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Paper Poster Session IV

Update on colistin & polymyxin B

Postantibiotic effect of colistin alone and combined with vancomycin or meropenem against *Acinetobacter baumannii* strains with well defined resistance mechanisms

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Background

The aim of this study was to determine in vitro synergy and postantibiotic effect (PAE) of colistin combined with other antibiotics (vancomycin and meropenem) against carbapenem-resistant *Acinetobacter baumannii* strains with defined resistance mechanisms. It was hypothesised that vancomycin and meropenem would prolong the PAE of colistin since it was previously found that they exert synergism with colistin in time-kill kinetics and also in clinical trials.

Methods

The experiments were performed on four *A. baumannii* strains with previously characterized carbapenem-hydrolyzing oxacillinases which included OXA-23, OXA-24, OXA-58 and OXA-143 positive strains. MICs of colistin, vancomycin and meropenem were determined by broth microdilution method. The interactions of two antibiotics were tested by checkerboard MIC technique, yielding the fractional inhibitory concentration index (FICI) as described previously. Time-kill experiments were carried out by exposing test cultures to colistin alone and combined with either vancomycin and meropenem and establishing bacterial numbers by viable counting. The PAE was calculated according to the following formula: $PAE = T - C$, where T is the time required for the viable counts of the antibiotic exposed cultures to increase by $1 \log_{10}$ and C is time required for the viable counts of the control cultures to increase by $1 \log_{10}$.

Results

The results of the checkerboard analysis indicated synergism between colistin and vancomycin with OXA-23 and OXA-24 positive strains (FICI of 0.5 and 0.25, respectively) but not with OXA-58 and OXA-143 (FICI of 1). Two well method revealed the growth of all strains at 0.25 x MIC of colistin alone but absence of growth when the strains were exposed to 2 x MIC of colistin alone and 0.25 x MIC and 2 x MIC of colistin combined with either vancomycin or meropenem confirming synergy with both drugs against all tested strains.

Colistin alone produced rapid bacterial killing with $1.5 \log_{10}$ (OXA-23, OXA-24) to $2 \log_{10}$ (OXA-58, OXA-143) reduction in bacterial counts after 1 h exposure. However, after initial killing no further reduction in CFU was noticed after first hour. Colistin combined with vancomycin demonstrated rapid bacterial killing with less than $1 \log_{10}$ (OXA-23, OXA-24) or no detectable bacterial counts (OXA-58, OXA-143) after 1 h exposure and with no regrowth within 24 h. Colistin combined with meropenem exerted reduction of 3 to $4 \log_{10}$ reduction of viable cells in all strains with no significant regrowth except in OXA-23 positive strain. Colistin alone exhibited negative with (OXA-143), short (0.3-1.1 h) (OXA-24 and OXA-58) or moderate (3.2 h) PAE (OXA-23). When combined with vancomycin the PAE was moderate (1.7-3.5 h) (OXA-23 and OXA-24) while with OXA-58 and OXA-143 positive strains it was not possible to calculate PAE due to no regrowth after exposure to antibiotics.

Conclusions

The duration of PAE in this study was strain dependent and the longest with OXA-23 producing organism. Combining of colistin with other antimicrobials can further prolong the PAE which could have a therapeutic significance.