Meropenem Breakpoints for *Acinetobacter* spp.

CLSI rationale document MR03
September 2019

Romney M. Humphries, PhD, D(ABMM)
Accelerate Diagnostics, Inc.
USA

Elizabeth Wood, PhD
Accelerate Diagnostics, Inc.
USA

On behalf of the CLSI Subcommittee on Antimicrobial Susceptibility Testing

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 CLSI agenda items submitted by the Working Group on AST Breakpoints.

2 Introduction

Meropenem is a member of the carbapenem group of β-lactam antimicrobial agents. β-lactams are characterized by a central four-membered, nitrogen-containing β-lactam ring, and the carbapenem subgroup has a 4:5 fused β-lactam ring, with a double bond between C-2 and C-3 and carbon instead of sulfur at C-1.[4] The mode of action occurs when the β-lactam ring binds to the transpeptidase active site of the penicillin-binding proteins (PBPs); PBPs facilitate the cross-linkage of the peptidoglycan layer of the bacterial cell wall.[5] When the β-lactam ring of the antibiotic binds to PBPs, cell wall synthesis cannot occur, and the bacterial cell dies because of osmotic instability or autolysis.[6]

The carbapenems have *in vitro* activity against gram-positive and gram-negative bacteria, including *Acinetobacter* spp., which are intrinsically resistant to ertapenem. *Acinetobacter* spp. have three mechanisms that contribute to doripenem, imipenem, and meropenem resistance, ie, carbapenem hydrolysis, alteration of outer membrane proteins, and resistance-nodulation-cell division–type efflux pumps.[4] *Acinetobacter baumannii* has a native chromosomal oxacillinase (OXA-51), which may be upregulated, resulting in carbapenem resistance. In addition, *Acinetobacter* spp. have acquired Ambler class A serine carbapenemases, class B metallo-β-lactamases, and class D oxacillinases. Of the class D oxacillinases, OXA-23–like, OXA-24–like, OXA-51 and its variants, OXA-58–like, OXA-143–like, and OXA-235–like, are associated with carbapenem resistance.[4]

Meropenem is approved by the US Food and Drug Administration (FDA) for the treatment of complicated skin or skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, and *Streptococcus agalactiae*; complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides thetaiotaomicron,* and *Peptostreptococcus* spp.; and bacterial meningitis caused by *Haemophilus influenzae, Neisseria meningitidis*, and penicillin-susceptible isolates of *Streptococcus pneumoniae*. Meropenem is frequently used off label to treat *Acinetobacter* spp. infections, because alternatives such as tigecycline or the polymyxins are potentially less effective and/or more toxic.

This document summarizes the data used by CLSI in 2013 to support the current meropenem breakpoints for *Acinetobacter* spp. In 2011, CLSI approved breakpoints for doripenem, at the request of the sponsor, Pfizer, who also requested that all carbapenems be reviewed for *Acinetobacter* spp. This effort was completed in 2013. Although the FDA recognizes current CLSI breakpoints for doripenem and imipenem for *Acinetobacter* spp., to date it has not recognized the CLSI meropenem breakpoints, and treatment of *Acinetobacter* spp. infections is not an on-label indication for meropenem. However, in clinical practice, meropenem is frequently used to treat these infections. Rates of resistance to meropenem may be high, and knowledge of meropenem susceptibility results is critical to inform the choice of meropenem over more-toxic (eg, colistin) or potentially less-effective (eg, tigecycline) agents. For current carbapenem breakpoints for *Acinetobacter* spp., see Table 1.

Table 1. Current CLSI Carbapenem Breakpoints[a]

Organism Group	Antimicrobial Agent	Interpretive Categories and MIC Breakpoints, µg/mL			
		S	SDD	I	R
Acinetobacter spp.	Doripenem	≤ 2	-	4	≥ 8
	Imipenem	≤ 2	-	4	≥ 8
	Meropenem	≤ 2	-	4	≥ 8

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

[a] Last reviewed June 2013; first published in CLSI document M100, 24th ed.

3 Standard Dosages and Pharmacokinetic Data

Pharmacokinetic data are available in the meropenem reference drug label. Susceptibility breakpoints were established using the dosages listed in Table 2.

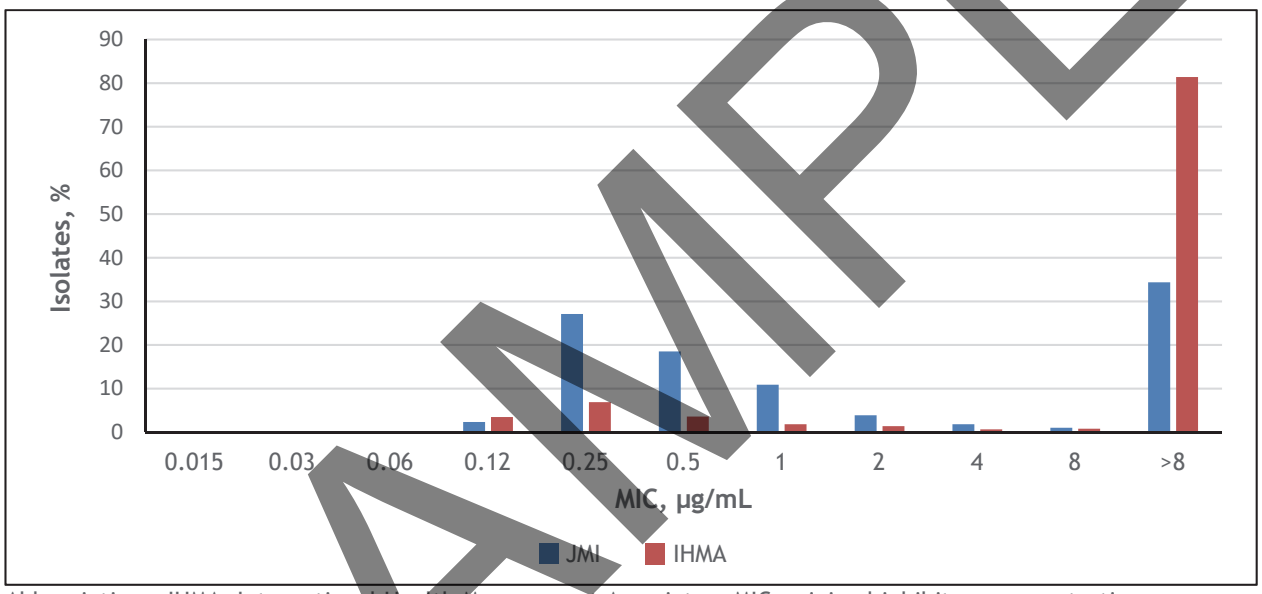
Table 2. Dosages Used for Breakpoint Determination[a]

Organism Group	Antimicrobial Agent	Dosages
Acinetobacter spp.	Doripenem	500 mg administered every 8 hours
	Imipenem	500 mg administered every 6 hours
	Meropenem	1 g administered every 8 hours or 500 mg administered every 6 hours

[a] See CLSI document M100.[2]

4 Minimal Inhibitory Concentration Distribution Data

Several datasets were reviewed for *Acinetobacter* spp. and meropenem MIC distributions in 2013. MIC distribution data are summarized in Table 3. Updated (2016–2018) MIC distributions were also obtained from JMI Laboratories and International Health Management Associates (IHMA) and are shown in Figure 1 and Table 3.



Abbreviations: IHMA, International Health Management Associates; MIC, minimal inhibitory concentration.

Figure 1. MIC Distribution Data for *Acinetobacter* spp. and Meropenem: JMI (United States 2016-2018, *N* = 772) and IHMA (Non-US 2016-2018, *N* = 7245).