# Polymyxin Breakpoints for Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

CLSI rationale document MR01
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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 Polymyxin Breakpoints for Enterobacterales, *P. aeruginosa*, and *Acinetobacter* spp. Ad Hoc Working Group to introduce new colistin and polymyxin B breakpoints for Enterobacterales and to support changes to the breakpoints for *Pseudomonas aeruginosa* and *Acinetobacter* spp.

## 2 Overview of Changes

This rationale document replaces the previous edition of the approved rationale document, MR01, 1st ed., published in 2018. Several changes were made in this edition, including:

- Revised title to reflect inclusion of polymyxin B along with colistin
- Added polymyxin B minimal inhibitory concentration (MIC) breakpoints for *P. aeruginosa* and *Acinetobacter* spp.
- Added colistin and polymyxin B MIC breakpoints for Enterobacterales
- Revised colistin and polymyxin B MIC breakpoints for *P. aeruginosa* and *Acinetobacter* spp.
- Added treatment guidance caveats
- Added historical CLSI polymyxin B MIC breakpoints for *P. aeruginosa* and *Acinetobacter* spp.

## 3 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 MR01.

## 4 Introduction

Polymyxin B and colistin (polymyxin E) are members of the polymyxin group of antimicrobial agents, large amphipathic cyclic lipopeptides that are positively charged at physiological pH.[4] The polymyxins act through electrostatic interaction with the lipopolysaccharide (LPS) component of the gram-negative cell wall, which leads to competitive displacement of the divalent cations that normally stabilize LPS. This disruption of outer membrane integrity results in cytoplasmic leakage and cell death.[4,5] The polymyxins are active against most gram-negative bacilli, including Enterobacterales (excluding *Proteus, Providencia, Morganella,* and *Serratia* spp.), *P. aeruginosa,* and *Acinetobacter* spp. *Neisseria* spp., *Brucella* spp., and *Burkholderia* spp. are intrinsically resistant to the polymyxins.[4] Polymyxin resistance primarily results from modification of the LPS target.[5] A transmissible form of resistance, mediated by plasmid-born *mcr* genes, has been described in the Enterobacterales.[5] There is complete cross-resistance between different polymyxins.[5]

Colistin is approved by the US Food and Drug Administration (FDA) for the treatment of acute or chronic infections caused by susceptible strains of gram-negative bacilli, particularly susceptible strains of *P. aeruginosa*.[6] Polymyxin B is FDA approved for the treatment of acute infections caused by susceptible strains of *P. aeruginosa*, meningeal infections caused by *Haemophilus influenzae,* urinary tract infections caused by *Escherichia coli,* and bacteremia caused by *Klebsiella aerogenes* and *Klebsiella pneumoniae*.[7] Colistin is approved by the European Medicines Agency for the treatment of serious infections due to selected aerobic gram-negative pathogens in patients with limited treatment options.[8]

In practice, both colistin and polymyxin B are relegated to salvage therapy for infections caused by multidrug-resistant isolates of *P. aeruginosa*, *Acinetobacter baumannii,* or carbapenem-resistant Enterobacterales. In these scenarios, polymyxin B and colistin are used primarily as part of combination therapy and should be used only when other antimicrobial agents are not active (eg, for metallo-β-lactamase–producing isolates of Enterobacterales) or available (eg, in countries where newer antimicrobial agents with specific activity against multidrug-resistant gram-negative bacteria have not yet been made clinically available).[9] Colistin is administered as the inactive prodrug, colistin methanesulfonate (CMS), whereas polymyxin B is administered in its active form.

For many years, CLSI did not publish Enterobacterales breakpoints for the polymyxins because of a dearth of clinical and PK-PD data that could be used to establish those breakpoints. However, CLSI recognized a need for guidance on how to best use these antimicrobial agents, despite the availability of new drugs demonstrating greater clinical efficacy. Specifically, CLSI recognized that new drugs are not available in all parts of the world. Also, it was recognized that there may be a need to rely on colistin or polymyxin B therapy when new drugs are not active. For these reasons, CLSI reviewed existing data, including a newly available international treatment guidance document,[9] which the ad hoc committee relied on during deliberations. The following caveats apply to the CLSI Enterobacterales, *P. aeruginosa,* and *Acinetobacter* spp. colistin and polymyxin B breakpoints:

- Clinical and PK-PD data suggest that these agents have limited clinical efficacy, regardless of MIC result.
- Alternative nonpolymyxin agents are strongly preferred when they are active *in vitro,* if available.
- Polymyxins should be used in combination with other active antimicrobial agents whenever possible.
- Colistin should be given with a loading dose and maximum renally adjusted doses as outlined in the international treatment guidance document.[9]
- Polymyxin B should be given at maximum doses, as outlined in the international treatment guidance document.[9]
- When given intravenously, polymyxin B and colistin are unlikely to be effective against pneumonia.
- The breakpoints in this document do not apply to inhaled formulations of colistin or polymyxin B.

The current colistin and polymyxin B breakpoints are listed in Table 1, and the historical breakpoints are listed in Table 2.

**Table 1. Current CLSI Colistin and Polymyxin B Breakpoints[a]**

| Organism Group | Antimicrobial Agent | Interpretive Categories and MIC Breakpoints, µg/mL | | | |
|---|---|---|---|---|---|
| | | S | SDD | I | R |
| Enterobacterales | Colistin | - | - | ≤2^[b] | ≥4 |
| | Polymyxin B | - | - | ≤2 | ≥4 |
| *P. aeruginosa* | Colistin | - | - | ≤2 | ≥4[c] |
| | Polymyxin B | - | - | ≤2 | ≥4 |
| *Acinetobacter* spp. | Colistin | - | - | ≤2 | ≥4 |
| | Polymyxin B | - | - | ≤2 | ≥4 |

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

[a] Last reviewed June 2019; first published in CLSI document M100, 30th ed.[2]

[b] Intermediate ranges denoted with a "^" for the applicable antimicrobial agents are based on the known ability of these agents to concentrate in the urine; some agents may also have the potential to concentrate at other anatomical sites (eg, epithelial lining).

[c] Last reviewed June 2016; first published in CLSI document M100, 27th ed.