Clinical Infectious Diseases

VIEWPOINTS

Piperacillin/Tazobactam Susceptibility Test Interpretive Criteria for Enterobacterales: Recommendations From the United States Committee on Antimicrobial Susceptibility Testing

Thomas P. Lodise,[1] Sujata M. Bhavnani,[2] Paul G. Ambrose,[2] Helio S. Sader,[3] David Andes,[4] and Jason M. Pogue[5]; on behalf of the US Committee on Antimicrobial Susceptibility Testing

[1]Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York, USA; [2]Institute for Clinical Pharmacodynamics, Inc, Schenectady, New York, USA; [3]JMI Laboratories, North Liberty, Iowa, USA; [4]Department of Medicine, Department of Medical Microbiology and Immunology, School of Medicine and Public Health and School of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin, USA; and [5]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA

(See the Editorial Commentary by Humphries on pages 1363–5.)

The in vitro susceptibility testing interpretive criteria (STIC) for piperacillin/tazobactam (TZP) against Enterobacterales were recently updated by the US Food and Drug Administration, Clinical and Laboratory Standards Institute, and European Committee on Antimicrobial Susceptibility Testing. The United States Committee on Antimicrobial Susceptibility Testing (USCAST) also recently reviewed TZP STIC for Enterobacterales and arrived at different STIC for Enterobacterales. Here, we explain our recommendations and rationale behind them. Based on our review of the available data, USCAST does not recommend TZP STIC for certain Enterobacterales species that have a moderate to high likelihood of clinically significant AmpC production (*Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes* only) or for third-generation cephalosporin-nonsusceptible Enterobacterales. USCAST recommends a TZP susceptibility breakpoint of ≤ 16/4 mg/L for third-generation cephalosporin-susceptible Enterobacterales and only endorses the use of extended infusion TZP regimens for patients with infections due to these pathogens.

Keywords. susceptibility; piperacillin/tazobactam; Enterobacterales; ESBL; AmpC.

Piperacillin/tazobactam (TZP) is recommended as a first-line treatment for Enterobacterales infections [1–3]. Despite its wide-scale use [4], there has been considerable debate on its role for infections caused by extended-spectrum β-lactamase (ESBL) and AmpC-producing Enterobacterales [5–7]. Data indicate that 15%–20% of *Escherichia coli* and *Klebsiella* spp. in the United States are third-generation cephalosporin-nonsusceptible (3GC-NS) [8–11], a phenotypic marker of ESBL expression, and that a majority of these isolates harbor CTX-M enzymes [12]. Although tazobactam is a potent inhibitor of most CTX-M enzymes [13–15], TZP has variable in vitro activity against ESBL-producing Enterobacterales [16–18]. The reduced TZP susceptibility against ESBL-producing Enterobacterales is multifactorial but driven in large part by the copresence of other β-lactamases [16, 18]. Concerns have also been raised regarding the use of TZP for Enterobacterales (eg, *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes*) that have a moderate to high likelihood of clinically significant AmpC production, given that tazobactam does not efficiently inhibit these enzymes [5, 19].

The in vitro susceptibility testing interpretive criteria (STIC) for TZP against Enterobacterales were recently updated by the US Food and Drug Administration (FDA) [20], Clinical and Laboratory Standards Institute (CLSI) [21, 22], and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [23] (Tables 1 and 2). The United States Committee on Antimicrobial Susceptibility Testing (USCAST) also recently convened to review TZP STIC for Enterobacterales. While USCAST appreciates the expertise of these organizations, USCAST arrived at different TZP STIC for Enterobacterales. Here, we explain our recommendations (Table 1), the rationale behind them, and the future research that is needed to further inform these STIC. Of note, USCAST did not discuss the optimal method for incorporating their proposed TZP STIC across clinical microbiologic laboratories in their deliberations. USCAST recognizes that many laboratories use obsolete breakpoints for a variety of reasons [24] and recommends that clinicians work with their

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Correspondence: T. P. Lodise, Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208-3492 (thomas.lodise@acphs.edu); J. M. Pogue, University of Michigan College of Pharmacy, 428 Church St, Ann Arbor, MI 48109-1065 (jmpogue@med.umich.edu).

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Table 1. United States Committee on Antimicrobial Susceptibility Testing, US Food and Drug Administration, Clinical and Laboratory Standards Institute, and European Committee on Antimicrobial Susceptibility Testing Susceptibility Test Interpretive Criteria for Piperacillin/Tazobactam Against Enterobacterales

	Current STIC (μg/mL) by Organization									
	United States Committee on Antimicrobial Susceptibility Testing		Clinical and Laboratory Standards Institute [21]			US Food and Drug Administration [20][a]			European Committee on Antimicrobial Susceptibility Testing [23][b]	
Enterobacterales	Susceptible	Resistant	Susceptible	Susceptible, dose dependent	Resistant	Susceptible	Intermediate	Resistant	Susceptible	Resistant
All Enterobacterales	No recommended STIC		≤ 8/4[c]	16/4[d]	≥ 32/4	≤ 8/4	16/4	≥ 32/4	≤ 8/4	> 16/4
Enterobacterales that have a moderate to high likelihood of clinically significant AmpC production	No recommended STIC									
Third-generation cephalosporin-nonsusceptible Enterobacterales	No recommended STIC									
Third-generation cephalosporin-susceptible Enterobacterales that do not have a moderate to high likelihood of clinically significant AmpC production[e]	16/4[f]	> 16/4								

Abbreviations: STIC, susceptibility test interpretive criteria.

[a]Clinical efficacy was shown for *Escherichia coli* and *Klebsiella pneumoniae*.

[b]Minimum inhibitory concentration of 16 mg/L is an area of technical uncertainty.

[c]Based on labeled dosing of 3.375 g or 4.5 g every 6 hours administered over 0.5 hours.

[d]Susceptible dose dependent. Based on a dose of 4.5 g every 6 hours over 3 hours or 4.5 g every 8 hours administered over 4 hours.

[e]Enterobacterales that have a moderate to high likelihood of clinically significant AmpC production due to an inducible chromosomal *ampC* gene include *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes*.

[f]This recommendation is based on a piperacillin/tazobactam dose of 4.5 g infused over 3 hours every 6 hours or 4.5 g infused over 4 hours every 8 hours.

Table 2. Previous Piperacillin/Tazobactam Susceptibility Testing Interpretative Criteria for Enterobacterales by Organization

Organization	Susceptible	Intermediate	Resistant
US Food and Drug Administration [20]	≤16/4	32–64	≥128/4
Clinical and Laboratory Standards Institute [21]	≤16/4	32–64	≥128/4
European Committee on Antimicrobial Susceptibility Testing [23]	≤8/4	16 (area of technical uncertainty)	>16/4
United States Committee on Antimicrobial Susceptibility Testing	Never addressed		

microbiologic departments to ensure the most clinically appropriate STIC are used for interpreting TZP susceptibility results.

Recommendation 1

USCAST does not recommend TZP STIC for Enterobacterales with a moderate to high likelihood of clinically significant AmpC production due to an inducible chromosomal *ampC* gene. This recommendation includes *E. cloacae*, *C. freundii*, and *K. aerogenes* only.

Rationale

This USCAST recommendation, which aligns with the recommendations of the current Infectious Diseases Society of America (IDSA) guidance on the treatment of antimicrobial-resistant gram-negative infections [5], was largely based on the high potential for selection of derepressed AmpC mutants during TZP treatment of patients with infections due to these pathogens and the lack of in vitro activity of TZP against these derepressed mutants. Tazobactam does not efficiently inhibit most AmpC β-lactamases [19, 25–27]. While the degree of AmpC production varies by Enterobacterales that possess a chromosomal *ampC* gene, there is a high potential for selection of derepressed AmpC mutants when administering a labile weak inducer such as piperacillin for treatment of infections due to *E. cloacae*, *C. freundii*, and *K. aerogenes* [6, 19, 28–32]. Although TZP is considered a weak AmpC inducer [33], derepressed mutants of these species are usually TZP-resistant [19].

The USCAST recommendation was also informed by the negative signals observed in the pilot (n = 72), multicentered, randomized, open-label trial that compared TZP with meropenem for definitive treatment of bloodstream infections caused by AmpC β-lactamase–producing Enterobacterales (MERINO-2) [34]. Overall, no significant difference in the primary composite failure outcome (30-day mortality, clinical failure, microbiological failure, or microbiological relapse) was observed between treatment groups. However, 53% of patients in the trial were infected with Enterobacterales that are unlikely to develop clinically significant AmpC expression (ie, *Citrobacter braakii*, *Morganella morganii*, *Serratia marcescens*, *Providencia* spp., or *Serratia* spp.) [28]. Among the subgroup of 32 patients with infections due to Enterobacterales with a moderate to high likelihood of clinically significant AmpC production (ie, *Enterobacter* spp.), a nonsignificantly higher proportion of patients in the TZP arm met the primary composite failure outcome (28% vs 7%, respectively; $P = .14$). These findings were consistent with those from a recent observational study that demonstrated significantly higher treatment failure rates among patients who received piperacillin ± tazobactam relative to those who received a carbapenem or cefepime for definitive treatment of wild-type AmpC β-lactamase–producing Enterobacterales bloodstream infections or pneumonia [35]. In this study, >75% of patients in the piperacillin group were infected with an Enterobacterales with a moderate to high likelihood of clinically significant AmpC production.

USCAST acknowledges that the results of several real-world observational studies have not conclusively demonstrated that there is a significant increase in failure with TZP relative to carbapenems for patients with these infections [36, 37]. However, these studies were small and suffered from significant confounding by indication where more severely ill patients received a carbapenem. These studies also included Enterobacterales species with a low risk of clinically significant AmpC production (eg, *S. marcescens*) and/or those that lacked a chromosomal AmpC enzyme altogether (eg, *Citrobacter koseri*), limiting their applicability. Of note, the USCAST recommendation only includes *E. cloacae*, *C. freundii*, and *K. aerogenes* and does not apply to other Enterobacterales (eg, *Hafnia alvei*, *Citrobacter youngae*, *Yersinia enterocolitica*) with a moderate to high likelihood of clinically significant AmpC production due to the dearth of TZP data against these pathogens. For use of TZP in the treatment of patients with infections due to these other AmpC β-lactamase–producing Enterobacterales with a moderate to high likelihood of clinically significant AmpC production, USCAST identified this as an area that merits further research.

Recommendation 2

USCAST does not recommend STIC for TZP against 3GC-NS Enterobacterales.

Rationale

This USCAST recommendation was based on its review of available microbiological, preclinical, in silico, and clinical data (predominately bloodstream infection data) and is in concordance with the recent recommendations of the IDSA Gram-Negative Guidance Panel [38]. TZP minimum inhibitory concentration (MIC) data for Enterobacterales from the US SENTRY Antimicrobial Surveillance Program (2020–2022) are shown in Figure 1. The tentative epidemiological cutoff (ECOFF) values

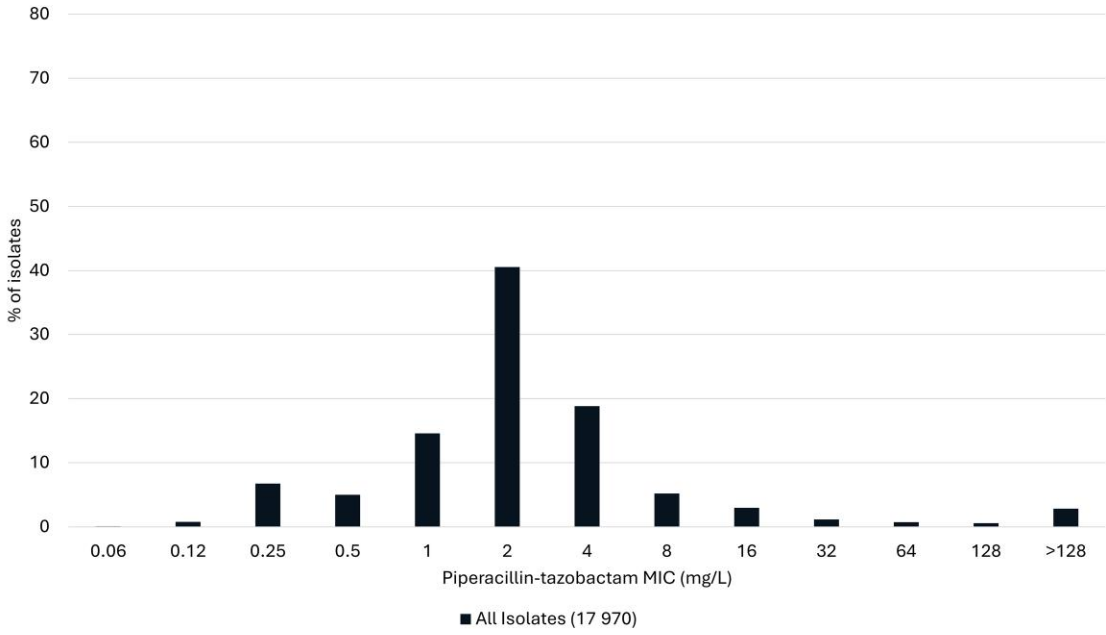

Figure 1. Piperacillin-tazobactam activity against Enterobacterales from US medical centers (2020–2022). Enterobacterales include *Escherichia coli* (n = 8750), *Klebsiella pneumoniae* (n = 5436), *Klebsiella oxytoca* (n = 1597), and *Proteus mirabilis* (n = 2187).

for thresholds from 95.0% to 99.9% were calculated for *Proteus mirabilis*, *E. coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae* and ranged from 0.5 to 1, 4 to 8, 4 to 8, and 8 to 16 mg/L, respectively (Supplementary Table 1). While these data suggest the ECOFF can be used to help inform the TZP susceptibility breakpoint for Enterobacterales, there were stark differences in the TZP MIC distributions between ceftriaxone-nonsusceptible (CRO-NS) and ceftriaxone-susceptible (CRO-S) isolates (Figure 2, Supplementary Figures 1–3). USCAST believed the highly discordant TZP MIC distributions between CRO-NS vs CRO-S Enterobacterales isolates limited the utility of the ECOFF in informing the TZP susceptibility breakpoint against 3GC-NS Enterobacterales.

Available preclinical pharmacokinetic/pharmacodynamic (PK/PD) data suggest that currently approved TZP dosing schemes are inadequate against the range of MIC values currently considered susceptible for 3GC-NS Enterobacterales. Using a piperacillin 50% free time above the MIC (piperacillin 50% $fT >$ MIC) as the PK/PD target associated with efficacy for TZP, most studies demonstrate that the probability of achieving this PK/PD target with TZP administered as a 0.5-hour intermittent infusion or ≥ 3-hour extended infusion is >90% for pathogens with MIC values ≤ 8/4 mg/L and ≤16/4 mg/L, respectively [39–44]. Although organizations have used this as part of their STIC justifications, there are 2 main issues with limiting the PK/PD assessment to this target. First, while generally accepted, data to support this $fT >$ MIC target for piperacillin are lacking [20]. Second, in addition to the piperacillin probabilty of target attainment profile, tazobactam exposures are a critical determinant in defining the PK/PD profile of TZP against 3GC-NS Enterobacterales as piperacillin is readily hydrolyzed by ESBLs. Data from hollow fiber infection models of ESBL-producing Enterobacterales infections indicate tazobactam exposures associated with intermittent-infusion or extended-infusion TZP regimens are insufficient for restoring the activity of piperacillin against 3GC-NS *E. coli* and *Klebsiella* spp. within the range of TZP MIC values currently considered susceptible by the FDA, CLSI, and EUCAST [20, 21, 23, 45, 46].

The failure demonstrated in these models can be explained by a close assessment of tazobactam PK/PD. The most informative preclinical PK/PD assessment of tazobactam was a 1-compartment in vitro infection model that examined a range of tazobactam doses in combination with piperacillin 4 g IV (intravenous; 0.5 hour) every 6 hours against 3 ESBL-producing strains of Enterobacterales (1 *E. coli* and 2 *K. pneumoniae*) with TZP MIC values of 4/4 mg/L, 2/4 mg/L, and 1/4 mg/L [47]. In this analysis, the percentage of time during the dosing interval that free tazobactam concentrations exceeded the TZP MIC value was identified as the PK/PD index most associated with activity. Importantly, free tazobactam concentrations had to exceed the TZP MIC value for 64% and 77% of the dosing interval to achieve net bacterial stasis and 1 $\log_{10}$ colony-forming unit reduction, respectively, when tazobactam was administered with piperacillin 4 g IV (0.5 hour) every 6 hours. In Monte Carlo simulations of critically ill [48] patients with estimated creatinine clearances (CL_{CR}) of 60–100 mL/min [27], the probabilities of achieving these critical tazobactam exposures associated with stasis and 1 $\log_{10}$ killing for TZP 4.5 g

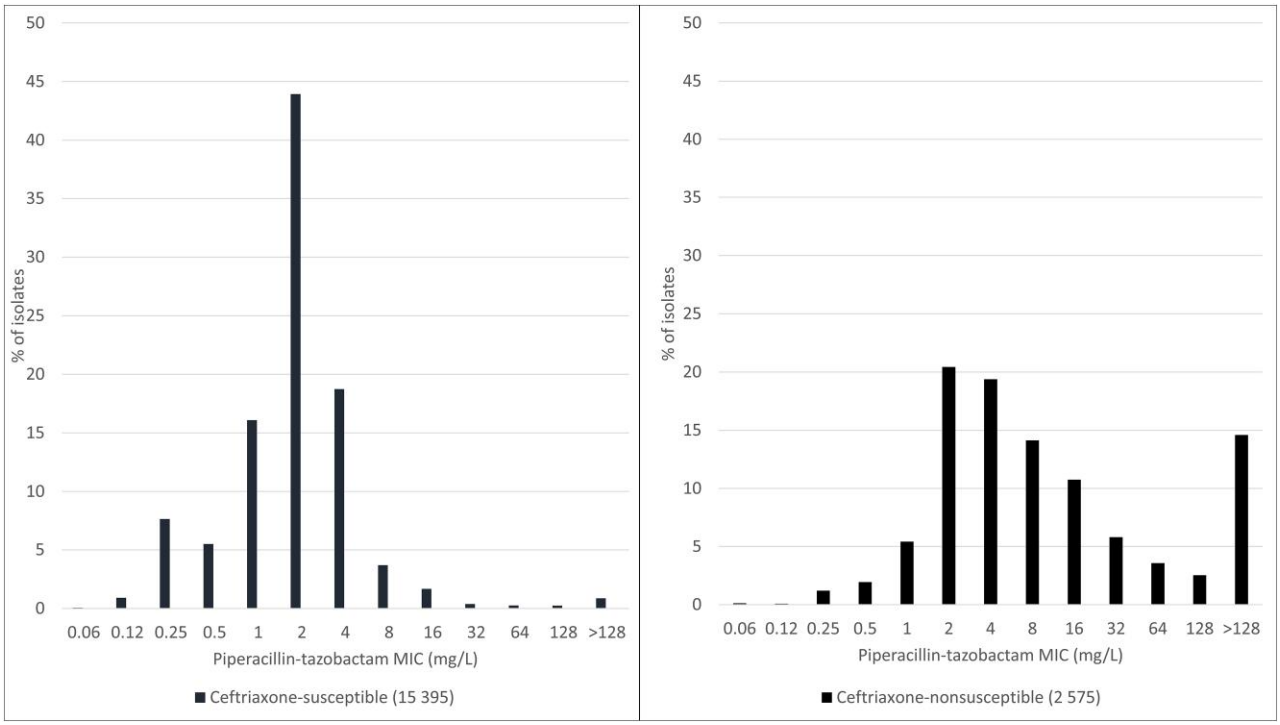

Figure 2. Piperacillin-tazobactam activity against Enterobacterales from US medical centers (2020–2022) stratified by ceftriaxone susceptibility. Enterobacterales include *Escherichia coli* (n = 8750), *Klebsiella pneumoniae* (n = 5436), *Klebsiella oxytoca* (n = 1597), and *Proteus mirabilis* (n = 2187). Enterobacterales were considered susceptible if the ceftriaxone MIC value was ≤1 mg/L. Enterobacterales were considered nonsusceptible if the ceftriaxone MIC value was ≥2 mg/L [21]. Abbreviation: MIC, minimum inhibitory concentration.

IV every 6 hours administered as an 0.5- or 3-hour infusion were less than approximately 90% for 3G-R Enterobacterales with TZP MIC values greater than 4/4 mg/L and 2/4 mg/L, respectively, depending on infusion duration and CL_{CR} (Supplementary Table 2). Considering that >50% of the observed TZP MIC values among 3G-R Enterobacterales in SENTRY were ≥4/4 mg/L (Figure 2), USCAST believes that even the most favorable interpretation of the in silico data [27] does not support the use of TZP in the treatment of patients with 3GC-NS Enterobacterales infections.

The USCAST recommendation was also informed by the MERINO trial [49], which compared definitive treatment with meropenem 1 g every 8 hours (0.5-hour infusion) or TZP 4.5 g every 6 hours (0.5-hour infusion) in adult patients with TZP-S, ceftriaxone-R (CRO-R) *E. coli*, or *K. pneumoniae* bloodstream infections. In this international, multicenter, open-label, randomized clinical trial, 30-day mortality was higher in the TZP arm relative to the meropenem arm (12.3% vs 3.7%, respectively; risk difference, 8.6%; 1-sided 97.5% confidence interval [CI], −α to 14.5%; $P = .90$ for noninferiority) [49]. Similar trends in favor of meropenem were demonstrated in the secondary outcomes of clinical cure, microbiological cure, and the development of resistance [49].

To investigate the potential reason(s) for the observed 30-day mortality differences between treatments in MERINO-1, post hoc analyses were performed, and an unexpectedly high rate of nonsusceptibility to TZP was demonstrated using broth microdilution at the central laboratory compared to Vitek or disk diffusion at the local site [50]. When the analysis was limited to patients with TZP-susceptible isolates via broth microdilution by the current FDA, CLSI, and EUCAST TZP susceptible breakpoint of ≤8/4 mg/L [20, 21, 23], 30-day mortality was still higher with TZP but no longer reached statistical significance (9% vs 5%, respectively; 95% CI, −2% to 11%). In the multivariate regression analyses, TZP MIC >16/4 mg/L was identified as the TZP MIC threshold best associated with 30-day mortality (30-day mortality was 50% [5 of 10] in patients with isolates that had TZP MIC values >16/4 mg/L vs 9% [13 of 147] in patients with isolates that had TZP MIC values ≤16/4 mg/L) [50].

While the findings from these post hoc clinical analyses support the FDA, CLSI, and EUCAST TZP susceptibility breakpoints [20, 21, 23], USCAST did not find them to be sufficient for endorsing a TZP susceptibility breakpoint of ≤8/4 mg/L for several reasons. First, initial isolates were only available in 84% of patients for the post hoc analysis, and 30-day mortality was higher among patients in the TZP arm with nonavailable vs available isolates (16.7% vs 11.5%, respectively) [50]. USCAST was concerned that this may have biased the findings in favor of TZP. Second, closer inspection of the 30-day mortality data by TZP MIC demonstrated that mortality exceeded 10% in

TZP-treated patients with CRO-R Enterobacterales that had a TZP MIC value of 2 mg/L. Among, TZP-treated patients with TZP MIC values ≤1 mg/L, 30-day mortality exceeded 25%. This "u-shaped" mortality curve as a function of increasing TZP MIC values weakens any association between TZP MIC and outcome in this study [50]. Third, although not powered to examine subgroups, the differences in 30-day mortality between TZP- and meropenem-treated patients in the original analyses were considerably more pronounced in sicker and/or more complicated populations [49]. Despite the well-recognized limitations associated with subgroup analyses, USCAST believed these populations were more representative of patients encountered in practice with 3GC-NS Enterobacterales bloodstream infections [51].

The USCAST recommendation was not unanimous, and 1 dissenting voter was concerned the available data were predominately related to patients with bloodstream infections and did not rule out the potential role of TZP for the treatment of patients with complicated urinary tract infections (cUTIs) due to 3GC-NS Enterobacterales as there is some evidence that supports TZP usage in this setting [52–55]. However, there are significant limitations to the observational studies that have addressed the role of TZP for cUTIs, most notably confounding by indication [52, 54, 55], and the lone cUTI randomized clinical trial had a small sample size, limiting interpretation [53]. Additionally, the tazobactam PK/PD concerns previously described remain relevant to cUTIs. While USCAST acknowledges that the role of TZP for 3GC-NS Enterobacterales in cUTIs remains unresolved, USCAST believed the most prudent recommendation at this time was not to have a TZP susceptibility breakpoint for 3GC-NS Enterobacterales given the uncertainties regarding the effectiveness of TZP in these patients.

The USCAST members were in full agreement that additional preclinical PK/PD studies with a more diverse group of 3GC-NS Enterobacterales isolates are needed to better understand the PK/PD of TZP against 3GC-NS Enterobacterales. If TZP use is supported by additional preclinical evidence, further randomized clinical trials would then be warranted to better quantify the efficacy of TZP for patients with 3GC-NS Enterobacterales infections. As part of these proposed studies, TZP should be evaluated in patients with less invasive 3GC-NS Enterobacterales infections, such as cUTIs, given the commonality of these infections and uncertainty of TZP's role for these patients. Of note, PETERPEN [56] is an ongoing, open-label, randomized clinical trial comparing extended-infusion TZP and meropenem for ESBL Enterobacterales bloodstream infections, and results of this study will help inform this conversation.

Recommendation 3

USCAST recommends that the STIC for TZP 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 are susceptible at MIC values ≤16/4 mg/L and resistant at MIC values >16/4 mg/L. This recommendation is based on TZP dosing regimens administered as an extended infusion (4.5 g infused over 3 hours every 6 hours or 4.5 g infused over 4 hours every 8 hours).

Rationale

The USCAST recommendations were primarily based on review of available microbiological and in silico data. TZP MIC distribution data from the SENTRY Antimicrobial Surveillance Program for CRO-S Enterobacterales (Figure 2) indicate that more than 95% of isolates have a TZP MIC ≤ 8/4 mg/L, supporting the FDA, CLSI, and EUCAST susceptibility breakpoint of ≤ 8/4 mg/L [20, 21, 23]. However, nearly 5% of CRO-S *K. pneumoniae* had a TZP MIC of 16/4 mg/L (Supplementary Figure 2), and USCAST therefore deemed that a 3GC-S Enterobacterales susceptibility breakpoint of ≤16/4 mg/L would be preferred if pharmacokinetically justified. USCAST endorses 2 extended-infusion TZP regimens (ie, 4.5 g infused over 3 hours every 6 hours or 4.5 g infused over 4 hours every 8 hours) for its proposed 3GC-S Enterobacterales susceptibility breakpoint given that the results of published target attainment analyses indicate the probability of achieving 50% piperacillin $fT > MIC$ with these extended-infusion TZP regimens is >90% for pathogens with TZP MIC values ≤ 16 mg/L [40, 42, 57, 58]. Of note, these are the same 2 extended-infusion TZP regimens recommended by CLSI for Enterobacterales with MIC values of 16/4 mg/L (susceptible-dose dependent) [21, 22]. However, UCSAST preferentially recommends TZP 4.5 g (3-hour infusion) every 6 hours for patients with CL_{CR} ≥ 100 mL/min based on Monte Carlo simulation studies that evaluated the effect of varying CL_{CR} on the observed probabilities of achieving 50% piperacillin $fT > MIC$ (Supplementary Table 3) [57, 59]. USCAST was opposed to the use of intermittent infusion TZP (4.5 g IV over 0.5 hours every 6 hours) for patients with 3GC-S Enterobacterales infections as the probability of achieving 50% $fT > MIC$ was <90% in simulated patients with (1) CL_{CR} ≥60 mL/min and TZP MIC of ≥8/4 mg/L, (2) CL_{CR} ≥80 mL/min and TZP MIC of ≥4/4 mg/L, and (3) CL_{CR} ≥100 mL/min and TZP MIC of ≥2/4 mg/L (Supplementary Table 3) [57, 59].

While piperacillin retains activity against most 3GC-S Enterobacterales, data from the SENTRY Antimicrobial Surveillance Program (2007– 2010) demonstrate that the addition of tazobactam increases the piperacillin susceptibility rates (at a breakpoint of ≤16/4 mg/L) from 86% to 97% for *K. pneumoniae* and from 53% to 97% for *E. coli* (Figure 3). Thus, the presence of tazobactam is not immaterial to the considerations that surround TZP breakpoints for 3GC-S Enterobacterales. USCAST acknowledges that there are limited preclinical data that characterize the PK/PD targets associated with efficacy for piperacillin alone and piperacillin in the presence of tazobactam against 3GC-S Enterobacterales [20].

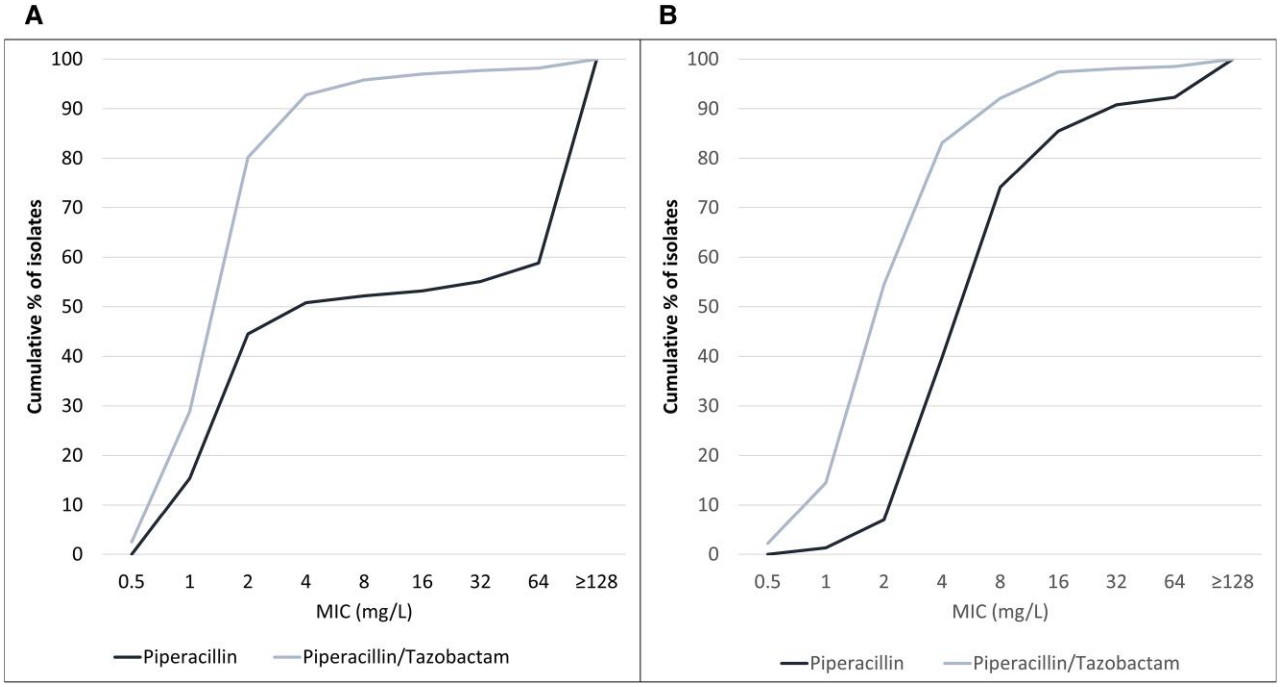

Figure 3. Activity of piperacillin and piperacillin/tazobactam against ceftriaxone-susceptible *Escherichia coli* (*A*) (4867 isolates) and ceftriaxone-susceptible *Klebsiella pneumoniae* (*B*) (2783 isolates) from North America medical centers (2007–2010). Enterobacterales were considered susceptible if the ceftriaxone MIC value was ≤1 mg/L. Abbreviation: MIC, minimum inhibitory concentration.

However, there are clinical data that suggest that critically ill patients with gram-negative infections who achieve 50% $fT >$ MIC with piperacillin and other β-lactams are more likely to have a positive clinical outcome [60–62].

Despite the notable data gaps, USCAST was in favor of these breakpoint recommendations based on the belief that use of TZP will largely be empiric for patients with 3GC-S Enterobacterales infections and that good stewardship practices will foster deescalation in most circumstances to a narrower agent when 3GCs demonstrate susceptibility. It is important to note that the 3GC-S Enterobacterales susceptibility breakpoint of ≤16/4 mg/L is contingent upon use of extended-infusion TZP. If institutions find administration of extended-infusion TZP infeasible, a reasonable susceptibility breakpoint with intermittent-infusion TZP would be 8/4 mg/L, as recommended by the FDA, CLSI, and EUCAST [20, 21, 23]. However, the probability of achieving 50% piperacillin $fT >$ MIC would be <90% for 3GC-S Enterobacterales with TZP MIC values ≤8 mg/L among some renal function subgroups with intermittent-infusion TZP (Supplementary Table 3) [57, 59]. Based on the Monte Carlo simulation studies that evaluated the effect of varying CL_{CR} on achieving 50% piperacillin $fT >$ MIC [57, 59], USCAST was not in favor of endorsing a TZP STIC for 3GC-S Enterobacterales that included a susceptible breakpoint for intermittent-infusion TZP dosing. USCAST unanimously agreed that additional preclinical PK/PD studies are needed to assess the piperacillin and tazobactam PK/PD targets associated with efficacy and using such targets to determine TZP dosing schemes necessary to ensure piperacillin's activity against 3GC-S Enterobacterales.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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