

Treatment with CSE-1034 (Elores™) in TheManagement of Community Acquired Pneumonia Due to Multi Drug Resistant *Pseudomonas aeruginosa*

ABSTRACT

Introduction:Community acquired pneumonia (CAP) is one of the important cause of mortality and morbidity. CAP is defined as an infection of the lung parenchyma that is not acquired in a hospital, long-term care facility, or other recent contact with the health care system. *Pseudomonas aeruginosa* (*P. aeruginosa*) is resistant to most antibiotics. This resistance is one of the main barriers in bacterial eradication and clinical cure of *Pseudomonas* infection. This delay in management of MDR *P.aeruginosa* with appropriate antibiotics,can lead to increased mortality and morbidity.

Case Presentation: Here we discuss a case of a CAP due to *P.aeruginosa* which clinically didn't respond to piperacillin-tazobactam & meropenem and was resistant to both classes of antibiotics. This was successfully treated with CSE-1034 (Ceftriaxone/Sulbactam/Disodium-edetate).

Conclusion:CSE-1034 (Elores™) proved to be safe and efficacious in treatment of a hospitalized patient with CAP due to MDR *P.aeruginosa*.

Keywords: MDR, Elores™, CAP, *Pseudomonas aeruginosa*, Disodium-edetate, CSE-1034

INTRODUCTION

Community acquired pneumonia (CAP) is associated with significant morbidity and mortality. CAP is defined as an infection of the lung parenchyma that is not acquired in a hospital, long-term care facility, or other recent contact with the health care system [1]. A retrospective study in Portugal showed that out of total hospitalized patients 3.7% were of CAP [2]. Diabetes is a risk factor for developing respiratory infections. There have been previous reports of association of diabetes with pneumonia [3]. 4-5 million cases of CAP per year were estimated. Out of these 25 % need hospitalization [4]. Only in USA, 915,900 episodes of CAP are reported each year in adults >65 years [5]. In India, in 2004, 89.5 deaths per 100,000 population were estimated to bedue to lower respiratory tract infection (LRTI) [6]. CAP is the second most common cause of

mortality in India [7]. In India, epidemiology of CAP in different region varies from each other. *Pseudomonas aeruginosa* is a gram negative aerobic bacterium belonging to family *Pseudomonadaceae*. Usually *Pseudomonas aeruginosa* (*P. aeruginosa*) is not a frequent pathogen in CAP but it was found most prevalent in one study conducted in Ludhiana [8,9,10]. *P.aeruginosa* is an opportunistic pathogen, mostly involved in nosocomial infections, but in severe CAP, prevalence of *P.aeruginosa* was found to be 1.8% to 8.3% with higher mortality rates [10]. *P. aeruginosa* isolates that cause infections are thought to express various virulence factors [11]. Pneumonia due to *P. aeruginosa* can be transmitted in hospitals by nursing staff, medical equipment, sinks, disinfectants, and food. *P. aeruginosa* is resistant to most of the antibiotics. This resistance is one of the main barriers in bacterial eradication and clinical cure of *Pseudomonas* infection [11]. This delay in management of MDR *P. aeruginosa* with appropriate antibiotics, can lead to increased mortality and morbidity [11,12].

Elores™ (Ceftriaxone/Sulbactam/Disodium-edetate) is an antibiotic adjuvant entity which has been found to be effective against MDR *P.aeruginosa* in CAP [13].

Here we are discussing a case of 69 year old male patient with diabetes and CAP due to MDR *P.aeruginosa* treated successfully with CSE-1034 (Elores™).

CASE PRESENTATION

A 69 year old male patient with medical history of diabetes and hypertension presented at our hospital with chief complaints of fever and weakness. At presentation, Vitals of patient were as follows: a) blood pressure 150/90 mmHg, b) pulse: 78/minute, body temperature: 101° F. Patient was presumptively diagnosed with community acquired pneumonia (CAP). Patient was given injection salbutamol stat at time of admission. He was empirically started with piperacillin-tazobactam on day of admission. On the second day meropenem was added to this regimen. For comprehensive management of CAP, other supportive treatment was also provided to patient. Patient was managed with injection pantoprazole 40 mg q24h and insulin, nebulization with salbutamol and ipratropium bromide q8h and nebulization with budesonide/formoterol q12h. Injection fluconazole 150 mg stat was given as prophylaxis for fungal infection. Chest X-ray of patient suggests pneumonia as shown in figure 1.

Hemogram showed TLC of 13000/cumm, Polymorphs: 80%, Lymphocytes:18 %, Monocytes:0%, Eosinophils:02 % on third day. Culture and susceptibility test showed the presence of multi drug resistant *P. aeruginosa*. Based on chest x-ray, blood counts, culture and susceptibility reports, patient was diagnosed with CAP. As patient didn't respond clinically to meropenem after 48 hours, CSE-1034 was initiated. CSE-1034 (Elores™) 3g q12h via IV infusion for 90 minutes was started for 3 days followed by Elores™ 1.5 g q12h for next 4 days. Fever normalized, WBC counts settled (6200/cumm) and the patient was discharged from the hospital on the 7th day.

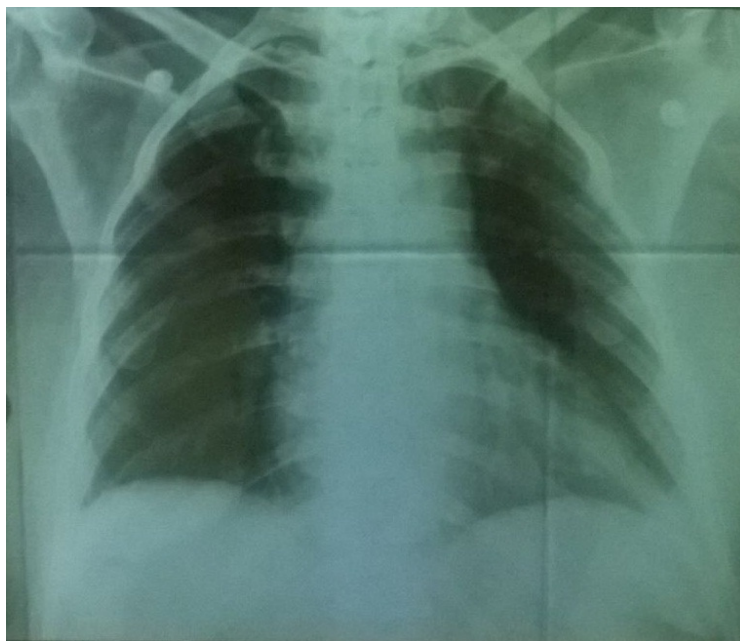


Fig.1 Chest X-ray at the time of admission

DISCUSSION

CAP due to *P.aeruginosa* is associated with higher mortality. Cases of CAP due to *P.aeruginosa* have been reported since 1960 [13]. Henderson et al., in 1992 reported two cases of CAP infection with *P.aeruginosa* of which both patients died in 36 h due to CAP [14]. In CAP due to *P. aeruginosa*, mortality is higher (30-35 %) and treatment is difficult because of development of resistance to traditional antibiotics used for treatment of CAP [13]. *P. aeruginosa* develop resistance by various mechanisms including over expression of efflux pump, Extended-Spectrum

β-Lactamases (ESBLs), Metallo-β-Lactamases (MBLs) and target site or outer membrane modification [12, 15].

In the present case, 69 year old male patient with CAP due to MDR *P. aeruginosa*. The patient also had a history of diabetes and hypertension. Diabetes is a risk factor for widespread dissemination of *P. aeruginosa* in the body[16]. Salbutamol was given as a bronchodilator to patient. Patient was started empirically on piperacillin-tazobactam and meropenem as per guidelines [17]. Culture and susceptibility report showed resistance to both of these antibiotics. C/S report showed *P. aeruginosa* was susceptible towards Elores™ (ceftriaxone/sulbactam/disodium-edetate).

CSE-1034 (Elores™) was selected based on established safety, efficacy, broad-spectrum activity against ESBL/MBL and culture and susceptibility testing. A study published in 2013 support use of Elores™ as it showed MBL and ESBL + MBL producing isolates of *P. aeruginosa* were resistant to most of antibiotics (piperacillin+tazobactam , imipenem, meropenem, ceftazidime and cefepime) except Elores™. CSE-1034 in MBL and ESBL + MBL producing isolates of *P. aeruginosa* showed significant susceptibility.[12]. Elores™ has synergistic action because of its components. Ceftriaxone is a third generation cephalosporin and sulbactam is β lactamase inhibitor. Disodium edetate helps in penetration and reduces the antibiotic resistance via reducing overexpression of efflux pump, enhances bacterial cell permeability, chelation of divalent ions and acting on other resistant mechanisms [18, 19]. In a phase 3 trial on 93 LRTI patients, Elores™ showed significantly higher clinical cure rate than the ceftriaxone group alone. When compared with ceftriaxone, Elores™ produced significantly less side effects [20]. Finally patient responded to Elores which helped this elderly patient to recover completely.

In present case study, Elores™ was used successfully in treatment of CAP due to multi drug resistant *P. aeruginosa* .

CONCLUSION

Increased incidence of CAP due to MDR pathogens increases morbidity and mortality. Due to increased antibiotic resistance clinicians face challenge in selecting antibiotics to treat infections due to for MDR *P. aeruginosa*. In the present case, Elores™ showed to be safe and efficacious in the treatment of a hospitalized patient with CAP due to MDR *P. aeruginosa*.

REFERENCES

1. Watkins IR, Lemonovich TL. Diagnosis and management of community-acquired pneumonia in adults. *Am Fam Physician*. 2011;83(11):1299-306.
2. Froes F, Diniz A, Mesquita M, Serrado M, Nunes B. Hospital admissions of adults with community-acquired pneumonia in Portugal between 2000 and 2009. *Eur Respir J*. 2013;41:1141–6.
3. Martins M, Boavida JM, Raposo JF, Froes F, Nunes B, Ribeiro RT, Macedo MP, Penha-Gonçalves C. Diabetes hinders community-acquired pneumonia outcomes in hospitalized patients. *BMJ Open Diabetes Res Care*. 2016;4(1):1-7.
4. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J, Sarosi GA, Torres A, Wilson R, Yu VL. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy. *Am J Resp Crit Care*. Med 2001; 163: 1730-54.
5. Jackson ML, Neuzil KM, Thompson WW, Shay DK, Yu O, Hanson CA, Jackson LA. The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clin Infect Dis*. 2004; 39:1642–50.
6. Epidemiology of Community-Acquired pneumonia.. *J Assoc Physicians India*. 2013; 61:7-8.
7. Soman R, Sunavala A. CAP in a Capsule. *J Assoc Physicians India*. 2013; 61:5.
8. Oberoi A, Aggarwal A. Bacteriological profile, serology and antibiotic sensitivity pattern of micro-organisms from community acquired pneumonia. *JK Science*. 2006;8:79–82.
9. Community-Acquired Pneumonia: Bacteriological Profile and Microbiological Investigations. *J Assoc Physicians India*. 2013; 61:9-11.

10. Cilloniz C, Gabarrús A, Ferrer M, Puig dela Bellacasa J, Rinaudo M, Mensa J, et al. Community-Acquired Pneumonia due to Multidrug and non-Multidrug resistant *Pseudomonas aeruginosa*. *Chest*. 2016. doi: 10.1016/j.chest.2016.03.042.
11. Yayan J, Ghebremedhin B, Rasche K. Antibiotic Resistance of *Pseudomonas aeruginosa* in Pneumonia at a Single University Hospital Center in Germany over a 10-Year Period. *PLoS One*. 2015;10(10):e0139836.
12. Chaudhary M, Payasi A. Rising antimicrobial resistance of *Pseudomonas aeruginosa* isolated from clinical specimens in India. *J Proteomics Bioinform*. 2013;6:5-9.
13. Hatchette TF, Gupta R, Marrie TJ. *Pseudomonas aeruginosa* community-acquired pneumonia in previously healthy adults: case report and review of the literature. *Clin Infect Dis*. 2000;31:1349–56.
14. Henderson A, Kelly W, Wright M. Fulminant primary *Pseudomonas aeruginosa* pneumonia and septicemia in previously well adults. *Intensive Care Med* 1992; 18:430–2.
15. Zavascki AP, Carvalhaes CG, Picao RC, Gales AC. Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: resistance mechanisms and implications for therapy. *Expert Rev Anti Infect Ther*. 2010;8: 71-93.
16. Knapp S. Diabetes and infection: is there a link? A minireview. *Gerontology*. 2013; 59, 99–104.
17. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell D, Dowell SF, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007; 44:27–72.
18. Chaudhary M, Payasi A. Ethylenediaminetetraacetic acid: A non antibiotic adjuvant enhancing *Pseudomonas aeruginosa* susceptibility. *Afr J Microbiol. Res*. 2012; 6(39): 6799-804.
19. Chaudhary M, Sudaroli M, Kumar S, Krishnaraju V. “Catering ESBL resistance challenge through strategic combination of Ceftriaxone, Sulbactam and Ethylenediaminetetra acetic Acid”, *Int J Drug Dev & Res*. 2012; 4(1): 72-81.

155 20. Chaudhary M, Payasi A. A randomized, open-label, prospective, multicenter phase- III
156 clinical trial of Elores™ in lower respiratory tract and urinary tract infections. *J Pharm*
157 *Res.* 2013;6(4):409–14.