Therapeutic Effect of Piperacillin-Tazobactam on Bacteremia Caused by Enterobacteriaceae Producing Extended-Spectrum Beta-Lactamase

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감사의 말씀

지난 2 년간 대학원 생활 중 부족한 제가 과연 석사 논문을 마칠 수 있을까 하는 많은 고민으로 시작도 어려워하던 찰나에 담임반 교수님이시자, 선뜻 저의 석사 논문 지도교수를 허락해주시면서 이 논문을 완성하기까지 시종 세심한 지도와 편달을 베풀어 주신 김영근 교수님께 깊은 감사를 드립니다.

연구기간 중 여러모로 지도와 격려 해주시면서 항상 저의 판단에 힘을 실어주시고 믿어주신 김효열 교수님 그리고 많은 조언의 말씀을 해주신 어영 교수님께 감사의 말씀 전합니다.

아울러 오늘에 이르기까지 무한한 사랑과 격려를 아끼지 않으신 부모님과 부족한 며느리를 아껴주시고 보듬어주신 시부모님 그리고 이 세상에서 가장 사랑하는 남편 김재혁을 비롯한 가족 모두에게도 깊은 감사를 드립니다.

저 자 씀

Contents

Table, Figure Contents

ABSTRACT

Therapeutic Effect of Piperacillin-Tazobactam on Bacteremia Caused by Enterobacteriaceae Producing Extended-Spectrum Beta-Lactamase

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The therapeutic effectiveness of piperacillin-tazobactam(TZP) in extended-spectrum beta-lactamase(ESBL) bacteremia is controversial. In this study, the treatment outcome of TZP versus carbapenems in patients with ESBL-producing Enterobacteriaceae bacteremia was compared.

Patients with ESBL-producing bacteremia from January 2014 to May 2018 in a single hospital in Republic of Korea were included. All Patients used empirical TZP in first place and ultimately received TZP or carbapenem for definite therapy for more than 48 hours after microbiology result of ESBL bacteremia was confirmed. This study aimed to evaluate 30-day mortality of patients treated with TZP versus carbapenem.

There were 401 patients with ESBL bacteremia during the study period, 59 of whom met eligiblility criteria. Time until fever subsides from definite therapy and

30-day mortality was significantly different between TZP and carbapenem group. Comparing survival and mortality group, Charlsons' comorbidity index, SOFA scores, carbapenem use were significantly different. There was no significant risk of mortality for patients receiving TZP for definite therapy to patients who transitioned to carbapenem (OR 0.13, 95% CI; 0.01-2.07). SOFA score at definite treatment was only significantly associated with 30-day mortality (OR 2.17, 95% CI; 1.40-3.37).

This study demonstrates that TZP can be used efficiently in definite treatment of patients with ESBL bacteremia compared to carbapenem.

Key words : Extended-spectrum beta-lactamase bacteremia, Piperacillin-tazobactam, Carbapenems, SOFA scores, 30-day mortality

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Chapter I Introduction

For the past decades, broad-spectum β-lactam resistant gram-negative bacteria has increased rapidly especially extended-spectrum β-lactamase (ESBL)-producing bacteria[1]. Antibiotics overuse, hospital cross-infection, the food chain, trade and human migration seem to have contributed to the recent dissemination of ESBLs [2]. The clinical outcomes of infections with ESBL-producing bacteria have been more detrimental compared to more susceptible organisms[3-7].

ESBL is a type of β-lactamases in which penicillin, cephalosporins and monobactams are hydrolyzed where cephamycins and carbapenems are stabilized. β-lactam/β-lactamase inhibitors such as piperacillin-tazobactam (TZP) demonstrated variable activity against ESBL-producing bacteria[8]. Previous studies have shown that carbapenems have superior clinical outcomes in ESBL bacteremia[9, 10]. However indiscrimant use of carbapenem in ESBL bacteremia has

consequently contributed to emergence of carbapenem-resistant bacteria[11, 12]. More therapeutic limitation has emerged for carbapenem-resistant bacteria[13] therefore in order to control multidrug-resistant bacteria and prevent the spread of ESBL endemicity, it is pivotal to identify effective alternative antibiotics for ESBL producing bacteria[14]. Current observational data have indicated that TZP may be an effective alternative antibiotic for reducing carbapenem resistant bacteria[9, 15, 16].

In this study, the purpose is aimed to compare therapeutic effectiveness of TZP and carbapenem in patients with ESBL-producing Enterobacteriaceae bacteremia.

Chapter II Methods

- **Study design and patients**

A retrospective cohort study was conducted at single hospital in Republic of Korea. Patients with ESBL bacteremia from January 2014 to May 2018 at Yonsei University Wonju Severance Christian Hospital were identified. The following inclusion criteria was fulfilled in each subject: age of more than 19 years old; presenting positive blood culture of ESBL producing Enterobacteriaceae; with empirical TZP in first place ultimately received TZP or carbapenem such as ertapenem, doripenem, imipenem, meropenem for definite therapy after microbiology result of ESBL bacteremia was confirmed. Also patients who were treated with definite therapy for more than 48 hours were included to evaluate proper result from sufficient use of definite therapy. Patients were excluded if they had polymicrobial bacteremia or used empirical antibiotics other than TZP. Subjects were followed up until discharge or death. Data were collected from the electronic medical records which included patient demographics, microbiology data, empirical and definitive antibiotic therapy, type of infection, source of bacteremia, Charlson's co-morbidity index, sequential organ failure assessment (SOFA) score, time until fever subsides from definite therapy and clinical outcomes (14 and 30-day mortality).

Patients with ESBL producing bacteremia isolated from at least one positive blood culture were included. Species identification was performed using MicroScan WalkAway System (Siemens Healthcare Diagnostics, Sacramento, CA, USA). Antimicrobial susceptibility testing and ESBL confirmatory testing were

performed using the broth microdilution method or the disk diffusion method, following the recommendations of the Clinical and Laboratory Standards Institute[17]. The study included patients with Enterobacteriaceae from at least one positive blood culture, with susceptible to both TZP and carbapenems.

Ethics waiver was obtained from Institutional Review Board for Human Research Yonsei University Wonju Severance Christian Hospital (approval no.CR318303). Informed consent was exempted and the protocol was adhered to the tenets of Declaration of Helsinki.

- **Definitions**

Empirical antibiotics therapy was referred as the use of antibiotics before susceptibility, started within 24 hours of blood culture with subsequent matching in vitro susceptibility and continued for at least 48 hours[14]. Definite antibiotics therapy was referred as the use of antibiotics after *in vitro* susceptibility was known[18]. Hosptial acquired bacteremia was defined by a positive blood culture obtained after 48 hours of admission[18]. Healthcare-associated bacteremia was defined as a positive blood culture obtained within 48 hours of hospital admission and if the patient fulfilled any healthcare associated risk factors such as prior hospital admissions in the last 90 days, nursing home residence, haemodialysis and intravenous chemotherapy[14], [19]. Healthcare-associated infection (HAI) included both hospital and healthcare associated bacteremia. Community-acquired bacteremia was defined as a positive blood culture obtained within 48 hours of hospital admission without any health associated risk factors.

Definition of fever is defined as a single oral temperature measurement of ≥ 38.3℃ or a temperature of ≥ 38.0℃ sustained over a 1 hour period[20]. Time until fever subsides was referred to the duration of febrile period from the start of the definite therapy.

- **Statistical analysis**

Baseline characteristics were summarized as number and percentage for categorical variables and median for continuous variables. Comparisons between the TZP versus carbapenem treatment group and survival and mortality group were analyzed by the Mann-Whitney U test for continuous variables and the Pearson Chi-square test for categorical variables. p-value of < 0.05 was considered significant.

A multivariable logistic regression model was used to identify significant risk factors contributing to 30-day mortality in patients with ESBL bacteremia. Covariates were selected from comparing between the group of survival and mortality. Covariates with significant difference on univariate analysis were included into the multivariate model. Significant covariates were type of infection, Charlsons' comorbidity index and SOFA score at definite treatment and variables with $p<0.1$ from univariate analysis were included in a multivariable logistic model for risk factors for 30-day mortality.

All statistical analyses were performed using the Statistical Package for Social Science software version 23.0 for Windows(IBM Corp., Armonk, NY, USA).

Chapter III Results

There were 401 patients with bacteremia cuased by Enterobacteriaceae producing ESBL during the study period, 64 of whom met eligible criteria. Five patients were excluded due to insufficient period of definite therapy, total 59 patients were enrolled in this study (Figure 1). Twenty two patients continued to use TZP (37%) and thirty seven patients were transitioned to carbapenem (63%) after susceptibility results were available. Carbapenem prescribed included ertapenem (2.7%), doripenem (10.8%), imipenem (5.4%), meropenem (81.1%).

Between TZP and carbapenem group, the median age was 75 years and 72 years respectively. There were 6 male (27.2%) patients in TZP group compared to 21 males (56.8%) patients in carbapenem group. Type of infection between two groups did not demonstrate significance (p=0.29) where there were 16 patients (43.2%) of HAI, 21 (56.8%) patients of community-acquired infection (CAI) in carbapenem group and 14 (63.6%) patients of HAI, 8 (36.4%) patients of CAI in TZP group. Charlsons' comorbidity index was also shown no significance.

Median SOFA score on admission period was 4.0 and 3.0 at definite treatment period in TZP group whereas both 4.0 in carbapenem group (p = 0.37, p = 0.28). In our study, source of bacteremia included urinary tract (41, 69.5%), respiratory (4, 6.8%), hepatobiliary (12, 20.3%) , catheter (1, 1.7%) and spine (1, 1.7%) and none of these sources were significantly different in TZP and carbapenem groups. Also none of *E.coli, K.pneumoniae* and other Enterobacteriaceae was significantly associated with empirical TZP and carbapenem use. The median time of definite therapy was 72 hours. Patients who were transitioned to carbapenem therapy had significantly prolonged febrile period than empirical TZP group (Table 1).

14-day mortality was first analyzed in order to exclude attributing mortality risk factors other than ESBL bacteremia but no significant difference was noted between TZP and carbapenem group (3[13.6%] vs. 4[19.0%]) (Table 1). However, considering the days of microbiologic response which were achieved in more than 14 days in some patients, we have decided to analyze additional 30-day mortality. There were 3 deaths (13.6%) in the TZP group and 12 deaths (32.4%) in the carbapenem group within 30 days, which showed significance (Table 1).

Risk factors affecting 30-day mortality were analyzed by comparing survival and mortality group. Median age of survival and mortality group was 74 years and 16 male patients (36.4%) were in survival group and 8 male patients (53.3%) in mortality group. Type of infection between two groups have not shown significance between survival and mortality groups where there were 21 patients (47.7%) of HAI, 23 patients (52.3%) of CAI in survival group and 9 patients (60%) of HAI, 6 patients (40%) of CAI in mortality group. Median Charlsons' comorbidity index in survival group was 4.0 and 7.0 in mortality group, showing significant difference ($p= 0.02$).

Median SOFA score on admission period was 3.5 and 2.0 at definite treatment period in survival group whereas 6.0 and 9.0 in mortality group ($p <0.01$). None of sources of bacteremia and pathogens was significantly different in survival and mortality groups. The median onset time for definite therapy was 72 hours. Patients who were transitioned to carbapenem therapy had no significantly prolonged time until fever subsides from definite therapy than survival group (Table 2).

In summary, risk factors for 30-day mortality were Charlsons's comorbidity index, SOFA scores and carbapenem use. After adjusting for age, sex and statistically significant variables from previous analysis, SOFA score at definite

treatment was only significantly associated with 30-day mortality (OR 2.17, 95% CI; 1.40-3.37) (Table 3). There was no significant risk of mortality for patients receiving TZP to patients who transitioned to carbapenem (OR 0.13, 95% CI; 0.01-2.07) (Table 3).

Figure 2 shows a Kaplan-Meier curve depicting bacteremia status for 30 days for patients receiving TZP compared with carbapenem therapy.

Chapter IV Discussion

This study found no significant difference in 30-day mortality between patients treated with TZP and carbapenem.

In this study, carbapenem group had more prolonged time until fever subsides from definite therapy compared to TZP group. This result can be explained by previous studies. Carbapenem using patients had high risk of mortality in ESBL-producing bacteremia [8, 10, 21]. Their comorbidity and severe septic conditions require more time than healthy individuals to overcome infection, including time to reach afebrile status from definite therapy.

In this study, higher mortality in carbapenem group was demonstrated (Table 1). Most of patients with extent bacteremia status were transitioned to carbapenem in later course of refractory diseases, which could contribute increment of number of carbapenem users and mortality. However, after adjusting other risk factors with significant difference such as type of infection, Charlsons's comorbidity index, SOFA score at definite treatment (Table 2), there was no significant increase of mortality for carbapenem group (Table 3). SOFA score at definite treatment was the only reliable factor to attribute to 30-day mortality in ESBL bacteremia which can be used as a clue to physicans to predict the prognosis in ESBL bacteremia.

It is important to notice the mortality rate (15/59, 25.4%) in the patients with ESBL-producing bacteremia in this study because high mortality rate can indicate the empiric use of TZP may affect the result in the study. In previous retrospective study of 394 patients of ESBL-producing bacteremia, 30-day mortality in empiric TZP was 30.9% [14], which shows similar mortality rate in this study (25.4%). Therefore empiric TZP use does not affect the results of this study.

Previous studies on the use of TZP for ESBL producing bacteria are controversial[10, 22]. In previous studies, high risk invasive ESBL-producing bacteria infected patients should be treated with carbapenem and carbapenems are the treatment of choice for severe ESBL bacteria induced infections[22]. In a prospective study of 85 cases of ESBL-producing *K. pneumonia* bacteremia, carbapenem monotherapy was significantly associated with reduction of 14-day mortality[10]. Also in a cohort study of 331 of patient with ESBL-producing bacteremia, empirical TZP received patients had 1.92 times increased risk of 14-day mortality compared to patients receiving empiric carbapenems[22].

Similar results with this study have been also reported in a prospective, observational study which evaluated 103 patients with ESBL producing E.coli bacteremia at 6 Spanish hospitals by Rodríguez-Baño. The patients in this study empirically received either β-lactam/β-lactamase inhibitor or carbapenem and did not show a significant difference in 30-day mortality between patients treated with a carbapenem and beta-lactam/beta-lactamase inhibitors both empirically and definitively (adjusted hazard ratio, 1.14 [95% CI, .29–4.40])[15].

In previous studies, controversy of TZP use in ESBL bacteremia underlies in concerning TZP activity that can be diminished by inoculum effect, slow metabolism and growth of high concentration of bacteria [23, 24]. Also other mechanisms of β-lactam resistance, such as AmpC β-lactamase production or additional ESBLs, reduce the efficacy of TZP by complicating the bacterial environment[8]. Therefore for treating ESBL producing bacteria, more data should be gathered to elucidate the optimal dosing of TZP.

It is important for physicians to use carbapenem carefully due to recent endemic appearance of carbapenem resistant bacteria[25-27]. Therefore empirical use of carbapenem should be carefully selected considering risk factors of patients

such as a previous history of infection by ESBL-producer, prolonged hospitalization or nursing centers, and recent TZP or cephalosporin exposure[28-30]. This study demonstrates that SOFA score at definite treatment was significantly associated with 30-day mortality. Therefore when deciding TZP over carbapenem in ESBL bacteremia, this study supports patients with low SOFA score can use TZP for empiric and definite therapy.

There are several limitations in this study. First, this is a single-center retrospective analysis which cannot be generalized to other institutions and we may not have been able to control all confounders which could affect the association of TZP and 30-day mortality in patients with ESBL-producing bacteremia. Second, there was limited number of patients enrolled in this study which could undermine the effect of carbapenem and TZP in definite therapy for treating ESBL bacteremia. For future reference, randomized controlled studies should be developed to analyze the impact of definite treatment of ESBL bacteremia using either TZP or carbapenem.

Chapter V Conclusion

Early appropriate empirical antibiotic use is crucial in order to diminish mortality from bacteremia[31]. This study demonstrates that piperacillin-tazobactam can be used efficiently in definite treatment of patients with ESBL bacteremia. Considering the emergence of carbapenem producing Enterobacteriaceae and until the development of alternative antibiotics for carbapenem, this study supports that TZP can be used as effective alternative antibiotics for treating ESBL bacteremia.

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Table 1. Baseline characteristics of 59 patients with extended-spectrum β-lactamase producing bacteremia treated with piperacillin-tazobactam or carbapenem therapy

Characteristics	TZP (N=22)	Carbapenem (N=37)	p value
Age, median (IQR)	75 (69-78)	72 (64-72)	0.18
Male sex	6 (27.2)	21 (56.8)	0.11
Type of Infection			0.29
Healthcare-associated	14 (63.6)	16 (43.2)	
Community-acquired	8 (36.4)	21 (56.8)	
Charlson's comorbidity index, median (IQR)	5.0 (4.5-6.7)	5.0 (4.5-6.3)	0.65
SOFA score on admission, median (IQR)	4.0 (2.7-5.6)	4.0 (3.7-5.6)	0.37
SOFA score at definite treatment, median (IQR)	3.0 (2.1-4.8)	4.0 (3.5-6.6)	0.28
Source of bacteremia			
UTI	14 (63.6)	27 (73.0)	0.17
Respiratory	1 (4.5)	3 (8.1)	0.30
Hepatobiliary	7 (31.8)	5 (13.5)	0.09
Catheter, spine	0 (0.0)	2 (5.4)	0.27
Pathogens			
E. coli	15 (68.2)	25 (67.6)	0.92
K .pneumoniae	4 (18.2)	8 (21.6)	0.53
Others (*S. marcescens, P. mirabilis)*	3 (13.6)	4 (10.8)	0.52
Onset time for definite therapy (hour), median (IQR)	72 (68-76)	72 (69-92)	0.95
Time until fever subsides from definite therapy (hour), median (IQR)	12 (6-24)	34 (24-80)	<0.01
14-day mortality	3 (13.6)	4 (19.0)	0.97
30-day mortality	3 (13.6)	12 (32.4)	<0.01

Abbreviations: TZP, piperacillin-tazobactam; IQR, inter quartile range

Data are no. of patients (%), unless otherwise indicated

Table 2. Characteristics of 59 patients with extended-sepectrum β-lactamase-producing bacteremia between survived and mortality group

Characteristics	Survive (N=44)	Mortality (N=15)	p value
Age, median (IQR)	74 (66-74)	74 (62-75)	0.70
Male sex	16 (36.4)	8 (53.3)	0.32
Type of Infection			0.08
Healthcare-associated	21 (47.7)	9 (60.0)	
Community-acquired	23 (52.3)	6 (40.0)	
Charlson's comorbidity index, median (IQR)	4.0 (4.2-5.6)	7.0 (5.6-8.4)	0.02
SOFA score on admission, median (IQR)	3.5 (3.0-4.8)	6.0 (4.9-7.4)	<0.01
SOFA score at definite treatment, median (IQR)	2.0 (2.0-3.4)	9.0 (7.2-11.9)	<0.01
SOFA score difference from admssion to at time of definite treatment, median (IQR)	-0.50 (-2.0 - -0.7)	3.0 (0.7-6.1)	<0.01
Source of bacteremia			
UTI	32 (72.7)	9 (60.0)	0.14
Respiratory	2 (4.5)	2 (13.3)	0.23
Hepatobiliary	8 (18.2)	4 (26.7)	0.20
Catheter, spine	2 (4.5)	0 (0.0)	0.16
Pathogens			
E. coli	30 (68.2)	10 (66.7)	0.84
K pneumoniae	8 (18.2)	4 (26.7)	0.49
Others (*S. marcescens, P. mirabilis)*	6 (13.6)	1 (6.7)	0.48
Onset time for definite therapy, median (IQR)	72 (71-90)	72 (64-73)	0.15
Time until fever subsides from definite therapy (hour), median (IQR)	10 (8-32)	11 (9-81)	0.72
Carbapenem use	25 (56.8)	12 (80.0)	0.01

Abbreviations: IQR, inter quartile range

Data are no. of patients (%), unless otherwise indicated

Table 3. Risk factors for 30-day Mortality among 59 Patients with extended-sepectrum β-lactamase producing bacteremia treated with piperacillin-tazobactam or carbapenem therapy

Variable	Multivariable analysis	
	OR, (95% CI)	p-value
Age	1.02 (0.93-1.12)	0.66
Male sex	0.33 (0.03-3.51)	0.36
Community-acquired infection	0.61 (0.06-6.26)	0.67
Charlson's comorbidity index	1.33 (0.79-2.22)	0.28
SOFA score at definite treatment	2.17 (1.40-3.37)	<0.01
Piperacillin-tazobactam use	0.13 (0.01-2.07)	0.15

Abbreviations: OR, Odds ratio; CI, confidence interval

Figure 1. Design of a study of patients receiving TZP vs. carbapenem therapy for ESBL bacteremia

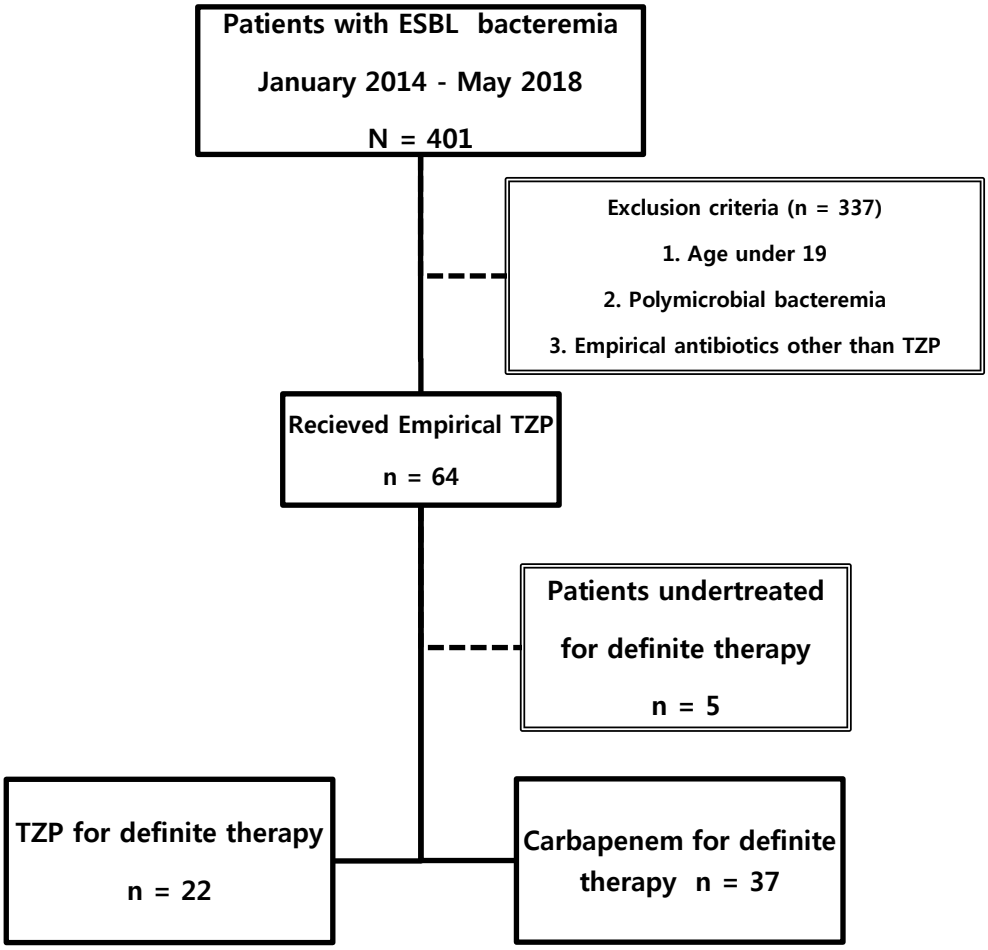
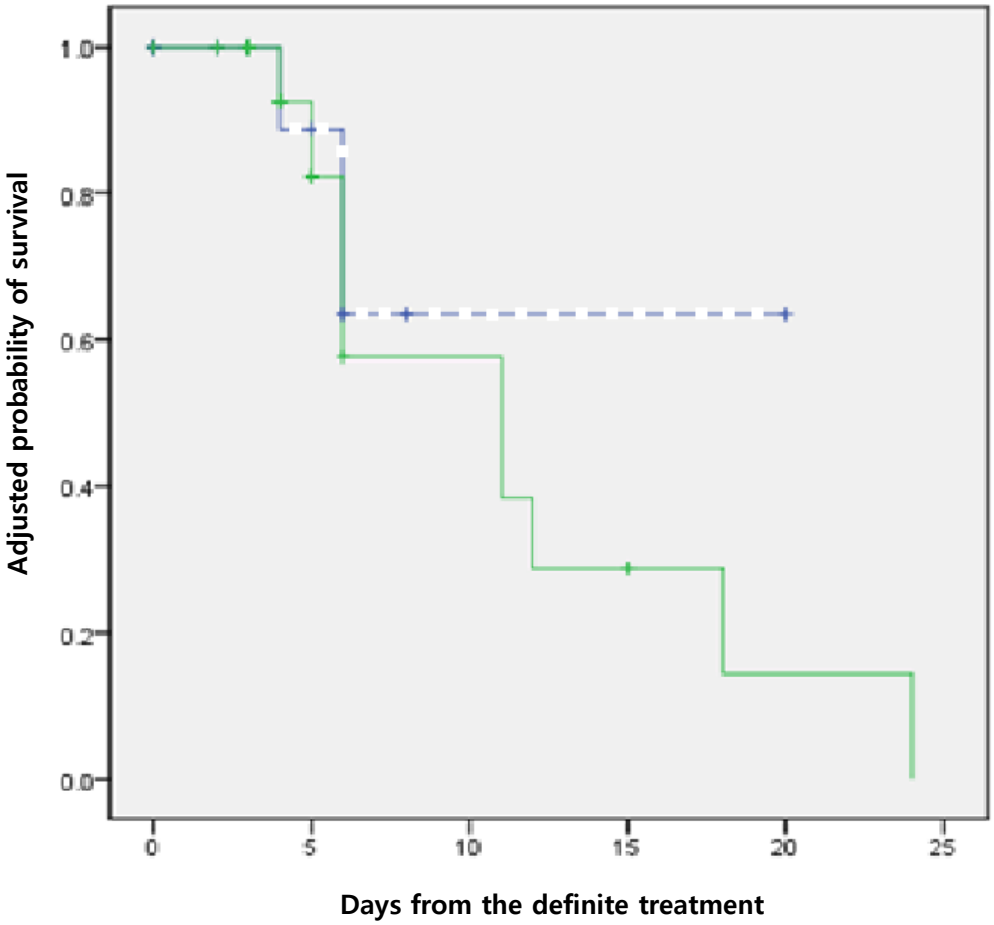


Figure 2. Probability of survival at day 30 for patients with ESBL producing bacteremia



Solid line represents patients with carbapenems; Dotted line represents patients who continued to maintain TZP; log-rank test = 0.43

국 문 요 약

Extended-Spectrum Beta-Lactamase 생성 장내세균(Enterobacteriaceae)에 의한 균혈증에서 피페라실린-타조박탐(Pipperacillin-Tazobactam)의 치료효과

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김 혜 경

ESBL 균혈증에서 piperacillin-tazobactam (TZP)의 치료 효과는 논란의 여지가 있다. 이 연구는 ESBL 생성 Enterobacteriaceae 균혈증 환자에서 TZP 와 carbapenems 의 치료 결과를 비교 하였다.

원주세브란스기독병원에서 2014 년 1 월부터 2018 년 5 월까지 ESBL 생성 균혈증 발생 환자를 대상으로 연구를 진행하였다. 모든 환자는 경험적 TZP 를 사용했고 ESBL 균혈증의 배양 결과 보고된 후 확정적 치료를 위해 TZP 또는 carbapenem 을 투여 받았다. 궁극적으로 TZP 로 치료받은 환자의 30 일 사망률을 carbapenem 과 비교 평가 하였다.

연구 기간 동안 ESBL 균혈증 환자 총 401 명이 있었고 그 중 59 명이 연구 선정 기준을 충족 시켰다. 확정적 치료 후 열이 가라 앉을 때까지의 시간과 30 일 사망률은 TZP 사용군과 carbapenem 사용 군간에 유의한 차이가 있었다. 생존군과

사망군을 비교 한 결과, Charlsons 의 합병증 지수, SOFA 점수, carbapenem 사용은 유의한 차이가 있었다. 하지만 다중 회귀분석을 통하여 의미 있는 변수들을 교정 후 확정적 치료로 carbapenem 을 사용한 환자군과 TZP 를 사용한 환자군의 사망 위험은 통계학적으로 유의하지 않았다 (OR 0.13, 95% CI; 0.01-2.07). 또한 확정적 치료 당시의 SOFA 점수는 30 일 사망률과 유의한 관련이 있었다 (OR 2.17, 95% CI; 1.40-3.37).

이 연구는 TZP 가 carbapenem 대신 ESBL 균혈증 환자의 확정적 치료에 효과적으로 사용될 수 있음을 증명하였다.

핵심되는 단어 : Extended-spectrum beta-lactamase 균혈증, Piperacillin-tazobactam, Carbapenems, SOFA scores, 30 일 사망률