Infect Chemother. 2022 Dec;54(4):722-732
https://doi.org/10.3947/ic.2022.0096
pISSN 2093-2340·eISSN 2092-6448

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Original Article

Impact of Inappropriate Empirical Antibiotic on Outcomes in Community-acquired Third Generation Cephalosporin Resistant *Enterobacterales* Bacteremia

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Received: Jun 22, 2022
Accepted: Sep 15, 2022
Published online: Dec 14, 2022

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Trial Registration
ClinicalTrials.gov Identifier: NCT03765749

ABSTRACT

Background: Currently, third generation cephalosporin resistant *Enterobacterales* (3GCRE) are becoming more common in community-acquired infection, leading to increasing consumption of carbapenems. Because community-acquired 3GCRE infections are generally less severe and of lower pathogenicity, the impact of inappropriate empirical antibiotics among patients with community-acquired 3GCRE bacteremia remains unknown.
Materials and Methods: This prospective cohort study included adult patients with 3GCRE bacteremia from April 2018 to December 2021. Participants were followed for 30 days to measure the primary outcome of mortality. Propensity score analysis was performed to adjust for treatment selection bias.
Results: A total of 155 patients met the eligible criteria (42 participants in the appropriate antibiotics group, and 113 participants in the inappropriate antibiotics group). Eight participants in the inappropriate antibiotics group never received appropriate antibiotics, three of whom died before microbiological results were made available. The most common clinical syndromes were urinary tract infection (56.8%) and biliary tract infection (22.6%). The overall 30-day mortality rate was 12.9%, 14.3% in the appropriate empirical antibiotics group and 12.4% in the inappropriate empirical antibiotics group. After propensity score weighted adjustment, the 30-day mortality rate in the inappropriate group was non-inferior to the appropriate group (mean difference 1.9%; 95% confidence interval: -10.1 - 14.0). From the multivariate analysis, acute respiratory failure and primary bacteremia were associated with 30-day mortality.
Conclusion: Among patients with community-acquired 3GCRE bacteremia, inappropriate empirical treatment given within 24 hours after the onset of bacteremia was non-inferior to appropriate antibiotics. In the setting of a high prevalence of 3GCRE carriage in community, adjustment to carbapenem might be tolerable among patients with community-acquired infections.

Trial Registration: ClinicalTrials.gov Identifier: NCT03765749

Keywords: Third generation cephalosporin-resistant Enterobacterales; Community-acquired infection; Bacteremia; ESBL

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Funding

This study was supported by the Division of Infectious Diseases, Department of Internal Medicine, Phramongkutklao Hospital (Funding number IDPMK 01301-61). The funder supported budget regarding the patient data collection process and all research equipment expenses, e.g., office supplies.

Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: WN, DC, VV. Data curation: WN, VV. Formal analysis: WN, VV. Funding acquisition: WN. Investigation: WN, DC, VV. Methodology: WN, DC, VV. Project administration: W.N. Resources: WN, DC, VV. Software: WN, VV. Supervision: WN, DC, VV. Validation: WN, VV. Visualization: WN, DC, VV. Writing - original draft: WN, VV. Writing - review & editing: WN, DC, VV.

INTRODUCTION

In the past decade, the incidence of third generation cephalosporin resistant *Enterobacterales* (3GCRE) infection has increased worldwide [1, 2]. The 3GCRE commonly occurs when these bacteria express third-generation cephalosporin beta-lactamase enzymes. These enzymes include extended-spectrum beta-lactamase (ESBL), AmpC enzymes, and OXA-type beta-lactamase [3]. Traditionally, this form of resistance is commonly found among patients with specific risk factors, such as recent hospitalization or exposure to broad-spectrum antibiotics [4]. However, an increasing incidence of 3GCRE intestinal carriage in the community has been described [5]. Spread of 3GCRE outside hospitals has in turn led to the increased use of inappropriate empirical antibiotics in community-acquired infections [6]. Inappropriate antibiotics use has been shown to be a significant risk factor for mortality in 3GRCE associated infections; in a systematic review, delayed appropriate antibiotics use of greater than 24 hours was associated with a 1.6 fold increase in mortality for patients infected with *Enterobacterales*, mainly 3GCRE [7]. Inappropriate antibiotics use is also associated with increased hospital length of stay in Gram-negative sepsis [8]. However, most studies have been conducted in patients with hospital-acquired and hospital-associated infections, which were associated with higher clinical severity and mortality.

Two studies in patients with community-onset 3GCRE bacteremia did not discover any association between inappropriate antibiotics use and mortality [9, 10]. These studies were conducted in the setting of low prevalence of community carriage at around 20%; and therefore, the majority of patients had a healthcare-associated infection [11]. Moreover, one of the studies analyzed only patients who received definitive treatment, excluding patients who might have died from inappropriate treatment before receiving definite treatment.

Because carbapenems are the treatment of choice for 3GCRE infections, community 3GCRE infection has led to an increased global carbapenem consumption and placed selection pressures for the emergence of carbapenem-resistant organisms [12, 13]. In Thailand, the rate of intestinal carriage of 3GCRE is more than 50%, leading to an increasing trend of carbapenem use for the management of community-acquired infection [14]. Antimicrobial stewardship in this setting has become challenging [15]. However, there is support that community - acquired 3GCRE strains are associated with lower pathogenicity [16]. Whether early inappropriate antibiotics use in community-acquired infection is associated with worse outcomes remains unknown. As there are no well-controlled prospective studies to address this issue, this study aimed to investigate whether early inappropriate empirical antibiotics use was non-inferior to appropriate antibiotics with respect to clinical outcomes in patients with community-acquired 3GCRE bacteremia.

MATERIALS AND METHODS

1. Study design

In this prospective cohort study, we enrolled adult patients (over 18 years) with the first onset of community-acquired monomicrobial 3GCRE bacteremia between April 2018 and December 2021 at Phramongkutklao Hospital, a 1,200-bed tertiary care university hospital in Bangkok, Thailand. Community-acquired infection was defined by the previously described criteria as those without: previous hospitalization within 90 days, previous antibiotics exposure within 90 days, history of hemodialysis or placement in a long-term health care

https://doi.org/10.3947/ic.2022.0096

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facility [17]. Exclusion criteria included participants who were pregnant or transferred out to another hospital within the first seven days after onset of bacteremia.

A list of patients with monomicrobial 3GCRE bacteremia were notified to the investigators every month by the hospital microbiological laboratory. Participants were subsequently assessed for eligibility and classified in two groups according to the appropriateness of empirical antibiotics use. Appropriate antibiotics were defined as antibiotics with *in vitro* activity against etiologic organisms according to laboratory susceptibility data. Empirical antibiotics were defined as antibiotics administered within the first 24 hours. Definite antibiotics were defined as antibiotics administered after the availability of antimicrobial susceptibility test.

Demographic data, preexisting medical conditions, source of bacteremia, source control measures, microbiological data, empirical treatment, definitive treatment, antibiotics de-escalation procedures, and outcome data for these eligible patients were retrieved from electronic medical records. Infectious diseases-trained physicians who provided patient care determined the source of infection and the appropriateness of source control measures. Mortality was assessed during the period of 30 days after the onset of bacteremia. Patients were routinely followed up by the hospital team after discharge and those who missed their appointment were assessed by telephone calls conducted by the study team. Those unable to be contacted were recorded as missing values after the time of the last known alive status. To minimize the effects of early death on length of stay, those who died during hospital admission were excluded from length of stay analysis.

Complications were defined within the first 24 hours after bacteremia. Septic shock was defined when norepinephrine was given. Acute kidney injury was defined as presence any of the following: increased serum creatinine ≥0.3 mg/dL within 48 hours, or increase in serum creatinine to ≥1.5 times baseline known or presumed to have occurred within the prior days [18]. Respiratory failure was defined when participants needed a mechanical ventilator or high flow oxygen. Disseminated intravascular coagulation (DIC) was defined when the DIC score endorsed by the International Society on Thrombosis and Haemostasis ≥5 points [19].

2. Ethics statement

The study protocol followed the guidelines of the Declaration of Helsinki and ethics approval was obtained from the Institutional Review Board Royal Thai Army Department. (IRB No R097h/61). This study was registered with the ClinicalTrials.gov, number NCT03765749. Informed consent was obtained in written forms from all participants or legal guardians in the study, either in person or by telephone call with the legal guardians in case participants had died before the enrolment.

3. Microbiological analysis

Bacterial isolates were collected in a clinical microbiology laboratory at the study hospital. Species identification was performed using Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Germany). Antimicrobial susceptibility testing was performed using the automated broth microdilution method (Sensititre, TREK Diagnostic Systems Inc, Cleveland, OH, USA) and was interpreted according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [20]. The 3GCRE was defined when *Enterobacterales* were resistant to at least one of the third-generation cephalosporins, *i.e.* ceftriaxone, ceftazidime, but had pan-susceptibility to carbapenems.

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4. Statistical analysis

This study was designed as a non–inferiority study. A previous study found that the stabilized propensity score weighted mortality among patients with appropriate and inappropriate antibiotics at 7.7 and 3.7%, respectively [9]. With 80% power, a one-sided alpha level of 0.025, and non-inferiority margin of 12%, 33 participants were required in the appropriate antibiotics group. Because the rate of appropriate treatment received was 30.4% [10], a total of 108 participants would be required. Therefore, we planned the enrolment period to take place over four years between April 2018 and 2021.

For categorical variables, Chi-square or Fisher's exact test was used, while Student's *t* test or the Mann-Whitney *U* was used to compare continuous variables. To adjust for treatment selection bias, propensity score analysis using the inverse probability of treatment weights (IPTW) was performed. Propensity scores were calculated based on multivariable logistic regression modeling including age, pulse rate, consciousness status, white blood cell count, respiratory failure, septic shock, disseminated intravascular coagulation, intraabdominal infection status, treatment with surgical drainage, time to first antibiotics, *Escherichia coli* infection, Pitt bacteremia score, and Charlson comorbidity index score. Sensitivity analysis was conducted to investigate the impact of never receiving appropriate antibiotics by excluding participants in the inappropriate antibiotics group who never received definite appropriate antibiotics.

For factors associated with 30-day mortality, potentially clinical significant predictors in the univariate analyses (*P*-value <0.05) were subsequently included in a multiple logistic regression model. For all analyses, a two-sided *P*-value <0.05 was considered significant. Data were analyzed using SPSS (Version 28, SPSS Inc, Chicago, IL, USA).

RESULT

During the study, a total of 694 isolates of monomicrobial 3GCRE bacteremia were notified by the microbiological laboratory, 155 cases of which met the eligible criteria (42 participants in the appropriate antibiotics group, and 113 participants in the inappropriate antibiotics group) as described in **Figure 1**. The majority of participants were male (58.1%), with 39.4% having a diagnosis of diabetes. The most common clinical syndromes were urinary tract infection (56.8%), and biliary tract infection (22.6%). Participants in the appropriate empirical antibiotics group had a significantly higher Charlson comorbidity index ($P = 0.002$). A trend toward a higher proportion of surgical drainage or early intervention for patients with urinary tract or biliary infection was observed in the inappropriate empirical antibiotics group (31.9% *vs.* 16.7%, $P = 0.06$). Baseline characteristics and severity of participants between the two groups are shown in **Table 1**.

Almost all participants in the appropriate antibiotics group received carbapenems, mainly ertapenem, for empirical and definitive treatment (92.9 and 95.2%, respectively). On the other hand, most participants in the inappropriate antibiotics group received ceftriaxone as empirical treatment and carbapenems as definitive treatment (88.5 and 82.3% respectively). Participants in the inappropriate antibiotics group received appropriate antibiotics with a median delay of 55 hours after the onset of bacteremia. Eight participants in the inappropriate antibiotics group never received appropriate antibiotics, three of whom

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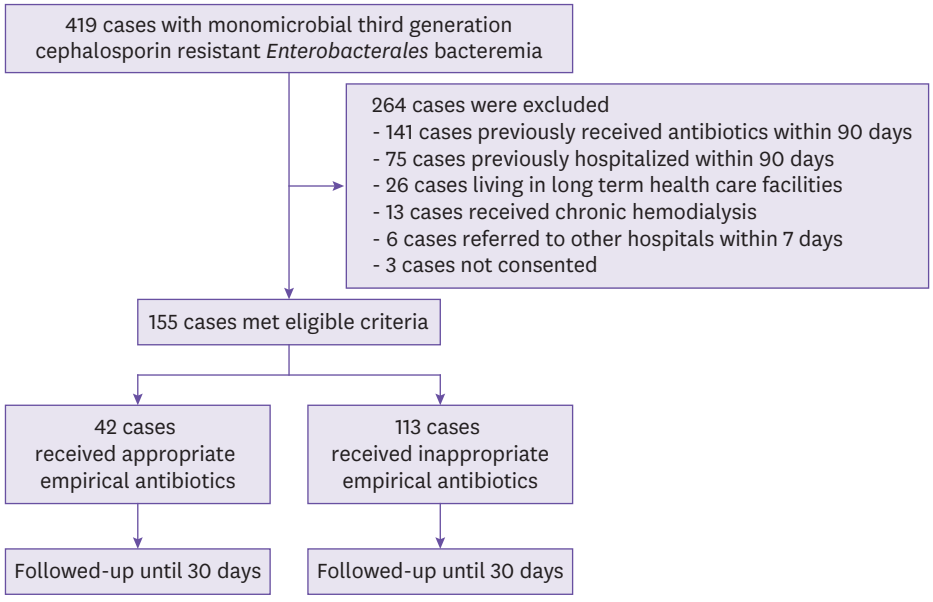

Figure 1. Participant enrolment.

died before the report of microbiological results was available. Antibiotics treatment of participants between the two groups are shown in **Table 2**.

E. coli was the most frequently isolated organism (85.8%). The overall 30-day mortality rate across both groups was 12.9%. The difference in mortality between the two groups was not statistically significant (14.3% *vs.* 12.4%, mean difference 1.9%; 95% confidence interval [CI]: -10.1 – 14.0%). The length of hospital stay and hospital mortality did not significantly differ between the two groups. After propensity score adjustment, the two groups were comparable regarding baseline characteristics and severity, except for underlying autoimmune diseases which were more common in the appropriate antibiotics group. The adjusted difference in mortality between the two groups was 1.6% (95% CI: -11.9 - 15.1%). The length of hospital stay and hospital mortality after adjusting were not statistically different between the two groups. The results of matching are shown in **Table 3**.

Sensitivity analysis which excluded 8 participants in the inappropriate antibiotics group never receiving definite appropriate antibiotics found the 30-day mortality of the appropriate group and inappropriate group was 14.9% and 10.1%, respectively. The adjusted difference in mortality between the two groups was 4.8% (95% CI: -7.8 - 17.4%).

Factors associated with 30-day mortality are shown in **Table 4**. In univariate analysis, cirrhosis, septic shock, acute respiratory failure, and primary bacteremia were significantly associated with mortality. In multivariate analyses, acute respiratory failure and diagnosis of primary bacteremia were associated with mortality. Inappropriate antibiotics use was not an independent risk factor for mortality.

https://doi.org/10.3947/ic.2022.0096

Table 1. Baseline characteristics, severity of participants in appropriate empirical antibiotics and inappropriate empirical antibiotics groups

Characteristics	Non-matching			Stabilized propensity score weighted		
	Appropriate empirical antibiotics (n = 42)	Inappropriate empirical antibiotics (n = 113)	*P*-value	Appropriate empirical antibiotics (n = 33.4)	Inappropriate empirical antibiotics (n = 107.8)	*P*-value
Male	24 (57.1)	66 (58.4)	0.887	19.8 (59.3)	65.6 (60.9)	0.812
Age (years)	78 (64 - 85)	72 (63 - 82)	0.346	71 (61 - 84)	73 (64 - 84)	0.910
Underlying diseases	42 (100)	109 (96.5)	0.575	33.4 (100)	104.0 (96.4)	0.573
Charlson comorbidity index score	2 (2 - 3)	1 (1 - 3)	0.002	2 (1 - 3)	2 (1 - 3)	0.273
Diabetes mellitus	18 (42.9)	43 (38.1)	0.586	13.1 (39.2)	41.5 (38.5)	0.912
Cirrhosis	3 (7.1)	4 (3.5)	0.586	0.9 (2.7)	4.2 (3.9)	1.000
Chronic kidney disease	10 (23.8)	21 (18.6)	0.389	8.8 (26.4)	20.8 (19.3)	0.381
Ischemic heart disease	8 (19)	10 (8.8)	0.470	6 (18)	11.7 (10.9)	0.287
Autoimmune disease	3 (7.1)	1 (0.9)	0.078	2.6 (7.8)	1 (0.9)	0.043
Cerebrovascular disease	8 (19)	18 (15.9)	0.061	5.6 (16.8)	17.7 (16.4)	0.894
Dementia	5 (11.9)	4 (3.5)	0.644	3.1 (9.3)	4.1 (3.8)	0.354
Solid malignancy	11 (26.2)	18 (15.9)	0.061	6.2 (18.6)	20 (18.6)	1.000
Hematological malignancy	0 (0)	4 (3.5)	0.145	0 (0)	3.1 (2.9)	1.000
Clinical parameters						
Mean arterial pressure	86.3 (75.7 - 97.3)	87.7 (76.7 - 98.3)	0.693	86 (78.7 - 97.3)	88 (76.3 - 98.3)	0.799
Body temperature	38.15 (36.7 - 39)	38 (37 - 38.7)	0.875	38.4 (37 - 39)	38 (37 - 38.8)	0.379
Pulse rate	108.5 (90 - 116)	97 (82 - 112)	0.167	106 (91 - 116)	97 (82 - 114)	0.492
Respiratory rate	20 (18 - 22)	20 (18 - 22)	0.706	20 (18 - 22)	20 (18 - 22)	0.423
Glasgow coma score	15 (15 - 15)	15 (15 - 15)	0.775	15 (15 - 15)	15 (15 - 15)	0.991
Oxygen saturation (%)	98 (93 - 99)	98 (96 - 99)	0.856	98 (95 - 99)	98 (96 - 99)	0.776
Sodium	136 (131 - 139)	135 (132 - 138)	0.955	136 (132 - 139)	135 (132 - 139)	0.973
Potassium	3.9 (3.6 - 4)	3.9 (3.43 - 4.08)	0.796	3.9 (3.66 - 4)	4 (3.43 - 4.08)	0.777
Creatinine	1.4 (0.8 - 2.1)	1.2 (0.85 - 2.1)	0.863	1.48 (0.8 - 2.77)	1.28 (0.85 - 2.1)	0.913
Hematocrit (%)	33.8 (30.6 - 37.1)	35 (29.6 - 39)	0.708	34.6 (33.1 - 37.7)	35 (29.6 - 39)	0.884
White blood cell (cells $\times 10^9$/L)	11.2 (9 - 1.6)	16 (10.7 - 19.4)	0.051	11.9 (9 - 19)	15.9 (10.7 - 19.2)	0.463
Platelet (cells $\times 10^9$/L)	220.5 (168 - 260)	196 (145 - 271)	0.667	221 (160 - 273)	196 (147 - 257)	0.454
Lactate (mmol/L)	2 (1.33 - 4)	2 (1.2 - 3.59)	0.808	2 (1.33 - 4)	2.11 (1.2 - 4)	0.903
Pitt bacteremia score	3 (2 - 6)	3 (2 - 4)	0.095	3 (2 - 6)	3 (2 - 4)	0.193
APACHE II score	11 (8 - 14)	11 (8 - 14)	0.906	12 (8 - 14)	11 (9 - 14)	0.808
Clinical syndrome						
Urinary tract infection	24 (57.1)	64 (56.6)	0.955	21.7 (65)	63.6 (59)	0.571
Biliary tract infection	7 (16.7)	28 (24.8)	0.293	4.6 (13.8)	23.3 (21.6)	0.387
Other intraabdominal infections	5 (11.9)	3 (2.7)	0.034	1.9 (5.7)	3.8 (3.5)	0.582
Skin and soft tissue infection	1 (2.4)	3 (2.7)	1.000	1.1 (3.3)	2.3 (2.1)	0.554
Primary bacteremia	3 (7.1)	8 (7.1)	1.000	2.4 (7.2)	7.8 (7.2)	1.000
Others	3 (7.1)	7 (6.2)	1.000	2.3 (6.9)	7.2 (6.7)	1.000
Complications	25 (59.5)	66 (58.4)	0.900	20 (59.9)	62.8 (58.3)	0.816
Septic shock	15 (35.7)	29 (25.7)	0.217	12.6 (37.7)	30 (27.8)	0.247
Acute kidney injury	16 (38.1)	47 (41.6)	0.694	14 (41.9)	44.2 (41)	0.863
Respiratory failure	13 (31)	24 (21.2)	0.207	10.7 (32.1)	25.3 (23.5)	0.295
Disseminated Intravascular Coagulation	11 (26.2)	37 (32.7)	0.433	10.4 (31.2)	34.5 (32)	0.873

Data are n (%), or median (IQR).

DISCUSSION

The results of this prospective cohort study indicated that inappropriate empirical antibiotics when given within 24 hours after the onset of bacteremia were non-inferior to appropriate antibiotics in terms of 30-day mortality, after adjusting for confounding factors using propensity score. Also, no differences were noted in length of hospital stay and hospital mortality between groups.

The overall 30-day mortality in this study (12.9%) was lower than that of recent studies for 3GCRE bacteremia reporting the incidence at 20 -30% [21, 22]. This may have been due to

https://doi.org/10.3947/ic.2022.0096

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Table 2. Antibiotics treatment among participants in appropriate empirical antibiotics and inappropriate empirical antibiotic groups

Antibiotics	Appropriate empirical antibiotics (n = 42)	Inappropriate empirical antibiotics (n = 113)
Antibiotic within 24 hours		
Piperacillin/tazobactam	2 (4.8)	0 (0.0)
Ertapenem	35 (83.3)	0 (0.0)
Imipenem/cilastatin	2 (4.8)	0 (0.0)
Meropenem	2 (4.8)	0 (0.0)
Ciprofloxacin	1 (2.4)	1 (0.9)
Ceftriaxone	6 (14.3)[a]	100 (88.5)
Azithromycin	0 (0.0)	1 (0.9)
Amoxicillin/clavulanate	0 (0.0)	1 (0.9)
Ceftazidime	0 (0.0)	1 (0.9)
None	0 (0.0)	9 (8.0)
Definite antibiotics with activity against 3GCRE		
Ertapenem	36 (85.7)	89 (78.8)
Imipenem/cilastatin	0 (0.0)	1 (0.9)
Meropenem	4 (9.5)	3 (2.7)
Ciprofloxacin	2 (4.8)	8 (7.1)
Trimethoprim/sulfamethoxazole	0 (0.0)	4 (3.5)
None	0 (0.0)	8 (7.1)

Data are n (%), 3GCRE: third generation cephalosporin resistant *Enterobacterales*.
[a]Ceftriaxone was not counted as an appropriate antibiotics but was given within 24 hours before the appropriate antibiotic.

Table 3. Causative organisms and mortality of participants in appropriate empirical antibiotics and inappropriate empirical antibiotics groups

Characteristics	Non-matching			Stabilized propensity score weighted		
	Appropriate empirical antibiotics (n = 42)	Inappropriate empirical antibiotics (n = 113)	*P*-value	Appropriate empirical antibiotics (n = 33.4)	Inappropriate empirical antibiotics (n = 107.8)	*P*-value
Organisms						
Escherichia coli	39 (92.9)	94 (83.2)	0.125	29.7 (89)	92.3 (85.6)	1.000
Klebsiella pneumoniae	3 (7.1)	13 (11.5)	0.560	3.69 (11.1)	10.43 (9.7)	0.743
Proteus mirabilis	0 (0.0)	3 (2.7)	0.563	0 (0.0)	2.54 (2.4)	1.000
Salmonella spp.	0 (0.0)	1 (0.9)	1.000	0 (0.0)	0.8 (0.7)	1.000
Citrobacter freundii	0 (0.0)	2 (1.8)	1.000	0 (0.0)	1.73 (1.6)	1.000
Interventions						
Time to empirical antibiotics (hours)	1 (0.15 - 2)	1 (0.25 - 3.25)	0.139	0.9 (0.08 - 2.05)	0.75 (0.25 - 3)	0.275
Time to appropriate antibiotics (hours)	1.1 (0.5 - 3)	55 (46 - 72)	0.0003	1.42 (0.5 - 3.1)	55.2 (46.5 - 72)	<0.0001
Surgical drainage	7 (16.7)	36 (31.9)	0.060	6.7 (20.1)	30.7 (28.5)	0.351
Clinical outcomes						
30-day mortality	6 (14.3)	14 (12.4)	0.754	5 (14.9)	14.3 (13.3)	0.762
Length of hospital stay	12 (9 - 18)	11 (8 - 16)	0.300	11 (7 - 15)	12 (8 - 17)	0.616
In-hospital mortality	8 (19)	17 (15)	0.547	5.4 (16.0)	17.3 (16.1)	0.919

Data are n (%), or median (interquartile range).

the lower virulence of community-acquired 3GCRE infection, as the two previous studies of community-onset 3GCRE bacteremia also found a lower incidence at 5-10% [9, 10]. Although the participants in this study had fewer severity factors, we included participants who died before receiving definite antibiotics which had been excluded from the previous studies [9, 10].

Inappropriate antibiotics use has been shown as a strong risk factor for mortality and increased length of hospital stay among patients mainly with hospital-acquired 3GRCE infections [7, 8]. On the contrary, this study showed that for patients with community-acquired 3GCRE bacteremia, inappropriate empirical antibiotics was non-inferior to appropriate antibiotics use. This is consistent with two previous studies in patients with community-onset bacteremia, including those with healthcare-associated infections. This

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Table 4. Results of the univariate and multivariate analysis of factors associated with 30-day mortality

Characteristics	Univariate analysis			Multivariate analysis	
	Non-survivors (n = 20)	Survivors (n = 135)	*P*-value	Adjusted RR	*P*-value
Male	11 (55)	79 (58.5)	0.766		
Age ≥75 years	11 (55)	63 (46.7)	0.486		
Escherichia coli bacteremia	18 (90)	115 (85.2)	0.741		
Underlying diseases	20 (100)	131 (97)	1.000		
Charlson comorbidity index score ≥2	13 (65)	73 (54.1)	0.359		
Diabetes mellitus	10 (50)	51 (37.8)	0.296		
Cirrhosis	3 (15)	4 (3)	0.046	1.7 (0.3 - 10.3)	0.578
Chronic kidney disease	4 (20)	27 (20)	1.000		
Ischemic heart disease	0 (0)	18 (13.3)	0.131		
Autoimmune disease	0 (0)	4 (3)	1.000		
Cerebrovascular disease	3 (15)	23 (17)	1.000		
Dementia	1 (5)	8 (5.9)	1.000		
Solid malignancy	6 (30)	23 (17)	0.165		
Hematological malignancy	1 (5)	3 (2.2)	0.428		
Clinical syndromes					
Urinary tract infection	8 (40)	80 (59.3)	0.105		
Biliary tract infection	2 (10)	33 (24.4)	0.149		
Other intraabdominal infections	2 (10)	6 (4.4)	0.275		
Skin and soft tissue infection	1 (5)	4 (3)	0.504		
Primary bacteremia	6 (30)	5 (3.7)	<0.0001	14.2 (3.1 - 65.3)	0.0007
Others	1 (5)	7 (5.2)	1.000		
Complications					
Septic shock	11 (55)	33 (24.4)	0.008	1.1 (0.3 - 4.4)	0.881
Respiratory failure	13 (65)	24 (17.8)	<0.0001	9.9 (3.2 - 30.7)	<0.0001
Interventions					
Appropriate empirical antibiotics	6 (30)	36 (26.7)	0.754	0.95 (0.3 - 3.1)	0.931
Surgical drainage	3 (15)	40 (29.6)	0.283		

Data are n (%).

may be explained by three reasons. First, the strains and virulence factors between hospital- and community-onset 3GCRE may be different, especially in patients with intraabdominal infections. For example, biliary tract obstruction found in 23% of participants with cholangitis was commonly thought to be the cause of bacteremia, not bacterial virulence [23]. This is in accordance with the previous 3GCRE carriage study in 188 patients from Sweden traveling to four regions with high 3GCRE prevalence, including Thailand [16]. The study showed that most isolates belonged to phylogroup A which were rarely associated with extraintestinal infections. No clinical infections were observed after 26 months of follow-up. Therefore, the community-acquired 3GCRE in the previous cohort showed a seemingly lower pathogenicity. Secondly, although the majority of participants presented extraintestinal infections presumably as a result of organisms with a higher pathogenicity; most were urinary tract infections. Urinary tract infections are well-known to be associated with lower mortality rates than infections from other anatomical sites [24]. Lastly, non-medical interventions such as the removal of infected foci or decompression of obstructions are essential aspects to treat infections and this was carried out promptly in 28% of patients in our cohort [25, 26].

Factors associated with mortality were consistent with those previously described [9, 10, 27]. After adjusting these factors, inappropriate empirical antibiotics use was not associated with increased mortality. The increased use of empirical carbapenems in response to increased prevalence of 3GCRE infections may be accompanied by rapid emergence of carbapenem resistant pathogens. Empirical carbapenem in community-acquired infection, even in the setting of high prevalence of 3GCRE carriage in community, should be discouraged.

https://doi.org/10.3947/ic.2022.0096

We describe the prospective cohort study to demonstrate the non-inferiority of inappropriate empirical antibiotics on the outcome of community-acquired 3GCRE bacteremia. However, our study encountered certain limitations. Firstly, this was an observational study, as it is impossible to design and enroll patients for randomized clinical trials due to the long turnaround time in the reporting of microbiological results. Therefore, unaccounted biases might have underestimated the true relationship between inappropriate antimicrobial therapy and mortality. For example, the prescribing physicians may have been affected by patients at a higher risk of death resulting in increased use of broader spectrum antibiotics. However, propensity score weighting was specifically used to reduce this selection bias and baseline characteristics between the two groups were not significantly dissimilar. Secondly, we did not demonstrate the mechanisms of resistance, strain, or virulent factors associated with the causative pathogens. Although this approach closely reflects real-world clinical practice, these findings may not be generalizable to settings with a different epidemiology of 3GCRE. Thirdly, this study was conducted in a large university hospital with a microbiological result alert system. The culture result turnaround time was relatively short, allowing the adjustment to appropriate antibiotics at the median time of only 55 hours in the inappropriate group. Therefore, the study results may not be generalizable to hospitals with longer microbiological result turnaround time. Finally, most patients presented low-inoculum infections such as urinary tract infections or those in which a reduced inoculum could be achieved through surgical intervention rather than high risk infections such as primary bacteremia or pneumonia. Therefore, whether inappropriate treatment is associated with higher mortality in these high-risk infections could not be concluded.

In summary, among patients with community-acquired 3GCRE bacteremia, inappropriate empirical treatment when given within 24 hours after the onset of bacteremia was non-inferior to appropriate antibiotics use. In the setting of a high prevalence of community 3GCRE carriage, adjustment to carbapenem might be tolerable for acute community-acquired infections.

ACKNOWLEDGMENT

We thank the Division of Microbiology, Department of Pathology, Phramongkutklao Hospital for bacterial isolation and standard antimicrobial susceptibility test.

REFERENCES

1. Belley A, Morrissey I, Hawser S, Kothari N, Knechtle P. Third-generation cephalosporin resistance in clinical isolates of *Enterobacterales* collected between 2016-2018 from USA and Europe: genotypic analysis of β-lactamases and comparative *in vitro* activity of cefepime/enmetazobactam. J Glob Antimicrob Resist 2021;25:93-101.
PUBMED | CROSSREF
2. Ling W, Furuya-Kanamori L, Ezure Y, Harris PNA, Paterson DL. Adverse clinical outcomes associated with infections by *Enterobacterales* producing ESBL (ESBL-E): a systematic review and meta-analysis. JAC Antimicrob Resist 2021;3:dlab068.
PUBMED | CROSSREF
3. Kim B, Seo MR, Kim J, Kim Y, Wie SH, Ki M, Cho YK, Lim S, Lee JS, Kwon KT, Lee H, Cheong HJ, Park DW, Ryu SY, Chung MH, Pai H. Molecular epidemiology of ciprofloxacin-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Korea. Infect Chemother 2020;52:194-203.
PUBMED | CROSSREF

4. Mohd Sazlly Lim S, Wong PL, Sulaiman H, Atiya N, Hisham Shunmugam R, Liew SM. Clinical prediction models for ESBL-*Enterobacteriaceae* colonization or infection: a systematic review. J Hosp Infect 2019;102:8-16.
PUBMED | CROSSREF

5. Bezabih YM, Sabiiti W, Alamneh E, Bezabih A, Peterson GM, Bezabhe WM, Roujeinikova A. The global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* in the community. J Antimicrob Chemother 2021;76:22-9.
PUBMED | CROSSREF

6. Clemenceau M, Ahmed-Elie S, Vilfaillot A, Chocron R, Compain F, Lebeaux D, Grohs P. Appropriateness of empirical antibiotic prescription for bloodstream infections in an emergency department from 2006 to 2018: impact of the spread of ESBL-producing *Enterobacterales*. Eur J Clin Microbiol Infect Dis 2022;41:71-7.
PUBMED | CROSSREF

7. Lodise TP, Zhao Q, Fahrbach K, Gillard PJ, Martin A. A systematic review of the association between delayed appropriate therapy and mortality among patients hospitalized with infections due to *Klebsiella pneumoniae* or *Escherichia coli*: how long is too long? BMC Infect Dis 2018;18:625.
PUBMED | CROSSREF

8. Battle SE, Bookstaver PB, Justo JA, Kohn J, Albrecht H, Al-Hasan MN. Association between inappropriate empirical antimicrobial therapy and hospital length of stay in Gram-negative bloodstream infections: stratification by prognosis. J Antimicrob Chemother 2017;72:299-304.
PUBMED | CROSSREF

9. Joo EJ, Park DA, Lee NR, Moon SY, Choi JK, Ko JH, Peck KR. Impact of appropriateness of empiric therapy on outcomes in community-onset bacteremia by extended-spectrum-β-lactamase producing Escherichia coli and *Klebsiella pneumoniae* definitively treated with carbapenems. Eur J Clin Microbiol Infect Dis 2017;36:2093-100.
PUBMED | CROSSREF

10. Kang CI, Wi YM, Ko KS, Chung DR, Peck KR, Lee NY, Song JH. Outcomes and risk factors for mortality in community-onset bacteremia caused by extended-spectrum beta-lactamase-producing *Escherichia coli*, with a special emphasis on antimicrobial therapy. Scand J Infect Dis 2013;45:519-25.
PUBMED | CROSSREF

11. Joo EJ, Kim SJ, Baek M, Choi Y, Seo J, Yeom JS, Ko KS. Fecal Carriage of antimicrobial-resistant *Enterobacteriaceae* in healthy Korean adults. J Microbiol Biotechnol 2018;28:1178-84.
PUBMED | CROSSREF

12. Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in different groups of patients. Clin Microbiol Infect 2019;25:932-42.
PUBMED | CROSSREF

13. McLaughlin M, Advincula MR, Malczynski M, Qi C, Bolon M, Scheetz MH. Correlations of antibiotic use and carbapenem resistance in enterobacteriaceae. Antimicrob Agents Chemother 2013;57:5131-3.
PUBMED | CROSSREF

14. Thamlikitkul V, Tangkoskul T, Seenama C. Fecal carriage rate of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* as a proxy composite indicator of antimicrobial resistance in a community in Thailand. Open Forum Infect Dis 2019;6:ofz425.
PUBMED | CROSSREF

15. Yoon YK, Kwon KT, Jeong SJ, Moon C, Kim B, Kiem S, Kim HS, Heo E, Kim SW; Korean Society for Antimicrobial TherapyKorean Society of Infectious DiseasesKorean Society of Health-System Pharmacist. Guidelines on implementing antimicrobial stewardship programs in Korea. Infect Chemother 2021;53:617-59.
PUBMED | CROSSREF

16. Ny S, Löfmark S, Börjesson S, Englund S, Ringman M, Bergström J, Nauclér P, Giske CG, Byfors S. Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study. J Antimicrob Chemother 2017;72:582-8.
PUBMED | CROSSREF

17. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791-7.
PUBMED | CROSSREF

18. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.
PUBMED | CROSSREF

19. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327-30.
PUBMED | CROSSREF

20. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 28th ed. CLSI supplement M100. Wayne, PA: CLSI; 2018.
21. Lim CL, Spelman D. Mortality impact of empirical antimicrobial therapy in ESBL- and AmpC-producing *Enterobacteriaceae* bacteremia in an Australian tertiary hospital. Infect Dis Health 2019;24:124-33.
PUBMED | CROSSREF
22. Sianipar O, Asmara W, Dwiprahasto I, Mulyono B. Mortality risk of bloodstream infection caused by either *Escherichia coli* or *Klebsiella pneumoniae* producing extended-spectrum β-lactamase: a prospective cohort study. BMC Res Notes 2019;12:719.
PUBMED | CROSSREF
23. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J 2007;83:773-6.
PUBMED | CROSSREF
24. Abe T, Ogura H, Kushimoto S, Shiraishi A, Sugiyama T, Deshpande GA, Uchida M, Nagata I, Saitoh D, Fujishima S, Mayumi T, Hifumi T, Shiino Y, Nakada TA, Tarui T, Otomo Y, Okamoto K, Umemura Y, Kotani J, Sakamoto Y, Sasaki J, Shiraishi SI, Takuma K, Tsuruta R, Hagiwara A, Yamakawa K, Masuno T, Takeyama N, Yamashita N, Ikeda H, Ueyama M, Fujimi S, Gando S; JAAM FORECAST group. Variations in infection sites and mortality rates among patients in intensive care units with severe sepsis and septic shock in Japan. J Intensive Care 2019;7:28.
PUBMED | CROSSREF
25. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for the Study of Infectious Diseases (KONSID). Risk factors for mortality and impact of broad-spectrum cephalosporin resistance on outcome in bacteraemic intra-abdominal infections caused by Gram-negative bacilli. Scand J Infect Dis 2011;43:202-8.
PUBMED | CROSSREF
26. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. Antimicrob Agents Chemother 2004;48:4574-81.
PUBMED | CROSSREF
27. Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, Citton R, D'Inzeo T, Fadda G, Cauda R, Spanu T. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Enterobacteriaceae*: importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother 2007;51:1987-94.
PUBMED | CROSSREF