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ePoster Session
Update on colistin PK/PD

Efficacy of colistin, alone and in combination with rifampicin, in a murine sepsis model due to carbapenemase-producing Klebsiella pneumoniae clinical strains

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Background: Treatment of severe infections caused by carbapenemase-producing *Klebsiella pneumoniae* (CPKp) is very complicated because these organisms very often present resistance to other families of antimicrobial agents, and combined therapy is frequently used. This approach seems to be associated with a lower mortality. The purpose of this study was to evaluate the *in vivo* activity of colistin (COL) alone and in combination with rifampicin (RIF) against four clinical isolates of CPKp, in a murine sepsis model.

Material/methods: Four clonally unrelated clinical isolates of CPKp, producing VIM-1, VIM-1+DHA-1(acquired AmpC β-lactamase), OXA-48+CTX-M-15 (extended spectrum β-lactamase) and KPC-3, respectively, were evaluated. Immunocompetent C57BL/6 female mice were used for the animal model. Pharmacokinetic/pharmacodynamic (PK/PD) parameters of RIF and COL were calculated (HPLC-MS/MS). The Bacteria Minimal Lethal Dose (DML) was characterized for each of the 4 strains. A murine sepsis model was used to carry out the efficacy studies. Groups of 15 infected animals were randomly assigned to the following treatment groups (3 days): Control (untreated), RIF (25 mg/kg/6h intraperitoneally [ip]); COL (20 mg/kg/8h, ip); and RIF+COL. All treatments were initiated 4 hours post-

inoculation. Bacterial counts in spleen, bacteraemia and mortality were analysed (ANOVA, post-hoc tests, and chi-square test); a $p < 0.05$ was considered significant.

Results: PK parameters of RIF and COL, respectively, were: Cmax (mg/L), 72.58 and 2.87; AUC_{0-24} (mg*h/L), 1103.58 and 14.41; $T_{1/2}$ (h), 19.33 and 1.1. PD parameters were: RIF (VIM-1, VIM-1+DHA-1, OXA-48+CTX-M-15 and KPC-3): AUC_{0-24}/MIC: 34.5, 8.60, 34.5 and 17.2, respectively; COL (VIM-1, VIM-1+DHA-1, OXA-48+CTX-M-15 and KPC-3): $fAUC_{0-24}$/MIC: 9.4, <0.15, 9.4 and 0.15. Bacterial counts in spleen of mice infected with VIM-1- and OXA-48+CTX-M-15-producing strains and treated with RIF alone were lower than controls, and the RIF+COL combination was better than controls and COL alone in mice infected with these CPKp, and better than the controls in those infected with the KPC-3-producing strain. The RIF+COL combination decreased the bacteraemia compared to controls monotherapies in mice infected with the VIM-1 producer. Finally, the mortality was lower in the RIF+COL group than in controls in mice infected with the KPC-3 producer, and than COL alone in those infected with OXA-48+CTX-M-15 and KPC-3 producers (Table 1). No treatment was effective in relation to bacterial count, bacteraemia and mortality for the mice infected with the VIM-1+DHA-1 producer.

Conclusions: The combination RIF+COL is effective in the bacterial clearance in spleen, and moderately in decreasing mortality and bacteraemia in systemic experimental infection by VIM-1-, OXA-48+CTX-M-15- and KPC-3- CPKp clinical isolates. No treatment was effective against the infection caused by the VIM-1+DHA-producing isolate.

Table 1: Therapeutic efficacy of rifampicin (RIF), colistin (COL) and the combination RIF+COL against four carbapenemase-producing *K. pneumoniae* clinical strains.

	VIM-1				VIM-1+DHA-1			
	Control	**RIF 100 mg/kg**	**COL 60 mg/kg**	**RIF+COL**	**Control**	**RIF 100 mg/kg**	**COL 60 mg/kg**	**RIF+COL**
Spleens Log CUF/g (Mean ± SD)	8.92 ± 0.46	**7.14 ± 0.48**[a]	8.60 ± 0.30	**6.01 ± 1.77**[a]	9.46 ± 0.32	9.68 ± 0.09	9.54 ± 0.34	7.64 ± 3.02
Bacteremia (%)	100 (9/9)	100 (8/8)	100 (15/15)	**53.33 (8/15)**[b]	100 (10/10)	100 (8/8)	100 (6/6)	**73.33 (11/15)**[b]
Mortality (%)	100 (9/9)	100 (8/8)	93.33 (14/15)	93.33 (14/15)	100 (10/10)	100 (8/8)	100(6/6)	73.33 (11/15)
	OXA-48+CTX-M-15				**KPC-3**			
	Control	**RIF 100 mg/kg**	**COL 60 mg/kg**	**RIF+COL**	**Control**	**RIF 100 mg/kg**	**COL 60 mg/kg**	**RIF+COL**
Spleens Log CUF/g (Mean ± SD)	9.56 ± 0.47	**8.24 ± 0.76**[a]	9.52 ± 0.55	**7.06 ± 2.50**[a]	10.19 ± 0.29	7.20 ± 2.96	9.19 ± 1.85	**6.76 ± 2.48**[d]
Bacteremia (%)	100 (10/10)	100 (10/10)	100 (15/15)	87.67 (13/15)	100 (10/10)	88.88 (8/9)	100 (8/8)	77 (13/15)
Mortality (%)	100 (10/10)	100 (10/10)	100 (15/15)	**73.33 (11/15)**[c]	100 (10/10)	**66.67 (6/9)**[d]	**75 (6/8)**[c]	**40 (6/15)**[d]

[a]: $p \leq 0.02$ compared with the control and the colistin groups.
[b]: $p < 0.05$ compared with the control, the rifampicin and the colistin groups.
[c]: $p \leq 0.03$ compared with the colistin group.
[d]: $p \leq 0.05$ compared with the control group.