LETTER TO THE EDITOR

Eternal Hunt: Unravelling the Challenge of CRE, the Quest for Perfection Continues!

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Dear Editor,

The article titled "The Comparative Efficacy of Ceftazidime–Avibactam with or without Aztreonam vs Polymyxins for Carbapenem-resistant Enterobacteriaceae Infections: A Prospective Observational Cohort Study" by Vijayakumar M et al. was read with great interest.[1] We appreciate the authors' research and want to express our views about the article.

Carbapenem-resistant Enterobacteriaceae (CRE) refers to organisms displaying resistance to either Meropenem or Imipenem or those Enterobacterales isolates producing carbapenemase enzymes.[2] Infections caused by these organisms are associated with high mortality rates among hospitalized patients, up to 50% in some studies.[3] Ceftazidime-Avibactam (CZT-AVI), Meropenem–Vaborbactam, Imipenem–Cilastatin–Sulbactam, Polymyxins, and Cefiderocol are preferred treatment options for invasive infections.[2] This study compared Ceftazidime–Avibactam with or without Aztreonam (AZT) vs Polymyxins for treating CRE.

Despite its demonstrated efficacy against NDM (New Delhi Metalloproteinase)-producing CRE, Ceftazidime-Avibactam with Aztreonam is typically reserved as a last-resort treatment for severe invasive infections.[4] This study did not discuss the degree of infection, especially regarding non-bloodstream diseases. In cases of urinary tract infections, it is uncertain whether they are upper or lower UTIs, and whether they are complicated. Uncomplicated lower UTIs due to CRE can be treated with a single dose of Colistin, Aminoglycosides, or Fosfomycin.[2]

Researchers did not mention the genotypic and phenotypic correlation of Carbapenem-resistant Enterobacteriaceae. Though studies have proven the role of Ceftazidime–Avibactam with Aztreonam in NDM subtypes, it is not 100%.[5] Hence, the summary of the sensitivity profile along with minimum inhibitory concentrations and genotype for both antibiotic groups would have clarified it. This study mentioned clinician discretion in choosing antibiotics based on the results of culture sensitivity testing and the specific Carbapenemase gene. Out of a total of 89 patients included in the study 2/3rd of patients received CAZ–AVI ± AZT, and only 1/3rd received Polymyxin. The study did not mention the reason for the difference in sample size of the groups.

This study had multiple primary outcomes, in our opinion, it should have considered a single composite primary outcome. There was mention of the duration of antibiotics and extension if needed. However, there was no mention of antibiotic policy in case there is no response or worsening despite *in vitro* sensitive antibiotics.[6] In ICU, it is common to have hospital-acquired infections and antibiotics need to be modified in case of any. There was no mention of such episodes of new HAI during antibiotic therapy and the antibiotic modifications if any.

It has been stated that CAZ–AVI ± AZT was used in patients with NDM infections, but 19 patients in the CAZ–AVI ± AZT group harbored both NDM and OXA 48 genes. The use of AZT in these patients is unclear because the overall number of NDM infections in the CAZ-AVI + AZT group does not equal the number of NDM infections in the CAZ-AVI ± AZT group.

We appreciate the efforts of the researchers in conducting this study. An ideal approach would be to use the genomics of bacteria to choose antibiotics,[5] and this is something that this study has used. However, its availability and affordability are an issue in India. We also emphasize that the site of infection, severity, and MIC of sensitive antibiotics should also be considered while choosing antibiotics despite bacterial genomics. High-end antibiotics like the one used in this study should be reserved for severe invasive multi-drug resistant infections. Further studies for genotype-phenotype correlation, site and severity-specific usage of antibiotics, and their efficacy are needed for multidrug-resistant organisms like CRE.

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