Evaluation of Effectiveness of Cefmetazole vs Meropenem for Invasive Urinary Tract Infections Caused by ESBL-Producing *Escherichia coli*: A Prospective Multicenter Observational Study

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K Hayakawa[1], K Uemura[2], Y Matsumura[3], A Sakurai[4], R Tanizaki[5], K Shinohara[3], T Hashimoto[6], H Kato[7], T Matono[8], R Hase[9], M Mawatari[10], H Hara[11], Y Hamada[12], S Saito[1], Y Doi[4]

[1] National Center for Global Health and Medicine; [2] University of Tokyo; [3] Kyoto University Hospital; [4] Fujita Health University Hospital; [5] Ise Municipal General Hospital; [6] Oita University Hospital; [7] Yokohama City University Hospital; [8] Iizuka Hospital; [9] Japanese Red Cross Narita Hospital; [10] Japanese Red Cross Medical Center; [11] Yokohama Brain and Spine Center; [12] Tokyo Women's Medical University Hospital

1-21-1 Toyama, Shinjuku-ku
Tokyo, 162-8655, Japan
kahayakawa@hosp.ncgm.go.jp

Background

- ESBL-producing *E. coli* (ESBLEC) continues to increase worldwide. For infection due to ESBLEC, no antimicrobial agent has clearly demonstrated therapeutic effectiveness that is comparable to carbapenem.
- Overuse of carbapenems may lead to an increase in carbapenem-resistant bacteria.
- Cefmetazole (CMZ) is active against ESBLEC, however, there are limited multicenter studies on the effectiveness of CMZ, potential carbapenem-sparing therapy for the treatment of ESBLEC.

Methods

- This prospective, observational study included patients hospitalized for invasive urinary tract infection (iUTI) due to ESBLEC between March 2020 and November 2021 at 10 centers in Japan, with either CMZ or meropenem (MEM) initiated within 96 hours of culture submission as definitive therapy, and continued for at least 4 days.
- The diagnosis of iUTI was made in patients with a fever of ≥37.5 ℃, symptom of pyelonephritis such as back pain, pyuria, and ESBLEC detected in urine (≥10^4 CFU/mL).
- Outcomes included clinical effectiveness (resolution of all clinical symptoms or improvement to pre-infection status) between day 4 to 6 of treatment（early）and between the final day of treatment and 2 days later (late), microbiological effectiveness (reduction to ≤10^3 CFU/mL) between day 4 to 6, and mortality.
- Outcomes were adjusted for the inverse probability of propensity scores (PS) for receiving CMZ or MEM treatment.
- Univariate analyses were performed using Fisher's exact test and the $\chi 2$ test (categorical variables) or Mann–Whitney U test (continuous variables).
- The collected strains were subjected to susceptibility testing by broth microdilution and identification of ESBL genes and clones by whole genome analysis.

Results

- 77 and 46 patients were included in the CMZ and MEM groups, respectively. In univariate analysis, the CMZ group was older than the MEM group and had more frequently resided in nursing home or LTCF prior to the admission. The MEM group had higher qSOFA, Pitt score, CRP, more frequent medical device use than the CMZ group (**Table 1**). Univariate analysis showed no difference in clinical effectiveness, and 30-day mortality was higher in the MEM group. In all cases with follow-up urine cultures (CMZ: n=57, MEM: n=22), both drugs were microbiologically effective.
- All tested isolates (n=120) were susceptible to MEM with low MIC (≤0.12 mg/L), and to CMZ with MICs ranging from ≤1 (n=85) to 8 mg/L (n=5) (**Table 2**).
- In all isolates, *bla*CTX-M was detected as the ESBL gene. The predominant CTX-M subtype was CTX-M-27 (49.2%), followed by CTX-M-15 (22.5%) and CTX-M-14 (20%). ST131 accounted for 72.5% of the clones, followed by ST1193, and the rest consisted of 18 different STs. ST131 clades comprised C1-M27 (35.8%), C1-non-M27 (15.8%), and C2 (11.7%) (**Table 3**).
- Dosing of CMZ and MEM is summarized in **Table 4**. In majority of patients, CMZ and MEM were used with adequate dosing based on the package insert, although no detailed recommendation is available for CMZ in patients with renal impairment.

Table 1. Comparison of clinical characteristics of invasive UTI between cefmetazole and meropenem treatment groups, univariate analysis[a]

Variables	CMZ (n = 77)	MEM (n = 46)	P value[b]
General patient demographics			
Age[c]	85 (76-91)	78 (69-85)	**0.002**
Male sex	27 (35.1)	23 (50)	0.13
Healthcare-associated exposure prior to admission			
Nursing home or LTCF residence	30 (39.5)	10 (21.7)	**0.049**
Hospitalisation in the past 3 months	16 (21.1)	16 (34.8)	0.136
Healthcare-associated exposure prior to ESBLEC isolation after admission			
Hospital onset	19 (24.7)	13 (28.3)	0.676
ICU stay	8 (10.5)	5 (10.9)	> 0.999
Surgery	5 (6.6)	6 (13)	0.328
Length of hospital stay before isolation of ESBLEC, days[c]	0 (0-4)	0 (0-11)	0.492
Presence of devices at the time of ESBLEC isolation			
CV/HD catheter	0 (0)	3 (6.5)	0.05
Urinary device[d]	17 (22.1)	19 (41.3)	**0.026**
Device other than CV/HD catheter or urinary device[e]	5 (6.5)	10 (21.7)	**0.021**
Acute and chronic conditions on admission			
Dependent functional status	55 (71.4)	21 (45.7)	**0.007**
Charlson's comorbidity index[c]	2 (1-4)	3 (2-3)	0.202
Any immunosuppressive status[f]	6 (7.9)	8 (17.8)	0.141
Urological complication	31 (40.8)	24 (52.2)	0.262
Antimicrobial exposure in the previous 1 month			
Any antimicrobial exposure	26 (33.8)	15 (32.6)	> 0.999
Beta-lactam antibiotics exposure	18 (23.4)	9 (19.6)	0.66
Clinical characteristics			
Polymicrobial culture[g]	23 (29.9)	17 (37)	0.433
Bacteremia due to ESBLEC	33 (42.9)	27 (58.7)	0.097
Severity of Infection			
qSOFA[c]	0 (0–1)	1 (0–2)	**0.003**
Pitt bacteremia score[c,h]	3 (0-3)	3 (3-3)	**0.01**
White blood cell ≥12000 (/μL)	17 (25.8)	17 (40.5)	0.138
CRP ≥10 (mg/dL)	27 (40.9)	27 (64.3)	**0.029**
Treatment			
Inadequate source control[i]	4 (5.2)	4 (8.7)	0.471
Outcome			
Clinically effective (early)	71 (92.2)	38 (82.6)	0.143
Clinically effective (late)	69 (95.8)	40 (90.9)	0.424
14-day mortality	0 (0)	1 (2.3)	0.379
30-day mortality	0 (0)	5 (12.5)	**0.008**
In-hospital mortality	2 (2.7)	6 (13.3)	0.051
Recurrence within 28 days	6 (8.1)	2 (4.8)	0.709
C. difficile infection within 28 days after treatment	2 (2.6)	2 (4.4)	0.628
LOS after isolation of ESBLEC among survivors, days[c]	15 (11-34)	19 (14-35)	0.117

Abbreviations: CV, central venous catheter/central venous port; HD, hemodialysis; LOS, Length of hospital stay; LTCF, long-term care facilities.
[a] Data are presented as number (%) unless indicated otherwise.
[b] Bold letters indicate statistically significant results (p <0.05).
[c] Median (interquartile range).
[d] Urinary device included urinary catheter, ureteral stent, and nephrostomy catheter.
[e] Including percutaneous endoscopic gastrostomy tube, tracheostomy tube, endotracheal tube, and nasogastric tube.
[f] Including one or more of the following at the time of culture: neutropenia (<500/μL), glucocorticoid/steroid use (doses greater or equal to an equivalent of 20 mg of prednisone per day for at least 1 month), chemotherapy or immunosuppressant use (such as antitumor necrosis factor α therapy, anti-IL-6 receptor/anti-CD20 monoclonal antibodies, selective T-cell costimulation blocker, methotrexate) in the previous 1 month, organ transplantation in the previous 3 months, or HIV infection.
[g] Isolation of additional bacteria other than ESBLEC from the same culture.
[h] Pitt bacteremia score was calculated only for bacteremic cases.
[i] Inadequate source control included undrained abscess and release of urinary tract obstruction.

Table 2 . Minimum inhibitory concentration of ESBLEC isolates (n=120)

	CFZ	CTX	CAZ	FEP	CMZ	FMOX	MEM	FRPM	ATM
MIC_{50}	>8	>16	4	8	≤1	≤0.12	≤0.12	1	8
MIC_{90}	>8	>16	16	>32	4	0.25	≤0.12	2	>16
	AMC	TZP	GEN	TOB	AMK	CIP	SXT	FOF	
MIC_{50}	8	2	≤4	≤4	≤16	>4	≤40	≤16	
MIC_{90}	16	8	>16	16	≤16	>4	>80	≤16	

MIC value is presented as mg/L. Abbreviations. AMK, amikacin; AMC, amoxicillin-clavulanic acid; ATM, aztreonam; CAZ, ceftazidime; CFZ, cefazolin; CIP, ciprofloxacin; CTX, cefotaxime; FEP, cefepime; FMOX, flomoxef; FOF, fosfomycin; FRPM, faropenem; GEN, gentamicin; SXT,trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin-tazobactam. Two isolates were missing from microbiological analyses. One isolate was not identified as ESBL-producing *E. coli* in the central laboratory analysis, and thus, excluded from the analysis (ESBL production of the *E. coli* isolate was confirmed at the local microbiological laboratory, with resistance to cefotaxime).

Table 3. Molecular characteristics of ESBLEC isolates (n=120)

MLST_ST[A]		CTX-M subtype		ST131 clade	
131	87 (72.5%)	27	59 (49.2%)	C1-M27	43 (35.8%)
1193	6 (5%)	15	27 (22.5%)	C1-non-M27	19 (15.8%)
38	5 (4.2%)	14	24 (20%)	C2	14 (11.7%)
95	3 (2.5%)	55	4 (3.3%)	A	8 (6.7%)
10	2 (1.7%)	8	2 (1.7%)	B	2 (1.7%)
69	2 (1.7%)	65	2 (1.7%)	C0	1 (0.8%)
393	2 (1.7%)	3	1 (0.8%)		
		104	1 (0.8%)		

[A] n=1 (0.8%) for ST12, 23, 73, 155, 162, 215, 450, 533, 648, 803, 1588, 5150, and 38SLV, respectively.

Table 4. Summary of cefmetazole or meropenem dosing in patients with invasive UTI due to ESBLEC

CMZ (n=77)						MEM (n=46)					
CrCl (mL/min) category	n (%)	Dose (g)	Q (hour)	n	Clinically non-effective (early)	CrCl (mL/min) category	n (%)	Dose (g)	Q (hour)	n	Clinically non-effective (early)
<10	2 (2.6%)	0.5	12	1	1	**<10**	5 (11%)	0.5	24	4	
		2	24	1				1	24	1	
10-29	20 (26%)	1	12	11		**10-25**	16 (35%)	1	12	6	1
		1	24	5				0.5	12	5	
		2	12	3	1			1	8	2	
		2	24	1				0.5	8	1	
30-50	26 (33.8%)	1	12	9				0.5	24	1	
		2	24	6				0.25	12	1	
		1	8	5	1	**26-50**	11 (24%)	1	12	6	2
		1	24	5				1	8	2	1
		2	12	1				0.5	12	2	
>50	29 (37.7%)	1	12	11				2	12	1	
		1	8	10	3	**>50**	14 (30%)	1	8	9	2
		2	12	4				0.5	12	2	2
		2	24	2				0.5	6	1	
		1	6	2				0.5	8	1	
								1	12	1	

Table 5. Empirical antibiotic treatment within 96 hours prior to cefmetazole or meropenem therapy

	None	SAM	CFZ	FEP	CRO	FQ	MEM	TZP
CMZ	22 (28.6%)	7 (3.1%)	1 (1.3%)	0	31 (40.3%)	4 (5.2%)	3 (3.9%)	9 (11.7%)
MEM	28 (60.9%)	3 (6.5%)	0	1 (2.2%)	7 (15.2%)	3 (6.5%)		4 (8.7%)
P value	0.001	0.742	>0.999	0.374	0.004	>0.999	NA	0.765

Abbreviations. CRO, ceftriaxone; FQ, fluoroquinolone (levofloxacin, ciprofloxacin, garenoxacin); NA, not available.
SAM, ampicillin-sulbactam. Other abbreviations are as Table 3.

Table 6. Propensity score-adjusted analyses[a] of clinical outcomes of invasive UTI: cefmetazole vs meropenem treatment groups

Variables	Adjusted Odds Ratio (95% confidence interval)	P value
Clinically effective (early)	0.479 (0.106-2.162)	0.334
Clinically effective (late)	1.782 (0.266-11.95)	0.548
14-day mortality	NA	
30-day mortality	<0.001 (NA)	<0.001
In-hospital mortality	0.147 (0.02-1.087)	0.060
Recurrence within 28 days	1.914 (0.2-18.279)	0.569

The propensity score was calculated using a nonparsimonious multivariate logistic regression model including the baseline characteristic variables (age, sex, healthcare exposure, hospital onset, ESBLEC bacteremia, polymicrobial isolation, Charlson comorbidity index, immunocompromised status, device use, qSOFA score, high CRP (as defined in Table 1). aOR for 14 day mortality is not available due to the small number of event. Abbreviation. NA, not available.

Results (cont)

- The comparison of empirical antibiotic treatment within 96 hours prior to the CMZ or MEM therapy revealed that empirical antibiotics were used more often in CMZ group than MEM group. However, no statistical difference was noted in the use of potentially effective antibiotics against ESBLEC, such as TZP (**Table 5**).
- After PS adjustment, clinical effectiveness did not differ between the two groups (**Table 6**). The risk of 30-day mortality was lower in CMZ group, whereas the risk of recurrence was similar in both groups.

Discussion

- Univariate analysis suggested that the MEM group may have been more severely ill, requiring higher levels of medical care, although the CMZ group included more elderly patients. Although the MEM group had a higher mortality rate, it was likely affected by differences in patient background as all deaths were accounted for, including non-infectious disease-related deaths.
- However, there was no difference in clinical effectiveness after adjusting for background factors using PS, and the 30-day mortality rate remained lower in the CMZ group. Of note, in this cohort, mortality in CMZ group was quite low.
- As limitations, although clinical and bacteriological effectiveness were similar in both groups, there were some missing data in the bacteriological effectiveness evaluation. Also, CMZ patients were enrolled more frequently than MEPM patients.

Conclusions

- CMZ is at least as effective as MEM for the treatment of iUTI, suggesting that it is a promising carbapenem-sparing therapy.
- Confirmation of effectiveness of both treatments based on objective measures in randomised control trial is needed.

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