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Combating antimicrobial resistance – Utility of antimicrobial combination therapy and/ or inhibitors

The range of antimicrobial agents that can be 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 $bla_{CTXM-15}$ that confers resistance to third-generation cephalosporins, and bla_{OXA-48}, bla_{NDM-1}, and bla_{KPC-2} that confer resistance to carbapenems. 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*. Nine clinical *Enterobacteriaceae* isolates were included in the study. One harboring $blaC_{TXM-15}$, one harboring *blaOXA-48*, one harboring bla_{KPC-2}, two harboring blaNDM-1 and $bla_{CTXM-15}$, and four harboring blaOXA-48 and $bla_{CTXM-15}$. Minimal inhibitory concentrations were determined for carbapenems 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. 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. The threat of antibiotic resistant bacterial infections remains viable; however, different approaches to therapy are available

Biography

Dr. Ghassan M. Matar is a Professor and Vice Chairperson in the Department of Experimental Pathology, Immunology & Microbiology, American University of Beirut. To present he published 101 articles in refereed international journals and received funding from various extramural sources. His research interests deal mainly with molecular mechanisms of resistance to antimicrobial agents in pathogenic bacteria, namely carbapenem resistance in ESBL and non-ESBL producing Enterobacteriaceae and assessment of combination using antimicrobial therapy with and without inhibitors or natural products, in infections caused by carbapenem resistant Enterobacteriaceae harboring various carbapenemase encoding genes.

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