Moxifloxacin	Rationale for the EUCAST clinical breakpoints, version 2.3	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.

Moxifloxacin is used to treat acute exacerbations of chronic bronchitis, community-acquired pneumonia and acute sinusitis. It is more potent than ciprofloxacin against streptococci including *Streptococcus pneumoniae* but is less potent against *Pseudomonas aeruginosa*.

1. Dosage

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

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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	5	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0.25
Acinetobacter spp	0	0	0	3	14	14	9	2	0	0	0	0	0	0	0	0	0	0	0	0.25
Bacteroides fragilis	0	0	0	0	0	1	13	137	466	156	61	32	49	13	3	0	0	0	0	2
Citrobacter spp	0	0	0	1	66	184	130	59	0	0	0	0	0	0	0	0	0	0	0	0.25
Enterobacter species	0	0	0	6	338	916	511	120	0	0	0	0	0	0	0	0	0	0	0	0.25
Enterococcus faecalis	0	0	0	0	0	12	90	741	213	36	18	0	0	0	0	0	0	0	0	1
Enterococcus faecium	0	0	0	0	0	4	9	16	18	58	77	0	0	0	0	0	0	0	0	1
Escherichia coli	0	0	4	51	126	215	53	9	0	0	0	0	0	0	0	0	0	0	0	0.25
Haemophilus influenzae	0	42	471	4870	2560	339	46	0	0	0	0	0	0	0	0	0	0	0	0	0.125
Haemophilus parainfluenzae	0	0	12	48	75	129	112	86	0	0	0	0	0	0	0	0	0	0	0	IE
Klebsiella pneumoniae	0	0	0	0	173	823	719	143	0	0	0	0	0	0	0	0	0	0	0	0.25
Klebsiella spp	0	0	0	0	162	548	412	144	0	0	0	0	0	0	0	0	0	0	0	0.25
Listeria monocytogenes	0	0	0	0	0	0	0	1	24	0	0	0	0	0	0	0	0	0	0	IE
Moraxella catarrhalis	0	0	1	27	563	1720	469	76	0	0	0	0	0	0	0	0	0	0	0	0.25
Morganella morganii	0	0	0	2	15	95	248	114	14	0	0	0	0	0	0	0	0	0	0	0.5
Neisseria gonorrhoeae	1	12	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.032
Neisseria meningitidis	0	0	10	20	18	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.064
Proteus mirabilis	0	0	0	0	10	73	331	1033	453	68	0	0	0	0	0	0	0	0	0	1
Proteus vulgaris	0	0	0	0	13	46	203	202	51	16	0	0	0	0	0	0	0	0	0	1
Providencia spp	0	0	0	0	0	6	24	15	4	0	0	0	0	0	0	0	0	0	0	IE
Pseudomonas aeruginosa	0	0	0	0	16	17	84	215	678	1540	742	430	0	0	0	0	0	0	0	4
Salmonella spp	0	0	0	0	0	11	15	1	0	0	0	0	0	0	0	0	0	0	0	IE
Serratia marcescens	0	0	0	0	0	6	10	44	27	4	7	4	0	2	0	0	0	0	0	1
Serratia spp	0	0	0	0	0	6	11	22	37	4	5	9	3	3	1	0	0	0	0	1
Staphylococcus aureus	0	0	0	57	598	560	232	43	0	0	0	0	0	0	0	0	0	0	0	0.25
Staphylococcus coagulase-negative	0	0	0	0	4	64	47	8	0	0	0	0	0	0	0	0	0	0	0	0.25
Staphylococcus epidermidis	0	0	0	0	268	817	463	87	0	0	0	0	0	0	0	0	0	0	0	0.25
Staphylococcus saprophyticus	0	0	0	0	1	0	42	5	0	0	0	0	0	0	0	0	0	0	0	0.25
Stenotrophomonas maltophilia	0	0	0	1	15	36	131	153	114	85	47	26	17	1	0	0	0	0	0	IE
Streptococcus agalactiae	0	0	0	0	2	3	61	148	18	0	0	0	0	0	0	0	0	0	0	0.5
Streptococcus pneumoniae	0	0	0	12	147	2772	12832	2730	187	0	0	0	0	0	0	0	0	0	0	0.5
Streptococcus pyogenes	0	0	0	0	1	42	468	176	43	0	0	0	0	0	0	0	0	0	0	0.5
Streptococcus viridans group	0	0	0	0	1	3	20	18	6	0	0	0	0	0	0	0	0	0	0	0.5

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							
		1/2		1/2		1/2	
Species related breakpoints							
Enterobacteriaceae	1/1					excluded	
Pseudomonas spp.	1/4					excluded	
Acinetobacter spp.	1/1					excluded	
Staphylococcus spp.	1/2					0.25/0.5	
Streptococcus spp.	1/2					1/2	
Streptococcus pneumoniae	1/2					1/2	1/2
Enterococcus spp	excluded					excluded	
Haemophilus, Moraxella spp.	1/2					0.25/0.5	1/-
Corynebacteria							
Neisseria meningitidis							
Neisseria gonorrhoeae							
Pasteurella multocida							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
Campylobacter spp.							
Helicobacter pylori							
Bacillus anthracis							

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

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4. Pharmacokinetics

Dosage	400 mg iv	400 mg oral		
Cmax (mg/L)	3.6 - 5.1	2.5 - 5.0		
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	8.2 - 15.4	8.3 - 15.6		
AUC24h (mg.h/L)	34.6 - 45.3	29.8 - 45.5		
Fraction unbound (%)	60	60		
Volume of distribution (L)	2.05 (L/kg)	3.08 (L/kg)		
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Wise R et al., Antimicrob. Agents Chemother. 1999; 43: 1508 • Stass H et al. J Antimicrob Chemother 1998; 43 Suppl.B: 83			

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5. Pharmacodynamics

	Streptococcus pneumoniae	Enterobacteriaceae	*Staphylococcus aureus*	
*f*AUC/MIC for bacteriostasis	30-40	80-100	25 - 30	
*f*AUC/MIC for 2 log reduction			60	
f/AUC/MIC from clinical data	30-40	80-100		
Comments	• Data are from non-neutropenic subjects, unless specified otherwise • Exposure response relationships for quinolones are considered to be comparable within the group • Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Ambrose PG, et al. Infect Dis Clin North Am 2003 17:529. • Ambrose PG, et al. Antimicrob Agents Chemother 2001 45:2793. • McGowan A, et al. J Antimicrob Chemother 1999 44:761			

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6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of Target Attainment for 400 mg x 1 oral are shown in Figure 1.

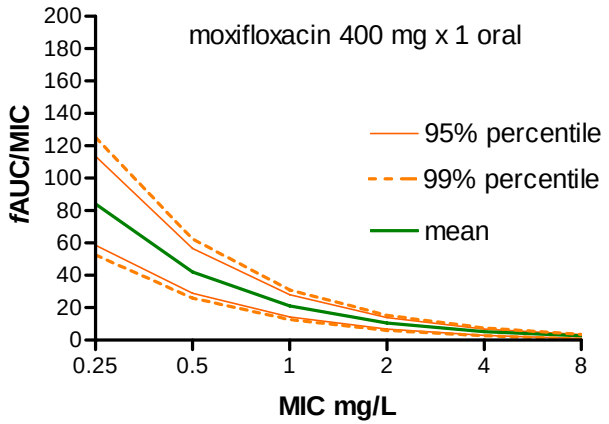

Figure 1. Probabilities of Target Attainment for moxifloxacin 400 mg x 1 oral.

The following pharmacokinetic parameters were used to obtain the PTA:
Volume of Distribution (Vd) 140L, CV 16%
Clearance (Cl) 11.5 L/h, CV 13%
Fraction unbound (Fu) 60%
Absorption rate coefficient (Ka) $2h^{-1}$
Bioavailability (F) 1.0

Results of simulations for the 400 mg IV dose do not markedly influence conclusions.

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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.

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8. Clinical breakpoints	
Non-species-related breakpoints	These have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. The column of non-species related breakpoints is for use only for species not included in the table. Breakpoints are S≤0.5 mg/L, R>1 mg/L. These render wild type Enterobacteriaceae, staphylococci, streptococci A, B, C and G, *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella* spp. susceptible.
Species-related breakpoints	For *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* the R breakpoint was set at R>0.5 mg/L (rather than 1 mg/L) since there were no data to support an intermediate category.
Species without breakpoints	*Pseudomonas* spp., *Acinetobacter* spp, *Enterococcus* spp. and anaerobic bacteria were considered poor targets for moxifloxacin therapy and for that reason did not receive breakpoints. *Neisseria* spp. and anaerobic bacteria were considered possible targets for moxifloxacin therapy but at present the evidence was considered insufficient to set breakpoints.
Dosage	Breakpoints apply to an oral and iv dose of 400 mg x 1.
Clinical qualifications	
Additional comment	

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9. Moxifloxacin - EUCAST clinical MIC breakpoints

These can be found at **http://www.eucast.org**

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10. Exceptions noted for individual national committees
None

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