Short Research Article

Efficacy of ceftriaxone+sulbactam+EDTA combination for complicated urinary tract infection patients: a retrospective case series.

Abstract

Background

In India, antimicrobial resistance (AMR) remains a major challenge for treatment of infectious diseases mainly due to inappropriate and high consumption of antibiotics.

Judicious choice of antibiotics and its optimistic utilization can be one of the potent ways to control the epidemic rise in AMR. The objective of this case series was to determine the clinical utility of antibiotic adjuvant entity (CSE-1034) (ceftriaxone+sulbactam+EDTA) in complicated urinary tract infection (cUTI) cases.

METHODS:

Patients suffering from multi-drug resistant (MDR) cUTIs and treated with CSE-1034 as monotherapy or combination therapy were screened and further analyzed. CSE-1034 therapy was started empirically in all these subjects and continued or discontinued based on culture sensitivity profile and clinical outcome. (State the statistical package used for sample analysis).

RESULTS:

20 culture-positive patients with mean age of 51±7.3 years were included in this case series. The most common pathogen isolated was *E. coli*(%) followed by *K. pneumonia* (%) and *A. baumannii* (%). Culture sensitivity profile has shown that pathogens isolated from all subjects showed no sensitivity to cefazolin, ceftriaxone, cefipime, 25% to pipericillin-tazobactam (pip-taz), 20% to cefaperozone+sulbactam, 5% to fluoroquinolones and 90% to meropenem. Sensitivity pattern of CSE-1034 and colistin was nearing 100%. 90% (18/20) patients treated empirically with CSE-1034 were cured with CSE-1034 monotherapy and 10% (2/20) with

CSE-1034+levofloxacin combination therapy.

Conclusion

From this case series, it can be suggested that CSE-134 alone or in combination with levofloxacin appears to be effective drug for treatment of MDR cUTI and can serve as effective replacement to pip-taz and β-lactam/β-lactam inhibitor combinations.

Key words: Complicated UTI, CSE-1034, Multi-drug resistance

Introduction

UTIs are the most common infections worldwide accounting for nearly 25% of all infections and affecting 150 million cases every year [1]. While cUTI compared with uncomplicated infection is caused by a wide range of pathogens including *Klebsiella* spp.,species *Enterococcus* spp. and *P. aeruginosa*; *E. coli* is the most common [2]. Based on the common causative agents, geographical location and other risk factors, the empirical antibiotic therapy for bacterial infections is started. In earlier days, simple antibiotics including pencillin and 3rd generation cephalosporins were reported to be effective against most of the bacterial isolates.(Not referenced). However, studies have shown that multiple antibiotic resistance in bacterial population has become growing clinical concern particularly in developing countries like India, and is currently recognized as a threat to public health [3][4]. Though MDR was mainly the concern of hospital settings, however, past few years have witnessed a rising AMR among community pathogens also.

cUTIs are frequently associated with high rate of recurrence and reinfection which increases the risk of MDR bacterial selection and propagation. UTIs complicated by MDR pathogens lead to uncertain treatment outcomes prolonging hospitalization and hospital-associated costs. Moreover, prolonged duration of UTIs could also lead to secondary infections including sepsis, severe sepsis or septic shock. UTI can be a focus of septic shock in 20-30% of the patients and the rate varies with the associated co-morbid diseases [5] and thus complicating the treatment further. The various lines of treatment for cUTIs include intravenous (IV) or oral antibiotics, including fluoroquinolones, cephalosporins and other β-lactams with or without β-lactamase inhibitors, pip-taz, aminoglycosides and the last resort drug, carbapenems [6]. However, treatment decisions for UTIs have become more difficult in the face of increased AMR to the commonly used antibiotics over the past few years.

The continuous rise in bacterial resistance to the available antimicrobial agents has inspired the development of new agents to treat these resistant infections. CSE-1034, a novel

combination of Ceftriaxone, sulbactam and EDTA has been recently developed and proposed as alternate to curb the AMR menace to some extent. The synergistic action of ceftriaxone and beta-lactamase inhibitor component with the non-antibiotic adjuvant EDTA acting as a catalyst, this drug has been reported to be affective against multiple type of MDR pathogens [7][8]. In this study, we discuss a series of 20 patients suffering from cUTI or urosepsis and treated successfully with CSE-1034.

Material and Methods

Adult patients (age ≥18 years) who were admitted to the hospital for the treatment of cUTI or urosepsis and received treatment for ≥3 days were evaluated in this case series study.

The main criteria for patient inclusion were 1) The primary diagnosis of cUTI and urosepsis based on various lab parameters and relevant signs and symptoms2) Isolation of pathogen at the baseline 3) Received CSE-1034 as an empirical therapy based on the risk of MDR pathogen isolation at the baseline 4) Received CSE-1034 at least for a period of≥3 days.

The cUTI included had at least three of the following signs and symptoms: fever (>38°C) and chills, increased frequency and urgency of urination, dysuria, costo-vertebral angle tenderness or abdominal tenderness, flank pain, or the presence of pyuria and colony count of $\geq 10^5$CFU/ml was must (Expunge).

Urosepsis diagnosis was made based on presence of symptoms mentioned above for cUTI. And additionally accompanied by hyperventilation, tachycardia, hypotension or impairment of consciousness or confusion.

Exclusion criteria included patients who 1) Received treatment for <72h 2) Died within 72h due to multiple complications other than antibiotic failure.

Information regarding demographic and baseline characters like gender, age, type and source of infection, causative pathogen, co-morbidities, antibiotic therapy, dose and duration for all the patients was retrieved from case history sheets.

Patients had undergone various hematological and biochemical investigations including Hb test, total leukocyte count (TLC), urine analysis, urine culture and blood

culture. Specimens including urine and blood were used for the isolation of baseline pathogens.

In vitro microbial susceptibility testing of the isolated pathogen was done using Kirby–Bauer disk diffusion method. Using breakpoints provided by manufacturer, anti-microbial susceptibility for CSE-1034 was performed. Criteria was <21mm- S, 14-20- I, ≤13- R.

The CSE-1034 dosage used was 3.0g every 12h in all patients.

The clinical response of the therapy was evaluated in terms of improvement in clinical parameters on daily basis and microbiological response on the basis of pathogen eradication. Patients were considered as clinically cured when a) afebrile b) No dysuria c) Normal total blood count.

Results

A total of 95 patients admitted for cUTI and urosepsis were screened, out of which 20 patients meeting our inclusion criteria were evaluated in this case series study. Male gender was observed in 45% (9) of the patients whereas female gender represented 55% (11) of the patients. The age ranged from 38 to 60 years, with a mean age of 51. Demographic analysis data for other parameters like weight, height, respiration rate, pulse rate, SBP, DBP and temperature is mentioned in detail in Table 1. Based on the type of infection, the patient disposition was UTI-15 and urosepsis-5. All the analyzed patients were meeting inclusion and exclusion criteria. The most common co-morbidities associated with patients at the time of hospitalization were hypertension and diabetes mellitus. *E. coli*(%) was the predominant pathogen isolated from 12 patients followed by *K. pneumoniae* in 5(%) and *A. baumannii* in 3 (%)cases.

In vitro microbial testing has shown that pathogens isolated at baseline from all the patients were multi-drug resistant and showed resistance to various classes of drugs including cefipime, cefazolin, ceftriaxone, amikacin. 25% (5/20) patients were reported to be sensitive to pip-taz, 20% (4/20) to cefaperozone+sulbactam, 15% (3/20) to fluoroquinolones and 90% (18/20) patients were sensitive to meropenem. Microbial susceptibility test to CSE-1034 has shown that all the patients were sensitive to CSE-1034. The per pathogen antibiotic susceptibility details to various drugs are (Recasr) tabulated in Table 2.

Antibiotic outcome

All the 20 subjects included in this case series study were started CSE-1034 empirically. The decision of starting CSE-1034 empirically was based on the previous hospital exposure and prescription of beta-lactam or beta-lactam/beta-lactam inhibitor (BL/BLI) combination in last 90 days.

90% (18/20) of the patients showed signs of clinical improvement on 3rd day of CSE-1034 therapy and were continued with same treatment regime. Successful clinical response was observed in all these patients at the end of therapy. The mean treatment duration among these 18 patients was 5.0 days±2.69 (SD). 2 (10%) patients who were sensitive to CSE-1034 but showed poor clinical response on 3rd day of CSE-1034 treatment, were switched to CSE-1034 and levofloxacin combination therapy. After 48h of the combination treatment, it was observed that the patient started responding to the treatment based on the laboratory investigations and their clinical condition started improving (Table 3). The mean treatment duration in patients cured with CSE-1034 and levofloxacin combination therapy was 7.0 days±2.88 (SD).

Overall assessment of the clinical response has shown that CSE-1034 monotherapy cured 90% patients alone and 10% patients in combination with levofloxacin. The assessment of microbiological response has shown the complete eradication of the pathogen isolated at the baseline was observed in all 20 patients (Table 4). (All tables are expected to follow results in order of importance).

Discussion

The trend of AMR among pathogens causing cUTI has risen in epidemic proportions and continues to increase posing serious challenge to clinicians [9][10]. Of main concern are gram-negative pathogens, as these are one of the main causes of both community- acquired and hospital acquired UTIs. These organisms can acquire genes that encode for multiple antibiotic resistance mechanisms, including extended-spectrum-lactamases (ESBLs), AmpC- β -lactamase, and carbapenemases [11]. The MDR previously limited mostly to hospital-acquired strains, have recently witnessed a rising trend in community-based infections also [12]. Though the exact figures of ESBL producing organisms is not known globally, prevalence in Indian subcontinent is estimated to be around 50% by various studies [13][14]. In view of these rising resistant pathogenic bacteria, a great effort is needed to develop new antibacterial approaches especially in the setting of multi- antibiotic resistant pathogens. We here in this case series report on promising results of the use of CSE-1034 therapy for treating MDR cUTI cases.

Normally, the recommended first line empiric treatment for community acquired UTI of moderate to severe grade is fluoroquinolones or ceftriaxone. In the present study, all the pathogens isolated at the baseline from the patients were observed to be resistant to different classes of antibiotics including cefazolin, cefipime, ceftriaxone. 85% isolates were observed resistant to fluoroquinolones. Next to these drugs, pip-taz or cefaperozone+sulbactam are the most commonly used drugs and the second line of empirical treatment. The sensitivity rate to pip-taz and cefaperozone+sulbactam were observed to be 25% and 20% making it an inappropriate choice for empirical therapy or 2nd line of empirical treatment for cUTI cases in our hospital. Similar to these findings, various studies in the past have documented that gram-negative bacterial infections are gaining resistance to various anti-microbial drugs including the drug of last resort carbapenems. The AMR data in India has shown the resistance against pip-taz has risen to 65-70% and about 55-60% against cefoperazone+sulbactam [15].The indiscriminate consumptions of pip-taz or BL/BLI combinations could be one of the vital reasons for the high AMR reported among the normally recommended second line of treatment for UTIs. The random use of antibiotics often provides the patient with only a transient amelioration of the UTI symptoms and increases the risk of recurrence with multi-resistant drug bacterial strains. AMR data at a tertiary trauma care center of India has reported that the resistance against the five classes of antimicrobials were carbapenems (50%), aminoglycosides (66%), fluoroquinolones (76%), third generation cephalosporins (88%), BL/BLI combinations (63%) and extra-drug resistance was reported in 27% isolated pathogens [16]. Depending on the pathogen type, the lowest resistance to carbapenems was reported in *E. coli* (8%) and highest equivalent to 74% in *Acinetobacter*. Resistance rate against meropenem observed in this case series was low equal to 10% which is comparatively low than reported in the above study (Clarify the study). The difference in the microbiological profile with *E.coli* being the commonly isolated pathogen in this case series can partly explain the high sensitivity rate to meropenem. In support of our observations, a retrospective study conducted over a 7-year period from 2008 to 2014 has shown that carbapenem resistance increased in *E. coli* from 7.8% to 11.5% and *K. pneumoniae* increased from 41.5% to 56.6% [17]. Moreover, the susceptibility profile of the pathogens identified depends on the flora of the hospital and the common antimicrobials prescribed there.

Interestingly, all the patients were reported to be sensitive to a new combination of drug, CSE-1034. The higher susceptibility to CSE-1034 could likely be the synergistic effect

of the three components. Disodium edetate, a non-antibiotic adjuvant , present in CSE-1034 chelates the divalent metal ions leading to membrane destablilization and enhanced penetration of drugs inside bacterial cells. The sulbactam component of CSE-1034 is known to have inherent activity against various bacterial infections. In line with our results, various studies in the past have also demonstrated higher efficacy of CSE-1034 against various bacterial infections including UTI. Since, our novel drug was shown to effectively cure all the patients treated with CSE-1034 alone or in combination with levofloxacin, it can be an effective treatment choice for cUTI cases. While 90% sensitivity was also reported towards meropenem, the rising trend of MBL-producing bacterial strains can turn out epidemic if carbapenem use is not restricted. The indiscriminate prescription of carbapenems has lately led to epidemic rise to carbapenem resistance which if left unchecked will leave us with no standard treatment regimens for MDR infections. One of the best ways to prevent this MBL spread is by judiciously prescribing carbapenems and replacing them with the alternate effective therapies available like CSE-1034. 100% sensitivity was also observed against colistin, however, colistin is never preferred as empirical treatment because of its nephrotoxic side-effects. Additionally, colistin has been preserved as the last resort drug for the Extra- drug resistant pathogens. The high sensitivity to colistin could more likely be the outcome of

its very restricted use and preserving it as the last line of treatment.

In total, all these results support that CSE-1034 is a valuable replacement of various BL/BLI combinations for the treatment of cUTI cases because of several associated advantages. First, CSE-1034 was observed to have excellent susceptibility profile qualifying it for empiric therapy. Secondly, all the patients treated with CSE-1034 empirically alone or in combination with levofloxacin therapy were completely cured. And most importantly, CSE-1034 is a combination of beta-lactam and beta-lactamase along with EDTA, and thus can help to spare the carbapenems as last line of treatment by reducing use of carbapenems.

(Authors interchanging sensitivity and resistance is confusing; l suggest using either sensitivity or resistance for proper communication of research outcome to readers).

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Table 1: Demographic and baseline characteristics of all study subjects (n=20).

Characteristics		(n=20)
Gender	Male, n (%)	9 (45)
	Female, n (%)	11 (55)
Age (year)	Mean±SD	51±7.3
Height (cm)	Mean±SD	167±9.14
Weight (kg)	Mean±SD	72±11.2
BP (mm of Hg)	Systolic (Mean±SD)	130±21.83
	Diastolic (Mean±SD)	80±13.18
Pulse (beats/min)	Mean±SD	100±10.68
Respiratory rate (/min)	Mean±SD	21.5±7.09
Diagnosis n (%)	UTI	15 (75)
	Urosepsis	5 (25)
Co-morbidities n (%)		
	DM	12 (60)
	Hypertension	08 (40)
	Hypothyroidism	04 (20)
	COPD	02 (10)
	Others	03 (15)
Pathogen n (%)		
E. coli	N (%)	12 (60)
K. pneumoniae	N (%)	05 (25)
A. baumannii	N (%)	03 (15)

*Others include CAD, gastritis, osteoporosis.

306 **Table 2. In-vitro antibiotic susceptibility testing of the pathogen isolated to various**
307 **antibiotics.**

(Antimicrobial agent are reported in % for reference purpose)

Antibiotic	*E. coli*		*K. pnuemoniae*		*A. baumannii*	
	Resistant	*Sensitive*	*Resistant*	*Sensitive*	*Resistant*	*Sensitive*
Cefipime	12 (%)	0	5	0	3	0
Cefazolin	12 (%)	0	5	0	3	0
Ceftriaxone	12 (%)	0	5	0	3	0
Pip.taz	9 (%)	3	4	1	2	1
Cefaperazone-	10 (%)	2	5	0	3	0
Sulbactam						
Fluoroquinolones	11 (%)	1	4	1	2	1
Meropenem	0	12	4	1	2	1
CSE-1034	0	12	0	5	0	3

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309 **Table 3: Hematology parameters (mean) of all the treatment groups before and after treatment.**
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Laboratory parameters	Screening	Completion	p-value
Hb (g %)	11.02±1.96	11.19±1.77	0.775
E.S.R (mm/h)	40.7±19.36	32.03±11.73	0.0949
T.L.C (/mm3)	10636.2±4647.05	9589.41±2956.01	0.4007
Lymphocytes (%)	12.23±5.03	20.17±8.52	0.0009
Blood Urea nitrogen (%)	19.5±10.07	13±8.52	0.025
S. Creatinine (mg/dl)	1.36±0.56	0.73±0.49	0.0005
S.G.P.T (U/L)	31.01±9.84	20.63±8.71	0.0011
S.G.O.T (U/L)	39.03±13.08	22.81±8.11	0.0001
A.L.P (U/L)	141.85±36.27	101.74±23.19	0.0002
International normalized ratio (INR)	0.91±0.12	0.95±0.10	0.259
Prothrombin time	11.4±1.17	11.7±1.24	0.44

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312 **Table 4. Display of outcomes based on the type of infection and pathogen.**

	CSE-1034	CSE-1034+Levofloxacin
Total		
Clinical cure	18/20 (90)	2/20 (10)
Clinical failure	2/20 (10)	0
Based on infection		
UTI	13/15 (86.7)	2/15 (13.3)
Urosepsis	2/5 (40)	3/5 (60)
Based on pathogen		
E. coli	12/12 (100)	0
K. pneumoniae	4/5 (80)	1/5 (20)
A. baumannii	2/3 (66.6)	1/3 (33.3)

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