Case Report

DOI: 10.7860/JCDR/2016/17544.7697

Microbiology Section

Antibiotic Adjuvant Therapy for Multi-Drug Resistant Carbapenemases Producing *Klebsiella pneumoniae* Associated Sepsis: A Case Study

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ABSTRACT

Rising resistance and spread of *K. pneumoniae* strains, create great concerns in treating sepsis patients due to high incidence of mortality and morbidity. The current study is a case of a 20-year-old male with sepsis and bilateral lung lesions infected with Multi-Drug Resistant (MDR) carbapenemase producing *K. pneumoniae* (KPC) showing resistance to carbapenem and polymyxin. Based on sensitivity report, patient was put on antibiotic adjuvant: Elores (ceftriaxone, sulbactam, disodium edetate) along with fluconazole for 10 days. Elores was instituted with remarkable recovery and patient was discharged.

Keywords: Elores, Enterobacteriaceae, ESBL, MBL

CASE REPORT

A 20-year-old male patient who was infected by KPC-producing *K. pneumoniae* was transferred to the Emergency Department of Government Medical College and Hospital, Chandigarh from a private hospital (Chandigarh), with chief complaints of fever and cough since one month. Patient had taken treatment of second generation cephalosporins and aminoglycosides from private clinics but did not respond well which further deteriorated his condition and progressed to sepsis. Patient was on initial treatment of meropenem and teicoplanin when admitted to emergency Department of Government Medical College and Hospital, Chandigarh, but there were no signs of improvement even after 7 days of treatment.

Overall condition of the patient was poor with hypo-tension, hypothermia, tachycardia, tachypnea, leucocytosis and anaemia. Vital signs were, blood pressure-70/40mmHg, pulse-116bpm, Respiratory rate- 22 breaths per min, temperature-36.4ºC. Laboratory reports revealed total leukocyte count of 430000/mm, haemoglobin 11.1g/dl and haematocrit 34.8%. Patients C-reactive protein level was deranged to 70mg/l and procalcitonin level were up to 10ug/l. Based on clinical presentation and laboratory reports patient was diagnosed as sepsis and immediately transferred to intensive care unit and resuscitated. Blood sample was taken for routine Investigations, culture and sensitivity. Chest X ray was advised and revealed bilateral cavitation in both lungs. Patient was put on colistin with fluconazole and linezolid but did not respond to the therapy. Laboratory culture and sensitivity reports revealed MDR *K. pneumoniae* with resistance to carbapenems, colistin and sensitivity to Elores. Thus initial antibiotic therapy was stopped and patient was put on Elores 3g b.i.d dose with fluconazole for 10 day along with other supportive therapy. Patient's condition improved gradually. Repeat laboratory test revealed normalized leukocyte count with reduced CRP (8mg/l) and procalcitonin levels (<0.25ug/l). Patient was haemodynamically stable and shifted to medicine ward for further monitoring and treatment. Patient was put on oral antibiotics and discharged on 17th day post admission with advice for regular follow-up.

DISCUSSION

Gram-negative bacteria have often been involved in the pathogenesis of sepsis [1]. Among Gram-negative pathogens, *Klebsiella pneumoniae* has increasingly been associated with hospital infections, especially in the Intensive Care Unit (ICU). Resistance of *K. pneumoniae* strains to broad-spectrum antibiotics, including carbapenems, is a matter of great concern [2]. The best therapeutic approach to KPC-producing organisms has yet to be defined as last resort of antibiotics like penem and colistin getting resistant to KPC. There are ongoing efforts to find out and try strategies which would improve outcome of this population [3].

Sepsis is an increasingly common cause of morbidity and mortality in critically ill patients. Despite advancement in surgical and critical care management, the projection of sepsis and subsequent multiple organ dysfunction has not improved mainly due to escalating resistance. Mortality rate among patients with severe sepsis and septic shock has been observed between 25% to 30% and 40% to 70% respectively, with increase in sepsis at an estimated annual rate of 1.5% [4]. Moreover, in a study from New Delhi, the ICU mortality with sepsis was reported 45.6% in young patients (< 60 years of age) [5]. *Klebsiella* species are common pathogens in ICUs, with infection of the lung, urinary tract and abdomen [6].

MDR, KPC producing *K. pneumoniae* due to inappropriate selection of antibiotic is a growing concern worldwide [3]. Carbapenems have been considered to be the last-line antimicrobial agents against MDR Gram-negative Bacteria, while recently increasing emergence of Carbapenemase-Producing Enterobacteriaceae (CPE) has been reported worldwide [7]. There are many carbapenemases involved in CPE isolates, in which carbapenemase producing *K. pneumoniae* plays a vital role in health care-associated infection [8]. In India, the prevalence of KPC producing *K. pneumoniae* is reported up to 33.3% [6].

Infections caused by KPCs have very limited options for treatment and often require the use of polymyxins, which fell into disuse in the 1970s due to high rates of nephrotoxicity [8]. An early diagnosis of sepsis followed by broad-spectrum antimicrobial therapies reduces mortality [9]. However, in the past few years, rising rates of treatment failure to such antimicrobial therapies caused the clinicians to see the alternative options to manage the current scenario.

In the present case patient was empirically put on meropenem and shifted to colistin, but did not responded to both the treatments.

Blood culture sensitivity test confirmed the presence of KPC producing *K. pneumoniae* which was resistant to both colistin and meropenem antibiotics but sensitivity to Elores. According to the susceptibility result, only Elores antibiotics could be used in this case. Patient was switched to Elores and the laboratory parameters improved from day 2 and recovered within 10 days of post Elores therapy.

In this case, patient was having bilateral lesions in the lung. During development of sepsis, bacteria damage lung epithelium and enter the bloodstream, inducing systemic inflammatory responses (for example, increased vascular permeability, leukocyte-endothelial adhesion, and activation of complement and clotting pathways) [2].

Elores is a combination of ceftriaxone, sulbactam and disodium edetate, having high susceptibility to ESBL and MBL producing pathogens including pathogens expressing NDM-1, VIM-1, KPC-2, IMP-1 [10]. The reason for enhanced susceptibility of Elores is synergistic activity of ceftriaxone, disodium edetate and sulbactam. Disodium edetate chelates the divalent ions required for the activity of MBLs thus de-activating the MBLs which in turn enhanced the susceptibility of Elores towards MBLs producing organisms [11,12].

Elores showed significant susceptibility against ESBLs and MBLs producing *K. pneumoniae* clinical isolates. In a study done on *K. pneumoniae* isolated from North Indian patients, Elores MICswere reported between 4-8 µg/ml in KPC producing pathogens, the time kill-curve of Elores demonstrated long and effective bactericidal activity (5-log reductions in the viable cell counts in 12hours) [11]. Apart from *invitro* studies, in a phase-III clinical trail on Elores, high susceptibility to all isolates positive with ESBL and MBL genes were observed, including KPC-2 [13]. Similarly, a retrospective study on 95 patients with LRTI, UTI and IAI with various Gram negative infections showed increasing prevalence of carbapenem resistant, while Elores showed excellent antibacterial activity against major Gram negative organisms identified including *Klebsiella* species (84%). Elores also showed higher clinical success rate of more than 75% as compared to meropenem 61% [14]. Very recently, its efficacy has also been demonstrated in complicated neurogenic bladder and multiloculated left pleural effusion case [15,16].

Hence, in view of the risk of spreading of ESBLs and MBLs resistant determinants in fatal diseases like sepsis, it is important to develop a new antibiotic combination that could be effective against ESBLs and MBLs producing strains. Antibiotic adjuvants like Elores could be a useful strategy in the current scenario.

CONCLUSION

Sepsis is a systemic infection that can lead to multi-organ failure and death. With increasing incidence of MDR Gram-negative pathogens and rise in KPC producing *K. pneumoniae* has created a therapeutic challenge in treating sepsis patients and raised a need for an antibiotic with novel mechanism of actions to tackle the current scenario. The present case report highlights the safety and efficacy of Elores: an antibiotic adjuvant entity with synergistic mechanism of action in managing MDR pathogens and can be considered as a drug of choice for treating KPC.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 27, 2015**
Date of Peer Review: **Dec 29, 2015**
Date of Acceptance: **Feb 19, 2016**
Date of Publishing: **Apr 01, 2016**