	0	23	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus gordonii</i>	0	0	13	4	6	0	1	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus infantarius</i>	0	0	1	1		0	0	0	0	0	0	0	0	0	0	0	0	0	ND	
<i>Streptococcus intermedius</i>	0	0	11	13	10	0	0	1	2	0	0	0	0	0	0	0	0	0	ND	

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Streptococcus milleri</i>	0	0	7	8	19	6	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus mitis</i>	1	4	65	95	88	49	25	7	20	5	0	3	2	1	0	0	0	0	0	0.12
<i>Streptococcus mutans</i>	0	0	10	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	0	11	35	35	7	4	8	6	1	1	0	0	0	0	0	0	0	0	0.12
<i>Streptococcus parasanguinis</i>	0	0	18	9	12	8	5	0	1	2	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	62	222	3992	812	434	517	1026	445	74	2	3	0	0	0	0	0	0	0	0	0.03
<i>Streptococcus porcinus</i>	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pyogenes</i>	38	140	2044	62	8	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0.03
<i>Streptococcus salivarius</i>	0	1	43	21	21	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0.06
<i>Streptococcus sanguinis</i>	1	2	28	17	23	5	3	1	0	1	0	0	0	0	0	0	0	0	0	0.06
<i>Streptococcus</i> spp. Group C	3	23	229	39	32	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03
<i>Streptococcus</i> spp. Group F	0	0	6	7	28	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0.06
<i>Streptococcus</i> spp. Group G	2	59	515	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03
<i>Streptococcus</i> spp. Viridans Group	3	7	218	227	226	85	41	40	24	10	0	1	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> spp. β -haemolytic	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus suis</i>	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus thermophilus</i>	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus uberis</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus vestibularis</i>	0	0	1	1	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Yersinia enterocolitica</i>	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	ND
<i>Yersinia</i> spp.	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	ND

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. Some combined distributions may include distributions truncated at concentrations below 512 mg/L. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

4. Breakpoints prior to harmonisation (mg/L) S_≤ / R_>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints	No previous breakpoints						
Species-related breakpoints	No previous breakpoints						
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Stenotrophomonas maltophilia</i>							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							
<i>Enterococcus</i> spp.							
Streptococcus groups A,B,C,G							
<i>Streptococcus pneumoniae</i>							
Viridans group streptococci							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Neisseria meningitidis</i>							
Anaerobes, Gram-positive							
<i>Clostridium difficile</i>							
Anaerobes, Gram-negative							
<i>Helicobacter pylori</i>							
<i>Listeria monocytogenes</i>							
<i>Pasteurella multocida</i>							
<i>Campylobacter</i> spp.							
<i>Corynebacterium</i> spp.							

5. Pharmacokinetics

Dosage (mg)	600 mg x 2 (60 min IV infusion) ¹	600 mg x 2 (60 min IV infusion) ² Mean ± SD	600 mg x 2 (60 min IV infusion) ² Mean ± SD	600 mg x 2 (60 min IV infusion) ³ Mean ± SD
C _{max} (mg/L)	22.7 ± 3.67	21.3 ± 4.1	31.8 ± 4.6	31.03 ± 7.50
C _{min} (mg/L)	0.39 ± 0.13			
Total body clearance (L/h)	8.70 ± 1.33	9.61 ± 1.40	5.74 ± 0.80	8.10 ± 1.54
T _{1/2} (h), mean (range)	2.0 ± 0.21	2.7 ± 0.4	3.1 ± 0.4	2.81 ± 0.39
AUC _{0-12h,ss} (mg.h/L)	61.3 ± 9.16	56.3 ± 8.9		65.45 ± 12.46
AUC _∞ (mg.h/L)	62.3 ± 9.50		94.1 ± 13.6	
Fraction unbound (%)	80 ± 6			
Volume of distribution (L/kg)	19.5 ± 2.98			
Comments (Cells are left empty when data are not readily available)	Phase I study in healthy adult volunteers; Steady state (ss) data; n=12	Phase I study in healthy adult volunteers; Steady state (ss) data; n=6	Phase I study in healthy elderly (≥65) volunteers; Single dose data; n=16	Phase I study in healthy adult volunteers; Steady state (ss) data; n=8
References	<ul style="list-style-type: none"> ¹Data on file, AstraZeneca. ²Riccobene T et al. J Clin Pharmacol 2014, [Epub ahead of print 22 Jan]; DOI: 10.1002/jcph.265 ³Riccobene T et al. Antimicrob. Agents Chemother. 2013;57:1496-1504 (in combination with avibactam) 			

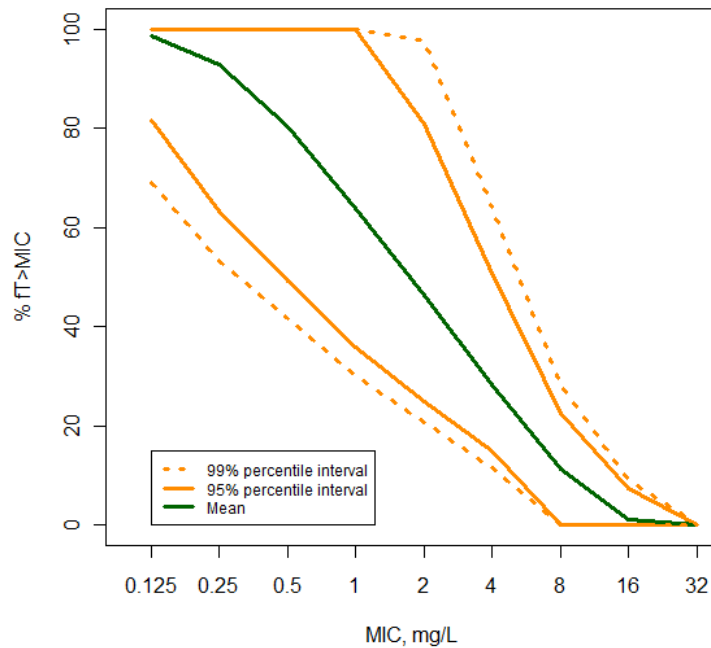
6. Pharmacodynamics

Preclinical data	Murine Thigh Infection Model ^{1,2} and an <i>in vitro</i> model ⁴		
	<i>S. aureus</i> ¹ (N= 4) / <i>S. aureus</i> ³ (N= 26) / <i>S. aureus</i> ⁴ (N= 8)	<i>S. pneumoniae</i> ¹ (N=5)	Enterobacteriaceae ^{2, 6} (N=4)
%T>MIC for bacteriostasis	26 (15-36) 26 ⁵ / 10 / 24.5 ⁵	35 (29-52)	48.5 (30-59)
%T>MIC for 1 log reduction	36 (18-44) 33 ⁵ / 18 / 27.8 ⁵	44 (33-59)	73 (39-89)
%T>MIC for 2 log reduction	51 (23-56) 45 ⁵ / 40 / 27.7 ⁵	51 (36-64)	NC
Clinical Data			
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not available. • The PK/PD index for ceftaroline efficacy is %fT>MIC and its magnitude (PK/PD target) was evaluated in murine thigh and lung infection models^{1,2,3} and an <i>in vitro</i> model⁴. The median (min-max) and mean values of the PK/PD target for <i>S. aureus</i>, and the median (min-max) of the PK/PD targets for <i>S. pneumoniae</i>, and <i>Enterobacteriaceae</i> (<i>E. coli</i> and <i>K. pneumoniae</i>) for bacterial stasis, 1-log₁₀ and 2-log₁₀ kills are calculated and shown below. The group mean for all <i>S. aureus</i> studies for bacterial stasis, 1-log₁₀ and 2-log₁₀ were 20.3%, 26.3%, and 37.6%, respectively. There were no appreciable differences in <i>in vivo</i> or <i>in vitro</i> efficacy (ie, log cfu reduction) of ceftaroline between methicillin-susceptible and methicillin-resistant isolates of <i>S. aureus</i>. • ⁵arithmetic mean values • ⁶Lung value not included in table • NC = Not calculated as 2-log₁₀ kill data were not available for strains <i>E. coli</i> ATCC 1894-1 and <i>K. pneumoniae</i> ATCC 43816 		
References	<ul style="list-style-type: none"> • 1. Andes D and Craig WA, <i>Antimicrob Agents Chemother</i> 2006; 50: 1376-1383 • 2. Li, J, Ambler JE, Sunzel M. P1610, 23rd ECCMID meeting (2013), Berlin, Germany. • 3. Keel RA, Crandon JL, Nicolau DP, <i>Antimicrob Agents Chemother</i> 2011; 55: 4028-4032 • 4. MacGowan AP et al., <i>Antimicrob Agents Chemother</i> 2013; 57: 2451. 		

7. Monte Carlo simulations and PK/PD breakpoints

Probabilities of target attainment (PTA) for ceftaroline 600 mg 1 h IV infusion x 2 in patients with cSSTI and CAP are shown in Figure 1.

Figure 1. Probabilities of target attainment for ceftaroline 600 mg 1 h IV infusion x 2



The PTA was obtained by Monte Carlo simulations using population PK models developed for ceftaroline fosamil and ceftaroline based on data from patients with cSSTI and CAP. A 3-compartment model with zero-order input, a rapid first-order conversion of ceftaroline fosamil to ceftaroline and a dual-phase absorption model with the same absorption rate constants for the intramuscular administration of ceftaroline fosamil best described the plasma ceftaroline fosamil concentration-time data. A 2-compartment model with first-order input (assuming complete conversion of ceftaroline fosamil to ceftaroline) and both first-order and Michaelis-Menten elimination best characterized the plasma ceftaroline concentration-time data. (Van Wart SA, Forrest A, Khariton T, Rubino CM, Bhavnani SM, Riccobene TA, Ambrose PG. Population pharmacokinetics of ceftaroline in patients with complicated skin and skin structure infections or community-acquired pneumonia. *J. Clin. Pharmacol.* 2013; 53: 1155–1167; Jianguo Li, Jane E. Ambler, and Maria Sunzel. Establishment of Non-species Specific Breakpoints of Ceftaroline - Application to *Staphylococcus aureus* and *Enterobacteriaceae*, P1610, 23rd ECCMID 2013, Berlin, Germany).

8. Clinical data

Complicated skin and soft tissue infections

A total of 1396 adults with documented complicated skin and soft tissue infections (cSSTI) were enrolled in two identical randomised, multi-centre, multinational, double blind registration studies comparing ceftaroline (600 mg administered intravenously over 60 minutes every 12 hours) with vancomycin plus aztreonam (1 g vancomycin administered intravenously over 60 minutes followed by 1 g aztreonam administered intravenously over 60 minutes every 12 hours). Patients with deep/extensive cellulites, a major abscess, a wound infection (surgical or traumatic), infected bites, burns or ulcers, or any lower extremity infection in patients with either pre-existing diabetes mellitus or peripheral vascular disease, were eligible for the studies. Treatment duration was 5 to 21 days. Ceftaroline was non-inferior to the comparator agents in infections caused by *S. aureus* (methicillin-susceptible and -resistant strains), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), *E. coli*, *K. pneumoniae* and *M. Morganii*.

Corey GR, et al. *J Antimicrob Chemother* 2010; 65(Suppl.): iv41–iv51.

Wilcox MH, et al. *J Antimicrob Chemother* 2010; 65(Suppl.): iv53–iv65. 2010.

Corey GR, et al. *Clin Infect Dis* 2010; 51: 641–50.

Community-acquired pneumonia

A total of 1240 adults with a diagnosis of community-acquired pneumonia (CAP) were enrolled in two randomized, multi-centre, multinational, double-blind registration studies comparing ceftaroline (600 mg administered intravenously over 60 minutes every 12 hours) with ceftriaxone (1 g ceftriaxone administered intravenously over 30 minutes every 24 hours). The studies were identical except that in one study both treatment groups received 2 doses of oral clarithromycin (500 mg every 12 hours) as adjunctive therapy starting on day 1. No adjunctive macrolide therapy was used in the second study. Patients with new or progressive pulmonary infiltrate(s) on chest radiography with clinical signs and symptoms consistent with CAP with the need for hospitalisation and intravenous therapy were enrolled in the studies. Treatment duration was 5 to 7 days. Ceftaroline was non-inferior to ceftriaxone in CAP caused by *S. pneumoniae*, *S. aureus* (methicillin-susceptible strains only), *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae* and *E. coli*.

File TM et al. *Clin Infect Dis* 2010; 51: 1395–1405.

9. Clinical breakpoints

PK/PD breakpoints	<p>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. PK/PD breakpoints have been termed “non-species-related breakpoints” but this has led to confusion and it has become clear that PK/PD breakpoints for some agents may differ for different organisms.</p> <p>A $fT > MIC$ target of 40% with a >99% target attainment rate and a target of 50% with a >95% target attainment rate for Enterobacteriaceae results in a susceptible breakpoint of 0.5 mg/l for a dosage of ceftaroline 600 mg 1 h IV infusion every 12 h. The $fT > MIC$ target is lower for <i>S. aureus</i> but EUCAST has taken the cautious approach in definition of the PK/PD breakpoint. There is currently no higher dose so the resistant breakpoint is >0.5 mg/l.</p>
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	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
Species-related breakpoints	Enterobacteriaceae	0.5	0.5	
	<i>Pseudomonas</i> spp.	-	-	These organisms were considered poor targets for ceftaroline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	<i>Stenotrophomonas maltophilia</i>	-	-	
	<i>Acinetobacter</i> spp.	-	-	
	<i>Staphylococcus</i> spp.	1	1	The breakpoints were increased to S ≤1 / R >1 mg/l in recognition of the slightly higher PK/PD breakpoint that might be appropriate for <i>S. aureus</i> and clinical data supporting good outcome in treatment of infections caused by MRSA with MICs up to 1 mg/L.
	<i>Enterococcus</i> spp.	-	-	These organisms were considered poor targets for ceftaroline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	Streptococcus groups A,B,C,G	Note ¹	Note ¹	1. Susceptibility is inferred from susceptibility to benzylpenicillin.
	<i>Streptococcus pneumoniae</i>	0.25	0.25	The breakpoints have been reduced as clinical outcome is unknown in patients infected with strains with MICs greater than 0.25 mg/l.
	Viridans group streptococci	-	-	Breakpoints were not set because these organisms are not included in the marketing authorisation for ceftaroline.
	<i>Haemophilus influenzae</i>	0.03	0.03	The breakpoints are essentially epidemiological cut-off values since clinical outcome is unknown in patients infected with strains with MICs greater than 0.03 mg/l.
	<i>Moraxella catarrhalis</i>	-	-	These organisms were considered poor targets for ceftaroline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	<i>Neisseria gonorrhoeae</i>	-	-	
	<i>Neisseria meningitidis</i>	-	-	
Anaerobes, Gram-positive	-	-		
<i>Clostridium difficile</i>	-	-		

	Anaerobes, Gram-negative	-	-	
	<i>Helicobacter pylori</i>	-	-	
	<i>Listeria monocytogenes</i>	-	-	
	<i>Pasteurella multocida</i>	-	-	
	<i>Campylobacter</i> spp.	-	-	
	<i>Corynebacterium</i> spp.	-	-	
Clinical qualifications	<p>Breakpoints apply only to complicated skin and soft tissue infections and community-acquired pneumonia.</p> <p>For community-acquired pneumonia, breakpoints for <i>S. aureus</i> relate to methicillin-susceptible isolates only.</p>			
Dosage	Breakpoints apply to ceftaroline 600 mg 1 h IV infusion every 12 h.			
Additional comment				

10. Exceptions noted for individual national committees
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None
