27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: P030 Colistin resistance: detection, mechanisms and synergy

**Category: 3c. Susceptibility testing methods**

23 April 2017, 13:30 - 14:30
P0654

## Polymyxin B-based combinations against multidrug-resistant Gram-negative bacteria

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**Background:** In last years, the increase of infections by multidrug resistant (MDR) gram - bacteria has limited the therapeutic options and increase the mortality of these infections. In search of more effective chemotherapeutic approaches, combination therapy is often employed with the expectation to increase antibacterial activity. Polymyxin B is an old antibiotic which retains in vitro activity against MDR gram – bacteria, albeit with some shortcomings such as toxicity and emergence of resistance. We therefore studied the in vitro combination of polymyxin B with 8 other antibiotics with different modes of action against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* MDR isolates.

**Material/methods:** Eighteen clinical isolates (4 *E. coli*, 5 *K. pneumoniae*,4 *P. aeruginosa* and 5 *A. baumannii*) with different resistance mechanisms (including KPC, VIM, CTXM, OXA, TEM, SHV, AmpC) were tested against polymyxin B alone and in combination with drugs targeting cell wall (temocillin, meropenem, fosfomycin), DNA (ciprofloxacin), RNA (rifampicin) and protein (amikacin, chloramphenicol, minocycline) synthesis. Two-fold serial dilutions of each drug were combined in 96 U-shaped microtitration plates in Mueller Hinton broth according to the ISO standard. For fosfomycin, medium was supplemented with glucose-6P. Plates were incubated for 18h and optical density was read at 630nm. The MIC of drugs alone and combination was determined as the lowest drug concentrations with <10% growth and interactions were assessed with the Fractional Inhibitory Concentration index (FICi). Combinations with FICi ≤0.5, 0.5-1, 1-4, ≥4 were classified as synergistic, additive, indifferent and antagonistic, respectively.

**Results:** The median (range) polymyxin B MICs were 2(1-64) mg/l for all isolates. Synergistic interactions were found for all combinations and some strains (6-33%) with highest frequency observed with rifampicin (33%) with median (range) FICi 0.3 (0.25-0.5), chloramphenicol (27%) with median (range) FICi 0.38 (0.25-0.5), and minocycline (17%) with median (range) FICi 0.15 (0.14-0.5). Most of the remaining combinations were additive (33-55%) most frequently observed with rifampicin (56%), amikacin (56%) and temocillin (50%). Overall, among all combinations additive/synergistic interactions were found for 61% (39-89)% of the isolates (mainly *A. baumannii* followed by *K. pneumoniae* and *E. coli* isolates) reducing polymyxin B MICs to 1 (0.125-4) mg/l. No antagonism was found.

**Conclusions:** Polymyxin B based combinations were additive to synergistic against MDR bacteria reducing the MIC of polymyxin B by 1-2 twofold dilutions. These results indicate a potential of clinically relevant increase in efficacy and reduction of toxicity by using polymyxin B combinations.