Original Research Article

A retrospective study to analyze the efficacy of ceftriaxone+sulbactam+EDTA combination for complicated urinary tract infections in diabetic patients.

Abstract

Objective

In general, infectious diseases are more frequent and/or serious in patients with diabetes mellitus, complicated further by antimicrobial resistance which potentially increases their morbi-mortality. The objective of this study was to determine the clinical utility of CSE-1034 (Ceftriaxone+Sulbactam+EDTA) in diabetic patients with complicated urinary tract infections (cUTIs).

Methods

Diabetic patients with cUTIs who received CSE-1034 as empiric therapy were screened and further analyzed. CSE-1034 therapy was started empirically in all these subjects and continued or discontinued based on culture susceptibility profile and clinical outcome. The statistical analysis was performed using Chi-square test.

Results

Out of 85 patients admitted for cUTI, 38 patients met our inclusion criteria and were included in this study. *E. coli* was the predominant pathogen isolated followed by *K. pneumoniae*. In vitro susceptibility testing has shown no susceptibility of baseline pathogens to levofloxacin, gentamicin, ceftriaxone, cefepime, cefazolin, 23.6% to pip-taz, 18.4-23.6% to beta-lactambeta-lactam inhibitor (BL/BLI) combinations, 63.1% to meropenem and 100% to CSE-1034. 92.1% of the patients were cured with CSE-1034 empiric therapy and 7.9% with alternate meropenem therapy.

Conclusion

From this study, it can be suggested that CSE-1034 alone appears to be effective drug for the treatment of multi-drug resistant cUTI in diabetic patients and can serve as effective alternate to meropenem and replacement for BL/BLI combinations.

Key words: Multi drug resistance; Extended Spectrum Beta-Lactamase; Metallo-β-lactamase; Gram-negative.

Introduction

Type 2 Diabetes mellitus (DM) is a heterogeneous group of disorders resulting from impaired insulin secretion or action leading to elevated levels of glucose. Other than the classical complications associated with DM, other outcomes include altered immune responses including impaired humoral immunity, decreased neutrophil action and reduced response of T cells [1 2 3 4]. Consequently, DM raises the risk of contracting infections, including the most common ones as well as those that almost only affect people with DM [2 5]. In addition to the associated repercussions, such infections may lead to serious manifestations and/or trigger DM complications.

Urinary tract is one of the most common infection site in individuals with DM. [25–27] Asymptomatic bacteriuria and symptomatic urinary tract infections (UTIs) are both reported to be more frequent in patients with type 2 diabetes than in the general population [6 7]. Available evidences also suggest that type 2 diabetes increases susceptibility to serious complications of UTI, including emphysematous conditions of the bladder or kidney, renal abscess, and renal papillary necrosis [8 9 10]. The different mechanisms that may contribute to the higher frequency of UTI and related complications among diabetic patients include impaired immune system, primarily diabetic nephropathy and cystopathy, recurrent vaginitis, incomplete bladder emptying, poor glycemic control, and higher glucose levels in the urine which may facilitate the growth of pathogenic organisms [5 7 8].

Given the increasing incidence of type 2 diabetes mellitus worldwide in recent years projected to be 380 million cases in 2025 and the clinical link between diabetic status and UTI risk and severity, a substantial burden of UTIs is going to increase [11]. Moreover, the high rates of antibiotic prescription in these patients, including broad-spectrum antibiotics, may

further induce the development of multi-drug resistant urinary pathogens [1213]. Ceftriaxone fortified with sulbactam and antibiotic resistance breaker "EDTA" (CSE-1034) is a newly approved antibiotic adjuvant entity for the treatment of infections caused by Extended Spectrum Beta-Lactamase/Metallo-β-lactamase (ESBL/MBL) producing gram negative pathogens [14 15 16 17]. In this study, we discuss a series of 25 diabetic patients suffering from cUTI and treated successfully with CSE-1034.

Material and Methods

Study population

The case history sheets of all the patients admitted to the hospital for treatment of bacterial infections between June 2016 to June 2017 were analyzed. Adult diabetic patients with age of ≥18 years and treated for cUTI were included in this retrospective study. The criteria for patient selection were 1) Diabetic patients diagnosed with cUTI based on various lab parameters and relevant signs and symptoms 2) Isolation of gram-negative pathogen at the base-line 3) Patients who received CSE-1034 at least for a period of ≥48h 3) Patients who received CSE-1034 as 2nd line of therapy.

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.

Patient analysis, antibiotic usage and outcomes

Information regarding demographic and baseline characters including gender, age, infection type and source, pathogen isolated, co-morbidities, antibiotic therapy, dose and duration for all the patients was retrieved from the case history sheets of the patients. Among all the cases analyzed, 25 patients who received CSE-1034 as empirical therapy and fulfilled the other above mentioned inclusion criteria were analyzed further.

Different specimens including urine and blood of the patients were tested for the diagnosis of etiological agent. Various hematological and biochemical investigations including Hb test, total leukocyte count (TLC), differential leukocyte count (DLC), liver function test (LFT), kidney function test (KFT) were carried out at the beginning and the end of treatment to evaluate the clinical progress of the patient and drug efficacy.

In-vitro microbial antibiotic-susceptibility testing (AST)

Kirby–Bauer disk diffusion method was used to test the microbial susceptibility of the antibiotics. Discs for various drugs including pip-taz, CSE-1034, meropenem and colistin were used and the results were interpreted as per the interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI) guidelines [18]. Depending on the breakpoints, the antimicrobial susceptibility of the pathogens involved was classified into susceptible, intermediate or resistant. Criteria for CSE-0134 was >21mm-S, 14-20-I, ≤13-R.

Antibiotic dosage

The dose of CSE-1034 used was 3.0g/12h. The progress of the therapy was evaluated in terms of improvement in clinical parameters on daily basis and at the end of treatment.

Definitions

Clinical success: The patient's response was considered as clinical success when, the patient recovered with either first line or 2nd line empiric antibiotic therapy.

Clinical failure: The response was considered as clinical failure when the patient was switched to other antibiotics or one or more antibiotics are added to the initial regime.

First line antibiotic therapy: It is defined as the regime started immediately after 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 culture susceptibility results.

Results

Out of 85 patients admitted for cUTI, 38 patients met our inclusion criteria and were included in this case series study. The characteristics of all the 85 cUTI patients which were screened and the subgroup patients with diabetes mellitus are presented in Table 1. Of the total patients screened, 55.3% of the patients consisted of males and 44.7% represented the female patients. However, in the subgroup of cUTI patients with diabetes mellitus, the male female ratio was 1:1. Overall, the mean age, systolic pressure, pulse and respiratory rates were similar in the two groups. However, the average weight and diastolic pressure was higher is cUTI patients with diabetes mellitus compared to the other group. For other

demographic features, refer to Table 1. The most common co-morbidities associated with cUTI patients which were screened at the time of hospitalization were diabetes mellitus, hypertension and hepatic disorders. 38 cUTI patients with diabetes mellitus were included in the final study analysis. In both the categories, *E. coli* was the predominant pathogen isolated followed by *K. pneumoniae*. Other isolated pathogens at the baseline included *A. baumannii* , *P. aeruginosa* and *P. mirabilis*. For further details, refer to Table 1.

Anti-microbial susceptibility testing has shown that baseline pathogens isolated from the patients were multi-drug resistant and were resistant to various classes of drugs including levofloxacin, gentamicin, ceftriaxone, cefepime and cefazolin. 23.6% (9/38) patients were reported susceptible to pip-taz, 18.4% (7/38) to cefaperozone-sulbactam, and 63.1% (24/38) to meropenem. In vitro susceptibility test to CSE-1034 has shown 100% susceptibility to CSE-1034. The per pathogen antibiotic susceptibility details to various drugs are tabulated in Table 2.

Antibiotic outcome

All the subjects included in this retrospective analysis received CSE-1034 empirically. Because of the hospital exposure in the last 90 days and prescription of beta-lactams or BL/BLIs before, CSE-1034 was started empirically in these patients by the concerned physician.

92.1% (35/38) of the patients who received CSE-1034 empiric therapy were observed to respond positively on the 3rd day of treatment and were continued on the same treatment therapy. These patients showed successful clinical response at the end of therapy and were completely cured. The average treatment duration in these 35 patients was 11.0 days±2.89 (SD).

2 (5.3%) patients who were started empirically with CSE-1034 but were found resistant after in vitro microbial susceptibility testing, were shifted to meropenem. 1 (2.6%) patients who showed poor clinical response to CSE-1034 therapy despite being CSE-1034-susceptible, were also switched to meropenem therapy (Figure 1).

After 48h of meropenem treatment, it was observed that all the three patients responded to the treatment based on the visible improvement in clinical conditions and laboratory investigations.

Overall assessment of the clinical response has shown that CSE-1034 monotherapy cured 92.1% patients alone. 7.9% patients were cured by meropenem treatment.

Discussion

In this study, 44.7% of the patients with cUTI were having diabetes as co-morbidity, which was comparatively little higher than reported in other Asian countries in various studies (range 13.0%–24.4%) [19] [20] [21]. However, in conformity to our observations, a UK-based observational study in a primary care setting on the incidence of UTIs have reported 60% increase in the risk of UTIs among patients with diabetes (n = 135,920) compared to 1:1 matched sample of patients without diabetes [22]. Another retrospective study based in China has reported the prevalence of UTIs in diabetic patients was 11.2% [23]. The relatively higher rate in our study could be because both male and female diabetic patients were included in our study, while the studies based in Asia generally included female diabetic patients. In our study, prevalence of UTIs in diabetic women was about double compared to diabetic men, which is related to the characteristics of female urinary tract. Beside the female gender, old age, BMI and diastolic pressure were also observed as risk factors of UTIs in diabetic patients; however, systolic pressure, and other demographic features had no relation with UTIs. The results were in accordance with previous studies [19] [23]. The most common pathogenic microorganisms isolated from UTI patients and cUTI patients with diabetes mellitus were similar and included *E. coli*, *K. pneumoniae* and *A. baumannii.* The results are similar to those of other studies [23] [24]. He *et al.* [23] and Li *et al.* [25] have reported *E. coli* and *K. pneumoniae* as the most common isolates from cUTI patients alone or with diabetes mellitus.

Regarding the antimicrobial resistance profile of uropathogens in the present study, it was observed that all the isolates were multi-drug resistant, resistant to different classes of antibiotics including levofloxacin, gentamicin, ceftriaxone, cefepime and cefazolin. Pip-taz or cefoperozone-sulbactam are the most common choices as 1st line of empirical treatment for patients suspected of hospital acquired infections. As only 18.4-23.6% patients were reported susceptible to BL-BLIs, thus it makes an inappropriate choice for empirical therapy or 2nd line of empirical treatment for cUTI cases in our hospital. Similar to our observations, 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 resistance against pip-taz has risen to 65-70% and about 55-60% against cefoperazone-sulbactam [26].The indiscriminate prescription of BL/BLI combinations can be one of the vital reasons for the high AMR reported among the normally recommended 1st line of treatment for UTIs. AMR data at a tertiary trauma care

center of India has reported the resistance against the five classes of antimicrobials as carbapenems (50%), aminoglycosides (66%), fluoroquinolones (76%), third generation cephalosporins (88%), BL/BLI combinations (63%) and extra-drug resistance was reported in 27% isolated pathogens [27]. Almost similar to above report, 36.9% were observed susceptible to meropenem in our study. Increase in carbapenems resistance has been linked with excessive carbapenem consumption. Hence selection pressure on carbapenems needs to be reduced either by reducing their consumption by using alternative drugs or developing newer therapeutic options. There are several publications about use of alternative agents for treating ESBL infections rather than carbapenems so as to reduce selection pressure without compromising clinical outcomes [28] .

Interestingly, all the patients were reported susceptible 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 [15 17]. Since, CSE-1034 was shown to effectively cure 92.1% of the patients alone, it can serve as effective choice of treatment for cUTI in diabetic patients.

CONCLUSION

Overall, the high carbapenem resistance reported among Gram-negative strains is a matter of grave concern and needs to be addressed at priority. The antibiotic Adjuvant Therapy scored over different β-lactam and β-lactamase inhibitor combinations and carbapenem*s* due to its resistance breaking mechanisms for the treatment of cUTI in diabetic patients.

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287 **Table 1: Patient baseline characteristics.**

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Characteristics		**(n=85)**	**(n=38)**
Gender	Male, n (%)	47 (55.3)	19 (50.0)
	Female, n (%)	38 (44.7)	19 (50.0)
Age		70±13.4	70±10.05
Weight (kg)	Mean±SD	70±13.75	77±12.8
Temperature (°F)	Mean±SD	98.6±1.02	98.6±1.31
BP (mm of Hg)	Systolic (Mean±SD)	130±19.58	130±17.9
	Diastolic (Mean±SD)	74±10.88	70±10.47
Pulse (beats/min)	Mean±SD	78±14.42	78±19.41
Respiratory rate (/min)	Mean±SD	18±3.89	18±2.95
Co-morbidities n (%)			
	DM	38 (44.7)	
	Hypertension	29 (34.1)	
	Hepatic disorders	12 (14.1)	
	Chronic kidney disease (CKD)	05 (5.9)	
	Others	07 (8.2)	
Baseline pathogen in urine n (%)			
	E. coli	42 (49.4)	19 (50.0)
	K. pneumoniae	22 (25.9)	8 (21.1)
	A. baumannii	11 (12.9)	5 (13.2)
	P. mirabilis	6 (7.1)	3 (7.9)
	P. aeruginosa	4 (4.7)	3 (7.9)

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293 **Table 2: Per pathogen type susceptibility pattern to different antibiotics.**

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Susceptibility (%)									
Clinical isolates	**No. of isolates**	**CSE-1034**		**Meropenem**		**Pip-Taz**		**Cefoperazone-Sulbactam**	
		S	**R**	**S**	**R**	**S**	**R**	**S**	**R**
E. coli	**19 (50.0)**	**19 (100)**	**0**	**15 (78.9)**	**4 (21.1)**	**4 (21.1)**	**15 (78.9)**	**2 (10.5)**	**17 (89.5)**
K. pneumoniae	**8 (21.1)**	**8 (100)**	**0**	**5 (62.5)**	**3 (37.5)**	**2 (25.0)**	**6 (75.0)**	**1 (12.5)**	**7 (87.5)**
A. baumannii	**5 (13.2)**	**5 (100)**	**0**	**2 (40.0)**	**3 (60.0)**	**1 (20.0)**	**4 (80.0)**	**1 (20.0)**	**4 (80.0)**
P. mirabilis	**3 (7.9)**	**3 (100)**	**0**	**1 (33.3)**	**2 (66.7)**	**1 (33.3)**	**2 (66.7)**	**1 (33.3)**	**2 (66.7)**
P. aeruginosa	**3 (7.9)**	**3 (100)**	**0**	**1 (33.3)**	**2 (66.7)**	**1 (33.3)**	**2 (66.7)**	**2 (66.7)**	**1 (33.3)**

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296 **Figure1: Flowchart elaborating the study structure and outcome.**
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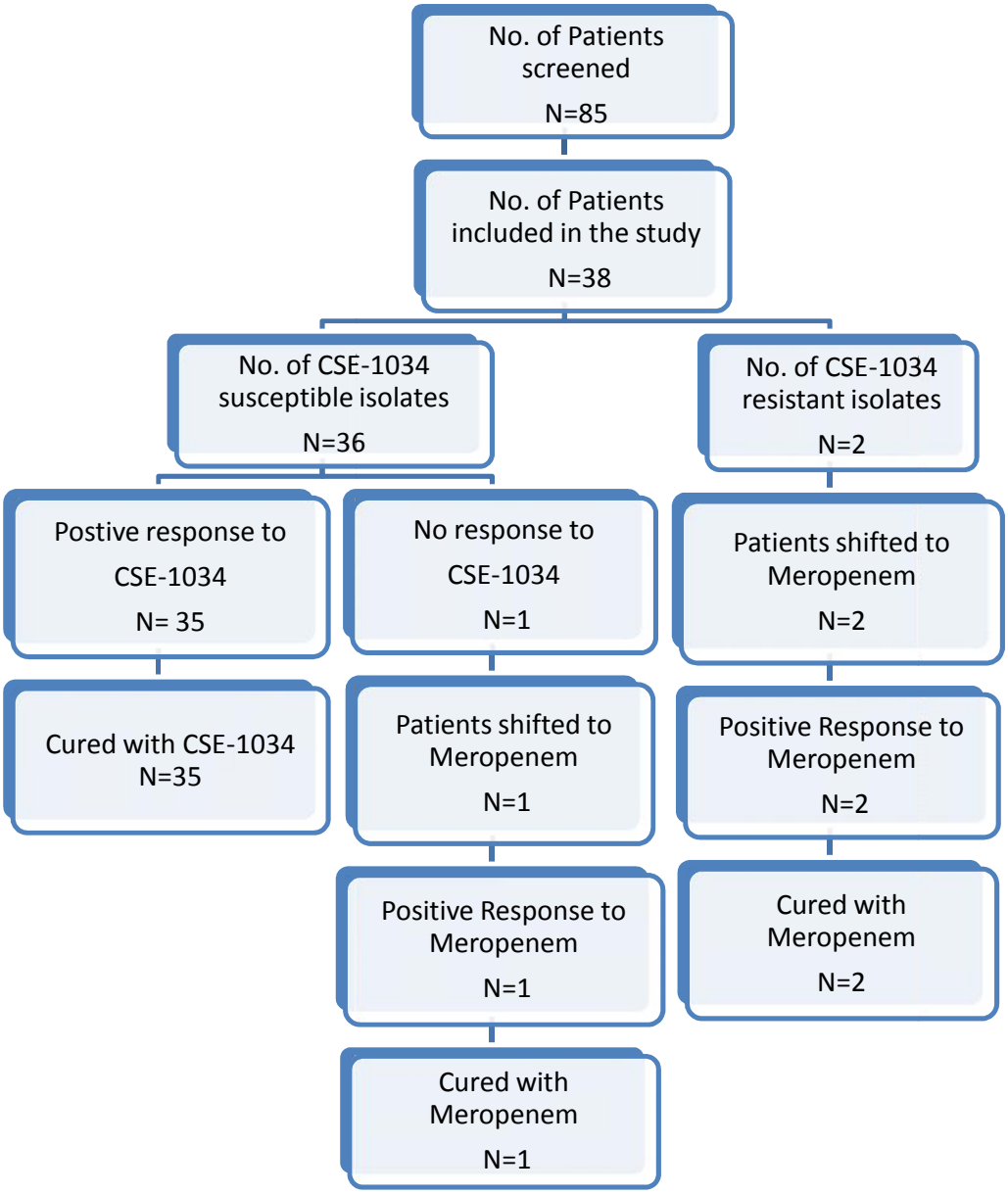

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