Cefazolin Breakpoints for Enterobacterales (Uncomplicated Urinary Tract Infections)

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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, 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 Oral Cephalosporin Ad Hoc Working Group to reassess cefazolin minimal inhibitory concentration (MIC) breakpoints for Enterobacterales for uncomplicated urinary tract infections (UTIs) 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 MR08.

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 affinities 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 for the treatment of[6]:

- Respiratory tract infections caused by *S. pneumoniae, Klebsiella* spp., *Haemophilus influenzae, S. aureus,* and group A β-hemolytic streptococci
- UTIs 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 to 8 hours
Mild infections caused by susceptible gram-positive streptococci	250-500 mg every 8 hours
Acute uncomplicated UTIs	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

Abbreviation: UTI, urinary tract infection.

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]

CLSI has established cefazolin as a surrogate agent to predict the activity of the oral cephalosporins (ie, cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef) in antimicrobial susceptibility testing (AST) against Enterobacterales isolates causing uncomplicated UTIs.[9,10] Data demonstrate that a cefazolin MIC ≤ 16 µg/mL (correlate zone diameter ≥ 15 mm) is an excellent predictor (97% to 100% accuracy) of susceptibility to these agents when testing *E. coli, K. pneumoniae,* and *P. mirabilis* for intended treatment of uncomplicated UTIs.[10] Cefdinir, cefpodoxime, and cefuroxime may be tested individually, because some isolates may be susceptible to these agents but resistant to cefazolin when applying the uncomplicated UTI cefazolin breakpoints.[10]

This rationale document summarizes interpretative data and information used by CLSI to establish cefazolin as a surrogate agent for oral cephalosporins, including cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef[10] (see Additional Resources, June 2013 CLSI meeting). Current CLSI urine-specific breakpoints are shown in Table 2.

Table 2. Current CLSI Urine-Specific Cefazolin Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL[b,c]			
		S	SDD	I	R
Enterobacterales (*E. coli*, *K. pneumoniae*, *P. mirabilis*)	Cefazolin	≤ 16	-	-	≥ 32

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last reviewed June 2013; first published in CLSI document M100, 24th ed.
[b] These breakpoints can be used to predict susceptibility to cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef.
[c] Breakpoints are based on a dosage regimen of 1 g administered every 12 h.

4 Standard Dosages and Pharmacokinetic Data

The standard dosages and PK data for cefaclor, cefazolin, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef are listed in Table 3.

Table 3. Dosages Used for Breakpoint Determination

Antimicrobial Agent	Dosages
Cefaclor[11]	250-500 mg every 8 hours
Cefazolin[6]	1-2 g (IM or IV) every 8 hours (1 g every 12 hours for uncomplicated UTIs), 2 g every 8 hours
Cefdinir[12,13]	300 mg every 12 hours or 600 mg every 24 hours
Cefpodoxime[14,15]	100-200 mg every 12 hours
Cefprozil[16]	250-500 mg every 12 hours
Cefuroxime[17,18]	125-500 mg every 12 hours
Cephalexin[19,20]	250-1000 mg every 6 hours
Loracarbef[21]	200-400 mg every 12 to every 24 hours (200 mg every 24 hours for uncomplicated UTIs)

Abbreviations: IM, intramuscular; IV, intravenous; UTI, urinary tract infection.