

## Levofloxacin: Rationale for EUCAST Clinical Breakpoints

<b>Current version</b>	<b>2.0</b>	<b>1 January 2021</b>
Previous version	1.5	22 August 2007

### 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.

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. Levofloxacin Rationale Document, version 2.0, 2021. <http://www.eucast.org/rd>."

## 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.

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

Levofloxacin breakpoints underwent revision in 2016.

## 1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	0.5 g x 1 oral 0.5 g x 1 iv	0.5 g x 1 oral	0.5 g x 1	0.5 g x 1 oral 0.5 g x 1 iv	-	0.5 g x 1
Maximum dose schedule	0.5 g x 1 oral 0.5 g x 2 iv	0.5 g x 2 oral	0.5 g x 1	0.5 g x 2 oral 0.5 g x 2 iv	-	0.5 g x 2
Available formulations	oral, iv	oral	oral/iv	oral, iv	-	oral, iv

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

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

## 3. Breakpoints prior to harmonisation (mg/L)

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI <sup>1</sup>
<b>General breakpoints</b>		1/4	0.5/4			2/2	
<b>Species related breakpoints</b>							
<i>Enterobacterales</i>	2/2					0.25/1	2/4
<i>Pseudomonas</i> spp.	2/2					2/2	2/4
<i>Stenotrophomonas maltophilia</i>							
<i>Acinetobacter</i> spp.	2/2						2/4
<i>Staphylococcus</i> spp.	2/2					0.06/2	1/2
<i>Enterococcus</i> spp.	Excluded <sup>2</sup>					0.5/2	2/4
Streptococcus groups A,B,C,G	2/2					Excluded <sup>2</sup>	2/4
<i>Streptococcus pneumoniae</i>	2/2	2/4				2/2	2/4
Viridans group streptococci							
<i>Haemophilus influenzae</i>	2/2					025/0.5	2/-
<i>Moraxella catarrhalis</i>	2/2					025/0.5	2/-
<i>Neisseria gonorrhoeae</i>	Nalidixic acid screen						
<i>Neisseria meningitidis</i>	2/2						0.03/0.06

Excluded = considered inappropriate to set a breakpoint, <sup>1</sup>CLSI breakpoints converted to European terminology

<b>4. Pharmacokinetics (PK)</b>						
<b>Dosage</b>	<b>0.5 g x 1 oral and iv</b>	<b>0.75 g x 1 oral &amp; iv</b>	<b>0.5 g x 1 iv (infected patients)*</b>	<b>0.5 g x 1 oral (healthy subjects)*</b>	<b>0.75 g x 1 iv (infected patients)*</b>	<b>0.75 g x 1 oral (healthy subjects)*</b>
C <sub>max</sub> (mg/L)	6.6-8.7	9.5				
C <sub>min</sub> (mg/L)		0.7				
Total body clearance (L/h)	9.3- 9.7		9.27	10.5	7.24	8.58
T <sub>½</sub> (h), mean (range)	8	7.6				
AUC <sub>0-12</sub> (mg.h/L)	48.6-72.5	61.3				
AUC <sub>0-24</sub> (mg.h/L)						
AUC <sub>0-∞</sub> (mg.h/L)						
Fraction unbound (%)	62-76					
Volume of distribution <sub>ss</sub> (L)	102	130				
Comments	<ul style="list-style-type: none"> <li>Pharmacokinetics are based on a single dose</li> </ul>					
References	<ul style="list-style-type: none"> <li>Preston et al., Antimicrob Agents Chemother 1998; 42: 1098</li> <li>Child et al., Antimicrob Agents Chemother 1995; 39: 2749</li> <li>Grant et al. J Clin Pharmacol 2001; 41: 206</li> <li>Sprandel et al., Antimicrob Agents Chemother 2004; 48: 4597</li> <li>Fish et al., Clin Pharmacokinet 1997; 32: 101</li> <li>*USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<a href="https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg">https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg</a>)</li> <li>Drusano et al., J Infect Dis 2004 189:1590-7</li> </ul>					

## 5. Pharmacodynamics (PD)

Index	Neutropenic Mouse Thigh						
	<i>Enterobacterales</i> (n=9)	<i>P. aeruginosa</i> (n=3)	<i>S. aureus</i> (n=7)	<i>S. pneumoniae</i> (n=5)			
<i>f</i> AUC/MIC for bacteriostasis	35.6	34.8	35.8	13.1			
<i>f</i> AUC/MIC for 1-log <sub>10</sub> reduction	67.4	47.3	68.7	21.0			
<i>f</i> AUC/MIC for 2-log <sub>10</sub> reduction	140	65.4	187	34.2			
Clinical <i>f</i> AUC/MIC for efficacy	72		-	33.8			
Comments	The clinical <i>f</i> AUC:MIC ratio of 72 (average <i>f</i> AUC:MIC ratio targets for efficacy of 87.5 and 61 for cirpofloxacin and levofloxacin, respectively) was used for <i>Enterobacterales</i> and <i>P.aeruginosa</i> .						
References	<ul style="list-style-type: none"> <li>USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<a href="https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg">https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg</a>)</li> </ul>						

## 6. Monte Carlo simulations

Monte Carlo simulations were conducted by USCAST using PK in healthy subjects and infected patients and PD parameters listed in Sections 4 and 5 as shown below

Population model from 172 patients with community-acquired infections, urinary, respiratory, and skin and skin-structure infections (Preston et al., Antimicrob Agents Chemother 1998; 42: 1098)

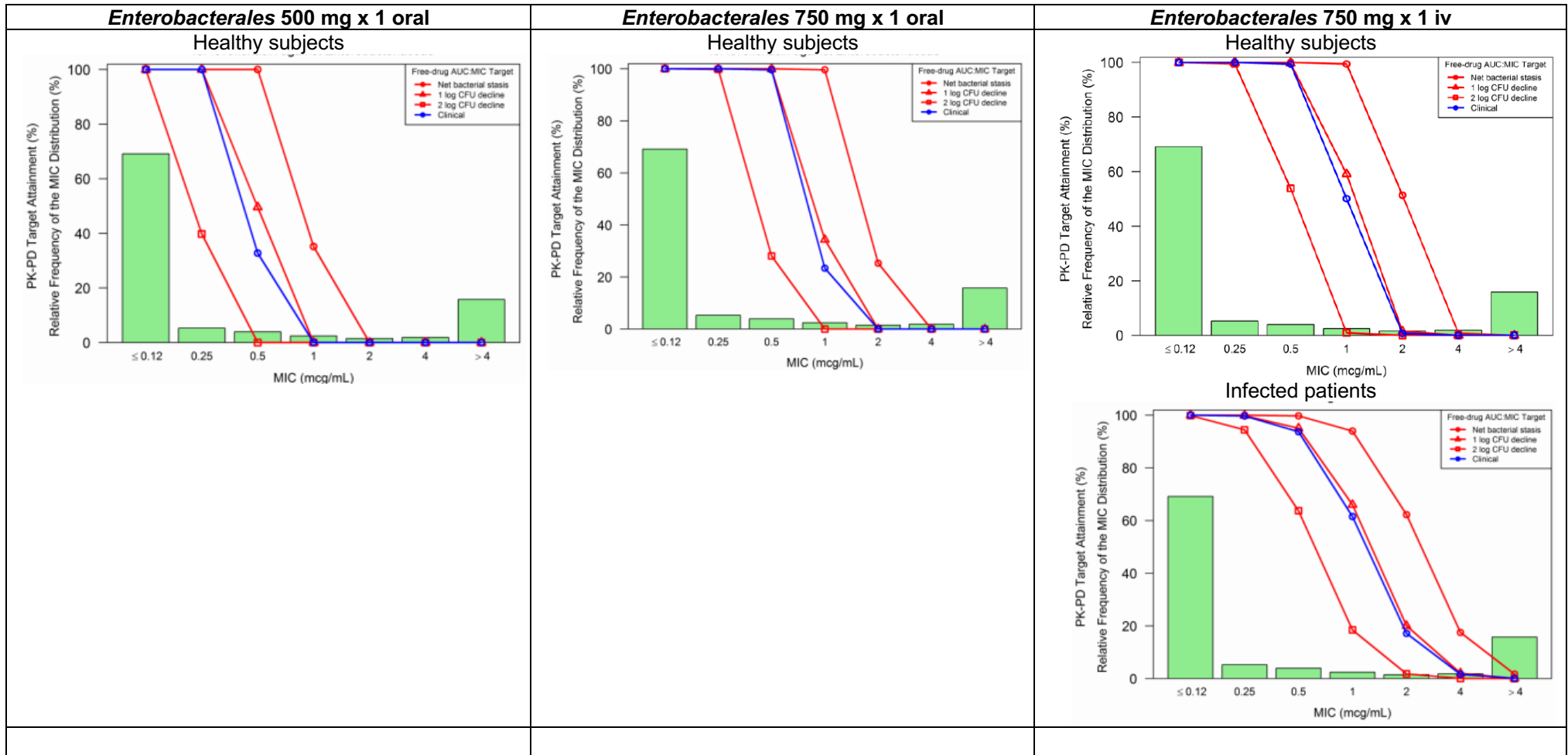
**Table 3-39.** Population PK parameters for levofloxacin (N=272)<sup>a</sup>

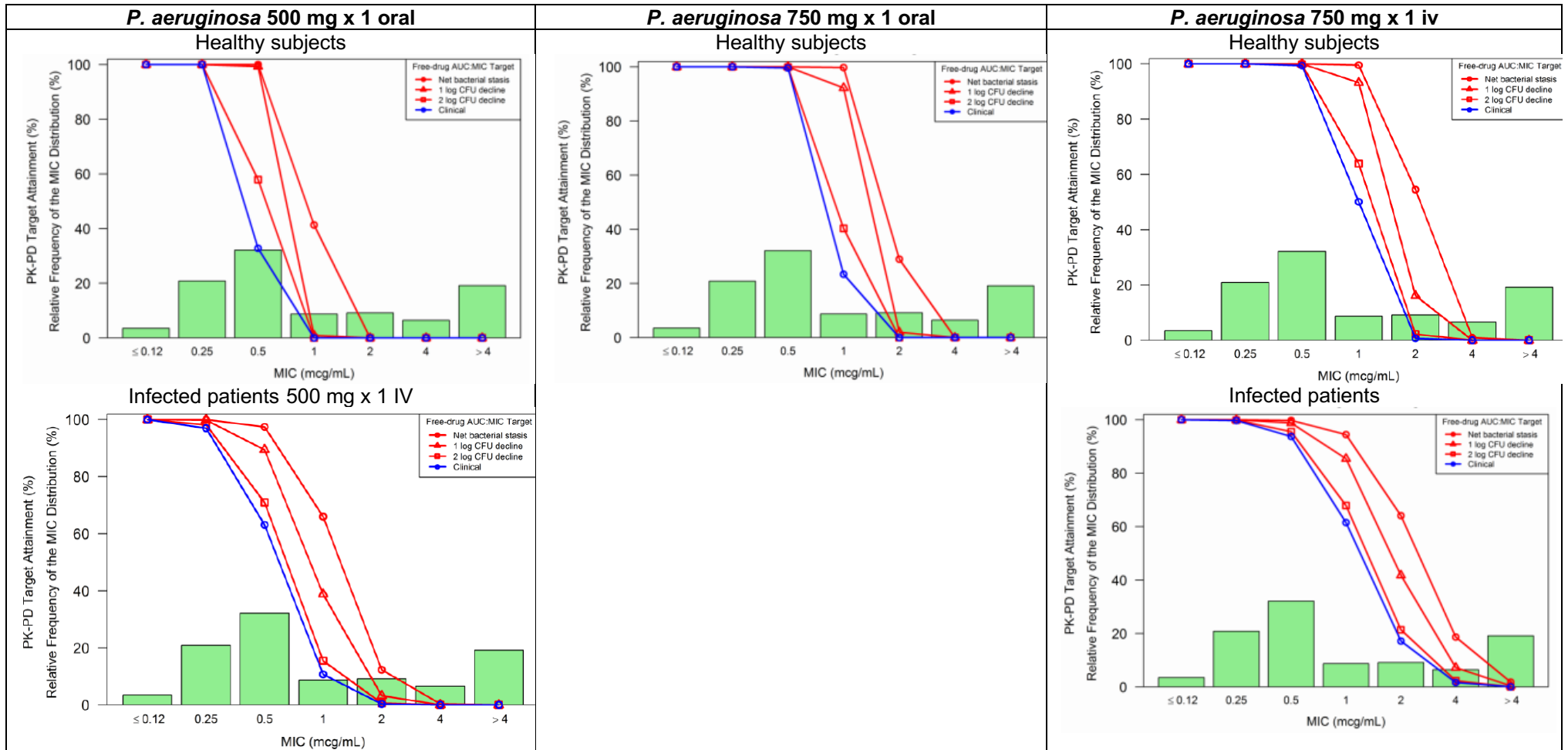
	$K_{CP}$ ( $h^{-1}$ )	$K_{PC}$ ( $h^{-1}$ )	VS (L/kg)	$CL_T$ (L/h)
Mean	0.487	0.647	0.836	9.27
Median	0.384	0.567	0.795	9.01
SD	0.378	0.391	0.429	4.31

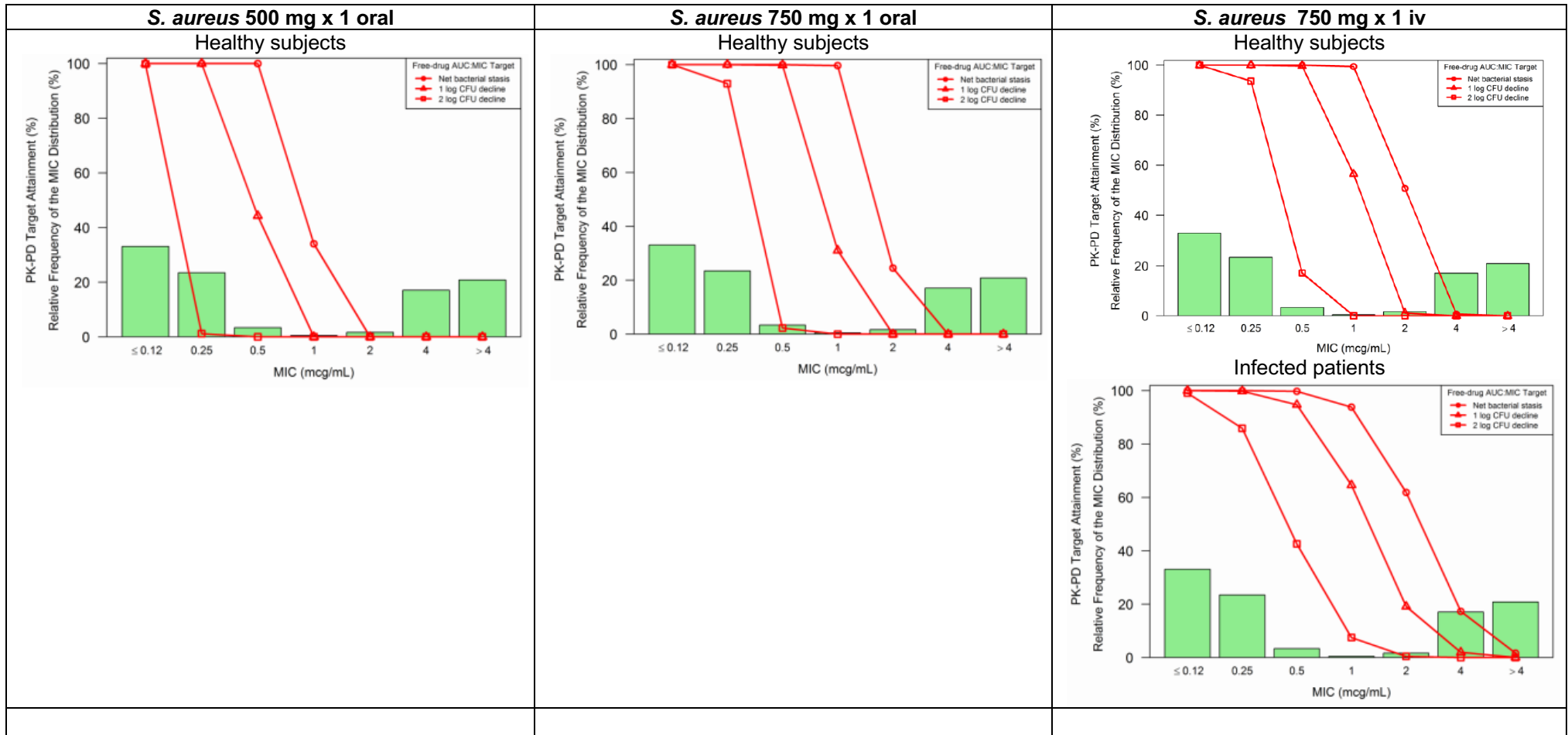
Population model from 58 acutely-ill patients treated with levofloxacin for hospital-acquired pneumonia (Drusano et al., J Infect Dis 2004 189:1590-7)

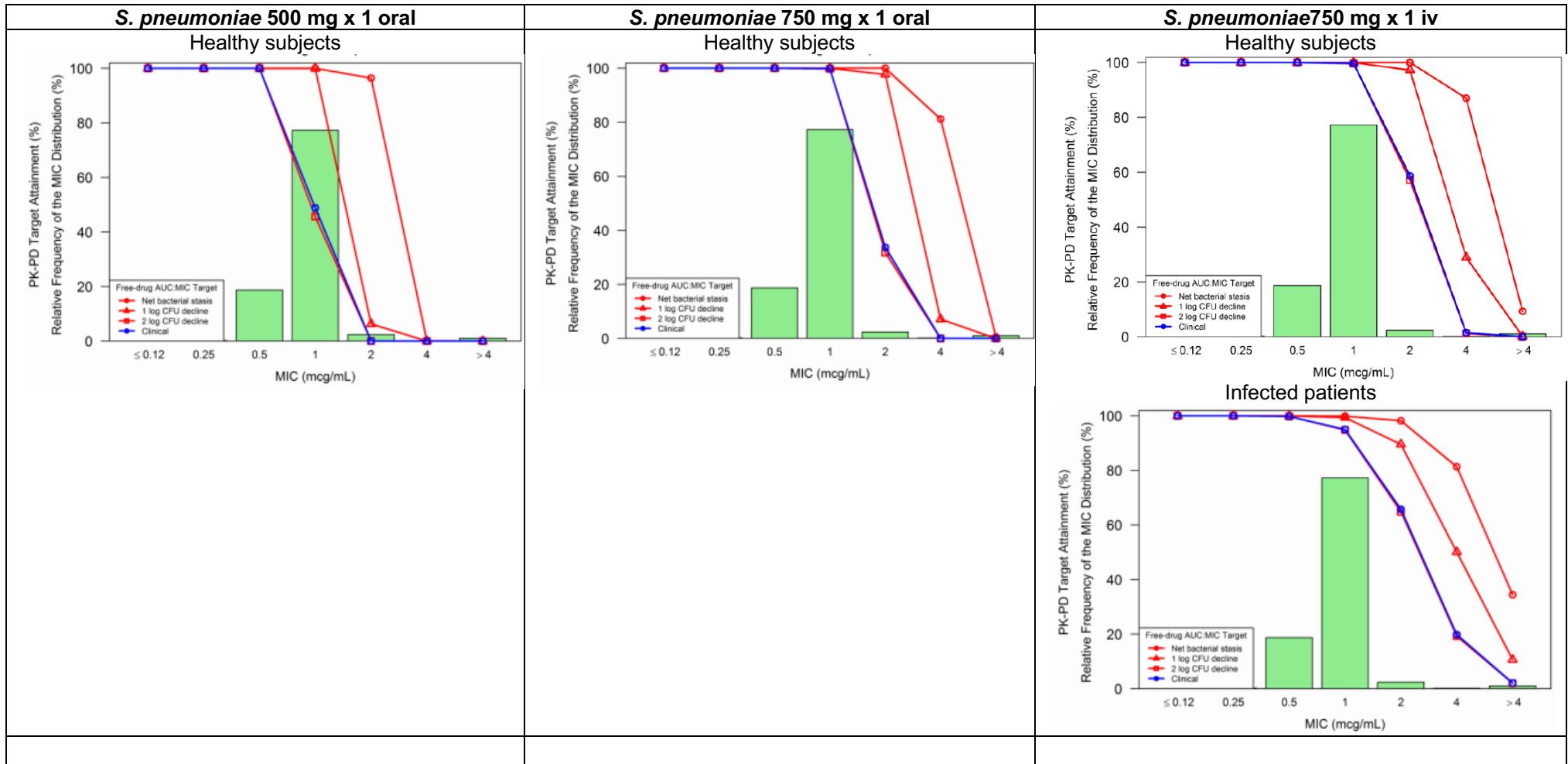
**Table 3-40.** Population PK parameter values derived from 58 patients with nosocomial pneumonia who were receiving levofloxacin (750 mg IV) as a 1.5 hour constant-rate infusion<sup>a</sup>

Unit	$V_c$ (L)	$K_{CP}$ ( $h^{-1}$ )	$K_{PC}$ ( $h^{-1}$ )	$CL_T$ (L/h)
Mean	34.4	7.65	6.07	7.24
Median	23.3	2.66	0.924	6.24
SD	33.5	9.59	12.0	4.36









**References**

- USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg>)
- Drusano et al., J Infect Dis 2004 189:1590-7

## 7. Clinical data

Extensive clinical data are available showing the relationship between exposure (AUC/MIC) and effect of quinolones (Ambrose PG, et al. Infect Dis Clin North Am 2003; 17: 529).

Drusano and colleagues constructed an exposure-response model based on 47 patients with hospital-acquired pneumonia treated with levofloxacin 750 mg IV every 24 hours [34]. The PK data were fitted by NPAG to a two-compartment model with a time limited zero-order IV input and first-order output. Logistic regression was used to model levofloxacin exposure (and other potential covariates) versus the probabilities of achieving clinical and microbiologic success. Logistic regression analysis revealed that only patient age and total-drug AUC:MIC ratio exceeding 87 had a significant effect on eradication of the pathogen ( $p < 0.001$ ). Achieving the breakpoint made the patient four times more likely to achieve eradication. The effect was greatest in patients aged 67 and older. Of particular interest, the authors suggested that in total that these data suggest a levofloxacin susceptibility breakpoint for of 0.5 Mg/L *Enterobacterales* and *P. aeruginosa* for levofloxacin. After adjusting for protein binding, the above-described total-drug AUC:MIC ratio targets for efficacy of 87 for cipro levofloxacin translated to free-drug AUC:MIC ratio targets of 61.

### References

- USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg>)
- Forrest et al., Antimicrob Agents Chemother 1993; 37:1065-1072

## 8. Clinical breakpoints (<http://www.eucast.org>)

PK/PD breakpoints (non-species related)	<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.</p> <p>S ≤0.5 mg/L    R &gt;1 mg/L</p>																																													
Species-related breakpoints	<table border="0"> <tr> <td><i>Enterobacterales</i></td> <td>S ≤0.5 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>Pseudomonas</i> spp.</td> <td>S ≤0.001 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>Acinetobacter</i> spp.</td> <td>S ≤0.5 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>Staphylococcus</i> spp.</td> <td>S ≤0.001 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>Enterococcus</i> spp.</td> <td>S ≤4 mg/L</td> <td>R &gt;4 mg/L (uncomplicated UTI only)</td> </tr> <tr> <td><i>Streptococcus</i> A B C G</td> <td>S ≤0.001 mg/L</td> <td>R &gt;2 mg/L</td> </tr> <tr> <td><i>S. pneumoniae</i></td> <td>S ≤0.001 mg/L</td> <td>R &gt;2 mg/L</td> </tr> <tr> <td><i>H. influenzae</i></td> <td>S ≤0.06 mg/L</td> <td>R &gt;0.06 mg/L</td> </tr> <tr> <td><i>M. catarrhalis</i></td> <td>S ≤0.125 mg/L</td> <td>R &gt;0.125 mg/L</td> </tr> <tr> <td><i>H. pylori</i></td> <td>S ≤1 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>P. multocida</i></td> <td>S ≤0.06 mg/L</td> <td>R &gt;0.06 mg/L</td> </tr> <tr> <td><i>A. sanguinicola</i> and <i>urinae</i></td> <td>S ≤2 mg/L</td> <td>R &gt;2 mg/L (uncomplicated UTI only)</td> </tr> <tr> <td><i>K. kingae</i></td> <td>S ≤0.125 mg/L</td> <td>R &gt;0.125 mg/L</td> </tr> <tr> <td><i>Aeromonas</i> spp.</td> <td>S ≤0.5 mg/L</td> <td>R &gt;1 mg/L</td> </tr> <tr> <td><i>Bacillus</i> spp. (not <i>anthracis</i>)</td> <td>S ≤0.001 mg/L</td> <td>R &gt;1 mg/L</td> </tr> </table>	<i>Enterobacterales</i>	S ≤0.5 mg/L	R >1 mg/L	<i>Pseudomonas</i> spp.	S ≤0.001 mg/L	R >1 mg/L	<i>Acinetobacter</i> spp.	S ≤0.5 mg/L	R >1 mg/L	<i>Staphylococcus</i> spp.	S ≤0.001 mg/L	R >1 mg/L	<i>Enterococcus</i> spp.	S ≤4 mg/L	R >4 mg/L (uncomplicated UTI only)	<i>Streptococcus</i> A B C G	S ≤0.001 mg/L	R >2 mg/L	<i>S. pneumoniae</i>	S ≤0.001 mg/L	R >2 mg/L	<i>H. influenzae</i>	S ≤0.06 mg/L	R >0.06 mg/L	<i>M. catarrhalis</i>	S ≤0.125 mg/L	R >0.125 mg/L	<i>H. pylori</i>	S ≤1 mg/L	R >1 mg/L	<i>P. multocida</i>	S ≤0.06 mg/L	R >0.06 mg/L	<i>A. sanguinicola</i> and <i>urinae</i>	S ≤2 mg/L	R >2 mg/L (uncomplicated UTI only)	<i>K. kingae</i>	S ≤0.125 mg/L	R >0.125 mg/L	<i>Aeromonas</i> spp.	S ≤0.5 mg/L	R >1 mg/L	<i>Bacillus</i> spp. (not <i>anthracis</i> )	S ≤0.001 mg/L	R >1 mg/L
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Species without breakpoints	<p>There is insufficient evidence to set breakpoints for levofloxacin:</p> <ul style="list-style-type: none"> <li>• Viridans group streptococci</li> <li>• <i>N. gonorrhoeae</i></li> <li>• <i>N. meningitidis</i></li> </ul> <p>The following species are considered poor targets for levofloxacin:</p> <ul style="list-style-type: none"> <li>• Anaerobes, gram-positive and gram-negative</li> </ul>																																													
Clinical qualifications																																														

Dosage(s) linked to breakpoints	Standard dosage: 0.5 g x 1 iv and oral High dosage: 0.5 g x 2 iv and oral
Additional comments	

### 9. Exceptions noted for individual national committees

None