Piperacillin-Tazobactam Breakpoints for Enterobacterales

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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 at a previously set breakpoint. 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 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 Working Group on Piperacillin-Tazobactam to reassess piperacillin-tazobactam breakpoints for Enterobacterales.

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 MR14.

3 Introduction

Piperacillin-tazobactam is a broad-spectrum β-lactam combination agent widely used in clinical practice for the treatment of gram-negative pathogens. It is composed of piperacillin, an ureidopenicillin, and tazobactam, a β-lactamase inhibitor. Piperacillin-tazobactam breakpoints were first published in CLSI document M100[2] in 1992. Over the next 30 years, the spectrum of β-lactamases found in Enterobacterales expanded to include those that are inhibited by tazobactam (eg, *TEM*, *SHV*, and *CTX-M* extended-spectrum β-lactamases [ESBLs]) and those that are poorly inhibited by tazobactam (eg, *OXA-1* and *OXA-30*).[4] In addition, over the past two decades, multiple studies using modern methods of PK/PD evaluation assessing predictable target attainment with optimized dosing strategies have been published, highlighting low probability of target attainment (PTA) for existing breakpoints. Lastly, a recent randomized controlled trial demonstrated clinical failure of piperacillin-tazobactam at minimal inhibitory concentrations (MICs) > 16 µg/mL.[5] This shift in epidemiology, coupled with mounting PK/PD and clinical outcome data, demonstrated the need to re-evaluate the breakpoints. The CLSI Working Group on Piperacillin-Tazobactam was convened to evaluate available evidence and possible revision of the piperacillin-tazobactam breakpoints for Enterobacterales. The historical piperacillin-tazobactam breakpoints are shown in Table 1.

Table 1. Historical CLSI Piperacillin-Tazobactam Breakpoints[a]

Test/ Report Group	Organism Group	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm[b]			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	I	R	S	I	R
B	Enterobacterales	≥ 21	18–20^	≤ 17	≤ 16/4	32/4–64/4^	≥ 128/4

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible.
Symbol: ^, designation for agents that have the potential to concentrate in the urine.
[a] Last published in CLSI document M100, 31st ed.
[b] Disk content 100/10 µg.

4 Standard Dosages and Pharmacokinetic Data

Table 2 provides the US Food and Drug Administration (FDA)–approved parenteral administration schedule for piperacillin-tazobactam in adult patients.

Table 2. Recommended Dosage Schedule for Piperacillin-Tazobactam in Adult Patients[6]

Renal Function	All Indications (except nosocomial pneumonia)[a,b]	Nosocomial Pneumonia[a,b,c]
CrCl > 40 mL/min	3.375 g every 6 h	4.5 g every 6 h
CrCl 20–40 mL/min[d]	2.25 g every 6 h	3.375 g every 6 h
CrCl < 20 mL/min[d]	2.25 g every 8 h	2.25 g every 6 h
Hemodialysis[e]	2.25 g every 12 h	2.25 g every 8 h
Continuous ambulatory peritoneal dialysis	2.25 g every 12 h	2.25 g every 8 h

Abbreviations: CrCl, creatinine clearance; h, hour; min, minute.
[a] Each piperacillin and tazobactam for injection 3.375-g single-dose vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam.
[b] Each piperacillin and tazobactam for injection 2.25 g single-dose vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam.
[c] Each piperacillin and tazobactam for injection 4.5-g single-dose vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam.
[d] CrCl for patients not receiving hemodialysis.
[e] 0.75 g should be administered following each hemodialysis session on hemodialysis days.

Table 3 shows the standard dosages of piperacillin-tazobactam based on 165 410 prescriptions.

Table 3. Standard Piperacillin-Tazobactam Dosages[a,7]

Dosage Regimen	Percentage
3.375 g every 8 h	37%
3.375 g every 6 h[b]	18%
3.375 g every 12 h	10%
4.5 g every 8 h	5%
4.5 g every 6 h[b]	4.5%

Abbreviation: h, hour.
[a] Based on 165 410 prescriptions.
[b] FDA-approved dosage.