Ceftaroline Breakpoints for *Staphylococcus aureus*

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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 Ceftaroline Breakpoint Ad Hoc Working Group to support the changes to the ceftaroline minimal inhibitory concentration (MIC) breakpoints for *Staphylococcus aureus* and introduce new resistant and susceptible-dose dependent (SDD) breakpoints.

2 Introduction

Cephalosporins are a large group 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]

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is an extended broad-spectrum cephalosporin with *in vitro* antibacterial activity against common gram-negative and gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*.[5] Ceftaroline fosamil is rapidly dephosphorylated to the active drug ceftaroline by plasma phosphates after intravenous administration.[6] Ceftaroline is available for parental administration.[7-9]

Methicillin resistance in *S. aureus* is typically mediated by acquisition of the *mecA* gene, which encodes for an altered PBP, PBP2a. PBP2a has a very low binding affinity for cephalosporins, rendering them ineffective as cell wall inhibitors in MRSA isolates.[6] Unlike other cephalosporins, ceftaroline exhibits a high binding affinity for PBP2a and is responsible for its bactericidal action against MRSA strains.[7,8]

Ceftaroline is approved by the US Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSI) caused by gram-positive and gram-negative bacteria, including *S. aureus* (methicillin-susceptible and MRSA isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae,* and *Klebsiella oxytoca*.[9] It is also approved for the treatment of community-acquired bacterial pneumonia caused by susceptible isolates of gram-positive and gram-negative microorganisms, including *S. pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, K. pneumoniae, K. oxytoca,* and *E. coli*.[9] Ceftaroline is approved by the European Medicines Agency (EMA) for the treatment of complicated skin and soft tissue infections and community-acquired bacterial pneumonia.[10]

Before 2019, CLSI published only susceptible and resistant breakpoints for ceftaroline for *Staphylococcus* spp. (last published in CLSI document M100, 28th ed.). It was then found that the ceftaroline breakpoint of 1 µg/mL was very close to the wild-type distribution and that many isolates showed higher breakpoints (2 and 4 µg/mL) in other parts of the world. Modeling and simulation analyses supported a change in the breakpoints to effectively treat *S. aureus* isolates with elevated MICs.
In January 2019, revisions to the ceftaroline breakpoints were published in CLSI document M100, 29th ed.[2] This rationale document describes these changes (see Tables 1 and 2).

Table 1. Current CLSI Ceftaroline Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL			
		S	SDD	I	R
Staphylococcus spp.[b]	Ceftaroline	≤ 1.0[c]	2-4[d]	-	≥ 8.0

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last reviewed June 2018; first published in CLSI document M100, 29th ed.[2]
[b] For reporting against *S. aureus* only, including MRSA.
[c] The breakpoint for susceptible is based on a dosage regimen of 600 mg administered every 12 h.
[d] The breakpoint for SDD is based on a dosage in adults of 600 mg every 8 h administered over 2 h.

Table 2. Historical CLSI Ceftaroline Breakpoints Replaced by Current Ceftaroline Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL			
		S	SDD	I	R
Staphylococcus spp.[b]	Ceftaroline	≤ 1.0[c]	-	2	≥ 4.0[c]

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last published in CLSI document M100, 28th ed.
[b] For reporting against *S. aureus* only, including MRSA.
[c] Breakpoints are based on a dosage regimen of 600 mg every 12 h.

3 Standard Dosages and Pharmacokinetic Data

The ceftaroline dosages used for breakpoint determination and population PK parameters in healthy volunteers are shown in Tables 3 and 4, respectively.

Table 3. Dosages Used for Breakpoint Determination

Breakpoint	Dosage	Reference
≤ 1.0 µg/mL (susceptible)	600 mg IV every 12 hours infused over 1 hour	FDA[9]
2-4 µg/mL (SDD)	600 mg IV every 8 hours infused over 2 hours	Outside the United States[11,a]

Abbreviations: FDA, US Food and Drug Administration; IV, intravenous; SDD, susceptible-dose dependent.
[a] Dryden M, Wilson D, Iaconis J, Gonzalez J. A phase III trial of ceftaroline fosamil 600 mg q8h versus vancomycin plus aztreonam in patients with cSSTI with systemic inflammatory response or underlying comorbidities. Presented at: 25th Annual Meeting of the European Society of Clinical Microbiology and Infectious Diseases; 25-28 April 2015; Copenhagen, Denmark. Abstract O193.

Table 4. Population PK Parameters in Healthy Volunteers After Administration of Ceftaroline 600 mg Every 8 Hours Infused Over 2 Hours[12,a] (Data from Matzneller P, Lackner E, Lagler H, et al. Single- and repeated-dose pharmacokinetics of ceftaroline in plasma and soft tissues of healthy volunteers for two different dosing regimens of ceftaroline fosamil. *Antimicrob Agents Chemother*. 2016; 60(6): 3617-3625.)

PK Parameter	Measurement[b]
C_{max}, mg/L	15.3 (2.7)
AUC_{0-24}, mg·h/L	133.0 (17.2)
fC_{max}, mg/L	12.2 (2.2)
$fAUC_{0-24}$, mg·h/L	103.9 (16.1)
T_{max}, h	2.1 (0.2)
$t_{1/2}$, h	1.7 (0.0)
V, L	32.3 (3.6)
$\%fT_{>MIC}$[c]	84.4 (4.0)

Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours for total ceftaroline; C_{max}, peak (maximum) total ceftaroline concentration; $fAUC_{0-24}$, area under the concentration-time curve from time zero to 24 hours for unbound (free) ceftaroline; fC_{max}, peak unbound (free) ceftaroline concentration; $\%fT_{>MIC}$, percentage of time during a dosing interval that free-drug concentration remains above the minimal inhibitory concentration; h, hours; MIC, minimal inhibitory concentration; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to the peak concentration; V, apparent volume of distribution.
[a] Unbound ceftaroline concentrations in plasma were calculated by assuming plasma protein binding of 20%.
[b] Values are shown as mean (SD).
[c] MIC 2 µg/mL.