EDITORIAL

Carbapenem-Sparing Therapy for Extended-Spectrum β-Lactamase–Producing *E coli* and *Klebsiella pneumoniae* Bloodstream Infection
The Search Continues

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Bloodstream infections due to *Escherichia coli* and *Klebsiella pneumoniae* are associated with significant morbidity, mortality, and financial costs.[1] Resistance to third-generation cephalosporins is increasing in these species both in the community and in health care settings.[2] The most common mechanism of third-generation cephalosporin resistance is production of an extended-spectrum β-lactamase (ESBL).[3] These enzymes render *E coli* and *K pneumoniae* nonsusceptible to nearly all cephalosporins and penicillins. Carbapenems, such as meropenem, remain active and are considered preferred agents for treatment of bloodstream infections due to ESBL-producing organisms. However, treatment with carbapenems creates selective pressure for development of carbapenem resistance, which is arguably the greatest contemporary antibiotic resistance threat. Thus, there is intense interest both in the development of new antibiotics and in the reassessment of older antibiotics for use as carbapenem alternatives.

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By definition, ESBLs are inhibited by β-lactamase inhibitors such as clavulanate and tazobactam. Because of this characteristic, β-lactam/β-lactamase inhibitors (BLBLIs) have been evaluated in several observational studies as carbapenem-sparing therapy for ESBL-producing bacterial infection. Results of these studies have been conflicting. In a large multinational cohort study, 30-day mortality was similar in patients with ESBL-producing bacteremia who were treated with either a BLBLI or a carbapenem for empirical therapy (ie, treatment before antibiotic susceptibility results are known, n = 365 patients) or definitive therapy (ie, treatment targeted to known antibiotic susceptibility, n = 601 patients), with mortality rates of 17.6% vs 20% (empirical therapy) and 9.8% vs 13.9% (definitive therapy), for BLBI and carbapenem treatment, respectively.[4] A systematic review and meta-analysis of 14 studies comparing BLBLIs or carbapenems for treatment of ESBL-producing bacterial bloodstream infections did not identify a significant difference in mortality between treatment groups. Mortality rates were 20.5% (109/531) vs 22.1% (121/547) in the empirical treatment group and 16.2% (32/199) vs 15.2% (115/767) in the definitive treatment group for BLBLI and carbapenem therapy, respectively, although heterogeneity among studies of definitive therapy was high.[5] In contrast, a large single-center, retrospective cohort study of 331 patients with ESBL-producing bacteremia found that the risk of 14-day mortality was greater in patients treated empirically with piperacillin-tazobactam (17% mortality) compared with those treated with a carbapenem (8% mortality).[6] Additional concerns from in vitro and animal models include the reduced activity of piperacillin-tazobactam in the presence of higher bacterial inoculums,[7,8] as can be seen in infections such as pneumonia. The discrepancies between outcomes of these and other studies have led to debate about the appropriate clinical uses of BLBLIs.[9]

The MERINO trial, results of which are reported in this issue of *JAMA*, was designed to help resolve this controversy.[10] In this study, Harris and colleagues[10] conducted an international noninferiority open-label randomized clinical trial to compare the effects of piperacillin-tazobactam (4.5 g every 6 hours) vs meropenem (1 g every 8 hours) given intravenously as definitive therapy on 30-day mortality for adult patients with ceftriaxone-resistant *E coli* or *K pneumoniae* bacteremia. Patients were randomized within 72 hours of blood culture collection and received study drug for a minimum of 4 days and a maximum of 14 days after randomization, with length of therapy determined by the treating physician. A conservative 5% noninferiority margin was used. As reported in the article by Harris et al,[10] a decision to terminate the study was made "by the study management team, after discussion with site investigators" on the grounds of harm and futility when the third prespecified interim review determined that it was highly unlikely that noninferiority could be demonstrated.

Results of the study are striking. A total of 391 patients were randomized and 378 were evaluable. Overall, the groups were balanced for baseline characteristics. Most episodes of bacteremia (86.2%) were due to *E coli*, 43.8% were community associated, and 54.8% had a urinary tract source. In the primary analysis population, all-cause 30-day mortality was 12.3% (23/187) in the piperacillin-tazobactam group and 3.7% (7/191) in the meropenem group, for an absolute risk difference of 8.6% (1-sided 97.5% CI, −∞ to 14.5%; P = .90 for noninferiority) and a number needed to harm of 12. Results were consistent in the per-protocol population, and adjustment for source of infection and Charlson Comorbidity Index score did not alter results significantly. No subgroup met the noninferiority margin (although the study was not powered for these analyses)

and the direction of risk favored meropenem in all subgroups and in every secondary analysis. Moreover, there was no evidence that piperacillin-tazobactam selected for less carbapenem resistance in subsequent infections, although the follow-up period was short and the number of secondary carbapenem-resistant infections reported was small.

The inability of the authors to demonstrate noninferiority of piperacillin-tazobactam to meropenem is particularly notable because several features of the pragmatic trial design and patient population favored a noninferiority effect. Empirical and step-down antibiotic therapy was not specified, and crossover of patients from one group to the other was allowed. For example, 13.8% of patients (26/188) in the piperacillin-tazobactam group received a carbapenem for empirical therapy, and 20.2% (38/188) received a carbapenem for step-down therapy. Acuity of illness was lower than expected: only 10 patients met criteria for a predefined high-risk category, 40.7% of patients had resolved signs of infection by the day of randomization, and the overall mortality rate was just 7.9%. In total, these results provide strong evidence against the noninferiority of piperacillin-tazobactam for definitive treatment of bacteremia due to ceftriaxone-resistant *E coli* and *K pneumoniae*.

An advantage of the pragmatic design of this trial is generalizability to a broad spectrum of acute care settings, although there may be some limitations. Only 2 patients were enrolled in North America, both in Canada. While the authors were careful to document that the dominant strains causing infection in this trial are common in North America, aspects of infection or clinical care in the United States may be different in ways that might limit the generalizability of the study to US patients.[6]

The authors' analysis of *E coli* and *K pneumoniae* isolates at a central laboratory yielded information that is useful for interpretation of study results. Only 3.9% of isolates were resistant to piperacillin-tazobactam. Mortality was unrelated to piperacillin-tazobactam resistance or to the minimum inhibitory concentration of piperacillin-tazobactam required to suppress bacterial growth, although the number of isolates in each minimum inhibitory concentration category was small. This is noteworthy, as earlier reports have suggested that poor response to piperacillin-tazobactam is seen primarily in ESBL-producing isolates with higher piperacillin-tazobactam minimum inhibitory concentrations.[11] While ESBL genes were confirmed in 85% of isolates, 10.2% carried an *ampC* gene and 2% carried genes for both enzymes. AmpC β-lactamases confer resistance to ceftriaxone but, unlike ESBLs, they are only minimally inhibited by tazobactam.[12] Genes for narrow-spectrum oxacillinases were detected in more than two-thirds of isolates tested. These enzymes have been found to reduce β-lactamase inhibition by tazobactam in vitro, although the effect on piperacillin-tazobactam in clinical settings is unknown.[13] Complex resistance backgrounds, such as those reported by Harris et al in the MERINO trial, are common in clinical isolates of *E coli* and *K pneumoniae*, and may limit the ability of routine susceptibility testing methods to predict clinical response to BLBLIs.

The MERINO trial has important implications for clinicians, clinical microbiologists, and antibiotic stewards. The study results provide clear evidence that piperacillin-tazobactam should not be used for definitive treatment of bloodstream infections due to ceftriaxone-resistant *E coli* or *K pneumoniae*, regardless of the patient population, source of infection, bacterial species, or response to initial empirical piperacillin-tazobactam therapy. In addition, the study suggests that reporting of piperacillin-tazobactam susceptibility for ceftriaxone-resistant *E coli* and *K pneumoniae* should include a caveat against its use in bacteremias. The study also left several questions unanswered, including whether piperacillin-tazobactam would be more effective if administered as extended infusion, and whether BLBLIs are noninferior to carbapenems for empirical treatment of bacteremia or for treatment of nonbacteremic ESBL-producing bacterial infection.

The goal of Harris and colleagues[10] was to demonstrate that piperacillin-tazobactam was a noninferior alternative for definitive treatment of bacteremia due to ceftriaxone-resistant *E coli* and *K pneumoniae*, thereby promoting less carbapenem use and reducing selective pressure for carbapenem resistance. The unexpected results of their study may instead have the opposite effect. How, then, can the use of carbapenems be decreased? First, as noted by the authors, the study results should not be extrapolated to newer BLBLIs, which require specific investigation of efficacy in randomized clinical trials. Second, studies of short-duration antibiotic treatment and noncarbapenem options for empirical and step-down therapy are needed to identify safe and effective regimens that limit carbapenem exposure.[14] New tools may soon be available, such as electronic decision support for antibiotic selection that calculates the estimated likelihood of antibiotic-resistant bacterial infection for each patient at the time of hospital admission.[15] Third, prevention of infection should be emphasized so as to reduce the need for antibiotic treatment altogether. The results of the MERINO trial make clear that piperacillin-tazobactam should no longer be considered an alternative to meropenem for definitive treatment of bloodstream infection due to ceftriaxone-resistant *E coli* or *K pneumoniae*.

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