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Evaluation of the clinical outcomes in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia during a nationwide shortage of cefazolin †

Atsushi Uda[1,2,*], Takeshi Kimura[1], Mari Kusuki[2], Ikuko Yano[1], Takayuki Miyara[2]

[1] Department of Infection Control and Prevention, Kobe University Hospital, Kobe 650-0017, Japan; hyakuta@med.kobe-u.ac.jp (M.K.)； miyarat@med.kobe-u.ac.jp (T.M.)

[2] Department of Pharmacy, Kobe University Hospital, Kobe 650-0017; kimutake@med.kobe-u.ac.jp (T.K.); iyano@med.kobe-u.ac.jp (I.Y.)

* Correspondence: a-uda@umin.ac.jp; Tel.: +81-78-382-5111 (A.U.)

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Abstract: Cefazolin is an essential antibiotic used for the treatment of bacteremia; in particular, it is recommended as a first-line agent for infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). In March 2019, problems with a major antibiotic supplier caused a critical shortage of cefazolin in Japan. In fact, in our hospital, the prescription of cefazolin was restricted (unless permitted by an infectious disease physician) between March 2019 and January 2020. The aim of this study was to evaluate the clinical outcomes of patients with MSSA bacteremia at a university hospital in Japan during cefazolin shortage. Details of antimicrobial use and patient data were extracted from the medical records and classified as pre-shortage (March 2018–January 2019) and post-shortage (March 2019–January 2020). Seventy-five patients were included in the study (pre-shortage group, n = 39; post-shortage group, n = 36); there were no significant differences between the demographic characteristics of the two groups. The percentage of patients that received cefazolin as definitive therapy, was significantly lower in the post-shortage group than that in the pre-shortage group (82% vs. 53%, $p = 0.012$). Of note, penicillins were more frequently administered as alternative therapy to the post-shortage group (10% vs. 53%, $p < 0.001$). However, no significant differences were observed between the clinical outcomes of the two groups. Therefore, in the treatment of MSSA-induced bacteremia, cefazolin shortage was associated with an increase in the use of penicillins as alternative agents, with no major changes in the clinical outcomes.

Keywords: antimicrobial shortage; cefazolin; bacteremia; methicillin-susceptible *Staphylococcus aureus*

1. Introduction

Methicillin-susceptible *Staphylococcus aureus* (MSSA), a common cause of hospital-acquired infections, is associated with poor clinical outcomes [1]. Cefazolin is classified as a first-generation cephalosporin with a narrow spectrum, which is used as a first-line antibiotic for treating patients with MSSA in Japan. Critical antimicrobial shortages have been a serious healthcare problem worldwide, and in March 2019, cefazolin shortage due to a supplier problem occurred in Japan [2], which affected infectious disease treatment in many hospitals. The Ministry of Health, Labor, and Welfare of Japan, therefore, issued a notice on using alternative antibiotics for treating specific infectious diseases [3]. The alternative antibiotics listed for treating MSSA bacteremia were ampicillin/sulbactam, third-generation cephalosporins (e.g., cefotaxime and ceftriaxone), vancomycin, and daptomycin. However, the overuse and misuse of broad-spectrum antibiotics risks

worsening the bacterial antimicrobial susceptibility, healthcare cost, and mortality rate [4,5]. Therefore, the use of narrow-spectrum antibiotics, such as penicillins, should be promoted. The impact of cefazolin shortage on the treatment of patients with MSSA bacteremia remains unclear. We aimed to evaluate the impact of cefazolin shortage on the clinical outcomes in patients with MSSA bacteremia at a university hospital.

2. Methods

2.1. Setting and patients

An observational study was retrospectively conducted between pre-shortage (March 2018–January 2019) and post-shortage (March 2019–January 2020) at Kobe University Hospital. Details of antimicrobial use and patient data were reviewed from the electronic medical records. Patients with MSSA bacteremia were characterized based on the identification of at least one MSSA in blood culture. We excluded the patients <18 years old or those with a polymicrobial blood culture.

2.2. Definition

The hospitalization ward, hemodialysis, invasive device use, and the quick Sequential Organ Failure Assessment (qSOFA) score were evaluated on bacteremia onset. Data pertaining to previous immunosuppression and recent surgery 30 days prior to bacteremia onset were collected. Definitive therapy was defined as the antibiotic therapy prescribed according to the microbiological data of *S. aureus* detected from blood culture. Time to fever resolution was calculated as the number of days from bacteremia onset until the blood temperature dropped below 37.5 °C. Time to white blood cell (WBC) normalization was defined as the number of days from bacteremia onset until the white blood cell count dropped below 8,600/μL. Treatment failure was defined as escalation to broad-spectrum antibiotics due to deteriorating condition, no defervescence within 14 days after bacteremia onset, or death within 30 days after bacteremia onset. The 30-day mortality was defined as death within 30 days of bacteremia onset.

2.3. Statistical analysis

The continuous and categorical variables were expressed as medians with interquartile ranges (IQRs) and frequency counts with percentages, respectively. The non-parametric and categorical variables were analyzed using the Mann–Whitney U-test and chi-square test, respectively. Statistical significance was set at $p < 0.05$. All parameters were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results and Discussion

A total of 75 patients were eligible for inclusion in this study (pre-shortage group, n = 39; post-shortage group, n = 36). Table 1 summarizes the demographic characteristics of the two groups. No significant differences were observed between the two groups with respect to sex, age, hospitalization ward, hospital stay before bacteremia onset, previous immunosuppression, recent surgery, hemodialysis, invasive device use, vasopressor use, and qSOFA score ≥2. Table 2 shows the percentage of patients in the two groups prescribed antibiotics as definitive therapy. The percentage of patients on cefazolin therapy was significantly lower in the post-shortage group than that in the pre-shortage group (82% vs. 53%, $p = 0.012$). Penicillins (including benzylpenicillin, ampicillin, ampicillin/sulbactam, and piperacillin/tazobactam) were frequently administered during the post-shortage period (10% vs. 53%, $p < 0.001$).

Table 1. Comparison of the demographic characteristics of patients with MSSA bacteremia

	Pre-shortage group (n = 39)	Post-shortage group (n = 36)	*p*
Male sex, n (%)	27 (69)	23 (64)	0.81
Age, median years (IQR)	69 (56–80)	69 (54–75)	0.54
Hospitalization ward, n (%)			
Medical ward	22 (56)	13 (36)	0.13
Surgical ward	14 (36)	15 (42)	0.78
Intensive Care Unit	3 (8)	8 (22)	0.15
Hospital stay before the onset of bacteraemia, median (IQR)	3 (0–20)	3 (0–21)	0.63
Previous immunosuppression, n (%)			
Immunosuppressive treatment	1 (3)	4 (11)	0.31
Corticosteroid treatment	11 (28)	7 (19)	0.54
Chemotherapy	7 (18)	2 (6)	0.2
Recent surgery, n (%)	4 (10)	4 (11)	1
Hemodialysis, n (%)	3 (8)	5 (14)	0.62
Invasive devices, n (%)			
Central venous catheter	8 (21)	13 (36)	0.21
Urinary tract infections	6 (15)	6 (17)	1
Mechanical ventilation	1 (3)	1 (3)	1
Vasopressor use, n (%)	7 (18)	6 (17)	1
qSOFA score ≥2, n (%)	12 (31)	14 (39)	0.62

IQR, interquartile ranges; qSOFA, quick Sequential Organ Failure Assessment

Table 2. Antibiotic definitive therapy, n (%)

	Pre-shortage group (n = 39)	Post-shortage group (n = 36)	*p*
Penicillins	4 (10)	19 (53)	<0.001
Cefazolin	32 (82)	19 (53)	0.012
Cefotiam	0 (0)	1 (3)	0.48
Ceftriaxon	0 (0)	2 (6)	0.23

Some patients were prescribed multiple type of antibiotics.

Antimicrobial shortage may pose serious threats to patient outcomes. Cefazolin, a first-generation cephalosporin, acts against both gram-positive and gram-negative bacteria and is recommended as an ACCESS group antibiotic on the WHO Model List of Essential Medicines [6]. Cefazolin is superior to vancomycin for treating methicillin-susceptible MSSA bacteremia [7] and used as the first-choice agent to treat MSSA because anti-staphylococcal penicillins (oxacillin and nafcillin) are not approved in Japan. In March 2019, Nichi-Iko Pharmaceutical Co., Ltd., a major supplier in Japan, announced that cefazolin supply was suspended because of manufacturing problems [2]. In response, the Japanese Ministry of Health, Labor, and Welfare listed broad-spectrum antibiotics as alternative therapy for infectious diseases caused by MSSA [3]. Since broad-spectrum antibiotics are associated with increased risk factors for the acquisition and development of resistant bacteria [8], using narrow-spectrum antibiotics should be encouraged via antimicrobial stewardship programs (ASPs). A previous cohort study has reported that penicillins could be alternative agents for the definitive treatment of penicillin-susceptible bacteremia with stable conditions [9]. We observed no significant differences in the use of broad-spectrum antibiotics, and vancomycin was not

prescribed as a definitive therapy. Meanwhile, penicillins were mainly prescribed to patients with mild or moderate bacteremia due to penicillin-susceptible *S. aureus*, leading to a significant increase in penicillin use. The prescription of cefazolin was restricted, particularly for patients vulnerable to severe illness or those with bacteremia caused by penicillin-resistant *S. aureus*.

In similar studies, piperacillin-tazobactam shortage in the USA increased meropenem prescription despite interventions via ASPs, but did not change therapy duration and mortality [10,11]. A previous retrospective study reported that alternative antimicrobial prophylaxis antibiotics, which consisted of broad-spectrum antibiotics, were associated with the increased risk for surgical site infection in spine surgery during cefazolin shortage in Japan [12]. Table 3 shows no significant differences in the clinical outcomes including time to fever resolution, time to WBC normalization, time to detect negative blood culture, persistent bacteremia ≥7 days, change to alternative antibiotics from definitive therapy, total duration of antibiotic therapy, treatment failure, hospital stay after the onset of bacteremia until discharge, 30-day mortality, and adverse drug reactions (e.g., diarrhea and skin rash) between the two groups. Among the four patients who died within 30 days of bacteremia onset, one died of malignancy and one of pneumonia in each group, indicating that there were no association between death and antimicrobial use. The prescriptions of penicillins are associated with a higher incidence rate of antimicrobial allergies than cephalosporins [13]. We found no significant differences in allergic rashes, but the sample size in this study was insufficient to assess adverse drug reactions.

Table 3. Clinical outcome in patients with MSSA

	Pre-shortage group (n = 39)	Post-shortage group (n = 36)	*p*
Time to fever resolution, median days (IQR)	2 (1–4)	3 (1–4)	0.98
Time to WBC normalization, median days (IQR)	4 (0–13)	2 (0–7)	0.28
Time to detect negative blood culture, median days (IQR)	5 (3–7)	4 (3–5)	0.47
Persistent bacteremia (≥7 days), n (%)	3 (8)	0 (0)	0.27
Change to alternative antibiotics from definitive therapy, n (%)	6 (15)	10 (28)	0.87
Total duration of antibiotic therapy, median days (IQR)	22 (16–35)	17 (15–33)	0.46
Treatment failure, n (%)	7 (18)	11 (31)	0.31
Hospital stay after the onset of bacteremia until discharge, median days (IQR)	35 (22–59)	32 (19–46)	0.68
30-day mortality, n (%)	2 (5)	2 (6)	1
Adverse drug reactions, n (%)			
Diarrhea	6 (15)	5 (14)	1
Skin rash	1 (3)	1 (3)	1

MSSA, methicillin-resistant *Staphylococcus aureus*; IQR, interquartile ranges; WBC, white blood cell

4. Conclusions

Due to cefazolin shortage, penicillin use has increased as an alternative agent for treating bacteremia caused by MSSA without changing the clinical outcomes.

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