UWTASP tele-antimicrobial stewardship program | echo

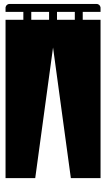
April 18th, 2025

Agenda

- The tale of Pip-tazo dosing
  - Rupali Jain, PharmD
- Case Discussions
- Open Discussion

FDA updated breakpoints for pip-tazo

- What is a breakpoint?
- Why is the FDA updating a breakpoint?
- Are there implications for using pip-tazo at my site?



The Minimum Inhibitory Concentration

Broth Dilution

The minimum inhibitory concentration (MIC):
The lowest concentration of a drug which prevents visible bacterial growth

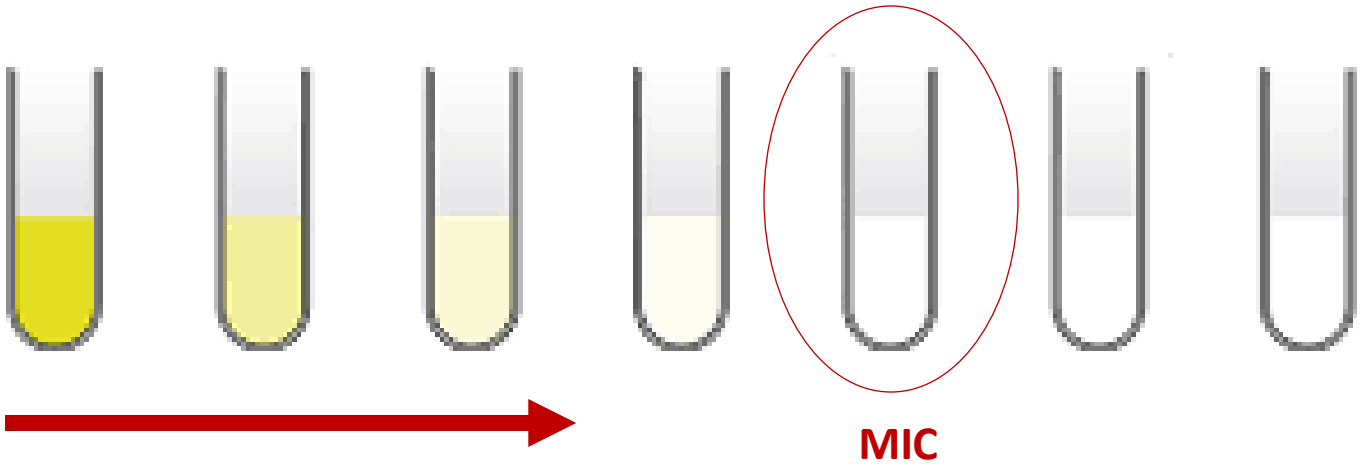


Image from: clinicalgate.com/antimicrobial-agents/ Accessed 7/23/18 SLIDE from ZKE

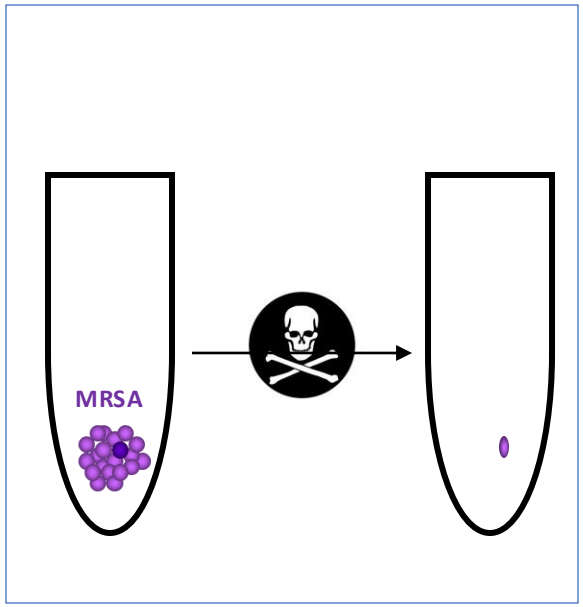
MIC ≠ Breakpoint

MIC is a number, Breakpoint is an interpretation (Susceptible/Intermediate/Resistant)

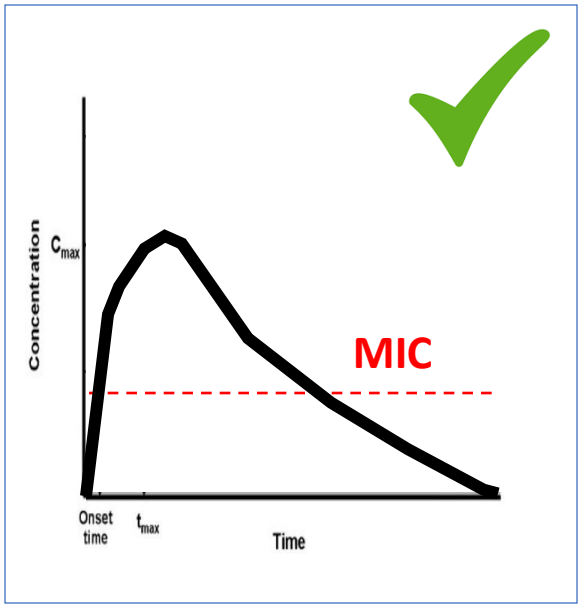
The Breakpoint:

Breakpoint setting integrates knowledge of **wild-type MICs**, assessment of antimicrobial **pharmacokinetics and pharmacodynamics**, and studies of **clinical outcomes** when the antimicrobial is used

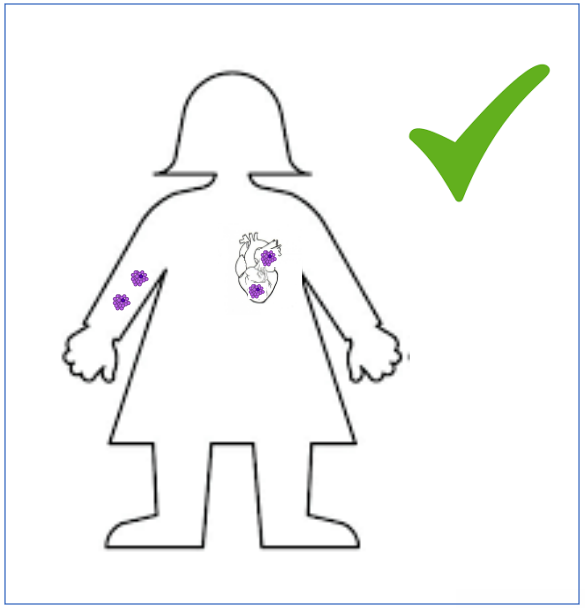
MIC



PK/PD

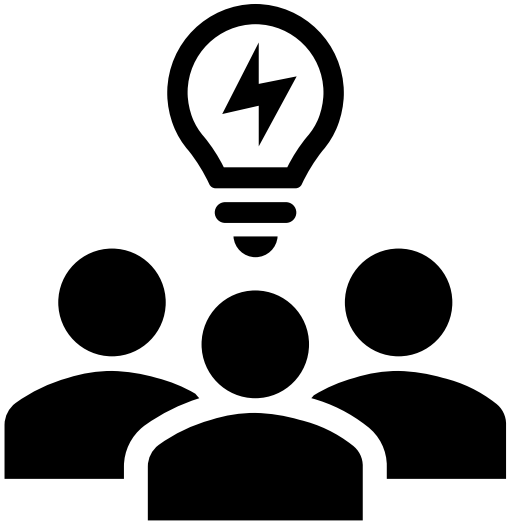


Clinical Outcomes



Turnidge J, Paterson DL. Setting and Revising Antibacterial Susceptibility Breakpoints. Clin Microbiol Rev 2007; 20(3):391-408. SLIDE from ZKE

Who are the CLSI?



Clinical Laboratory Standards Institute

Non-profit organization that brings together varied perspectives and expertise of the Laboratory community

Develops medical laboratory standards and guidelines

Develop standards that promote accurate antimicrobial susceptibility testing, appropriate reporting

Piperacillin-Tazobactam Breakpoints for Enterobacterales

CLSI

CLSI rationale document MR14
February 2022

CLSI proposed new breakpoints

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.

Table 6. Excerpt From CLSI document M100[2] Table 2A, Zone Diameter and MIC Breakpoints for Enterobacterales[a]

Test/ Report Group	Antimicrobial Agent	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm[b]			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	SDD	R	S	SDD	R
B	Piperacillin-tazobactam	≥ 25	21–24	≤ 20	≤ 8/4	16/4	≥ 32/4

Abbreviations: MIC, minimal inhibitory concentration; R, resistant; S, susceptible, SDD, susceptible-dose dependent.
[a] Breakpoints for susceptible are based on a dosage regimen of 3.375-4.5 g administered every 6 hours as a 30-minute infusion. Breakpoints for SDD are based on a dosage regimen of 4.5 g administered every 6 hours as a 3-hour infusion or 4.5 g administered every 8 hours as a 4-hour infusion.
[b] Disk content 100/10 µg.

This shift in epidemiology, coupled with mounting PK/PD and clinical outcome data, demonstrated the need to re-evaluate the breakpoints.

FDA recognizes Pip-tazo dosing needs updating

Zosyn was approved in 1998!

- Dosing was based on indication NOT MIC values

Resistance is evolving

Beta-lactamases are smart

- Prolonging the infusion helps

FDA Rationale for Piperacillin-Tazobactam Breakpoints for Enterobacterales

FDA has completed their review of the rationale document titled, "Piperacillin-Tazobactam Breakpoints for Enterobacterales" (MR14, February 2022), submitted by the Clinical and Laboratory Standards Institute (CLSI) to the public docket, FDA-2017-N-5925-0012, in March 2022.

Piperacillin-tazobactam is a combination of piperacillin, a penicillin-class antibacterial and tazobactam, a β-lactamase inhibitor, indicated for the treatment of:

- Intra-abdominal infections in adult and pediatric patients 2 months of age and older
- Nosocomial pneumonia in adult and pediatric patients 2 months of age and older
- Skin and skin structure infections in adults
- Female pelvic infections in adults
- Community-acquired pneumonia in adults

For nosocomial pneumonia in adults, piperacillin-tazobactam is approved at 4.5 g every 6 hours administered by intravenous infusion over 30 minutes (min). For all other indications in adults, piperacillin-tazobactam is approved at 3.375 g every 6 hours administered by intravenous infusion over 30 min.

FDA Rationale for Piperacillin-Tazobactam Breakpoints for Enterobacterales | FDA

Dosing varies across the country

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

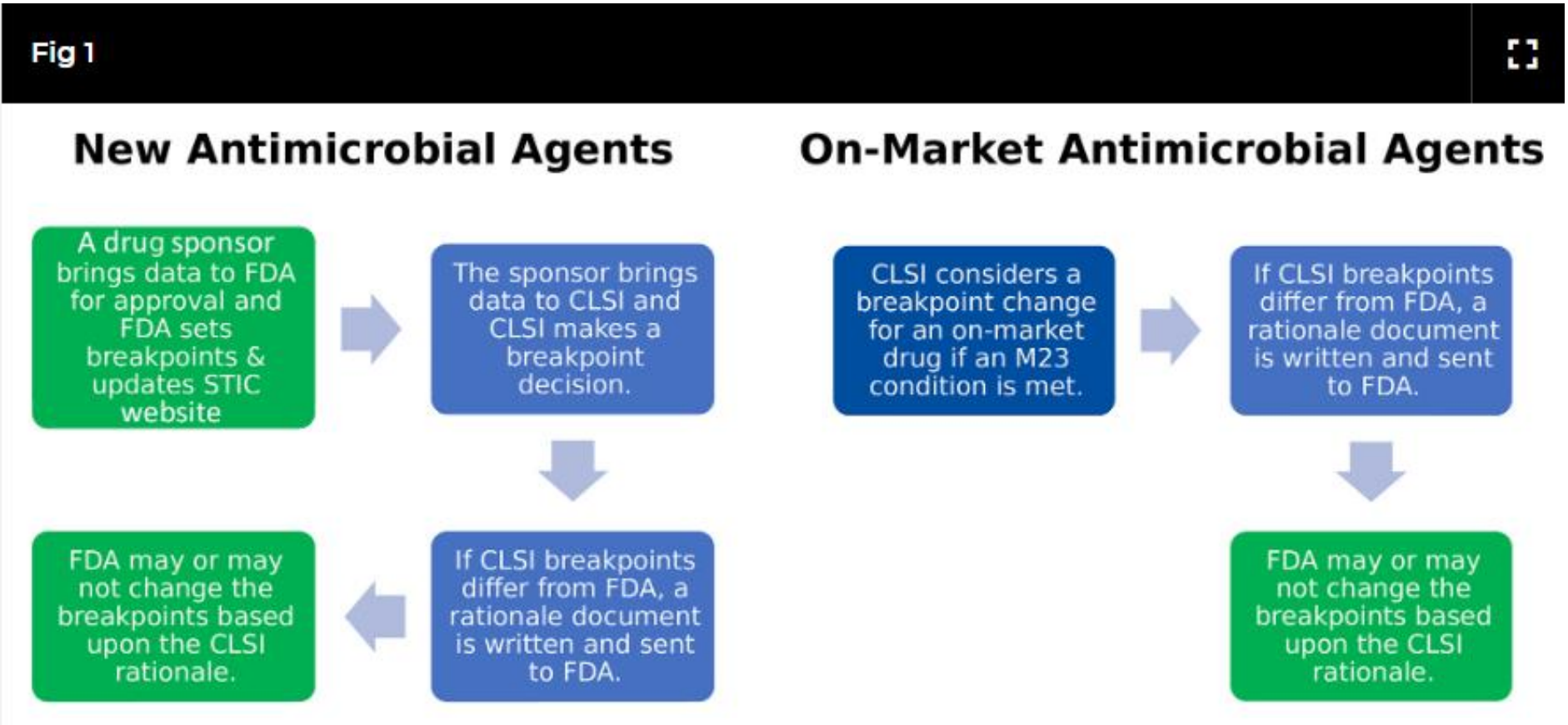
Dosage Regimen	Percentage
3.375 g every 8 h	37%
3.375 g every 6 h[b]	18%
3.375 g every 12 h	10%
4.5 g every 8 h	5%
4.5 g every 6 h[b]	4.5%

Abbreviation: h, hour.

[a] Based on 165 410 prescriptions.

[b] FDA-approved dosage.

FDA vs CLSI breakpoints



FDA only allows a commercial Antimicrobial Susceptibility Testing devices to report FDA-recognized breakpoints

Patel JB, et al 2023. Updating breakpoints in the United States: a summary from the ASM Clinical Microbiology Open 2022. J Clin Microbiol 61:e01154-22.https://doi.org/10.1128/jcm.01154-22

Here's deal: FDA vs CLSI

Organization	Susceptible	Intermediate	Susceptible-Dose Dependent	Resistant
	MIC, mcg/mL			
CLSI	</= 8		16	>/= 32
FDA	</=8	16		>/= 32
EUCAST	</=8			>8
USCAST	</=16			>16

FDA, however, does not accept an SDD breakpoint of 16 mcg/mL because available PK-PD and clinical data are insufficient to support the proposed SDD breakpoint.

No clinical studies have directly evaluated the efficacy of piperacillin-tazobactam extended infusions in patients with infections caused by Enterobacterales isolates with an MIC of 16 mcg/mL.

SDD vs Intermediate

Susceptible Dose Dependent

- Only applies when multiple approved dosing exist
- Expect same clinical response as, "Susceptible" if higher or more frequent dosing is used

Intermediate

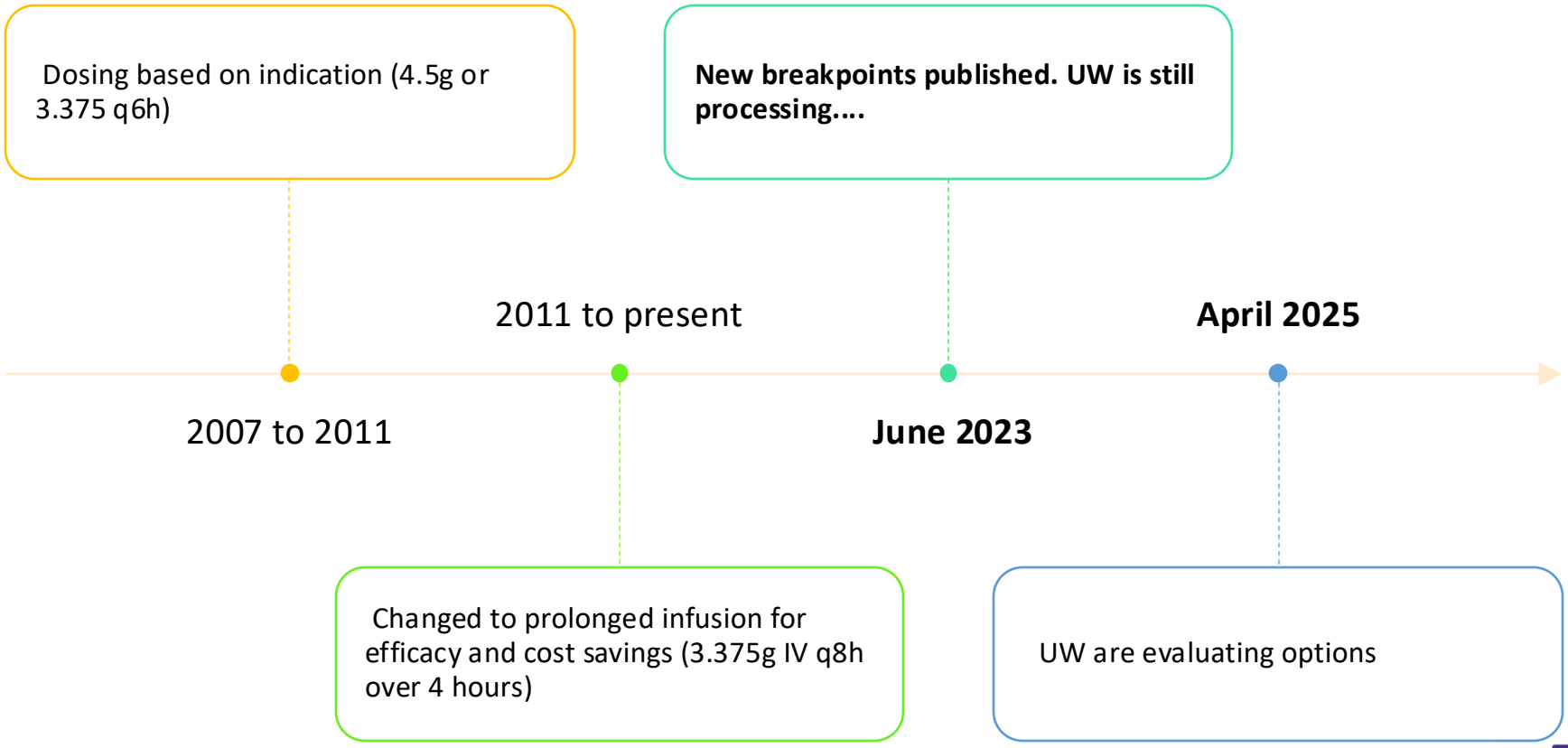
Implies clinical efficacy in body sites where:

- Drugs are physiologically concentrated but response may be lower
- Higher than normal dose can be use
- allows for inherent variability

What is UW Medicine doing?

Pip-tazo dosing for all patients regardless of organism
4.5g IV x1 over 30min
3.375g IV q8h (over 4 hours)
considered equivalent to 4.5g IV q6h over 30 min

Pip-tazo dosing history at UWM



What dose are you using?

a. Pip-tazo 3.375g IV q6h infused over 30 minutes
b. Pip-tazo 4.5g IV q6h infused over 30 minutes
c. Pip-tazo 4.5g IV q8h infused over 3-4 hours
d. Pip-tazo 3.375g IV q8h infused over 3-4 hours
e. Something else

BUT are we using the correct dose?

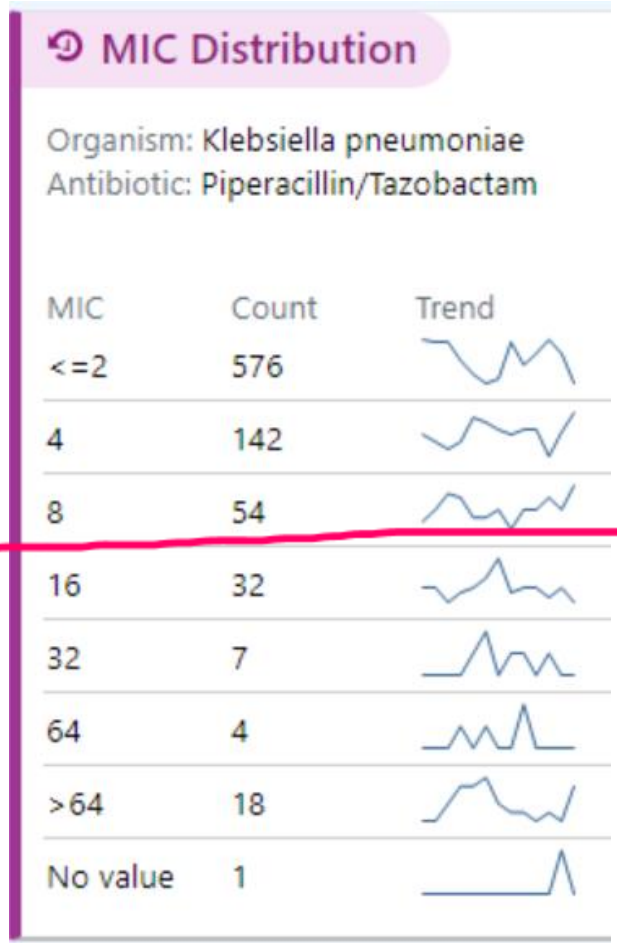
Table 5. Summary of Studies Investigating Piperacillin-Tazobactam PK and PD Data

Dosage	Infusion Time	MIC With ≥ 90% PTA[a]	
3.375 g every 6 h	30 min	≤ 8 µg/mL[10-12]	OK!
4.5 g every 6 h	30 min	≤8 µg/mL[12-15]	
3.375 g every 8 h	4 h	≤8 µg/mL[14-17]	UW
4.5 g every 8 h	4 h	≤8 µg/mL[12-15]	
4.5 g every 8 h	4 h	≤ 16 µg/mL[12,14,17,18]	
4.5 g every 6 h	3 h	≤ 16 µg /mL[12,13,18,19]	

UWM uses
CLSI breakpoint (MIC =8) and current dosing matches FDA /CLSI recommendation

If MIC </=16 (SDD), then higher dosing warranted

How often will UW underdose based on MIC?

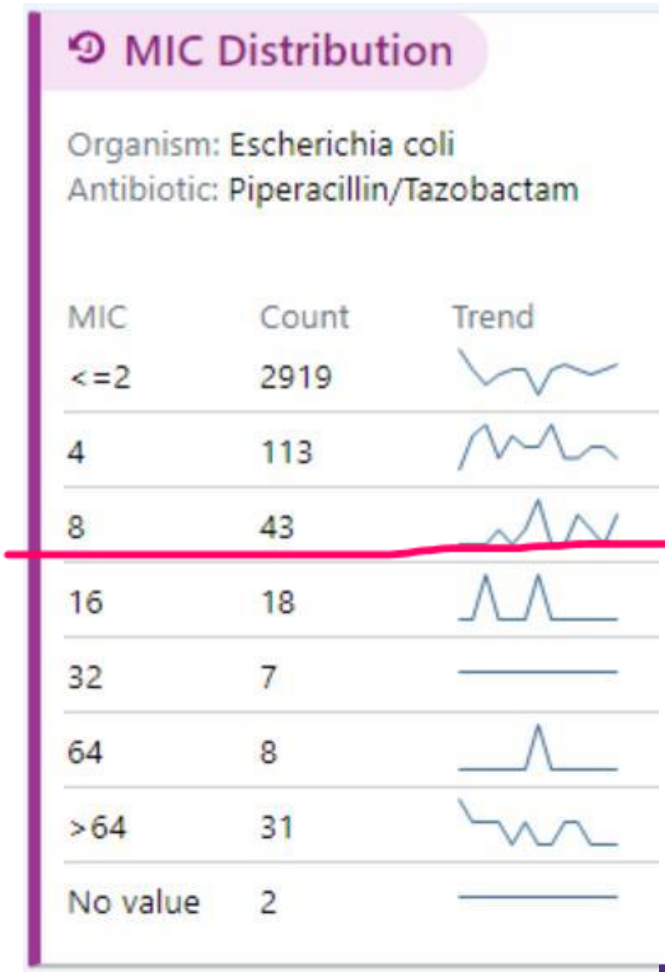


MIC Distribution

Organism: Klebsiella pneumoniae
Antibiotic: Piperacillin/Tazobactam

MIC	Count	Trend
<=2	576	
4	142	
8	54	
16	32	
32	7	
64	4	
>64	18	
No value	1	

Klebsiella MIC </=8 : 92%
(772/834)



MIC Distribution

Organism: Escherichia coli
Antibiotic: Piperacillin/Tazobactam

MIC	Count	Trend
<=2	2919	
4	113	
8	43	
16	18	
32	7	
64	8	
>64	31	
No value	2	

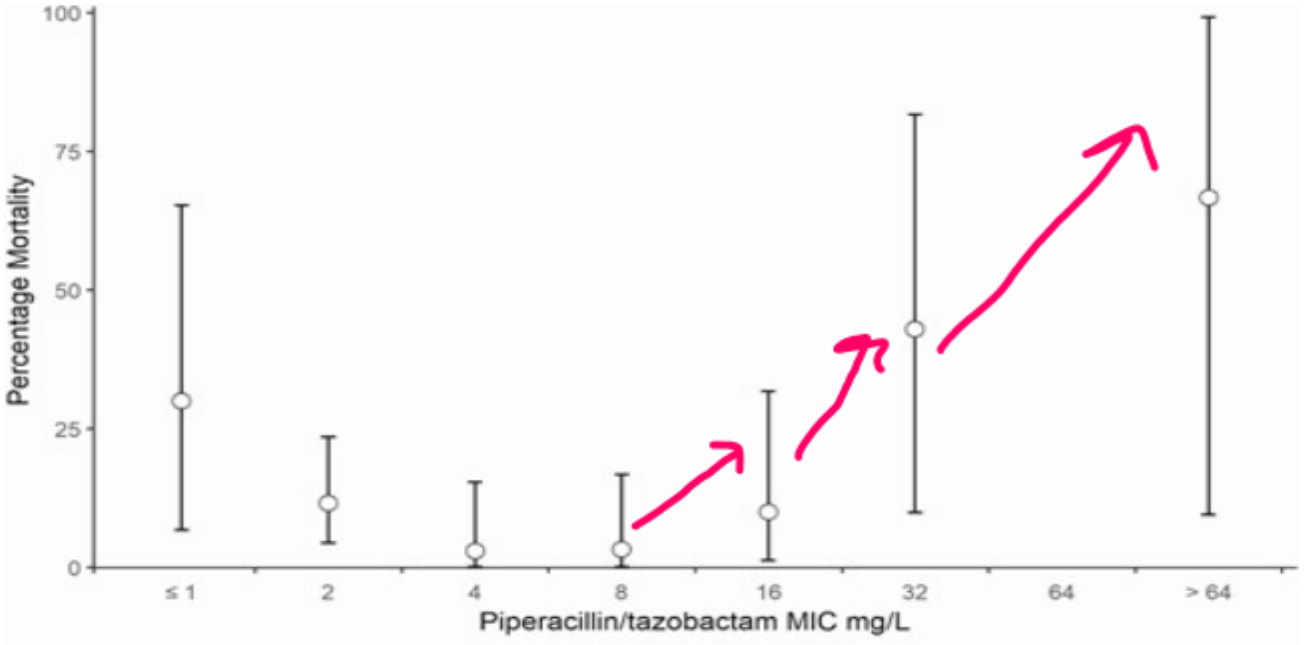
E.coli MIC </=8 : = 97%
(3075/3141)

What is the consequence?

Association Between Minimum Inhibitory Concentration, Beta-lactamase Genes and Mortality for Patients Treated With Piperacillin/Tazobactam or Meropenem From the MERINO Study FREE

A Henderson, D L Paterson ✉, M D Chatfield, P A Tambyah, D C Lye, P P De, R T P Lin, K L Chew, M Yin, T H Lee ... Show more

standard dose used in the MERINO trial was 4.5g Q6H (30 min)

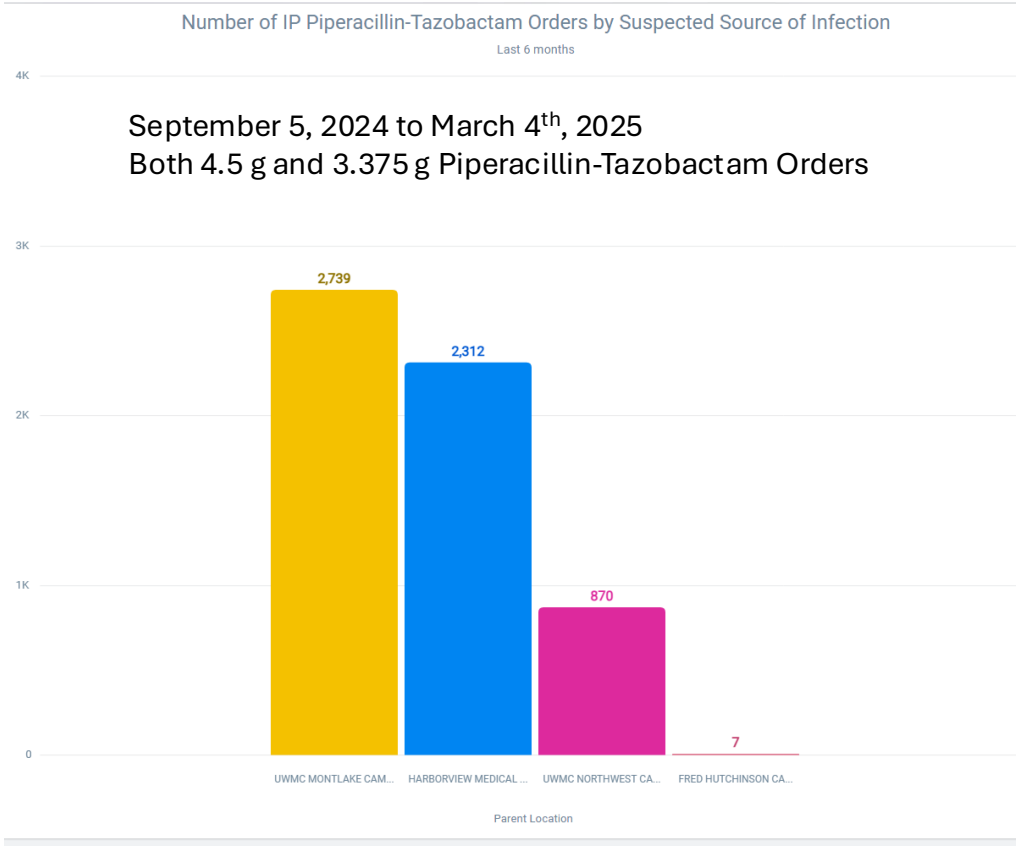


Assessment of UW dosing

CLSI	MIC </=8 (Susceptible)	MIC </= 16 (SDD)	MIC >/= 32
Pip-tazo	3.75g IV q8h over 4 hours	4.5 g q8h over 4-hour infusion OR 4.5 g q6h over 3-hour infusion	Do not use
	UWM standard dosing	RISK area	

Should we change our dosing to accommodate the risk areas?
Should all patients get 4.5g IV q8h over 4 hours?

Piperacillin-tazobactam Usage by Facility and Indication



Number of Orders for Top 3 Indications at each Facility

UWMC
GI: 770
Pulmonary: 390,
Sepsis: 380

HMC
SSTI: 806,
Pulmonary: 367
Sepsis: 316

NW
Other/Unknown Source: 194,
SSTI: 140,
GI: 134

Two ways of the pip-tazo

$$

Requires additional pharmacy
labor to attach vial
RN to activate vial

$

What are the costs?

6 months: 20,000 doses over the system	Actual costs from last 6 months	Comments
Scenario 1: keep current dosing and current product (4.5g premix, 3.375 premix)	$200,000	
Scenario 2: keep current dosing and change product (3.375 MB Plus)	$120,000	How difficult is it to change from frozen to mini-bag plus? Increased labor costs not accounted for
Scenario 3: Change dosing and keep current product (pre-mix 4.5g)	$260,000	
Scenario 4 : change dosing and Change product (4.5 g MB Plus)	$140,000	How difficult is it to change from frozen to mini-bag plus? Increased labor costs not accounted for

How would you advise UW?

a) Keep dosing as is: 3.375g IV q8h over 30 min
b) Increase to 4.5g IV q8h over 4 hours for everyone
c) Re-evaluate in 6 months
d) I don't know

Risk vs Benefit of changing dosing

Risks:

- Patient harms
- Giving more drug than needed
- Future impact unknown

Benefits:

- Better patient outcomes
- Cost savings !?!
- Align with FDA/ CLSI
- Align with teritary references

Conclusion

- Breakpoints are confusing IN GENERAL
  - The interplay between FDA and CLSI is ALSO confusing
- Your site probably does not need to change dosing based on resistance
  - Opportunity to chat with your lab!
- UW Medicine is still deciding
- PS there is a breakpoint update for Pseudomonas

of infection is used, resulting in a likely clinical cure.

• **susceptible-dose dependent (SDD)** – a category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosage regimen that is used in the patient. To achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosage regimen (ie, higher doses, more frequent doses, or both, or extended infusion) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum, literature-supported dosage regimen because higher exposure gives the highest probability of adequate coverage of an SDD isolate. Table 2 Dosages lists the doses used when establishing SDD categories. The drug label should be consulted for recommended doses and adjustment for organ function; **NOTE:** The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are supported by the literature, widely used clinically, and/or approved and for which sufficient data to justify the designation exist and have been reviewed. This category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins. See Appendix E for additional information.

• **intermediate (I)** – a category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and/or for which response rates may be lower than for susceptible isolates; **NOTE:** An I with a ^ in Tables 2 indicates agents that have the potential to concentrate in the urine. The I^ is for informational use only. The decision to report I^ is best made by each laboratory based on institution-specific guidelines and in consultation with appropriate medical personnel. The I category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

CLSI

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.