Short Communication

Does Quick Sepsis-Related Organ Failure Assessment Suggest the Use of Initial Empirical Carbapenem Therapy in Bacteremia Caused by Extended-Spectrum β -Lactamase-Producing Bacteria? :A Multicenter Case-Control Study

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SUMMARY: We hypothesized that quick Sequential Organ Failure Assessment (qSOFA) would be associated with 30-day mortality in bacteremia caused by extended-spectrum β -lactamase (ESBL)-producing bacteria and might be a selection criterion for the use of carbapenem as initial empirical therapy. A multicenter retrospective study was conducted in six hospitals. All patients who had bacteremia due to ESBL-producing bacteria were included in the study. Multivariable logistic regression analysis was performed to analyze 30-day mortality as the main outcome. A total of 203 adult patients were identified with bacteremia caused by ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*. In multivariate logistic regression analysis, bacteremia caused by ESBL-producing *K. pneumoniae* or *P. mirabilis* (odds ratio [OR] 5.07, 95% confidence interval [CI] 1.64–15.56), underlying liver disease (OR 3.38, 95% CI 1.09–10.00), and underlying solid cancer (OR 3.45, 95% CI 1.27–9.69) were associated with 30-day mortality. In a subgroup analysis, empirical non-carbapenem therapy was associated with 30-day mortality in bacteremia caused by ESBL-producing *K. pneumoniae* or *P. mirabilis*. Our results suggest that the qSOFA score is not a selection criterion for the use of carbapenem in initial empirical therapy.

Extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae* are recognized as a global threat because bloodstream infections (BSIs) caused by ESBL-producing *Enterobacteriaceae* are associated with high mortality and increased hospital costs (1,2). Although the consumption of carbapenems is correlated with an increasing prevalence of antimicrobial-resistant bacteria (3), initial empirical carbapenem therapy is important for critically ill patients with ESBL-producing *Enterobacteriaceae* bacteremia (1). The quick Sepsis-related Organ Failure Assessment (qSOFA) score was developed to promptly identify infected patients who are at a risk of mortality (4). However, there have been no data to suggest a relationship between the qSOFA score and 30-day mortality in bacteremia caused by ESBL-producing bacteria. We hypothesized that the qSOFA score is associated with 30-day mortality in this condition and might be a selection criterion for the use of carbapenem as initial empirical therapy.

A multicenter retrospective cohort study was conducted among all patients with bacteremia caused by

ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* from January 2012 to December 2016 in 6 hospitals located in Niigata, Japan (Kaetsu Hospital, 261 beds; Niigata Kouseiren Sado General Hospital, 354 beds; Kashiwazaki General Hospital and Medical Center, 400 beds; Saiseikai Niigata Daini Hospital, 425 beds; Niigata City General Hospital, 676 beds; and Nagaoka Red Cross Hospital, 649 beds). The study was approved by the institutional review board of each participating hospital. The patients' demographic and clinical characteristics were reviewed and recorded (Table 1). The severity of illness was calculated using the qSOFA (4). Only the first bacteremia episode for each patient was included. Bacteremia was defined as an infection with ESBL-producing *E. coli*, *K. pneumoniae*, or *P. mirabilis* isolates from blood cultures. Antimicrobial susceptibility and ESBL confirmatory tests were performed using the microdilution or disk diffusion method according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (5). Isolates categorized as intermediate by antimicrobial susceptibility testing were considered to be resistant. Empirical therapy was defined as the initial antimicrobial therapy initiated before the results of blood culture were reported. Definitive therapy was defined as antimicrobial therapy that was administered 2–5 days after the initiation of empirical therapy. Appropriate therapy was defined as the use of antimicrobials based on in vitro susceptibility testing. Infections occurring 48 h or more after hospital admission were defined as hospital-

Received June 29, 2018. Accepted October 11, 2018.

J-STAGE Advance Publication October 31, 2018.

DOI: 10.7883/yoken.JJID.2018.272

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Dose qSOFA Suggest the Use of Carbapenem?

Table 1. Baseline characteristics and outcomes for groups with qSOFA scores <2 and ≥2

	qSOFA score <2 (n = 137)	qSOFA score ≥2 (n = 66)
Age, yr, mean ± SD	77 ± 14	80 ± 11
Sex, n male (%)	80 (58)	37 (56)
Body weight, kg, mean ± SD	57 ± 18	61 ± 20
Pathogen, n (%)		
<i>E. coli</i>	119 (87)	54 (82)
<i>K. pneumoniae</i>	15 (11)	10 (15)
<i>P. mirabilis</i>	3 (2)	2 (3)
Primary site of infection, n (%)		
Urinary tract	67 (49)	41 (62)
Biliary tract	30 (22)	14 (21)
Other	40 (29)	11 (17)
Total duration of antibiotics therapy, days, mean ± SD	12 ± 7	12 ± 5
Received appropriate initial empirical therapy, n (%)	67 (49)	38 (58)
Carbapenem	56 (41)	34 (52)
Piperacillin-tazobactam	5 (4)	3 (5)
Cefmetazole	2 (2)	0 (0)
Quinolones	4 (3)	1 (2)
Received appropriate definitive therapy, n (%)	101 (74)	50 (76)
Hospital-acquired infection, n (%)	64 (47)	24 (36)
Underlying disease, n (%)		
Cardiovascular disease	24 (18)	12 (18)
Pulmonary disease	12 (9)	9 (14)
Renal disease	26 (19)	8 (12)
Liver disease	20 (15)	5 (8)
Neurological disease	52 (38)	28 (42)
Solid cancer	47 (34)	11 (17)
Hematologic malignancy	16 (12)	3 (5)
Death within 30 days, n (%)	14 (10)	9 (14)

Continuous variables are reported as means and standard deviations; categorical variables are reported as frequencies and percentages.

acquired infections. JMP9 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. Multivariate modeling was performed using logistic regression with a stepwise backward-forward selection ($P < 0.25$) procedure to identify the independent factors associated with 30-day mortality. Variables included in the multivariate analysis were pathogen, primary site of infection, total duration of antibiotics therapy, hospital-acquired infection, qSOFA score ≥ 2, underlying disease, appropriate initial empirical therapy, initial empirical carbapenem therapy, and appropriate definitive therapy. Additionally, based on multivariate analysis results, we performed a subgroup analysis among patients with bacteremia caused by *K. pneumoniae* or *P. mirabilis*, underlying liver disease, or underlying solid cancer. The same variables were used for the subgroup multivariate analysis, with the exception of pathogen and underlying disease (because subgroup patients were limited by these variables). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. $P < 0.05$ was considered to be statistically significant.

Of 221 patients with BSIs due to ESBL-producing bacteria, 18 were excluded because of antimicrobial

Table 2. Multivariate logistic regression analysis of factors associated with 30-day mortality

	Odds ratio	95%CI	P
<i>E. coli</i>	1		
<i>K. pneumoniae</i> or <i>P. mirabilis</i>	5.07	1.64–15.56	0.01
No liver disease	1		
Liver disease	3.38	1.09–10.00	0.04
No solid cancer	1		
Solid cancer	3.45	1.27–9.69	0.02

CI, confidence interval.

Table 3. Multivariate logistic regression subgroup analysis of factors associated with 30-day mortality among patients with bacteremia caused by *K. pneumoniae* or *P. mirabilis*, underlying liver disease, or solid cancer

	Odds ratio	95%CI	P
Empirical carbapenem therapy	1		
Empirical non-carbapenem therapy	15.00	1.80–124.67	0.01
Non-hospitalization-onset	1		
Hospitalization-onset	3.02	1.01–10.03	0.048

CI, confidence interval.

treatment administered within 48 h. Therefore, 203 patients (58% male) with a median age of 80 years (range 20–100 years) and median body weight of 55 kg (range 22–103 kg) were included in the study: 137 (67%) and 66 (33%) patients had qSOFA scores < 2 and ≥ 2, respectively. Among the included patients, bacteremia was caused by ESBL-producing *E. coli* (85%), *K. pneumoniae* (12%), and *P. mirabilis* (2%). Primary sites of infection were the urinary tract (53%), biliary tract (22%), and other (25%). Eighty-eight patients (43%) had hospital-acquired infections. The median duration of antibiotic therapy was 12 days (range 3–42 days). Eight patients (4%) received combination antibiotic therapy. Twenty-three patients (11%) died within 30 days. Baseline characteristics and outcomes for groups with qSOFA scores < 2 and ≥ 2 are shown in Table 1.

In multivariate logistic regression analysis, bacteremia caused by *K. pneumoniae* or *P. mirabilis* (OR 5.07, 95% CI 1.64–15.56), underlying liver disease (OR 3.38, 95% CI 1.09–10.00), and underlying solid cancer (OR 3.45, 95% CI 1.27–9.69) were significantly associated with 30-day mortality (Table 2). In the subgroup of patients who had bacteremia caused by *K. pneumoniae* or *P. mirabilis*, underlying liver disease, or underlying solid cancer ($n = 92$), the incidences of death within 30 days were 10/53 (19%) and 9/39 (23%) among those who received appropriate and non-appropriate initial empirical therapy, respectively. Additionally, the 30-day mortalities were 7/44 (16%) and 12/48 (25%) among those who received initial carbapenem and non-carbapenem empirical therapy, respectively. In multivariate logistic regression analysis, empirical non-carbapenem therapy (OR 15.00, 95% CI 1.80–124.67) and hospital-acquired infection (OR 3.02, 95% CI 1.01–10.03) were significantly associated with 30-day mortality (Table 3).

Our study indicates that the qSOFA score was not associated with 30-day mortality for bacteremia caused by ESBL-producing bacteria. Our findings are similar to

those of a previous study conducted among patients in intensive care units, in which the qSOFA score was not associated with in-hospital mortality (6). Thus, the qSOFA score is not a selection criterion for the use of carbapenem as initial empirical therapy. In contrast to our results, the in-hospital mortality rate was higher in patients with sepsis who tested positive for qSOFA than those who tested negative (4). This difference may be due to the fact that our study was conducted among patients with bacteremia but not sepsis. In addition, because the qSOFA is a screening tool for sepsis, it is not a replacement for systemic inflammatory response syndrome, and so is not part of the definition of sepsis (7). Thus, initial empirical antimicrobials should be carefully selected for patients who have underlying disease or other factors (8,9).

Bacteremia caused by *K. pneumoniae* or *P. mirabilis*, underlying liver disease, and underlying solid cancer were significantly associated with 30-day mortality in multivariate analysis. Our subgroup analysis suggested that patients with these characteristics as well as those with hospital-acquired infections should receive initial empirical carbapenem therapy, although initial appropriate empirical therapy was not associated with 30-day mortality. In a previous study, carbapenem therapy was associated with significantly lower 14-day mortality in bacteremia caused by *K. pneumoniae* (8). Additionally, liver disease is associated with 30-day mortality (9), and solid cancer patients have been identified as a high-risk population for infection with ESBL-producing bacteria (10). Moreover, hospital-acquired infections are associated with a high risk of ESBL-producing bacteria colonization (11). Therefore, initial empirical carbapenem therapy might be recommended for such patients.

Our study has several limitations. First, this is a retrospective observational study; therefore, hidden bias may exist. Furthermore, patients who are critically ill or have many underlying diseases might be more likely to be administered empirical carbapenem therapy by their physician. Second, our study could not assess the severity of illness without the qSOFA because we could not access the required data to perform the SOFA. Third, we did not

evaluate combination therapy in this study; however, a few patients who received combination therapy (4%) were included in the study group.

In conclusion, our results suggest that the qSOFA score is not a selection criterion for the use of carbapenem as initial empirical therapy.

Conflict of interest None to declare.

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