Use of β -Lactam/ β -Lactamase Inhibitors for Extended-Spectrum- β -Lactamase Infections: Defining the Right Patient Population

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ABSTRACT In a multicenter, multinational observational study that included neutropenic patients with bloodstream infections by extended-spectrum- β -lactamase-producing species, Gudiol et al. (Antimicrob. Agents Chemother. 61:e00164-17, 2017, <https://doi.org/10.1128/AAC.00164-17>) demonstrated that β -lactam/ β -lactamase inhibitors are effective treatment options. A review of this work, however, reminds us that some lingering questions remain for specific high-risk subgroups.

KEYWORDS ESBL, MDRGN, Gram negative, meropenem, piperacillin-tazobactam

Over the last several years, the pendulum has swung in the understanding of the treatment of invasive extended-spectrum- β -lactamase (ESBL) infections. In the past, the inoculum effect observed *in vitro* (1, 2), data from animal studies (3, 4), coexpression of additional β -lactamases not effectively inhibited by β -lactamase inhibitors (β LI) (5), and concerns regarding inadequate pharmacokinetic-pharmacodynamic drug target attainment with standard β -lactam (β L)/ β LI dosing regimens (6, 7) have tempered the enthusiasm for prescribing these agents for the treatment of invasive ESBL infections. However, more recently, and in large part due to the multicenter efforts led by several Spanish investigators (8, 9), such concerns have been largely alleviated. It has been shown that for many patients with invasive ESBL infections, β L- β LI treatments are safe and effective options.

The study by Gudiol and colleagues is a welcome addition to the literature as it further defines the populations for which β L/ β LIs can be considered for the treatment of ESBL infections (10). The investigators compared β L/ β LIs to carbapenems in a cohort of neutropenic patients with ESBL bacteremia and hematological malignancies. This is a subgroup that had traditionally been left unaddressed in previous observational studies (8, 9, 11–15). The investigators used propensity-score matching to limit bias from confounding by indication. Evaluating treatment effects from observational data can be problematic as a number of prognostic factors (e.g., severity of illness, underlying medical conditions, source of bacteremia, microbial characteristics, provider characteristics, etc.) can influence the decision to prescribe β L/ β LIs or carbapenems for patients with ESBL-producing bloodstream infections.

Although propensity-score matching is a sophisticated technique that attempts to mimic the equality of study groups provided by randomized control trials, a drawback of this approach is that it almost inevitably leads to reductions in sample sizes. In this case, the investigators began with 174 patients in the empirical-therapy cohort and were left with 35 pairs of patients after propensity-score matching. Similarly, propensity-score matching yielded 15 matched pairs in the definitive-therapy cohort from an initial 251 patients.

Accepted manuscript posted online 5 June 2017

Citation Tamma PD, Villegas MV. 2017. Use of β -lactam/ β -lactamase inhibitors for extended-spectrum- β -lactamase infections: defining the right patient population. Antimicrob Agents Chemother 61:e01094-17. <https://doi.org/10.1128/AAC.01094-17>.

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For the article discussed, see <https://doi.org/10.1128/AAC.00164-17>.

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In the propensity-score-matched empirical-therapy group, the 30-day mortality rates, the primary outcome, were 20% and 11% for the β L/ β LI and carbapenem groups, respectively. In the propensity-score-matched definitive-therapy group, the 30-day mortality rates were 13% for the β L/ β LI group and 7% for the carbapenem group. Although neither of these differences was statistically significant, the absolute differences in mortality rates remind us that these cohorts were likely underpowered to identify differences in 30-day mortality, if such differences existed.

An important caveat to consider with this work is the generalizability of the findings. As an example, there is no mention of patients with deep-seated sources of infection who may have had difficulty achieving source control. The most frequent sources of bloodstream infections, which accounted for approximately 90% of cases, were intestinal translocation, catheter-related bloodstream infections (where catheter removal presumably occurred), and urinary tract infections (where high concentrations of antibiotics are expected). It is unclear how effective β L/ β LI would be in neutropenic patients with “high-inoculum” infections such as intra-abdominal abscesses, endovascular infections, osteoarticular infections, and hospital-acquired pneumonias. Similarly, only approximately 15% of the cohort experienced profound neutropenia, with absolute neutrophil counts of fewer than 100 neutrophils/mm³. Furthermore, although a description of the propensity-score-matched cohort was not provided, only about 10% to 20% of patients were likely to be severely ill.

Additionally, approximately three-quarters of patients were infected with *Escherichia coli*. It is unknown whether microbial characteristics (e.g., immunogenicity of the *Klebsiella pneumoniae* capsule) or specific β -lactamase characteristics (e.g., inhibitor-resistant SHV β -lactamases, etc.) or the presence of other virulence factors on mobile genetic elements might lead to differences in the behavior of other ESBL-producing *Enterobacteriaceae* compared to ESBL-producing *E. coli*. Indeed, in a large, multicenter study by Gutiérrez-Gutiérrez et al. (9), ESBL-producing *K. pneumoniae* was independently associated with higher mortality than ESBL-producing *E. coli*. Similarly, in another observational study using propensity-score analysis in which poorer outcomes were observed in the β L/ β LI group, almost 70% of patients were infected with ESBL-producing *K. pneumoniae* (14).

Despite these issues of limited sample size and generalizability, this work addresses an important gap in knowledge related to the treatment of ESBL infections in neutropenic patients with hematologic malignancies. As this is a population repeatedly exposed to broad-spectrum antibiotics and to the health care environment, which is highly conducive to the dissemination of plasmid-mediated resistance mechanisms, these investigators remind us that carbapenem-sparing regimens should be favored over carbapenem regimens whenever possible for both empirical and targeted treatment of infections. Their findings suggest that, for neutropenic patients with mild to moderate ESBL bloodstream infections or from sites clearly amenable to source control, β L/ β LI, when active *in vitro* and appropriately dosed, are a reasonable treatment option.

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