Fluoroquinolone Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa*

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1 Foreword

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Using the CLSI voluntary consensus process, the Subcommittee on Antimicrobial Susceptibility Testing develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting. The subcommittee reviews data from various sources and studies (eg, *in vitro*, pharmacokinetic-pharmacodynamic [PK-PD], and clinical studies) to establish antimicrobial susceptibility test methods, breakpoints, and quality control (QC) ranges.

The details of the necessary and recommended data for selecting appropriate breakpoints and QC ranges, and how the data are presented for evaluation, are described in CLSI document M23.[1] CLSI antibacterial breakpoints are provided in CLSI documents M100[2] and M45.[3]

Over time, a microorganism's susceptibility to an antimicrobial agent may decrease, resulting in a lack of clinical efficacy and/or safety. In addition, microbiological methods, QC parameters, and the manner in which breakpoints are established may be refined to ensure more accurate results. Because of these types of changes, CLSI continually monitors and updates information in its documents. Although CLSI standards and guidelines are developed using the most current information available at the time, the field of science and medicine is always changing; therefore, standards and guidelines should always be used in conjunction with clinical judgment, current knowledge, and clinically relevant laboratory test results to guide patient treatment. For more information, visit www.clsi.org.

This CLSI rationale document is based on CLSI agenda items submitted by the CLSI-EUCAST Joint Fluoroquinolone Ad Hoc Working Group.

2 Introduction

Ciprofloxacin and levofloxacin are members of the fluoroquinolone group of antimicrobial agents. The fluoroquinolones possess a fluorinated 4-quinolone nucleus.[4] The bactericidal action of fluoroquinolones results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are necessary for bacterial DNA replication, transcription, repair, and recombination.[5] The fluoroquinolones, including ciprofloxacin and levofloxacin, have *in vitro* activity against gram-negative and gram-positive bacteria, including the *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii, Yersinia pestis,* methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multidrug-resistant organisms), and *Bacillus anthracis*.[5,6]

Fluoroquinolone resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV (termed the quinolone resistance–determining regions), decreased outer membrane permeability, or altered efflux.[6] Plasmid-mediated resistance mechanisms, including the *qnr* genes, have increased in frequency among some *Enterobacteriaceae*. Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to 10^{-6}.[5] Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (ie, range 10^{-10} to 10^{-9}).[6]

Ciprofloxacin and levofloxacin are approved by the US Food and Drug Administration for the treatment of acute or chronic infections due to gram-positive and gram-negative bacteria, including nosocomial and community-acquired pneumonia, skin and skin structure infections, urinary tract infections, chronic bacterial prostatitis, inhalation anthrax, and plague. Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects. Therefore, for uncomplicated urinary tract infection, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis, use should be reserved for patients with no alternative treatment options.[5,6]

For current and past fluoroquinolone breakpoints for *Enterobacteriaceae* and *P. aeruginosa*, see Tables 1 and 2, respectively.

Table 1. Current CLSI Fluoroquinolone Breakpoints*

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤ 0.25	-	0.5	≥ 1
	Levofloxacin	≤ 0.5	-	1	≥ 2
P. aeruginosa	Ciprofloxacin	≤ 0.5	N/A	1	≥ 2
	Levofloxacin	≤ 1	N/A	2	≥ 4

* Last reviewed January 2018; first published in CLSI document M100, 29th ed.[2]
Abbreviations: I, intermediate; N/A, not applicable; R, resistant; S, susceptible; SDD, susceptible-dose dependent.

Table 2. Historical CLSI Fluoroquinolone Breakpoints Replaced by Current Fluoroquinolone Breakpoints*

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤ 1	-	2	≥ 4
	Levofloxacin	≤ 2	-	4	≥ 8
P. aeruginosa	Ciprofloxacin	≤ 1	N/A	2	≥ 4
	Levofloxacin	≤ 2	N/A	4	≥ 8

* Last published in CLSI document M100, 28th ed.
Abbreviations: I, intermediate; N/A, not applicable; R, resistant; S, susceptible; SDD, susceptible-dose dependent.

3 Standard Dosages and Pharmacokinetic Data

Ciprofloxacin and levofloxacin dosages used to determine breakpoints are shown in Table 3.

Table 3. Dosages Used for Breakpoint Determination*

Organism Group	Drug	Dose
Enterobacteriaceae	Ciprofloxacin	400 mg IV or 500 mg PO administered every 12 hours
	Levofloxacin	750 mg IV or PO every administered every 24 hours
P. aeruginosa	Ciprofloxacin	400 mg IV administered every 8 hours
	Levofloxacin	750 mg IV or PO administered every 24 hours

* See CLSI document M100.[2]
Abbreviations: IV, intravenous; PO, oral.

Population pharmacokinetic (PK) parameters for ciprofloxacin and levofloxacin are shown in Tables 4, 5, and 6. For levofloxacin, Table 5 parameters are based on data derived from patients treated for community-acquired infections, while Table 6 parameters are derived from patients with life-threatening infections treated in the hospital setting.

Table 4. Population PK Parameters for Ciprofloxacin by Iterative Two-Stage Analysis[7] (Reprinted from Forrest A, Ballow CH, Nix DE, Birmingham MC, Schentag JJ, Development of a population pharmacokinetic model and optimal sampling strategies for intravenous ciprofloxacin, *Antimicrob Agents Chemother*, 1993, Vol 37/No 5, pp. 1065-1072, doi: 10.1128/AAC.37.5.1065. Reproduced with permission from American Society for Microbiology.)

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

Abbreviations: % CV, coefficient of variation expressed as a percentage; CL_D, distributional clearance of the central compartment; CL_T, total plasma clearance; PK, pharmacokinetic; $T_{1/2\beta}$, terminal half-life; V_β, volume of distribution that when associated with terminal rate constant for elimination will provide the correct clearance; V_C, central volume of distribution; V_P, distributional clearance of the peripheral compartment.

Table 5. Population PK Parameters for Levofloxacin ($N = 272$)[8] (Reprinted from Preston SL, Drusano GL, Berman AL, et al., Levofloxacin population pharmacokinetics and creation of a demographic model for prediction of individual drug clearance in patients with serious community-acquired infection, *Antimicrob Agents Chemother*, 1998, Vol 42/No 5, pp. 1098-1104, doi: 10.1128/AAC.42.5.1098. Reproduced with permission from American Society for Microbiology.)

Unit	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	0.596	0.795	9.01
SD	0.378	0.391	0.429	4.31

Abbreviations: CL_T, total plasma clearance; K_{CP}, transfer rate between the central compartment and the peripheral compartment; K_{PC}, transfer rate between the peripheral compartment and the central compartment; PK, pharmacokinetic; SD, standard deviation; VS, slope of the mean volume of distribution of the central compartment to body weight.