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AUTHOR REPLY

Reply to Shapiro, "Cefepime/Enmetazobactam Is a Clinically Effective Combination Targeting Extended-Spectrum β-Lactamase-Producing *Enterobacterales*"

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The emergence of bacterial resistance, mainly due to the widespread presence of β-lactamase enzymes, is an important health concern. The use of β-lactamase inhibitors is probably the main strategy available for restoring the effectiveness of β-lactam antibiotics. However, the emergence of new β-lactamases, such as extended-spectrum β-lactamases (ESBLs) and carbapenemases, is a new worldwide problem.

Fortunately, new extended-spectrum inhibitors have emerged in recent years in the fight against multidrug resistance in bacteria. Thus, the efficacy of the novel β-lactamase inhibitors enmetazobactam, zidebactam, and taniborbactam is being evaluated, and promising results for these inhibitors in combination with cefepime have been obtained in phase III clinical trials.

As S. Shapiro indicates in his letter (1) in response to our study (2), the prevalence of ESBLs in *Enterobacterales* is higher than that of carbapenemases; however, we must not forget that carbapenemases are the main challenge when treating an infection with β-lactam antibiotics and, regardless of their prevalence, are associated with high rates of mortality (3). Most of the carbapenemases, such as KPC (class A), VIM, IMP, and NDM (class B), and OXA-48 (class D), are not inhibited by the majority of inhibitors approved by clinical agencies. Therefore, the objective of our study (2) was to evaluate the efficacy of the novel combinations of cefepime and these inhibitors against a collection of 400 carbapenemase-producing isolates of *Enterobacterales*. It is essential to test the new inhibitors against these worrisome carbapenemases in order to identify the best therapeutic options in the near future.

Cefepime/enmetazobactam is known to be a potential carbapenem-sparing agent with activity against ESBLs, as is also, e.g., cefepime/tazobactam (4, 5). This aspect is neither questioned nor evaluated in our study. However, we consider that the evaluation of enmetazobactam (along with other novel inhibitors) against a broad collection of carbapenemase-producing *Enterobacterales* is of interest to readers of *Antimicrobial Agents and Chemotherapy* and to clinical microbiologists in general.

Regarding S. Shapiro's opinion about the cefepime breakpoints used in the study, we would like to point out that breakpoints have not yet been defined for these new combinations of β-lactamase inhibitors with cefepime. Thus, in order to facilitate interpretation of the results obtained, we, following CLSI criteria, used cefepime MIC values of ≤2 and ≥16 mg/L as breakpoints to define "susceptible" and "resistant" categories, respectively (6).

Finally, concerning the last comment in the letter, about KPC-carrying isolates, we point out that previous studies have also observed that cefepime/enmetazobactam presented moderate activity against KPC-producing *Klebsiella pneumoniae* isolates (7–9). As indicated in the text and Table 2 in our report and in Table S2 in its supplemental material, the MICs of cefepime and cefepime/enmetazobactam for KPC-carrying isolates are determined by the clonality of the isolates. The non-ESBL-producing *K. pneumoniae* isolates mostly belong to sequence type 512 (ST512), whereas the KPC- and ESBL-producing isolates mostly belong

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to ST307. The non-ESBL-producing isolates were cefepime/enmetazobactam resistant; however, as indicated in the report, this was probably due to inactivating mutations identified in OmpK35 and OmpK36, which do not appear in ST307 (cefepime/enmetazobactam susceptible) (Table S2) (2). We consider very unlikely the hypothesis of downregulation of KPC gene expression in the presence of ESBL suggested by S. Shapiro.

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