In vitro activity of colistin alone and in combination with imipenem, rifampicin and tigecyclin against carbapenemase-producing Enterobacteriaceae isolated from blood cultures

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Background: Despite the relevance of carbapenemase-producing Enterobacteriaceae infections especially bloodstream infections there are a scarce number of studies to evaluate in vivo the efficacy of combinations therapies. The aim of this study was to investigate the in vitro activities of colistin, imipenem, rifampicin, and tigecycline alone and in combination against carbapenemase-producing Enterobacteriaceae isolated from blood cultures in Tunisia.

Materials/methods: 148 CPE strains (123 OXA-48-like, 27 NDM, 3 NDM + OXA-48-like, 1VIM) isolated from blood cultures in the laboratory of Habib Bourguiba hospital between 2009 and 2015 were studied. The MICs were determined by the broth microdilution. Bactericidal and synergistic activity of colistin alone and in combination with tigecyclin, imipenem and rifampicin was measured by time-kill curves and Chequerboard method. Accordingly, the fractional inhibitory concentration (FIC) index was calculated and complete synergy was defined as FIC ≤0.5. Bactericidal activity was defined as ≥3-log10 CFU/mL reduction of the initial bacterial count.

Results: Colistin (MIC50, 0.25; MIC90, >32 µg/mL; 79.97% susceptible) and tigecyclin (MIC50, 1; MIC90, 2 µg/mL; 81.82% susceptible) were more active against the studied CPE strains than imipenem (MIC50, 2; MIC90, 8 µg/mL; 53.9% susceptible), meropenem (MIC50, 4; MIC90, 16 µg/mL; 45.5% susceptible), and amikacin (MIC50, 8; MIC90, 32 µg/mL; 66.3%).

Chequerboard method showed that synergy was detected in 112/148 (75.7%), 36/148 (24.3%), 32/148 (21.6%) of the strains for colistin + rifampicin, colistin + tigecycline, and colistin + imipenem, respectively. The synergy was significantly higher in colistin-resistant strains, 63% vs 14.4% for colistin + tigecycline and colistin + rifampicin, 96.7% vs 70.3%.

By time kill studies, all colistin combinations showed bactericidal activity against all colistin-susceptible strains except for 6 strains with colistin + tigecycline (antagonism). However, the colistin combinations showed bactericidal activity against 24/30 (80%), 4/30 (13.3%), 2/30 (7%) of the colistin-resistant strains for colistin + rifampicin, colistin + imipenem and colistin + tigecyclin, respectively. The triple combinations colistin + rifampicin + imipenem or colistin + rifampicin + tigecycline were bactericidal against 96% of strains.

Conclusions: Our in vitro data suggest that colistin combinations especially with rifampicin might be a valid therapeutic option against CPE, even in the presence of colistin resistance.