Ofloxacin	Rationale for the EUCAST clinical breakpoints, version 1.4	22nd August 2007

Introduction

The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1960s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against Gram-negative pathogens. The newer fluoroquinolone agents have enhanced intrinsic activity against Gram-positive organisms and anaerobes and improved pharmacokinetic characteristics in comparison with preceding derivatives. Emergence of resistance is mainly due to mutations in the QRDR region where phenotypic resistance arises as a result of stepwise mutations. Microorganisms with one mutation may exhibit elevated fluoroquinolone MICs that are sometimes difficult to distinguish from wild-type MIC distributions. Other low level resistance mechanisms include increased activity of efflux pumps, Qnr proteins (capable of protecting DNA gyrase from quinolones) and inactivating enzymes.

EUCAST has defined clinical breakpoints for the fluoroquinolones ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), norfloxacin (NOR) and ofloxacin (OFL). They are with few exceptions available in all European countries. Older fluoroquinolones which are available only in few countries or in topical preparations have not been addressed.

Some fluoroquinolones are available for both oral and intravenous therapy while others are available for oral therapy only. This is reflected in the breakpoints.

Ofloxacin is used to treat simple and complicated urinary tract infections, chronic prostatitis, uncomplicated genital infections, respiratory tract infections, enteric fever and gastroenterits infections and ocular infections.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	400 x 1 oral 400 x 1 iv	200 x 2 oral 200 x 2 iv	200 x 2	200 x 2 oral	200 x 2 oral 200 x 2 iv	200 x 2 oral
Maximum dose schedule (mg)	400 x 2 oral 400 x 2 iv	400 x 2 oral 300 x 2 iv	400 x 2	400 x 2 oral	300 x 3 oral 400 x 3 iv	400 x 2 oral
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv

2. MIC distributions and epidemiological cut-off (ECOFF) values

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Acinetobacter baumannii	0	0	0	0	2	4	67	43	21	6	12	2	5	0	0	0	0	0	0	1
Acinetobacter spp	0	0	0	1	2	6	47	61	40	21	6	1	10	13	13	30	0	0	0	1
Aeromonas hydrophila	0	0	2	16	6	1	0	0	0	0	0	0	1	0	0	0	0	0	0	IE
Burkholderia cepacia	0	0	0	0	0	0	0	1	2	1	7	2	1	2	0	0	0	0	0	IE
Campylobacter jejuni	0	0	0	0	0	0	1	19	5	7	2	0	1	3	1	4	0	0	0	IE
Citrobacter spp	0	0	0	0	8	65	59	17	16	4	4	1	7	1	1	0	0	0	0	0.25
Enterobacter spp	0	0	0	1	34	266	321	49	36	37	16	18	3	1	1	0	0	0	0	0.25
Enterococcus faecalis	0	0	0	0	0	0	0	0	4	161	341	36	4	7	8	84	0	0	0	4.0
Enterococcus faecium	0	0	0	0	0	0	0	0	1	3	4	9	3	6	15	22	0	0	0	IE
Escherichia coli	0	0	0	3	196	1159	397	47	49	61	19	5	93	8	10	3	0	0	0	0.25
Haemophilus influenzae	0	0	3	258	2994	336	15	3	0	0	1	0	0	0	0	0	0	0	0	0.064
Helicobacter pylori	0	0	0	0	0	0	0	7	13	1	0	0	0	0	0	0	0	0	0	IE
Klebsiella pneumoniae	0	0	0	0	11	81	119	14	5	8	10	1	4	0	0	0	0	0	0	0.25
Klebsiella spp	0	0	0	0	14	169	331	60	23	46	32	6	12	2	0	2	0	0	0	0.25
Legionella pneumophila	0	0	3	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
Listeria monocytogenes	0	0	0	0	0	0	0	0	0	3	57	7	0	0	0	0	0	0	0	IE
Moraxella catarrhalis	0	0	0	0	6	21	235	4	0	0	0	0	0	0	0	0	0	0	0	0.25
Morganella morganii	0	0	0	3	11	54	83	16	6	0	0	0	0	0	0	6	0	0	0	0.5
Neisseria gonorrhoeae	0	0	22	58	16	15	2	0	2	5	0	0	0	0	0	0	0	0	0	0.064
Plesiomonas shigelloides	0	0	0	17	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
Proteus mirabilis	0	0	0	0	1	83	617	242	31	10	20	10	6	6	6	10	0	0	0	0.5
Proteus vulgaris	0	0	0	0	6	114	77	12	0	0	0	1	0	0	0	0	0	0	0	0.25
Providencia spp	0	0	0	1	6	33	34	48	45	20	6	4	2	3	5	1	0	0	0	IE
Pseudomonas aeruginosa	0	0	0	0	3	5	26	89	513	434	230	146	111	36	30	102	0	0	0	2.0
Salmonella spp	0	0	0	0	0	0	67	41	0	2	1	0	0	0	0	0	0	0	0	0.25
Serratia spp	0	0	0	0	1	8	15	45	31	9	3	8	3	0	1	0	0	0	0	IE
Shigella spp	0	0	0	0	6	64	3	0	0	0	0	0	0	0	1	0	0	0	0	IE

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Staphylococcus aureus	0	0	0	0	3	5	150	1225	744	90	20	33	284	176	60	38	0	0	0	1
Staphylococcus coagulase negative	0	0	0	0	0	1	11	338	201	42	4	17	46	69	25	16	0	0	0	1
Staphylococcus epidermidis	0	0	0	0	1	1	3	110	144	6	4	22	285	0	0	0	0	0	0	1
Staphylococcus saprophyticus	0	0	0	0	0	0	0	0	0	17	1	0	0	0	0	0	0	0	0	IE
Stenotrophomonas maltophilia	0	0	0	0	0	0	1	0	13	14	10	4	2	0	0	0	0	0	0	IE
Streptococcus agalactiae	0	0	0	0	0	0	0	0	2	86	81	6	0	0	0	0	0	0	0	4.0
Streptococcus group C	0	0	0	0	0	0	0	0	0	48	14	0	0	0	0	0	0	0	0	IE
Streptococcus group G	0	0	0	0	0	0	0	0	3	50	19	1	0	0	0	0	0	0	0	IE
Streptococcus pneumoniae	0	0	0	0	0	0	0	10	71	859	3268	190	1	7	6	0	0	0	0	4
Streptococcus pyogenes	0	0	0	0	0	0	0	0	17	154	104	14	0	0	0	0	0	0	0	4
Streptococcus viridans group	0	0	0	0	0	0	0	0	1	21	76	19	3	1	0	1	0	0	0	IE
Yersinia enterocolitica	0	0	0	0	0	8	33	1	0	1	0	0	0	0	0	0	0	0	0	IE

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. When there is insufficient evidence (IE) no epidemiological cut-off has been determined.

3. Breakpoints prior to harmonisation (mg/L) S≤/R>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI[1]
General breakpoints							
		1/4	1/4	1/2	0.5/2	1/2	
Species related breakpoints							
Enterobacteriaceae	2/2				0.5/2	0.25/1	2/4 (U)
Pseudomonas spp	2/8				excluded	excluded	2/4 (U)
Acinetobacter spp.							
Staphylococcus spp.	2/2				0.12/2	0.25/2	2/4
Streptococcus spp.	2/2	excluded			0.25/2	excluded	2/4
Streptococcus pneumoniae	2/2	excluded			0.25/2	0.25/2	2/4
Enterococcus spp.	excluded	excluded			0.25/4	0.25/2	
Haemophilus, Moraxella spp.	2/2				excluded	0.25/0.5	2/-
Corynebacteria							
Neisseria meningitidis	excluded				0.12/0.25	excluded	
Neisseria gonorrhoeae	nalidixic acid				0.12/0.25	0.06/0.25	0.25/1
Pasteurella multocida							
Anaerobes, Gram-positive	excluded				excluded	excluded	
Anaerobes, Gram-negative	excluded				excluded	excluded	
Campylobacter spp.							
Helicobacter pylori							
Bacillus anthracis							

excluded = considered inappropriate to set a breakpoint
[1]CLSI breakpoints converted to EUCAST terminology

4. Pharmacokinetics

Dosage (mg)	400 x 1 oral	400 x 1 iv	600 mg x 1 oral	
Cmax (mg/L)				
Cmin (mg/L)				
Total body clearance (L/h)		12		
T ½ (h), mean (range)	5	5.6	7.0	
AUC24h (mg.h/L)	28	32.6 (0 -12 h)		
Fraction unbound (%)	75	75	75	
Volume of distribution (L)	102	99		
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Lockley et al., J Antimicrob Chemother 1984; 14: 647 • Klepser et al., Antimicrob Agents Chemother 1995; 39: 2503 • Zlotos et al., J Pharmac Sci 1998; 87: 215 • Lode H et al., Antimicrob Agents Chemother 1987; 31: 1338			

5. Pharmacodynamics

	Enterobacteriaceae	*Pseudomonas aeruginosa*	*Streptococcus pneumoniae*	
*f*AUC/MIC for bacteriostasis	30 - 40		30 - 40	
*f*AUC/MIC for 2 log reduction	80 -100			
f/AUC/MIC from clinical data	80 -100	100	30 - 40	
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Ambrose et al., Antimicrob Agents Chemother 2001 45:2793 • Ambrose et al. Infect Dis Clin North Am 2003 17:529			

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilties of Target Attainment (PTA) for 500 mg x 2 oral are shown in Figure 1.

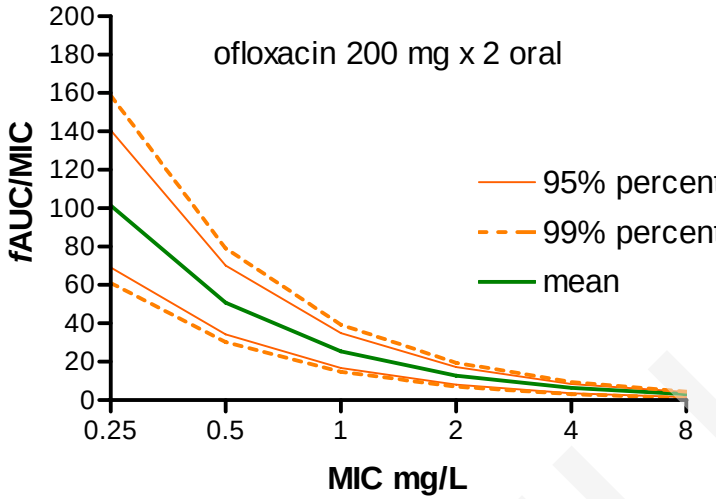

Figure 1. Probabilities of Target Attainment for Ofloxacin 200 mg x 2 oral.

The following pharmacokinetic parameters were used to obtain the PTA:
Volume of Distribution (Vd): 99L, CV 15%
Clearance (Cl): 12 L/h, CV 15%
Fraction unbound (Fu): 75%
Absorption rate coefficient (Ka): $2h^{-1}$
Bioavailability (F): 1

Results of simulations for the 200 mg x 2 iv dose do not markedly influence conclusions.

7. Clinical data

Extensive clinical data are available showing the relationship between exposure (AUC/MIC) and effect of quinolones, in particular for pneumococci. These data are summarized in section 5.

8. Clinical breakpoints

Non-species-related breakpoints	Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Breakpoints are S≤0.5 mg/L, R>1 mg/L. These render wild type Enterobacteriaceae, *Staphylococcus* spp.*, Haemophilus influenzae, Moraxella catarrhalis* and *Neisseria gonorrhoeae* susceptible.
Species-related breakpoints	The wild type MIC distributions of most Enterobacteriaceae, including salmonellae, exhibit MIC values <0.125 mg/L. A breakpoint of ≤0.5 mg/L allows low-level quinolone resistant Enterobacteriaceae to be categorized as susceptible to ofloxacin. For *Staphylococcus* spp. the S/I breakpoint was increased to 1 mg/L to avoid dividing wild type MIC distributions. Therefore these breakpoints relate to the higher dosages of ofloxacin. For *S. pneumoniae* more than 95% of wild type strains have MICs of 0.5, 1, 2 or 4 mg/L, which means that neither of the non-species-related values can be used as a breakpoint without causing major splitting of the wild type distribution and thus problems with the reproducibility of S, I and R categorisation. A breakpoint of S≤0.125 mg/L categorises wild type *S. pneumoniae* as intermediate to ofloxacin and a breakpoint of R>4 mg/L categorises non-wild type *S. pneumoniae* as resistant to ciprofloxacin. Both consequences were intended. The breakpoints allow some fluoroquinolone resistant *Haemophilus influenzae* and *Moraxella catarrhalis* to be categorized as susceptible to ofloxacin. Laboratories may screen these species for fluoroquinolone resistance by testing with a nalidixic acid 30 µg disc.
Species without breakpoints	*Pseudomonas* spp.*, Acinetobacter* spp.*, Streptococcus* spp.*, Enterococcus* spp.*,* and anaerobic bacteria were considered poor targets for ofloxacin therapy and for that reason did not receive breakpoints. *Neisseria meningitidis* was considered a possible target for ofloxacin prophylaxis but at present the evidence was considered insufficient to set breakpoints.
Clinical qualifications	
Dosage	Breakpoints apply to an oral dose of 200 mg x 2 to 400 mg x 2 and an intravenous dose of 200 mg x 2 to 400 mg x 2.
Additional comment	

9. Ofloxacin - EUCAST clinical MIC breakpoints

These can be found at **www.eucast.org**

10. Exceptions noted for individual national committees

None