

Ciprofloxacin: Rationale for EUCAST Clinical Breakpoints

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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>.

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Delafloxacin 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.

Ciprofloxacin is used to treat complicated and uncomplicated urinary tract infections, acute and chronic bacterial prostatitis, gonorrhoea, lower respiratory tract infections, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections and blood stream infections, mainly involving gram-negative organisms including *Pseudomonas aeruginosa*. It is also used in infectious diarrhoea caused by susceptible bacteria when antibacterial therapy is indicated. Other than in cystic fibrosis patients, its use in paediatric patients is still a matter of debate.

Ciprofloxacin breakpoints underwent revision in 2016.

1. Dosage

	UK	France	Netherlands	Germany	Norway	Sweden
Most common dose	0.5 g x 2 oral 0.4 g x 2 iv	0.5 g x 2 oral 0.4 g x 2 iv	0.25 g x 2 oral 0.4 g x 2 iv	0.5 g x 2 oral 0.2 g x 2 iv	0.25-0.5 g x 2 oral 0.4 g x 2 iv	0.5 g x 2 oral 0.4 g x 2 iv
Maximum dose schedule	0.75 g x 2 oral 0.4 g x 3 iv	0.75 g x 2 oral 0.4 g x 3 iv	0.75 g x 2 oral 0.4 g x 3 iv	0.75 g x 2 oral 0.4 g x 2 iv	0.75 g x 2 oral 0.4 g x 3 iv	0.75 g x 2 oral 0.4 g x 3 iv
Available formulations	oral, iv	oral, iv	oral, iv	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 ¹
General breakpoints	ND	1/2	1/2	1/2	0.125/2	1/2	
Species related breakpoints							
<i>Enterobacterales</i>	1/1				0.12/2	0.12/1	1/2
<i>Pseudomonas</i> spp.	1/4					1/1	1/2
<i>Acinetobacter</i> spp.						1/1	1/2
<i>Staphylococcus</i> spp.	1/1				0.12/2	0.06/2	1/2
<i>Streptococcus</i> spp.	1/1	excluded			0.12/2	0.12/2	excluded
<i>Streptococcus pneumoniae</i>	0.12/2	excluded			0.12/2	0.12/2	excluded
<i>Enterococcus</i> spp.	excluded	excluded			0.12/2	0.12/2	1/2
<i>Haemophilus/Moraxella</i> spp.	1/1				0.12/0.5	0.12/0.25	1/-
<i>Corynebacterium</i> spp.						excluded	
<i>Neisseria meningitidis</i>	1/1				0.06/0.12	0.03/0.25	
<i>Neisseria gonorrhoeae</i>	0.06/-		0.06/1		0.06/0.12	0.06/0.25	0.06/0.5
<i>Pasteurella multocida</i>						0.12/0.25	
Anaerobes, Gram-positive	excluded					excluded	
Anaerobes, Gram-negative	excluded					excluded	
<i>Campylobacter</i> spp.	1/1						
<i>Helicobacter pylori</i>	2/2						
<i>Bacillus anthracis</i>							0.5/-

Excluded = considered inappropriate to set a breakpoint, ¹CLSI breakpoints converted to European terminology

4. Pharmacokinetics (PK)

Dosage	0.4 g x 2 iv	0.5 g x 2 oral	0.75 g x 2 oral	0.2 g x 2 to 0.4 g x 3*
C _{max} (mg/L)	3.2	2.3 - 2.8	3.2 - 3.9	
C _{min} (mg/L)				
Total body clearance (L/h)	26.8			38 (CV 24%)
T _{1/2} (h), mean (range)	(4.2 - 4.3)	(2.5 - 3.9)	4.0	6.5 (1.6-22)
AUC ₀₋₁₂ (mg.h/L)				
AUC ₀₋₂₄ (mg.h/L)	21 - 29	19.2 - 19.8	39	
AUC _{0-∞} (mg.h/L)				
Fraction unbound (%)	70 - 80	70 - 80	70 - 80	70 (range 60-80)
Volume of distribution _{ss} (L)	100 - 180			0.69 L/kg (CV 26%)
References	<ul style="list-style-type: none"> • Drusano et al., Antimicrob Agents Chemother 1987; 31:860 • Dudley et al., Antimicrob Agents Chemother 1987; 31:1782 • Crump et al., Antimicrob Agents Chemother 1983; 24:784 • Bergan et al., Antimicrob Agents Chemother 1986; 29:298 • Zlotos et al., J Pharm Sci 1998; 87:215 • Catchpole et al., J Antimicrob Chemother 1994; 33:103 • de Marie et al., Int Care Med 1998; 24:343 • *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 			

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 ₁₀ reduction	67.4	47.3	68.7	21.0			
<i>f</i> AUC/MIC for 2-log ₁₀ 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 ciprofloxacin and levofloxacin, respectively) was used for <i>Enterobacterales</i> and <i>P.aeruginosa</i> .						
References	<ul style="list-style-type: none"> USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg) 						

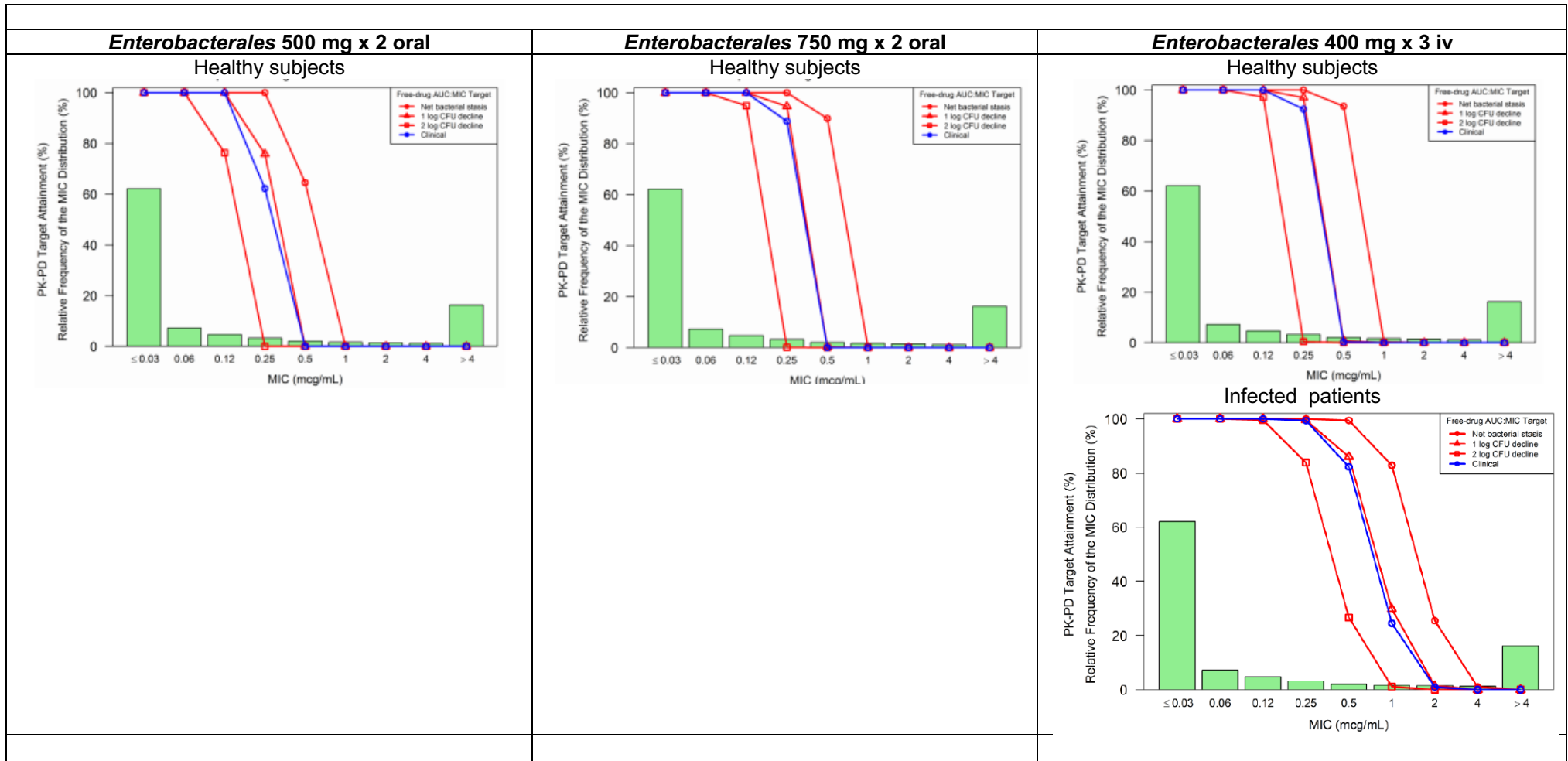
6. Monte Carlo simulations

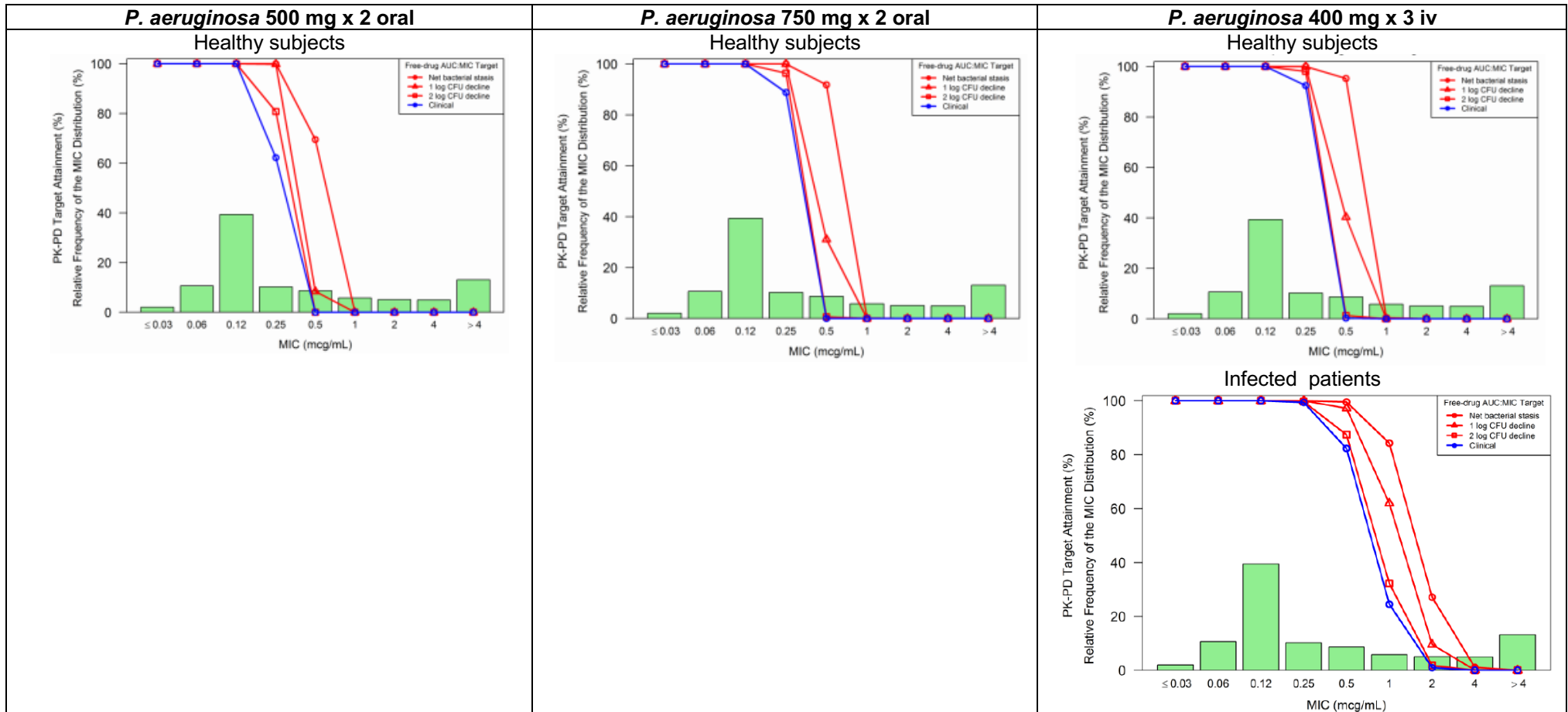
Monte Carlo simulations were conducted by USCAST using PK in healthy subjects and infected patients and in vivo PD parameters listed in Sections 4 and 5 as shown in the Tables below.

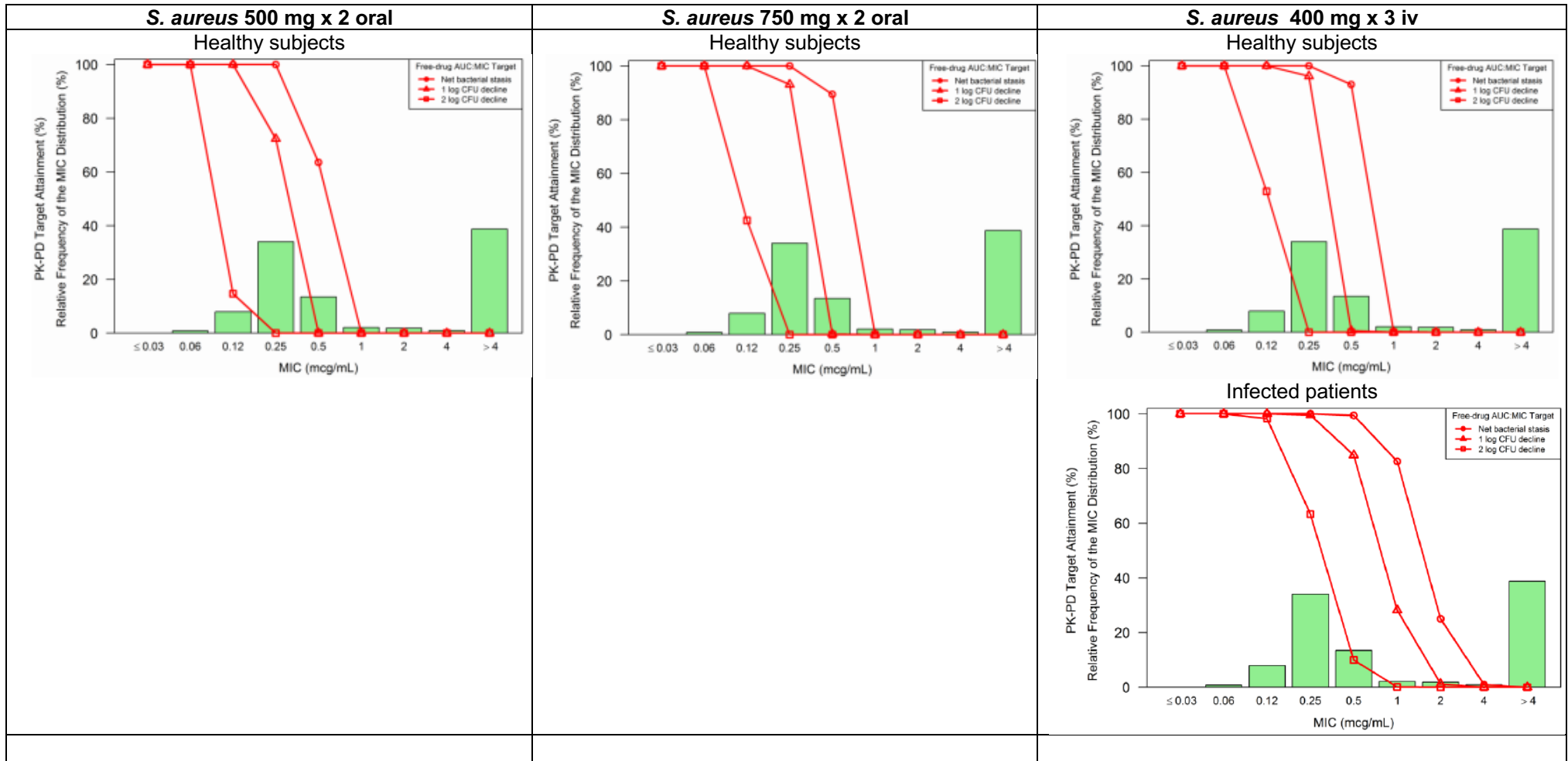
Table 3-37. Population PK parameter values by iterative two-stage analysis^a

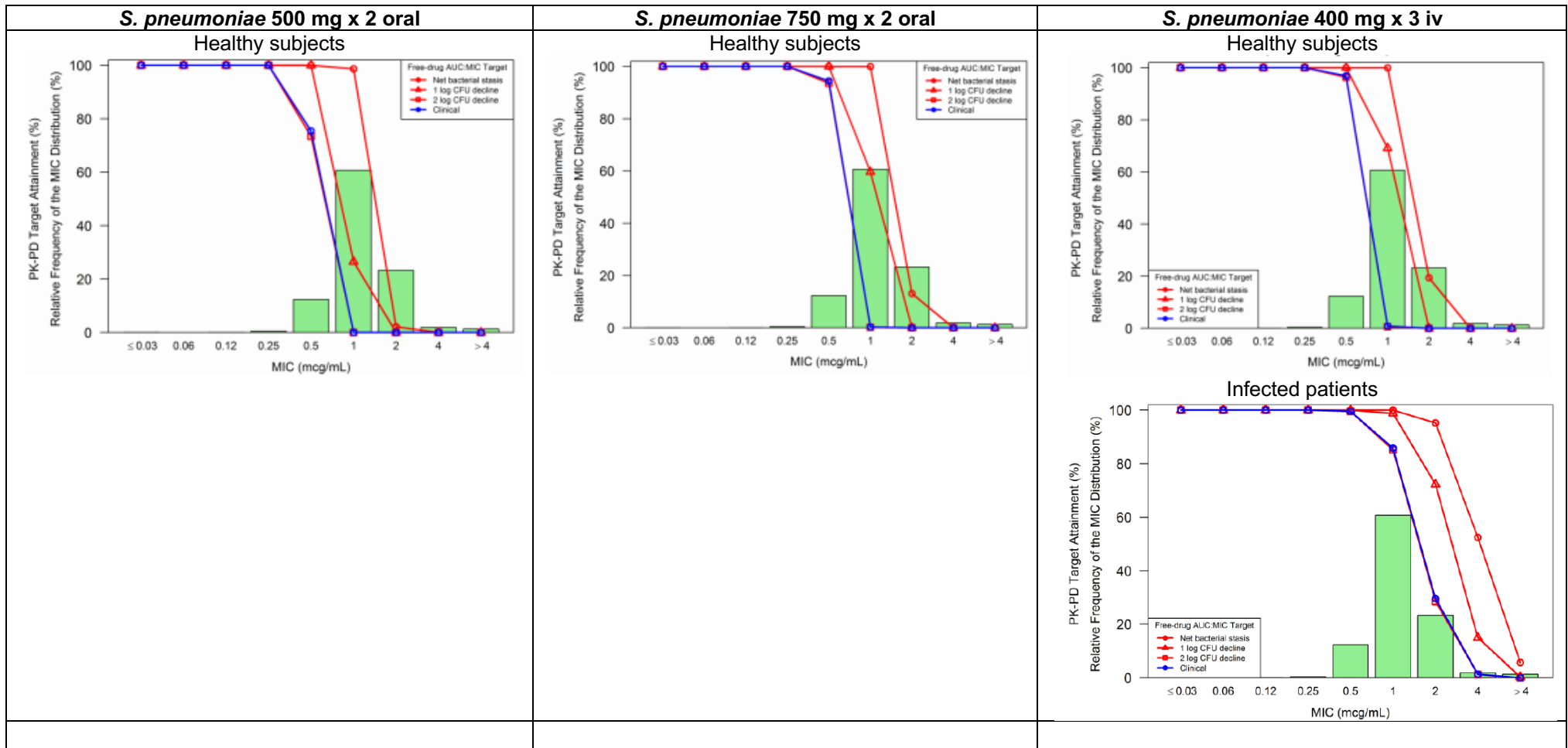
Parameter	Mean	Interpatient %CV	Range
V_c (L/kg)	0.69	26	0.2-1.2
V_p (L/kg)	0.51	33	0.2-2.0
V_β (L/kg)	2.0	31	0.96-5.0
CL_D (L/h/1.73 m ²)	38	24	16-64
CL_T (L/h/1.73 m ²)	17	44	4.4-37
$T_{1/2\beta}$ (h)	6.5	50	1.6-22

Forrest et al., Antimicrob Agents Chemother 1993; 37:1065-1072









References

- USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg>)

7. Clinical data

Extensive clinical data are available showing the relationship between exposure (AUC/MIC) and effect of quinolones, in particular for *Enterobacteriales*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. These data are shown in section 5. Much of the data come from the hospital-acquired pneumonia study by Forrest et al., described below.

Hospital-Acquired Pneumonia

Forrest and colleagues developed a PK-PD model based upon data from 74 acutely ill patients treated with ciprofloxacin IV dosing regimens ranging between 0.2 g every 12 hours and 0.4 g every 8 hours [33]. The PK data were fit by iterative two-stage analysis, assuming a linear two-compartment model. Logistic regression was used to evaluate the relationship between ciprofloxacin exposure (and other potential covariates) and the probabilities of achieving clinical or microbiologic success. Relationships between the same variables and time to bacterial eradication were also assessed using proportional hazards regression. A total-drug AUC:MIC ratio of 125 was found to be a significant breakpoint for probabilities of both clinical and microbiologic success. Total-drug AUC:MIC ratios of 125 (19 patients) and less were associated with percent probabilities of clinical and microbiologic success of 42 and 26%, respectively. Total-drug AUC:MIC ratio greater than 125 (45 patients) were associated with probabilities of clinical and microbiological success of 80% ($p < 0.005$) and 82% ($p < 0.001$), respectively.

There were two significant breakpoints in the time-to-bacterial-eradication data. Total-drug AUC:MIC ratios below 125 (21 patients) were associated with a median time to eradication exceeding 32 days. Total-drug AUC:MIC ratios of 125 to 250 (15 patients) were associated with median time to eradication of 6.6 days and total-drug AUC:MIC ratios above 250 (28 patients) were associated with median time to eradication was 1.9 days (groups differed; $p < 0.005$). Of particular interest, the authors stated that in total, these data suggested a ciprofloxacin susceptibility breakpoint of 0.25 µg/mL.

In invasive infections with *Salmonella* spp. there is increasing evidence of clinical failure of ciprofloxacin treatment in cases where there is reduced susceptibility (indicated by resistance to nalidixic acid) due to the acquisition of at least one mutation in *gyrA*.

The risk of ciprofloxacin resistant mutants or of an increase in resistance levels is higher when there is already reduced susceptibility to this antibiotic.

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 ≤0.25 mg/L R >0.5 mg/L</p>		
Species-related breakpoints	<p><i>Enterobacteriales</i> <i>Salmonella</i> spp. <i>Pseudomonas</i> spp. <i>Acinetobacter</i> spp. <i>Staphylococcus</i> spp. <i>Enterococcus</i> spp. <i>H. influenzae</i> <i>M. catarrhalis</i> <i>N. gonorrhoeae</i> <i>N. meningitidis</i> <i>P. multocida</i> <i>C. jejuni</i> and <i>coli</i> <i>Corynebacterium</i> spp. (not <i>diphtheriae</i>) <i>A. sanguinicola</i> and <i>urinae</i> <i>K. kingae</i> <i>Aeromonas</i> spp. <i>Bacillus</i> spp. (not <i>anthracis</i>)</p>	<p>S ≤0.25 mg/L S ≤0.06 mg/L S ≤0.001 mg/L S ≤0.001 mg/L S ≤0.001 mg/L S ≤4 mg/L S ≤0.06 mg/L S ≤0.125 mg/L S ≤0.03 mg/L S ≤0.03 mg/L S ≤0.06 mg/L S ≤0.001 mg/L S ≤0.001 mg/L S ≤2 mg/L S ≤0.06 mg/L S ≤0.25 mg/L S ≤0.001 mg/L</p>	<p>R >0.5 mg/L (ATU = 0.5 mg/L) R >0.06 mg/L R >0.5 mg/L R >1 mg/L R >1 mg/L R >4 mg/L (uncomplicated UTI only) R >0.06 mg/L R >0.125 mg/L R >0.06 mg/L R >0.03 mg/L (prophylaxis only) R >0.06 mg/L R >0.5 mg/L R >1 mg/L R >2 mg/L (uncomplicated UTI only) R >0.06 mg/L R >0.5 mg/L R >0.5 mg/L</p>
Species without breakpoints	<p>The following species are considered poor targets for ciprofloxacin:</p> <ul style="list-style-type: none"> • <i>Streptococcus</i> A B C G • <i>S. pneumoniae</i> • Viridans group streptococci • Anaerobes, gram-positive and gram-negative 		

Clinical qualifications	There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by <i>Salmonella</i> spp with low-level fluoroquinolone resistance (MIC>0.06 mg/L). EUCAST has suggested that the epidemiological cut off value (S ≤0.06, R >0.06 mg/L) be used in <i>Salmonella</i> spp. systemic infections.
Dosage(s) linked to breakpoints	Standard dosage: 0.5 g x 2 oral; 0.4 g x 2 iv High dosage: 0.75 g x 2 oral; 0.4 g x 3 iv
Additional comments	None

9. Exceptions noted for individual national committees

None