Mortality Attributable to Mismatch with In Vitro Susceptibility of Empirical Antibiotics in Patients with Bacterial Bloodstream Infections

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Background: Empirical antibiotic therapy mismatching with susceptibility of identified pathogens is common despite widespread use of broad-spectrum antibiotics in bacterial bloodstream infections (BSIs). However, it remains challenging in evaluating the clinical impact of the mismatch on mortality due to patient heterogeneity and time-varying treatment decisions.

Methods: Electronic medical data from all 43 public hospitals in Hong Kong (2012-2021) were used to identify inpatient BSI events receiving empirical antibiotics. A marginal structural Cox model with inverse-probability weighting estimated associations between mismatched empiric treatment and both BSI-associated and in-hospital mortality overall, and with BSI-associated mortality in prespecified subgroups.

Results: Among 140,951 BSI events, 20,970 (15%) received mismatched empiric therapy. It was more frequent in BSIs caused by clinically prioritized AMR phenotypes in targeted pathogens, including carbapenem-resistant or extended-spectrum cephalosporin-resistant *K. pneumoniae* and Methicillin-resistant *S. aureus* (MRSA). It was independently associated with an increased risk of BSI-associated (HR: 1.13, 95% CI: 1.09–1.18) and in-hospital mortality (1.13, 1.08–1.16). BSI-associated mortality was higher in several subgroups, including hospital-onset BSI (HR 1.22, 95% CI 1.16−1.29), non-severe BSI (1.13, 1.06–1.21), and severe BSI with shock (1.18, 1.10–1.27), as well as in gram-negative BSIs (e.g., *E. coli*, *K. pneumoniae*, *Proteus spp.*, and *Acinetobacter spp.*). Increased BSI-associated mortality was also observed for non-clinically prioritized phenotypes, including *Proteus spp.* (HR 1.67, 95% CI 1.35–2.07), *K. pneumoniae* (1.37, 1.14–1.64), and *E. coli* (1.19, 1.08–1.31).

Conclusion: Mismatched empirical antibiotic therapy was frequently observed and associated with a higher mortality in BSIs caused by pathogens with various AMR profiles. It underscores the importance of optimizing empirical antibiotic selection to mitigate the clinical impact of AMR.