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Use of Elores™ in Guiding Successful Treatment of Ventilator Associated Pneumonia Due to Multi Drug Resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*

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Authors' contributions

Both the authors have equal contribution in this case report. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Increased antimicrobial resistance of *Acinetobacter baumannii* (*A. baumannii)* and *Klebsiella pneumoniae* (*K. pneumoniae*), is of great concern worldwide. Management of Ventilator associated pneumonia (VAP) due to MDR poses a challenge for clinicians.
Case Presentation: Here we are discussing a case of 47 year old male patient diagnosed with VAP due to *A. baumannii* and *K. pneumoniae*. Use of Elores™ (Ceftriaxone/Sulbactam/Disodium-edetate) as antibiotic for the treatment of VAP due to MDR pathogen *K. pneumoniae* and *A. baumannii* resulted in clinical cure of infection.
Conclusion: Elores™ can be considered as a safe and efficacious antibiotic to treat MDR gram negative pathogens in VAP.

Keywords: Ceftriaxone/Sulbactam/Disodium-edetate; antibiotic resistance; Acinetobacter baumannii; Klebsiella pneumoniae; CSE1034; ventilator associated pneumonia (VAP).

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1. INTRODUCTION

Pneumonia is an inflammation of the lung, caused by bacteria, viruses, and fungi infection. Ventilator associated pneumonia (VAP) is one of the most common nosocomial infections in critical care [1]. Approximately 9 -27% patients who are ventilated mechanically go on to develop VAP. These account for 5 cases per 1000 ventilator days [1]. VAP is defined as pneumonia that occurs 48 hours or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count) and detection of a causative agent [2]. VAP is very severe condition and has very high mortality rate ranging from 0–50% [2,3,4]. Prevalence of VAP in brain injured patient has been observed up to 40% [5]. *Acinetobacter baumannii* (*A. baumannii*) and *Klebsiella pneumoniae (K. pneumoniae) are* the predominant etiological agents for VAP. Multi drug resistant (MDR) pathogens increase the mortality rate in VAP [6,7].

A. baumannii is an aerobic non motile lactose negative and gram negative coccobacillus [8,9]. Prevalence of MDR *A. baumannii* has increased in nosocomial infections in last decades [10]. In pneumonia due to MDR *A. baumannii* infections, the mortality rate to the tune of 65 % [11]. In India, Shete et al. in 2010 reported 11.6% cases of VAP due to *Acinetobacter baumannii* [12]. VAP infections due to MDR *A. baumannii* are difficult to treat because of resistance to a number of antibiotics [13]. Various risk factors for *A. baumannii* include receipt of mechanical ventilation, prolonged hospitalization, exposure to intensive care unit (ICU), surgery, the severity of disease, intubation, exposure to antibiotics etc [14]. Infections with *A. baumannii* are usually associated with increased duration and cost of hospitalization [15].

K. pneumoniae belongs to Enterobacteriaceae family and is present in the natural environment and in mammal's mucosal surfaces [16]. *K. pneumoniae* is another gram negative pathogen causing nosocomial infections and mortality with this virulent pathogen has been reported up to 70% [17]. A study in Newyork reported the prevalence of ESBL positive isolates of *K. pneumoniae* to be 34% [18]. *K. pneumoniae* can cause both early-onset and, more commonly, late-onset sepsis, hospital-acquired pneumonia, urinary tract infections (UTIs), and surgical site infections [16,19]. In the USA, about 20% of *K. pneumoniae* are resistant to third generation cephalosporins in ICUs [20].

Elores™ (Ceftriaxone/ Sulbactam/ Disodium-edetate) is an antibiotic adjuvant entity effective in lower respiratory tract infections against various MDR pathogens. It can decrease antibiotic resistance via reducing overexpression of efflux pumps, increasing membrane permeability, biofilms eradication etc. [21].

In the present case report, we discuss a case of VAP due to multiple pathogens secondary to Left frontotemporal bleeding with intraventricular extension. This case demonstrated cure with the use of Elores™.

2. CASE REPORT

A 47 year old male patient was admitted to our hospital on ventilator support. The patient was unconscious at the time of presentation and had a medical history of hypertension. The patient was put on ventilator. The patient had Glasgow Coma Scale (GCS) EI VT M2. The patient had respiratory rate: 20/minute, SPO_2:98% (on oxygen), blood pressure: 210/120 mmHg, pulse:90/minute and body temperature: 98.2° F. Systemic examination revealed CVS: S1 S2 normal, Abdomen: soft and bowl sounds present, Chest: bilateral air entry. No pedal edema was observed. Blood investigations showed TLC: 11000/cumm and deranged renal function test (RFT). CT brain showed massive left temporal and intraventricular bleed. Cerebral angiography was conducted which showed normal study with no arteriovenous malformation (AVM)/ aneurysm.

Based on clinical, radiological, hematological and biochemical investigations, the patient was diagnosed of Left frontotemporal bleeding with intraventricular extension.

The patient was operated for left frontotemporoparietal (FTP) decompressive craniotomy with evacuation of left frontotemporal clot with external ventricular drain EVD placement, right frontal horn placement on the day of admission. A subgaleal drain was placed under the scalp to allow drainage of collected blood. After surgery, the patient was shifted to neurosurgery ICU for further management. The patient was tracheostomised for prolonged ventricular support. The patient was conservatively managed with Tab amlodipine 5 mg in the morning and 10 mg in the evening,

Tab Pantoprazole 40 mg q 24 h, Phenytoin 40 mg q 24 h, Prazosin 2.5 mg q 12 h, Telmisartan 80 mg q 24 h. Post operative CT brain was done which showed post operative changes with left FTP decompressive craniotomy with evacuation of clot with a decrease in mass effect. Deranged renal function test (RFT) values were corrected with hydration.

During hospitalization, the patient had febrile episodes for which tracheal secretion samples were sent for culture and susceptibility testing. All the cultures were sterile and the patient was empirically started on a broad spectrum antibiotic. Initially, febrile episodes were considered due to intra ventricular hemorrhage (IVH) and Ibuprofen was started. CT brain was repeated at regular intervals which showed changes of resolution with decreased mass effect and no significant increase in the size of ventricles. Despite the use of broad spectrum, antibiotics fever continued to persist, so repeated samples were sent for culture and sensitivity on 14th day of admission. The patient was empirically given meropenem q8h for three days. C/S for tracheal secretion showed growth of multi drug resistant (MDR) *K. pneumoniae* and *A. baumannii* resistant to most of the antibiotics including carbapenems as shown in Table 1. Thus this patient was diagnosed of VAP on 14th day of hospitalization. Based on C/S report patient was started with Elores™ (CSE1034) 3 g bd for 14 days. Supportive treatment was given to the patient for comprehensive management. The patient was afebrile, blood counts (TLC: 4800/cumm) were settled and culture was sterile after use of Elores™. The patient had gradual neurological recovery and his blood counts settled, so he was gradually weaned off from the ventilator after giving wean off trial. The patient responded well to the treatment given.

The patient was discharged in a hemodynamically stable condition. At the time of discharge, patient was tracheostomised on room air, afebrile, GCS: E4 VT M5-6, right hemiplegia, tolerating feed with adequate output.

3. DISCUSSION

Respiratory infections especially nosocomial infections are associated with significant morbidity and mortality. *K. pneumoniae* and *A. baumannii* are predominant pathogens associated with higher mortality and morbidity especially in nosocomial pneumonia [10,22,23].

Table 1. Culture and susceptibility report of tracheal secretion sample

S. no	Antibiotic/Isolated pathogen	*A. baumannii*	*K. pneumoniae*
1	Amikacin	Sensitive	Sensitive
2	Amoxicillin and clavulanic acid	-	Resistant
3	Ampicillin	-	Resistant
4	Aztreonam	Resistant	-
5	Cefepime	-	Resistant
6	Cefoperazone+ sulbactam	Resistant	Resistant
7	Ceftazidime	Resistant	-
8	Ceftriaxone	-	Resistant
9	Cefuroxime	-	Resistant
10	Ciprofloxacin	Resistant	Resistant
11	Cotrimoxazole	Resistant	Sensitive
12	Colistin	Sensitive	Sensitive
13	Ertapenem	-	Resistant
14	Gentamicin	Resistant	Sensitive
15	Imipenem	Resistant	Resistant
16	Levofloxacin	Resistant	-
17	Meropenem	Resistant	Resistant
18	Piperacillin+Tazobactam	Resistant	Resistant
19	Polymyxin B	Sensitive	Sensitive
20	Ticarcillin+clavulanic acid	Resistant	-
21	Tigecycline	Resistant	Sensitive
22	Elores™	Sensitive	Sensitive

Acinetobacter species and *K. pneumoniae* pose resistance by different mechanisms. These pathogens possess resistance to antibiotics via following mechanisms (a) antimicrobial-inactivating enzymes (ESBL,MBL, AmpC, OXA type enzymes) (b) reduced access to bacterial targets via over expression of efflux pump which actively remove broad range of antimicrobial agents from the cell. (c) Alteration in porin channels inhibits entry of antibiotics into the cell. (d) mutations that change targets or cellular function [14]. These pathogens have the ability to acquire genes from other pathogens, leading to resistance over a period in these pathogens [14,24]. These MDR *A. baumannii* and *K. pneumoniae* are resistant towards most of the antibiotics.

In the present case, the patient had febrile episodes during hospitalization after surgery of left FTP decompressive craniotomy. The patient was started empirically with meropenem for 3 days. Early and accurate microbiological identification and susceptibility evaluation are crucial in order to optimize antibiotic therapy. But the report of culture and susceptibility testing showed both pathogens were resistance towards meropenem, so it was discontinued. Elores™ 3 g q 12 h via IV infusion for 90 minutes was started. Colistin because of nephrotoxicity (10-20% cases) should not be prescribed in patients when other alternatives are available [25]. Colistin is used in combination with other antibiotics as mortality rate is higher when given as monotherapy. It is selected only when all other drugs are resistant in culture and susceptibility testing or due to failure of other antibiotics. Thus colistin is used only as a last resort [25, 26]. Polymyxin B also has side effects of neurotoxicity and nephrotoxicity [27]. The incidences of nephrotoxicity were up to 14% with polymyxin B therapy [28,29]. Due to deranged renal function tests, Amikacin, colistin & Polymyxin B were not used due to toxicity concerns. Elores™ was selected because of its safety and efficacy profile [21].

Elores™ showed enhanced susceptibility to both pathogens. Ceftriaxone is a third generation cephalosporin, while sulbactam is ß lactamase inhibitor. Disodium edetate enhances the membrane permeability, chelates divalent ions required for activity of MBLs and biofilm eradication [30]. In a study on biofilms, Minimum biofilm eradication concentration (MBEC) for Elores™ was 8 to 16 µg/ml while for other antibacterial agents (piperacillin+tazobactam, ceftriaxone, ceftriaxone+sulbactam and cefoperazone+ sulbactam), it was 64 to 4096 µg/ml [31]. Elores™ showed significant susceptibility against *Klebsiella pneumoniae* and *Acinetobacter baumannii* [24,30,31,32] In a phase 3 trial on 93 LRTI patients, Elores™ showed significantly better clinical cure and bacterial eradication as compared to ceftriaxone [21].

Thus Elores™ is efficacious and safe antibiotic adjuvant for treatment of VAP due to MDR pathogens like *K. pneumoniae* and *A. baumannii.*

4. CONCLUSION

Treatment of VAP due to MDR multiple pathogens like *K.* pneumoniae and *A.* baumannii poses a challenge for the physician. Due to limited options, the need for safe and efficacious antibiotic arises. In the present case, Use of Elores™ as antibiotic for the treatment of VAP due to MDR pathogen *Klebsiella pneumoniae* and *Acinetobacter baumannii* resulted in clinical cure of the patient. Elores™ can be considered as an efficacious therapeutic option for MDR gram negative pathogen in VAP.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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