Journal of Advances in Medicine and Medical Research

26(5): 1-7, 2018; Article no.JAMMR.40164
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Retrospective Case Series Analysis of Clinical Outcomes Associated with Management of Severe Community Acquired Pneumonia Cases *due to K. pneumoniae* with CSE-1034

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Authors' contributions

This work was carried out in collaboration between all authors. Author RK designed the study, wrote the protocol and first draft of the manuscript. Authors DM and RA performed the statistical analysis and managed the analyses of the study. Author RA manage the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/40164
Editor(s):
(1) Chan-Min Liu, School of Life Science, Xuzhou Normal University, Xuzhou City, China.
(2) Nicolas Padilla-Raygoza, Professor, Department of Nursing and Obstetrics, Campus Celaya Salvatierra University of Guanajuato, Mexico.
Reviewers:
(1) Masaaki Minami, Nagoya City University, Japan.
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(3) Sheikh Mohd Saleem, Government Medical College, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/24515

Short Research Article

Received 17th February 2018
Accepted 26th April 2018
Published 8th May 2018

ABSTRACT

Background: In India, the rapid emergence of multi-drug resistance among community acquired pneumonia (CAP) causing pathogens contributes to the seriousness of these infections and is currently a major treatment-related issue. The objective of this case series was to determine the clinical efficacy of antibiotic adjuvant entity (CSE-1034: Ceftriaxone+Sulbactam+EDTA) in severe CAP cases.
Methods: Severe CAP patients due to *K. pneumoniae* who were hospitalized and treated with CSE-1034 as monotherapy or combination therapy were screened and further analyzed. CSE-1034 therapy was started in all these subjects based on culture sensitivity (C/s) profile and continued or discontinued depending on clinical response.

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Results: 25 *K. pneumoniae* culture-positive patients with mean age of 52 years were included in this case series. C/s profile has shown that pathogens isolated from all subjects were completely resistant to amikacin, cefazolin, ceftriaxone, pipericillin-tazobactam (pip-taz) and cefoperazone/sulbactam. Sensitivity pattern of CSE-1034 was 100% and meropenem was 85%. The C/s reports and clinical response to CSE-1034 were in concordance in 92% patients. 23/25 (92%) patients treated with CSE-1034 were cured with CSE-1034 monotherapy and 2/25 (8%) with CSE-1034+colistin combination therapy.

Conclusion: From this case series, it can be presumed that CSE-1034 can serve as effective replacement to BL/BLI combinations and appears to be effective drug for treatment of severe CAP cases.

Keywords: K. pneumonia; CSE-1034; multi-drug resistance; community acquired pneumonia.

1. INTRODUCTION

Community acquired pneumonia (CAP) remains the most prevalent infectious diseases among humans worldwide despite the availability of range of anti-microbials. Though exact figures are not known, it is estimated that the incidence rate of CAP ranges from 1.6/1000 to 16/1000 annually and as much as 20% of them require hospitalization [1]. The etiological profile of CAP varies in different geographical locales and could also vary in same region over a period of time. Moreover, patients with severe CAP have distinct and different etiological pathogens than patients with other forms of pneumonia [1,2]. Similarly, the likely pathogen involved is also determined by the associated co-morbidity and age of the patient [1]. *K. pneumoniae* is among the common gram-negative bacteria encountered by physicians worldwide and is frequent etiology of severe CAP cases [3,4]. Moreover, it has been proven to be an independent risk factor for mortality in severe CAP cases. Its distribution as a CAP pathogen is uneven across the world with a highest incidence in developing countries and very infrequent cause of CAP in the United States and Europe [1,5]. A recent multicenter prospective study conducted in several Asian countries showed *K. pneumoniae* accounted for 15.4% of the pathogens responsible for hospitalized CAP, just after *S. pneumoniae* [5].

In recent years, the sensitivity profile of CAP pathogens including *K. pneumoniae* have undergone drastic shifts. Many of the CAP cases are increasingly reported resistant to traditionally used antibiotics and the pathogen profile of CAP is shifting to resistant type [6,7]. Resistance to broad spectrum β-lactams, mediated by extended spectrum β-lactamases (ESBLs), metallo β-lactamases (MBL) and AmpC β-lactamases (AmpC) enzymes is now a critical concern for the development of therapies against *K. pneumoniae* infections. This high rate of resistance has greatly limited the therapeutic options and has raised the need to explore alternate therapeutic strategies and save the future of antibiotics. Various reports have suggested that CSE-1034 therapy may be a suitable approach to reduce the frequency of drug resistance in microbes [8][9].This retrospective observational study is aimed to explore a new combination drug CSE-1034 (Ceftriaxone + Sulbactam with adjuvant Disodium edetate) as a carbapenem-sparing option in the management of moderate to severe CAP cases due to *K. pneumoniae*. The evaluation has been carried out on the basis of clinical and microbiological response.

2. MATERIALS AND METHODS

2.1 Study Design

The subjects included in this retrospective case series were patients suffering from CAP due to *K. pneumoniae* and treated between Jan. 2016 to Dec. 2016. The study was conducted as per guidelines for observational studies and the ethical principles of Declaration of Helsinki. Informed consent from the patients was not required because of retrospective nature of study.

2.2 Study Population

25 adult subjects in the age group of ≥18 years fulfilling the inclusion criteria were included in the study. The main inclusion criteria were a) primary diagnosis of CAP based on relevant signs and symptoms and various laboratory parameters b) Blood, sputum or pleural fluid cultures results confirming isolation of *K. pneumoniae* at the baseline c) received CSE-1034 as empirical treatment or after 3 days based on C/s report d) hospitalized for more than 5 days. Subjects who died within 72 hours due to multiple

complications other than antibiotic failure were excluded from the analysis.

CAP was identified in patients by the presence of various symptoms which includes fever (>100.4 F), leukocytosis (>12,000 WBC/mL), chest pain, cough and dyspnea, bronchial breath sounds, rales or egophony and abnormal chest radiographs.

2.3 Data Collection and Analysis

The department's patient file archive was used to identify the patients and retrieve the data needed. All necessary required information including demographic and baseline characters like gender, age, infection type, source of infection, causative pathogen, dosage and regime of antibiotic therapy were retrieved and analyzed.

CSE-1034 was initially either empirically or after 3 days based on C/s report in all the selected subjects based on the clinical presentation and the decision of treating physician. All the patients received CSE-1034 after C/s test and CSE-1034 was continued/discontinued further based on clinical response.

The clinical response of treatment was evaluated in terms of improvement in infection-related signs and symptoms after 3 days of treatment initiation and at the end of the treatment. All the patients were eligible to switch over to other treatment regimen depending on the microbial sensitivity data and clinical response.

2.4 Antibiotic Dosage

A dose of 3.0 g/12h of CSE-1034, 1.0 g/8h of meropenem and colistin with a loading dose of 9 MIU followed by BD doses of 4.5 MIU were used. Standard dose adjustment as per requirement was done for colistin.

2.5 *In-vitro* Microbial Antibiotic-susceptibility Testing

To test the antimicrobial susceptibility of the pathogen isolated from the subjects, Kirby-Bauer disk diffusion method/Vitek automated system were used. The results were interpreted as per the interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI) standards. The anti-microbial susceptibility for CSE-1034 was performed as per breakpoints provided by manufacturer. Criteria was <21mm- S, 14-20- I, ≤13- R.

2.6 Definitions

Clinical success: The patient's response was considered as clinically successful when, the patient recovered with either first line empiric antibiotic therapy or a step down from the initial therapy.

Clinical failure: An individual case was defined as clinical failure when the patient was switched to other antibiotics or one or more antibiotics is added to the initial regime.
First line antibiotic therapy: It is defined as the regime started at the beginning after the admission to the hospital.

Second-line antibiotic therapy: It is defined as the addition of one or more antibiotics to the initial regime or a complete or partial replacement of the initial antibiotic with another parenteral antibiotic regime depending on microbial sensitivity results.

2.7 Statistical Analysis

All the statistical analysis was performed using Chi-square test. P values were two-tailed and a value of <0.05 was considered as statistically significant.

3. RESULTS

3.1 Demographic Characters

A total of 120 CAP patients admitted for treatment were screened, out of which 25 patients meeting our inclusion criteria, were evaluated in this case series study. The male sex was predominant and observed in 60% population whereas female population represented 45% (9) patients. The mean age was 52 ranging from 45 to 70 years. The details of various other demographic parameters like weight, height, respiration rate, pulse rate, systolic blood pressure, diastolic blood pressure and temperature are mentioned in Table 1. All the analyzed patients were meeting inclusion and exclusion criteria. The most common co-morbidities associated with patients at the time of hospitalization were diabetes mellitus and liver diseases.

In vitro microbial testing has shown that pathogens isolated at baseline from the patients were completely resistant to various classes of drugs including cefipime, cefazolin, ceftriaxone, pip-taz and cefaperoxone+sulbactam.

Table 1. Demographic and baseline characteristics of all study subjects (n=25)

Characteristics		(n=20)
Gender	Male, n (%)	14 (56)
	Female, n (%)	11 (44)
Age (year)	Mean±SD	59±6.30
Height (cm)	Mean±SD	164±8.74
Weight (kg)	Mean±SD	72±10.40
BP (mm of Hg)	Systolic (Mean±SD)	129±21.53
	Diastolic (Mean±SD)	82±12.19
Pulse (beats/min)	Mean±SD	100±11.81
Respiratory rate (/min)	Mean±SD	22.5±8.90
Co-morbidities n (%)	DM	13 (52)
	Hypertension	09 (36)
	Liver disorders	08 (32)
	COPD	02 (8)

Table 2. Hematology parameters (mean) of all the treatment groups before and after treatment

Laboratory parameters	Screening	Completion	p-value
Hb (g %)	12.52±1.88	13.19±1.52	0.775
E.S.R (mm/h)	39.50±17.89	31.53±11.33	0.0949
T.L.C (/mm3)	10246.20±4244.85	8959.31±2956.01	0.4007
Lymphocytes (%)	11.93±4.53	21.27±7.92	0.0009
Blood Urea nitrogen (%)	20.56±9.77	12±7.32	0.025
S. Creatinine (mg/dl)	1.26±0.46	0.72±0.34	0.0005
S.G.P.T (U/L)	30.18±8.46	18.53±7.11	0.0011
S.G.O.T (U/L)	37.03±14.28	21.51±7.11	0.0001
A.L.P (U/L)	132.55±33.57	100.47±21.34	0.0002

Microbial susceptibility test has shown that all the patients were sensitive to CSE-1034 and 90% were sensitive to meropenem. The sensitivity to colistin was 100%.

Although 90% patients showed sensitivity to meropenem also, but based on antibiotic stewardship policy of hospital, CSE-1034 is preferred over meropenem and meropenem is reserved for CSE-1034 non-sensitive cases in need.

3.2 Prior Antibiotic Therapies given and Antibiotic Outcome

The classes of the prior antibiotics received by the patients prior to CSE-1034 therapy were pip-taz or cefoperazone/sulbactam (15–pip-taz; 10–cefoperazone/sulbactam). All the 25 subjects included in this case series study were started CSE-1034 based on the reports of culture sensitivity testing. 88% (22/25) of the patients responded to the treatment and showed signs of clinical improvement after 48h of CSE-1034 therapy. These patients were continued on the same treatment regimen and were reported to be completely cured at the end of therapy. The mean treatment duration among these 22 patients was 8.0 days ±2.89 (SD). 3 (12%) patients who were sensitive to CSE-1034 but showed poor clinical response to CSE-1034 treatment regimen, were switched to CSE-1034 and colistin combination therapy. After 48h of the combination treatment, it was observed that the patient started responding and their clinical condition improved. The mean treatment duration in patients cured with CSE-1034 and colistin combination therapy was 9.0 days±3.47 (SD).

Overall assessment of clinical response has shown that CSE-1034 cured 88% of the patients as monotherapy and 12% were cured in combination with colistin. Microbiological response has shown complete eradication of the pathogen at baseline in all 20 patients.

4. DISCUSSION

K. pneumoniae is one of the common gram-negative bacteria involved in severe CAP cases

accounting for 10% cases and is also an independent risk factor for mortality rate ranging from 20% to 53%. The rapidly emerging multi-drug resistant strains among CAP causing pathogens is becoming a serious problem and contributes to the seriousness of these infections. β-lactam antibiotics were one of the most common antimicrobials prescribed for the treatment of various bacterial infections including CAP. However, due to excessive consumption of β-lactam antibiotics in routine clinical practice, a series of ESBLs have emerged. ESBLs are the enzymes produced by Gram-negative bacilli which can hydrolyze β-lactam antibiotics containing an oxy-imino group. Moreover, the location of ESBLs on large plasmids having other antimicrobial resistant genes, makes most of the ESBL producing organisms resistant to various other sets of drugs also. As β-lactam antibiotics are inhibited by β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam, they were later replaced by BL+BLIs combinations to overcome ESBL resistance [10,11,12]. Parallel, to BL+BLI combinations, carbapenems are also the mainstay of therapy for ESBL infections. Although both carbapenems and BL+BLIs combinations played an important role in the treatment of ESBL infections, a considerable failure of BL+BLI combination and carbapenems has been reported worldwide [10]. The various mechanisms of carbapenem resistance are production of carbapenemases, changes in outer membrane proteins and over expression of drug efflux pumps [13]. In view of the rising anti-microbial resistance, new antibacterial approaches are needed to deal these infections especially MDR pathogens. We here in this case series report a successful treatment of severe CAP patients with CSE-1034.

The present study retrospectively analysed data sheets of 25 patients diagnosed with CAP due to *K. pneumonia* and treated with CSE-1034. The analysis of data retrieved demonstrated the use of BL+BLI combinations as the empirical therapy in these patients which failed to respond and the patients were switched over to CSE-1034 therapy. The failure of patients to respond to BL+BLI combinations, which was supported by culture sensitivity reports also, clearly categorize these infections as multi-drug resistant *K. pneumoniae* infections. In appropriate or delayed empirical anti-microbial therapy is still a significant problem associated with treating different bacterial infections and is associated with increased mortality and morbidity rate. Studies on various infections have documented higher mortality in patients who received inappropriate therapy. Though the treatment outcome in patients switched from inappropriate to appropriate therapy is better than for patients who remained on inappropriate therapy, but the benefit is not as par with the patients started on appropriate therapy empirically.

The culture sensitivity reports and clinical response to CSE-1034 were in concordance in 92% of the patients. 2 patients who failed to respond despite being sensitive to CSE-1034 were cured with a combination therapy of CSE-1034 and colistin. The sensitivity of these multi-drug resistant pathogens to CSE-1034 can be attributed to different mechanisms through which CSE-1034 targets various bacteria. The higher sensitivity to CSE-1034 could likely be the synergistic effect *of ceftriaxone, sulbactam and EDTA.* In addition to the routine anti-microbial activity of ceftriaxone and sulbactam, the non-antibiotic adjuvant, EDTA mediates various antimicrobial effects by chelating divalent metal ions located in the outer membrane causing destabilization of outer membrane, de-activates carbapenemases by chelating zinc ions and chelates Mg^{2+}ions required for conjugation process [14]. Moreover, CSE-1034 is also reported to down-regulate the expression of *MexAB-OprM* and *AcrAB-tolC* efflux pumps [15,16]. Though, culture sensitivity reports has shown 85% sensitivity of pathogen isolates to meropenem also, however the indiscriminate use of carbapenems has led to epidemic rise in MBL-producing bacterial strains, which if left unchecked will leave us with no treatment option for MDR infections. The judicious prescription of carbapenems and replacing them with the alternate effective therapies available like CSE-1034 can be only way to save this epidemic rise in carbapenem resistance. The results of this case series clearly support the use of CSE-1034 in treating serious cases of CAP where normal BL-BLIs combinations are increasing reported to fail and to spare carbapenems for extreme cases.

5. CONCLUSION

Overall, this case series study suggests that CSE-1034 can be an effective replacement for BL/BLI combinations including pip-taz and cefaperaxone-sulbactam for the treatment of CAP cases. Moreover, CSE-1034 is a combination of β-lactam and β-lactamase along with EDTA and thus can help to

spare the carbapenems as last line of treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/24515