Piperacillin/Tazobactam Breakpoints
Enterobacterales and *P. aeruginosa*

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Executive Committee, USCAST
Background

- Piperacillin/tazobactam (TZP) is a β-lactam/β-lactamase inhibitor combination that is currently recommended as an empiric treatment for infections due to Enterobacterales and *P. aeruginosa*.\(^1\)-\(^4\)

- Despite its wide use, there has been considerable debate on its role for infections caused by extended spectrum β-lactamase-producing Enterobacterales (ESBL-E) and AmpC-producing Enterobacterales (AmpC-E).\(^5\)-\(^8\)

- Data indicates that 15-20% of *E. coli* and *Klebsiella* spp. in the US are ceftriaxone resistant (CRO-R), a phenotypic marker of ESBL-E, and the majority harbor CTX-M enzymes.\(^9\)-\(^13\)

- Tazobactam (TAZ) inhibits most CTX-M enzymes, but TZP has variable in vitro activity against ESBL-E.\(^14\)-\(^19\)
  - The reduced TZP susceptibility is driven in large part by the co-presence of other β-lactamases (i.e., AmpC or OXA-1) and it is estimated that upwards of 50% of CTX-M bearing Enterobacterales co-harbor other β-lactamases.\(^17\)

- Concerns have also been raised with TZP for Enterobacterales (i.e., *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes*) that have a moderate to high likelihood of clinically significant AmpC production given that TAZ does not efficiently inhibit these enzymes.\(^6\), \(^20\)
<table>
<thead>
<tr>
<th>Organization</th>
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<th>Interpretive Categories and MIC Breakpoints, µg/mL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>CLSI(^21,22)</td>
<td>Enterobacterales</td>
<td>≤8/4(^a)</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em>(^c)</td>
<td>≤16/4</td>
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<tr>
<td>EUCAST(^23)</td>
<td>Enterobacterales(^e)</td>
<td>≤8/4</td>
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<td></td>
<td><em>Pseudomonas spp.</em>(^f)</td>
<td>≤0.001/4</td>
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</table>

\(^a\) Based on labeled dosing of 3.375 grams or 4.5 grams every 6 hours administered over 0.5 hours.

\(^b\) Susceptible dose-dependent. Based on a dose of 4.5 grams every 6 hours over 3 hours or 4.5 grams every 8 hours administered over 4 hours.

\(^c\) Breakpoint is based on piperacillin (alone or in combination with tazobactam) are based on a piperacillin dosage of at least 3 grams every 6 hours.

\(^d\) Designation for agents that have the potential to concentrate in the urine.

\(^e\) MIC of 16 mg/L is an area of technical uncertainty (ATU)

\(^f\) Susceptible, increased exposure: A microorganism is categorised as "Susceptible, Increased exposure*" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
# Susceptibility Testing Interpretative Criteria Recommended by USCAST

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Abbreviations: 3GC-R, third generation cephalosporin resistant; 3GC-S, third generation cephalosporin susceptible.

<sup>a</sup>3GC-S Enterobacterales that do not have a moderate to high likelihood of clinically significant AmpC production due to an inducible chromosomal AmpC gene

<sup>b</sup>This recommendation is based on a TZP dose of 4.5 grams infused over 3 hours every 6 hours
Recommendation 1*

USCAST does not recommend a TZP susceptibility breakpoint for Enterobacterales species (i.e., *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes*) that have a moderate to high likelihood of clinically significant AmpC production due to an inducible chromosomal AmpC gene.

Voted 12-0 in favor of no susceptibility breakpoint

*Pending open comment period
Rationale for USCAST Recommendation

- Tazobactam does not efficiently inhibit most AmpC β-lactamases.\(^{20, 24-26}\)

- High potential for selection of derepressed AmpC mutants when administering a labile weak inducer like piperacillin for treatment of infections due to Enterobacterales species that have a moderate to high likelihood of clinically significant AmpC production (i.e., *E. cloacae*, *C. freundii*, and *K. aerogenes*).\(^{7,20, 27-31}\)
  - Although TZP is a weak AmpC inducer, derepressed mutants of these species are usually TZP-resistant.\(^{20,32}\)
Use of TZP Versus Meropenem in Patients with Bloodstream Infections Due to AmpC-Producing Enterobacterales

- Negative signal observed with TZP in pilot multi-centered, randomized, open-label study that compared TZP versus meropenem for definitive treatment of bloodstream infections caused by AmpC β-lactamase-producing Enterobacterales (MERINO-2).

- Primary composite outcome: 30-day mortality, clinical failure, microbiological failure, or microbiological relapse.
Considerations with USCAST Recommendation

- USCAST acknowledges that the results of real-world observational studies have not conclusively demonstrated that there is a significant increase in failure with TZP treatment relative to carbapenems for patients with moderate to high production AmpC-E infections.\(^{34-35}\)

  - Studies were of limited sample size.
  - High risk confounding by indication as more severely ill patients received a carbapenem.
  - Studies also often included species with a low risk of clinically significant AmpC production (e.g., *Serratia marcescens*) and/or those lacking a chromosomal AmpC enzyme altogether (e.g., *Citrobacter koseri*).
Recommendation 2*

USCAST does not recommend a susceptibility breakpoint for TZP against 3GC-R Enterobacterales

Voted 11-1 in favor of no susceptibility breakpoint

*Pending open comment period
TZP Activity Against *E. coli* (8,750), *K. pneumoniae* (5,436), *K. oxytoca* (1,597), and *P. mirabilis* (2,187) from US Medical Centers from 2020-2022
TZP Activity Against *E. coli, K. pneumoniae, K. oxytoca, and P. mirabilis* from US Medical Centers Stratified by Ceftriaxone (CRO) Susceptibility (2020-2022)
TZP Activity Against CRO-R *E. coli, K. pneumoniae, K. oxytoca, and P. mirabilis* from US Medical Centers Stratified by CRO Susceptibility (2020-2022)

**Graph 1:**
- **Y-axis:** % of isolates
- **X-axis:** Piperacillin-tazobactam MIC (mg/L)
- **Legend:**
  - Black: Ceftriaxone-susceptible (15,395)

**Graph 2:**
- **Y-axis:** % of isolates
- **X-axis:** Piperacillin-tazobactam MIC (mg/L)
- **Legend:**
  - Blue: Ceftriaxone-nonsusceptible (2,575)
Probability of Achieving 50% Free Time Above the MIC (fT>MIC) for TZP 4.5 g IV Q6 Hours (0.5- or 4-hr infusions) and TZP 18 g/daily as Continuous Infusion
Determination of the Tazobactam (TAZ) Exposure Required for Piperacillin (PIP) Efficacy Against ESBL-Producing Enterobacterales

- TAZ exposures are the critical determinant in defining the PK/PD profile of TZP against ESBL-producing Enterobacterales.
  - PIP is readily hydrolyzed by ESBL
- Data from in vitro PK/PD models of ESBL-producing Enterobacterales infections indicate that TAZ exposures associated with standard doses of TZP, administered as 0.5 or 4-hour infusions, are insufficient for restoring the activity of piperacillin against 3GC-R *E. coli* and *Klebsiella spp.* within the range of MIC values currently considered susceptible.37-41
Data from in-vitro PK/PD models of clinical ESBL-producing Enterobacterales indicate percentage of time during dosing interval that free TAZ concentrations exceed the PIP MIC with TAZ 4 mcg/mL ($f_T > \text{MIC}_{\text{TZP}}$) is the PK/PD driver for TAZ with PIP.\(^{38}\)

- 64% $f_T > \text{MIC}_{\text{TZP}}$ were required to achieve bacterial stasis with PIP 4 g IV Q6H.
- 77% $f_T > \text{MIC}_{\text{TZP}}$ were required to achieve 1-log\(_{10}\) CFU/ml reduction with PIP 4 g IV Q6H.

Tazobactam exposures are insufficient for restoring the activity of piperacillin against ESBL-producing *E. coli* and *Klebsiella* spp. within the range of MIC values currently considered susceptible by CLSI and EUCAST.
Meropenem Versus TZP for Treatment of Patients with CRO-R *E. coli* or *Klebsiella* spp. Bloodstream Infections (MERINO TRIAL)\(^{42}\)

<table>
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<tr>
<th>Design</th>
<th>International, multicenter, open-label, parallel group, randomized, non-inferiority trial</th>
</tr>
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<tr>
<td>Population</td>
<td>Adults with ≥1 positive blood culture with ceftriaxone-non-susceptible <em>E. coli</em> or <em>Klebsiella</em> spp. susceptible to TZP* (2014-2017)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Definitive Treatment with Meropenem 1g IV q8h (30-minute infusion) or TZP 4.5g IV q6h (30-minute infusion)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>All-cause mortality at 30 days post randomization</td>
</tr>
</tbody>
</table>
| Results | Treatment assignment: MEM (n=191) TZP (n=188)  
Phenotypic ESBL confirmed in 86% of isolates  
Mean APACHE-II score higher in Meropenem group vs. TZP group  
\* 21.0 vs. 17.9, respectively  
Mortality: Meropenem: 3.7% (7/191) vs. TZP: 12.3% (23/187)  
\* Difference 8.6%; one-sided 97.5% CI to 14.5 |

*Note: Bacterial identification to species level was performed using standard laboratory methods and susceptibility testing was performed at local sites using standard methodologies.*
Secondary Analyses in MERINO

- Clinical and Microbiological response at Day 4 was lower in TZP patients vs. meropenem patients.
  - TZP: 68.4% vs meropenem: 74.6% (-6.2 risk difference; 95% CI: -15.5 to 3.1)

- Measures of Failure were higher in TZP patients vs. meropenem patients.
  - Microbiologic relapse: TZP: 4.8% vs meropenem: 2.1% (2.7 risk difference; 95% CI: -1.1 to 7.1)
  - Secondary infections: TZP: 8.0% vs. meropenem: 4.2% (3.8 risk difference; 95% CI: -1.1 to 9.1)
    - TZP: 12 patients with TZP or meropenem-resistant organism and 3 with Clostridium difficile infection.
    - Meropenem: 6 patients with TZP or meropenem-resistant organism and 2 with Clostridium difficile infection

- Differences in 30-day mortality between TZP and meropenem in more difficult to treat populations.
  - Pitt score ≥ 4 (TZP: 27.8% vs. meropenem: 0%)
  - Health care–associated infection (TZP: 16.8% vs. meropenem: 3.7%)
  - Non-urinary tract source of infection (TZP: 18.8% vs. meropenem: 4.8%)
  - Immune compromise (TZP: 19.6% vs.meropenem: 2.5%)
Post-Hoc Analysis of MERINO

- Minimum inhibitory concentrations (MIC) testing and enzyme whole genome sequencing were performed at central laboratory
- N=320 primary blood cultures (278 *E.coli*, 42 *K. pneumoniae*) from 379 pts (84%)

**Finding #1:** TZP MICs using broth microdilution were higher than observed with MERINO testing (Vitek2, disk diffusion)

When TZP-resistant isolates were excluded, mortality difference decreased to 5% (95% CI -1 to 10)

**Finding #2:** CTX-M predominated (n=273), OXA also common (n=102)

Higher modal TZP MICs for OXA-containing isolates compared with those with ESBL alone (8 mg/L vs. 2 mg/L, p<0.001)

Results of Testing at Central Laboratory: 6% of TZP isolates were resistant and 20% had a TZP MIC of 16 mg/L
TZP MIC >16 mg/L was identified as the optimal MIC breakpoint associated with 30-Day Mortality
Among the 157 microbiologic assessable patients who received TZP, 18 died (11.5%)

Of 96 patients with CCS <3, 1 died

Of 61 patients with CCS ≥ 3, 17 died (27.9%)

- 32 UTI patients: 18.8% died
- 29 non-UTI patients: 37.9% died
The USCAST recommendation was not unanimous.

Dissenting voter did not rule out the potential role for TZP for treatment of complicated urinary tract infections (cUTIs) due to 3GC-R Enterobacterales as there is some evidence supporting TZP in this setting.44-47

Other members cited the high potential for biases in observational studies, limited RCT data, and TAZ with PIP PK/PD data as reasons for not supporting TZP as an option for 3GC-R Enterobacterales cUTIs.

USCAST unanimously agreed that further research is required to better define the TZP susceptibility breakpoints for 3GC-R Enterobacterales.

Additional need for pre-clinical PK/PD studies that include a more diverse group of 3GC-R Enterobacterales.

If use of TZP is supported by additional pre-clinical evidence, further randomized clinical trials would then be warranted to better quantify the efficacy of TZP for patients with 3GC-R Enterobacterales infections, including those with less invasive infections (i.e., cUTIs).
Recommendation 3*

USCAST recommends the TZP susceptibility breakpoint against 3GC-S Enterobacterales that do not have a moderate to high likelihood of clinically significant AmpC production due to an inducible chromosomal AmpC gene is ≤ 16/4 and resistance is >16/4 mg/L.

This recommendation is based on a TZP dose of 4.5 grams IV infused over 3 hours every 6 hours

Voted 11-1 in favor of both the susceptibility breakpoint and dosing recommendations

*Pending open comment period
TZP Activity Against CRO-S *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* from US Medical Centers (2020-2022)

The ECOFF for TZP against each Enterobacteriales spp. is ≤ 8 mg/L
PK/PD Rationale

- Although the ECOFF supports a susceptibility breakpoint of ≤ 8/4 mg/L, USCAST was in favor of a TZP susceptibility breakpoint of ≤ 16/4.

- USCAST Recommendation based on PK/PD modeling studies indicate that the probability of achieving 50% fT>MIC with extended TZP 4.5 g/6h (3h IV infusion) is >90% for pathogens with MIC values ≤ 16 mg/L.\(^{36, 48-53}\)

  - USCAST was opposed to the use of standard TZP regimens for patients with 3GC-S Enterobacterales infections.
Probability of Target Attainment of TZP dosing regimens stratified by CL\textsubscript{CR} and MIC

<table>
<thead>
<tr>
<th>CL\textsubscript{CR} (ml/min)</th>
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<tr>
<td></td>
<td>0.25 0.5 1 2 4 8 16 32</td>
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<tr>
<td>120</td>
<td>0.96 0.94 0.90 0.83 0.73 0.57 0.6 0.13 0.99</td>
<td>0.99 0.99 0.99 0.99 0.99 0.96 0.62 0.11</td>
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<tr>
<td>100</td>
<td>0.98 0.96 0.93 0.88 0.81 0.67 0.46 0.19 0.99</td>
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</tr>
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<td>80</td>
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TZP 4.5 g/6 h, 3 h IV infusion required for ≥ 90% at MIC of 16 mg/L
Activity of PIP and TZP Against CRO-S (CLSI 2022) *E. coli* (4867 Isolates) and *K. pneumoniae* (2783 Isolates) From North America Medical Centers (2007-2010)
PK/PD of TZP Against 3GC-S Enterobacterales

- The presence of TAZ lowers the PIP MIC$_{50/90}$ by several log$_2$ dilutions, indicating the TAZ is not immaterial for TZP MICs against 3GC-S Enterobacterales.

- To date, no pre-clinical PK/PD infection model studies have defined the TAZ PK/PD target in the presence of PIP and there are scant clinical data that has evaluated outcomes by TZP MIC among patients with CRO-S Enterobacterales.

- Standard and prolonged TZP regimens were found to have rapid and sustained bactericidal activity across 7 days in an in vitro dynamic hollow-fiber infection model study of a 3GC-S, non-ESBL-producing *E. coli* with a TZP MIC of 2 mg/L.$^{40}$
Considerations with USCAST Recommendations

- USCAST voted 11-1 in favor of these recommendations.
  - Based on the belief that use of TZP will largely be empiric for patients with 3GC-S Enterobacterales infections and good stewardship practices will foster de-escalation in most circumstances to a narrower agent.

- The lone dissenting vote was due to concerns that many institutions will not routinely administer extended infusion TZP and/or will lack the resources for aggressive de-escalation.

- It is important to note that these susceptibility breakpoints are contingent upon a TZP dose of 4.5 g every six hours as a three-hour infusion.
  - If institutions find this infeasible, a reasonable susceptibility breakpoint with TZP 4.5 grams every six hours as a 30-minute infusion would be 8 mg/L, as recommended by the CLSI and EUCAST.\(^{21-23}\)

- USCAST unanimously agreed that pre-clinical PK/PD studies are needed to determine optimal TAZ and TZP dosing schemes necessary to restore PIP’s activity against 3GC-S Enterobacterales.
Recommendation 4*

USCAST recommends that the TZP susceptibility breakpoint against *Pseudomonas aeruginosa* is ≤ 16/4 and resistance is >16/4 mg/L.

This recommendation is based on a TZP dose of 4.5 grams IV infused over 3 hours every 6 hours.

Voted 12-0 in favor of both the susceptibility breakpoint and dosing recommendations.

*Pending open comment period*
### Probability of Target Attainment of TZP dosing regimens stratified by CL\textsubscript{CR} and MIC

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TZP 4.5 g/6h, 3h IV infusion required for ≥ 90% at MIC of 16 mg/L
Considerations with USCAST Recommendations

- USCAST voted 12-0 in favor of these recommendations.
- It is important to note that these susceptibility breakpoints are contingent upon a TZP dose of 4.5 g IV every six hours as a three-hour infusion.
- Pre-clinical PK/PD studies are needed to determine optimal TZP target against contemporary *P. aeruginosa* isolates with varying resistant determinants in the context of modern-day in vitro surveillance data.
- Future breakpoint decisions should ultimately be guided by high quality clinical data, if it becomes available.
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References

1. ZOSYN® (piperacillin and tazobactam) for injection, for intravenous use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050684s88s89s90_050750s37s38s39lbl.pdf.


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