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O0730 In vitro pharmacodynamics of fosfomycin-based combinations against clinical isolates of carbapenem-resistant Klebsiella pneumoniae and Enterobacter species

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Background: The lack of new antibiotics against carbapenem-resistant Enterobacteriaceae (CRE) infections has led to renewed interest in “old” antibiotic fosfomycin for systemic CRE infections. However, heteroresistance and emergence of resistance against fosfomycin had been observed *in vitro*. This study aimed to evaluate the *in vitro* pharmacodynamics of fosfomycin-based combinations against CRKP and CRENT.

Materials/methods: Time-kill studies (TKS) were performed with 10 well-characterised CRKP and CRENT (3 *E. cloacae* and 2 *E. aerogenes*) (Figure 1). These isolates harboured various carbapenemases such as OXA-181, KPC-2 and NDM; with porin loss and/or efflux up-regulation. 24h TKS were conducted with 10^5 CFU/mL at baseline with clinical achievable concentrations (mg/L) of amikacin (65), aztreonam (24), levofloxacin (8), cefepime (50), polymyxin B (2), rifampicin (4), tigecycline (2), ertapenem (15), imipenem (12.5), meropenem (20), doripenem (26), piperacillin-tazobactam (35/7) singly and in combination with fosfomycin (160), in the presence of glucose-6-phosphate (25).

Results: All isolates demonstrated regrowth against fosfomycin alone at 24h, including isolates that are susceptible to fosfomycin (KP1, ENT2 – ENT5). Against CRKP, fosfomycin + polymyxin B were bactericidal against 3/5 isolates (KP1, KP2, KP3) and fosfomycin + doripenem, imipenem or meropenem were bactericidal against 4/5 isolates (KP1, KP2, KP3, KP5). Fosfomycin + tigecycline was the only bactericidal combination against all CRKP isolates. Fosfomycin in combination with multiple different antibiotics were bactericidal against all CRENT except against ENT1. We observed a higher frequency of combinations that were bactericidal in isolates with fosfomycin MICs ≤16mg/L. No correlation was observed between the frequency of combinations that were bactericidal and types of resistance mechanisms.

Conclusions: Fosfomycin monotherapy was associated with regrowth in CREs, including those with low fosfomycin MICs. While bactericidal fosfomycin-based combinations differ between and within bacterial species, most fosfomycin-based combinations appeared to be effective against CREs with fosfomycin MICs ≤16mg/L. Further investigations with a hollow-fibre infection model should be carried out to evaluate possible emergence of resistance with fosfomycin-based antibiotic combinations in CREs with low fosfomycin MICs.

Figure 1. Antimicrobial drug susceptibilities and resistance mechanisms of the ten CRE isolates

Isolate	Resistance Mechanisms		MIC (mg/L)											
	Carbapenemases	Others	IPM	MEM	DOR	ETP	AMK	T2P	FEP	ATM	LVX	PMB	TGC	FOF
KP1	NDM-1	fosA, SHV-11, TEM, CTX-M-15, OXA-1, OXA-9, efflux pump	≥32	≥32	≥32	≥32	≥128	≥128/4	≥64	≥128	≥32	8	2	16
KP2	OXA-181	fosA, SHV-28, TEM-1C, CTX-M-15, CMY-4, OXA-1, OXA-9, efflux pump, porin loss	≥32	≥32	≥32	≥32	≥128	≥128/4	≥64	≥128	≥32	1	4	512
KP3	KPC-2	fosA, SHV, TEM, efflux pump	≥32	≥32	16	≥32	16	≥128/4	≥64	≥128	≥32	4	2	16
KP4	NDM-1, OXA-181	fosA, SHV, TEM-1B, CTX-M-15, CMY-4, porin loss	≥32	≥32	≥32	≥32	≥128	≥128/4	≥64	≥128	≥32	16	1	64
KP5	OXA-232	fosA, SHV, TEM	8	≥32	16	≥32	≥128	≥128/4	≥64	≥128	≥32	≥32	1	128
ENT1	NDM	fosA, SHV, TEM, CTX-M, porin loss	≥32	≥32	≥32	≥32	16	≥128	≥64	≥128	8	8	1	64
ENT2	KPC-2	SHV-12, TEM-1B, CTX-M-15, OXA-1, porin loss, efflux pump	≥32	≥32	16	≥32	8	≥128	≥64	≥128	4	8	2	4
ENT3	NDM-7	CTX-M-15, ACT-7, OXA-1, efflux pump	≥32	≥32	≥32	≥32	≥128	≥128	≥64	≥128	16	8	2	0.5
ENT4	KPC-2	TEM, CTX-M, porin loss	16	≥32	8	16	8	≥128	≥64	≥128	1	8	0.5	8
ENT5	NDM	fosA, TEM, CTX-M, efflux pump	≥32	≥32	≥32	≥32	≥128	≥128	≥64	≥128	≥32	0.5	2	16

KP = *K. pneumoniae* ; EC = *E. cloacae* ; IPM = imipenem; MEM = meropenem; DOR = doripenem; ETP = ertapenem; AMK = amikacin; T2P = piperacillin-tazobactam; FEP = cefepime; ATM = aztreonam; LVX = levofloxacin; PMB = polymyxin B; TGC = tigecycline; FOF = fosfomycin