Cefazolin Breakpoints for Enterobacterales (Systemic Infections)

CLSI rationale document MR07
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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 data compiled by the CLSI *Enterobacteriaceae* Ad Hoc Working Group to reassess cefazolin minimal inhibitory concentration (MIC) breakpoints for Enterobacterales for systemic infections and introduce new intermediate and resistant MIC breakpoints supported by higher dosage treatment regimens for cefazolin.

2 A Note on Terminology

As of January 2020, the term *Enterobacteriaceae* has been replaced with Enterobacterales. For consistency with CLSI document M100,[2] Enterobacterales is used in MR07. In some instances (eg, the name of the working group that originally compiled the data), *Enterobacteriaceae* is necessarily retained.

3 Introduction

Cephalosporins are a large class of antimicrobial agents that contain a six-membered dihydrothiazine ring moiety fused to a β-lactam ring with broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria. These compounds are derivatives of 7-aminocephalosporanic acid, with various modifications at several ring positions that result in differences in antimicrobial activity, β-lactamase stability, and pharmacokinetic (PK) properties.[4] The bactericidal action of cephalosporins is mediated by their strong binding affinity for penicillin-binding proteins (PBPs). This affinity leads to the inhibition of bacterial cell wall synthesis and, ultimately, cell death.[4]

Cefazolin is a parenterally administered, first-generation cephalosporin that exhibits bactericidal activity against a wide variety of gram-positive and gram-negative bacteria, including methicillin-susceptible *Staphylococcus aureus* (MSSA), coagulase-negative *Staphylococcus* spp., penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus* spp., *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.[5]

Cefazolin is approved by the US Food and Drug Administration (FDA) for the treatment of[6]:

- Respiratory tract infections caused by *S. pneumoniae, Klebsiella* spp., *Haemophilus influenzae, S. aureus*, and group A β-hemolytic streptococci
- Urinary tract infections caused by *E. coli, P. mirabilis, Klebsiella* spp., and some strains of *Enterobacter* and *Enterococcus*
- Skin and skin structure infections caused by *S. aureus*, group A β-hemolytic streptococci, and other strains of *Streptococcus*
- Biliary tract infections caused by *E. coli, Streptococcus, P. mirabilis, Klebsiella* spp., and *S. aureus*
- Bone and joint infections caused by *S. aureus*
- Genital infections caused by *E. coli, P. mirabilis, Klebsiella* spp., and some strains of *Enterococcus*
- Septicemia caused by *S. pneumoniae, S. aureus, P. mirabilis, E. coli,* and *Klebsiella* spp.
- Endocarditis caused by *S. aureus* and group A β-hemolytic streptococci
- Perioperative prophylaxis

The FDA-approved parenteral administration schedule for cefazolin in adult patients is shown in Table 1.

Table 1. Recommended Dosage Schedule for Cefazolin in Adult Patients[6] (FDA. Cefazolin for injection USP prescribing information.)

Type of Infection	Dosage
Moderate to severe infections	0.5-1 g every 6-8 hours
Mild infections caused by susceptible gram-positive streptococci	250-500 mg every 8 hours
Acute uncomplicated urinary tract infections	1 g every 12 hours
Pneumococcal pneumonia	500 mg every 12 hours
Severe life-threatening infections (eg, endocarditis, septicemia)	1-1.5 g every 6 hours

The predominant mechanisms of resistance to cefazolin in gram-negative bacteria include decreased bacterial uptake of cefazolin into the cell or production of β-lactamases that enzymatically hydrolyze and inactivate β-lactam antibiotics.[7] Cefazolin is a useful de-escalation agent for the treatment of many invasive and noninvasive infections caused by susceptible isolates of *E. coli, Klebsiella* spp. (excluding *Klebsiella aerogenes*), and *P. mirabilis*.[8,9] Current and historical CLSI breakpoints for cefazolin are shown in Tables 2 and 3.

Table 2. Current CLSI Cefazolin Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL[b]			
		S	SDD	I	R
Enterobacterales	Cefazolin	≤ 2	-	4	≥ 8

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last reviewed June 2010; first published in CLSI document M100, 21st ed.
[b] Breakpoints are based on a dosage regimen of 2 g administered every 8 h.

Table 3. Historical CLSI Cefazolin Breakpoints Replaced by Current Cefazolin Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL[b]			
		S	SDD	I	R
Enterobacterales	Cefazolin	≤ 1	-	2	≥ 4

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last published in CLSI document M100, 20th ed.
[b] Breakpoints are based on a dosage regimen of at least 1 g every 8 h.

4 Standard Dosage and Pharmacokinetic Data

The cefazolin dosage used for breakpoint determination is shown in Table 4. According to the FDA-approved prescribing information, the cefazolin dosage goes up to 1.5 g every six hours, which is equivalent to 2 g every eight hours.[6]

Table 4. Dosage Used for Breakpoint Determination[a]

Antimicrobial Agent	Dosage
Cefazolin	2 g IV every 8 hours

Abbreviation: IV, intravenous.
[a] CLSI document M100, 30th ed.[2]

Following IV administration of 1 g cefazolin in healthy volunteers, mean serum concentrations peaked at approximately 185 µg/mL and were approximately 4 µg/mL at eight hours.[6] The serum half-life for cefazolin is approximately 1.8 hours following IV administration.[6] Plasma PK parameters in healthy volunteers (N = 12) following a single 15-minute IV infusion of cefazolin 2 g are shown in Table 5.[6] Safety of 2- to 4-g doses of cefazolin have been demonstrated.[10-13]

Table 5. Plasma PK Parameters of Cefazolin in Healthy Volunteers[6] (FDA. Cefazolin for injection USP prescribing information.)

PK Parameter	Measurement[a]
C_{max}, µg/mL	280.9 (45.9)
$AUC_{0-\infty}$, (µg·h/mL)	509.9 (89.3)
T_{max}, h	0.25 (0.25-0.33)[b]
$t_{1/2}$, h	2.01 (0.28)
CL, L/h	4.03 (0.68)
V_z, L	11.50 (1.53)

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve extrapolated to infinity; CL, total clearance; C_{max}, maximum plasma concentration; h, hours; $t_{1/2}$, apparent plasma terminal elimination half-life; T_{max}, time to maximum plasma concentration; V_z, volume of distribution.
[a] Values are shown as mean (SD).
[b] T_{max} reported as median (range).