Double-carbapenem therapy for systemic infections caused by carbapenemase-producing *Klebsiella pneumoniae*

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A. Oliva, M.T. Mascellino, A. Cipolla, F. Gizzi, A. D'Abramo M. Iannetta, C.M. Mastroianni, V. Vullo.
Sapienza University, Rome (IT). Department of Public Health and Infectious Diseases
E-mail: alessandra.oliva81@gmail.com

Background

Infections caused by carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) are associated with high mortality rate and limitations of therapeutic options.

Objective

Aim of the study was to evaluate the *in-vivo* and *in-vitro* activity of double carbapenem regimen in patients with systemic infections due to CP-Kp.

Methods

Over a 2-years period, subjects who underwent therapy with double-carbapenem regimen (ertapenem+ high dosage of meropenem) because of systemic infections due to CP-Kp at "Sapienza" University of Rome were included in the study. For each subject, clinical and demographic characteristics were collected. Strain identification and antimicrobial susceptibility testing were performed throughout VITEK-2. Carbapenemase production was phenotypically confirmed by modified Hodge test and double disk synergy with oxacillin, dipicolinic and boronic acid was used to identify the type of carbapenemase. Broth macrodilution method (BMD) was used to perform the minimal inhibitory concentrations (MICs) of ertapenem (ERT) and meropenem (MEM). Synergy was *in-vitro* investigated throughout checkerboard method and killing tests by evaluating the FIC Index (∑FIC: FICA + FICB= MICA+B/MICAalone + MICB+A/MICBalone) and the difference in CFU/mL compared to the growth control, respectively. Complete synergism was defined as FIC≤0.5, partial synergism as FIC>0.5<1, additivity as FIC≥1<2, antagonism as FIC≥2

Results

Table1. Characteristics of patients (n=10) treated with double carbapenem regimen (Ertapenem 1 gr/die plus Meropenem 2gr every 8h).

	Age, years (mean) /sex	Apache score III/Charls on Index	Type of infection	Mode of infection acquisition	Previous hospitalization or carbapenem therapy (within 12 months)	Clinical presentation	Duration of double carbapenem therapy (mean), days	Outcome
Pts (n=10)	61±12/ 7M,3F	31/3.8	Bloodstream infections (4/10, 40%); urinary tract infections (4/10, 40%); Pneumonia (1/10, 10%); cutaneous abscessus (1/10, 10%)	HA 6/10 (60%); HCA 4/10 (40%); CA 0/10 (0%)	8/10 (80%)	sepsis/severe sepsis/septic shock 6/10 (60%)	14±4	Clinical success 8/10 (80%); death 2/10 (20%)*

HA: Hospital-acquired; HCA: health-care associated; CA: community-acquired.
*: One patient died for CP-Kp sepsis; one patient died because of his comorbidity.

Table2. Microbiological analyses of CP-Kp strains (n=10) isolated from patients with systemic infection.

	Type of carbapenemase	ERT/MEM MICs (VITEK-2), □g/mL	ERT/MEM MICs (BMD), □g/mL	ERT+MEM Complete Synergy (checkerboard method), FIC INDEX <0.5	ERT+MEM Partial Synergy (checkerboard method), FIC INDEX 0.5-<1	ERT+MEM Additivity (checkerboard method), FIC INDEX >1-<2	ERT+MEM Antagonism (checkerboard method), FIC INDEX >2	ERT+MEM Synergy and bactericidal activity at 24h (killing study)
Strains (n=10)	KPC	>8/>16	128/128	3/10 (30%)	4/10 (40%)	3/10 (30%)	0/10 (0%)	6/10 (60%) MEM0.5x+ERT1x; 7/10 (70%) MEM 1x+ERT1x; 8/10 (80%) MEM 2x+ERT1x

Killing tests showed a synergistic and bactericidal activity at concentrations of ERT1x+MEM 0.5x, ERT 1xMIC+MEM 1xMIC and ERT 1xMIC+MEM 2xMIC.

Conclusions

A previous hospitalization and therapy containing carbapenem-based regimen are risk factors for infections due to CP-Kp. Double-carbapenem regimen could be a promising option in selected patients in whom other antimicrobials cannot be administered because of resistance or toxicity, even in the presence of severe infections (sepsis/severe sepsis/septic shock). Despite a high level of carbapenem resistance, the high dosage of MEM together with the action of ERT as a carbapenemase suicide inhibitor might explain the efficacy of this combination both *in-vitro* and *in-vivo*.

References

Oliva A, D'Abramo A, D'Agostino C, Iannetta M, Mascellino MT, Gallinelli C, Mastroianni CM, Vullo V. 2014. Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant Klebsiella pneumoniae bloodstream infections. J Antimicrob Chemother. 69(6):1718-2**0.**
Bulik CC, Nicolau DP. 2011. Double-carbapenem therapy for carbapenemase-producing Klebsiella pneumoniae. Antimicrob Agents Chemother. 55: 3002-4.
Giamarellou H, Galani L, Baziaka F, Karaiskos I. 2013. Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant Klebsiella pneumoniae. Antimicrob Agents Chemother. 57: 2388-90.
Oliva A, Mascellino MT, Cipolla A, D'Abramo A, De Rosa A, Savinelli S, Ciardi MR, Mastroianni CM, Vullo V. Therapeutic strategy for pandrug-resistant Klebsiella pneumoniae severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen. Int J Infect Dis. 2015 Apr;33:132-4.