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Original Article

Comparison of the efficacy of cefmetazole and meropenem for patients with extended-spectrum beta-lactamase-producing *Escherichia coli* bacteremia: a single-center experience

Tomoyuki Kato[1], Emi Ono[1], Yoko Hiroshima[1], Kaoru Nagata[2], Shinichirou Suzaki[3], Takashi Yamazaki[4], Masayuki Nagasawa[1,5]

[1]*Antimicrobial Stewardship Team, Musashino Red Cross Hospital, Tokyo, Japan*

[2]*Department of General Practice, Musashino Red Cross Hospital, Tokyo, Japan*

[3]*Department of Emergency and Critical Care Medicine, Musashino Red Cross Hospital, Tokyo, Japan*

[4]*Department of Orthopedics, Musashino Red Cross Hospital, Tokyo, Japan*

[5]*Department of Pediatrics, Musashino Red Cross Hospital, Tokyo, Japan*

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Abstract

Background: We retrospectively investigated whether cefmetazole (CMZ) was equivalently as effective as meropenem (MEPM) for treating bloodstream infections with extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-*E. coli*).

Methods: From 2012 through 2017, ESBL-*E. coli* were cultured from the blood of 74 patients at our institute. Excluding 17 ineligible patients, 31 patients were treated with CMZ and 26 patients were treated with MEPM as definitive therapy. The primary infection site was the urinary tract in 37 patients, the abdomen in 4, and undetermined in 16.

Results: There was no significant difference between both groups with respect to sex differences, Sequential Organ Failure Assessment (SOFA) score and Pitt bacteremia score, except for age (CMZ vs. MEPM: 79.5±13.4 vs. 71.4±15.5 years; p=0.045) and the frequency of undetermined infection site (CMZ vs. MEPM: 5/36 vs. 11/26; p=0.028). There was no significant difference in 30-day mortality after treatment between the CMZ and MEPM groups (4/31 vs. 3/26; p=0.88). Furthermore, there was no recurrence within 30 days after treatment in both groups. Multivariate analysis revealed that the SOFA score was significantly (p=0.026) and the undetermined infection focus was relatively (p=0.055) associated with 30-day mortality after treatment.

Conclusions: CMZ for bloodstream infections with ESBL-*E. coli* originating in the urinary tract may be as effective as MEPM when the SOFA score is not high.

Keywords: bacteremia, beta-lactamase, cefmetazole, meropenem, organ dysfunction score

Address for Correspondence: Masayuki Nagasawa, Department of Pediatrics, Musashino Red Cross Hospital, 1-26-1, Kyonan-cho, Musashino-city, Tokyo 180-8610, Japan. E-mail: mnagasawa.ped@tmd.ac.jp

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Introduction

Bloodstream infection is a clinically serious condition with a high mortality rate, and thus, rapid intervention with proper antibiotics is required [1]. *Escherichia coli* is a common enteric bacterium that causes bloodstream infections in both community and health care units [2]. The incidence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, including ESBL-producing *E. coli* (ESBL-*E. coli*), has increased worldwide [3].

In general, carbapenems are recommended for treating infections with ESBL-producing *Enterobacteriaceae* [4,5]. However, the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) is of high concern and is associated with increased consumption of carbapenems [6]. Therefore, the proper use of antibiotics is important and recommended to reduce the prevalence of CRE.

Cephamycins such as cefmetazole (CMZ) are effective against ESBL-producing bacteria *in vitro* [7]. Recent clinical papers reported that CMZ was as effective as carbapenems for treating urinary tract infections due to ESBL-producing *Enterobacteriaceae* [8]. However, although carbapenems are still recommended for the empirical treatment of clinically severe cases [9,10], no study has reported the significant superiority of carbapenems to cephamycins.

Therefore, we evaluated and compared the efficacy of CMZ and meropenem (MEPM) as a definitive therapeutic antimicrobial agent for treating bloodstream infections with ESBL-*E. coli.*

Methods

From January 2012 through December 2017, ESBL-*E. coli* were cultured from the blood of 74 patients at our hospital [Figure 1]. Among them, five patients died before the results of the blood culture could be obtained, six were transferred and untraceable and three were determined to be contaminants. In the other three patients, neither CMZ nor MEPM was used even after the blood culture results. Excluding these 17 patients, 57 patients were enrolled in this study [Figure 2].

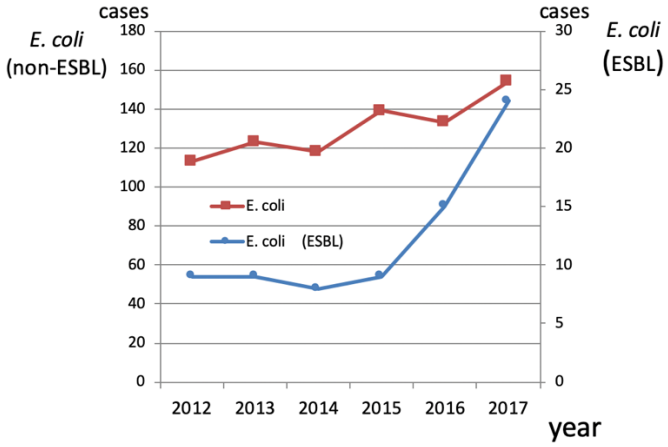

Figure 1. Cases of bacteremia with ESBL-producing and non-producing *Escherichia coli* between 2012 and 2017.

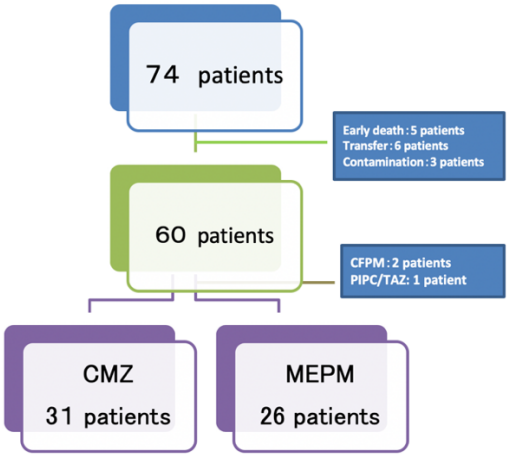

Figure 2. Flow chart of patient enrollment in this study.
CMZ: Cefmetazole, MEPM: Meropenem, CFPM: Cefepime, PIPC/TAZ: Piperacillin/Tazobactam.

Medical information was retrospectively obtained from the clinical records of 57 patients. To evaluate the status of the patients, the Sequential Organ Failure Assessment (SOFA) score [11], which is usually used to track a patient's condition during their stay in an intensive care unit, and the Pitt bacteremia score (PBS) [12] were used as markers of severity and prognosis.

ESBL-*E. coli* was isolated using the broth microdilution method according to the break-point criteria advocated by the Clinical and Laboratory Standard Institute [13,14] and was confirmed using AmpC/ESBL differential discs (Kanto Chemical Co. Inc., Japan). The primary endpoint was death within 30 days after initiating treatment.

Statistical analysis

For the statistical analysis, a Chi-square test, Mann-Whitney U test and logistic regression were performed. All statistical analyses were performed using Excel Statistics version 6.0 (Microsoft Corporation, Redmond, WA, USA). Analysis items with p-values <0.05 were considered statistically significant.

Ethical assessment

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the institutional review board of our hospital. The aim of the study was explained to the patients and informed consent was obtained via the opt-out method.

Results

As shown in Figure 1, the number of cases of ESBL-*E. coli* bloodstream infection remained unchanged between 2012 and 2015 but increased from 2016, compared with the slight increase in the incidence of ESBL-nonproducing *E. coli* bloodstream infection.

CMZ was used in 31 patients and MEPM in 26 patients as definitive therapy after obtaining the blood culture results. There was no significant change in the preference for selecting CMZ or MEPM according to age (data not shown). The summarized profile of the 57 patients is presented in Table 1. There were no significant differences between both groups with respect to sex differences, the SOFA score and PBS, except for age (CMZ vs. MEPM: 79.5±13.4 vs. 71.4±15.5 years; p=0.045) and the frequency of undetermined infection site (CMZ vs. MEPM: 5/36 (16%) vs. 11/26 (42%); p=0.028).

Table 1. Characteristics and outcomes of patients treated with CMZ or MEPM

	CMZ	MEPM	p-value
Number	31	26	
Male (N, %)	14 (45%)	16 (62%)	0.22
Age (years)	79.5 ± 13.4	71.4 ± 15.5	**0.045**
Death (<30 days)	4 (13%)	3 (12%)	0.88
Primary focus			
Urinary tract	23 (74%)	14 (54%)	0.11
Intra-abdominal	3 (10%)	1 (4%)	0.39
Undetermined	5 (16%)	11 (42%)	**0.028**
SOFA	2.6 ± 2.4	3.5 ± 2.4	0.15
PBS	0.9 ± 1.4	1.5 ± 1.7	0.13
Shock	4 (13%)	5 (19%)	0.51
Multiple pathogens	2 (6%)	6 (23%)	0.07

CMZ: Cefmetazole, MEPM: Meropenem, SOFA: Sequential Organ Failure Assessment, PBS: Pitt bacteremia score.

The urinary tract was identified as the primary infection site in 37 patients, the abdomen in 4, and undetermined in 16. MEPM was preferentially used in patients with undetermined infection focus [Table 1]. The mortality rate was higher among patients with undetermined primary infection focus than in those with the urinary tract or abdomen as the primary infection site (5/16 (31.3%) vs. 2/41 (4.9%), p=0.006). Regarding the initial choice of antimicrobial agents, various antimicrobial agents effective against gram-negative bacteria were used [Table 2], and there seemed to be no constant preferential selection. For interpretation, MEPM was not used in the CMZ group as an empiric therapy because the effect of MEPM was completely negligible in the CMZ group.

Table 2. Antibiotics initially selected for the patients of CMZ and MEPM group

CMZ group		MEPM group	
Initial treatment		Initial treatment	
CMZ	8	CMZ	4
CTRX	8	CTRX	6
CTM	4	CTM	4
CEZ	2	CEZ	4
CAZ	1	CAZ	1
CFPM	1	CFPM	3
PIPC/TAZ	5	PIPC/TAZ	2
ABPC/SBT	2	ABPC/SBT	2
Total	31	Total	26

CMZ: Cefmetazole, MEPM: Meropenem, CTRX: Ceftriaxone, CTM: Cefotiam, CEZ: Cefazolin, CAZ: Ceftazidime, CFPM: Cefepime, PIPC/TAZ: Piperacillin/Tazobactam, ABPC/SBT: Ampicillin/Sulbactam.

CMZ was initially used and changed to MEPM in four cases arbitrarily after ESBL-*E. coli* bloodstream infection was confirmed. Three of four patients had a high SOFA score with a shock when blood culture samples were taken [Table 3] and were considered serious. Multiple pathogens were cultured from the blood of eight patients. MEPM was preferentially used to treat these patients, and mortality was associated with the SOFA score in these eight patients (data not shown).

Table 3. Profile of four patients in whom CMZ was changed to MEPM as a definitive therapy

Age (years)	Death (<30 days)	Shock	Primary focus	SOFA	PBS
45	No	Yes	Undetermined	8	6
79	No	No	Urinary tract	3	2
64	No	Yes	Urinary tract	6	4
86	No	Yes	Intra-abdominal	5	3

SOFA: Sequential Organ Failure Assessment, PBS: Pitt bacteremia score.

Table 4. Multivariate analysis for risk factors of death within 30 days

	Odds ratio	95% CI		p-value
		Lower limit	Upper limit	
Antibiotics	33.73	0.499	2277	0.102
SOFA	4.128	1.180	14.43	**0.026**
Shock	0.150	0.001	17.55	0.435
PBS	0.545	0.213	1.395	0.206
Undetermined focus	53.05	0.912	3085	0.055

SOFA: Sequential Organ Failure Assessment, PBS: Pitt bacteremia score.

There was no significant difference in the 30-day mortality rate after treatment between the CMZ and MEPM groups [Table 1]. The SOFA score was significantly higher among dead patients than among survivors (5.86±2.27 vs. 2.64±2.17; p<0.004), but there was no significant difference in PBS (1.71±1.89 vs. 1.12±1.55; p=0.421). The SOFA score was higher among cases with undetermined infection focus (4.00±6.53) than among those with the urinary tract (2.65±5.51) and abdomen (2.75±2.91) as infection foci, without statistical significance. The multivariate analysis revealed that the SOFA score was significantly (p=0.026) and the undetermined infection site was relatively (p=0.055) associated with 30-day mortality after treatment [Table 4]. No patients had a recurrent infection within 30 days in both groups.

Discussion

In this study, the urinary tract was the most common primary infection site (37/57, 64.9%) as previously reported [13]. ESBL-producing *Enterobacteriaceae* colonize the intestinal tract of healthy subjects and are reported to eventually cause bloodstream infections [15,16]. It is considered that healthy subjects acquire ESBL-producing *Enterobacteriaceae* via domestic animals and food or environmental exposure [17], and the spread of ESBL-producing *Enterobacteriaceae* among the population is a matter of concern these days [18].

As shown in Figure 1, the number of patients in whom ESBL-*E. coli* was cultured from the blood has increased at our hospital since 2016. It is speculated that the improper use of antimicrobial agents among healthy subjects leads to an expansion of ESBL-producing *Enterobacteriaceae* by pharmacological selection and eventually results in an increased incidence of infection with this pathogen. As the universal use of carbapenems is prohibited along with the creation of antimicrobial stewardship programs, it becomes important to make a proper diagnosis and evaluate infection with ESBL-producing *Enterobacteriaceae*. As an initial choice, various antimicrobial agents effective against gram-negative bacteria were used [Table 2], and there seemed to be no constant preference in the selection of initial antibiotics. At our institute, the choice of definitive therapy was based on the result of *in vitro* sensitivity data for ESBL-producing *Enterobacteriaceae* and not on the site of infection.

Although a previous report clearly showed that CMZ was clinically effective for urinary tract infection with ESBL-*E. coli* [8], the efficacy of CMZ for bloodstream infections with ESBL-*E. coli* is not still confirmed. In this study, CMZ was sufficiently effective and feasible for treating bloodstream infections with ESBL-*E. coli*. Although fatal cases were observed frequently among patients with undetermined infection focus, there was no significant difference in the mortality rate between the CMZ (2/5, 40%) and MEPM (3/11, 27.3%) groups (p=0.61). However, CMZ was initially used among four patients and changed to MEPM arbitrarily after bloodstream ESBL-*E. coli* infection was confirmed. Three of four patients had high SOFA scores with a shock when blood culture samples were obtained, and the primary infection focus was undetermined in two patients. As mentioned above, the SOFA score was higher among patients with undetermined primary infection focus in this cohort. Consequently, these four patients survived, which might be explained by the fact that MEPM was somehow superior to CMZ in managing serious infections.

The multivariate analysis revealed that death within 30 days after treatment was significantly associated with the SOFA score but not with the choice of antimicrobial agent (CMZ or MEPM). However, there seemed to be an arbitrary choice of MEPM rather than CMZ for patients with serious infections in this cohort; thus, we have to interpret our results with caution.

The SOFA score was devised to evaluate the degree of organ damage in septicemic patients and the mortality rate of patients with high SOFA scores was predicted to be high. Several studies have reported a positive association of SOFA score or quick SOFA score, which is devised for the screening of septic patients outside intensive care units [19], with an increased mortality rate [20-22]. However, other studies have reported no relationship between quick SOFA score and the mortality rate of inpatients with ESBL-producing bacteremia [23,24]. This discrepancy might be explained by the pathologic difference between sepsis and bacteremia; however, further studies will be necessary in the future.

In our retrospective study, we concluded that CMZ may be as effective as MEPM for treating patients with ESBL-*E. coli* bacteremia originating in the urinary tract if the SOFA score is not high.

Conflict of interest

There are no conflicts of interest to declare for all of the authors.

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