JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

The Lebanese LSIDCM

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

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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 *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*.

Methodology: Nine clinical *Enterobacteriaceae* isolates were included in the study. One harboring *bla*$_{CTXM-15}$, one harboring *bla*$_{OXA-48}$, one harboring *bla*$_{KPC-2}$, two harboring *bla*$_{NDM-1}$ and *bla*$_{CTXM-15}$, and four harboring *bla*$_{OXA-48}$ 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.

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.

J Infect Dev Ctries 2018; 12(2S):14S. doi:10.3855/jidc.10099

(Received 21 December 2017 – Accepted 22 December 2017)

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Conflict of interests: No conflict of interests is declared.