Predicting effective antimicrobial combination treatment in vivo with microcalorimetry screening

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The worldwide emergence of antibiotic resistance calls for effective exploitation of existing antibiotics. Antibiotic combinations with different modes of action can synergize for successful treatment. In the present study, we used microcalorimetry screening to identify synergistic combination treatments against clinical MDR isolates. The synergistic effects were validated in a murine infection model.

The synergy of meropenem combined with colistin, rifampicin or amikacin was tested on 12 isolates (1 Escherichia coli, 5 Klebsiella pneumoniae, 3 Pseudomonas aeruginosa and 3 Acinetobacter baumannii) in an isothermal microcalorimeter measuring metabolic activity. One A. baumannii strain was tested with two individual pairings of antibiotic combinations. The microcalorimetric data were used to predict in vivo efficacy in a murine peritonitis/sepsis model. NMRI mice were inoculated intraperitoneally and after 1 h treated with saline, drug X, drug Y or X+Y. Bacterial load was determined by cfu in peritoneal fluid and blood after 4 h.

In vitro, of the 13 combinations tested on the 12 strains, 3 of them exhibited a synergistic reduction in MIC (23% n = 3/13), 5 showed an additive effect (38.5% n = 5/13) and 5 had indifferent or antagonistic effects (38.5% n = 5/13). There was a significant correlation (P = 0.024) between microcalorimetry-screening FIC index values and the log reduction in peritoneal fluid from mice that underwent combination treatment compared with the most effective mono treatment. No such correlation could be found between chequerboard and in vivo results (P = 0.16).

These data support microcalorimetic metabolic readout to predict additive or synergistic effects of combination treatment of MDR infections within hours.

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