Combating antimicrobial resistance using antimicrobial combination therapy and β–lactamase inhibitors

Bassam El-Hafi¹,², Sari Shawki Rasheed¹,², Noor Salloum¹,², Antoine Abou Fayad¹,², George Farah Araj²,³, Ghassan Matar Matar¹,²

¹ Department of Experimental Pathology, Immunology and Microbiology, American University of Beirut, Beirut, Lebanon
² Center for Infectious Disease Research (CIDR), American University of Beirut Medical Center, Beirut, Lebanon
³ Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Abstract
Introduction: The range of antimicrobial agents used to treat bacterial infections is becoming limited with the constant increase in antimicrobial resistance (AMR). Several genetic factors underlie AMR, including β-lactamase-encoding genes such as blaCTXM-15 that confers resistance to third-generation cephalosporins, and blaOXA-48, blaNDM-1, and blaKPC-2 that confer resistance to carabapenems. Remaining treatment approaches for such resistant infections include antimicrobial combination therapy and the use of β-lactamase inhibitors. This study assesses the molecular effects of such treatment approaches on antimicrobial resistant Enterobacteriaceae clinical isolates in vitro and in vivo.

Methodology: Nine clinical Enterobacteriaceae isolates were included in the study. One harboring blaCTXM-15, one harboring blaOXA-48, one harboring blaKPC-2, two harboring blaNDM-1 and blaCTXM-15, and four harboring blaOXA-48 and blaCTXM-15. Minimal inhibitory concentrations were determined for carabapenems with β-lactamase inhibitors: avibactam, Ca-EDTA, and relebactam. Synergism between antibiotic combinations was determined by double disc diffusion when using colistin with several antibiotics. In vitro and in vivo gene expression levels were done on these combinations with and without inhibitors.

Results: The use of meropenem, imipenem, and ertapenem with the selected β-lactamase inhibitors restored isolate susceptibility in 100%, 87.5%, and 25% of the cases, respectively. Antimicrobial synergism was mostly detected between colistin and meropenem, fosfomycin, or tigecycline. Survival studies revealed the survival of most mice receiving antimicrobial combination therapy with inhibitors as compared to the controls. Overall gene expression levels of resistance genes were variable depending on treatment.

Conclusions: The threat of antibiotic resistant bacterial infections remains viable; however, different approaches to therapy are available.

Key words: antimicrobial resistance; combination therapy; beta-lactamase inhibitor.