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Benefits of Aerosolized Colistin for Ventilator-Associated Pneumonia: Absence of Proof Versus Proof of Absence?

To the Editor—We read with great interest the retrospective matched case-control study by Kofteridis et al. In this study, intravenous (IV) colistin with and without aerosolized colistin were compared for the treatment of ventilator-associated pneumonia (VAP). The authors concluded that the addition of aerosolized colistin to IV colistin did not provide additional therapeutic benefit to patients with VAP due to multidrug-resistant gram-negative bacteria. The authors should be commended for their efforts in addressing this clinical question, which challenges clinicians worldwide. We would like to add our perspectives and considerations to the discussion.

To arrive at the authors’ conclusion, 2 important points (which could potentially confound the results of the study) should be clarified: (1) the timing of initiation of colistin therapy and (2) concurrent use of antibiotics. It is important to clarify whether colistin was started as empirical therapy at the onset of pneumonia (ie, before culture results were known) or as directed by the culture and susceptibility testing results (in which a delay of 2–5 days would typically be expected). Because the length of time to initiation of appropriate therapy is an important determinant of VAP outcome, one could argue that adding aerosolized colistin to the treatment regimen would not confer substantial benefit late in the clinical course of the disease, due to the inoculum effect observed with colistin.

Furthermore, reporting of concurrent antibiotic therapy (regardless of the susceptibility of the strains) could also be important, in view of the potential synergy or antagonism with various combinations.

In addition, the sample size of this study is one of our major concerns, as also pointed out by Paterson et al. To further elaborate on this, the reported VAP-related mortality was 26% (among those treated with IV colistin) and 16% (among those treated with IV and aerosolized colistin), which did not meet a conventional threshold of statistical significance ($P = .289$). However, the type II (beta) error is in excess of 75% using the reported sample size of 43 in each arm. In other words, if the claim is that aerosolized colistin did not offer any additional VAP-related mortality benefit to patients, there is a greater than 3 in 4 chance that the conclusion would be incorrect. Hence, we are unable to arrive at the authors’ conclusion independently on the basis of the data presented.

Before applying the results in clinical practice, it may also be prudent to compare the study results to what was previously known. The clinical success rate in the IV colistin group was 60.5%, which is much higher than the 25% success rate reported by Levin et al. Furthermore, a recent study reported benefits (clinical cure) associated with treatment with IV plus aerosolized colistin, compared with treatment with IV colistin alone (79.5% vs 60.5%; $P = .025$). Although the study results are thought-provoking, we believe that more concrete clinical data are needed to clarify the effectiveness and safety of concomitant administration of aerosolized and IV colistin in patients with VAP.

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Andrea L. Kwa, Matthew E. Falagas, Argyris Michalopoulos, and Vincent H. Tam

1Department of Pharmacy, Singapore General Hospital, Singapore, 2Alfa Institute of Biomedical Science and, 3Intensive Care Unit, Henry Dunant Hospital, Athens, Greece, 4Tufts University School of Medicine, Boston, Massachusetts and, 5Department of Clinical Sciences and Administration, University of Houston College of Pharmacy, Houston, Texas

References


Correspondence: Vincent H. Tam, PharmD, University of Houston College of Pharmacy, 1441 Moursund St, Houston, TX 77009 (vtam@uh.edu).

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