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RESPONSE TO LETTER

Synergistic Effect of Ceftazidime-Avibactam with Aztreonam on Carbapenemase-Positive *Klebsiella pneumoniae* MBL+, NDM+ [Response to Letter]

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Dear editor

Thank you for the valuable and insightful comments provided by Pathak et al. In response to the very important issues raised, we would like to emphasize that *Klebsiella pneumoniae* MBL+ strains with an additional resistance mechanism, ie, ESBL or AmpC production, were found in isolates from patients in both groups. When ceftazidime-avibactam therapy was used in combination with aztreonam, we observed better final results in terms of reduced mortality compared to the group where the alternative treatment was used. The limitation of our study is the single-center nature of the work and the size of the group.[1] This is why it is crucial to publish studies addressing similar issues. However, the study did not include patients with MBL and KPC. Assessing the effectiveness of therapy in such cases is justified and driven by the fact that avibactam inhibits KPC beta-lactamase, while aztreonam acts against MBL. However, Klebsiella pneumoniae KPC strains resistant to ceftazidime with avibactam have been reported, hence the need to determine synergism in vitro.[2,3]

With the launch of aztreonam-avibactam, breakpoints for aztreonam-avibactam susceptibility testing using the disk diffusion method are available as of May 2024.[4] In the absence of this method, the preferred approach remains the determination of in vitro synergism, ideally prior to the initiation of therapy. It should be noted that in many countries worldwide, the aztreonam-avibactam combination is still not available, necessitating the use of ceftazidime-avibactam combined with aztreonam as a substitute therapy.

The broth disk elution method is as accessible as the synergy testing method using the E-test/disk on Mueller-Hinton agar, and in our view, both methods can currently be used interchangeably, ideally simultaneously.

The lack of correlation between in vitro results and clinical outcomes may be due, among other factors, to pharmacokinetic differences in patients, particularly those in critical condition. However, the potential discrepancy does not obviate the need to determine the drug synergism in the laboratory.

Undoubtedly, to optimize treatment, it is essential to monitor both the therapeutic outcomes and to clearly define the preferred method for determining ceftazidime-avibactam synergism with aztreonam (or aztreonam with avibactam) in vitro.[5] However, it is important to note the reported instances of *Klebsiella pneumoniae* strains producing KPC beta-lactamase resistant or less susceptible to ceftazidime-avibactam.[2,3,6] On the other hand, the use of colistin carries numerous potential risks, and importantly, colistin therapy should be combined with another antibiotic active against the tested strain, which is sometimes impossible.[7] Furthermore, beta-lactam antibiotics are preferred for the treatment of most infections due to their favorable pharmacokinetic-pharmacodynamic profile, which also supports the choice of aztreonam-avibactam therapy over other alternative regimens. It is likely that such therapy will limit the spread of multidrug-resistant strains.[8]

Disclosure

The authors report no conflicts of interest in this communication.

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