Bloodstream Infection Caused by Extended-Spectrum \( \beta \)-Lactamase–Producing Gram-Negative Bacteria: How to Define the Best Treatment Regimen?

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Extended-\( \beta \)-lactamases (ESBLs), found chiefly among *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus* species, are a diverse group of bacterial enzymes that share the ability to hydrolyze third-generation cephalosporins and aztreonam, yet are inhibited by the commercially available \( \beta \)-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) \([1]\). Since the discovery of the first ESBL-producing *K. pneumoniae* in Germany nearly 30 years ago, gram-negative bacteria expressing ESBLs have posed a very serious therapeutic challenge \([2]\). We have learned, from the cost of human life, the tremendous clinical significance carried by the presence of ESBLs.

The molecular epidemiology of ESBL-producing gram-negative bacteria has evolved dramatically in the past decades. After an early dominance of ESBLs belonging to the TEM and SHV \( \beta \)-lactamases, we have seen in the past decade the global emergence of CTX-M–type enzymes \([3]\). Presently, in *E. coli* the CTX-M \( \beta \)-lactamases far outnumber the TEM and SHV types, and are linked with the dissemination of the “high-risk clone” sequence type (ST) 131, associated with increased virulence \([4]\). In addition, novel \( \beta \)-lactamases of the PER, OXA, VEB, GES, BES, TLA, and SFO families have only added more complexity to this challenging area (http://www.lahey.org/Studies/). We know from systematic molecular surveys that genes that encode for ESBLs are usually found on large plasmids accompanied by genetic determinants of resistance against other antibiotics, such as aminoglycosides, sulfa drugs, and fluoroquinolones. We have also become aware that patients who develop colonization or infection with these pathogens often are previously treated with fluoroquinolones and third-generationcephalosporins, usually are seriously ill, and are exposed heavily to nosocomial interventions and environment \([5]\). It is interesting that despite our longstanding knowledge of these risk factors, the correlation between cephalosporin use and the emergence of ESBLs persists. Additionally, there are many ongoing issues related to the detection of ESBLs in clinical microbiology laboratories, including a recent shift from phenotypic confirmation with clavulanic acid to lowering cephalosporin breakpoints \([6]\). These difficulties are highlighted by pathogens such as *K. oxytoca* where detection of ESBL production in the laboratory is problematic, as the ESBL phenotype is mediated by the hyperproduction of a chromosomal enzyme called K1 that hydrolyzes some cephalosporins but not others \([7]\).

The prolonged time that transpires between the initial detection of bacterial infection and the eventual determination of minimum inhibitory concentrations (MICs) and detection of ESBLs in the laboratory dictates a period of “empiric therapy.” Thus, defining appropriate therapy for suspected or confirmed infections caused by ESBL-producing organisms remains an elusive goal. Nevertheless, there are some certainties. To start, studies from some time ago show that carbapenems should be regarded as the drugs of choice for serious infections caused by ESBL-producing organisms; clearly, oximinocephalosporins are a poor choice against these pathogens \([8]\).

The role of other agents is not as well defined. Despite its superior ability to readily penetrate gram-negative cells,
Importantly, we know from several clinical studies that cefepime performs less satisfactorily than carbapenems in the treatment of ESBL-producing organisms responsible for bloodstream infection and nosocomial pneumonia [11–13]. This is in contrast with infections caused by Enterobacteriaceae that constitutively express AmpC β-lactamases; cefepime, unlike other cephalosporins, has poor affinity for these enzymes and stands as a good option for the treatment of infections caused by AmpC-producing organisms, provided ESBLs are not in the background [14, 15].

What about β-lactam/β-lactamase inhibitor combinations? There is clear in vitro demonstration of the ability of β-lactamase inhibitors to inactivate ESBLs [16]. There are, however, also misgivings given the potential role of the inoculum effect, more apparent with piperacillin-tazobactam than with amoxicillin–clavulanic acid [17]. PK/PD models may support the use of piperacillin/tazobactam for ESBL-producing E. coli, especially if resorting to high doses and prolonged infusions, but are much less encouraging for K. pneumoniae [18]. In fact, several observational studies ranging from case descriptions to multivariate analyses report treatment failures when piperacillin-tazobactam is used to treat infections caused by ESBL-producing K. pneumoniae [19, 20].

In this issue of Clinical Infectious Diseases, Tamma et al present the results of a retrospective observational study comparing empiric treatment of bloodstream infection caused by ESBL-producing E. coli, Klebsiella species, and Proteus species with piperacillin-tazobactam vs carbapenems; the authors found that empiric treatment with piperacillin-tazobactam was associated with increased risk of mortality at 14 days (adjusted hazard ratio, 1.92 [95% confidence interval, 1.07–3.45]). However, we also know from other retrospective observational studies by Rodriguez-Baño et al that piperacillin-tazobactam and amoxicillin–clavulanic acid are equivalent to carbapenems for the empiric and definite treatment of bloodstream infection caused by ESBL-producing E. coli [21].

Why the discrepancy? What are the real differences between the analyses? Certainly, both groups of drugs should be effective. Carbapenems, by a process that is poorly appreciated, are “trapped” in the active site of β-lactamases for prolonged periods of time and act as inhibitors, in a similar fashion to tazobactam and clavulanic acid. Additionally, carbapenems and piperacillin or amoxicillin are all excellent β-lactams that readily inactivate penicillin-binding proteins. Mechanistically, at least, there are no clear differences between the 2 classes of drugs. Similarly, both studies demonstrate methodological soundness, notwithstanding their observational design. In both instances, the investigators chose to match the treatment and comparator groups according to a propensity score derived from the probability of receiving the treatment, which is the current gold standard among the strategies to analyze observational data. This attempts to overcome the selection bias inherent to observational studies, where treatment is chosen by clinicians and not randomly allocated as in experimental studies, resulting in imbalances between the treatment groups.

Perhaps conflicting observations arise because the objects that are being contemplated are so different in terms of (1) source of infection, (2) genetic background of the pathogen, and (3) regional molecular epidemiology. In studies supporting the efficacy of piperacillin-tazobactam for the treatment of ESBL-producing gram-negative bacteria from Spain and beyond, we see a concentration of attention on E. coli predominantly arising from the urinary and biliary tracts [21, 22]. In the Tamma et al study, we see a collection of strains that include not only E. coli, but also K. pneumoniae, K. oxytoca, and Proteus mirabilis, while central lines and pneumonia are the most common sources of bacteremia. These contrasting distributions may especially matter, because respiratory tract infections imply a high inoculum of bacteria in a compartment where penetration of antibiotics may be impaired, whereas urinary tract infections have a more moderate inoculum and β-lactams easily concentrate in the urine. Furthermore, there may be differences in permeability, virulence determinants, and host predilection between the different bacterial species, as well as variations in the type, quantities, and expression of β-lactamases. A recent survey of ESBLs in the United States found that CTX-M-15 and CTX-M-14 are the most common ESBLs both in E. coli and K. pneumoniae, and that K. pneumoniae frequently co-harbors several types of SHV-like ESBLs. Of note, OXA-1/30, which can confer resistance to both piperacillin and tazobactam, is frequently associated with CTX-M-15 both in E. coli and K. pneumoniae [23]. Surveys in Spain have also revealed the increasing importance of this mechanism in E. coli ST131, but also demonstrate its association with bacteremia from non–urinary tract and non–biliary tract sources [24]. The presence of OXA-1/30 and CTX-M-15 in the emergent E. coli ST131 may complicate the therapeutic role of β-lactam/β-lactamase inhibitor combinations in the future.

How do we reconcile these conflicting observations and decide treatment for our patients? Based on the available evidence, carbapenems may be the best “empiric therapy” for patients with serious bloodstream infections caused by ESBL-producing bacteria with a “complex genetic background,” including K. pneumoniae.
and multiple β-lactamas. Combinations of β-lactams with β-lactamase inhibitors remain an effective treatment option for bloodstream infections caused by ESBL-producing E. coli originating from the urinary tract, or with low MICs (≤2 µg/mL in the case of piperacillin-tazobactam). Clues that may guide us in this decision can be gleaned from a thoughtful consideration of the clinical presentation, risk factors, and antecedent microbiology, with careful inspection of the results of the antibiogram. When incorporated into the clinic, the results of rapid molecular screening may reveal just how complex the β-lactamase background really is. Even then, we may not be able to anticipate the role of efflux pumps, loss of porin channels, and alterations in penicillin-binding proteins that conspire to thwart our best diagnostic and therapeutic efforts.

This landscape will change, not only as the result of the adoption of rapid molecular diagnostics, but also as new therapies enter the arena. The ability to rapidly determine the identity of the causative agent of bacteremia and its resistance mechanisms promises to shorten the period of empiric therapy from 3.5 days, as in the present study, to 1 day or less. Novel β-lactamase inhibitors with activity against ESBLs, such as avibactam and relebactam, are in advanced stages of clinical development. Ceftolozane-tazobactam, a new cephalosporin combined with an established β-lactamase inhibitor, recently received approval by the US Food and Drug Administration for the treatment of urinary tract and intrabdominal infections. In vitro data and PK/PD simulations indicate that the addition of tazobactam extends the activity of ceftolozane to include “most” ESBL producers, with improved efficacy over piperacillin-tazobactam. This drug could certainly position itself as a carbapenem-sparing agent in the treatment of infections caused by ESBL-producing bacteria. However, in some rare strains with high resistance, the reduction in MICs afforded by the inhibitor is insufficient to attain susceptibility [25]. A randomized controlled trial to compare piperacillin-tazobactam to meropenem for the definitive treatment of bloodstream infection caused by ceftriaxone non-susceptible E. coli and Klebsiella sp. is underway (MERINO trial, Professor D. L. Paterson, NCT02176122). This and other studies conducted on isolates whose genetic background has been defined precisely, will determine the future role of β-lactam/β-lactamase inhibitor combinations vs carbapenems in the treatment of serious infections caused by ESBL-producing organisms, and help preserve and enhance the utility of our antibiotic armamentarium.

Notes

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