Can We Really Use β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Infections Caused by Extended-Spectrum β-Lactamase–Producing Bacteria?

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(See the article by Rodríguez-Baño et al, on pages 167–74.)

In this issue a provocative study authored by Jesús Rodríguez Baño and colleagues asserts that the β-lactam/β-lactamase inhibitor (BLBLI) combinations piperacillin/tazobactam and amoxicillin/clavulanate are suitable for the treatment of certain patients with bloodstream infections due to Escherichia coli possessing extended-spectrum β-lactamases (ESBLs). The authors examined patients with infections originating mostly from the urinary and biliary tracts and included both community- and hospital-acquired infections. In the case of patients treated with piperacillin/tazobactam, we read that deaths attributed to infection did not occur when the minimum inhibitory concentration (MIC) of ESBL-producing E. coli against that drug was ≤2 mg/L. Weren’t infections due to ESBL-producing bacteria supposed to be treated with carbapenems?

As clinicians, we readily appreciate that this study has significant implications for our daily practice. These findings challenge us to revisit a fundamental therapeutic approach against antibiotic-resistant bacteria and reward us with a needed alternative to carbapenems for the treatment of ESBL-producing E. coli bloodstream infections. Beyond that, this study may herald a renaissance of BLBLI therapy in the era of “bad bugs, no drugs.”

For years, the paradigm of how to treat Gram-negative bacteria–producing ESBL was shaped by the link between clinical outcomes and antibiotic MICs. On the one hand, increased mortality in the setting of elevated cephalosporin MICs, due to the hydrolytic effects of ESBLs, disqualifies the use of extended-spectrum cephalosporins (eg, ceftazidime, cefotaxime, and ceftriaxone) [1]. On the other hand, favorable outcomes result from treatment with carbapenems, which retain low MICs and are stable in the presence of ESBLs [2]. Alternatives are acceptable only if their MICs are well below the resistance breakpoint, a rare occurrence for fluoroquinolones. Piperacillin/tazobactam and amoxicillin/clavulanate are “stable” against ESBLs, because these enzymes are readily inactivated or inhibited by tazobactam and clavulanate. In the clinical microbiology laboratory, this results in much lower MICs of BLBLI combinations than β-lactams alone. This property is further manifest in the simple double disc diffusion test where, for instance, ceftazidime’s zone of inhibition is increased by clavulanate.

Why, then, have we avoided using BLBLI combinations to treat infections caused by ESBL-producing organisms even when the MICs indicate susceptibility? First, there are concerns about the increase in piperacillin/tazobactam MICs when bacterial inocula reach 10⁷ colony-forming units/mL. Second, the presence of other mechanisms of β-lactam resistance in a given strain, such as AmpC enzymes (eg, CMY-2, FOX-5, ACT-1), hyperproduction and specific mutations of non-ESBL enzymes (eg, SHV or TEM), or additional ESBLs, may provide a “complex background” that reduces the activity of BLBLIs. Third, pharmacokinetic/pharmacodynamic studies indicate that conventional doses of BLBLIs do not achieve “targets” associated with satisfactory outcomes. Finally, the published record on the use of BLBLIs for the treatment of infections caused by ESBL-producing organisms is limited and of heterogeneous quality [3].

Rodríguez Baño et al, coping with the onslaught of ESBL-producing E. coli in their Spanish communities, provide us with their clinical experience framed in...
cohort studies of patients treated with carbapenems and BLBLIs. Their observations allow us to refine the treatment paradigm for infections caused by E. coli harboring ESBLs, without rejecting our previous assumptions about BLBLIs and ESBLs. To begin with, the cohort of patients treated with BLBLIs, although bacteremic, predominantly had low-inoculum infections (in the case of the urinary tract) or infections in which a reduction of the inoculum could be achieved through surgical intervention (in the case of the biliary tract), rather than infections with high inocula such as pneumonia. Additionally, nationwide investigations of the molecular epidemiology of cephalosporin-resistant E. coli in Spain reveal the predominance of CTX-M (72%) and SHV-12 (27%) among ESBLs [4]. In contrast, there is a much lower prevalence of AmpC enzymes (<5%) [5]. Thus, 89% and 69% of ESBL-producing E. coli remain susceptible to piperacillin/tazobactam and amoxicillin/clavulanate, respectively. Furthermore, the investigators were careful to administer high doses of piperacillin/tazobactam (4.5 grams intravenously every 6 hours), following stochastic models predicting clinical success with that dose against susceptible isolates [6]. A corollary “secret” is that ESBLs, especially CTX-Ms, are readily inhibited by higher amounts of tazobactam; larger amounts of piperacillin exceed the capacity of the CTX-M β-lactamase to readily hydrolyze it [7]. In the end, this study revalidates the link between MIC, antibiotic dose, and clinical outcome in infections caused by ESBL-producing E. coli: mortality at 30 days in patients empirically treated with 4.5 grams of piperacillin/tazobactam intravenously every 6 hours was only 4.5% if the MIC was ≤4 mg/L, and 23% if the MIC was >4 mg/L.

Clinicians in the United States and elsewhere may be able to use these data to spare the use of carbapenems for the treatment of infections caused by ESBL-producing E. coli, but this will not be easy. Most immediately, a commonly used automated system of antibiotic susceptibility testing may fail to reliably detect piperacillin/tazobactam resistance in ESBL-producing E. coli [8], imposing the need for manual determination of the MIC as a prerequisite for piperacillin/tazobactam therapy. Because amoxicillin/clavulanate is not available in the parenteral formulation in the United States, its role may be limited to “step-down” oral therapy in selected cases. Relying on piperacillin/tazobactam to treat ESBL-producing organisms instead of carbapenems exerts broad selective pressure, against Pseudomonas aeruginosa included; in contrast, ertapenem, an option among carbapenems, is potentially less selective [9]. Although CTX-M enzymes predominate globally, significant regional variations occur in the resistance determinants of E. coli that may hamper the activity of BLBLIs. For instance, CMY-type β-lactamase–producing E. coli strains are as common as ESBL-producing strains in certain areas of the United States [10].

In this post hoc analysis of prospective cohorts, the “sickest” patients were treated with carbapenems more often than with BLBLIs. This is an indicator of other potential differences between the groups, which is a recognized bias of this type of study. The random allocation of treatments can overcome this limitation, and this would indeed be the best way to compare BLBLIs and carbapenems for the treatment of infections produced by ESBL-producing bacteria. Nevertheless, there is a lot to learn from cohorts like the one formed by Rodríguez Baño et al. In fact, similar studies are urgently needed to elucidate the impact on treatment decisions and outcomes of a genetic background that may include AmpC and ESBLs, but also serine carbapenemases (ie, KPC) and metallo-β-lactamases (eg, NDM-1). This will become especially relevant as we realize the potential of rapid molecular diagnostic methods to detect these traits and incorporate them into clinical practice [11].

The current crisis in antibiotic development demands such advances. It also imposes a reappraisal of therapeutic strategies that have been successful in the past. In this regard, the current generation of BLBLIs continues to offer important dividends, as revealed by Rodríguez Baño et al. The changing landscape of bacterial resistance dictates that future generations of BLBLIs will have to target organisms harboring KPC and NDM-1. The most clinically advanced novel β-lactamase inhibitor is avibactam, formerly known as NXL104. Avibactam is a potent inhibitor of both class A and class C β-lactamases (including ESBLs, AmpCs, and KPC), and it has been paired with ceftazidime and ceftaroline to conduct phase 2 clinical trials [7]. The combination of aztreonam and avibactam is of special interest because it offers a potential option against organisms harboring NDM-1, in addition to class A and class C β-lactamases (note that aztreonam is stable against metallo-β-lactamases) [12]. Indeed, we look forward to the further clinical advancement of these compounds and to new developments of BLBLI combinations.

Notes

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