Clinical efficacy of intravenous colistin therapy in combination with ceftazidime in severe MDR P. aeruginosa systemic infections in two haematological patients

**Efficacia clinica della combinazione colistina più ceftazidime nelle infezioni gravi da P. aeruginosa multiresistente in due pazienti ematologici**

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**INTRODUCTION**

Colistin (polymyxin E) is a polypeptide antibiotic discovered in 1949, active against most Gram-negative aerobic bacteria. It is active against *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, *Enterobacter* spp, *Klebsiella* spp, *Citrobacter* spp but not against *Burkholderia cepacia*, *Proteus* spp and *Providencia* spp. Colistin is considered bactericidal in a concentration-dependent mode although this activity has not always been demonstrated [1, 2]. In the past its use was restricted to topical formulation by the high incidence of nephrotoxicity when given intravenously [3, 4]. In the last few decades it has been used systemically or by aerosol only for lung infections in patients with cystic fibrosis [5, 6]. The emergence of bacteria resistant to most classes of commercially available antibiotics and the shortage of new antimicrobial agents active against gram negative bacteria have led to a reconsideration of colistin [1]. Colistin has been used once again especially in intensive care units where gram-negative bacterial infections are more frequent [7-9].

In recent years we have observed an increased incidence of multi-drug resistant *P. aeruginosa* infections among patients admitted to the Ospedale Unico della Versilia, Viareggio, (LU) Italy, especially to the Haematologic Unit. The use of colistin in haematological patients is rarely described and it is generally used for oral selective intestinal decontamination; frequent renal impairment due to chemotherapy and other toxic drugs is cause for concern in these patients when treated intravenously with drugs considered particularly toxic such as colistin [10]. Several reports during the early years of use of this medication, mainly in the 1960s, left the medical community with the impression that the medication is very toxic.

The present study describes a retrospective analysis of colistin use in two haematological patients with systemic, severe infections by multi-resistant strains of *P. aeruginosa*. The study was designed to assess the effectiveness and safety of colistin.

**CLINICAL REPORTS**

PATIENT 1. A 64-year-old male patient was admitted in October 2004 to the Ospedale Unico della Versilia for febrile neutropenia a week after a chemotherapy cycle (FLAI) for acute myeloid leukaemia. Twelve years before admission a non-Hodgkin lymphoma of the
lumbar spine was diagnosed and treated with radiotherapy and chemotherapy (CHOP) for 6 cycles. One year before admission the patient underwent colon resection for stenosis due probably to the previous radiotherapy. The surgery was complicated by peritonitis due to *Pseudomonas aeruginosa* and the patient was treated with piperacillin/tazobactam for two months. Six months before admission pancytopenia developed. The patient was therefore subjected to BOM which demonstrated AREB myelodysplasia.

One month before admission a myeloid acute leukaemia (LAM-M0) was diagnosed; cytogenetic study of the bone marrow demonstrated translocation of chromosome 17 with chromosome 21.

Seven days before admission a chemotherapy cycle with fludarabine, cytarabine, and idarubicin was administered. The day of admission after the collection of blood cultures, an empiric antibiotic therapy with imipenem (3 g per day), vancomycin (2 g per day) and voriconazole (400 mg per day after a loading dose) was started due to severe neutropenia (100 neutrophils per µl). Several blood cultures were positive for an ESBL producing strain of *E. coli* but fever was still present. After a few days vancomycin-resistant *E. faecium* septicaemia was demonstrated and vancomycin replaced with linezolid 1200 mg per day orally and voriconazole stopped. After 5 days a zoster of the ophthalmic branch of the left trigeminus nerve developed and acyclovir therapy was started (30 mg/kg per day intravenously). Leucopenia with profound and prolonged neutropenia was still present after 21 days of this therapy when a spontaneous acute painful arthritis of the left knee developed. The specimen obtained from the knee arthrocentesis grew MDR *P. aeruginosa* susceptible only to colistin and intermediate to ceftazidime, cefepime and piperacillin/tazobactam.

The patient was treated for 45 days with colistin intravenous 1 million IU every 12 hours plus ceftazidime 3 g intravenous every 8 hours. Imipenem and linezolid were stopped. The clinical condition improved with complete remission of the arthritis. The creatinine level at the beginning of colistin therapy was 0.9 mg/dl, the highest level reached during therapy was 1.3 mg/dl and at the end of therapy a level of 0.8 mg/dl was found. No other adverse event was demonstrated. Neutropenia stopped 10 days after the end of colistin therapy and after another 10 days the patient was discharged from hospital without fever.

**PATIENT 2.** A 65-year-old female patient was admitted in February 2005 to the Ospedale Unico della Versilia for severe anaemia and leucopenia. Seven years before admission Horton’s arteritis was diagnosed and treated with steroids. One year before admission a right pneumonia was found and treated at home with antibiotic therapy for ten days. A BOM revealed an acute lymphoblastic leukaemia (Philadelphia +). Chemotherapy with the scheme called Hyper-CVAD was started. Seven days after this therapy, during profound neutropenia (neutrophils: 60/µl) the patient developed nausea, vomit, abdominal pain and fever. An abdomen sonography was able to demonstrate a thickening of the colon and small intestine wall (11 mm); hence a diagnosis of typhlitis was made [11]. Empirically a therapy with ceftazidime (3 g every 8 hours intravenously), vancomycin (2 g per day) and fluconazole (400 mg per day intravenously) was given. The day after a blood culture proved positive for *P. aeruginosa*, susceptible only to colistin and ceftazidime and intermediate to aztreonam, cefepime and piperacillin/tazobactam. Due to the persistence of fever after three days, colistin was administered intravenously 1 million UI every 12 hours, vancomycin was stopped. After two days a complete defervescence was obtained and abdomen symptoms disappeared. This therapy was administered for 12 days when the fever re-started associated with deterioration of renal function (creatinine 2 mg/dl) without the presence of cylinders at urine analysis. Empirically aztreonam and caspofungin was started instead of ceftazidime, colistin and fluconazole. The renal function returned normal, the fever disappeared but after three days the patient died of cardiac arrest. Autopsy was not performed.

**DISCUSSION**

There are few experimental and clinical studies in the literature regarding the synergistic activity of colistin with other antimicrobial agents against MDR gram-negative bacteria [1]. The combinations of colistin with other an-
tipseudomonal agents against MDR P. aeruginosa were more effective than colistin alone in 53 patients with cystic fibrosis and with exacerbation of chronic pulmonary infections [5]. Kasiakou et al. used colistin intravenously to treat fifty patients with 54 episodes due to MDR gram-negative rod infections due to A. baumannii (51.9%), P. aeruginosa (42.6%) and K. pneumoniae (3.7%) with a clinical response of 66% and deterioration of renal failure of 8%.

Our data regarding two haematological patients with difficult-to-treat infections are in agreement with the above results [8]. Our previous experience demonstrated that a colistin/rifampin combination had synergistic bactericidal activity against MDR P. aeruginosa strains in 4 patients. Furthermore the combination was effective also from a clinical point of view in the 4 patients studied [2]. In this setting the colistin/ceftazidime combination was synergistic from a clinical point of view, obtaining a clinical response in two severe systemic infections in patients with reduced host defence. Indeed, patients with leukaemia and undergoing chemotherapy have infections that are very difficult to treat for several reasons: I) neutropenia, II) reduction in immunoglobulin level, III) reduction in cellular immunity, IV) drug toxicity.

The most common adverse effects of colistin therapy are nephrotoxicity and neurotoxicity, renal toxicity mainly includes acute tubular necrosis that might be demonstrated by the presence of showing cylinders in urinary sediment. In these two leukaemic patients, we used colistin for 45 and 12 days intravenously. Only in the second patient did we observe a reversible deterioration of renal function but without the presence of cylinders at the urine examination.

Colistin in the form of colistimethate sodium (also called colistin methansulphonate) for intramuscular use is a drug already present in Italian formulary. When we opted to start therapy with colistin, intravenous use was chosen in order to avoid the reduction of drug concentration especially in patients with a low platelets count like leukaemics where intramuscular injection is not indicated. Therefore the off-label use of the drug was explained to the patient who was asked for oral informed consent, since the same molecule used for the intramuscular injection, colistimethate sodium, is also the form usually administered for intravenous use. Because the drug was already present in the Italian formulary no permission was sought from the Ethical Committee.

In leukaemic patients, prospective studies on the therapeutic use of intravenous colistin for difficult-to-treat severe gram-negative infections are warranted.

Key Words: Colistin, P. aeruginosa, systemic infection, haematological patients

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**SUMMARY**

Nosocomial infections due to MDR P. aeruginosa are an increasing problem. Therapeutical options are few. We describe two haematological patients with severe neutropenia and systemic infection due to MDR P. aeruginosa treated successfully with colistin plus ceftazidime. Severe adverse events were not described.

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**RIASSUNTO**

Le infezioni nosocomiali gravi causate da P. aeruginosa multiresistente sono sempre più frequenti. Le opzioni terapeutiche sono sempre più limitate. Gli autori descrivono due casi di infezioni gravi da P. aeruginosa MDR in pazienti ematologici con profonda neutropenia, trattati con colistina endovenosa più ceftazidime con risoluzione del quadro clinico. Non sono stati osservati gravi effetti collaterali.
REFERENCES