DR MARGUERITE LOUISE MONOGUE (Orcid ID : 0000-0001-8251-458X)
DR EMILY L. HEIL (Orcid ID : 0000-0002-6644-6684)

Article type : Invited Commentary

(Insert SIDP logo)

Title: The role of tazobactam-based combinations for the management of infections due to Extended-spectrum β-lactamase-producing Enterobacterales

Marguerite L Monogue*[1,2], Emily L Heil[3,4], Samuel L Aitken[5,6], Jason M Pogue[7]

[1]Department of Pharmacy, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [2]Division of Infectious Diseases and Geographic Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [3]University of Maryland Medical Center, Department of Pharmacy Services, Baltimore, Maryland, USA, [4]University of Maryland School of Pharmacy, Department of Pharmacy Practice and Science, Baltimore, Maryland, USA, [5]Department of Pharmacy; Michigan Medicine; Ann Arbor, MI, USA, [6]Department of Clinical Pharmacy, University of Michigan College of Pharmacy; Ann Arbor, MI, USA, [7]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, USA.

*Corresponding author:
University of Texas Southwestern Medical Center at Dallas
Department of Pharmacy
6201 Harry Hines Blvd
Dallas, Texas 75390
mmonogue@utexas.edu

Acknowledgements: The SIDP Publications and Podcasts Committee developed the concept for this manuscript, identified expert authors, provided peer review throughout its composition, and approved its final form. The SIDP Board of Directors also reviewed and approved the manuscript at each stage in its development, including its final form.
We would like to acknowledge Shamir Kalaria for his assistance with tazobactam pharmacokinetic/pharmacodynamic simulations in critically ill patients.

Conflict of Interest: MLM and JMP serve as consultants to Merck. All other authors declare no conflicts of interest.

Keywords: Tazobactam, Piperacillin, Ceftolozane, extended-spectrum β-lactamases, Enterobacterales, pharmacokinetics, pharmacodynamics, microbiome

Abstract (168/300 words): Extended-spectrum β-lactamase (ESBL) producing Enterobacterales are a global threat to public health due to their antimicrobial resistance profile and consequently, their limited available treatment options. Tazobactam is a sulfone β-lactamase inhibitor with *in vitro* inhibitory activity against common ESBLs in Enterobacterales, including CTX-M. However, the role of tazobactam-based combinations in treating infections caused by ESBL-producing Enterobacterales remains unclear. In the United States, two tazobactam-based combinations are available, piperacillin-tazobactam and ceftolozane-tazobactam. We evaluated and compared the roles of tazobactam-based combinations against ESBL-producing organisms with emphasis on pharmacokinetic/pharmacodynamic exposures in relation to MIC distributions and established breakpoints, clinical outcomes data specific to infection site, and considerations for downstream effects with these agents regarding antimicrobial resistance development. While limited data with ceftolozane-tazobactam are encouraging for its potential role in infections due to ESBL producing Enterobacterales, further evidence are needed to determine its place in therapy. Conversely, currently available microbiologic, pharmacokinetic, pharmacodynamic, and clinical data do not suggest a role for piperacillin-tazobactam, and we caution clinicians against its usage for these infections.

I. Introduction (7555 words)

First identified in the early 1980s, extended-spectrum β-lactamases (ESBLs) are predominately a group of Ambler molecular class A β-lactamase enzymes that hydrolyze penicillins, oxyimino-cephalosporins and aztreonam, and are typically encoded by plasmid-borne genes.[1] ESBLs have increased in frequency in both inpatient and outpatient settings worldwide. The United States Centers for Disease Control and Prevention considers ESBLs to be a serious threat to public health that were associated with nearly 200,000 cases and 9,100 deaths in 2017 with an estimated $1.2 billion in attributable health costs.[2] Over 200 ESBLs have been characterized, and are found most commonly in *E. coli* and *K. pneumoniae*, but can be found in a wide range of Enterobacterales and other gram-negative organisms including *Pseudomonas aeruginosa*.[3]

Carbapenems have traditionally been viewed as the gold-standard treatment for serious ESBL-producing (ESBL+) Enterobacterales infections, but widespread utilization of carbapenems has driven carbapenem-resistance which poses a serious threat to public health.[1,4,5] Between 2000 and 2010, data from 71 countries demonstrated that consumption of carbapenems increased by 45%.[6] While the spread of carbapenem resistance is multifactorial, the potential to use carbapenem-sparing treatments for ESBL+ infections is an antimicrobial stewardship priority. While ceftazidime-avibactam displays potent *in vitro* activity and has demonstrated efficacy against a wide variety of ESBL infections, the use of this agent is generally reserved for carbapenem-resistant Enterobacterales, notably Klebsiella Pneumoniae Carbapenemase (KPC) or OXA-48-like carbapenemase producing strains.[7–14]

Tazobactam-containing therapies are of particular interest given tazobactam's more narrow spectrum inhibitory properties and the changing epidemiology of ESBLs. The majority of ESBLs used to be derived from TEM-1, TEM-2 and SHV-1; however, CTX-M-type ESBLs have undergone rapid global spread and are the most prevalent ESBL encountered in *E. coli* and *K. pneumoniae* in most settings.[3,15] CTX-M enzymes are inhibited by tazobactam with almost 10-fold greater activity than clavulanic acid.[1,3,16,17] The purpose of this article is to understand the potential role of tazobactam-containing combinations for the management of ESBL+ Enterobacterales infections. This will be accomplished by a thorough review of the pharmacology, pharmacokinetics, and pharmacodynamics of tazobactam, the clinical data for tazobactam based combinations for ESBL+ Enterobacterales infections, and comparative selective pressure considerations for tazobactam based combinations and carbapenems.

II. Tazobactam Overview

Pharmacology of Tazobactam

The role of β-lactam-β-lactamase inhibitor combinations (BLBLIs) is for the inhibitor to restore the antimicrobial activity of their partner β-lactam compound when it is labile to hydrolysis by a given β-lactamase. Following Food and Drug Administration (FDA)-approvals of clavulanate and sulbactam, tazobactam was the third BLI brought to market by 1993.

Although structurally similar to β-lactam antimicrobials, traditional β-lactamase inhibitors possess specific structural differences that enhance their ability to inhibit β-lactamase enzymes. Tazobactam is a penicillinate sulfone β-lactamase inhibitor as defined by the sulfone within the five-membered ring (**Figure 1)**. This heteroatom serves as the leaving group responsible for the opening of the second ring and creating the intermediate that allows for hydrolysis of the β-lactamase.[18,19] Furthermore, tazobactam exhibits a triazole group at the C-2 β-methyl position. This structural difference is hypothesized to improve tazobactam's inhibition by decreasing the concentration required to inhibit 50% of the β-lactam mediated hydrolysis by a particular β-lactamase, also known as the 50% inhibitory concentration (IC_{50}), and dissociation rates against Ambler class A and specific class C β-lactamases.[18,20]

Tazobactam's inhibitory spectrum includes many Ambler class A β-lactamases (TEM-, SHV-, and CTX-M-type) and some class C (AmpC-type) β-lactamases.[18,21] Notably, not all β-lactamases and inhibitors are created equal, as demonstrated in **Table 1** by the varying IC_{50s} of tazobactam, clavulanic acid, and sulbactam.[22–28] While tazobactam demonstrates low IC_{50} values against TEM- and SHV-type enzymes; its enhanced inhibitory activity against CTX-M-15, the most common ESBL present in Enterobacterales, is notable.[23–25,27,28] Tazobactam lacks meaningful activity against KPC-type and most Ambler class B, C, and D enzymes. While tazobactam's IC_{50} values provide insight into enzyme inhibitory effect, there are limitations associated with the interpretation of these values.[18] Instead, clinical decisions are often influenced by the minimum inhibitory concentration (MIC) and the susceptibility breakpoint of the combination product.

Dosing and susceptibility testing

In the United States, tazobactam is available intravenously in combination with piperacillin, a ureidopenicillin, or ceftolozane, an antipseudomonal cephalosporin. Piperacillin-tazobactam is formulated in an 8:1 ratio. Standard, non-renally adjusted doses, range from 3.375 grams (g) to 4.5 g every 6 to 8 hours (h). Ceftolozane-tazobactam is available in a 2:1 ratio and dosing ranges from 1.5 g to 3 g every 8 h.[29,30]

Clinically, tazobactam is administered in a predefined ratio with the partner β-lactam and thus, as with any drug, concentrations vary over a dosing interval. However, *in vitro* susceptibilities—as determined by the MIC of the combination product—use a fixed tazobactam concentration of 4 μg/mL, irrespective of fluctuations in the concentration of the partner β-lactam. Consequently, this fixed tazobactam concentration is reflected in the established piperacillin-tazobactam or ceftolozane-tazobactam susceptibility breakpoints.

For Enterobacterales, the Clinical & Laboratory Standards Institute (CLSI) susceptibility breakpoints for piperacillin-tazobactam and ceftolozane-tazobactam are ≤ 16/4 μg/mL and ≤ 2/4 μg/mL, respectively.[31] Notably, the piperacillin-tazobactam breakpoint set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is more conservative at an MIC of ≤ 8/4 μg/mL. These breakpoints fall at or above the epidemiologic cutoff for these organisms; however, susceptibility defined by the breakpoint does not guarantee a wild-type organism (e.g. the absence of an ESBL-producer).[32,33]

Using these breakpoints, both piperacillin-tazobactam and ceftolozane-tazobactam demonstrate *in vitro* susceptibility against ESBL+ Enterobacterales. In a collection of 63 ESBL+ *E. coli* bloodstream infections, with CTX-M-15 and CTX-M-27 representing the majority of the ESBLs, approximately 98% of the organisms demonstrated susceptibility to piperacillin-tazobactam with MICs < 16/4 μg/mL. However, consistent with the inhibitory profile of tazobactam, the percentage of piperacillin-tazobactam susceptible isolates decrease if the isolates co-carry AmpC (Ambler class C) or OXA-1 (Ambler class D) enzymes in addition to the ESBL.[34] Likewise, a collection of urine and bloodstream ESBL + *E. coli* isolates demonstrated 81% and 70% susceptibility to piperacillin-tazobactam, respectively.[35] Overall, the data suggest that the majority of ESBL+ *E. coli* isolates are piperacillin-tazobactam susceptible at current breakpoints; however, this is not the case for *Klebsiella* species.[36–38] North American data from 2010–2014 demonstrated 69% of ESBL+ *E. coli* isolates were piperacillin-tazobactam susceptible compared with only 26.9% of *Klebsiella* spp. isolates.[39] Similar trends were

observed in the Asia-Pacific region.[38] Limited *in vitro* data exists beyond ESBL+ *E. coli* and *Klebsiella* species.

Ceftolozane-tazobactam displays potent *in vitro* activity against *E. coli* and *K. pneumoniae* producing CTX-M-14 and CTX-M-15 ESBLs with over 70% of the organisms inhibited at an MIC of ≤ 2/4 µg/mL.[40] Shortridge D. *et al.* demonstrated that 88% of ESBL positive Enterobacterales displayed MICs of ≤ 2/4 µg/mL.[41] Similar to what is observed with piperacillin-tazobactam, ceftolozane-tazobactam MICs tend to be lower against ESBL+ *E. coli* isolates than against *K. pneumoniae* ESBL+ isolates.[42–44] In general, ceftolozane-tazobactam is more potent than piperacillin-tazobactam with MIC_{50}/MIC_{90} values against ESBL+ isolates being several dilutions lower **(Table 2).**[42,45–53] In fact, greater *in vitro* activity is demonstrated with ceftolozane-tazobactam despite having lower susceptibility breakpoints. This is due to ceftolozane demonstrating greater stability to hydrolysis by common ESBLs than piperacillin. Against low, moderate, and high levels of CTX-M-15 production in *E. coli* isolates, the MICs (in the absence of tazobactam) of ceftolozane were 4, 16, and 64 µg/mL compared to 128, >256, >256 µg/mL, with piperacillin.[54,55] In other words, ceftolozane is less reliant than piperacillin on tazobactam's inhibitory properties, and this will be an important pharmacokinetic and pharmacodynamic consideration as described below.

III. Pharmacokinetic and Pharmacodynamic Considerations

Optimization of an antimicrobial's pharmacokinetics (PK) and pharmacodynamics (PD) is an essential component to the clinical success of an agent, as it impacts clinical efficacy and patient safety.[56] Pharmacokinetics describes the movement of drug throughout the body over time. Pharmacodynamics defines the relationship between drug concentration and pharmacologic or toxicologic effect.[57] Traditional indices employed to describe this antimicrobial concentration/effect relationship are 1) the ratio of the peak free drug concentration to the MIC (fC_{max}/MIC); 2) the ratio of the area under the free drug concentration-time curve to the MIC (fAUC/MIC); or 3) the percentage of the free drug concentration that exceeds the MIC over a defined time period (fT>MIC). However, β-lactamase inhibitor PK/PD is complex and often non-traditional, falling under the shadow of the partner β-lactam's PK/PD.[58,59] It is important to note that this may or may not be reflected in current susceptibility breakpoints. For example, the piperacillin breakpoint of 16 µg/mL is largely based on PK/PD considerations with commonly

applied piperacillin dosing strategies; that is, the ability to achieve piperacillin *f*T>MIC targets in patients. The piperacillin-tazobactam breakpoint is 16/4 µg/mL*, solely because the piperacillin breakpoint is 16 µg/mL*, irrespective of whether or not a fixed concentration of 4 µg/mL of tazobactam in a test tube is reflective of the restorative ability of commonly employed doses of tazobactam to reestablish the activity of piperacillin if the MIC is ≤ 16/4 µg/mL. Understanding and application of inhibitor PK/PD is of critical importance to determining the utility of tazobactam based combinations in patients.

The limitations of β-lactamase inhibitor PK/PD are multifaceted. First, the ability to dose the inhibitor as an individual agent in the clinical setting is dictated by the partner agent given the compounds are formulated as a single product. For example, optimizing exposures of the β-lactam partner via tactics such as increasing the dose or extending the infusion consequently also impacts the PK/PD of the inhibitor. Second, the partner β-lactam's concentration, and ultimately restorative effect, is highly dependent on the ratio of β-lactamase inhibitor to β-lactamase production, which is a dynamic, fluctuating environment. Unfortunately, the rationale for the products ratio between parent β-lactam and inhibitor with tazobactam based combinations is lacking.[55,60] Third, there is a lack of consistent methodology for quantifying the inhibitor effect dynamically. Not only to account for the changes in tazobactam concentration, but also the changes in the "concentration" of the β-lactamase. The degree of β-lactamase transcription varies across both individual and populations of bacteria. The BLI effect has been described as direct enzyme inhibition or enhancement of the antimicrobial activity of the partner β-lactam. Additionally, any experiment that assesses the ability of an inhibitor to restore the activity of a parent drug is going to be dependent on the amount of parent drug given, which can further complicate translation of the findings to the patient level if the amount of parent drug given in the experiment is different from the amount given to patients as part of the fixed dose combinations. Current approaches to characterize the PK/PD of β-lactamase inhibitors include normalizing the β-lactamase inhibitor exposures required to the BLBLI combination MIC, a defined "threshold", or a dynamic/instantaneous MIC.[60–63] In this setting, the term "threshold concentration" refers to a serum concentration of the BLI (i.e. tazobactam) that target exposures need to be normalized to that may or may not be reflected in the combination product MIC (e.g. *f*T> 1 µg/mL of tazobactam or a *f*T > piperacillin/tazobactam MIC). For the purpose of this review, we will focus on studies utilizing clinically relevant doses and threshold concentrations

that can be determined with basic microbiologic susceptibility data that are provided to the treating clinician.

Piperacillin-tazobactam PK/PD targets:

The first studies to describe the PK/PD of tazobactam in combination with piperacillin utilized 24-h one-compartment *in vitro* infection models.[54,64] In the first study by Nicasio and colleagues, three *E. coli* strains with varying levels of CTX-M-15 production (low, moderate, high) were exposed to dose-fractionated, free-drug concentrations of tazobactam. Piperacillin was infused into the model at doses equivalent to exposures in patients with 2 g or 4 g every 6 hours. Using Hill-type models and nonlinear least-squares regression, the correlations of change in bacterial density ($\log_{10}$ CFU/mL) to *f*AUC, *f*C_{max}, and *f*T > threshold were determined. The PK/PD index best associated with tazobactam efficacy was *f*T > threshold ($r^2 = 0.84$); importantly however, the threshold concentration changed as the CTX-M-15 transcription level increased. These threshold concentrations ranged from 0.25 to 2 μg/mL for the three isolates. Tazobactam *f*T > threshold exposures of 45, 63, and 85% were required to restore the ability of piperacillin to achieve net bacterial stasis, 1, and 2 $\log_{10}$ CFU/mL reduction at 24 hours.[54]

While this study was informative, three main limitations restrict application to patient care. First, there would be no way of clinically knowing if there was low, medium, or high β-lactamase production occurring; therefore, the threshold tazobactam concentration to target would be unknowable. Second, the investigators did not translate the threshold concentrations to piperacillin-tazobactam MICs, which is the only clinically available threshold concentration to practitioners. Without knowing how to use these thresholds in the context of MIC, clinical decisions cannot be made. Third, the various experiments that developed these threshold concentrations administered two different piperacillin background doses. As previously described, the amount of tazobactam necessary to restore the activity of piperacillin, will depend on how much piperacillin is present. As some of the threshold concentrations described were determined in the backdrop of half (2 g every 6 hours) of the daily dose of piperacillin, it is unclear how to apply these findings to a clinical scenario where twice as much piperacillin is administered.

To overcome these limitations, Vanscoy and colleagues sought to determine the "real world" tazobactam exposure required to restore piperacillin's activity (4 g every 6 hours

administered as a 30-minute infusion) against three clinical Enterobacterales isolates that had not only the presence of ESBLs, but also other resistance mechanisms including other β-lactamases and porin/efflux alterations. The authors demonstrated that once again tazobactam's *f*T > threshold was the PK/PD exposure that optimally restored piperacillin's antibacterial activity. Importantly however, they demonstrated that similar to the traditional PK/PD indices, the threshold concentration that was the most predictive threshold was the piperacillin-tazobactam MIC (MIC_{TZP}). Tazobactam *f*T > MIC_{TZP} exposures of 64 and 77% were required to restore the ability of standard dose piperacillin to achieve bacterial stasis and 1 $\log_{10}$ CFU/mL reduction. This study utilized traditional piperacillin dosing, providing a clean interpretation of the tazobactam effect. Furthermore, the PK/PD index predictive of efficacy is not different than our traditional PK/PD indices, allowing for easy clinical translation.[64]

Ceftolozane-tazobactam PK/PD targets:

As the previous studies demonstrated, the isolate and the level of enzyme production can dictate tazobactam target exposures. The partner β-lactam that is paired with tazobactam adds an additional layer of complexity, as the stability of each β-lactam antimicrobial against various β-lactamases differs.[65] As previously discussed, ceftolozane-tazobactam tends to be more potent than piperacillin-tazobactam against Enterobacterales as ceftolozane is more stable to hydrolysis than piperacillin and therefore, tazobactam PK/PD targets will differ when combined with ceftolozane compared to those with piperacillin.[42,45,66,67] Using identical *E. coli* producing CTX-M-15 isolates from the *in vitro* study by Nicasio and colleagues, VanScoy and colleagues conducted a similar *in vitro* model with ceftolozane as the partner β-lactam (in place of piperacillin).[55] In the dose fractionation studies, ceftolozane was administered as 125 mg, 500 mg, and 1,000 mg every 8 hours for the isolates with low, moderate, and high-β-lactamase expression, respectively. Similar to piperacillin-tazobactam, *f*T > threshold was the exposure that best correlated with efficacy ($r^2 = 0.94$). However, both the threshold concentrations (0.05 to 0.25 µg/mL) and target exposures relative to those thresholds were lower in this model than when combined with piperacillin, reflecting the enhanced stability of ceftolozane. Tazobactam *f*T > threshold exposures of 35, 50, and 70% were required to restore the ability for ceftolozane to achieve net bacterial stasis, 1, and 2 $\log_{10}$ CFU/mL reduction at 24 hours.[55] As described above

with piperacillin, the lack of a clinically translatable reference point for exposure, and various doses of ceftolozane used in this study limited the clinical applicability of these data.

Acknowledging the threshold concentrations varied between isolates, VanScoy and colleagues further attempted to improve the clinical translatability of this measurement by correlating threshold with MIC. Similar to the aforementioned work with piperacillin-tazobactam, seven clinical isolates and one ATCC strain with varying levels of CTX-M-15, AmpC, porin, and efflux expression were used. In the PK/PD analysis, the ceftolozane dose was 1,000 mg for isolates with ceftolozane-tazobactam MICs of 0.5/4 and 1/4 µg/mL and 2,000 mg for ceftolozane-tazobactam MICs of 2/4 and 4/4 µg/mL. The *f*T > threshold of tazobactam required to restore the ability of ceftolozane to achieve bacterial stasis, 1-$\log_{10}$, and 2-$\log_{10}$ CFU reductions were 65.9, 77.3, and 90.2%. Importantly, the authors were again able to relate the threshold concentration necessary to the ceftolozane-tazobactam MIC provided to clinicians. The threshold concentration that best equated with restoration was the product of 0.5 and the ceftolozane-tazobactam MIC (MIC_{CT} * 0.5).[62] For example, if the ceftolozane-tazobactam MIC is 2/4 µg/mL, this would be mean that the threshold concentration of tazobactam is 1 µg/mL. This study improves the clinical applicability of the data given both that the threshold exposure necessary is translated to clinically reported MICs, and since ceftolozane was administered at clinically relevant doses. It is important to note however that some of the isolates had the threshold concentration determined in the background of standard dose (1000 mg every 8 hours) ceftolozane, and thus if high dose is employed, lower thresholds of tazobactam may be demonstrated due to the increased dose of ceftolozane administered.

Tazobactam PK/PD target summary:

Based on *in vitro* data, **Table 3** summarizes the thresholds needed for various tazobactam based combinations. Unfortunately, no clinical data exists validating the exposures of tazobactam required for the treatment of infections caused by β-lactamase producing organisms. The available PK/PD data demonstrate that species, type of β-lactamase, quantity of β-lactamase production, and the stability of the partner β-lactam to hydrolysis by these enzymes affect the tazobactam exposures required to optimize efficacy. Unfortunately, based on the standard ratios administered, tazobactam concentrations are inherently lower than piperacillin or ceftolozane; however, the required *f*T > threshold exposures to restore bacterial kill are much higher for

tazobactam compared with its β-lactam partners, leading to potential issues with susceptibility breakpoints driven by the partner β-lactam.[67,68]

To further understand and translate susceptibility of tazobactam combinations a detailed assessment at tazobactam pharmacokinetics with commonly employed doses is necessary. Unfortunately, data on the pharmacokinetics of tazobactam are extremely limited to healthy volunteer data found in the prescribing information for both piperacillin-tazobactam and ceftolozane-tazobactam and small studies in infected patients. The following section will discuss what is known about tazobactam pharmacokinetics and ultimately try and relate this to the exposures needed and appropriate susceptibility breakpoints.

Tazobactam Pharmacokinetics:

Healthy volunteer pharmacokinetics:

Per the piperacillin-tazobactam package insert after a dose of 4.5 g (4 g of piperacillin 500 mg of tazobactam) every 6 hours (30-minute infusion) the tazobactam PK profile is described by a maximum free tazobactam serum concentration (C_{max}) of ~ 24 μg/mL, a drug clearance of 12.4 L/h, a volume of distribution of 14.7 L, and a half-life of 0.82 h. In the context of maximizing tazobactam exposure, the greatest PK limitations of tazobactam are its relatively low serum concentrations and short half-life.[69,70] Using package insert based dosing, the highest MIC at which tazobactam will restore bacterial stasis (tazobactam 64% $fT > MIC_{TZP}$) and 1 log kill (tazobactam 77% $fT > MIC_{TZP}$) of piperacillin are 1/4 and 0.5/4 μg/mL, respectively. This is problematic given the piperacillin-tazobactam MIC_{50} against ESBL+ *E. coli* organisms is ≥ 4/4 μg/mL and the CLSI susceptible breakpoint for Enterobacterales is 16/4 μg/mL **(Table 3)**.

In the FDA approved ceftolozane-tazobactam dose of 3 g (2 g ceftolozane, 1 g tazobactam) every 8 hours (60-minute infusion), tazobactam exposures appear to be more in line with those required to restore activity than with piperacillin-tazobactam due to its higher dose (3 g tazobactam/day) longer infusion (60-minute), and lower susceptibility breakpoint (2/4 μg/mL). Comparing heathy volunteer PK data, 1000 mg of tazobactam with ceftolozane versus 500 mg of tazobactam with piperacillin has higher clearance (20.9 vs. 12.4 L), larger volume of distribution (23.7 vs. 14.7 L), and slightly longer half-life (1.02 vs. 0.82 h). However, the 1000 mg dose has a lower free C_{max} (20 vs. 24 μg/mL), likely reflecting the duration of infusion (60 vs. 30 minutes). Again applying basic pharmacokinetic equations to these values and translating to target

ceftolozane-tazobactam exposures of 66% and 77% *f*T > (MIC_{CT} * 0.5), the highest achievable MIC to restore bacterial stasis and 1-log kill of ceftolozane are 2/4 and 1/4 µg/mL, respectively, with high dose ceftolozane-tazobactam demonstrating less of a disconnect between the susceptibility breakpoint and the achievable exposures than with piperacillin.[62]

When reviewing the aforementioned package insert based estimations, it is important to note that these are simply estimations based on average values (i.e. the 50% percentile). PK/PD probability of target attainment (PTA) studies have much higher standards for determining whether or not exposures will be reliably achieved in a population of patients, and a PTA of 90% is considered the standard for whether or not an MIC can be targeted at a given dose. While these robust simulations of the BLI have not been performed with piperacillin-tazobactam or ceftolozane-tazobactam, they have been simulated with healthy volunteer pharmacokinetic data in a phase 1 study of cefepime-tazobactam, and these findings further highlight the concerns with tazobactam doses, exposures, and breakpoints. In this cefepime-tazobactam model, tazobactam doses of 2 g every 8 hours as a 90-minute infusion (twice the daily dose given with ceftolozane and three times the daily dose given with piperacillin) will only have a PTA of ~90% or greater for achieving the threshold exposures associated with restoring stasis or 1-log_{10} kill with piperacillin or ceftolozane up to a threshold concentration of 0.5 µg/mL. This would suggest that even at these higher tazobactam doses administered as a prolonged infusion (which enhances the time above a threshold concentration), appropriate breakpoints for piperacillin-tazobactam and ceftolozane-tazobactam, would be 0.5/4 µg/mL and 1/4 µg/mL, respectively.[71]

Infected patients pharmacokinetics:

While healthy volunteer PK data provide insight into expected drug exposures, these are not the patients who ultimately receive the drug. Therefore, it is essential to understand how PK is altered across different populations, especially infected patients, to better understand if the chosen doses achieve our target PK/PD exposures; or perhaps more importantly, what MIC values can be targeted with the current labeled doses. Tazobactam PK data, in combination with ceftolozane, has been assessed from infected patients, including those with nosocomial pneumonia, as part of the recent drug development program for this combination. Volumes of distribution appear ~2-fold higher in infected patients compared with healthy volunteers, while clearance was consistent regardless of infection status. A higher volume of distribution will

ultimately result in lower C_{max} concentrations and potentially compromise PK/PD target attainment. However, these PK changes will also lead to a longer half-life, which depending on achieved C_{max} values, might afford longer time above threshold concentrations.[72,73] Additional data followed by robust pharmacokinetic simulations are needed in these specific patient populations to further appreciate the importance of these changes in PK in relation to optimizing tazobactam exposure in combination with ceftolozane.

Tazobactam exposures, in combination with piperacillin, have recently been explored in a real world study in critically ill patients.[74] Tazobactam plasma samples from eighteen patients in the intensive care unit were used to develop a 1-compatment pharmacokinetic model. While maximal free concentrations were, on average, similar, drug clearance was lower in infected patients with normal renal function when compared with healthy volunteers (5.3 L/h vs. 12.4 L/h).[69] Using the population PK model from this study, we performed a 1,000 patient Monte Carlo Simulation and assessed the tazobactam PTA for 77% *f*T > various threshold concentrations of tazobactam (the 1-log kill threshold exposures for piperacillin-tazobactam and ceftolozane-tazobactam) with both labeled doses of 500 mg every 6 hours (30-minute infusion) or 1000 mg every 8 hours (60-minute infusion) **(Figure 2)**. For both of these tazobactam dosing regimens, the highest threshold concentration where ~90% PTA was achieved was 2 μg/mL. Notably, this threshold is higher than those estimated from PK in healthy volunteers, likely due to the difference in drug clearance. While these data would support current ceftolozane-tazobactam Enterobacterales susceptibility breakpoints, they would suggest that a more appropriate piperacillin-tazobactam susceptibility breakpoint would be 2/4 μg/mL. Importantly this simulation was based on a small population of critically ill patients. A larger cohort is needed to validate these findings. Furthermore, the PK of tazobactam was only performed in the presence of piperacillin. Future analyses should include patients receiving both ceftolozane or piperacillin in combination with tazobactam as the PK of the BLI is potentially impacted by the partner β-lactam.

PK/PD summary

The differences in tazobactam exposures, in addition to the ESBL stability of the partner β-lactam, must be taken into consideration when evaluating the clinical outcomes of tazobactam-based therapy for the treatment of ESBL+ infections.[33,75,76] Unfortunately, the rationale for

clinically recommended doses and fixed ratios remains largely unsupported by PK/PD. Although limited tazobactam PK/PD data exists, available healthy volunteer PK/PD would suggest breakpoints for piperacillin-tazobactam 4.5 g every 6 hours (30-minute infusion) of 0.5/4 μg/mL and ceftolozane-tazobactam 3 g every 8 hours (60-minute infusion) of 1/4 μg/mL. Small studies in critically ill patients suggest higher MICs may be targeted but more robust data are needed. While ceftolozane-tazobactam's CLSI breakpoint of 2/4 μg/mL may be within reach depending on patient-specific PK, piperacillin-tazobactam's CLSI breakpoint of 16/4 μg/mL makes adequate tazobactam exposure unattainable, highlighting potential clinical failure concerns for "susceptible" β-lactamase producing organisms. Further pharmacokinetic and clinical data are urgently needed to optimize tazobactam's efficacy against β-lactamase producing organisms.

IV. Clinical Data

Early *in vitro* and clinical data hinted that tazobactam-based therapies may be inadequate for ESBL+ organisms, particularly high-inoculum infections. One small retrospective analysis of 21 patients with culture confirmed ESBL+ infections found patients treated with piperacillin-tazobactam had only 56% treatment success rate despite reported *in vitro* susceptibility.[77] Time-kill studies showed cefepime, imipenem and meropenem demonstrated bactericidal activity against ESBL+ isolates but piperacillin-tazobactam showed bactericidal killing against only 1 ESBL+ isolate investigated. At high inoculum, cefepime and piperacillin-tazobactam were unable to maintain activity against any of the ESBL+ isolates unlike the carbapenems.[78] These data reinforced the paradigm that carbapenems were the drug of choice for invasive ESBL infections. This dogma was not significantly challenged until the early 2010's.

Piperacillin-tazobactam for ESBL bacteremia

Between 2012-2016, a series of retrospective, observational trials comparing β-lactam/β-lactamase inhibitors (largely piperacillin/tazobactam) and carbapenems for the empiric and/or definitive treatment of bacteremia due to ESBL+ Enterobacterales were performed (Table 4) with conflicting results. Interpretation of the findings from these trials is challenging and limited by significant heterogeneity in the source of bacteremia, a range of both piperacillin/tazobactam doses administered and MIC distributions of the Enterobacterales causing infection, significant confounding by indication where sicker or more complicated patients received carbapenems, and

a substantial amount of cross-over between treatment arms (empiric piperacillin/tazobactam followed by definitive carbapenem therapy) in some of the publications.[79–84]

In general, piperacillin/tazobactam fared comparably to carbapenems in studies that assessed empiric and definitive therapy cohorts separately,[79,83] those that primarily included patients with urinary or biliary sources of bacteremia,[79,80,83] and those where piperacillin/tazobactam dosing was high and MIC distributions were low.[79,80] Conversely, significant concerns with piperacillin/tazobactam were raised in studies that focused on empiric use,[81] those that had a larger percentage of patients with higher burden sources (e.g. pneumonia and central line),[81,82] and those that utilized lower piperacillin/tazobactam doses and/or had higher MIC distributions.[80–82]

The conflicting findings and the significant confounding by indication in these retrospective analyses precluded the ability for conclusive recommendations for piperacillin-tazobactam for ESBL bacteremia. The MERINO trial, a prospective, multi-center, international, open-label, randomized controlled non-inferiority study, was hoped to be the definitive answer to this question. Adult patients with ESBL + bacteremia, defined as ceftriaxone-nonsusceptible *E.coli* or *K. pneumoniae,* were randomized to meropenem (1000 mg every 8 hours as a 30-minute infusion) or piperacillin-tazobactam (4.5 g IV every 6 hours as a 30-minute infusion) within 72 hours of blood culture collection. Isolates had to be susceptible to both study drugs according to local laboratory susceptibility testing protocols. The study set out to enroll 454 patients to demonstrate non-inferiority of piperacillin-tazobactam with a primary outcome of 30-day all-cause mortality. However, the trial was stopped early when an interim analysis showed increased mortality in the piperacillin-tazobactam group compared to the meropenem group (12.3% vs 3.7%, risk difference 8.6%; p=0.004).

Interestingly this mortality difference was demonstrated despite the study population largely consisting of 'less severe' infections, with <10% of patients in the ICU and a median Pitt bacteremia score of 1 for both groups. The secondary endpoint of clinical and microbiologic success at day 4 also favored meropenem patients (74.6% vs. 68.4%), however the study was underpowered to assess this endpoint. Mortality rates in patients receiving piperacillin/tazobactam were similar in patients with MICs ≤2 μg/mL (14.5%) or >2 μg/mL (12.7%).[76]

A post-hoc analysis re-evaluated outcomes based on MIC after a central lab performed broth microdilution MIC testing for 157/188 patients who received piperacillin-tazobactam and 163/191 patients who received meropenem. For isolates that initially tested piperacillin-tazobactam susceptible at the study site, but were confirmed to be piperacillin-tazobactam resistant (MICs >16 μg/mL), mortality was higher in piperacillin-tazobactam treated patients (5/10, 50%) than those with susceptible isolates (13/147, 8.8%); p=0.002.[33] The authors highlighted how the differences in the MERINO trial between piperacillin-tazobactam and meropenem became less pronounced when limited to isolates "susceptible" to both drugs (13/147 (8.8%) vs. 6/155 (3.9%). However, it is important to note that mortality rates were still twice as high for patients receiving piperacillin-tazobactam. Furthermore, mortality rates were the highest (9/61; 14.8%) for patients receiving piperacillin-tazobactam with low MICs (≤ 2 mg/L), thereby limiting the relationship demonstrated between MIC and outcome. This study also highlights the potential clinical impact of isolates that co-harbor other β-lactamase enzymes, such as narrow spectrum oxacillinases (OXA). The potential presence of other resistance mechanisms should be considered when evaluating the efficacy of tazobactam-based combinations.

Regardless of the role susceptibility testing may have played in amplifying the results, the striking difference in mortality rates, as well as numerically worse clinical and microbiological success rates in this study certainly gives pause to the use of piperacillin-tazobactam for ESBL+ gram-negative bloodstream infections, even in the 'lower-risk' bacteremic patients with low-inoculum sources of infection.

Piperacillin-tazobactam for ESBL urinary tract infections

Although piperacillin-tazobactam fared poorly for bacteremia, the question remains whether or not it is appropriate for less severe infections without bacteremia. While multiple retrospective studies exist addressing the potential role for piperacillin-tazobactam for the treatment of urinary tract infections, the majority of them are limited by small numbers, diagnostic uncertainty, and/or the inclusion of bacteremic patients. Sharara and colleagues recently performed a retrospective multicenter observational study comparing clinical outcomes of adults hospitalized with pyelonephritis (without bacteremia) caused by ESBL+ Enterobacterales who were primarily treated with piperacillin-tazobactam versus carbapenems, using an inverse probability of treatment weighted propensity score analysis. Patients were

included if they received study medication within 48 hours of the time of the initial culture and it was continued for at least 72 hours. The primary outcome of recurrent cystitis or pyelonephritis occurred in 9/44 (20%) patients receiving piperacillin-tazobactam compared to 35/141 (25%) patients receiving a carbapenem. Similarly, there was no difference in the secondary outcomes of resolution of symptoms within 7 days (OR 1.79; 95% CI 0.50 – 6.46) or 30-day mortality (OR 0.38; 95% CI 0.05 – 3.06) in patients receiving piperacillin-tazobactam or meropenem, respectively. While these data suggest a potential role for piperacillin-tazobactam for ESBL pyelonephritis they suffer from significant limitations, similar to the initial bacteremia data that limit their interpretations. Although adjusted for in propensity score, some important comorbidities were more numerically frequent in the carbapenem group, notably as it related to immunocompromising conditions. Furthermore, patients in the piperacillin-tazobactam group were more likely to be started on study drug within 24 hours (95.5% vs 79.4%), more likely to transition to oral stepdown therapy (20% vs. 7.8%), and received shorter durations of therapy. Moreover, the methods required 72 hours of study drug and disallowed switches to the other treatment arm. Therefore, any patient started on piperacillin-tazobactam and switched to a carbapenem would be ineligible for inclusion in this cohort, biasing the results towards patients responding to empiric piperacillin-tazobactam therapy.[85] These subtle differences in confounding by indication between the groups are reflected by numerically better results for every study endpoint in piperacillin-tazobactam treated patients compared to those who received the gold-standard carbapenem regimen and limit any inferences that can be made.

Ceftolozane-tazobactam for ESBL infections

Although there are currently no comparative real-world or randomized controlled trial data comparing ceftolozane-tazobactam to carbapenems specifically for ESBL infections, there are some subgroup data from FDA registry trials comparing ceftolozane-tazobactam's efficacy versus levofloxacin (complicated urinary tract infections) and meropenem (intrabdominal infections, and hospital acquired bacterial pneumonia). Popejoy and colleagues reported on the efficacy of ceftolozane-tazobactam (1.5 grams every 8 hours) versus comparators for ESBL+ Enterobacterales from the urinary tract and intra-abdominal infection trials. For the endpoint of clinical cure at test of cure, ceftolozane-tazobactam was superior to levofloxacin for complicated urinary tract infections (53/54 (98%) vs. 38/46 (83%); p = 0.01) and similar to meropenem for

complicated intra-abdominal infections (23/24 (96%) vs. 23/26 (89%); p > 0.05) due to ESBL+ Enterobacterales.[86]

Most recently, ceftolozane-tazobactam (3 g every 8 hours) was studied versus meropenem (1000 mg every 8 hours) for the treatment of nosocomial pneumonia. ESBL+ Enterobacterales were isolated from 157 (31%) patients in the study, 54 of which (32%) were resistant (defined as an MIC >4/4 μg/mL) to ceftolozane-tazobactam. Twenty-eight-day mortality in patients with ESBL+ Enterobacterales was similar between patients receiving ceftolozane tazobactam (18/84, 21%) and meropenem (21/73 (29%)) (difference 7.3% (-6.1 to 20.8). Clinical cure rates at test of cure were also similar between the groups (48/84 (57%) vs. 45/73 (62%); - 4.5 (-19.3 to 10.7)) for ceftolozane-tazobactam and meropenem, respectively. Interestingly, clinical cure with ceftolozane-tazobactam was demonstrated in 33/53 (62%) isolates with MICs ≤4/4 mg/L compared with 15/31 (48%) above 4/4 μg/mL. Similar clinical cure rates (63% and 60%) were seen in patients who received meropenem, regardless of ceftolozane-tazobactam susceptibility.[75]

While these initial data are encouraging, more evidence is needed to support the role of ceftolozane-tazobactam for invasive ESBL infections and to ultimately change the current standard of care. The MERINO III trial, comparing ceftolozane-tazobactam and meropenem for bloodstream infections due to ESBL and/or AmpC producing Enterobacterales plans to begin enrolling soon and will help fill this data void.

V. Considerations for collateral damage

One of the principal arguments for consideration of tazobactam-based combinations for infections due to ESBL+ Enterobacterales is the notion that their "carbapenem-sparing" nature will decrease the selective pressure for carbapenem-resistance and thus limit the urgent threat to public health of carbapenem-resistant organisms, most notably CRE. While this would represent an important consideration if supported by evidence, it is of critical importance that this theory is fully vetted and deliberated.

Impact of tazobactam-based combinations and carbapenems on the human microbiome

At a surface level, the spectrum of activity of piperacillin-tazobactam, ceftolozane-tazobactam, and the carbapenems are broadly similar, with each having activity against common

Enterobacterales, *P. aeruginosa*, as well as gram-positives, and anaerobic organisms for piperacillin-tazobactam and carbapenems. Both piperacillin-tazobactam and carbapenems appear to generally lead to a decrease in the relative abundance of Enterobacterales and increase the relative abundance of *Enterococci*, consistent with their known spectrum of activity.[87,88] The effects of piperacillin-tazobactam and the carbapenems on anaerobic bacteria, including Bacteroides spp., are more variable.[88] No data are available regarding the effect of ceftolozane-tazobactam on the microbiome. The clinical impact of these microbiome changes, along with the significance of any minor differences between agents, is not known.

Mechanistic basis of selection of carbapenem resistance in patients treated with tazobactam-based combinations and carbapenems

In general, there are two pathways by which a patient may become infected or colonized with carbapenem-resistant pathogens following treatment for a defined infection. In the first case, a pre-existing organism may develop one or more spontaneous mutations or other genetic changes that are associated with antimicrobial resistance, with no need for acquisition of exogenous resistance elements or colonization by pre-existing antimicrobial-resistant mutants.[89,90] In the Enterobacterales, spontaneous carbapenem resistance appears to develop primarily as a result of outer membrane porin loss or alterations in patients with previous ESBL or AmpC-producing organisms and subsequent carbapenem exposure.[91–94] This resistance pathway leads to a phenotypically carbapenem-resistant organism without carbapenemase genes; such organisms typically have lower-level resistance to carbapenems than do carbapenemase producers.[95] Whether this mechanism is exclusively related to carbapenem exposure or if tazobactam based combinations may exert similar selective pressure is unclear and is an active area of investigation.

The second pathway requires host acquisition of a genetically distinct organism harboring a resistance element. Acquisition of this organism may precede antimicrobial exposure, with subsequent antimicrobial use selecting for infection with the organism, or acquisition may occur following administration when an ecologic niche for new organisms has been carved out. In contrast to spontaneous resistance mutations, which cause infections typically limited to a single host, acquisition of foreign antimicrobial resistant pathogens leads to epidemic spread, as was seen with the KPC-harboring ST258 *K. pneumoniae.*[96–98] Given the overlapping spectrums of

activity of tazobactam based combinations and carbapenems, it would be expected that these agents would have a similar propensity to lead to antimicrobial resistance by these mechanisms.

Comparative clinical data for carbapenems and tazobactam based combinations for selection of carbapenem-resistant organisms

Unfortunately, data assessing the comparative impact of treatment of ESBL infections with tazobactam-based combinations or carbapenems on the subsequent isolation of CRE or any piperacillin-tazobactam-resistant organism are limited. Two comparative studies have investigated the isolation of resistant organisms on subsequent clinical cultures, however, the data in both cases are incomplete and no analyses have systematically examined colonization with carbapenem-resistant organisms.

In the MERINO trial, Harris and colleagues investigated the incidence of secondary infections with a meropenem- or piperacillin tazobactam–resistant organism in patients randomized to either piperacillin-tazobactam or meropenem, which they defined as growth of a meropenem- or piperacillin tazobactam–resistant gram-negative organism from any clinical specimen collected from day 4 after randomization to day 30. The rates of isolation of either a meropenem- or piperacillin tazobactam–resistant gram-negative organism was 12/187 (6.4%) in patients receiving piperacillin-tazobactam and 6/191 (3.1%) in patients receiving meropenem. The authors further stated that rates of carbapenem-resistant organism isolation were not different (3.2% vs 2.1%) between the groups. Furthermore, only four patients in the study had isolation of meropenem- or piperacillin tazobactam–resistant gram-negative organisms from future blood cultures. All four of these patients were in the piperacillin-tazobactam arm (one with a meropenem-susceptible *E. coli*, two with meropenem-resistant *K. pneumoniae* and one with a carbapenem-resistant *A. baumannii*). In addition to the small numbers, an important consideration when interpreting these data is that in the piperacillin-tazobactam cohort 14% of patients received empiric therapy and 20% of patients received "step-down" therapy with a carbapenem, which could influence the selection of future resistant isolates.[76]

In the retrospective cohort study by Sharara and colleagues comparing piperacillin-tazobactam and carbapenems for pyelonephritis caused by ESBL+ Enterobacterales a secondary outcome was isolation of a carbapenem-resistant (ertapenem, meropenem, or imipenem) organism in the 30 days following treatment initiation. 1/47 (2%) of piperacillin-tazobactam

616 treated patients had isolation of a carbapenem-resistant organism (*P. aeruginosa*) versus 11/141
617 (8%; p= 0.09) of those receiving carbapenems (3 *E. coli*, 4 *K. pneumoniae*, 3 *P. aeruginosa*, and
618 1 *A. baumannii*). These data are suggestive that selection of carbapenem resistant organisms may
619 be more common in patients treated with carbapenems, however, there are important limitations
620 to consider in interpreting these data. These include likely confounding by indication biasing
621 against the carbapenems, the lack of clarity of whether a history of carbapenem-resistant
622 organisms prior to the study were considered, and no assessment of isolation of piperacillin-
623 tazobactam resistant organisms. [85]
624 The relative impact of piperacillin-tazobactam versus carbapenems on antimicrobial
625 resistance in general, versus carbapenem resistance specifically, remains unclear. As this section
626 illustrates, there is a lack of a clear theoretical rationale why tazobactam based combinations
627 would be expected to be less likely to select for carbapenem-resistant organisms than
628 carbapenems, and the relative effect of selection of piperacillin-tazobactam or ceftolozane-
629 tazobactam resistant organisms. There are limited clinical data available comparing the two and
630 to date, the only randomized study assessing these therapies failed to demonstrate any signal that
631 decreased selection of carbapenem resistance with piperacillin-tazobactam does occur.
632
633 VI. **Conclusions and future directions**
634 Continued β-lactam use for the treatment of gram-negative infections is threatened by
635 increasing antimicrobial resistance, including ESBLs. BLIs, like tazobactam, may serve an
636 essential role in reducing carbapenem use by protecting partner β-lactam antibiotics from
637 degradation and ultimately inactivity against these ESBL+ organisms. Optimizing tazobactam's
638 inhibition potential is reliant on many factors, including the partner β-lactam antimicrobial and
639 tazobactam-specific PK/PD.
640 Ceftolozane-tazobactam appears to offer several PK/PD advantages over piperacillin-
641 tazobactam when treating ESBL+ organisms. First, ceftolozane-tazobactam demonstrates more
642 potent *in vitro* activity against ESBL+ Enterobacterales, with lower MIC_{50} and MIC_{90} values,
643 which is likely due to ceftolozane's enhanced stability to hydrolysis. Second, more tazobactam is
644 given over a longer infusion when used in combination with ceftolozane based on standard
645 doses. Third, ceftolozane-tazobactam's achievable "threshold" concentrations based on standard
646 doses fall within the realm of the agent's established breakpoints, while piperacillin-tazobactam

breakpoints may be several-fold higher than the achievable "thresholds" for ESBL+ organisms. All of these factors play a role in tazobactam's probability of PK/PD target attainment for susceptible organisms. Based on these differences, tazobactam when combined with ceftolozane may be more reliable in achieving appropriate exposures in respect to potential MICs of ESBL+ organisms. The clinical data for ceftolozane-tazobactram, while limited to industry sponsored trials in specific disease states, are supportive of this and are encouraging.

For piperacillin-tazobactam, the story is much more concerning. From a PK/PD perspective even use of "high dose" piperacillin-tazobactam raises alarms. Using data from healthy volunteers the highest attainable MIC, where tazobactam can restore the activity of piperacillin is 0.5/4 μg/mL. When applying the more favorable PK profile of this dosing regimen that was present in critically ill patients due to a decreased drug clearance, this PK/PD breakpoint increases to 2/4 μg/mL. To put these values into perspective, of the 9,916 ESBL+ phenotype *E. coli* listed in the SENTRY online database only 0.6% and 35.1% have piperacillin/tazobactam MIC's ≤ 0.5/4 and 2/4 μg/mL, respectively.[99] The situation is even more dire when looking at the 8,160 ESBL+ phenotype *K. pneumoniae* isolates in this database where 0.1 and 5.4% are inhibited at MIC values of 0.5/4 and 2/4 μg/mL respectively. When these PK/PD limitations are combined with the failure of piperacillin-tazobactam in the MERINO trial it is difficult to see a clear path forward for piperacillin/tazobactam for systemic infections due to ESBL+ producing Enterobacterales.

So the question is where do we go from here? Given the red flags with piperacillin-tazobactam and concerns of what widespread ceftolozane usage may do to *P. aeruginosa* susceptibilities it appears prudent that rather than rushing into decisions based on the current limited data, focus should be placed on appropriate BLBLI drug development. For both agents, more robust pre-clinical PK/PD analyses are urgently needed. The PK/PD target exposures discussed here were only assessed against *E. coli* isolates. It is important to understand if the tazobactam exposure requirements change based on organism and different β-lactamase(s) present. Furthermore, *in vivo* studies validating these exposures currently do not exist. For piperacillin-tazobactam, it will be interesting to understand if extended or continuous infusions of piperacillin-tazobactam can better change the trajectory for that combination. Given that prolonged/continuous infusions will optimize the PK of both the parent beta-lactam and the inhibitor it is possible that a combination of lower thresholds (due to prolonged infusions of

piperacillin) and the ability to optimize the time above these thresholds (due to prolonged infusions of tazobactam) might improve PTA at higher MIC values. Additionally, as the analyses by VanScoy and colleagues only determined threshold exposures for isolates with MICs up to 4/4 µg/mL, assessment should be performed to determine if threshold exposures of tazobactam translate to the piperacillin-tazobactam MIC in the same way at higher MICs. Work should also be performed to understand tazobactam pharmacokinetics in infected, hospitalized patients. Only if results of these pre-clinical analyses are favorable, should further studies be initiated assessing piperacillin-tazobactam in these patients. Of note, the PETERPEN trial comparing piperacillin-tazobactam and meropenem for bacteremia due to third generation cephalosporin resistant Enterobacterales is ongoing (NCT03751967) and will further inform this discussion.

For ceftolozane-tazobactam the path forward has different landmines. While PK/PD and clinical data are encouraging, further PTA analyses of tazobactam exposures in critically ill patients in the FDA registry trials will better describe the ability to achieve threshold exposures at different MIC targets with this agent, and MERINO 3 will provide outcomes data in ESBL+ bacteremia. The bigger question for ceftolozane-tazobactam, and even piperacillin-tazobactam should it be able to move forward, is whether or not the "collateral damage" with this combination is superior, inferior, or neutral when compared to the carbapenems. As ceftolozane use is preferred for DTR *P. aeruginosa*[100], careful study of the comparative resistance selection of these agents will be important to critically assess if the desire for carbapenem-sparing therapies will backfire leading to increased resistance to other last line agents. Therefore, in the absence of compelling data that these agents are effective for the treatment of infections due to ESBL + Enterobacterales, appropriate setting of susceptibility breakpoints, and supportive data that there is in fact a collateral damage benefit to tazobactam based combinations, carbapenems should remain the preferred treatment for any ESBL + infection warranting intravenous beta-lactam therapy.

References

1. Paterson DL, Bonomo RA. Extended-Spectrum β-Lactamases: a Clinical Update. *Clin Microbiol Rev*. 2005;18(4):657-686. doi:10.1128/CMR.18.4.657-686.2005

2. CDC. The biggest antibiotic-resistant threats in the U.S. Centers for Disease Control and Prevention. Published November 14, 2019. Accessed January 20, 2020. https://www.cdc.gov/drugresistance/biggest-threats.html

3. Bush K, Jacoby GA. Updated Functional Classification of β-Lactamases. *Antimicrob Agents Chemother*. 2010;54(3):969-976. doi:10.1128/AAC.01009-09

4. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev*. 2012;25(4):682-707. doi:10.1128/CMR.05035-11

5. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013. *JAMA*. 2015;314(14):1479-1487. doi:10.1001/jama.2015.12480

6. Boeckel TPV, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis*. 2014;14(8):742-750. doi:10.1016/S1473-3099(14)70780-7

7. Mendes RE, Castanheira M, Woosley LN, Stone GG, Bradford PA, Flamm RK. Molecular β-lactamase characterization of Gram-negative pathogens recovered from patients enrolled in the ceftazidime-avibactam phase 3 trials (RECAPTURE 1 and 2) for complicated urinary tract infections: Efficacies analysed against susceptible and resistant subsets. *Int J Antimicrob Agents*. 2018;52(2):287-292. doi:10.1016/j.ijantimicag.2018.04.001

8. Zhanel GG, Lawson CD, Adam H, et al. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. *Drugs*. 2013;73(2):159-177. doi:10.1007/s40265-013-0013-7

9. Isler B, Ezure Y, Romero JLG-F, Harris P, Stewart AG, Paterson DL. Is Ceftazidime/Avibactam an Option for Serious Infections Due to Extended-Spectrum-β-

Lactamase- and AmpC-Producing Enterobacterales?: a Systematic Review and Meta-analysis. *Antimicrob Agents Chemother*. 2020;65(1). doi:10.1128/AAC.01052-20

10. Haidar G, Clancy CJ, Chen L, et al. Identifying Spectra of Activity and Therapeutic Niches for Ceftazidime-Avibactam and Imipenem-Relebactam against Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother*. 2017;61(9). doi:10.1128/AAC.00642-17

11. van Duin D, Bonomo RA. Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2016;63(2):234-241. doi:10.1093/cid/ciw243

12. Sousa A, Pérez-Rodríguez MT, Soto A, et al. Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae. *J Antimicrob Chemother*. 2018;73(11):3170-3175. doi:10.1093/jac/dky295

13. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2019;68(3):355-364. doi:10.1093/cid/ciy492

14. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections. *Open Forum Infect Dis*. 2019;6(12):ofz522. doi:10.1093/ofid/ofz522

15. Rossolini GM, D'Andrea MM, Mugnaioli C. The spread of CTX-M-type extended-spectrum β-lactamases. *Clin Microbiol Infect*. 2008;14:33-41. doi:10.1111/j.1469-0691.2007.01867.x

16. Walther-Rasmussen J, Høiby N. Cefotaximases (CTX-M-ases), an expanding family of extended-spectrum beta-lactamases. *Can J Microbiol*. 2004;50(3):137-165. doi:10.1139/w03-111

17. Bonnet R. Growing Group of Extended-Spectrum β-Lactamases: the CTX-M Enzymes. *Antimicrob Agents Chemother*. 2004;48(1):1-14. doi:10.1128/AAC.48.1.1-14.2004

18. Drawz SM, Bonomo RA. Three Decades of β-Lactamase Inhibitors. *Clin Microbiol Rev*. 2010;23(1):160-201. doi:10.1128/CMR.00037-09

19. Therrien C, Levesque RC. Molecular basis of antibiotic resistance and β-lactamase inhibition by mechanism-based inactivators: perspectives and future directions. *FEMS Microbiol Rev*. 2000;24(3):251-262. doi:10.1111/j.1574-6976.2000.tb00541.x

20. Bonomo RA, Rudin SA, Shlaes DM. Tazobactam is a potent inactivator of selected inhibitor-resistant class A beta-lactamases. *FEMS Microbiol Lett*. 1997;148(1):59-62. doi:10.1111/j.1574-6968.1997.tb10267.x

21. Soon RL, Lenhard JR, Bulman ZP, et al. Combinatorial Pharmacodynamics of Ceftolozane-Tazobactam against Genotypically Defined β-Lactamase-Producing Escherichia coli: Insights into the Pharmacokinetics/Pharmacodynamics of β-Lactam-β-Lactamase Inhibitor Combinations. *Antimicrob Agents Chemother*. 2016;60(4):1967-1973. doi:10.1128/AAC.02635-15

22. Pérez-Llarena FJ, Vázquez-Ucha JC, Kerff F, et al. Increased Antimicrobial Resistance in a Novel CMY-54 AmpC-Type Enzyme with a GluLeu217-218 Insertion in the Ω-Loop. *Microb Drug Resist Larchmt N*. 2018;24(5):527-533. doi:10.1089/mdr.2017.0017

23. Naumovski L, Quinn JP, Miyashiro D, et al. Outbreak of ceftazidime resistance due to a novel extended-spectrum beta-lactamase in isolates from cancer patients. *Antimicrob Agents Chemother*. 1992;36(9):1991-1996. doi:10.1128/aac.36.9.1991

24. Payne DJ, Cramp R, Winstanley DJ, Knowles DJ. Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important beta-lactamases. *Antimicrob Agents Chemother*. 1994;38(4):767-772. doi:10.1128/aac.38.4.767

25. Shen Z, Ding B, Bi Y, et al. CTX-M-190, a Novel β-Lactamase Resistant to Tazobactam and Sulbactam, Identified in an Escherichia coli Clinical Isolate. *Antimicrob Agents Chemother*. 2017;61(1). doi:10.1128/AAC.01848-16

26. Khan A, Faheem M, Danishuddin M, Khan AU. Evaluation of Inhibitory Action of Novel Non β-Lactam Inhibitor against Klebsiella pneumoniae Carbapenemase (KPC-2). *PLoS ONE*. 2014;9(9). doi:10.1371/journal.pone.0108246

27. Faheem M, Rehman MT, Danishuddin M, Khan AU. Biochemical Characterization of CTX-M-15 from Enterobacter cloacae and Designing a Novel Non-β-Lactam-β-Lactamase Inhibitor. *PLoS ONE*. 2013;8(2). doi:10.1371/journal.pone.0056926

28. Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother*. 1993;37(4):851-858. doi:10.1128/aac.37.4.851

29. Xiao AJ, Miller BW, Huntington JA, Nicolau DP. Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia. *J Clin Pharmacol*. 2016;56(1):56-66. doi:10.1002/jcph.566

30. Sime FB, Lassig-Smith M, Starr T, et al. Population Pharmacokinetics of Unbound Ceftolozane and Tazobactam in Critically Ill Patients without Renal Dysfunction. *Antimicrob Agents Chemother*. 2019;63(10). doi:10.1128/AAC.01265-19

31. M100Ed31 | Performance Standards for Antimicrobial Susceptibility Testing, 31st Edition. Clinical & Laboratory Standards Institute. Accessed August 12, 2021. https://clsi.org/standards/products/microbiology/documents/m100/

32. EUCAST: Clinical breakpoints and dosing of antibiotics. Accessed December 30, 2019. http://www.eucast.org/clinical_breakpoints/

33. Henderson A, Paterson DL, Chatfield MD, Tambyah PA, Lye DC, De PP, Lin RTP, Chew KL, Yin M, Lee TH, Yilmaz M, Cakmak R, Alenazi TH, Arabi YM, Falcone M, Bassetti M, Righi E, Ba R, Kanj SS, Bhally H, Iredell J, Mendelson M, Boyles TH, Looke DFM, Runnegar NJ, Miyakis S, Walls G, Ai Khamis M, Zikri A, Crowe A, Ingram PR, Daneman NN, Griffin P, Athan E, Roberts L, Beatson SA, Peleg AY, Cottrell KK, Bauer MJ, Tan E, Chaw K, Nimmo GR, Harris-Brown T, Harris PNA; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. Clin Infect Dis. 2020 Oct 27:ciaa1479. doi: 10.1093/cid/ciaa1479. PMID: 33106863.

34. Livermore DM, Day M, Cleary P, et al. OXA-1 β-lactamase and non-susceptibility to penicillin/β-lactamase inhibitor combinations among ESBL-producing Escherichia coli. *J Antimicrob Chemother*. 2019;74(2):326-333. doi:10.1093/jac/dky453

35. Kumar D, Singh AK, Ali MR, Chander Y. Antimicrobial Susceptibility Profile of Extended Spectrum β-Lactamase (ESBL) Producing Escherichia coli from Various Clinical Samples. *Infect Dis*. 2014;7:1-8. doi:10.4137/IDRT.S13820

36. Jobayer M, Afroz Z, Nahar SS, Begum A, Begum SA, Shamsuzzaman S. Antimicrobial Susceptibility Pattern of Extended-spectrum Beta-lactamases Producing Organisms Isolated in a Tertiary Care Hospital, Bangladesh. *Int J Appl Basic Med Res*. 2017;7(3):189-192. doi:10.4103/ijabmr.IJABMR_28_16

37. Al Mously N, Al Arfaj O, Al Fadhil L, Mukaddam S. Antimicrobial susceptibility patterns of ESBL Escherichia coli isolated from community and hospital-acquired urinary tract infections. Journal of Health Specialties. 4. 133. 10.4103/1658-600X.179829.

38. Jean S-S, Coombs G, Ling T, et al. Epidemiology and antimicrobial susceptibility profiles of pathogens causing urinary tract infections in the Asia-Pacific region: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2010-2013. *Int J Antimicrob Agents*. 2016;47(4):328-334. doi:10.1016/j.ijantimicag.2016.01.008

39. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. *Int J Antimicrob Agents*. 2014;43(4):328-334. doi:10.1016/j.ijantimicag.2014.01.007

40. Titelman E, Karlsson IM, Ge Y, Giske CG. In vitro activity of CXA-101 plus tazobactam (CXA-201) against CTX-M-14– and CTX-M-15–producing Escherichia coli and Klebsiella pneumoniae. *Diagn Microbiol Infect Dis*. 2011;70(1):137-141. doi:10.1016/j.diagmicrobio.2011.02.004

41. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial Activity of Ceftolozane-Tazobactam Tested Against Enterobacteriaceae and Pseudomonas aeruginosa with Various Resistance Patterns Isolated in U.S. Hospitals (2013–2016) as Part of the Surveillance Program: Program to Assess Ceftolozane-Tazobactam Susceptibility. *Microb Drug Resist*. 2017;24(5):563-577. doi:10.1089/mdr.2017.0266

42. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Enterobacteriaceae and Pseudomonas aeruginosa with Various Resistance Patterns Isolated in U.S. Hospitals (2011-2012). *Antimicrob Agents Chemother*. 2013;57(12):6305-6310. doi:10.1128/AAC.01802-13

43. Saran O, Sulik-Tyszka B, Basak GW, Wróblewska MM. Activity of Ceftolozane/Tazobactam Against Gram-Negative Rods of the Family Enterobacteriaceae and Pseudomonas Spp. Isolated from Onco-Hematological Patients Hospitalized in a Clinical Hospital in Poland. *Med Sci Monit Int Med J Exp Clin Res*. 2019;25:305-311. doi:10.12659/MSM.913352

44. Pazzini C, Ahmad-Nejad P, Ghebremedhin B. Ceftolozane/Tazobactam Susceptibility Testing in Extended-Spectrum Betalactamase- and Carbapenemase-Producing Gram-Negative Bacteria of Various Clonal Lineages. *Eur J Microbiol Immunol*. 2019;9(1):1-4. doi:10.1556/1886.2019.00001

45. Sutherland CA, Nicolau DP. Susceptibility Profile of Ceftolozane/Tazobactam and Other Parenteral Antimicrobials Against Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa From US Hospitals. *Clin Ther*. 2015;37(7):1564-1571. doi:10.1016/j.clinthera.2015.05.501

46. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and Pseudomonas aeruginosa collected from patients with bloodstream infections isolated in United States hospitals (2013-2015) as part of the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) surveillance program. *Diagn Microbiol Infect Dis*. 2018;92(2):158-163. doi:10.1016/j.diagmicrobio.2018.05.011

47. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial Activity of Ceftolozane-Tazobactam Tested Against Enterobacteriaceae and Pseudomonas aeruginosa with Various Resistance Patterns Isolated in U.S. Hospitals (2013-2016) as Part of the Surveillance Program: Program to Assess Ceftolozane-Tazobactam Susceptibility. *Microb Drug Resist Larchmt N*. 2018;24(5):563-577. doi:10.1089/mdr.2017.0266

48. Sader HS, Castanheira M, Streit JM, Flamm RK. Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalized with bloodstream infections in United States medical centers (2015-2017). *Diagn Microbiol Infect Dis*. 2019;95(3):114850. doi:10.1016/j.diagmicrobio.2019.06.002

49. Sader HS, Flamm RK, Carvalhaes CG, Castanheira M. Comparison of ceftazidime-avibactam and ceftolozane-tazobactam in vitro activities when tested against gram-negative bacteria isolated from patients hospitalized with pneumonia in United States medical centers (2017-2018). *Diagn Microbiol Infect Dis*. 2020;96(3):114833. doi:10.1016/j.diagmicrobio.2019.05.005

50. Pfaller MA, Shortridge D, Sader HS, Flamm RK, Castanheira M. Ceftolozane-tazobactam activity against drug-resistant Enterobacteriaceae and Pseudomonas aeruginosa causing

healthcare-associated infections in Australia and New Zealand: Report from an Antimicrobial Surveillance Program (2013-2015). *J Glob Antimicrob Resist*. 2017;10:186-194. doi:10.1016/j.jgar.2017.05.025

51. Pfaller MA, Shortridge D, Sader HS, Gales A, Castanheira M, Flamm RK. Ceftolozane-tazobactam activity against drug-resistant Enterobacteriaceae and Pseudomonas aeruginosa causing healthcare-associated infections in Latin America: report from an antimicrobial surveillance program (2013-2015). *Braz J Infect Dis Off Publ Braz Soc Infect Dis*. 2017;21(6):627-637. doi:10.1016/j.bjid.2017.06.008

52. Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and Pseudomonas aeruginosa causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012-15). *J Antimicrob Chemother*. 2017;72(5):1386-1395. doi:10.1093/jac/dkx009

53. Castanheira M, Doyle TB, Mendes RE, Sader HS. Comparative Activities of Ceftazidime-Avibactam and Ceftolozane-Tazobactam against Enterobacteriaceae Isolates Producing Extended-Spectrum β-Lactamases from U.S. Hospitals. *Antimicrob Agents Chemother*. 2019;63(7). doi:10.1128/aac.00160-19

54. Nicasio AM, VanScoy BD, Mendes RE, et al. Pharmacokinetics-Pharmacodynamics of Tazobactam in Combination with Piperacillin in an In Vitro Infection Model. *Antimicrob Agents Chemother*. 2016;60(4):2075-2080. doi:10.1128/AAC.02747-15

55. VanScoy B, Mendes RE, Nicasio AM, et al. Pharmacokinetics-pharmacodynamics of tazobactam in combination with ceftolozane in an in vitro infection model. *Antimicrob Agents Chemother*. 2013;57(6):2809-2814. doi:10.1128/AAC.02513-12

56. Rizk ML, Bhavnani SM, Drusano G, et al. Considerations for Dose Selection and Clinical Pharmacokinetics/Pharmacodynamics for the Development of Antibacterial Agents. *Antimicrob Agents Chemother*. 2019;63(5). doi:10.1128/AAC.02309-18

57. Jarrell AS, Kruer RM, Johnson D, Lipsett PA. Antimicrobial Pharmacokinetics and Pharmacodynamics. *Surg Infect*. 2015;16(4):375-379. doi:10.1089/sur.2014.180

58. Crass RL, Pai MP. Pharmacokinetics and Pharmacodynamics of β-Lactamase Inhibitors. *Pharmacotherapy*. 2019;39(2):182-195. doi:10.1002/phar.2210

59. Monogue ML, Nicolau DP. Pharmacokinetics-pharmacodynamics of β-lactamase inhibitors: are we missing the target? *Expert Rev Anti Infect Ther*. 2019;17(8):571-582. doi:10.1080/14787210.2019.1647781

60. Ambrose PG, Lomovskaya O, Griffith DC, Dudley MN, VanScoy B. β-Lactamase inhibitors: what you really need to know. *Curr Opin Pharmacol*. 2017;36:86-93. doi:10.1016/j.coph.2017.09.001

61. Louie A, Castanheira M, Liu W, et al. Pharmacodynamics of β-lactamase inhibition by NXL104 in combination with ceftaroline: examining organisms with multiple types of β-lactamases. *Antimicrob Agents Chemother*. 2012;56(1):258-270. doi:10.1128/AAC.05005-11

62. Vanscoy B, Mendes RE, McCauley J, et al. Pharmacological basis of β-lactamase inhibitor therapeutics: tazobactam in combination with Ceftolozane. *Antimicrob Agents Chemother*. 2013;57(12):5924-5930. doi:10.1128/AAC.00656-13

63. Bhagunde P, Chang K-T, Hirsch EB, Ledesma KR, Nikolaou M, Tam VH. Novel modeling framework to guide design of optimal dosing strategies for β-lactamase inhibitors. *Antimicrob Agents Chemother*. 2012;56(5):2237-2240. doi:10.1128/AAC.06113-11

64. VanScoy BD, Rubino CM, McCauley J, et al. Determination of the tazobactam exposure required for piperacillin efficacy using a one-comparement in vitro infection model. Boston (MD): ASM Microbe; 2016.

65. Livermore DM. Determinants of the activity of β-lactamase inhibitor combinations. *J Antimicrob Chemother*. 1993;31(suppl_A):9-21. doi:10.1093/jac/31.suppl_A.9

66. Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs*. 2014;74(1):31-51. doi:10.1007/s40265-013-0168-2

67. 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

68. Craig WA, Andes DR. In Vivo Activities of Ceftolozane, a New Cephalosporin, with and without Tazobactam against Pseudomonas aeruginosa and Enterobacteriaceae, Including Strains with Extended-Spectrum β-Lactamases, in the Thighs of Neutropenic Mice. *Antimicrob Agents Chemother*. 2013;57(4):1577-1582. doi:10.1128/AAC.01590-12

69. Zosyn Package Insert. Published online May 2012. Accessed March 22, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050684s055s061_050750s016s020lbl.pdf

70. Zerbaxa Package Insert. Published online September 2020. Accessed March 22, 2021. https://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf

71. Muller A, Bhagwat S, Patel M, et al. Development of a population model of tazobactam including high doses. Boston (MA): ASM Microbe; 2016.

72. Zhang Z, Patel YT, Fiedler-Kelly J, Feng H-P, Bruno CJ, Gao W. Population Pharmacokinetic Analysis for Plasma and Epithelial Lining Fluid Ceftolozane/Tazobactam Concentrations in Patients With Ventilated Nosocomial Pneumonia. *J Clin Pharmacol*. 2021;61(2):254-268. doi:10.1002/jcph.1733

73. Nicolau DP, De Waele J, Kuti JL, et al. Pharmacokinetics and Pharmacodynamics of Ceftolozane/Tazobactam in Critically Ill Patients With Augmented Renal Clearance. *Int J Antimicrob Agents*. Published online February 7, 2021:106299. doi:10.1016/j.ijantimicag.2021.106299

74. Kalaria SN, Gopalakrishnan M, Heil EL. A Population Pharmacokinetics and Pharmacodynamic Approach To Optimize Tazobactam Activity in Critically Ill Patients. *Antimicrob Agents Chemother*. 2020;64(3). doi:10.1128/AAC.02093-19

75. Kollef MH, Nováček M, Kivistik Ü, et al. Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. 2019;19(12):1299-1311. doi:10.1016/S1473-3099(19)30403-7

76. Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. *JAMA*. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

77. Burgess DS, Hall RG, Lewis JS, Jorgensen JH, Patterson JE. Clinical and Microbiologic Analysis of a Hospital's Extended-Spectrum β-Lactamase-Producing Isolates Over a 2-Year Period. *Pharmacother J Hum Pharmacol Drug Ther*. 2003;23(10):1232-1237. doi:10.1592/phco.23.12.1232.32706

78. Burgess DS, Hall RG. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-esbl producing klebsiella pneumoniae. *Diagn Microbiol Infect Dis*. 2004;49(1):41-46. doi:10.1016/j.diagmicrobio.2003.11.007

79. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á, Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2012;54(2):167-174. doi:10.1093/cid/cir790

80. Retamar P, López-Cerero L, Muniain MA, Pascual Á, Rodríguez-Baño J, ESBL-REIPI/GEIH Group. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli. *Antimicrob Agents Chemother*. 2013;57(7):3402-3404. doi:10.1128/AAC.00135-13

81. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2015;60(9):1319-1325. doi:10.1093/cid/civ003

82. Ofer-Friedman H, Shefler C, Sharma S, et al. Carbapenems Versus Piperacillin-Tazobactam for Bloodstream Infections of Nonurinary Source Caused by Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae. *Infect Control Hosp Epidemiol*. 2015;36(8):981-985. doi:10.1017/ice.2015.101

83. Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, et al. A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2016;60(7):4159-4169. doi:10.1128/AAC.00365-16

84. Ng TM, Khong WX, Harris PNA, et al. Empiric Piperacillin-Tazobactam versus Carbapenems in the Treatment of Bacteraemia Due to Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae. *PLOS ONE*. 2016;11(4):e0153696. doi:10.1371/journal.pone.0153696

85. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tamma PD. Is Piperacillin-Tazobactam Effective for the Treatment of Pyelonephritis Caused by Extended-Spectrum β-Lactamase-Producing Organisms? *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2020;71(8):e331-e337. doi:10.1093/cid/ciz1205

86. Popejoy MW, Paterson DL, Cloutier D, et al. Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae: a pooled analysis of Phase 3 clinical trials. *J Antimicrob Chemother*. 2017;72(1):268-272. doi:10.1093/jac/dkw374

87. Zimmermann P, Curtis N. The effect of antibiotics on the composition of the intestinal microbiota - a systematic review. *J Infect*. 2019;79(6):471-489. doi:10.1016/j.jinf.2019.10.008

88. Bhalodi AA, van Engelen TSR, Virk HS, Wiersinga WJ. Impact of antimicrobial therapy on the gut microbiome. *J Antimicrob Chemother*. 2019;74(Suppl 1):i6-i15. doi:10.1093/jac/dky530

89. MacDougall C. Beyond Susceptible and Resistant, Part I: Treatment of Infections Due to Gram-Negative Organisms With Inducible β-Lactamases. *J Pediatr Pharmacol Ther JPPT*. 2011;16(1):23-30.

90. Lister PD, Wolter DJ, Hanson ND. Antibacterial-Resistant Pseudomonas aeruginosa: Clinical Impact and Complex Regulation of Chromosomally Encoded Resistance Mechanisms. *Clin Microbiol Rev*. 2009;22(4):582-610. doi:10.1128/CMR.00040-09

91. Lee Y, Choi H, Yum JH, et al. Molecular Mechanisms of Carbapenem Resistance in Enterobacter cloacae Clinical Isolates from Korea and Clinical Outcome. *Ann Clin Lab Sci*. 2012;42(3):281-286.

92. Shropshire WC, Aitken SL, Pifer R, et al. β-lactamase Amplification and Porin Loss Drive Progressive β-lactam Resistance in Recurrent ESBL Enterobacteriaceae Bacteremia. *bioRxiv*. Published online April 23, 2019:616961. doi:10.1101/616961

93. Adler M, Anjum M, Andersson DI, Sandegren L. Influence of acquired β-lactamases on the evolution of spontaneous carbapenem resistance in Escherichia coli. *J Antimicrob Chemother*. 2013;68(1):51-59. doi:10.1093/jac/dks368

94. Tängdén T, Adler M, Cars O, Sandegren L, Löwdin E. Frequent emergence of porin-deficient subpopulations with reduced carbapenem susceptibility in ESBL-producing Escherichia coli during exposure to ertapenem in an in vitro pharmacokinetic model. *J Antimicrob Chemother*. 2013;68(6):1319-1326. doi:10.1093/jac/dkt044

95. Tamma PD, Huang Y, Opene BNA, Simner PJ. Determining the Optimal Carbapenem MIC That Distinguishes Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother*. 2016;60(10):6425-6429. doi:10.1128/AAC.00838-16

96. Satlin MJ, Chavda KD, Baker TM, et al. Colonization With Levofloxacin-resistant Extended-spectrum β-Lactamase-producing Enterobacteriaceae and Risk of Bacteremia in Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2018;67(11):1720-1728. doi:10.1093/cid/ciy363

97. Pitout JDD, Nordmann P, Poirel L. Carbapenemase-Producing Klebsiella pneumoniae, a Key Pathogen Set for Global Nosocomial Dominance. *Antimicrob Agents Chemother*. 2015;59(10):5873-5884. doi:10.1128/AAC.01019-15

98. Nicolas-Chanoine M-H, Bertrand X, Madec J-Y. Escherichia coli ST131, an Intriguing Clonal Group. *Clin Microbiol Rev*. 2014;27(3):543-574. doi:10.1128/CMR.00125-13

99. JMI Laboratories. SENTRY Antimicrobial Surveillance Program. Accessed March 20, 2021. https://sentry-mvp.jmilabs.com/

100. Pranita DT Samuel L Aitken, Robert A Bonomo, Amy J Mathers, David van Duin, Cornelius J Clancy. AMR Guidance. Accessed March 22, 2021. https://www.idsociety.org/practice-guideline/amr-guidance/

Figure 1. Structure of Tazobactam

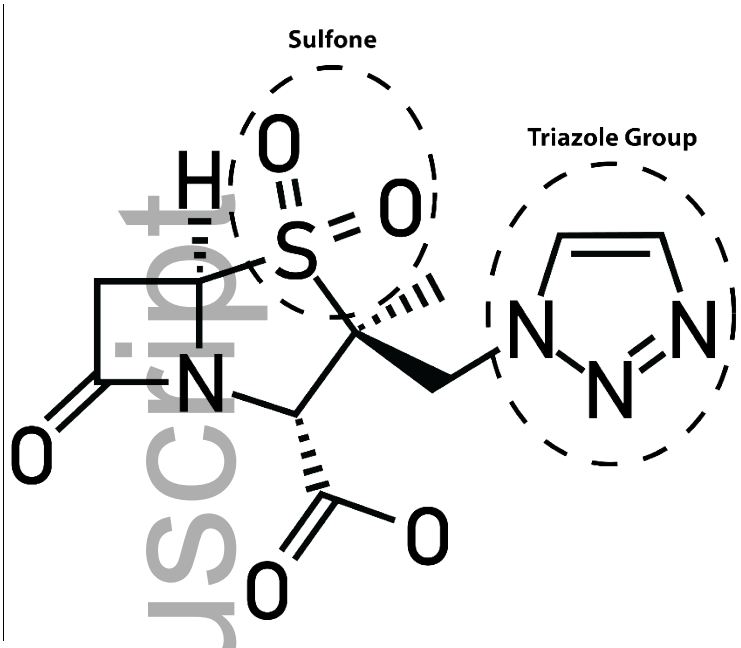
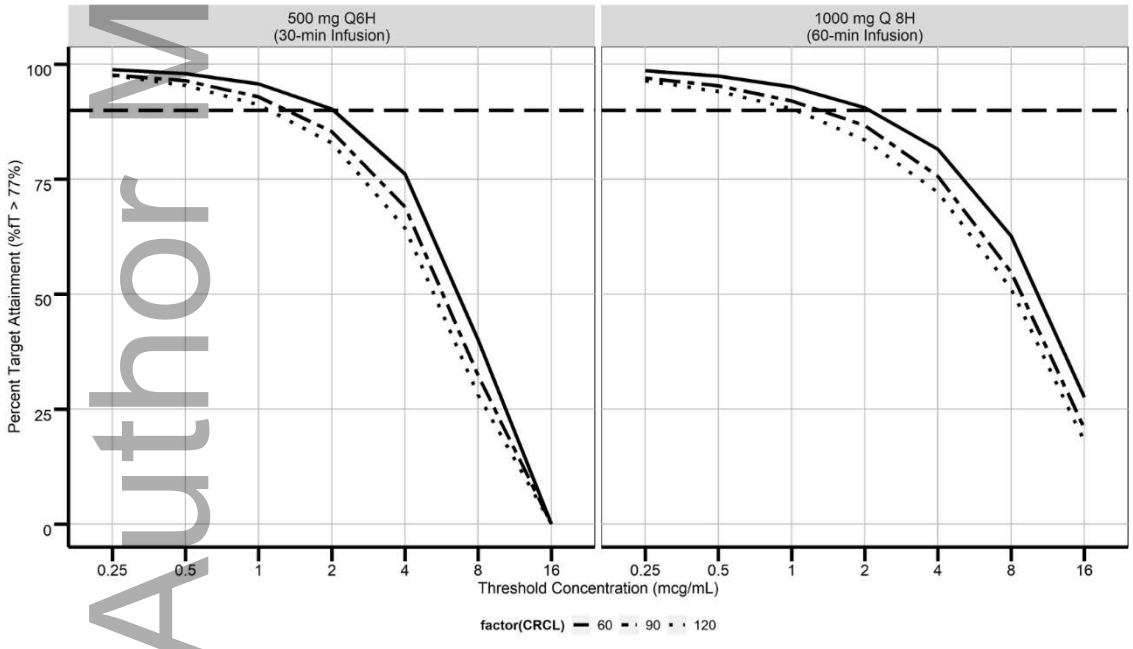


Figure 2. Percent Target Attainment of Tazobactam across Thresholds in Critically Ill Patients



Percent Target Attainment of Tazobactam across Thresholds in Critically Ill Patients

Tazobactam 500 mg every 6 hours

	MIC (μg/mL)						
	0.25	0.5	1	2	4	8	16
CrCl 60 mL/min	99	98	96	90	76	40	0
CrCl 90 mL/min	98	96	93	85	69	32	0
CrCl 120 mL/min	98	95	91	83	64	28	0
Tazobactam 1000 mg every 8 hours							
	MIC (μg/mL)						
	0.25	0.5	1	2	4	8	16
CrCl 60 mL/min	99	97	95	91	82	63	28
CrCl 90 mL/min	97	95	92	87	76	55	21
CrCl 120 mL/min	96	94	90	84	72	51	18

Table 1. Inhibition of β-lactamases by Tazobactam, IC_{50} (nM)[16,22–28]

Characteristic Active Site	Molecular Class	β-lactamase	Tazobactam	Clavulanic Acid	Sulbactam	Reference
Serine	A	TEM-1	40	90	610	[24]
			97	90	900	[23]
		TEM-2	50	180	8700	[24]
			17	22	2400	[28]
		TEM-3	10	30	30	[24]
			5	11	21	[28]
		TEM-5	280	30	1200	[24]
		TEM-6	170	120	450	[24]
		TEM-7	180	100	620	[24]
		TEM-9	340	290	900	[24]
			77	9	270	[23]
		TEM-10	80	30	340	[24]
			87	4.4	940	[23]
		TEM-26	77	8.4	350	[23]
		TEM-E1	20	50	640	[24]

		TEM-E2	50	90	1600	[24]
		TEM-E3	60	20	200	[24]
		TEM-E4	40	60	790	[24]
		SHV-1	140	30	170	[24]
			150	12	12000	[28]
		SHV-2	130	50	2800	[24]
		SHV-3	100	40	2700	[24]
		SHV-5	80	10	630	[24]
		CTX-M-1	16	80	550	[16]
		CTX-M-8	10	36	4000	[16]
		CTX-M-15	1	14	212	[27]
			6	9	--	[16]
			1500	3400	5800	[25]
		CTX-M-14	5-8	33-60	500-34500	[16]
		CTX-M-16	8	30	4500	[16]
		CTX-M-55	600	800	1400	[25]
		CTX-M-190	46200	500	77300	[25]
		KPC-2	98790	136930	106090	[26]
	C	P99	8.5	>100000	5600	[28]
		S2	6000	51000	52000	[28]
		CMY-2	1640	30800	5840	[22]
		CMY-54	370	186000	757	[22]
	D	OXA-1	1400	1800	4700	[24]
		OXA-2	10	1400	140	[24]
		OXA-4	5600	8400	16000	[24]
		OXA-5	250	3100	18000	[24]

		OXA-6	1700	1600	5100	[24]
		OXA-7	610	360	40000	[24]
Metallo (Zn^{2+})	B	CcrA	400,000	>500,000	>500,000	[28]
		Sme-1	3,000	14,000	3,300	[28]
		L1	>400,000	>400,000	>400,000	[28]

nM, nanomolar

Table 2: *In vitro* activity of piperacillin-tazobactam compared with ceftolozane-tazobactam against ESBL+ Enterobacterales[47–52]

		Piperacillin-Tazobactam		Ceftolozane-Tazobactam		
Organism	Location	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Reference
Enterobacterales, ESBL+	United States	4/4	64/4	0.5/4	4/4	[48]
	United States	8/4	64/4	0.5/4	8/4	[49]
	United States	8/4	>64/4	0.5/4	4/4	[47]
	United States	4/4	64/4	0.5/4	2/4	[53]
	Europe	8/4	>64/4	0.5/4	8/4	[52]
	Australia and New Zealand	8/4	>64/4	0.5/4	2/4	[50]
	Latin America	8/4	>64/4	0.5/4	>32/4	[51]

MIC_{50}, Minimum Inhibitory Concentration required to inhibit the growth of 50% of organisms; MIC_{90}, Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms; ESBL+, ESBL-producing

Table 3: Target PK/PD exposures of tazobactam-based combination therapies in relation to *in vitro* potency against Enterobacterales[47,62,64]

Combination	CLSI breakpoint, Enterobacterales	$MIC_{50,}$ MIC_{90} (µg/mL) against Enterobacterales[a]	$MIC_{50,}$ MIC_{90} (µg/mL) against ESBL+ *E. coli*[a]	$MIC_{50,}$ MIC_{90} (µg/mL) against ESBL+ *K. pneumoniae*[a]	PK/PD Index	Stasis	1-log_{10} kill	2-log_{10} kill
Piperacillin-Tazobactam[41,64]	≤ 16/4, S 32/4-64/4, I ≥ 128/4, R	2/4, 16/4	4/4, 64/4	16/4, >64/4	*f*T>threshold (MIC_{TZP})	63.9%	77.4%	100%
Ceftolozane-Tazobactam[47,62]	≤ 2/4, S 4/4, I ≥ 8/4, R	0.25/4, 1/4	0.5/4, 2/4	1/4, 16/4	*f*T>threshold (MIC_{CT} * 0.5)	65.9%	77.3%	90.2%

ESBL+, ESBL-producing; I, intermediate; MIC, minimum inhibitory concentration; NA, not applicable, R, resistant; S, susceptible

[a] Isolates from the United States

Table 4. Clinical outcomes of tazobactam-based combination therapies for the treatment of ESBL+ infections

Reference, year	Study type	Comparator antimicrobial	Most common BLBLI dose (percent of cohort)	Number of patients in BLBLI cohort	Infection type	Percent of patients with urinary source of infection	TZP MIC_{50}	Outcome(s), BLI vs. carbapenem
Piperacillin-tazobactam								
[77]2003[A]	Retrospective case series	--	N/A	9	Mixed	N/a	N/A	Clinical cure, 56%

[79]2012[B]	Post hoc analysis of six prospective cohort studies	Carbapenem	4.5 g q6h (>90%)	72 (35 TZP)	Blood	72.2[C]	2/4	Mortality (30 day), ETC 9.7% vs. 19.4% (p=0.1); DTC 9.3% vs. 16.7%, p=0.1
[80]2013		--		39	Blood	28.2	4-8/4	BLBLI 30-day mortality 17.9% (overall); 0% (low MIC) vs. 41.1% (intermediate/high MIC), p=0.002
[81]2015	Retrospective cohort	Carbapenem	3.375 g q6h, 30-min infusion (61%)	103	Blood	19.4	8/4	Mortality (14 day), 17% vs. 8%, HR 1.92 (95% CI 1.07–3.45)
[82]2015	Retrospective cohort	Carbapenem	N/A	10	Blood	0	8/4	Mortality (30 day), 60% vs. 34%, p=0.10
[83]2016[D]	Retrospective cohort	Carbapenem	4.5 g q8h (47%)	170	Blood	45.3	N/A	Mortality (30 day), ETC 17.6% vs. 20% (p =0.6) DTC: 9.8% vs 13.9%, (p = 0.28)
[84]2016	Retrospective cohort	Carbapenem	3.375 g q6h, 30-min infusion (61%)	94	Blood	52.1	N/A	Mortality (30 day), 30.9% vs. 29.8%; p=0.89
[76]2018	Randomized	Meropenem	4.5 g q6h, 30-	188	Blood	54.8	2/4	Mortality (30 day),

	clinical trial		min infusion (100%)					12.3% vs. 3.7%; p=0.004
[85]2020	Retrospective multicenter cohort	Carbapenem	3.375 g q6h (81%)	45	Pyelonephritis	100	2/4	Recurrent infection (30 days), 20% vs. 25%; p=0.52; Mortality (30 day), 4% vs. 7%; p=0.36
Ceftolozane-tazobactam								
[86]2017	Post hoc analysis of randomized controlled trials	Meropenem (intra-abdominal), levofloxacin (UTI)	1.5 g q8h (100%)	78	UTI/intra-abdominal	67	0.5/4	Clinical cure, UTI, 98% vs. 83%; p=0.01; intra-abdominal, 96% vs. 89%; p>0.05
[75]2019	Post hoc analysis of randomized controlled trial	Meropenem	3 g q8h (100%)	84	Ventilated pneumonia	0	0.5/4[E]	Mortality (28 day), 21% vs. 29%; 95% CI, −6.1% to 20.8%

--, not applicable; BLBLI, β-lactam-β-lactamase inhibitor; DTC, definitive therapy cohort; ETC, empirical therapy cohort; N/A, not available; q*h; every * hours; TZP, piperacillin-tazobactam; UTI, urinary tract infection

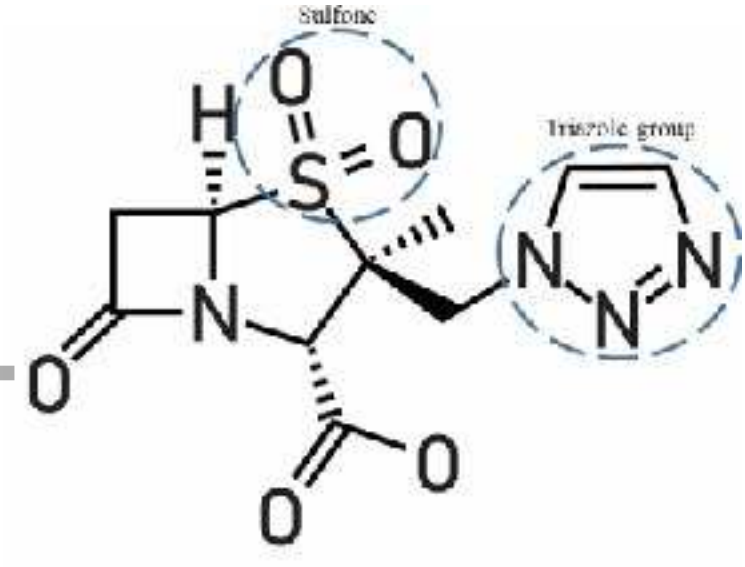
[A]Alone or in combination with a fluoroquinolone or an aminoglycoside

[B]Amoxicillin-clavulanate include in BLBLI analysis

[C]Includes biliary source

[D]Amoxicillin- clavulanate and ampicillin-sulbactam included in BLBLI analysis

[E]Not specific to ESBL+ isolates



phar_2623_f1.tif