Clinical features and outcomes of patients with polymyxin- and carbapenem-resistant Klebsiella pneumoniae infections treated with tigecycline or amikacin

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Background: The increasing rates of resistance to polymyxins in carbapenem-resistant Klebsiella pneumoniae (CR-KP) represent a serious threat to effective antimicrobial therapy. Amikacin and tigecycline have been among the few drugs showing in vitro activity against polymyxin- and CR-KP (PCR-KP). We aimed to evaluate clinical features and outcomes of patients treated with amikacin-, tigecycline- or both antimicrobials-containing schemes.

Material/methods: Patients hospitalized from January/2015 to March/2016 with a PCR-KP infection were included. Exclusion criteria were <18 years and death <48 hours from the infection onset. The primary outcome was clinical cure at day 15th from infection onset (CC15) defined by survivor status plus afibrile status ≥72 hours, normal leukocyte count, no vasoactive drug and no antimicrobial against Gram-negative.

Results: Thirty-one patients were included: 14 (45%) female, mean age=57±17 years; median Charlson score= 2 (IQR= 0-4); median baseline creatinine clearance= 80ml/min (IQR= 29-125); 6 (19%) were intensive care unit patients. Twenty-nine (94%) were infected by KPC-producing PCR-KP (polymyxin B [PMB] MIC
time >90%= 16/32mg/L, range= 4-128mg/L). The most common sites of infections were urinary tract (12), intra-abdominal (7), lung (6), central venous catheter (4), primary bloodstream (2) and skin/soft tissue (1); 9 (29%) presented bacteremia. Eighteen (58%) fulfilled CC15 criteria; 14-,
30-, and in-hospital mortality rates were: 10% (3), 19% (6) and 42% (13). All but two patients had a KPC-producing polymyxin-susceptible CR-KP recovered before infection and 6 (19%) were previously colonized by a KPC-producing PCR-KP; 11 (35%) were treated with PMB 30 days before PCR-KP infection. Twenty-seven (87%) were treated with an amikacin-containing scheme (all but two isolates were susceptible / CLSI breakpoint) and 18 (58%) with a tigecycline-containing one (MIC$_{50-90}$ = 1/2mg/L; one with MIC=16mg/L); 14 (45%) received both; 20 (65%) received PMB and 23 (74%) meropenem (all MICs ≥32mg/L) in their schemes. No significant association was found between any treatment scheme and CC15. The median from infection onset to the beginning of amikacin and tigecycline was 3 (IQR, 0-4) and 3 (1-6), respectively. Thirteen (68%) of 19 patients treated with tigecycline-containing schemes were treated with double-dose regime. The mean dose of amikacin was 15.6±6.0 mg/kg/day. Excluding urinary tract infections, CC15 was 47% (9/19). Eighteen had a same site culture collected after therapy, PCR-KP was recovered in 9 (50%): 5 (56%) from urine. The number of patients precludes a multivariate analysis. Bias of indications cannot be excluded.

**Conclusions:** Using strict criteria for clinical cure, in this small cohort of mostly mild PCR-KP infections, CC15 was just above 50% and was less than a half when urinary tract infections were excluded. In-hospital mortality was high, possibly indicating the severity of patients infected by these isolates.