

O0692 **Efficacy of fosfomycin in combination with colistin or meropenem in carbapenemase producing *Klebsiella pneumoniae* experimental osteomyelitis**

Azzam Saleh-Mghir¹, Aurélien Dinh*¹, William Mouton⁷, Marie-Clémence Verdier², Idir Ghout³, Pierre Tattevin⁴, Frederic Laurent⁵, Anne-Claude Crémieux⁶

¹UMR U1173 Inserm-Université Versailles St-Quentin-Hôpital Raymond Poincaré, Service de Maladies Infectieuses, Garches, France, ²Laboratoire de Pharmacologie Biologique, Hôpital Pontchaillou, CHU de Rennes, Rennes, France, ³URC Paris-Ouest, Laboratoire de Bio statistiques, Hôpital Ambroise Paré, BOULOGNE-BILLANCOURT, France, ⁴Hôpital Pontchaillou, CHU de Rennes, Service de Maladies Infectieuses et Réanimation Médicale, Rennes, France, ⁵Laboratoire de Bactériologie, Hôpital de la Croix Rousse, Centre National de Référence des Staphylocoques Unité Inserm 851, Faculté de Médecine Lyon Est, Lyon, France, ⁶Hôpital Saint Louis- Université Paris-Diderot, Paris, France, ⁷International Centre for Infectiology Research INSERM U1111 - CNRS UMR5308 - ENS Lyon - Lyon 1 University, Team "Staphylococcal pathogenesis", Lyon, France

Background: Optimal treatment of carbapenemase-producing *Klebsiella pneumoniae* osteomyelitis is poorly defined. We studied the efficacy of fosfomycin combined with colistin or meropenem *in vitro* and *in vivo* in a new experimental model of osteomyelitis.

Materials/methods: KPC-99YC is a clinical strain intermediate to meropenem (MIC 4 mg/L), susceptible to colistin (MIC 1 mg/L), and fosfomycin (MIC 32 mg/L). Time-kill curves were performed at 4 MICs. Plasma antibiotic concentrations were measured in uninfected rabbits, to select doses equivalent to those used in humans (H). An osteomyelitis was induced in rabbits by tibial injection of a sclerosing agent followed by 10⁹ CFU/mL (0.2 mL) of KPC-99YC. Treatment started 14 days after inoculation, for 7 days, in 4 groups of 12 rabbits: (1) control group, (2) colistin 150 000 IU/kg tid im (equivalent to 3 M IU tid in H), (3) fosfomycin (F) 150 mg/kg bid im (4 g tid in H) + colistin (4) fosfomycin + meropenem 80 mg/kg sc tid (1 g tid in H). Three days after the end of treatment, crushed bones were sampled to quantify residual bacterial concentrations. Colistin-resistant strains were checked on bone homogenates of colistin-treated animals.

Results: *In vitro*, colistin alone was rapidly bactericidal. However, regrowth occurred after 9 h. When fosfomycin was added to colistin, the bactericidal effect was complete with no regrowth. Meropenem alone was poorly bactericidal. The addition of fosfomycin to meropenem had an incomplete bactericidal effect, with a low residual viable inoculum up to 9 h. *In vivo*, rabbits treated with colistin alone were not different from controls with a median (IQR) bacterial count of 5.67 (4.96, 6.16) log₁₀ CFU/g of bone, and no sterile bone at D24. Colistin resistant strains emerged in one rabbit. Meropenem plus fosfomycin was not superior to controls (p=0.927). In contrast, in agreement with time-kill curves, colistin plus fosfomycin reduced bone bacterial density (p<0.001), and no colistin-resistant strain emerged.

Conclusions: *In vitro* and *in vivo*, the combination of fosfomycin plus colistin was the most effective treatment of KPC-producing *K. pneumoniae* complex infections.