



## Correspondence



# The Efficacy of Penicillins with $\beta$ -lactamase Inhibitor or Cefmetazole against Pneumonia in which ESBL-Producing Bacteria were Isolated from Sputum

Akihiko Goto , Kosaku Komiya , Kazufumi Hiramatsu , and Jun-ichi Kadota

Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, Oita, Japan

## OPEN ACCESS

Received: Jun 10, 2021

Accepted: Aug 13, 2021

### Corresponding Author:

Kosaku Komiya, MD, MPH, PhD

Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan.

Tel: +81-97-586-5804

E-mail: komiyakh1@oita-u.ac.jp

Copyright © 2021 by The Korean Society of Infectious Diseases, Korean Society for Antimicrobial Therapy, and The Korean Society for AIDS

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Akihiko Goto

<https://orcid.org/0000-0002-4875-9599>

Kosaku Komiya

<https://orcid.org/0000-0002-8679-1661>

Kazufumi Hiramatsu

<https://orcid.org/0000-0001-9846-7116>

Jun-ichi Kadota

<https://orcid.org/0000-0003-4482-9948>

► See the article “Characteristics and Clinical Outcomes of Extended-Spectrum beta-lactamase-producing *Klebsiella pneumoniae* Bacteremia in Cancer Patients” in volume 52 on page 59.

Dear Editor:

A report in the present journal focused on the characteristics for bloodstream infections caused by extended spectrum  $\beta$ -lactamase (ESBL)-producing bacteria [1]. The authors indicated that an inappropriate empirical antibiotic therapy was not related to higher mortality. As the authors mentioned, physicians at this institution generally do not begin with carbapenem unless the patient is critically-ill or is expected to be at an increased risk of multidrug-resistant bacterial infection. We totally agree with the authors' idea and want to encourage discussion about non-carbapenem-based regimens for ESBL-producing bacteria. Interestingly, another report also showed no significant difference in mortality between the carbapenem-based and non-carbapenem-based regimens for bloodstream infections caused by ESBL-producing bacteria [2]. Some studies demonstrated the equivalent efficacy of penicillins with  $\beta$ -lactamase inhibitor or cefmetazole (CMZ) to carbapenem in the treatment of ESBL-producing bacterial infections [3, 4].

However, these studies focused on bloodstream infections and there is no evidence of the efficacy of non-carbapenem antibiotics in the treatment of pneumonia. Due to the fact that pneumonia may be one of the major causes for bacteremia, study to assess the efficacy of non-carbapenem antibiotics is required. We herein aimed to compare the efficacy of  $\beta$ -lactamase inhibitor or CMZ to that of carbapenem in patients with pneumonia in whom ESBL-producing bacteria were isolated from the sputum samples.

We retrospectively included consecutive patients with pneumonia in whom ESBL-producing bacteria (*Escherichia coli* or *Klebsiella pneumoniae*) were isolated from sputum from January 2010 to March 2020 at the Department of Respiratory Medicine, Oita University Hospital. In this study, pneumonia was defined based on the criteria of the American Thoracic Society/ Infectious Diseases Society of America guidelines [5]. Pneumonia was diagnosed based on clinical signs and symptoms, including cough and fever, as well as infiltrates revealed through chest radiography or chest CT. Patients were divided into a carbapenem group and a non-carbapenem group (piperacillin-tazobactam [TZP], ampicillin-sulbactam [SAM],

**Ethical Approval**

The study protocol was approved by the Institutional Ethics Committee of Oita University Hospital, Oita, Japan (Approval Number: 1943; Approval Date: 28 September 2020).

**Conflicts of Interest**

No conflicts of interest.

**Author Contributions**

Conceptualization: AG, KK. Supervision: KH, JK. Writing – original draft: AG. Writing - review & editing: AG, KK.

CMZ). Patient data - including the gender, age, and underlying diseases, laboratory data, presence of respiratory failure, and antibacterial agents used - were obtained from clinical records. The definition of respiratory failure was SpO<sub>2</sub> <90% without oxygen inhalation. "Improvement" was defined in accordance with a previous reference [6]. Statistical analyses were performed using the IBM SPSS statistics ver. 22 software package (IBM SPSS, Tokyo, Japan). Comparisons between these groups were performed using t-tests for continuous variables and  $\chi^2$ -tests for categorical variables. *P*-values of <0.05 were considered to indicate statistical significance.

Twenty-nine patients with pneumonia from whom ESBL-producing bacteria were isolated from sputum were included. Twelve patients were treated by carbapenem and 17 patients were treated by other antibiotics (SAM, n = 10; TZP, n = 4; and CMZ, n = 3). No significant difference was found in therapeutic effect between the two groups (Table 1). Patients treated by non-carbapenem antibiotics had high serum albumin levels and a good oxygenation status.

Given these results, non-carbapenem antibiotics, penicillins with  $\beta$ -lactamase inhibitor or CMZ could be a candidate option for the treatment of pneumonia in which ESBL-producing bacteria were isolated from sputum at least for non-severe cases. However, this study has some limitations to be discussed. First, a multivariate analysis is required for adjusting other patient characteristics when treatment regimens are independently associated with clinical outcomes, but the analysis could not be conducted due to the small sample size of this study. Second, it was difficult to determine whether the isolated bacteria reflected bacterial infection or colonization. Although the sputum quality might be a clue to resolve this issue, it was not assessed due to the retrospective nature of this study. Nevertheless, the results of this study seem to support the findings of Nham et al. [1]. A large prospective study focusing on the sputum quality is needed to validate these results.

**Table 1.** Comparison of the carbapenem drug and alternative drug groups.

	Carbapenem (n = 12)	Alternative (n = 17)	<i>P</i> -value
Gender, female	1 (8)	0 (0)	0.414
Age, years	73.5 (69.5 - 81.5)	71 (67 - 81)	0.838
WBC, /mm <sup>3</sup>	10,305 (8,205 - 12,845)	8,260 (6,670 - 11,590)	0.118
Neutrophil, /mm <sup>3</sup>	8,682 (6,711 - 11,519)	7,002 (4,776 - 9,962)	0.087
Lymphocyte, /mm <sup>3</sup>	816 (345 - 992)	952 (610 - 1,079)	0.605
CRP, mg/dl	5.69 (1.64 - 13.86)	3.28 (0.96 - 4.57)	0.069
Alb, g/dl	2.44 (2.26 - 2.83)	3.46 (2.66 - 3.80)	0.047
ALT, IU/L	18.4 (11.5 - 23.8)	19.2 (14.1 - 28.4)	0.545
eGFR, mL/min/1.73m <sup>2</sup>	66.1 (58.9 - 91.5)	68.5 (63.9 - 74.2)	0.428
Interstitial pneumonia	4 (33)	2 (12)	0.198
COPD	3 (25)	8 (47)	0.273
Cardiac diseases	3 (25)	2 (12)	0.622
Diabetes mellitus	7 (58)	7 (41)	0.462
Respiratory failure	10 (83)	6 (35)	0.022
Isolated bacteria			0.622
<i>Escherichia coli</i>	9 (75)	15 (88)	
<i>Klebsiella pneumoniae</i>	3 (25)	2 (12)	
Improvement	9 (75)	13 (76)	1.000

Data are presented as the number (%) or median (interquartile range).

WBC, white blood cell; CRP, C-reactive protein; Alb, albumin; ALT, alanine transaminase; eGFR, estimate glomerular filtration rate; COPD, chronic obstructive pulmonary disease.

## REFERENCES

1. Nham E, Huh K, Cho SY, Chung DR, Peck KR, Lee NY, Kang CI. Characteristics and clinical outcomes of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteremia in cancer patients. *Infect Chemother* 2020;52:59-69.  
[PUBMED](#) | [CROSSREF](#)
2. Benanti GE, Brown ART, Shigle TL, Tarrand JJ, Bhatti MM, McDanel PM, Shelburne SA, Aitken SL. Carbapenem versus cefepime or piperacillin-tazobactam for empiric treatment of bacteremia due to extended-spectrum- $\beta$ -lactamase-producing *Escherichia coli* in patients with hematologic malignancy. *Antimicrob Agents Chemother* 2019;63:e01813-8.  
[PUBMED](#) | [CROSSREF](#)
3. Muhammed M, Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Comparison between carbapenems and  $\beta$ -lactam/ $\beta$ -lactamase inhibitors in the treatment for bloodstream infections caused by extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae*: a systematic review and meta-analysis. *Open Forum Infect Dis* 2017;4:ofx099.  
[PUBMED](#) | [CROSSREF](#)
4. Fukuchi T, Iwata K, Kobayashi S, Nakamura T, Ohji G. Cefmetazole for bacteremia caused by ESBL-producing enterobacteriaceae comparing with carbapenems. *BMC Infect Dis* 2016;16:427.  
[PUBMED](#) | [CROSSREF](#)
5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44 Suppl 2:S27-72.  
[PUBMED](#) | [CROSSREF](#)
6. Vardakas KZ, Siempos II, Grammatikos A, Athanassa Z, Korbila IP, Falagas ME. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ* 2008;179:1269-77.  
[PUBMED](#) | [CROSSREF](#)