**Effectivity of a double-carbapenem regimen for the treatment of a KPC-producing Klebsiella pneumoniae infection in an immunocompromised patient.**

**Background**

In recent years, the number of infections due to carbapenemase-producing Enterobacteriaceae, especially KPC Klebsiella pneumoniae, has been extensively reported. Within the carbapenemase family are the most clinically significant carbapenemases: the KPC, VIM and IMP. These enzymes are associated with increasing resistance to almost all classes of antibiotics, posing a significant public health concern. Carbapenemase-producing K. pneumoniae (CPKP) is associated with a high mortality rate (30-50%), and optimal regimens are not yet well defined. CPKP frequently co-express additional resistance determinants that confer resistance to several antibiotic families other than beta-lactams. This situation represents an important threat to public health since therapeutic options against these infections are limited. Combined therapy with more than one antibiotic is recommended nowadays according to retrospective studies. Recently, double-carbapenem regimens have been suggested and used as an alternative to treat extensively drug-resistant CPKP. However, results limited evidence of the effectiveness of simultaneous administration of two carbapenems to treat CPKP infections among immunocompromised patients.

**Microbiological methods**

**Microbiological results**

**Case History**

A 35-year-old Spanish woman with acute myeloid leukemia diagnosed four months ago (myeloid sarcoma form: neutropenic, ovarian and uterine location), was admitted in August 2015 to receive an allo-HCT (unrelated donor), after conditioning chemotherapy regimen. Previously, she had received anti-infective prophylaxis with fluoroacetic, azithromycin and amphotericin B and immunosuppressive therapy (IT) with tacrolimus. In this admission, she presented a neutropenic colitis (absolute neutrophil count, ANC, was 0 cell/mc/c) the same day that progenitor cell infusion was performed.

The patient was treated with piperacillin/tazobactam empirically and teicoplanin due to a previous Enterobacteriaceae bloodstream infection. Bacterial cultures were negative at the time and she did not receive any more antibiotics for the moment. On post-allo-HCT day 6, she remained febrile and showed diarrhea. Blood cultures done on that day remained negative, whereas in the urine culture grew a Carbapenemase-producing K. pneumoniae (CPKP) (>100,000 cfu per ml) which was resistant to imipenem and susceptible to gentamicin and colistin (table 1 and 2).

Despite the susceptibility to aminoglycosides, she was not evaluated initially at the urine isolation, piperacillin-tazobactam was empirically replaced by these antibiotics. Twenty-four hours later, the patient persisted febrile with chills and hypotension (no vasopressor and inotropic support was needed). ANC remained at 0 cell/mm3, creatinine was 0.54mg/dl and C-reactive protein was 13.5mg/ml. At this moment, in the blood culture grew the same CPKP now is growing in a renal screening but not at central venous catheter cultures.

**Clinical progression**

This patient was considered to be at a high risk of potential antibiotic-induced nephrotoxicity (thrombocytopenia, neutropenia, early allo-HCT and use of other nephrotoxic drugs), so colistin was avoided, due to a lack of alternative regimens, and on the basis of synergy studies and on previous successful experiences by other authors, double-carbapenem regimen with imipenem and meropenem was started. Carbapenem dosage and positioning was chosen in consensus with previous experiences based on selecting P/F/T/R features: ertapenem (1 g every 24h) was followed one hour later by high dose of meropenem (2 g every 8h, in 3h extended infusion). This regimen was given during 14 days, in the absence of adverse effects. The patient became afebrile in less than 48h and urine cultures and blood cultures underwent negative. The patient achieved clinical and microbiological success and was discharged 2 weeks later.

**In vitro synergy testing**

**In vivo synergy testing**

**Conclusions**

Carbapenemase-producing K. pneumoniae bloodstream infections generally have a poor outcome, with a high mortality in immunocompromised patients and high treatment failure rates. We describe a case of a neutropenic patient who developed a carbapenemase-producing K. pneumoniae bloodstream infections immediately after allo-HCT. Taking into account the in vitro synergy effect of two carbapenems combination, the patient was treated simultaneously with ertapenem and meropenem, achieving clinical and microbiologic success. To our knowledge, this is the first reported case of the successful use of a double-carbapenem regimen in a neutropenic patient. The double-carbapenem regimen could be an effective strategy with little toxicity, especially useful when only nephrotic drugs are available. The treatment of these infections should be individualized, a process in which the collaboration with the Microbiology Laboratory is essential to evaluate therapeutic alternatives.