Is Cefoxitin a Carbapenem Sparing Agent in the Management of Urinary Tract Infections Caused by ESBL Producing *Enterobacterales*?

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Abstract

Background: Cefoxitin has shown in vitro activity against Extended-Spectrum β-Lactamase (ESBL) producing *Enterobacterales*. Outcome data regarding cefoxitin as a carbapenem sparing agent in the management of urinary tract infections (UTI) are scarce. We sought to evaluate the clinical and microbiologic efficacy of cefoxitin as compared to ertapenem. **Methods:** A retrospective observational study was conducted at our quaternary care institution between May 2015 and March 2019. We identified all patients who received cefoxitin for the treatment of UTI during the study period and used Charlson Comorbidity Index to select a matching cohort from patients who received ertapenem. Primary end points were clinical and microbiological cure. **Results:** Thirty patients who received cefoxitin were matched with 55 patients who received ertapenem. Clinical cure was marginally in favor of ertapenem: 83.2% in cefoxitin group versus 96.8% in ertapenem group ($P = .042$). However, 90-day recurrence was in favor of cefoxitin: 13.5% in cefoxitin group versus 34.8% in ertapenem group ($P = .045$). Microbiologic cure was not significant between the 2 groups with 88.6% success in cefoxitin versus 100% in ertapenem. Additionally, the group difference on 30-day recurrence or relapse rates and the 90-day mortality rate were not clinically significant. **Conclusion:** Cefoxitin achieved similar microbiologic cure rate when compared to ertapenem for the treatment of UTI caused by ESBL-producing *Enterobacterales*. No significant differences were found in 30-day recurrence/relapse or mortality rates. Larger randomized controlled trials are required to identify the clinical sittings in which cefoxitin could be used as a carbapenem-sparing agent in the treatment of UTI.

Keywords

cefoxitin, ESBL, carbapenem, sparing, UTI

Introduction

Extended-spectrum β-lactamase (ESBL) producing *Enterobacterales* such as *Klebsiella pneumoniae* and *Escherichia coli* have been recognized as a global microbiologic threat due to their antimicrobial resistance.[1] ESBL resistance genes, found in the plasmid, encode the bacterial resistance against third generation cephalosporins and monobactams.[2-4] These bacteria usually possess other genes encoding resistance to different antibiotic classes, such as aminoglycosides, macrolides, sulfonamides, and fluoroquinolones.[1,2,5] Carbapenems are considered the antibiotics of choice for such resistant strains.[6,7] However, the over-utilization of carbapenems as empiric therapy in response to ESBL-producing organisms' have led to the emergence of carbapenemase-producing *Enterobacterales* (CPE).[8,9]

Therefore, to reduce carbapenem overuse, alternative antimicrobial agents of narrower spectrum should be considered whenever feasible. At our institution, ertapenem is considered the formulary carbapenem.

Cefoxitin is a cephamycin antibacterial agent with time-dependent bactericidal activity. Cephamycins are classified as second generation cephalosporins with reasonable activity against E. coli, P. mirabilis, and *Klebsiella* as well as

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Bacteroides spp.[10-12] Cefoxitin has several indications including treatment of UTI.[10] Cefoxitin has shown in vitro activity against ESBL producing organisms which could be rendered to its resistance to hydrolysis by β-lactamase-producing organisms.[13] It has been proposed as a potential alternative for carbapenems in the treatment of UTI caused by ESBL-producing bacteria.[14]

Despite the well documented in vitro activity of cefoxitin against ESBL producing organisms, to date, a limited number of relatively small studies have evaluated its clinical efficacy of cefoxitin in treating ESBL producing organisms in humans.[12] The limited available evidence demonstrated encouraging results for the use of cefoxitin in treating UTIs caused by ESBL-producing bacteria. However, a major drawback is the small sample size of these studies.[14-17] Furthermore, cefoxitin is not listed as a treatment option for urinary tract infections caused by ESBL producing organisms in the latest Infectious Diseases Society of America (IDSA) guidelines.[18]

At our quaternary care hospital, the incidence of ESBL producing organisms is around 30%, hence our Antimicrobial Stewardship Program (ASP) team advocates sparing carbapenems by using alternative agents such as cefoxitin and aminoglycosides to treat UTI caused by these resistant organisms.[19] Therefore, we sought to evaluate the clinical and microbiologic efficacy of cefoxitin compared to ertapenem as the standard of care.

Methods

This retrospective observational study was conducted at our quaternary care institution between May 2015 and March 2019. Data collection was started after the receipt of the hospital's Research Ethics Committee approval number A-2019-024. We included all admitted adults (≥18 years) who had confirmed UTI due to ESBL-producing organisms and received cefoxitin for most of the treatment duration (as defined below). Cefoxitin patients were matched to patients who received ertapenem during the same study period using the Charlson Comorbidity Index (CCI) at a 1:2 ratio. We excluded asymptomatic and colonized patients as well as ambulatory patients who were treated with oral agents. Primary end points were clinical and microbiologic cure, while secondary end points included relapse or recurrence within 30 and 90 days and 90-day mortality.

Variables' Definition

Patients who received cefoxitin therapy for most of the duration of treatment are those who received cefoxitin either for the full duration of therapy or as a de-escalation therapy (ie, after 48-72 hours of empiric therapy-once susceptibility results were finalized). Urinary tract infection was defined as presence of bacteria in the urine that can't be accounted for by contamination with accompanying signs and symptoms

of infection. Clinical cure was defined as absence of signs and symptoms of UTI (mainly; dysuria, hematuria, and fever) in 72 hours from start of the antibiotic as documented by the physicians with no further need for additional antibiotic therapy. Relapse/recurrence; re-emergence of signs and symptoms of infection and microbiological confirmation for same or different organism. Clinical failure was defined as persistence of functional urinary symptoms more than 72 hours in the presence of repeat positive cultures, and/or clinician documentation of failure. Microbiologic cure was defined as negative repeat culture during or immediately after end of therapy. Relapse or recurrence was defined as positive repeat urinary culture for the same organism accompanied by clinical symptoms of UTI within 30 and 90 days. The laboratory at our hospital screen for ESBL using the Vitek-2 system then confirm with the E-test (ceftazidime and ceftriaxone with and without clavulanic acid), then divide the minimum inhibitory concentration (MIC) with and without clavulanate to get the results.

Data Collection

All data were collected from the electronic medical record system; patient's demographics (age, gender, race, weight, and height) and co-morbidities were collected for the analysis of baseline characteristics. Infection parameters (vitals and white blood cell count (WBCs)), urine analysis, urine culture, and cultures from the blood or other sites, were all documented. Additional data collected included any antimicrobials, duration of therapy, length of hospital stay, and mortality. Charlson Comorbidity Index was used to identify patients who were treated with ertapenem during the same period.

Statistical Analysis

Prior to data analysis, baseline/demographics and outcomes analyses, in all instances where continuous variables were examined, the Shapiro-Wilk test was used to examine normality (alpha criteria of .05). The null hypothesis was retained in all instances (admittedly possibly due to small sample size), so when examining group differences on continuous variables, we focused on mean differences (not median differences).

Groupings were based on the administered antimicrobial: cefoxitin or ertapenem. Baseline and demographic comparisons between the groups were performed. When the baseline/demographic variables of interest were continuous, dichotomous, or categorical with more than 2 groups, independent samples *t*-tests, Fisher's exact tests, and chi-squared tests respectively were used to assess group differences.

Unadjusted group differences on dichotomous and continuous outcomes were assessed using Fisher's exact test and independent samples *t*-test respectively. Adjusted/conditional group differences on the dichotomous outcome/

Table 1. Demographics and Baseline Characteristics of the Study Sample.

Characteristic	Cefoxitin (n = 30)	Ertapenem (n = 55)	P value
Gender (%)			.11
Female	40 (12)	58.1 (32)	
Age (mean ± SD) years	68.03 ± 18.26	74.82 ± 12.798	.049
BMI (mean ± SD)	28.58 ± 5.51	28.82 ± 6.76	.87
DM (%)	63.33 (19)	74.55 (41)	.28
CAD (%)	20 (6)	18.18 (10)	.84
Hypertension (%)	53.33 (16)	81.82 (45)	.0068
Dyslipidemia (%)	53.33 (16)	60 (33)	.55
Liver disease (%)	13.33 (4)	12.73 (7)	.94
Cerebrovascular accident (%)	36.67 (11)	10.91 (6)	.0069
COPD (%)	10 (3)	25.45 (14)	.1
CHF (%)	26.67 (8)	21.82 (12)	.62
Mechanically ventilated (%)	13.33 (4)	3.64 (2)	.12
Renal function			.225
Normal renal function (%)	43 (13)	50.9 (28)	
Acute kidney injury (%)	13.3 (4)	5.4 (3)	
Chronic kidney disease (%)	30 (9)	40 (22)	
Acute on of chronic kidney disease (%)	10 (3)	0.36 (2)	
End stage kidney disease (%)	3.3 (1)	0	
Chronic respiratory failure (%)	20 (6)	7.27 (4)	.09
Foley catheter at time of infection (%)	63.3 (19)	42 (23)	.077
Organism in first culture			.686
E. coli (%)	56.6 (17)	60 (33)	
Klebsiella spp. (%)	43.3 (13)	36.3 (20)	
Both E. coli and Klebsiella spp. (%)	0	3.6 (2)	
Concomitant antibiotic (%)	6.7 (2)	0	.122
Charlson Comorbidity Index (mean ± SD)	5.87 ± 2.56	6.53 ± 2.58	.26
Antibiotic dose in gram (mean ± SD)	1.433 ± 0.5	1.01 ± 0.36	NA
Frequency in hour (mean ± SD)	9.73 ± 5.53	23.93 ± 4.25	NA
WBC at therapy initiation × 10^9/L (mean ± SD)	12.96 ± 5.17	11.32 ± 5.92	.21
Temperature at therapy initiation °C (mean ± SD)	37.33 ± 0.73	37.32 ± 1.07	.95
CRP at therapy initiation in mg/L (mean ± SD)	52.09 ± 59.86	87.79 ± 80.12	.08
Procalcitonin at therapy initiation in ng/mL (mean ± SD)	0.1648 ± 0.16	0.19 ± 0.33	.75

Note. BMI = Body Mass Index; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; DM = diabetes mellitus.

endpoint variables were assessed using logistic regression. Continuous outcome/endpoint variables, adjusted/conditional group differences were assessed using OLS regression. Group values were adjusted by CCI via the inclusion of this score as a grand-mean centered covariate in the respective regression models. Thus, regression models estimating adjusted/conditional group differences consisted of only 3 terms: an intercept term, dichotomous drug group indicator, and the grand-mean centered CCI covariate.

We note that though we limited the sample to a narrow range on the CCI and further attempted to statistically equate groups on the CCI via regression adjustments, the cefoxitin/ertapenem group comparisons were potentially impacted other confounding variables not explicitly included in the study design plan or analytic strategies discussed. A 2-tailed alpha criteria of .05 was used to determine statistical significance in all instances. All analyses were performed using Microsoft R Open version 3.5.2.

Results

Patients demographics and baseline characteristics are illustrated in Table 1. Thirty patients met the inclusion criteria and received cefoxitin during the study period (18, 60% males). Fifty-five matched controls were included in the analysis (23, 42% males). There was no statistically significant difference in baseline characteristics and demographics between the groups with exception of age, hypertension, and cerebrovascular accident as described in Table 1. All patients had either cystitis, pyelonephritis, or catheter related UTI. The mean age of the cefoxitin group was 68 ± 18.3 versus 74.8 ± 12.8 for the ertapenem group (*P* = .049), while 82% of

Table 2. MIC to Cefoxitin in Both Groups.

	Cefoxitin group MIC to cefoxitin	Ertapenem group MIC to cefoxitin
E. coli MIC		
4 mg/L or less	15	21
8 mg/L	2	7
16 mg/L	0	2
32 mg/L	0	1
64 mg/L	0	3
Klebsiella MIC		
4 mg/L or less	13	11
8 mg/L	0	6
16 mg/L	0	2
34 mg/L	0	1
64 mg/L	0	1

Note. Two patients in ertapenem group grew both organisms so were accounted for twice.

the ertapenem group had hypertension as compared to 53% in cefoxitin group ($P = .0068$), and 36% of the cefoxitin group had cerebrovascular accident as compared to 10% in the ertapenem group (0.0069). There was no significant difference in CCI between the groups (cefoxitin score 5.87 ± 2.56 vs 6.53 ± 2.58 for ertapenem; $P = .26$). Twenty-three patients received cefoxitin in the acute care units and 7 in the Intensive Care Unit (ICU) and similarly 41 patients received ertapenem in the acute care units and 14 in the ICU. Table 2 represent the MIC to cefoxitin in both groups.

Adjusted group comparisons (tables 3 and 4) indicate that cefoxitin had similar outcomes when compared to ertapenem for the following endpoints: microbiological cure, vasopressor use, 30-day recurrence/relapse, mortality, days of therapy, days to inflammatory markers normalization, and days to defervescence. However, statistically significant adjusted group differences were found for clinical cure (OR = 0.16, $P = .042$) and relapse/recurrence within 90 days (OR = 0.29, $P = .045$). Specifically, clinical cure was marginally in favor of ertapenem: 83.2% in cefoxitin group versus 96.8 % in ertapenem group. Ninety-day recurrence was in favor of cefoxitin: 13.5% in cefoxitin group versus 34.8% in ertapenem group.

The organisms causing UTI in this study are listed in Table 1. Out of the 30 patients in the cefoxitin group, 8 patients received cefoxitin for the full duration of treatment, 17 patients were treated empirically with other antimicrobials then switched to cefoxitin. Empiric therapies included; ertapenem (9), ciprofloxacin (2), meropenem (1), or piperacillin/tazobactam (1), or others (4). Empiric therapy was administered for a duration of 48 to 72 hours while awaiting culture results, which was then switched to cefoxitin for the rest of therapy duration. Three out of 30 patients failed cefoxitin therapy; 1 had persistent *Klebsiella* and grew *Actinobacteria* in the sputum, the antibiotic was changed to colistin, and another patient expired. Four out of 30 patients were switched to an alternative therapy due to related infections; 2 with pneumonia for which 1 switched to ciprofloxacin and the other to piperacillin/tazobactam. A third patient grew pseudomonas in the sputum and was switched to ciprofloxacin. Four of the 30 patients (including 2 of the failed cefoxitin therapy) were switched to different antibiotics due to other infections, one of them due to pneumonia and was switched to ciprofloxacin and the other to piperacillin/tazobactam. A third patient was switched to ciprofloxacin due to concomitant infection with *Pseudomonas* in sputum. Two patients in the cefoxitin group received concomitant antibiotic therapy not related to UTI (vancomycin for cellulitis and azithromycin for chronic obstructive pulmonary disease exacerbation).

Ertapenem was 1 g intravenously (IV) daily (reduced to 500 mg IV daily in patient with eGFR < 30 mL/minute/m^2) and the most commonly used of cefoxitin was 1 to 2 g every 6 hours and reduced to 1 to 2 g every 12 to 24 hours in patients with compromised renal function. Of patients who had repeat cultures which showed persistent bacteria (cefoxitin = 3 *Klebsiella* Spp., and ertapenem = 2 *Klebsiella* Spp., and 1 *E. coli*).

Discussion

Although this topic has been studied before, due to lack of large scale controlled clinical trials, we aimed to corroborate the available evidence by adding to the literature the results of our retrospective analysis which included a relatively larger number of patients with UTI's with mixture of organisms.

This study sought to evaluate the efficacy of cefoxitin in treating UTI secondary to ESBL-producing *Enterobacterales*. Adjusted group comparisons indicate that cefoxitin had similar outcomes when compared to ertapenem for microbiological cure, vasopressors use, relapse or recurrence within 30 days, mortality, days of therapy, days to inflammatory markers normalization, and days to defervescence. Statistically significant adjusted group differences were found for clinical cure (OR = 0.16, $P = .042$) and relapse/recurrence within 90 days (OR = 0.29, $P = .045$). These findings suggest that cefoxitin could be a carbapenem sparing agent in the treatment of simple and complicated UTI caused by ESBL-producing *Enterobacterales*. Of note, our institution protocol/policy recommends high dose (cefoxitin 2 g IV every 6 hours) to achieve the pharmacokinetics/pharmacodynamics target; however, clinicians have used different doses.

Cephamycins such as cefoxitin, cefotetan, and cefmetazole are not substrates for ESBL class of inactivating enzymes, hence, they retain their in vitro activity against such organisms in absence of other mechanisms of resistance (such as AmpCs, porin mutations). However clinical data about the use of this class is scarce.[16,20,21] A limited number of reports stated that the use of cephamycins may result in collateral resistance to both cephamycins and ertapenem secondary to the emergence of porin mutations and acquisition of plasmid-mediated AmpC enzymes.[22]

Table 3. Group Comparison on Dichotomous Outcomes.

Outcome variable	Drug	N (patients)	% Experiencing outcome	P^	% Experiencing outcome	Coefficient	Std. error	Odds ratio (95% CI)	P
			Group comparison		Adjusted/conditional group comparison*				
Clinical cure	Ertapenem	55	96.4	.091	96.8	−1.823	0.896	0.16 (0.03-0.94)	.042
	Cefoxitin	30	83.3		83.2				
Microbiological cure	Ertapenem	16	100.0	.192	100.0	−19.130	4077.160	$	.996
	Cefoxitin	13	84.6		88.6				
Vasopressor use (in critically ill patients)	Ertapenem	55	12.7	.250	12.8	−1.497	1.101	0.22 (0.03-1.94)	.174
	Cefoxitin	30	3.3		3.2				
Relapse/ recurrence within 30 days	Ertapenem	55	18.2	.999	18.1	−0.133	0.611	0.88 (0.26-2.90)	.828
	Cefoxitin	29	17.2		16.2				
Relapse/ recurrence within 90 days	Ertapenem	55	34.5	.070	34.8	−1.229	0.613	0.29 (0.09-0.97)	.045
	Cefoxitin	29	13.8		13.5				
Mortality within 90 days	Ertapenem	55	0.0	.122	0.0	21.539	5243.711	$	.997
	Cefoxitin	30	6.7		1.8				

^Calculated using Fisher's exact test.
*Adjusted/conditional group differences performed by including the Charlson Comorbidity Index as a covariate in the logistic regression model.
$Unidentified due to perfect alignment in 1 or more cells.

Table 4. Group Comparison on Continuous Outcomes.

Outcome variable	Drug	N (patients)	Mean	SD	P^	Mean	Coefficient	Std. error	95% CI of mean dif.	P
			Group Comparison			Adjusted/conditional group comparison*				
Days of therapy	Ertapenem	55	6.64	2.69	.124	6.61	−0.806	0.564	(−1.91 to 0.30)	.157
	Cefoxitin	30	5.77	1.98		5.81				
Days to WBC normalization	Ertapenem	13	3.85	3.00	.560	3.80	−0.758	1.102	(−2.96 to 1.45)	.499
	Cefoxitin	10	3.20	1.93		3.04				
Days to defervescence	Ertapenem	17	1.47	0.72	.131	1.51	1.003	0.509	(−0.02 to 2.02)	.064
	Cefoxitin	4	2.25	1.50		2.51				

^Calculated using independent samples t-test.
*Adjustment in group differences performed by including the Charlson Comorbidity Index as a covariate in the Ordinary Last Square (OLS) regression model.

Few small studies tried to address the use of cefoxitin in management of UTI secondary to ESBL-producing organisms. For instance, Demonchy et al,[14] conducted a single-arm prospective study to evaluate the use of cefoxitin in 23 patients with UTI secondary to ESBL-producing *Enterobacterales.* The investigators reported success in all patients (3 of them had pyelonephritis). Nineteen of the 23 patients achieved clinical cure at 3 and 6 months. Moreover, 13/23 patients at 3 months and 9/19 patients at 6 months achieved microbiological cure. The authors recommended to use cefoxitin as a carbapenem sparing agent. However, the results were not compared to controls. In another prospective study, Mambie et al,[15] followed 15 patients with UTI (10 prostatitis, 3 pyelonephritis, and 2 cystitis) for 28 days. Nine out of 10 patients achieved clinical and microbiological cure. In the studies, Resistance or treatment relapse was not documented in either

of the studies.[14,15] Furthermore, Pilmis et al[16] evaluated cefoxitin in 17 patients with ESBL UTI. The investigators reported that there was no difference in clinical or microbiological outcomes for patients who received cefoxitin compared with those who received carbapenems or other antimicrobials. However, resistance strains against cefoxitin were reported in 3 patients during the study period. In another retrospective study by Kernéis et al,[17] out of the 33 patients with ESBL-producing organisms (23 UTI), 30 had favorable clinical outcomes at 48 hours. In this study, microbiological failures occurred in 6 cultures and resistance to cefoxitin was reported in 2 strains of *K. pneumoniae*. In all of the previously mentioned studies, Cefoxitin was safe and effective in all of the trials above with the exception of nonserious skin rash reported in 2 studies of the 4 studies.[14-17] These findings match ours, however, in our study, we

matched the cases with retrospective controls who received ertapenem.

Most recently, More recently, Senard et al in a relatively larger multicenter, retrospective trial compared cefoxitin with carbapenems in 50 male patients (n=23 cefoxitin and n=27 carbapenem). Median follow-up was 63 days. The investigators compared 23 patients in the cefoxitin arm and 27 patients in the carbapenems arm with 63 days median follow up duration. The investigators matched both arms with propensity score analysis. The clinical and microbiological success in both groups did not show statistical significance (clinical cure 72.9% vs 81.5%) or microbiological cure (57.9% vs 50%), respectively.[23] Although these findings are similar to our study, our sample was somewhat larger, included both male and female subjects, critically ill patients with long-term indwelling catheters, and both *E. coli* and *Klebsiella* sp. In addition to MIC for better applicability. Additionally, in our study, we included the microorganisms' MICs for better applicability. These studies along with ours confirm the need to consider cefoxitin in the management of UTI secondary to ESBL producing organisms.

The limitations of our study were its retrospective design, small sample size, selection bias. In addition, 17 patients received an antibacterial agent prior to switching to cefoxitin which could have interfered with our outcome. However, relapse rate in those patients was not different from whom received ertapenem for the full duration of therapy. Further, although cefoxitin doses used varied widely, they were still in compliance with the manufacturers package insert dosing recommendation. Finally, although we used CCI for control selection, we could not account for severity and complexity of the disease.

Conclusion

Our study showed that cefoxitin could be potentially a reasonable alternative to ertapenem in the treatment of UTI caused by ESBL-producing *Enterobacterales*. Large randomized controlled studies are needed to determine its optimal utilization as a carbapenem-sparing agent in the treatment of UTI caused by resistant pathogens.

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