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O0574 Azidothymidine is bactericidal against carbapenem-resistant Enterobacteriaceae and produces synergistic activity in combination with colistin against multidrug-resistant Enterobacteriaceae

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Background: Bacterial infections remain the leading killer worldwide which is worsened by the continuous emergence of antibiotic resistance. In particular, antibiotic-resistant Gram-negative bacteria are prevalent and are extremely difficult to treat. Reusing of existing drugs and rejuvenating the therapeutic potential of existing antibiotics represent an attractive novel strategy. Azidothymidine (AZT) is an anti-retroviral drug which is used in combination with other antivirals to prevent and to treat HIV/AIDS. AZT is also active against Gram-negative bacteria but has not been developed for that purpose. Here we investigated the efficacy of AZT against a variety of antibiotic resistant Enterobacteriaceae. We also tested the ability of AZT to enhance the potency of currently used antibiotics particularly colistin against antibiotic-resistant including NDM-1 Enterobacteriaceae.

Materials/methods: Bacterial strains were antibiotic resistant Gram-negative clinical isolates including *Escherichia coli* and *Klebsiella pneumoniae* from Asia, colistin resistant mcr-1 *E. coli* strains and DNM-1 Enterobacteriaceae. Bacterial strains were grown in nutrient broth and on tryptone soya agar.

Minimum inhibitory concentration (MIC) was determined by broth dilution method in cation-adjusted Mueller Hinton Broth following the Clinical and Laboratory Standards Institute guidelines.

The chequerboard method was used for the measurement of combination effects of AZT with colistin against colistin-sensitive and -resistant Gram-negative strains.

For time-kill-curve test, different concentrations of drugs alone or in combination were added to bacterial suspension which was incubated at 37ºC for 24 hours. Viability after drug exposure were determined at different time points by CFU counting and expressed as Log CFU/mL.

Results: We found that AZT was active against NDM-1 *E. coli* and *K. pneumoniae* with MIC ranged from 0.25 to 4 mg/L. Fractional inhibitory concentration index demonstrated that AZT synergised with colistin against MDR, NDM-1 and mcr-1 *E. coli* and *K. pneumoniae*, showing synergy against 61% of ESBL *E. coli*, 87% of ESBL *K. pneumoniae*, 100% of NDM-1 strains and 92% of mcr-1 *E. coli*. Time-kill analysis demonstrated significant synergistic activities when a low level of AZT was combined with colistin.

Conclusions: AZT is bactericidal against NDM-1 *E. coli* and *K. pneumoniae*. AZT in combination with colistin produced synergistic activities against ESBL, NDM-1 and mcr-1 producing Enterobacteriaceae.