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Effectiveness of Cefmetazole vs Meropenem for Invasive Urinary Tract Infections Caused by Extended-Spectrum β-Lactamase-Producing *Escherichia coli*

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Abstract

Cefmetazole is active against extended-spectrum β-lactamase-producing *Escherichia coli* (ESBLEC) and is a potential candidate for carbapenem-sparing therapy. This multicenter, observational study included patients hospitalized for invasive urinary tract infection due to ESBLEC between March 2020 and November 2021 at 10 facilities in Japan, for whom either cefmetazole or meropenem was initiated as a definitive therapy within 96 hours of culture collection and continued for at least 3 days. Outcomes included clinical and microbiological effectiveness, recurrence within 28 days, and all-cause mortality (14-day, 30-day, in-hospital). Outcomes were adjusted for the inverse probability of propensity scores for receiving cefmetazole or meropenem. Eighty-one and forty-six patients were included in the cefmetazole and meropenem groups, respectively. Bacteremia accounted for 43% of the cefmetazole group, and 59% of the meropenem group. The crude clinical effectiveness, 14-day, 30-day, and in-hospital mortality for patients in the cefmetazole and meropenem groups were 96.1% vs 90.9%, 0% vs 2.3%, 0% vs 12.5%, and 2.6% vs 13.3%, respectively. After propensity score adjustment, clinical effectiveness, the risk of in-hospital mortality, and the risk of recurrence were similar between the two groups (p=0.54, p=0.10, and p=0.79, respectively). In all cases with available data (cefmetazole : n=61, meropenem : n=22), both drugs were microbiologically effective. In all isolates, $bla_{\text{CTX-M}}$ was detected as the extended-spectrum β-lactamase gene. The predominant CTX-M subtype was CTX-M-27 (47.6%). Cefmetazole showed clinical and bacteriological effectiveness comparable to meropenem against invasive urinary tract infection due to ESBLECs.

Keywords: Antimicrobial resistance; carbapenem; E. coli; urinary tract infection; cephamycin

Introduction

Third-generation cephalosporin-resistant (3GCR) *Escherichia coli* has been increasing worldwide. The reported median 3GCR rate of bacteremia due to *E. coli*, which is one of the two sustainable development goals for antimicrobial resistance indicators, was 36.6% (interquartile range [IQR], 17.5–58.3) according to the recent global surveillance report (1). Based on data from 2167 medical institutions in Japan, 3GCR *E. coli* was isolated from 3.7% of hospitalized patients (i.e., approximately 100,000 patients per year). The 3GCR rate of *E. coli* has continually been increasing (26.8% in 2017 and 28.3% in 2020) (2). Extended-spectrum β-lactamase (ESBL) production is the main mechanism by which *E. coli* acquires resistance to third-generation cephalosporins (1). Carbapenems are the first-line treatment option for infections due to ESBL-producing *E. coli* (ESBLEC). However, increased carbapenem usage may exert selective pressure on the indigenous flora, leading to disadvantages including an increase in carbapenem-resistant bacteria (3). Therefore, there is a need for effective and targeted carbapenem-sparing therapy for ESBLEC infection. The most promising carbapenem-sparing therapy was piperacillin-tazobactam; however, a recent international randomized clinical trial was not able to demonstrate its non-inferiority to meropenem (MEM) (4).

Cefmetazole (CMZ), a semisynthetic cephamycin antibiotic, is stable against hydrolysis by ESBLs and exhibits antibacterial activity against ESBL-producing bacteria (5), making it a promising candidate for carbapenem-sparing therapy. Although it is no longer available in many countries, CMZ is available in Japan and is commonly used to treat infections due to ESBLEC, including invasive urinary tract infections (iUTI). Data on the effectiveness of CMZ for this indication are only available from retrospective single-center or oligo-center studies (6-9). Additionally, despite its wide range of approved doses (1–4 g/day in patients with normal renal function, no dosage recommendation in the package insert for renal

impairment), there are limited data on appropriate, evidence-based dosing (8, 10). CMZ contains an *N*-methyl-tetrazole-thiol side chain, which inhibits vitamin K epoxide reductase and may inhibit synthesis of vitamin K-dependent coagulation factors (11). Real world data on adverse events of CMZ, including coagulopathy, are also scarce (11, 12).

This study aimed to determine the clinical effectiveness of CMZ against iUTI due to ESBLEC compared to MEM. Microbiological characteristics of ESBLEC, optimal dosing of CMZ, and adverse events were also evaluated.

Materials and Methods

Study design and patients

This prospective, observational study was conducted at 10 hospitals in Japan between March 2020 and November 2021. Adult patients (age ≥20 years) were eligible for enrollment if they met all three of the following criteria (a, b, c).

a) Clinical diagnosis of iUTI (a-1 and a-2)

a-1) Clinical symptoms of any of the following

- Fever of ≥37.5 ℃, or symptom of pyelonephritis such as low back pain, lateral abdominal pain, and renal pain including costovertebral angle tenderness (13)
- Sepsis due to UTI with Quick Sepsis-related Organ Failure Assessment (qSOFA) score ≥1 (14)

a-2) Presence of pyuria

b) Microbiological diagnosis

- ESBLEC detected in urine culture ($\geq 10^4$ CFU/mL)
- If ESBLEC was detected in blood culture only, no other source of infection other than

the urinary tract

c) Antibiotic treatment

- Either CMZ or MEM initiated within 96 hours of culture collection as definitive therapy and continued for at least 3 calendar days.

Detailed exclusion criteria are available in the supplementary document. The doses of CMZ and MEM were determined at the discretion of each facility.

Clinical data collection and definition

The clinical data were collected from electronic medical records and predefined definitions were used for each condition (supplementary document).

Outcomes

Outcomes, which are detailed in the supplementary material, included clinical and microbiological effectiveness, recurrence within 28 days from the start of either antibiotic, and all-cause mortality (14-day, 30-day, in-hospital). The primary outcome was clinical effectiveness between day 4 and 6 of treatment (early treatment period). Clinical effectiveness was defined as resolution or improvement of clinical symptoms (e.g. fever, low back pain, lateral abdominal pain, renal pain including costovertebral angle tenderness, tachypnea, low blood pressure, altered mental status) to pre-infection baseline, as determined by an infectious disease specialist (15).

Microbiology

Bacterial identification and susceptibility testing were conducted using MicroScan WalkAway (Beckmann-Coulter, Germany) (six facilities), VITEK2 (bioMérieux, France) (one facility),

and BD phoenix (Beckton Dickinson, USA) (one facility). MALDI Biotyper (Bruker, Bremen, Germany) was also used for bacterial identification in one facility. Bacteria isolated from enrolled patients were sent to the central laboratory based at Kyoto University Graduate School of Medicine for further analysis. At the central laboratory, antibiotic susceptibility was evaluated by broth microdilution (BMD) using a Dry Plate Eiken (Eiken, Tokyo, Japan) according to CLSI guidelines (16). The results were interpreted using the 2021 CLSI breakpoints (15). Detailed microbiological analyses are described in the supplementary material.

Pharmacokinetic/pharmacodynamic analysis

The pharmacokinetic and pharmacodynamic parameters of CMZ and MEM were calculated using the model reported by Tomizawa *et al.* (17). Creatinine Clearance (CrCl) was calculated based on the Cockcroft-Gault equation (18). The time above MIC (TAM) was calculated using the MIC value obtained from each patient and its simulated CMZ and MEM concentration. MIC values determined by BMD at the central laboratory were used for the analysis. Phoenix NLME version 8.1 (Certara, Princeton, NJ, USA) was used for the pharmacokinetic simulation to calculate the TAM.

Statistical analyses

The inverse probability of treatment weight (IPTW) method was used to adjust for baseline confounders of CMZ and MEM treatment (Supplementary Table 1). Detailed information on statistical analyses is available in the supplementary document.

Ethics

The study was approved by the institutional review board at the National Center for Global

Health and Medicine (No. NCGM-G-003389-00). The opt-out recruitment method was used, and the requirement for informed consent was waived.

Data availability

Data are available upon reasonable request with the permission of participating facilities. The sequences determined in this study have been deposited in the GenBank/ENA/DDBJ Sequence Read Archive database (PRJNA976817).

Results

Comparison of clinical characteristics

Eighty-one and forty-six patients were included in the CMZ and MEM groups, respectively. In univariable analysis, the CMZ group was older, had dependent functional status more often than the MEM group, and had more frequently resided in nursing home or long–term care facilities (LTCF) prior to admission (Table 1). Diabetes was more common in the MEM group than the CMZ group. Use of indwelling device (central venous catheter/central venous port/hemodialysis [CV/HD] catheter, and device other than CV/HD catheter and urinary device) was more prevalent in the MEM group than the CMZ group. The number of days from onset to CMZ or MEM initiation was lower in the MEM group than CMZ group. The MEM group was more likely to be in an intensive care unit (ICU) than the CMZ group on the day of MEM or CMZ initiation. The MEM group had higher qSOFA score, Pitt score, white blood cell count, and C-reactive protein (CRP) level than the CMZ group on the day of MEM or CMZ initiation. The number of days from CMZ or MEM initiation to fever resolution was similar between the two groups (CMZ vs MEM group: 2 days [IQR: 1-6] vs 3 days [1-9]), whereas leukocytosis (CMZ vs MEM group: 3 [4.5%] vs 11 [25.6%]), and high CRP (≥10 mg/dL) (5 [7.6%] vs 16 [37.2%]) were more commonly observed in the early treatment period in the

MEM group than the CMZ group (Supplementary Table 2).

Antibiotic treatment

The antibiotic treatment given is summarized in Table 2. Total duration of study drug as well as total duration of all antibiotics were similar between the two groups. Empirical antibiotic treatment was used more frequently in the CMZ group than the MEM group, with ceftriaxone use significantly more common in the CMZ group than the MEM group. No statistical difference was noted in the empiric use of potentially effective antibiotics against ESBLEC, such as piperacillin-tazobactam (TZP). MEM was used in 3 cases (3.7%) of the CMZ group as empiric therapy.

Switch from definitive therapy with CMZ or MEM to another antibiotic therapy was more frequent in the MEM group than the CMZ group ($p<0.001$). No significant differences were found between the two groups regarding the individual antimicrobial agents switched. CMZ replaced MEM in 34.5% (n=16) of the MEM group. For two patients who received MEM after CMZ, one patient clinically improved but was changed to MEM due to liver dysfunction, and in the other, CMZ was clinically and microbiologically effective prior to the switch to MEM.

MIC and susceptibility of isolated ESBLEC

All tested isolates (n=124) were susceptible to MEM with low MIC (≤0.12 mg/L). The MICs to CMZ ranged from ≤1 (n=86) to 8 mg/L (n=5) (Table 3). Susceptibility rates to β-lactam/β-lactamase inhibitors, such as amoxicillin-clavulanate and TZP were 77.4% (n=96) and 96% (n=119), respectively. The highest MIC of TZP was 16 mg/L (n=5 [4%]). Susceptibility to ciprofloxacin was as low as 15.3% (n=19), and approximately half (n=66, 53.2%) of the isolates were resistant to trimethoprim-sulfamethoxazole. Among

aminoglycosides, amikacin was the most active agent with all 124 isolates testing susceptible.

Molecular characteristics of isolated ESBLEC

In all isolates, *bla*$_{\text{CTX-M}}$ was detected as the ESBL gene (Table 4). The predominant CTX-M subtype was CTX-M-27 (n=59, 47.6%), followed by CTX-M-15 (n=30, 24.2%) and CTX-M-14 (n=25, 20.2%). ST131 accounted for 73.4% (n=91) of the clones, followed by ST1193 (n=6, 4.8%), and the rest comprised 18 different sequence type (STs). ST131 clades included C1-M27 (n=43, 47.3%), C1-non-M27 (n=20, 22%), C2 (n=17, 18.7%), and A (n=8, 8.8%).

Genes for the following other β-lactamases were detected: TEM-1, 26 (21%); OXA-1, 14 (11.3%); TEM-190, 1 (0.8%); TEM-135, 1 (0.8%). Genes for pAmpC was detected in only one isolate (DHA-1), and the CMZ MIC of the isolate was ≤1 mg/L.

Outcome

The all-cause 30-day and in-hospital mortality rates were higher in the MEM group than the CMZ group (n=5 [12.5%] vs 0, n=6 [13.3%] vs n=2 [2.6%], respectively). The median days from the completion of the treatment to the recurrence was 11 days (range, 6–27) in the CMZ group and 11 days (range, 8–14) in the MEM group. In all cases with follow-up urine cultures, both drugs were microbiologically effective. *Clostridioides difficile* infection (CDI) within 4 weeks after the end of treatment was observed in 2 (2.5%) patients in the CMZ group and 1 (2.2%) patient in the MEM group. Days from CMZ treatment to CDI onset were 4 days and 26 days in the two CMZ patients, respectively, and the onset of CDI could not be determined in the patient in the MEM group. Carbapenem-resistant Enterobacterales was not detected in any clinical specimens within 4 weeks of the end of treatment in either group.

Mortality rates for bacteremic patients due to ESBLEC were similar between the two

groups: 14-day mortality, 0 vs 0; 30-day mortality, 0 vs 2 (9.1%); in-hospital mortality, 0 vs 2 (7.4%) for the CMZ and MEM groups, respectively.

After PS adjustment, clinical effectiveness did not differ between the two groups both in the early (adjusted odds ratio [aOR]: 0.63 [95% confidence interval: 0.15–2.75], p=0.54) and late treatment periods (aOR: 1.83 [0.26–12.75], p=0.54) (Table 5). Adjusted odds ratio for 14-day mortality was not available due to the small number of events. The risk of 30-day mortality was lower in CMZ group (aOR: <0.01 [95% confidence interval: NA], p<0.01), whereas and the risk of in-hospital mortality, recurrence, and LOS after isolation of ESBLEC among survivor were similar in both groups (aOR: 0.20 [0.03-1.36], p=0.10; aOR: 1.36 [0.14–12.93], p=0.79; p=0.23, respectively).

Pharmacokinetic/pharmacodynamic analysis

Dosing of CMZ and MEM with TAM is summarized in Table 6. Except for one patient in the CMZ group with CrCl of 32 mL/min for whom CMZ (2g q 24 h) was infused over 120 minutes, CMZ and MEM was infused over 30 minutes (CMZ: 19 [23.5%], MEM: 7 [15.2%]) or 60 minutes (CMZ: 61 [75.3%], MEM: 39 [84.8%]). In the MEM group, TAM was 100% in all cases. In all 6 cases where CMZ was clinically ineffective in the early treatment period, TAM of CMZ was 100%.

Adverse events

Regarding adverse events considered related to CMZ or MEM, 3 patients in the CMZ group had liver dysfunction (Grade 1: n=2, Grade 2: n=1) and 1 patient had skin rash (Grade 1); 1 patient in the MEM group had non-CDI diarrhea (Grade 4).

Data were available for 35 patients (CMZ: 18, MEM: 17) for prothrombin time (PT) and 33 patients (CMZ: 17, MEM: 16) for activated partial thromboplastin time (APTT) in the

early treatment period. Compared to the pre-treatment period, no significant increase was observed for PT (median increase presented as fold-change [IQR]; CMZ: 1 [0.8–1.1], MEM 0.9 [0.8–1], p=0.291) or APTT (CMZ: 0.9 [0.8–1.1], MEM 0.9 [0.8–1.2], p= 0.801) in either group in the early treatment period. Data were available for 19 patients (CMZ: 14, MEM: 5) for PT and 19 APTT (CMZ: 14, MEM: 5) in the late treatment period. Compared to pre-treatment, there was no significant increase for PT (CMZ: 1 [0.9–1], MEM 0.9 [0.7–1.1], p value 0.781) or APTT (CMZ: 1 [0.9–1.1], MEM 1.2 [1–1.6], p=0.064) in either group in the late treatment period.

Discussion

This observational study showed that CMZ was as effective as MEM in a cohort of patients with iUTIs caused by ESBLEC. This study includes the largest number of patients and was conducted at the largest number of facilities among studies that examined the effectiveness of CMZ for ESBLEC to date (6-9). Among previous reports, three studies compared the effectiveness of CMZ with that of carbapenems, and in all three studies CMZ was as effective as carbapenems. However, only one study adjusted for background factors using propensity scores (9). In that study focusing on ESBLEC bloodstream infection (BSI) (hereafter referred to as CF-CARBA study) (9), patients treated with CMZ were included as part of the combined CMZ and flomoxef group (CF), where flomoxef is an oxacephem agent with activity against ESBLEC that is approved for clinical use in Japan. The unadjusted 30-day mortality rates in the definitive treatment cohort were 9.3% in the carbapenem group and 5.1% in the CF group, and 7.0% and 7.4%, respectively, after PS adjustment. The median age of patients was approximately 10 years higher in the present study than the CF-CARBA study. The CF-CARBA study included more immunocompromised patients. The present study also included patients other than those with bacteremia, and the 30-day unadjusted mortality rate

was lower in the CMZ group than in the CF-CARBA study, but higher in the MEM group than the CF-CARBA study. Intriguingly, the 30-day mortality rate in the MEM group was lower when only the patients with BSI due to ESBLEC were included, to almost the same level as in the CF-CARBA study. Although identifying the cause of death was outside this study's scope, it is possible that causes of death not directly related to infection were also involved, which may have contributed to the lower mortality associated with the CMZ group than the MEM group, even after PS adjustment. Despite the use of slightly different criteria, the two studies were consistent in demonstrating high clinical effectiveness of CMZ against ESBLEC infection.

The dosing of CMZ was also examined in this study. In this cohort, the MIC of CMZ for all ESBLEC strains available for analysis (n=124) was ≤8 mg/L. In the majority of cases, a dose of 1 g q 8 h for patients with CrCl >50 mL/min and 1 g q 12 h for CrCl 30–50 mL/min resulted in a TAM >50%, which is the pharmacodynamic target associated with effectiveness in the treatment of ESBLEC infections (19). Clinical failure occurred in patients with high TAM in both the MEM and CMZ groups, which is consistent with our previous report (8) and may be more related to the patients' underlying conditions than the intrinsic efficacy of the antibiotics. Of the six patients in the CMZ group and the eight patients in the MEM group for whom study drugs were clinically ineffective, microbiologically effectiveness was confirmed in all patients for whom microbiological evaluation was possible (4 patients in the CMZ group and 6 patients in the MEM group). There was no clear difference between CMZ and MEM in safety, including coagulation function tests. CMZ is reportedly associated with coagulopathy and increased hemorrhagic events (11, 12), but we did not observe a signal in our relatively small cohort.

We also performed a molecular microbiological analysis. In concordance with the global distribution, ST131 was the major ST in this study. However, nearly half of the CTX-M

311 gene subtypes were CTX-M-27. CTX-M-14, which differs from CTX-M-27 by only one
312 nucleotide, accounted for 20%. The global pandemic subtype CTX-M-15 accounted for only
313 24%, and the ST131 clade C1-M27, accounted for approximately 50%, confirming a unique
314 genetic background of ESBLECs in Japan (20). These molecular epidemiological differences
315 may explain the much lower detection rate of $bla_{\text{OXA-1}}$ (11.3%) in this cohort compared to the
316 MERINO trial cohort (67.6%) (4). As the presence of $bla_{\text{OXA-1}}$ is associated with higher MICs
317 of TZP (21), our study suggests that the results of the MERINO trial may not be directly
318 applicable in Japan.
319 CMZ is hydrolyzed by AmpC and strains producing this group of enzymes are
320 resistant to this agent. In the present study, pAmpC was detected in only 0.8% (n=1). In a
321 previous report from Japan, co-production of ESBL and pAmpC genes was relatively rare (5).
322 3GCR *E. coli* with a CMZ MIC of 16 mg/L are considered susceptible by CLSI criteria (16),
323 but increasing rates of pAmpC production among *E. coli* strains with CMZ MICs of 16 mg/L or
324 higher have been reported (5), which should be noted when interpreting MIC data.
325 The antimicrobial agents prescribed prior to study drug administration differed
326 between the two groups, with MEM initiated more often without prior drug administration and
327 CMZ administered more frequently after other drugs, especially ceftriaxone. The propensity to
328 receive TZP, which might still be effective for ESBLEC, did not differ between the two groups.
329 The patients in the MEM group tended to be more ill at the initiation of the study drug
330 administration than the CMZ group (e.g., higher qSOFA score, Pitt bacteremia score, and CRP
331 levels; more patients in ICU). These differences were considered when adjusting for PS.
332 Approximately one-third of patients in the MEM group were later de-escalated to CMZ to
333 complete the treatment. Since the switch occurred when treatment of the acute phase of
334 infection had already been completed, it is unlikely to have affected the study outcome.

This study has certain limitations. Due to the observational nature of the study, there were some missing data regarding some parameters including microbiological effectiveness. The significant difference in 30-day mortality does not reflect superiority of CMZ over MEM, but rather the fact that there were few deaths in the CMZ group. Although PS was used to minimize the baseline differences between the two groups, there may be residual differences that could not be fully adjusted as the mortality risk at baseline seemed to differ substantially between the two groups.

This study has shown that the clinical and bacteriological effectiveness of CMZ was comparable to MEM in the treatment of iUTI cases caused by ESBLEC in a cohort that included more than 40% of patients with concomitant bacteremia. In addition, an appropriate dosing strategy of CMZ was developed. Based on these findings, CMZ appears to be a safe and effective alternative to MEM without increase in mortality, however, a randomized clinical trial (RCT) is necessary to conclusively demonstrate this; one is currently in progress (22).

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Conflict of interest

The Authors declare that there is no conflict of interest.

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448 **Tables**

449 **Table 1. Comparison of clinical characteristics of invasive urinary tract infection**

450 **between cefmetazole and meropenem treatment groups [a] (n=127)**

	CMZ (n=81)	MEM (n=46)
Patient demographic and comorbid conditions		
Age	85 (76–90)	78 (69–85)
Male sex	28 (34.6)	23 (50)
Dependent functional status	58 (71.6)	21 (45.7)
Cardiovascular disease	11 (13.6)	11 (23.9)
Cerebrovascular accident	25 (31.3)	10 (21.7)
Dementia	27 (33.3)	8 (17.4)
Connective tissue disease	6 (7.4)	9 (19.6)
Mild liver disease	8 (9.9)	1 (2.2)
Moderate to severe kidney disease	2 (2.5)	2 (4.3)
Diabetes mellitus	15 (18.5)	17 (37)
Solid tumor (localized)	13 (16)	11 (23.9)
Solid tumor (metastatic)	6 (7.4)	3 (6.5)
Leukemia or lymphoma	0 (0)	2 (4.3)
Charlson comorbidity index	2 (1–4)	3 (2–3)
Any immunosuppressive status	6 (7.5)	8 (17.8)
Urological complication	33 (41.3)	24 (52.2)
Healthcare exposure prior to ESBLEC isolation		
Nursing home or LTCF residence	32 (40)	10 (21.7)
Hospitalization in the previous 3 months	17 (21.3)	16 (34.8)
Hospital onset[b]	19 (23.5)	13 (28.3)
Length of hospital stay before isolation of	0 (0–3)	0 (0–11)

ESBLEC, days		
Surgery after admission prior to ESBLEC isolation	5 (6.3)	6 (13)
CV/HD catheter	0 (0)	3 (6.5)
Urinary device[e]	20 (24.7)	19 (41.3)
Device other than CV/HD catheter and urinary device[d]	5 (6.2)	10 (21.7)
Any antimicrobial exposure in the previous 1 month	27 (33.3)	15 (32.6)
Clinical characteristics and severity of infection		
Bacteremia due to ESBLEC	35 (43.2)	27 (58.7)
Polymicrobial culture[e]	25 (30.9)	17 (37)
Fever on the day of onset	72 (90)	41 (89.1)
Pain[f] on the day of onset	10 (12.5)	12 (26.1)
Days from onset to microbiological test	0 (0–1)	0 (0–2)
Days from onset to CMZ or MEM initiation	2 (0–3)	0 (0–2)
Fever on the day of CMZ or MEM initiation	41 (50.6)	26 (57.8)
ICU stay on the day of CMZ or MEM initiation	1 (1.2)	8 (17.4)
qSOFA on the day of CMZ or MEM initiation	0 (0–1)	1 (0–2)
Pitt bacteremia score[g] on the day of CMZ or MEM initiation	3 (0–3)	3 (3–5)
WBC on the day of CMZ or MEM initiation (/μL)	8900 (6563–12598)	10825 (7405–16318)
Leukocytosis on the day of CMZ or MEM initiation	19 (27.1)	17 (40.5)
CRP on the day of CMZ or MEM initiation (mg/dl)	7.3 (4.2–14.5)	13.2 (5.5–23.8)

CRP ≥10 (mg/dL)	30 (42.9)	27 (64.3)

Abbreviations: CMZ, cefmetazole; CV, central venous catheter/central venous port; ESBLEC, ESBL–producing *E. coli*; HD, hemodialysis; ICU, intensive care unit; LTCF, long–term care facilities, MEM, meropenem, WBC, white blood cell.

Note. "Fever" is defined as temperature equal or higher than 37.5 ºC, "leukocytosis" is defined as WBC>12000 μL.

a Data are presented as number (%) or median (interquartile range) unless indicated otherwise.

b Defined as length of hospital stay before isolation of ESBLEC equal or longer than 4 days.

c Urinary device includes urinary catheter, ureteral stent, and nephrostomy catheter.

d Including percutaneous endoscopic gastrostomy tube, tracheostomy tube, endotracheal tube, and nasogastric tube.

e Isolation of additional bacteria other than ESBLEC from the same culture.

f Pain includes lower back pain, lateral abdominal pain, and renal pain (including costovertebral angle tenderness).

g Pitt bacteremia score is calculated only for bacteremic cases.

Table 2. Comparison of outcomes of invasive urinary tract infection between cefmetazole and meropenem treatment groups [a] (n=127)

	CMZ (n=81)	MEM (n=46)
Outcome		
Clinically effective (early)	75 (92.6)	38 (82.6)
Clinically effective (late)[b]	73 (96.1)	40 (90.9)
Microbiologically effective (early)[c]	61 (100)	22 (100)
Microbiologically effective (late)[c]	9 (100)	5 (100)
14–day mortality[d]	0 (0)	1 (2.3)
30–day mortality[d]	0 (0)	5 (12.5)
In–hospital mortality[d]	2 (2.6)	6 (13.3)
Recurrence within 28 days	6 (8.3)	2 (5.6)
LOS after isolation of ESBLEC among survivors, days	15 (11–34)	19 (14–35)
Days from CMZ or MEM initiation to fever resolution	2 (1–6)	3 (1–9)
Defervescence from CMZ or MEM initiation to early treatment period	29 (39.7)	14 (31.8)
Inadequate source control	4 (4.9)	4 (8.7)
Dependent functional status on discharge	52 (68.4)	23 (57.5)
Discharge to home	36 (46.2)	22 (55)
Clostridiodes difficile infection within 28 days after treatment	2 (2.5)	1 (2.2)
CRE isolation within 28 days after treatment	0 (0)	0 (0)

Abbreviations: CMZ, cefmetazole; CRE, carbapenem-resistant Enterobacterales; ESBLEC, ESBL–producing *E. coli*; LOS, length of hospital stay; MEM, meropenem.

Note. "Early" indicates early treatment period, and "late" indicates late treatment period, and "fever" is defined as temperature equal or higher than 37.5 ºC.

a Data are presented as number (%) or median (interquartile range) unless indicated otherwise.

b Data are missing for 5 (CMZ) and 2 (MEM) cases.

c Data are available for 83 (CMZ 61. MEM 22) (early) and 14 (CMZ 9 MEM 5) (late) cases.

d Data are missing for 6/2 (CMZ/MEM) for 14–day mortality, 16/6 (CMZ/MEM) for 130–day mortality, and 4/1 (CMZ/MEM) case for in–hospital mortality.

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468 **Table 3. Details of antibiotic treatment**

Variable	CMZ (n=81)	MEM (n=46)	P value[a]
Total duration of study drug, median (IQR)	8 (6–12)	9 (5–12)	0.920
Total duration of all antibiotics, median (IQR)	11 (8–14)	12 (10–16)	0.087
Empiric therapy[b]			
None	24 (29.6%)	28 (60.9%)	**0.001**
AMP	1 (1.2%)	0	>0.999
SAM	8 (9.9%)	3 (6.5%)	0.745
TZP	9 (11.1%)	4 (8.7%)	0.768
CFZ	1 (1.2%)	0	>0.999
CRO	33 (40.7%)	8 (17.4%)	**0.01**
FEP	1 (1.2%)	1 (2.2%)	>0.999
MEM	3 (3.7%)	NA	NA
FQ[c]	2 (2.5%)	2 (4.3%)	0.62
Oral cephalosporin[d]	2 (2.5%)	0	0.534
Treatment continuation after study therapy[e]			
Any	16 (19.8%)	24 (52.2%)	**<0.001**
SAM	1 (1.2%)	0	>0.999
AMC	0	1 (2.2%)	0.362
TZP	1 (1.2%)	0	>0.999
CMZ	NA	16 (34.8%)	NA
MEM	2 (2.5%)	NA	NA
FQ[c]	4 (4.9%)	1 (2.2%)	0.653

SXT	7 (8.6%)	1 (2.2%)	0.257
Other[f]	1 (1.2%)	2 (4.3%)	0.297

Abbreviations. AMC, amoxicillin–clavulanic acid; AMP, ampicillin; CFZ, cefazolin; CRO, ceftriaxone; FEP, cefepime; FQ, fluoroquinolone (levofloxacin, ciprofloxacin, garenoxacin); NA, not available; SAM, ampicillin–sulbactam; SXT, trimethoprim–sulfamethoxazole; TZP, piperacillin–tazobactam.

a Bold font indicates statistically significant results ($p < 0.05$).

b Empiric therapy was defined as antibiotics active against Gram-negative bacteria that have been used within 96 hours prior to the start of the study drug (i.e., CMZ or MEM). Four patients (3 in CMZ group and 1 in MEM group) received two antibiotics, and both antibiotics were counted separately.

c FQs include 2 levofloxacin, one ciprofloxacin, and one garenoxacin in empiric treatment, and 3 levofloxacin and one ciprofloxacin in treatment continuation.

d Oral cephalosporin include one cefditoren pivoxil and one cefcapene pivoxil.

e Two patients (1 in CMZ group and 1 in MEM group) received two antibiotics, and both antibiotics were counted separately for each antibiotics category.

f Including one patient each treated with fosfomycin and minocycline (MEM group) and one patient who received CFZ (CMZ group).

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Table 4. MIC and susceptibility of isolated ESBLEC (mg/L) (n=124)

	AMC	TZP[b]	CFZ[c]	CTX	CAZ	FEP	CMZ[d]	FMOX	ATM
MIC_{50}	8/4	2/4	>8	>16	4	8	≤1	≤0.12	8
MIC_{90}	16/8	8/4	>8	>16	16	>32	4	0.25	>16
Susceptible, number[a], (%)	96 (77.4%)	119 (96%)	0	1 (0.8%)	63 (50.8%)	29 (23.4%)	124 (100%)		31 (25%)

	MEM	IMP	FRPM	GEN	TOB	AMK	CIP	SXT	FOF[e]
MIC_{50}	≤0.12	≤1	1	≤4	≤4	≤16	>4	≤2/38	≤16
MIC_{90}	≤0.12	≤1	2	>16	16	≤16	>4	>4/76	≤16
Susceptible, number, (%)	124 (100%)	124 (100%)		99 (79.8%)	99 (79.8%)	124 (100%)	19 (15.3%)	66 (53.2%)	120 (96.8%)

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.

a Susceptibility results were interpreted using the 2021 CLSI breakpoints.

b TZP breakpoint MIC ≤ 8/4 mg/L was used for susceptible category.

c CFZ breakpoint MIC ≤ 2 mg/L was used for susceptible category.

d MIC distribution of CMZ is as follows: ≤1 mg/L (n=86, 69.4%), 2 mg/L (n=23, 18.5%), 4 mg/L (n=10, 8%), 8 mg/L (n=5, 4%)

e Fosfomycin MICs were measured by broth microdilution in the presence of glucose-6-phosphate (25 mg/L in the medium).

474 **Table 5. Molecular characteristics of isolated ESBL-producing E. coli (n=124)**

MLST_ST[a]		CTX-M subtype		ST131 clade (n=91)	
131	91 (73.4%)	27	59 (47.6%)	C1-M27	43 (47.3%)
1193	6 (4.8%)	15	30 (24.2%)	C1-nM27	20 (22%)
38[b]	6 (4.8%)	14	25 (20.2%)	C2	17 (18.7%)
95	3 (2.4%)	55	4 (3.2%)	A	8 (8.8%)
10	2 (1.6%)	8	2 (1.6%)	B	2 (2.2%)
69	2 (1.6%)	65	2 (1.6%)	C0	1 (1.1%)
393	2 (1.6%)	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, and 5150, respectively.

b including one isolate with single locus variant of ST38.

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476 **Table 6. Propensity score-adjusted analyses of clinical outcomes of invasive UTI: cefmetazole vs**

477 **meropenem treatment groups**

Variables	Adjusted Odds Ratio (95% confidence interval)	P value
Clinically effective (early)	0.63 (0.15–2.75)	0.54
Clinically effective (late)	1.83 (0.26–12.75)	0.54
14-day mortality	NA	NA
30-day mortality	<0.01 (NA)	<0.01
In-hospital mortality	0.20 (0.03–1.36)	0.10
Recurrence within 28 days	1.36 (0.14–12.93)	0.79
LOS after isolation of ESBLEC among survivors	NA	0.23

Abbreviations. LOS, length of stay; NA, not available.

The propensity score was calculated using a nonparsimonious multivariable logistic regression model including the baseline characteristic variables (age, sex, nursing home or LTCF residence, hospitalization in the past 3 months, surgery after admission prior to ESBLEC isolation, hospital onset, ESBLEC bacteremia, polymicrobial isolation, Charlson comorbidity index, immunocompromised status, urological complication, device other than CV/HD catheter and urinary device, qSOFA score, any empiric therapy before initiation of CMZ or MEM, and CRP ≥10 mg/dl [as defined in Table 1]. The adjusted Odds Ratio for 14-day mortality is not available owing to the small number of events. NA, not available.

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481 **Table 7. Summary of cefmetazole or meropenem dosing in patients with invasive urinary tract infection due to ESBL-producing *E. coli***

CMZ (n=81)								MEM (n=46)					
CrCl (mL/min) category	n (%)	Dose (g)	Interval (h)	No.	MIC, median (range)	TAM for each regimen, median (IQR)	Clinically ineffective (early), no.	CrCl (mL/min) category	n (%)	Dose (g)	Interval (hour)	No.	Clinically ineffective (early), no.
<10	3 (3.7%)	0.5	12	1	≤1	100	1	<10	5 (11%)	0.5	24	4	
		1	24	1	4	99.8				1	24	1	
		2	24	1	≤1	100		10–25	16 (35%)	1	12	6	1
10–29	20 (24.7%)	1	12	11	≤1 (≤1–4)	100 (100–100)				0.5	12	5	
		1	24	5[a]	NA (≤1–4)	80.9 (64.7–96)				1	8	2	
		2	12	3	2 (≤1–	100	1			0.5	8	1	

					8)	(100–100)							
		2	24	1	2	82.9				0.5	24	1	
30–50	29 (35.8%)	1	8	8	≤1 (≤1–2)	100 (100–100)	4			0.25	12	1	
		1	12	9	≤1 (≤1–4)	100 (84.6–100)		26–50	11 (24%)	1	12	6	2
		1	24	5	≤1 (≤1–2)	65 (55.6–90.2)				1	8	2	1
		2	12	1	2	100				0.5	12	2	
		2	24	6	≤1 (≤1–8)	58.5 (43.0–62.6)				2	12	1	
>50	29 (35.8%)	1	6	2	≤1 (≤1–<1)	100 (100–100)		>50	14 (30%)	1	8	9	2
		1	8	10[a]	≤1 (≤1–2)	50				0.5	12	2[a]	2
		1	12	11	≤1	57.8				0.5	6	1	

				(≤1–8)	(41.5–82.4)					
	2	12	4	≤1 (≤1–<1)	95.2 (89.6–100)		0.5	8	1	
	2	24	2	NA (2–8)	43.6	(32.8–NA)	1	12	1	

Abbreviations. NA, not available. TAM, time above MIC.

a For one case per each category, TAM could not be calculated; two isolates were missing from microbiological analyses at the central laboratory. 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 reported in the hospital microbiological laboratory, with resistance to cefotaxime).