Daptomycin Breakpoints for Enterococci

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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 Ad Hoc Working Group to Reassess Daptomycin Breakpoints for Enterococci to change minimal inhibitory concentration (MIC) breakpoints and introduce new resistant and susceptible-dose dependent (SDD) breakpoints supported by higher dosage treatment regimen options for daptomycin.

2 Introduction

Daptomycin is a parenterally administered, cyclic lipopeptide antibiotic with rapid, concentration-dependent bactericidal activity against a wide variety of gram-positive bacteria, including enterococci, vancomycin-resistant enterococci (VRE), staphylococci, and methicillin-resistant *Staphylococcus aureus* (MRSA).[4,5] The bactericidal action of daptomycin is mediated by a distinct mechanism that involves calcium-dependent insertion of the molecule into the bacterial cytoplasmic membrane.[6] This process leads to rapid disruption of the bacterial cell membrane without causing cell lysis or penetration of the molecule into the cell cytoplasm.[7]

Daptomycin is approved by the US Food and Drug Administration (FDA) for the treatment of complicated skin and soft-tissue infections caused by staphylococci, streptococci, and vancomycin-susceptible *Enterococcus faecalis* at a dose of 4 mg/kg/day and for bacteremia caused by *S. aureus*, including right-sided infective endocarditis, at a dose of 6 mg/kg/day.[8] Because its activity is inhibited by pulmonary surfactant,[8,9] daptomycin is not indicated for the treatment of pneumonia.[10]

Although daptomycin lacks an approved indication from the FDA to treat *Enterococcus faecium,* because of limited treatment options, it is frequently used to manage vancomycin-resistant *E. faecium* infections.[11] There is general agreement that daptomycin doses of 4 to 6 mg/kg body weight used for staphylococcal infections are inadequate to treat vancomycin-resistant *E. faecium* infections, because *E. faecium* daptomycin MICs are 4- to 8-fold higher than those for staphylococci.[9,12,13] Many clinicians use increased doses of daptomycin (8 to 12 mg/kg/day) to treat serious *E. faecium* infections.[14] The Infectious Diseases Society of America (IDSA) provides the following advice for using high-dose daptomycin[14]:

- **MRSA bacteremia and endocarditis:** daptomycin 8 to 10 mg/kg/day (recommended by some experts)
- **Persistent MRSA bacteremia and vancomycin treatment failures:** high-dose daptomycin (10 mg/kg/day)
- **Native-valve endocarditis caused by staphylococci:** daptomycin ≥ 8 mg/kg/day
- **Endocarditis caused by ampicillin-resistant VRE:** daptomycin 10 to 12 mg/kg/day (may be considered)

Reports of daptomycin resistance among enterococci are becoming more common.[15-18] However, the daptomycin resistance mechanisms in enterococci have not been fully elucidated and appear to emerge through various genetic events.[11] Additionally, reports of daptomycin nonsusceptibility among enterococci have been growing, in particular *E. faecalis* and *E. faecium*.[19] The observed nonsusceptibility largely occurs with prolonged treatment and in infections with high bacterial burdens and may occur in the absence of previous daptomycin exposure.[19] Before 2019, CLSI published only a susceptible breakpoint for *Enterococcus* spp. (last published in CLSI document M100, 28th ed.). In January 2019, revisions to the daptomycin breakpoints were published in CLSI document M100, 29th ed.[2] Following publication, the subcommittee re-evaluated these breakpoints and approved additional revisions. These updates were published in a revision to CLSI document M100, 29th ed.,[2] in March 2019. This rationale document describes both changes (see Tables 1 and 2).

Table 1. Current CLSI Daptomycin Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL			
		S	SDD	I	R
E. faecium only	Daptomycin	-	≤ 4[b]	-	≥ 8
Enterococcus spp. (other than *E. faecium*)	Daptomycin	≤ 2[c]	-	4	≥ 8

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible-dose dependent.

[a] Last reviewed January 2019; first published in CLSI document M100, 29th ed. (March 2019 revision).[2]

[b] The breakpoint for SDD is based on a dosage regimen of 8-12 mg/kg administered every 24 h in adults and is intended for serious infections due to *E. faecium*. Consultation with an infectious diseases specialist is recommended.

[c] The breakpoint for susceptible is based on a dosage regimen of 6 mg/kg administered every 24 h in adults.

Table 2. Historical CLSI Daptomycin Breakpoints Replaced by Current Daptomycin Breakpoints

Year Last Published	Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL			
			S	SDD	I	R
2018[a]	*Enterococcus* spp.	Daptomycin	≤ 4[b]	-	-	-
2019[c]	*Enterococcus* spp.	Daptomycin	≤ 1[d]	2–4[e]	-	≥ 8

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible-dose dependent.
[a] Last published in CLSI document M100, 28th ed.
[b] Breakpoints are based on a dosage regimen of 4-6 mg/kg/day.
[c] Last published in CLSI document M100, 29th ed. (January 2019).[2]
[d] The breakpoint for susceptible is based on a dosage regimen of 6 mg/kg per day in adults.
[e] The breakpoint for SDD is based on a dosage regimen of 8-12 mg/kg per day in adults and is intended for serious infections due to *Enterococcus* spp. Consultation with an infectious diseases specialist is recommended.

3 Standard Dosages and Pharmacokinetic Data

The daptomycin dosages used for breakpoint determination and single-dose pharmacokinetics of daptomycin in healthy volunteers are shown in Tables 3 and 4, respectively.

Table 3. Dosages Used for Breakpoint Determination

Organism Group	Antimicrobial Agent	MIC Breakpoint (Interpretive Category)	Dosage	References
Enterococcus other than *E. faecium*	Daptomycin	≤ 2 µg/mL (S)	4–6 mg/kg/day in adults	8
E. faecium	Daptomycin	≤ 4 µg/mL (SDD)	8–12 mg/kg/day in adults	20–22

Abbreviations: MIC, minimal inhibitory concentration; S, susceptible; SDD, susceptible-dose dependent.

Table 4. Single-Dose Daptomycin Pharmacokinetics in Healthy Volunteers[a,20]

Dose, mg/kg	C_{max}, µg/mL (% CV)	$AUC_{0-\infty}$, µg · h/mL (% CV)	$t_{1/2}$, h (% CV)	CL_{wp}, mL/h/kg (% CV)	V, mL/kg (% CV)
6	95.7 (31.8)	729.8 (32.2)	7.5 (10.9)	9.9 (12.5)	105.9 (13.3)
8	106.2 (20.0)	773.3 (20.3)	7.3 (18.4)	10.1 (24.0)	102.9 (11.8)
10	129.7 (11.3)	1013.5 (16.2)	8.4 (12.0)	9.9 (20.7)	117.2 (11.5)
12	164.8 (7.4)	1269.2 (22.2)	7.8 (12.1)	10.0 (23.7)	111.1 (13.7)

Abbreviations: $AUC_{0-\infty}$, area under the concentration time curve from 0 to infinity; CL_{wp}, plasma clearance normalized for body weight; C_{max}, maximum concentration of drug in serum; $t_{1/2}$, half-life; % CV, coefficient of variation expressed as a percentage; V, volume.
[a] All values are means.