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Point-Counterpoint: Piperacillin-tazobactam should be used to treat infections with ESBL-positive organisms

Audrey Schuetz, MD[a], Sergio Reyes Salcedo[b], MD, and Pranita D. Tamma[c], MD, MHS.

[a] Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine and Science, Rochester, MN

[b] Bacterial Resistance and Hospital Epidemiology, International Center for Medical Research and Training – CIDEIM, Cali, Colombia

[c] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION

Beta-lactam/beta-lactamase inhibitor combinations (BLBLIs) are among the most controversial classes of antibiotic agents available for the treatment of infections caused by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria (ESBL-GNR). Piperacillin-tazobactam (PTZ) is one of the most frequently utilized antibiotic agents for empiric gram-negative bacterial coverage and remains active against a large proportion of ESBL-GNR. Furthermore, good antimicrobial stewardship practices encourage the use of carbapenem-sparing treatment regimens for infections due to ESBL-GNR. As rapid diagnostics are increasingly used in the clinical microbiology laboratory and have the capability of detecting CTX-M type or other ESBL resistance mechanisms, this issue continues to be pertinent. Some data imply reduced efficacy of PTZ against ESBLs. Several factors may affect a clinician's choice to use BLBLI including the isolate's minimum inhibitory concentration (MIC), the site and severity of infection, and the type of resistance mechanism. These factors will be explored in this review of the pros and cons of BLBLI treatment of invasive infections due to ESBL-producing bacteria, as well as how laboratories should report results for BLBLIs for these organisms as it relates to antimicrobial stewardship. In this point-counterpoint Dr. Audrey Schuetz provides the pro point of view and Drs. Sergio Reyes Salcedo and Pranita Tamma provide the con, counter-point, view.

POINT

In this era of increasing focus on antimicrobial stewardship, clinicians and laboratorians are asking whether it is worth revisiting use of BLBLIs for treatment of infections due to ESBL-GNR. Over time, carbapenems have become the first-line treatment option for infections due to ESBL-GNR (1). Increasing use of carbapenems has led to an increase in carbapenem-resistant Gram-negative bacteria. Literature supporting clinical efficacy of carbapenems has largely driven this preference. Clinicians and laboratorians alike are currently reassessing the possibility of treatment of ESBLs with piperacillin-tazobactam. It is well recognized that the *in vitro* susceptibility to clavulanate used in the past as a confirmatory test for ESBL production may not, in fact, translate to *in vivo* susceptibility and clinical efficacy. However, healthcare is entering an era of limited antibacterial treatment options and rising antimicrobial resistance. There are fewer and fewer antimicrobial treatment options available, and interest has been renewed in potential use of antimicrobials which were largely dismissed in the past.

Publications assessing the efficacy of BLBLIs for treatment of urinary tract infections due to ESBL-GNR support the efficacy of BLBLIs for this application. One of the earliest retrospective observational studies of PTZ treatment for infections due to ESBL-GNR showed clinical success of PTZ therapy in 6/6 patients with urinary tract infections, regardless of the isolate's minimum inhibitory concentration (MIC) to PTZ (2). Organisms in this study included ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Support for BLBLI therapy of ESBL-GNR from urinary sources was also demonstrated in a retrospective study of ESBL-producing *E. coli* and *K. pneumoniae* infections (3). In this study, 522 infections due to ESBL-GNR were included, the majority (55%) of which were urinary tract infections. Clinical success of non-carbapenem therapy (80% of which was BLBLI therapy, primarily cefoperazone-sulbactam) was similar to that of carbapenem therapy, at 79.6% versus 85.7% (p=0.15). A recent randomized controlled trial comparing PTZ, cefepime and ertapenem for the treatment of urinary tract infections due to ESBL-producing *E. coli* also supports PTZ as effective treatment for such infections when the isolate tests susceptible (4). A total of 66 patients received either

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PTZ or ertapenem in that study. PTZ MICs were susceptible, ranging between 4 and 16 µg/mL (MIC ≤16 µg/mL is the susceptible breakpoint for Enterobacteriaceae according to the Clinical and Laboratory Standards Institute) (5). Clinical success rates were similar between PTZ and ertapenem (31/33 [93.9%] with PTZ and 32/33 [97.0%] with ertapenem; p=0.50). Microbiologic success, defined as failure to recover *E. coli* on urine culture performed on day 10-14 post-treatment, was achieved in 97.0% (32/33) of both treatment groups, and 28-day mortality was also the same between the treatment groups at 6.1% (2/33).

Thus, the evidence seems fairly strong supporting use of BLBLIs for treatment of ESBL-GNR causing urinary tract infections, provided the organism's MIC tests within the susceptible range. There is also evidence that some non-urinary source infections may respond to BLBLI therapy when the isolate's MIC is within the susceptible range. In the study by Gavin et al. mentioned above which had demonstrated successful PTZ therapy for ESBL-GNR urinary tract isolates, successful treatment outcome with PTZ was also seen in 10/11 (91%) patients with non-urinary source infections (including blood, sputum, skin and soft tissue, and other sources) when the organisms demonstrated MICs ≤16 µg/mL (2). When the PTZ MIC exceeded 16 µg/mL for isolates of non-urinary source infections, clinical success was 1/5 (20%).

Observational studies comparing carbapenem therapy to BLBLI therapy for bloodstream infections (BSIs) due to ESBL-GNR show more disparate results (6, 7). In a retrospective observational study of 11 ESBL-producing *Proteus mirabilis* bloodstream infections, only 1/4 (25%) BSIs treated with BLBLIs (including PTZ, amoxicillin-clavulanate or ampicillin-sulbactam) responded to therapy (6). On the other hand, 5/5 BSIs due to non-ESBL-producing isolates responded to BLBLI therapy (p=0.02). All BSIs treated with a carbapenem responded to therapy, regardless of ESBL production. An international prospective observational study of *K. pneumoniae* BSIs in 1996-1997 demonstrated that the efficacy of carbapenems was superior to non-carbapenem β-lactam therapy including BLBLIs (7). Of the 49 *K. pneumoniae* BSI episodes treated with monotherapy which was considered active in vitro, 2/49 (4%) received PTZ therapy, while two other patients received ticarcillin-clavulanate therapy. Mortality at 14 days was 3.7% (1/27) with carbapenem therapy but was 50% (2/4) with BLBLI therapy (both patients

84 treated with PTZ died). Although the numbers of patients treated with BLBLIs in these studies
85 were relatively small, BLBLI therapy compared less favorably to carbapenem therapy in the
86 treatment of BSIs due to ESBL-GNR.

87 Other studies assessing use of BLBLI therapy for BSI due to ESBL-GNR have shown
88 conflicting results (8-10). Authors of a retrospective observational study of BSIs due to ESBL-
89 GNR compared mortality of patients treated with BLBLIs versus those treated with
90 carbapenems (8). Of the 33 patients treated with BLBLIs (either PTZ or amoxicillin-clavulanate)
91 to which the isolates displayed in vitro susceptibility, 4 (12%) died as compared to 1/28 (3.6%)
92 who were treated with carbapenems. Despite the trend in mortality difference, use of a BLBLI
93 for therapy was not associated with a significant increase in mortality (OR 0.55; 95% CI, 0.19-
94 1.55). In another retrospective study of ESBL-GNR BSI, empirical treatment with BLBLIs
95 (primarily PTZ in this study) was associated with a higher but not statistically significant higher
96 mortality of 38% (6/16 died) as compared to no deaths after empiric carbapenem therapy
97 (0/10) (9). In fact, 5/6 PTZ-treated patients who died had isolates with PTZ MICs in the
98 susceptible range of ≤16 μg/mL.

99 One of the largest and most recent trials comparing PTZ therapy to carbapenem therapy
100 demonstrated poorer outcomes of PTZ therapy in patients with ESBL-GNR bacteremia (10). In
101 this single-center retrospective study of 213 patients, 103 (48%) received PTZ and 110 (52%)
102 received carbapenems. Seventeen (17%) deaths occurred in the PTZ group, and 9 (8%) in the
103 carbapenem group. The adjusted risk of death for patients who received PTZ therapy was 1.92
104 times higher at 14 days compared to patients who received carbapenem therapy (95% CI, 1.07-
105 3.45). In this study, approximately 44% of BSIs were central-lined associated in both treatment
106 groups, and there was also a high proportion patients with pneumonia as the source of
107 bacteremia. These differences in sources may be significant when comparing to other BSI
108 studies in which ESBL-GNR strains are arising predominantly from urinary or biliary sources.
109 Such is the case with a large post hoc analysis of six prospective studies of BSI caused by ESBL-
110 producing *E. coli* comparing BLBLI therapy with carbapenem therapy (11). In the definitive
111 therapy cohort (in which antibiotics were given after susceptibility reports were released), 54

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patients received BLBLI (18 PTZ and 36 amoxicillin-clavulanate) and 120 received a carbapenem. Morality rates at 30 days were similar (9.3% BLBLI and 16.7% carbapenem; p >0.2) for the definitive cohort. However, in the empirical treatment group (in which antimicrobial therapy was administered prior to release of susceptibility results) after adjustment for the propensity score in a Cox regression model, BLBLI therapy showed a hazard ratio for increased mortality of 1.14 (CI, 0.29-4.40; p=0.84). Notably, in this study, high dose PTZ (4.5 gm IV every 6 hours) was given instead of the standard dosing of 3.375 gm IV every 6 hr. This higher dosage may favor less mortality difference between the groups. Mortality in this study was also associated with non-urinary and non-biliary sources of bacteremia.

Tied to the debate on treatment of ESBL infections with BLBLIs is the laboratory's role in labeling isolates as ESBLs and the manner in which BLBLIs are reported for ESBLs. First, should the laboratory perform ESBL confirmatory testing? CLSI has stated that it is unnecessary to perform routine ESBL testing if a laboratory is using the current (e.g., lower) breakpoints for cephalosporins and aztreonam. Breakpoints for these antimicrobials were revised in January 2010, and most commercial AST systems have adopted these revised breakpoints. Prior to this change, laboratories confirmed the presence of an ESBL phenotypically, because results of certain cephalosporins, aztreonam, and penicillins had to be edited to resistant if the isolate proved to be an ESBL-GNR. Breakpoint-setting organizations have stated that confirmatory testing for ESBLs may still be useful for epidemiologic or infection control purposes such as placement of the patient on contact precautions (5). However, with the increasing focus on carbapenem-sparing therapy, and the rising concern of BLBLI treatment for some infections caused by ESBLs, it seems advisable to once again perform ESBL confirmatory testing on isolates A single surrogate marker for ESBL production, such as ceftriaxone resistance, is not sufficient to detect all ESBLs. The ESBLs are a heterogenous group; fewer than 1000 ESBLs are estimated to have been identified, many of which have different hydrolyzing abilities for different β-lactams (KB, personal communication) (12). In fact, the heterogeneity of ESBLs is reflected in the manner in which phenotypic confirmatory ESBL testing is performed, with the use of more than one antimicrobial agent to improve sensitivity of detection. Additionally, reliance on surrogate antimicrobial agents is imprecise due to the inherent MIC variability in test systems.

Variability in MICs over four or more doubling dilutions even in reference broth dilution testing has been noted for ESBLs in particular (13). Given the heterogenous nature of ESBLs and the variability in MICs with different antibiotics, as well as the clinical evidence supporting PTZ treatment for some infections due to ESBL-GNR, it would seem prudent to perform ESBL confirmatory testing on suspected isolates.

The second issue in ESBL reporting is the manner in which laboratories report BLBLIs for ESBL-GNR. This issue was debated in the past when ESBLs were first recognized, and cases of PTZ treatment failure for ESBL-GNR were reported. At the time, laboratories took a variety of approaches to reporting PTZ, including automatically reporting it as resistant; reporting the MIC and interpretive category with a linked comment stating the possibility of inadequacy of PTZ treatment; reporting solely the MIC without an interpretation; and, finally, not including PTZ in the report at all. Given the new knowledge we have gained concerning adequacy of PTZ treatment of some types of infections due to ESBL-GNR, laboratories should reassess the manner in which they are reporting PTZ and other BLBLIs for ESBL-GNR. Some laboratories may consider appending a comment to the PTZ report of ESBL isolates warning of the inadequacy of treatment for certain types of infections such as bloodstream infections. Others may wish to only report PTZ on non-sterile sources. Such laboratory decisions should involve infectious diseases practitioners, pharmacists, and the infection control team.

In summary, clinical efficacy data of BLBLIs for therapy of ESBL-GNR are generally drawn from retrospective and observational studies. These studies show that choice of therapy depends on the site and severity of infection. A recent randomized clinical trial supports the use of PTZ for treatment of urinary tract infections due to ESBL-producing *E. coli* (4). However, randomized controlled trials specifically comparing carbapenems to BLBLIs for treatment of serious infections due to ESBL-GNR are lacking. The data currently available are limited by relatively small numbers of patients. Although a few studies of bloodstream ESBL infections demonstrate no significant difference in mortality or clinical outcome, the majority of studies favor carbapenem therapy over BLBLIs for BSI. The single large prospective cohort study by Rodruiguez-Bano et al. that failed to demonstrate significant differences in mortality between

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BLBLI and carbapenem therapy for BSI was based on higher dosing of PTZ (11). Based on these clinical data, it is appropriate to consider treatment of urinary tract infections due to ESBL-producing Enterobacteriaceae with PTZ if the isolate tests susceptible. There is even some evidence, though not strong, supporting the use of BLBLI for therapy of BSIs associated with sources that are urinary or biliary in origin. Finally, laboratories should review both the need for confirmatory testing of ESBLs and the manner in which PTZ (or other BLBLIs) are reported on such isolates. Clinical and laboratory evidence support performance of confirmatory ESBL testing on suspicious organisms in order to guide appropriate clinical therapy. With the increasing pressure to focus on antimicrobial stewardship, it is appropriate that laboratories and clinicians alike explore alternative options to carbapenems for treatment of infections due to ESBL-GNR.

Audrey Schuetz

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COUNTERPOINT

With the ongoing global rise in ESBL infections and the need to preserve the efficacy of carbapenems (1), the mounting body of clinical evidence indicating PTZ is an effective option for patients with invasive ESBL-GNR infections appears to be welcome news (2-5). Previously, the inoculum effect - albeit largely confined to experimental data (6-9), co-production of additional β-lactamases not effectively inhibited by β-lactamase inhibitors (10), and concerns regarding inadequate pharmacokinetic-pharmacodynamic drug target attainment with standard βLβLI dosing regimens (11-12) led to restrained enthusiasm when considering PTZ for the treatment of invasive ESBL-GNR infections. However, there are some stark contrasts between available observational data indicating equal efficacy between PTZ and carbapenems for the treatment of ESBL-GNR bloodstream infections (2-5) and those that suggest PTZ results in poorer outcomes (13, 14). These differences should give us pause when considering PTZ for the treatment of invasive ESBL-GNR.

First, the majority of patients in studies supporting the use of PTZ had “low inoculum” sources of bloodstream infections (e.g., biliary or urinary sources where the bacterial inoculum was anticipated to be ≤ 10^5 CFU/mL), (6-9) ranging from approximately 60 to 90% (2-5). This is

in contrast to studies showing inferior outcomes with PTZ use where the minority (roughly 15-30%) of bloodstream infections were from low inoculum sources (13, 14). It seems intuitive that for infections where relieving an obstruction is arguably the most important component of infection management (i.e., biliary sources) or sites where antibiotic concentrations are expected to be particularly high (i.e., urine) that antibiotic therapy may not need to be as "aggressive." These are likely more amenable to pathogen eradication than pneumonia, intra-abdominal collections, deep wound infections, or endovascular infections. Second, ≤15% of patients in ESBL-GNR bloodstream studies supporting PTZ use were critically-ill (2-5), whereas, one-third to over a half of patients in studies suggesting suboptimal outcomes with PTZ required ICU care (13, 14). Furthermore, studies favoring PTZ generally included isolates with relatively low PTZ MICs (~2 mcg/ml) (2-5). In contrast, the median minimum inhibitory concentrations (MICs) in studies indicating inferior outcomes with PTZ approached susceptibility breakpoints (13, 14).

The species of ESBL- GNR may also be an important determinant of the efficacy of βLβLI treatment. *E. coli* was the predominant pathogen (70-100%) in studies demonstrating similar clinical outcomes between PTZ and carbapenems for ESBL-GNR (2-5). This is in contrast to studies with the opposite conclusions in which other *Enterobacteriaceae* were recovered with equal or greater frequency (13-14). Tazobactam has been shown to have increased activity against *E. coli* compared to *K. pneumoniae*. The addition of tazobactam to ceftolozane yielded an $MIC_{50/90}$ of 0.5/4 mcg/ml and 4 />32 for large numbers of *E. coli* and *K. pneumonia*e isolates, respectively (15). In a large, multicenter study, ESBL-producing *K. pneumoniae* was independently associated with higher mortality than ESBL-producing *E. coli* (3). Similarly, in an observational study that identified poorer outcomes in the βLβLI group, almost 70% of patients were infected with ESBL-producing *K. pneumoniae* isolates (14). Disparities in outcomes across studies may be related to inherent differences in the molecular epidemiology associated with these organisms (i.e., *bla*CTX-M-types are more often associated with *E. coli* whereas *bla*SHV-types are more commonly associated with other *Enterobacteriaceae*). Additionally, it is unknown if there are microbial characteristics, β-lactamase characteristics (e.g., inhibitor-

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resistant SHV β-lactamases, etc.), or the presence of other virulence factors on mobile genetic elements that might contribute to differences in the conduct of ESBL-producing *E. coli* compared to other ESBL-producing *Enterobacteriaceae*. Or, perhaps, *E.coli* may simply be a proxy for urinary sources of bloodstream infections whereas other *Enterobacteriaceae* may be more representative of complex sites of infection such as intra-abdominal collections.

Synthesizing available clinical data, although PTZ may be an effective agent for the treatment of invasive ESBL infections in patients who are not critically ill, with lower inoculum infections, and lower piperacillin MICs, one cannot infer that PTZ is effective beyond these parameters based on available observational data. Hopefully, lingering questions will be answered by the MERINO study, the first randomized controlled trial to address the question of meropenem vs. PTZ for ESBL bloodstream infections (16).

The question then arises as to whether ESBL confirmatory testing is value-added in guiding treating decisions. A number of healthcare facilities have abandoned confirmatory ESBL testing, in accordance with Clinical and Laboratory Standards Institute (CLSI) guidance (17). This has left many clinicians puzzled as to when ESBLs may be produced. Ceftriaxone nonsusceptibility is often used as a proxy for ESBL presence and when ceftriaxone MICs greater than 1 mcg/ml are observed, carbapenem therapy is frequently pursued. While it is true that ESBL-producers are likely to have ceftriaxone MICs in the nonsusceptible range, not all *Enterobacteriaceae* with ceftriaxone MICs in the nonsusceptible range are ESBL producers (18). ESBL confirmatory testing can be helpful by taking the guesswork out of deciding if an isolate is ESBL-producing, potentially leading to the avoidance of unnecessary carbapenem therapy. Additionally, the current PTZ CLSI breakpoint is ≤16 mcg/and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint is ≤8 mcg/ml. ESBL isolates with PTZ MICs nearing the breakpoints may not respond as favorably to PTZ as isolates with lower PTZ MICs (19-20). Knowing when *Enterobacteriaceae* with PTZ MICs in these higher ranges are ESBL-producing is helpful to guide clinicians towards alternate regimens. Taken together, we

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believe that performing ESBL confirmatory testing can favorably impact antibiotic prescribing decisions.

Sergio Reyes Salcedo and Pranita D. Tamma

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SUMMARY

Points of Agreement

1. The decision to use PTZ to treat an infection with an ESBL-GNR is complex and requires consideration of the source of the infection, the severity of the infection, the organism, the MIC of the organism, and the dosage of antibiotic used.
2. PTZ may be effective for treating invasive ESBL-GNR infections in patients who are not critically ill, with lower inoculum of infection and a lower MIC (≤ 2 ug/ml).
3. The strongest data supporting the use of a BLBLI for treating infections caused by ESBL-GNR is with urinary tract infections and possibly biliary tract infections.
4. BLBLIs appear to be less effective than carbapenem therapy for blood stream infections due to ESBL-GNR.
5. If PTZ is used for these infections, the laboratory should report MIC data and perform ESBL confirmatory testing, as to provide clinicians with optimal information for clinical decisions.
6. Laboratories that perform ESBL confirmatory testing should consider including a comment that PTZ therapy may be inadequate for treating blood stream infections or other serious infections.

Issues to be resolved

1. The efficacy of BLBLIs for blood stream infections due to ESBL-producing organisms needs to be assessed in a large multi-center trial. The ongoing MERINO study, a randomized controlled trial of PTZ versus meropenem for the treatment of bloodstream infections due to these organisms, should provide much needed data on appropriate treatment options.
2. Similar studies are needed for other types of infections, such as intra-abdominal infections.
3. Outcomes studies assessing of the clinical utility of rapid molecular methods for detecting ESBL-producing organism are needed to assist clinical laboratories in determining the ideal approach to confirming ESBL producing organisms.

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