

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.

Norfloxacin is used to treat uncomplicated urinary tract infections.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	400 x 2	400 x 2	400 x 2	400 x 2		400 x 2
Maximum dose schedule (mg)	400 x 2		400 x 2	400 x 2		400 x 2
Available formulations	oral	oral	oral	oral		Oral

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	
<i>Acinetobacter</i> spp	0	0	0	0	0	1	1	1	3	12	11	6	2	1	0	0	0	0	0	0	IE
<i>Enterobacter</i> spp	0	0	0	0	2	27	7	1	0	0	0	2	0	1	0	1	1	0	0	0	0.25
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	2	6	120	91	5	9	10	15	0	0	0	0	8
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	0	1	1	2	3	3	4	4	0	0	0	0	IE
<i>Escherichia coli</i>	0	0	0	0	2	29	12	0	4	1	0	0	0	0	1	1	0	0	0	0	0.25
<i>Klebsiella</i> spp	0	0	0	0	1	14	7	1	3	2	1	0	0	0	0	0	0	0	0	0	0.25
<i>Listeria monocytogenes</i>	0	0	0	0	0	0	0	0	0	0	0	11	13	1	0	0	0	0	0	0	0.25
<i>Proteus mirabilis</i>	0	0	0	0	0	16	6	2	1	0	0	0	0	0	0	0	0	0	0	0	0.25
<i>Providencia</i> spp	0	0	0	0	5	33	7	2	1	0	0	1	0	0	0	0	0	0	0	0	0.25
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	6	49	139	38	17	8	0	0	0	1	0	0	0	0	2
<i>Staphylococcus aureus</i>	0	0	0	0	0	0	0	3	44	140	49	4	1	5	6	20	0	0	0	0	4
<i>Staphylococcus coagulase negative</i>	0	0	0	0	0	0	0	2	10	22	5	1	0	1	0	0	0	0	0	0	4
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	0	0	0	10	9	0	0	0	0	0	0	0	0	IE
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	0	0	0	0	5	13	8	4	3	0	0	0	0	IE
<i>Streptococcus agalactiae</i>	0	0	0	0	0	0	0	0	0	0	0	5	14	0	0	0	0	0	0	0	IE
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	0	0	0	0	9	57	287	299	47	2	0	0	0	0	0	16
<i>Streptococcus viridans</i>	0	0	0	0	0	0	0	0	0	0	1	4	5	14	3	1	2	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							
		1/2	1/2	1/2		1/4	
Species related breakpoints							
Enterobacteriaceae	4/4 (U)					0.5/1	4/8 (U)
<i>Pseudomonas</i> spp.						excluded	4/8 (U)
<i>Staphylococcus</i> spp.						0.5/4	4/8 (U)
<i>Enterococcus</i> spp.	4/4 (U)					0.5/4	4/8 (U)

excluded = considered inappropriate to set a breakpoint

U = urinary tract infections only

¹CLSI breakpoints converted to EUCAST terminology

4. Pharmacokinetics

Dosage	400 x 2 oral			
C _{max} (mg/L)	1.45			
C _{min} (mg/L)				
Total body clearance (L/h)				
T _½ (h), mean (range)	3.25			
AUC _{24h} (mg.h/L)				
Fraction unbound (%)	75			
Volume of distribution (L)				
Comments	<ul style="list-style-type: none">Two values are given where references differ. Cells are left empty when data are not readily available.			
References	<ul style="list-style-type: none">Wise et al, J Antimicrob Chemother 1984 ; 14C: 25Wise, J Antimicrob Chemother 1984; 13B: 59Naber et al, Antimicrob Agents Chemother 1998; 42:1659Zlotos et al J Pharmac Sci 1998; 87: 215			

5. Pharmacodynamics

fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comment	• No data available			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

There are not enough pharmacodynamic data available to justify Monte Carlo simulations. The Pk/Pd target is unknown.

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7. Clinical data

Norfloxacin has been shown to be efficacious in treatment of uncomplicated urinary tract infections caused by Enterobacteriaceae. There are insufficient data on infections caused by *Pseudomonas* spp and *Acinetobacter* spp.

8. Clinical breakpoints

Non-species-related breakpoints	Because Pk/Pd data are unavailable, no non-species related breakpoints are given.
Species-related breakpoints	Breakpoints are S _≤ 0.5 mg/L, R _{>} 1 mg/L. These breakpoints render wild type Enterobacteriaceae susceptible.
Species without breakpoints	<p><i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>, <i>Neisseria meningitidis</i> and anaerobic bacteria are considered poor targets for norfloxacin therapy and for that reason did not receive breakpoints.</p> <p><i>Neisseria gonorrhoeae</i> is considered a possible target for norfloxacin therapy but at present the evidence is considered insufficient to set breakpoints.</p>
Clinical qualifications	Norfloxacin breakpoints relate to the use of norfloxacin in urinary tract infections.
Dosage	Breakpoints apply to an oral dose of 400 mg x 2.
Additional comment	

9. Norfloxacin - EUCAST clinical MIC breakpoints

For quinolone breakpoints – see www.eucast.org

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10. Exceptions noted for individual national committees
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None

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