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Cefepime/Enmetazobactam Is a Clinically Effective Combination Targeting Extended-Spectrum β-Lactamase-Producing *Enterobacterales*

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Vázquez-Ucha et al. present interesting data on the potentiation of cefepime by some β-lactamase inhibitors in clinical development (1). However, a side-by-side comparison of cefepime synergism toward carbapenemase-producing *Enterobacterales* by enmetazobactam and by zidebactam or taniborbactam is misleading. Whereas zidebactam and taniborbactam were designed to overcome resistance attributable to class A, B, and D carbapenemases, enmetazobactam is a novel penicillanic acid sulfone β-lactamase inhibitor targeting enterobacterial extended-spectrum β-lactamases (ESBLs). Cefepime was chosen as a partner for enmetazobactam (which entered development prior to the appearance of either zidebactam or taniborbactam) based on the cephalosporin's antibacterial spectrum (including good antipseudomonal activity), presumptive enhanced porin penetrance, and intrinsic resistance to hydrolysis by AmpCs and OXA-48-like enzymes.

Since its introduction several decades ago, the activity of tazobactam has waned in the face of new, more aggressive ESBLs (2), and cefepime/enmetazobactam was developed as a carbapenem-, diazabicyclooctane-, and cyclic boronate-sparing β-lactam/β-lactamase inhibitor combination to supplant piperacillin/tazobactam for treating recalcitrant infections attributable to ESBL-producing (as well as AmpC- and OXA-48-like-producing) *Enterobacterales* without driving the emergence and dissemination of carbapenem resistance. The efficacy of cefepime/enmetazobactam has been demonstrated in preclinical studies (3, 4) and clinical trials (5).

Carbapenemases capture most of the alarmist headlines but, fearmongering aside, the global prevalence of carbapenem (meropenem) resistance among *Enterobacterales* is only 3.3%, distributed predominantly among KPCs (~1.5% global prevalence), metallo-β-lactamases (MBLs) (0.4% to 0.7% global prevalence), and OXA-48-like enzymes (~0.6% global prevalence) (6, 7), whereas the global prevalence of ESBL-producing but non-carbapenemase-resistant phenotypes among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* collected during 2018 and 2019 were 30.0% and 25.4%, respectively (8). From a global perspective, ESBL-mediated β-lactam resistance trumps carbapenem-mediated β-lactam resistance, and a bactericidal non-carbapenem/non-diazabicyclooctane/non-cyclic boronate antibiotic with a β-lactam-like safety profile for treating infections attributable to diverse ESBL-producing *Enterobacterales* remains an unmet medical need.

Clinical development of cefepime/enmetazobactam was conducted with truculent enterobacterial infections in mind and, considering this combination's projected posology, the lower "% isolates with MICs values" boundary for cefepime/enmetazobactam in Vázquez-Ucha et al.'s Tables 1 and 2 should have been the susceptible, dose-dependent (SDD) value for cefepime of 4 to 8 mg/L rather than the susceptible (S) value of ≤2 mg/L (9).

It is curious that 94.1% of Vázquez-Ucha et al.'s *Enterobacterales* isolates harboring both KPC and ESBL genes were susceptible to cefepime/enmetazobactam at a MIC of ≤2 mg/L, raising the possibility that, at least in their strain panel, the copresence of an ESBL gene

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downregulated the expression of the KPC gene to a level where the isolates were essentially just ESBL producers. This observation is worthy of further exploration.

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