Is Extended or Continuous Infusion of Carbapenems the Obvious Solution to Improve Clinical Outcomes and Reduce Mortality?

To the Editor—We have read with great interest the meta-analysis by Falagas et al regarding “clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems [CBP]...
and piperacillin/tazobactam [P/T]" [1] and would like to make some comments.

First, the authors concluded that "extended or continuous infusion of CBP and P/T results in lower mortality." However, in figure 3 of their article, this conclusion is only valuable for P/T but is not statistically significant for CBP (risk ratio = 0.66; 95% confidence interval, .34–1.30).

Second, the quality of studies reported on CBP could be questioned: among 6 studies, 1 was an abstract (with imipenem/cilastatin or meropenem used differently without data about dosage) and 1 was published as a letter to the editor (not a full article) [2, 3]. Important variations were noted between studies, rendering conclusions difficult to translate in daily clinical practice. For example, the total daily dose ranged from 1 g to 4 g for meropenem; indications for treatment ranged from bacteremia to intensive care unit–acquired pneumonia (including 1 study with “moderate community-acquired pneumonia,” which is usually not an indication for CBP); and severity of the underlying infection or minimum inhibitory concentration (MIC) of the pathogens were not available in all the publications.

Third, extended or continuous infusions were considered equivalent for both drugs, as the time that the concentration of the antibiotic remains above the MIC (T > MIC) is the pharmacodynamic parameter associated with effectiveness for all β-lactams. However, the T > MIC for bactericidal killing is 30%–40% and 50%–60% for CBP and P/T, respectively, and postantibiotic effect is considered for CBP but not for P/T [4, 5]. Moreover, CBP appears to be the most unstable of the β-lactams for continuous infusion, such that its use should be considered only under strict conditions including cold packs to store the drug throughout the infusion, or changing the medication cartridge every 6–8 hours [6, 7]. Theoretically, these reasons could favor extended infusion for CBP and continuous infusion for P/T.

Finally, 3 additional papers have been recently published on that topic, 1 with meropenem alone and 2 with various β-lactams including meropenem and P/T [8–10]. None of these studies found a significant difference in term of mortality, and clinical cure was higher in the continuous or prolonged group only in 1 study [9].

In conclusion, current literature do not favor extended or continuous infusion of CBP in terms of improved clinical cure and reduced mortality, as it could be for P/T. This could be explained by pharmacokinetic/pharmacodynamic differences among β-lactams, such as duration of T > MIC, drug stability, or level of concentration at the site of infection. We fully agree with the conclusion of the authors that well-designed randomized controlled prospective trials are urgently needed to determine the optimal method for delivery of β-lactams in an area of declines in new antimicrobial development and increasing rates of resistance.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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