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RESEARCH ARTICLE

EFFECTIVE MANAGEMENT OF CRITICAL HAP PATIENT INFECTED WITH MDR *ACINETOBACTER BAUMANNII* WITH MULTIPLE CO-MORBIDITIES

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ABSTRACT

Emergence of multi drug resistance (MDR) strains of *Acinetobacter baumannii* (*A. baumannii*), resistant to most of the available antibacterial drugs is of great concern globally. Management of the infections caused by these MDR strains especially pneumonia is a great challenge for physicians and clinical microbiologists. In the present study, we discuss a case of a 71 year old male patient diagnosed with MDR *A. baumannii* pneumoniae with known co-morbidities of *CKD*, hypertension, diabetis mellitus and *coronary artery disease* (CAD) treated with a newer antibiotic adjuvant entity: Elores (ceftriaxone+sulbactam+disodium edetate) and recovered well.

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INTRODUCTION

Patients with chronic kidney disease (CKD) or under hemodialysis are more at risk for pneumonia than the general population especially with associated co-morbidities like diabetes, cardiovascular disease, asthma, and chronic obstructive pulmonary disease (Chou *et al*., 2014). Mortality and morbidity is high in patients of CKD with co-morbidities of cardiovascular events, pneumonia and other bacterial infections. Patients undergoing long-term hemodialysis are 36% more prone to pneumonia. Mortality risk was shown to be directly associated with hospital acquired MDR pneumonia especially in critically ill patents infected with Acinetobacter baumannii (Viasus *et al*., 2011). Pneumonia due to a hospital acquired MDR bacteria is one of the most dreadful hindrance that occurs in the critical care setting. Several studies reported enhanced risk of mortality in critically ill patients when the occurrence of pneumonia is due to a multidrug-resistant pathogens (Shete *et al*. 2010; Chaudhary and Payasi, 2013a). Pneumonia caused by Acinetobacter spp. are predominant especially in patients hospitalized for longer duration of time and critically ill patients (Shete *et al*. 2010; Edis *et al*., 2010).

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Acinetobacter baumannii (A. baumannii) is also the most prevalent organism in the respiratory secretions collected from ICUs (Edis *et al*., 2010). In a study by Jaggi *et al*. (2012) reported A. baumannii as a predominant pathogen contributing up to 30.4% of hospital acquired infections. MDR A. baumannii species poses a daunting challenge for physicians and clinical microbiologists because of it's natural ability to survive in a hospital environment and surfaces for extended periods of time and frequent cause for healthcare-associated fatal infections (Shete *et al*. 2010). A. baumannii harbors multiple mechanisms of drug resistance. The mechanism of resistance to β-lactam agents in *A. baumannii* involves: production of a variety of chromosomal or plasmid-mediated β-lactamases (ESBL/MBLs), reduced access to bacterial targets (due to decreased outer membrane permeability, mutations that change cellular functions (efflux pumps overexpression and biofilm formation on the surface of various implants and also in the environment (Manchanda *et al*., 2010). A combination of several resistant mechanisms existing within the same isolate has also been observed (Shete *et al. 2010;* Manchanda *et al.,* 2010).

A unique feature of A. baumannii is rapid acquisition of antibiotic-resistance mechanisms to various groups of antimicrobials including aminoglycosides, fluoroquinolones and carbapenems.[6] In India antibiotic resistance to

A. baumannii is increasing at an alarming rate leading to increased morbidity, mortality and treatment costs in ICU settings. A tertiary care hospital in India reported 89.6% carbapenem resistance *A. baumannii* from the entire hospital, same clinical isolates from the ICU patients showed 93.2% resistance to carbapenems (Jaggi *et al.,* 2012). From the last decade, the epidemiological, clinical, prognostic and therapeutic characteristics of *A. baumannii* isolated from infected patients have been reported in the literature. The most alarming problems encountered during this period are the organism's ability to accumulate diverse mechanisms of resistance towards all commercially available antibiotics coupled with the lack of new antimicrobial agents in the pipeline (Jaggi *et al.,* 2012). We are presenting a critical case of pneumonia caused by MDR A. baumannii in a patient with CKD, undergoing hemodialysis with co-morbidities of hypertension and Type II diabetes mellitus, which failed to respond to last resort of antibiotics like carbapenems and BL+BLI combination and successfully treated with Antibiotic Adjuvant Entity Elores.

Case presentation

A 71 year old male with known case of CKD, hypertension, diabetis mellitus and coronary artery disease **(**CAD) arrived at our emergency department with complaints of difficulty in breathing and severe cough. On general examination, the overall condition of the patient was poor, had tachypnea and tachycardia. After initial stabilization and evaluation, patient was advised high-resolution computed tomography (HRCT) of chest, USG abdomen with 2D echo and shifted to medical intensive care unit (MICU) for further management. HRCT chest revealed, collapse consolidation of the left lower lobe basal segment with pleural effusion, few centrilobular nodules in the superior segment of left multiple enlarged mediastinal lymph nodes of infective etiology. USG abdomen revealed bilateral (B/L) kidneys smaller in size showing echogenicity with loss of CMD and B/L pleural effusion. 2 D ECHO revealed concentric left ventricular hypertrophy (LVH) with regional wall motion abnormalities (RWMA) in mild and basal inferoseptal hypokinesia with grade-II left ventricular diastolic dysfunction (LVDD) and trace tricuspid regurgitation (TR).

Based on patients history, general examination and radiological findings, he was immediately put on hemodialysis with broad spectrum antibiotic coverage of piperacillin-tazobactam and clarithromycin. Cardiology consultation was done. Ivabradine, antihypertensives and antiplatelets treatment was initiated taking into consideration his old CAD post percutaneous transluminal coronary angioplasty **(**PTCA). During hospital stay patient had persistent respiratory distress, hypoxemia and dry cough. Serial chest X rays revealed left sided patch with fluid overload. Patient was managed with intermittent biphasic positive airway pressure (BIPAP) support with high FIO2 requirement with regular hemodialysis with ultra filtration. In view of his deteriorating condition and raising counts, patients sputum, urine and blood samples were re-sent to culture and sensitivity testing and antibiotics were steeped to meropenem and teicoplanin. Though on steeped up antibiotic therapy, patient started producing copious amount of thick muddy sputum. Blood and urine cultures were sterile, while sputum culture yielded MDR A. baumannii with sensitive only to colistin and Elores. Considering the patients old age and CKD history, colistin was deferred to be added (nephrotoxicity and higher chances of neuromuscular weakness). Patient was put on 3g Elores with 90 min infusion for 8 days.

Patients condition gradually improved, with improvement in FiO_2 and clearing of infiltrative patch was observed under X ray image. Patient was de-escalated to Elores 1.5g BD along with supportive therapy. Patients relatives were informed about the seriousness of the condition and chances of recurrence of infection. Deranged renal function was taken care by regular hemodialysis. On the 9^{th} day post de-escalation, patient suddenly showed waxing and waning in his respiratory parameters and raising of TLC with copious secretions. Suspecting hospital acquired super-infection, chest X-ray was advised and revealed developing patch over right lung. Considering the nosocomial infection and deteriorating condition of the patient, colistin 9 MIU loading dose along with Elores 3g intravenous infusion was started. Health to risk benefits of colistin were explained to family, especially the neurotoxicity and nephrotoxicity effect considering CKD, diabetes and lowered immune response which could lead to longer ICU stay, respiratory muscle weakness and patient being more prone to ventilator dependency.

Patient was on slight recovery phase post 5 days of antibiotic therapy. But suddenly patients condition deteriorated, showing signs of drowsiness and disorientation. ABG revealed respiratory acidosis and hemodynamic instability. Patient was immediately intubated and put on assisted ventilation on ACMV mode and given inotropic support. Blood and urine cultures were sterile. Chest X-ray revealed fluid overload and patch on right side also. Repeated screening ECHO and ECG with cardiac enzymes was done, but failed to reveal any acute cardiac event. During this stage of illness, he had complete kidney shutdown with anuric status. Hemodialysis was being done with ultra-filtration on every alternate day. Antibiotic dosage was modified accordingly with other supportive therapies. Respiratory acidosis and hemodynamic instability were effectively managed. Patient started showing recovery and was extubated after counseling the family, explaining a high chance of re-intubation in case of poor respiratory efforts or retention of secretions. Post extubation he remained conscious, had cough reflex, but wasn't able to expectorate out. Needed intermittent NIV support.

He was continued on supportive care, antibiotics and dialysis for renal parameters and dehydration. Serial chest X-ray report showed decreased consolidation in both lung, with improvement in lab parameters, declining counts, minimal NIV support. Patient was monitored for few days and requested discharge against medical advise. On the previous night of discharge patient again had respiratory distress, requiring NIV support, stat hemodialysis with ~ 3.5 liters ultra filtration was done. Post this event he was comfortable, on oxygen via nasal prongs at the rate of 4L/min. But with episode of respiratory distress, requiring NIV support, with retaining orotracheal secretions, poor muscle mass and having respiratory muscle weakness. Received hemodialysis with ~3.5 liters. Total leukocyte count raised to 24000x 10^6 micro-liters of blood.

Sputum samples were sent for microscopic examination. Microscopy revealed few yeast cells, suggestive of fungal infection. Thus along with colistin and Elores, patient was put on fluconazole. Post revised antibiotic therapy and supportive treatment, improvement in the condition of patient was noted. Antibiotics were deescalated. Colistin and fluconazole were stopped and Elores continued 3g BD for next 5 days and then de-escalated to 1.5 g BD along with active physiotherapy, steam inhalation and supportive therapy. When lab parameters were within normal limits and patients overall condition improved, he was discharged, with advise for regular hemodialysis and follow-up.

DISCUSSION

In the present case, patient was with CKD, under going hemodialysis and developed nosocomial MDR neumonia along with co-morbidities of hypotension and Type II diabetes mellitus. Patient with CKD and diabetes mellitus complication have increased susceptibility to pulmonary infections. The reasons for patients with CKD or under hemodialysis particularly susceptible to pulmonary infections are reduced carbon monoxide transfer, decreased inspiratory muscle strength and impaired phagocytic cell function (Sarnak and Jaber, 2001). Studies also reported that end-stage renal disease is associated with a decreased lymphocyte proliferation and increased immune dysfunction in patients with decreased glomerular filtration rate (Viasus *et al*., 2011). The mechanisms underlying development of pneumonia among diabetic patients may include decreased leukocyte function and harmful effects of hyperglycemia (Kornum *et al*., 2007).

Sarnak and Jaber (2001), reported pulmonary infectious mortality rates are 14-16 times higher in dialysis patients than in the general population. Chou *et al*. (2014) reported the incidence rate of pneumonia to be 65.6 per 1000 person-years in patients with CKD compared to 28.4 per 1000 person-years in patients without CKD. The common risk factors among patients with CKD associated with pneumonia are old age, diabetes, cardiovascular disease, asthma and chronic obstructive pulmonary disease (Chou *et al*., 2014; Viasus *et al*., 2011). Common organism associated with decreased immune system are specifically Gram-negative non-fermentors like A. baumannii and *Pseudomonas aeruginosa* along with *Enterobacteriaceae.*

A. baumannii is one of the most important pathogens causing nosocomial pneumonia, predominantly in patients with underlying lung diseases, prolonged mechanical ventilation, prior broad spectrum antibiotic treatment, recent major surgery and prolonged bed ridden patients in ICU (Chen *et al*., 2001).
A unique feature of A. baumannii is rapid acquisition of antibiotic-resistance mechanisms. A. baumannii have become increasingly resistant to almost currently available antibacterial agents used to treat A. baumannii infections include aminoglycosides, fluoroquinolones and carbapenems. In recent years, there have been numerous reports on MDR A. baumannii from hospital settings in India. Production of β-lactamases has been one of the important resistance mechanism of A. baumannii**,** *with h*igh prevalence of ESBLs (up to 85%) and MBLs (up to 59%) in India. Efflux pump over expression, membrane impermeability, structural change in PBP, drug inactivation, decreased permeability and more than one mechanisms of resistance existing within the same isolate contributes to MDR. The mortality rate in patients suffering from A. baumannii infections is approximately 75% associated with frequent treatment failures (Chaudhary and Payasi, 2013a).

In our case, patient was initially treated with empirical antibiotic therapy with piperacillin/tazobactam and clarithromycin, antibiotic regimen was changed to meropenem and teicoplanin in view of patient critical condition and deranged laboratory parameters indicating rise in infection. But patient still produced thick muddy sputum, indicating resistance and reduced susceptibility to penems and piperacillin/tazobactam against A. baumannii. This was confirmed in our case as culture and sensitivity of sputum samples revealed MDR A. baumannii and sensitive only to colistin and Elores. Similarly, Chaudary *et al*., reported up to 85.7% resistance to meropenem and piperacillin/tazobactam against carbapenemase producing A. baumannii isolated from respiratory secretion (Chaudhary and Payasi, 2013a).

In view of patient age and CKD, colistin was being deferred to be used as an initial drug of choice in the current case, considering its nephrotoxicity and induce respiratory muscle weakness (Spapen *et al*., 2011). Elores was consider the drug of choice based on the establishing safety and efficacy report and antibiogram of the hospital (Chaudhary and Payasi, 2013b), though colistin was added in the treatment regimen at an later stage to prevent the chances of sepsis development. Elores shows enhanced susceptibility towards *A. baumannii* through synergistic activity of ceftriaxone plus sulbactam and antibiotic adjuvant entity disodium edetate. Disodium edetate chelates the divalent ions required for the activity of MBLs and alters the outer membrane permeability which in turn increased penetration of drug inside the bacterial cells (Chaudhary and Payasi, 2013b). Apart from these activities, Disodium edetate in Elores may reduce expression of mRNA responsible for efflux pump over expression by controlling the ATP concentration in bacteria (Chaudhary *et al*., 2012), effectively inhibiting curli formation and bacterial adhesion in biofilm formation (Chaudhary and Payasi, 2012).

Phase-III clinical trial on Elores reported clinical cure rate of 91.30% (42/46) and bacterial eradication 97.05% (33/34) in LRTI patients including pneumonia (Chaudhary and Payasi, 2013b). Manu Chaudhary *et al*. (2013) reported sensitivity of ESBL producing *A. baumannii* clinical isolates from clinical settings in India, Elores showed 89.5% sensitivity, where as meropenem and piperacillin/tazobactam showed 65.4% and 40.4% respectively. Hence, new option like novel antibiotic adjuvant entity Elores provide promising safer solution for treating MDR organisms in renally compromised patients when other broad spectrum antibiotics (piperacillin/tazobactam, clarithromycin, teicoplanin and meropenem) fail to respond.

Conclusion

Challenges in treating renal impaired patients undergoing hemodialysis with serious infection of MDR pathogens has always been a challenge for the physicians, especially with co-

morbidity like diabetes which favors a suitable environment for bacterial growth. Considering the limited treatment options available for treating such serious patients, a need for a safe and effective antibiotic arises. The present case highlights the importance of newer antibiotic adjuvant entities in treating MDR pathogens, especially A. baumannii as an efficacious and safe drug of choice which can be used as monotherapy or in combination with other broad spectrum antibiotics.Based on the evidence of the present case, Elores can be considered as an effective and safe choice in treatment of hospital acquired MDR pathogens especially A. baumannii expressing various mechanisms of resistance to multiple drugs.

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