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Antimicrobials: In vitro antibacterial susceptibility and drug interaction studies

The detection of synergy of colistin combinations against Gram-negative bacterial pathogens using an E-test methodology

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Objectives: Infections due to multi-drug resistant (MDR) pathogens have become a therapeutic challenge. As few new antibacterial agents being evaluated, the potential synergy of presently available drugs exhibits increasing interest. The objective of this study was to detect the possible synergistic activity of the unconventional combination of colistin with daptomycin against Gram negative type strains and MDR clinical isolates. We studied also the potential synergy of colistin plus meropenem versus MDR *Klepsiella pneumoniae* strains.
Methods: Thirty one clinical isolates, resistant not only to carbapenems but to most other antimicrobial classes, were tested. Specifically, 11 *Acinetobacter baumannii*, 10 *Pseudomonas aeruginosa* and 10 *K. pneumoniae* strains as well as respective antibiotic susceptible type strains, were selected to evaluate the colistin/daptomycin synergy. The *K. pneumoniae* clinical isolates were also used to study the synergistic activity between colistin and meropenem. Identification and susceptibility testing were performed using the Vitek 2 system (bioMerieux, France). MICs of colistin, meropenem and daptomycin were determined by E-test (AB Biodisk), according to CLSI and EUCAST breakpoints. Synergy testing was performed in triplicate by an E-test MIC/MIC ratio method. The fractional inhibitory concentration index (FICI) was calculated: synergy <= 0.5, indifference >0.5-4 and antagonism >4. Boronic acid and EDTA test methodologies were used for detecting *K. pneumoniae* isolates producing KPC or MBL casbapenemases, respectively.
Results: All isolates had a daptomycin MIC >256 μg/mL, as expected. The MIC range of colistin was 0.047-128, 0.5-1 and 0.047-64 μg/mL for *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* isolates, respectively. All *K. pneumoniae* clinical strains were meropenem resistant (MICs 8->32 μg/mL) by producing KPC (50%) and MBL (50%) carbapenemases. The distribution of the results of the synergy testing is shown in the following table:

		SYNERGY n, %, FICI range	INDIFFERENCE n, %, FICI range	ANTAGONISM n, %, FICI range
Colistin/ daptomycin	*A. baumannii* (n=13)	3, 23, 0.1-0.5	10, 77, 0.9-2	–
	P. aeruginosa (n=11)	–	5, 63, 2-4	3, 37, 5
	K. pneumoniae (n=11)	1, 9, 1	10, 91, 1.2-3.7	–
Colistin/ meropenem	*K. pneumoniae* (n=10)	10, 100, 0.1-0.5	–	–

Additionally, considering the colistin/daptomycin combination, all *A. baumannii* isolates demonstrated a reduction in the MIC of colistin, while in 5 strains the MIC of daptomycin was decreased down to the level of 16 μg/mL. The colistin/meropenem combination, was able to remarkably reduce the MIC of meropenem in all *K. pneumoniae* isolates to less than the susceptibility breakpoint for 2 strains.
Conclusions: Regimens containing daptomycin may confer therapeutic benefit for treating infections due to MDR *A. baumannii* strains. More extensive work with far more isolates is needed to confirm this impression as well as to investigate whether the in vitro synergy translates into in vivo effectiveness.