Piperacillin-Tazobactam Breakpoints for *Pseudomonas aeruginosa*

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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 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^	≥ 28/4
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]

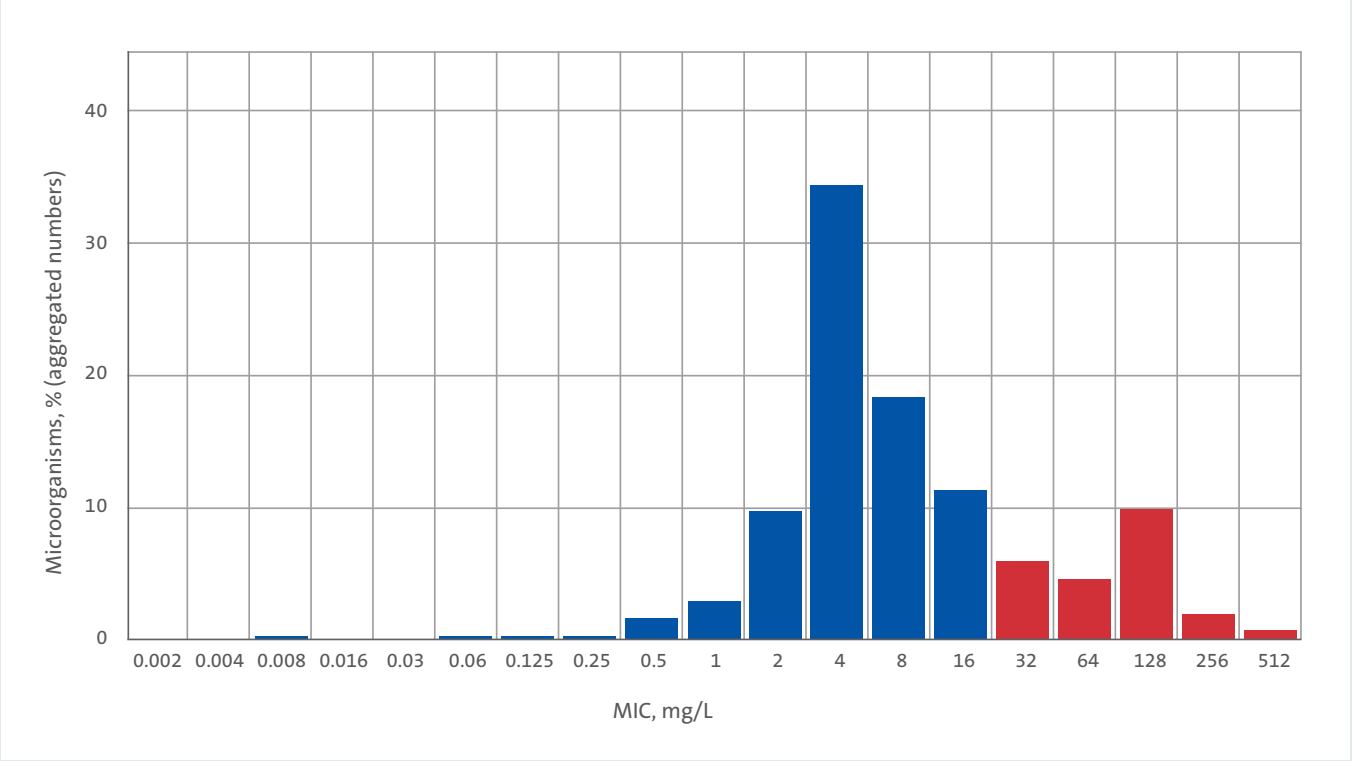
Dosage Regimen	Percentage
4.5 g every 6 h[b]	4.5%
4.5 g every 8 h	5%
3.375 g every 12 h	10%
3.375 g every 6 h[b]	18%
3.375 g every 8 h	37%

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

4 Minimal Inhibitory Concentration Distribution Data

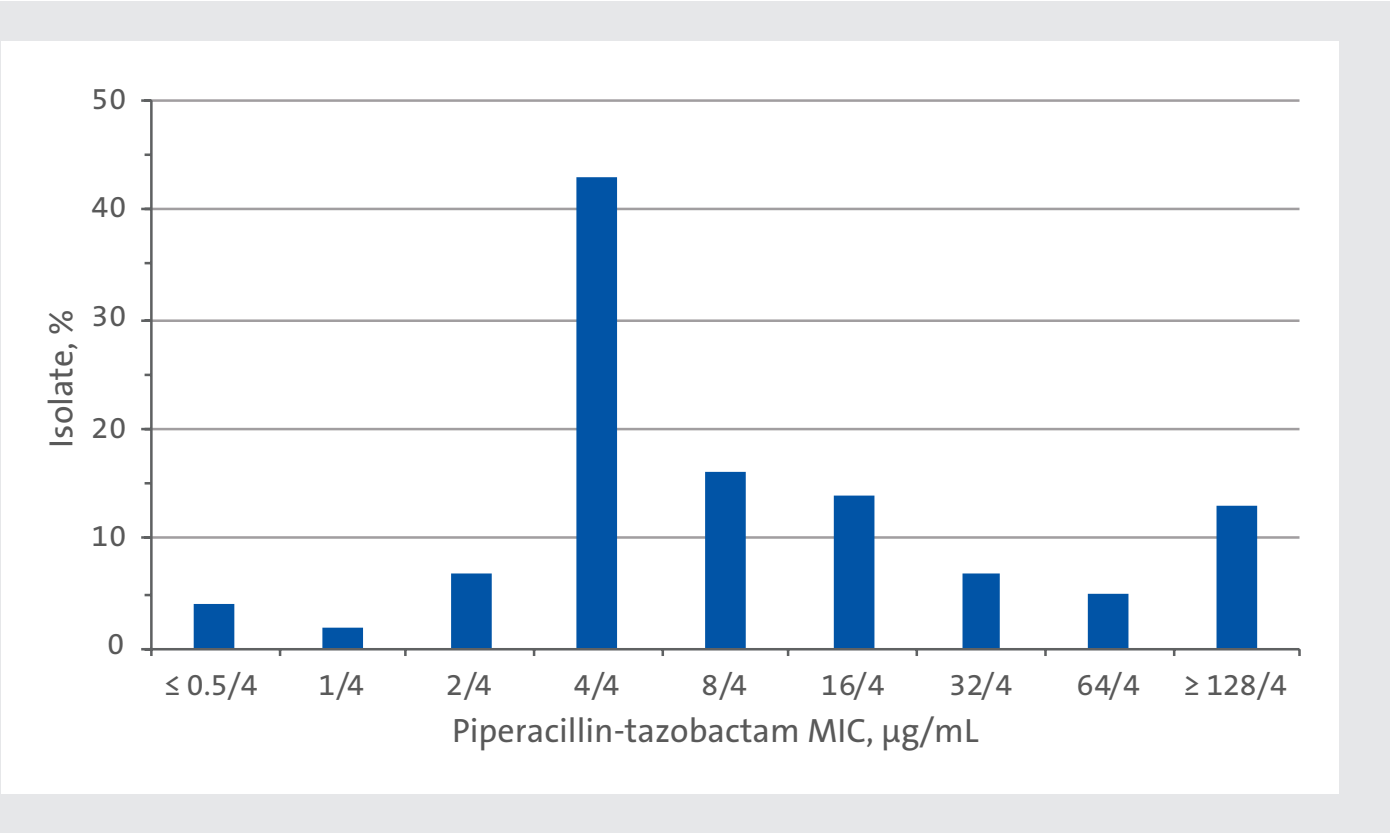
Aggregate data, including 29 971 MIC observations from 58 distributions, were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (see Figure 1).[7] An epidemiological cutoff value (ECV or ECOFF) of 16/4 µg/mL was demonstrated for piperacillin-tazobactam against *P. 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).



Abbreviation: MIC, minimal inhibitory concentration.

Figure 1. Piperacillin-Tazobactam MIC Distribution Against *Pseudomonas aeruginosa*.[7] Blue bars indicate wild-type organisms, and red bars indicate non-wild-type organisms. (European Committee on Antimicrobial Susceptibility Testing [EUCAST]. MIC and zone diameter distributions and ECOFFs. Accessed 12 January 2023. https://www.eucast.org/mic_distributions_and_ecoffs/)



Abbreviation: MIC, minimal inhibitory concentration.

Figure 2. JMI SENTRY Surveillance Database Aggregate Piperacillin-Tazobactam MIC Distribution Against *Pseudomonas aeruginosa*[8] (Data from JMI Laboratories. MVP report of activity of piperacillin-tazobactam against 34,667 *Pseudomonas aeruginosa* isolates in the SENTRY program, United States 2012-2022. Accessed 12 January 2023. sentry-mvp.jmilabs.com)

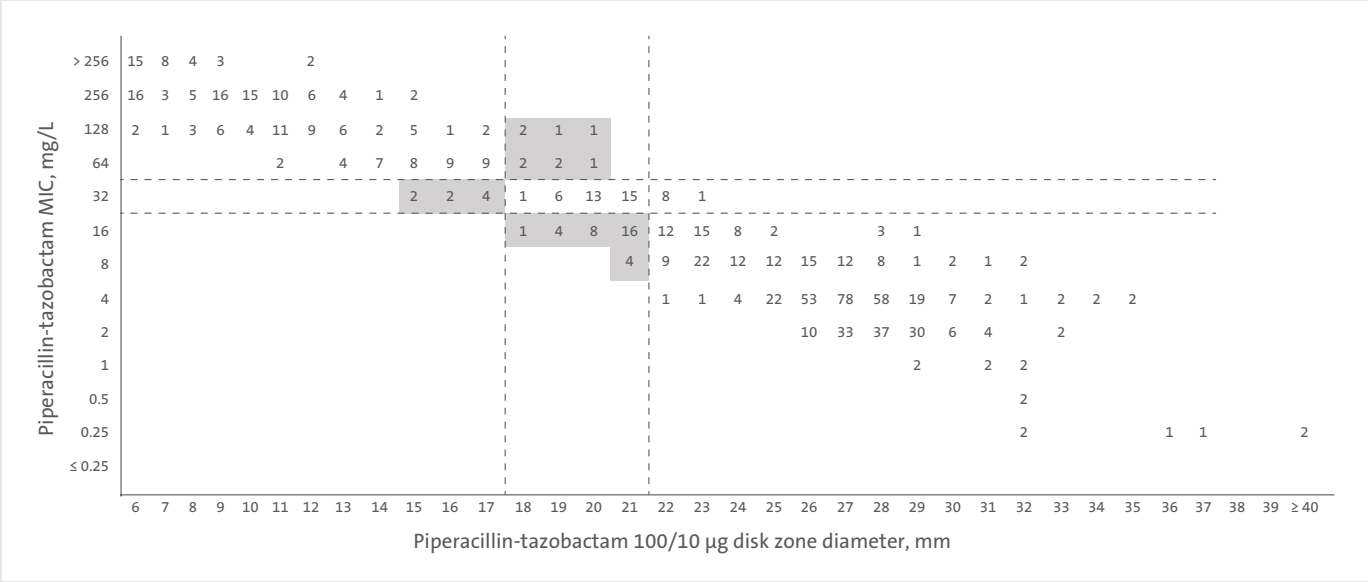
5 Disk Diffusion Zone Diameter Compared With Minimal Inhibitory Concentration Correlates

Data comparing disk diffusion zone diameters with MICs were obtained from the 2012 piperacillin-tazobactam breakpoint revision against *P. aeruginosa* and reanalyzed according to tentative 2023 breakpoints. Piperacillin-tazobactam broth microdilution MICs were compared with 100/10 µg disk zone diameters against 820 isolates of *P. aeruginosa*. Table 4 shows error rates at tentative MIC susceptible breakpoints of ≤ 16/4 µg/mL, intermediate breakpoints of 32/4 µg/mL, and resistant breakpoints of ≥ 64/4 µg/mL. Figure 3 shows error rates of tentative disk zone diameter correlates at susceptible breakpoints of ≥ 22 mm, intermediate breakpoints of 18 to 21 mm, and resistant breakpoints of ≤ 17 mm. Minor error rates for the ≥ I+2 and ≤ I–2 MIC ranges as calculated by the error rate–bound method each exceeded the acceptable thresholds of ≤ 5% (see Table 4).[10] Disks showed a tendency to more frequently overcall isolates that were considered susceptible by broth microdilution (n = 33) as intermediate, compared with undercalling isolates that were resistant by broth microdilution (n = 9) as intermediate. The slight revision of the susceptible zone diameter from ≥ 21 mm to ≥ 22 mm caused 20 of these minor errors but was made to reduce the likelihood that disk testing would incorrectly categorize isolates with MICs of 32 µg/mL as susceptible (see Figure 3).

Table 4. Summary of Error Rates for Piperacillin-Tazobactam 100/10 µg Disks vs MICs at Tentative 2023 *Pseudomonas aeruginosa* Breakpoints

MIC Range	Number of Isolates	Error Rates, n (%)		
		Very Major	Major	Minor
≥ I+2	152	0	N/A	26 (17.1)
I±1	166	0	0	51 (30.7)
≤ I–2	222	N/A	0	50 (22.5)
Total	540	0	0	127 (23.5)

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; N/A, not applicable.



Abbreviation: MIC, minimal inhibitory concentration.

Figure 3. Disk Diffusion Zone Diameter Correlates to Piperacillin-Tazobactam MICs Against *Pseudomonas aeruginosa* at Tentative 2023 CLSI Breakpoints. Correlates are based on 820 isolates included in the 2012 CLSI breakpoint revision data. Gray-shaded cells represent minor errors.

6 Pharmacokinetic/Pharmacodynamic Data

Evaluation of available piperacillin-tazobactam PK/PD data against *P. aeruginosa* resulted in findings similar to those described for Enterobacterales,[4] with some notable differences. First, preclinical data clearly demonstrate that the addition of tazobactam to piperacillin does not affect the MIC or antibacterial activity or efficacy against *P. aeruginosa,* allowing pharmacometric studies to focus on the PTA of piperacillin alone at a threshold of 50% $fT_{>MIC}$.[11-15] This ≥ 50% $fT_{>MIC}$ threshold is based on the maximal bactericidal activity of penicillins overall and is supported by preclinical and clinical PK/PD studies of piperacillin against *P. aeruginosa.* Although some preclinical *in vitro* and/or *in vivo* studies of piperacillin-tazobactam support a target of ≥ 40% $fT_{>MIC}$ for bactericidal activity, all published pharmacometric studies capable of estimating PTA and thereby assisting in breakpoint revision utilized an $fT_{>MIC}$ threshold of ≥ 50% (see Table 5). A thorough search did not yield primary literature that described utilization of any target other than 50% $fT_{>MIC}$, outside some clinical studies in critically ill patients targeting 100% $fT_{>MIC}$.[16-20] Also, because the 2012 revision of CLSI M100 (CLSI M100-S22) set the susceptibility breakpoint at the ECV of ≤ 16/4 µg/mL, PK/PD analyses centered around identifying optimal dose-exposure thresholds for the susceptible and intermediate categories. Doses listed in CLSI M100[2] indicate the drug exposure at which an MIC breakpoint was determined and are not intended to be comprehensive dosing recommendations. Given the number of possible piperacillin-tazobactam dosing regimens available, a

more evidence-based, parsimonious, and/or standard dosage regimen was favored when appropriate (eg, 4.5 g every 8 hours over 4 hours vs 3.375 g every 6 hours over 4 hours).[18,21,22] Extended-infusion dosing (over 3 to 4 hours) of the 4.5 g dose every 6 to 8 hours was optimal for achieving ≥ 90% PTA at MICs ≤ 16/4 µg/mL. No dosage regimen demonstrated acceptable PTA at MICs ≥ 32/4 µg/mL in patients with normal renal function (ie, creatinine clearance ≤ 120 mL/min), regardless of study methodology or infusion duration.

Table 5. Summary of PK/PD Studies Investigating Piperacillin-Tazobactam Achievable MIC Targets for ≥ 90% PTA at 50% $fT_{>MIC}$

Dosage	Infusion Time	Maximum Achievable MIC, µg/mL
3.375 g every 6 h[21,23-28]	30 min	8/4
4.5 g every 8 h[21-24]	30 min	8/4
4.5 g every 6 h[21,22,29-31]	30 min	8/4
4.5 g every 6 h[26,32]	30 min	16/4
3.375 g every 8 h[22,30,33-35]	4 h	8/4
4.5 g every 8 h[21,22,26,29,30]	4 h	8/4
4.5 g every 8 h[21,30,34,36]	4 h	16/4
4.5 g every 6 h[21,22,29,31,36]	3 h	16/4

Abbreviations; h, hour; MIC, minimal inhibitory concentration; min, minute.

7 Clinical Efficacy

Clinical data providing insights into piperacillin-tazobactam MIC correlations with clinical outcomes of patients treated with piperacillin-tazobactam for *P. aeruginosa* infections are limited to observational studies. In a study of 34 adults with *P. aeruginosa* bacteremia with piperacillin-tazobactam MICs of 32/4 to 64/4 µg/mL, 86% 30-day mortality was observed for patients receiving piperacillin-tazobactam compared with 22% for patients receiving other antipseudomonal β-lactam agents.[37] Piperacillin-tazobactam dosing used in the study was not provided. None of the patients received extended-infusion piperacillin-tazobactam.

In a study of 170 children with *P. aeruginosa* bacteremia, a 30-day mortality of 24% and 9%, respectively, was demonstrated in children with piperacillin MICs 32/4 to 64/4 µg/mL and ≤ 16/4 µg/mL.[38] Approximately 20% of children received piperacillin 400 mg/kg per day, and the remainder received 300 mg/kg per day. Dosages were equally distributed between the two MIC categories and were appropriately adjusted for all children with renal impairment. None of the children were prescribed extended-infusion or continuous-infusion piperacillin. Differences in outcomes by piperacillin dosages were not evaluated.

A third study in which 78 patients with *P. aeruginosa* bacteremia or pneumonia were evaluated indicated favorable outcomes in 43% of patients with piperacillin-tazobactam MICs ≥ 32/4 µg/mL compared with 94% of patients with piperacillin-tazobactam MICs ≤ 16/4 µg/mL.[39] The microbiological effect after treatment was used to determine the efficacy of various piperacillin-tazobactam dosing regimens. In 28 of 30 patients with pseudomonal pneumonia receiving piperacillin-tazobactam 4.5 g every 8 hours, the microbiological efficacy was 93% when the MIC was ≤ 16 µg/mL and 50% (5 of 9 patients) and 0% (0 of 3 patients) with MICs 32 µg/mL ($P < 0.05$) and 64 µg/mL, respectively. In 11 of 11 patients with bacteremia receiving piperacillin-tazobactam as 4.5 g either three times a day or four times a day, the microbiological efficacy was 100% when the MIC was < 16 µg/mL and 33% (1 of 3 patients) and 0% (0 of 3 patients) with MICs 32 µg/mL and ≥ 64 µg/mL, respectively.

Finally, a study of 354 episodes of *P. aeruginosa* bacteremia demonstrated in-hospital mortality of 34% and 21%, respectively, in patients with piperacillin-tazobactam MICs 32/4 to 64/4 µg/mL and ≤ 16/4 µg/mL, respectively.[40] Dosing of piperacillin-tazobactam was 4.5 g every 6 hours (23% of patients), 3.375 g every six hours (51% of patients), and ≈ 3.375 g every 8 hours (26% of patients), all as standard infusions. Differences in outcomes by piperacillin-tazobactam dosing were not evaluated.

Limitations exist with the available clinical data, including likely selection bias influencing treatment assignment, generally small sample sizes, and heterogenous piperacillin-tazobactam dosing. Moreover, no studies have investigated the association of extended-infusion piperacillin-tazobactam on patient outcomes. Although not all studies achieved statistical significance in demonstrating poorer outcomes for patients infected with *P. aeruginosa* isolates with piperacillin-tazobactam MICs ≥ 32 µg/mL, the preponderance of data indicate a clinical failure signal for *P. aeruginosa* isolates with MICs ≥ 32 µg/mL treated with piperacillin-tazobactam.

8 Committee Rationale for the Breakpoint

With a combination of the available evidence, PK/PD data indicate that appropriate target attainment with MICs 16/4 µg/mL is unlikely to be achieved with standard-infusion piperacillin-tazobactam but can be achieved with extended-infusion piperacillin-tazobactam. PK/PD and clinical outcomes data indicate that MICs ≥32/4 µg/mL are associated with unacceptably low PTA and increased mortality. These data led to CLSI recategorizing piperacillin-tazobactam against *P. aeruginosa* as susceptible for MICs ≤ 16/4 µg/mL, intermediate for MICs 32/4 µg/mL, and resistant for MICs ≥64/4 µg/mL, based on the dosing shown in Table 5. Although the 4.5 g every 6 hours dosage regimen can be administered as a standard (30-minute) or extended (3-hour) infusion for susceptible isolates, based on PK/PD data, the standard infusion is preferred for isolates with an MIC ≤ 8/4 µg/mL and the extended infusion is preferred for isolates with an MIC 16/4 µg/mL. The intermediate breakpoint of 32/4 µg/mL for piperacillin-tazobactam against *P. aeruginosa* is meant only to account for technical variability inherent to susceptibility testing and does not imply dose-dependent susceptibility. Administration of piperacillin-tazobactam against *P. aeruginosa* isolates with MIC 32/4 µg/mL is not advised.

9 Final Table Entry

Table 6 shows the final table entry from CLSI M100.[2]

Table 6. Excerpt From CLSI M100[2] Table 2B-1, Zone Diameter and MIC Breakpoints for *Pseudomonas aeruginosa*[a]

Antimicrobial Agent	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm[b]			Interpretive Categories and MIC Breakpoints, µg/mL		
	S	I	R	S	I	R
Piperacillin-tazobactam	≥ 22	18-21^	≤ 17	≤ 16/4	32/4	≥ 64/4

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible.
[a] Susceptible breakpoints are based on a dosage regimen of 4.5 g administered every 6 hours over 30 minutes or over 3 hours. Intermediate breakpoints are only to provide a buffer zone to prevent small uncontrolled technical factors from causing major discrepancies in interpretations.
[b] Disk content 100/10 µg.

10 Voting Record

MIC breakpoints: approved in January 2022 (11 approved, 2 opposed, 0 abstained, 0 absent).

Disk diffusion zone diameter breakpoints: approved in January 2022 (13 approved, 0 opposed, 0 abstained, 0 absent).

11 References

1 CLSI. *Development of* In Vitro *Susceptibility Test Methods, Breakpoints, and Quality Control Parameters*. 6th ed. CLSI guideline M23. Clinical and Laboratory Standards Institute; 2023.

2 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 33rd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2023.

3 CLSI. *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*. 3rd ed. CLSI guideline M45. Clinical and Laboratory Standards Institute; 2016.

4 Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Breaking down the breakpoints: rationale for the 2022 Clinical and Laboratory Standards Institute revised piperacillin-tazobactam breakpoints against Enterobacterales. *Clin Infect Dis.* 2023. doi:10.1093/cid/ciac688

5 US FDA. Piperacillin and tazobactam for injection. Accessed 23 October 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/065446s000lbl.pdf

6 Premier Applied Sciences® Premier Inc. Premier Healthcare Database: Data That Informs and Performs. Accessed 1 November 2023. https://learn.premierinc.com/white-papers/premier-healthcare-database-whitepaper

7 European Committee on Antimicrobial Susceptibility Testing (EUCAST). MIC and zone diameter distributions and ECOFFs. 2023. Accessed 31 October 2023. https://www.eucast.org/mic_distributions_and_ecoffs/

8 JMI Laboratories. MVP report of activity of piperacillin-tazobactam against 34,667 *Pseudomonas aeruginosa* isolates in the SENTRY program. 2023. Accessed 12 January 2023. sentry-mvp.jmilabs.com

9 Kahlmeter G, Turnidge J. How to: ECOFFs—the why, the how, and the don'ts of EUCAST epidemiological cutoff values. *Clin Microbiol Infect*. 2022;28(7):952-954. doi:10.1016/j.cmi.2022.02.024

10 Humphries RM, Abbott AN, Hindler JA. Understanding and addressing CLSI breakpoint revisions: a primer for clinical laboratories. *J Clin Microbiol.* 2019;57(6). doi:10.1128/jcm.00203-19

11 Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis.* 2007;44(1):79-86. doi:10.1086/510079

12 Hyatt JM, Nix DE, Stratton CW, Schentag JJ. *In vitro* pharmacodynamics of piperacillin, piperacillin-tazobactam, and ciprofloxacin alone and in combination against *Staphylococcus aureus, Klebsiella pneumoniae, Enterobacter cloacae,* and *Pseudomonas aeruginosa. Antimicrob Agents Chemother.* 1995;39(8):1711-1716. doi:10.1128/aac.39.8.1711

13 Strayer AH, Gilbert DH, Pivarnik P, Medeiros AA, Zinner SH, Dudley MN. Pharmacodynamics of piperacillin alone and in combination with tazobactam against piperacillin-resistant and -susceptible organisms in an *in vitro* model of infection. *Antimicrob Agents Chemother.* 1994;38(10):2351-2356. doi:10.1128/aac.38.10.2351

14 Li C, Nicolau DP, Lister PD, Quintiliani R, Nightingale CH. Pharmacodynamic study of β-lactams alone and in combination with β-lactamase inhibitors against *Pseudomonas aeruginosa* possessing an inducible β-lactamase. *J Antimicrob Chemother.* 2004;53(2):297-304. doi:10.1093/jac/dkh057

15 Bulik CC, Tessier PR, Keel RA, Sutherland CA, Nicolau DP. *In vivo* comparison of CXA-101 (FR264205) with and without tazobactam versus piperacillin-tazobactam using human simulated exposures against phenotypically diverse gram-negative organisms. *Antimicrob Agents Chemother.* 2012;56(1):544-549. doi:10.1128/aac.01752-10

16 Heil EL, Nicolau DP, Farkas A, Roberts JA, Thom KA. Pharmacodynamic target attainment for cefepime, meropenem, and piperacillin-tazobactam using a pharmacokinetic/pharmacodynamic-based dosing calculator in critically ill patients. *Antimicrob Agents Chemother.* 2018;62(9). doi:10.1128/aac.01008-18

17 Taccone FS, Laterre PF, Dugernier T, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care.* 2010;14(4):R126. doi:10.1186/cc9091

18 Udy AA, Lipman J, Jarrett P, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? *Crit Care.* 2015;19(1):1-9.

19 Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. β-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent β-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med.* 2016;42(10):1535-1545. doi:10.1007/s00134-015-4188-0

20 Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients—are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis.* 2014;58(8):1072-1083. doi:10.1093/cid/ciu027

21 Thabit AK, Grupper M, Nicolau DP, Kuti JL. Simplifying piperacillin/tazobactam dosing: pharmacodynamics of utilizing only 4.5 or 3.375 g doses for patients with normal and impaired renal function. *J Pharm Pract.* 2017;30(6):593-599. doi:10.1177/0897190016684453

22 Felton TW, Hope WW, Lomaestro BM, et al. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. *Antimicrob Agents Chemother.* 2012;56(8):4087-4094. doi:10.1128/aac.00521-12

23 Li C, Kuti JL, Nightingale CH, Mansfield DL, Dana A, Nicolau DP. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. *J Antimicrob Chemother.* 2005;56(2):388-395. doi:10.1093/jac/dki243

24 Lodise TP Jr, Lomaestro B, Rodvold KA, Danziger LH, Drusano GL. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. *Antimicrob Agents Chemother.* 2004;48(12):4718-4724. doi:10.1128/aac.48.12.4718-4724.2004

25 Occhipinti DJ, Pendland SL, Schoonover LL, Rypins EB, Danziger LH, Rodvold KA. Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. *Antimicrob Agents Chemother.* 1997;41(11):2511-2517. doi:10.1128/aac.41.11.2511

26 Kim MK, Xuan D, Quintiliani R, Nightingale CH, Nicolau DP. Pharmacokinetic and pharmacodynamic profile of high dose extended interval piperacillin-tazobactam. *J Antimicrob Chemother.* 2001;48(2):259-267. doi:10.1093/jac/48.2.259

27 Burgess DS, Waldrep T. Pharmacokinetics and pharmacodynamics of piperacillin/tazobactam when administered by continuous infusion and intermittent dosing. *Clin Ther.* 2002;24(7):1090-1104. doi:10.1016/s0149-2918(02)80021-2

28 Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD. Pharmacokinetics of piperacillin-tazobactam: intermittent dosing versus continuous infusion. *Int J Antimicrob Agents.* 2005;25(1):62-67. doi:10.1016/j.ijantimicag.2004.08.012

29 Alobaid AS, Wallis SC, Jarrett P, et al. Population pharmacokinetics of piperacillin in nonobese, obese, and morbidly obese critically ill patients. *Antimicrob Agents Chemother.* 2017;61(3). doi:10.1128/aac.01276-16

30 Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB. Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. *J Clin Pharmacol.* 2015;55(8):899-908. doi:10.1002/jcph.505

31 El-Haffaf I, Caissy JA, Marsot A. Piperacillin-tazobactam in intensive care units: a review of population pharmacokinetic analyses. *Clin Pharmacokinet.* 2021;60(7):855-875. doi:10.1007/s40262-021-01013-1

32 Mattoes HM, Capitano B, Kim MK, et al. Comparative pharmacokinetic and pharmacodynamic profile of piperacillin/tazobactam 3.375G Q4H and 4.5G Q6H. *Chemotherapy.* 2002;48(2):59-63. doi:10.1159/000057663

33 Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy.* 2006;26(9):1320-1332. doi:10.1592/phco.26.9.1320

34 Shea KM, Cheatham SC, Wack MF, Smith DW, Sowinski KM, Kays MB. Steady-state pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by prolonged infusion in hospitalised patients. *Int J Antimicrob Agents.* 2009;34(5):429-433. doi:10.1016/j.ijantimicag.2009.07.004

35 Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of optimal renal dosage adjustments for traditional and extended-infusion piperacillin-tazobactam dosing regimens in hospitalized patients. *Antimicrob Agents Chemother.* 2010;54(1):460-465. doi:10.1128/aac.00296-09

36 Merino-Bohórquez V, Docobo-Pérez F, Valiente-Méndez A, et al. Population pharmacokinetics of piperacillin in non-critically ill patients with bacteremia caused by Enterobacteriaceae. *Antibiotics (Basel).* 2021;10(4):348. doi:10.3390/antibiotics10040348

37 Tam VH, Gamez EA, Weston JS, et al. Outcomes of bacteremia due to *Pseudomonas aeruginosa* with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. *Clin Infect Dis.* 2008;46(6):862-867. doi:10.1086/528712

38 Tamma PD, Turnbull AE, Milstone AM, Hsu AJ, Carroll KC, Cosgrove SE. Does the piperacillin minimum inhibitory concentration for *Pseudomonas aeruginosa* influence clinical outcomes of children with pseudomonal bacteremia? *Clin Infect Dis.* 2012;55(6):799-806. doi:10.1093/cid/cis545

39 Yamagishi Y, Terada M, Ohki E, Miura Y, Umemura T, Mikamo H. Investigation of the clinical breakpoints of piperacillin-tazobactam against infections caused by *Pseudomonas aeruginosa*. *J Infect Chemother.* 2012;18(1):127-129. doi:10.1007/s10156-011-0285-3

40 Gentry CA, Williams RJ, 2nd. A propensity score-matched analysis of the impact of minimum inhibitory concentration on mortality in patients with *Pseudomonas aeruginosa* bacteraemia treated with piperacillin/tazobactam. *Int J Antimicrob Agents.* 2017;49(3):333-338. doi:10.1016/j.ijantimicag.2016.11.018

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