Piperacillin-Tazobactam Breakpoints for *Pseudomonas aeruginosa*

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On behalf of the Working Group on Piperacillin-Tazobactam and 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 [PK/PD], and clinical studies) to establish antimicrobial susceptibility test methods, breakpoints, and QC ranges.

The details of the necessary and recommended data for selecting appropriate breakpoints and QC ranges, as well as how the data are presented for evaluation, are described in CLSI M23.[1] CLSI antibacterial breakpoints are provided in CLSI M100[2] and CLSI M45.[3]

Over time, a microorganism's susceptibility to an antimicrobial agent can decrease, resulting in a lack of clinical efficacy and/or safety. Also, microbiological methods, QC parameters, and the manner in which breakpoints are established might 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 Working Group on Piperacillin-Tazobactam to reassess piperacillin-tazobactam breakpoints against *Pseudomonas aeruginosa*.

2 Introduction

Piperacillin-tazobactam is a broad-spectrum β-lactam/β-lactamase inhibitor combination agent widely used in clinical practice as empiric and/or definitive therapy against gram-negative pathogens, including *P. aeruginosa*. It is composed of piperacillin, a ureidopenicillin, and tazobactam, a β-lactamase inhibitor. Piperacillin-tazobactam breakpoints against *P. aeruginosa* were first published in CLSI M100[2] in 1992 and subsequently revised in 2012. Since then, multiple studies using modern PK/PD methods to assess the probability of target attainment (PTA) with optimized dosing strategies have been published, highlighting low PTA at minimal inhibitory concentrations (MICs) > 16 µg/mL.[4] The CLSI Working Group on Piperacillin-Tazobactam reevaluated available evidence for possible revision of the piperacillin-tazobactam breakpoints against *P. aeruginosa* in 2022. The historical piperacillin-tazobactam breakpoints are shown in Table 1.

Table 1. Historical CLSI Piperacillin-Tazobactam Breakpoints Against *Pseudomonas aeruginosa*

Year	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm[a]			Interpretive Categories and MIC Breakpoints, µg/mL		
	S	I	R	S	I	R
1992	≥ 18	-	≤ 17	≤ 64/4	-	≥ 128/4
2012[b]	≥ 21	15-20^	≤ 14	≤ 16/4	32/4-64/4^	≥ 128/4
2023	≥ 22	18-21^	≤ 17	≤ 16/4[c]	32/4	≥ 64/4

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible.
Symbol: ^ designates agents that have the potential to concentrate in urine.
[a] Disk content 100/10 µg.
[b] Based on a piperacillin-tazobactam dosage regimen of ≥ 3.375 g given every 6 hours.
[c] Based on a piperacillin-tazobactam dosage regimen of 4.5 g every 6 hours as a 30-minute or 3-hour infusion.

3 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[a,5]

Creatinine Clearance, mL/min[b]	Nosocomial Pneumonia[c,d,e]	All Other Indications[d,e]
> 40	4.5 g every 6 h	3.375 g every 6 h
20–40	3.375 g every 6 h	2.25 g every 6 h
< 20	2.25 g every 6 h	2.25 g every 8 h
Intermittent hemodialysis[f]	2.25 g every 8 h	2.25 g every 12 h
Continuous ambulatory peritoneal dialysis	2.25 g every 8 h	2.25 g every 12 h

Abbreviations: h, hour; min, minute.
[a] Doses infused over 30 minutes.
[b] Creatinine clearance for patients not receiving hemodialysis.
[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 piperacillin and tazobactam sodium equivalent to 0.5 g tazobactam.
[d] 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 piperacillin and tazobactam sodium equivalent to 0.375 g tazobactam.
[e] 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 piperacillin and tazobactam sodium equivalent to 0.25 g tazobactam.
[f] A supplemental dose of 0.75 g should be administered following each hemodialysis session on hemodialysis days.

Table 3 shows the most commonly used dosages of piperacillin-tazobactam based on 165 410 prescriptions.

Table 3. Most Commonly Used Piperacillin-Tazobactam Dosages in Adult Patients[a,6]

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

Abbreviation: h, hour.
[a] Infusion duration not reported.
[b] FDA-approved dosage.

4 Minimal Inhibitory Concentration Distribution Data

Aggregate data, including 29 971 MIC observations from 58 distributions, were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (see Figure 1).[7] An epidemiological cutoff value (ECV or ECOFF) of 16/4 µg/mL was demonstrated for piperacillin-tazobactam against *P. aeruginosa*. These data aligned with those obtained from the JMI SENTRY Surveillance database of 34 667 observations demonstrating a 97.5% ECV of 16/4 µg/mL (see Figure 2).[8]

Breakpoints set below the ECV reduce the ability of antimicrobial susceptibility testing methods to reliably distinguish between interpretive categories, potentially leading to unacceptably high error rates (ie, misclassification of susceptible and nonsusceptible isolates).[9] Importantly, the *P. aeruginosa*-specific ECV was one $\log_2$ dilution higher than the Enterobacterales ECV and corresponding susceptibility breakpoint of ≤ 8/4 µg/mL, thereby preventing breakpoint harmonization across these organism groups (see Figure 2).