Evaluation of the Benefits of De-Escalation for Patients with Sepsis in the Emergency Intensive Care Unit

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ABSTRACT – Purpose. Although the 2016 Japanese guidelines for the management of sepsis recommend de-escalation of treatment after identification of the causative pathogen, adherence to this practice remain unknown. The objective of this study was to evaluate the benefits of de-escalating treatment for sepsis patients at an advanced critical care and emergency medical centre. **Methods**. Based on electronic patient information, 85 patients who were transported to the centre by ambulance, and diagnosed with sepsis between January 2008 and September 2013 were enrolled and evaluated. Patients were divided into two groups with and without de-escalation, and comparisons were conducted for several variables, including length of hospital stay, and length of antibiotic administration. Two types of subgroup analysis were conducted between patients with septic shock or positive blood cultures. Statistical analysis was conducted using chi-square and Mann-Whitney U tests. **Results**. The length of hospital stay after diagnosis was significantly shorter for the de-escalation group than for the non-de-escalation group. In the subgroup analysis, de-escalation for blood culture-positive patients was beneficial in terms of the length of hospital stay and length of antibiotic administration. **Conclusions**. The findings of this study suggest that sepsis treatment de-escalation is beneficial for treatment efficacy and appropriate use of antibiotics.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (1). The reported mortality rates for sepsis are 25–30% and 40–70% for septic shock (2). Improving the survival rates for severe sepsis and septic shock requires not only treatment of the infection but also intensive care of the organ dysfunction and associated pathologies that occur successively. The treatment guidelines for sepsis are stipulated in the international guidelines for the management of sepsis (3), with descriptions of antimicrobial therapy, surgical management, and combined therapy.

During the treatment of sepsis, lower mortality rates have been associated with shorter periods between the recognition of the pathology and administration of antibiotics; in particular, a significantly lower mortality rate has been reported when antibiotics were administered within 1 hour of diagnosis (4). Therefore, swift administration of antibiotics based on empiric treatment is crucial following diagnosis (5). However, excessive use of antibiotics has been associated with the appearance of resistant bacteria and risk of destroying the patient's normal bacterial flora (6). Therefore, after

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administering empiric treatment, identification of the causative pathogen and, when the drug sensitivity is known, de-escalation to more narrow-spectrum antibiotics is recommended. The antimicrobial de-escalation is definded as change to a narrow spectrum antibacterial drug or reduce the type of antimicrobial drug (7). The successful use of antibiotics in de-escalation has indicated that such use does not increase the recurrence or mortality rates for sepsis (8, 9), which results in improvements in survival rates and length of hospital stay in cases of ventilator-associated pneumonia (7). Further, de-escalation has also been reported as a safe strategy even for patients with severe sepsis and septic shock admitted to the intensive care unit (ICU) (10).

A number of clinical studies regarding de-escalation for patients with bacteraemia or traumatic injury have been undertaken (11-15). However, the outcomes of de-escalation of sepsis patients in the emergency domain have not been examined. Therefore, this study aimed to investigate the benefits of de-escalation specific to sepsis in the emergency domain, by retrospectively studying sepsis treatment at the advanced critical care and emergency medical centre (hereafter, emergency intensive care unit [EICU]) and evaluating the de-escalation rates and suitability of empiric treatment.

METHODS

Patients and data

Information was collected from electronic patient medical record terminals at the hospital pharmacy. Patients who were diagnosed with sepsis and received treatment at the EICU between January 2008 and September 2013 were eligible. Patients aged <18 years or who did not receive proactive treatment were excluded. In addition, patients who were de-escalated after being transferred from the EICU to other hospital wards were excluded from the comparison of outcomes by de-escalation status.

Variables included sex, age, height, weight, body mass index (BMI), the condition for which patients were transported to the hospital and any complications, lactic acid levels, Acute Physiology and Chronic Health Evaluation (APACHE II) score (16), and Sequential Organ Failure Assessment (SOFA) score (17). Items used to distinguish between empiric treatment and de-escalation were the date and time of sepsis diagnosis, date of identification of the causative pathogen, antibiotics used, drug sensitivity of the causative pathogen, and the presence of neutropenia (data not shown). Outcomes included the length between the diagnosis of sepsis and discharge from the EICU (days), patient outcome (mortality rate) prior to discharge or transfer, and length of antibiotic administration (days).

Empiric treatment by doctors was defined as administration of suitable antibiotics during the period between the diagnosis of sepsis and identification of the causative pathogen. De-escalated patients were those for whom suitable empiric treatment was conducted and who met the following three criteria: clinical improvement in condition, identified causative pathogen receptive to more narrow-spectrum antibiotics, and no sustained neutropenia ($<1000/mm^3$) or other serious immunodeficiency.

De-escalation was carried out based on the identification of the bacteria. A flow diagram on the timeline, from transportation to the emergency room to de-escalation, is presented in supplementary figure 1. In this study, de-escalation was defined as a change to more narrow-spectrum antibiotics or a reduction in the types of antibiotics used after identification of the causative pathogen and its drug sensitivity. Criteria for de-escalation followed those reported by Kollef et al. (9). Evaluation of the utility of de-escalation was conducted by dividing the subjects into two groups based on de-escalation and comparing and assessing the mortality rate, length of hospital stay (days), and length of antibiotic administration (days) between the two groups.

STATISTICAL ANALYSIS

The Student's t test, Welch's t test, or Mann-Whitney U test was used for comparing continuous variables, as appropriate. To compare categorical variables, the chi-square test was performed.

Comparisons were only conducted for those with available data for lactic acid levels, APACHE II score, and SOFA score. Two types of sub-group analysis were conducted, where the patients were further classified into those with septic shock, or those with positive blood culture only, to compare the influence on de-escalation outcome. $P < 0.05$ was considered significant.

Ethical considerations in research

The survey content and methods to protect personal information were approved by the Okayama University Hospital Ethics Committee and in accordance with the stipulations on the handling of patient personal information (Ethics Committee Registration Number: 969)

RESULTS

Rate of de-escalation

Empiric treatment was conducted for all 85 patients with sepsis, and de-escalation was considered suitable for 60 patients (Fig. 1). De-escalation was conducted for 21 (35.0%) of these patients.

Characteristics of de-escalation and non-de-escalation groups

Patient background by de-escalation and non-de-escalation status is provided in Table 1. Median age, sex distribution, median BMI, median lactic acid level, mean APACHE II score, median SOFA score, and the median time (in days) from the first blood collection and the identification of the microbes was not significantly different between the groups. The patients' complaints at the time of transportation are presented in supplementary Table 1. The non-de-escalation group contained more patients with liver failure and renal failure, compared to that of the de-escalation group. The number of users taking antibiotics before and after de-escalation is shown in Supplementary Table 2. As a result of the de-escalation, the relative proportion of carbapenem antibiotics that were used (such as Imipenem/Cilastatin and Piperacillin/Tazobactam) decreased, while the relative proportion of beta-lactam antibiotic usage increased.

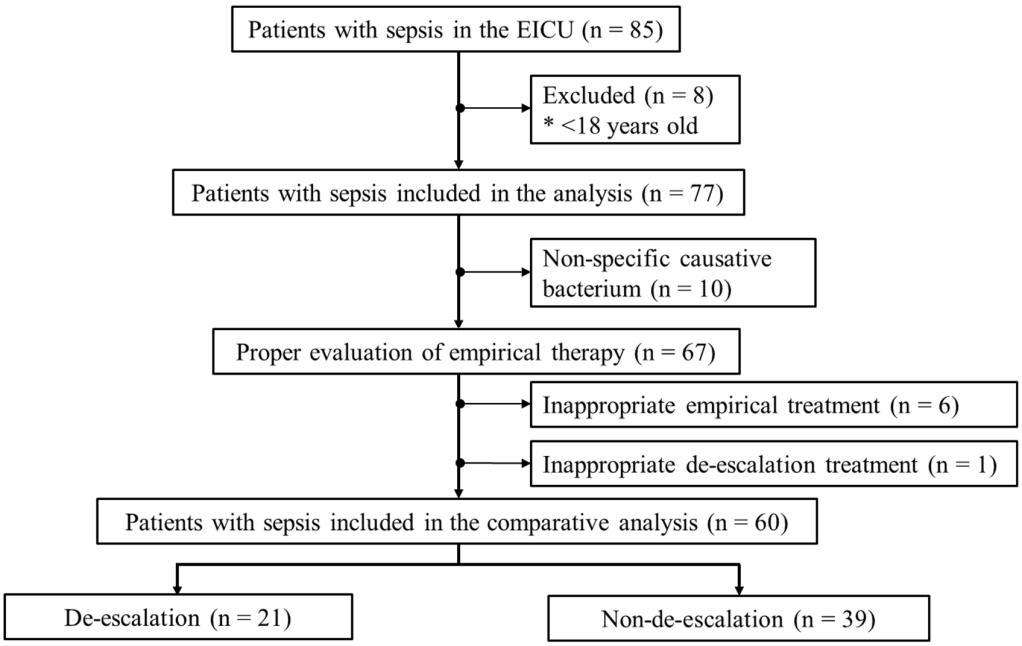

Figure 1. De-escalation for patients with sepsis

Table 1. Patient characteristics by de-escalation status

Values are reported as median (range), mean ± standard deviation, or n.

	De-escalation group	Non-de-escalation group	p value
Age (years)	61.1 (23–89)	69.0 (20–89)	0.053
Sex			
Male	13	29	0.315
Female	8	10	
BMI (kg/m^2)	20.9 (10.74–30.42)	21.0 (10.65–60.35)	0.11
Lactic acid level (mmol/L)	1.9 (0.7–7.1)	2.3 (0.7–19.0)	0.27
APACHE II score	17.5 ± 5.0	19.0 ± 8.1	0.485
SOFA score	6.5 (2–13)	7.5 (2–15)	0.936
Median days before identification of the microbes	4 (2-9)	3 (2-8)	0.187

Comparison of outcomes by de-escalation and non-de-escalation groups

Mortality rate and length of antibiotic administration were not significantly different between the two groups, although they were both higher in the non-de-escalation group (Table 2).

The median length of hospital stay was significantly longer in the non-de-escalation group (26 days) than in the de-escalation group (12 days; p = 0.028).

Subgroup analysis

In the group of patients with septic shock, the rate of de-escalation was 33.3% (10/30). Mortality rate, length of hospital stay, and length of antibiotic administration did not differ by de-escalation status (Table 3).

In the group of patients with only positive blood cultures, the rate of de-escalation was 39.0% (16/41). Mortality rate, length of hospital stay, and length of antibiotic administration were all superior for the de-escalation group. The differences in the length of hospital stay and length of antibiotic administration were significant (Table 4).

Table 2. Comparison of outcomes by de-escalation status

	De-escalation group (n = 21)	Non-de-escalation group (n = 39)	p value
Mortality rate (Death/Survival)	9.5% (2/19)	23.1% (9/30)	0.227
Length of hospital stay (days)	12 (4–138)	26 (5–204)	0.028
Length of antibiotic therapy (days)	12 (4–34)	16 (5–71)	0.071

Values are reported as median (range) or a percentage.

Table 3. Influence of de-escalation in patients with septic shock

	De-escalation group (n = 10)	Non-de-escalation group (n = 20)	p value
Mortality rate (Death/Survival)	10.0% (1/9)	40.0% (8/12)	0.204
Length of hospital stay (days)	11 (7–51)	21 (5–81)	0.184
Length of antibiotic therapy (days)	10 (6–21)	15 (5–70)	0.26

Values are reported as median (range) or a percentage.

Table 4. Influence of de-escalation in blood culture-positive patients

	De-escalation group (n = 16)	Non-de-escalation group (n = 25)	*p* value
Mortality rate (Death/Survival)	12.50% (2/14)	24.0% (6/19)	0.448
Length of hospital stay (days)	11 (4–138)	26 (5–204)	0.030
Length of antibiotic therapy (days)	12 (4–34)	16 (5–71)	0.041

Values are reported as median (range) or a percentage.

DISCUSSION

The percent of de-escalation in the treatment of patients with sepsis in the EICU was 35.0% (21/60), similar to the results of previous studies conducted (11-14). Reasons not to de-escalate may have included difficulty controlling antimicrobial treatment of sepsis.

Regarding the benefits of de-escalation, the length of hospital stay was significantly shorter for the de-escalation group than for the non-de-escalation group. Because the reason for discharge from the EICU was improved symptoms, the results indicate that those with the swiftest improvement in symptoms had the shortest hospital stays; in other words, the severity of the patient's condition may have biased the results. However, the significant difference between the de-escalation and non-de-escalation groups despite no bias in severity indicates that de-escalation contributed to the shorter

hospital stay. Therefore, treatment de-escalation might be beneficial for patients with sepsis.

The length of antibiotic administration is important for evaluating the appropriate use of antibiotics. Long-term antibiotic administration prolongs hospital stays and treatment duration and adversely affects prognosis for some patients owing to side effects such as microbial substitution due to resistant bacteria or the resistant bacteria themselves. As such, the duration of antibiotic administration for bacteraemia and other conditions is generally limited to 14 days (18). The median length of antibiotic administration in the present study was 12 days for the de-escalation group, compared with 16 days for the non-de-escalation group, indicating a tendency for de-escalation to help shorten the length of antibiotic administration.

Given that shorter antibiotic administration may be correlated with the duration of hospital stay, a subgroup analysis was conducted between patients with septic shock or who were blood culture positive, which are considered to have a major influence on the decision for de-escalation. The selection of antibiotics depends on whether there is sufficient time to reflect the results of blood culture tests. In the present study, no significant difference was observed in the length of hospital stay or antibiotic administration based on de-escalation status for patients with septic shock. However, for blood culture-positive patients, the length of hospital stay and length of antibiotic administration were significantly shorter for the de-escalation group. The guidelines recommend drawing blood cultures prior to commencing antibiotics in all cases of sepsis.[3] Further, the aseptic collection of sample specimens from the possible infection source site for smear tests and culture identification and sensitivity tests is also recommended (19-21). The results of the present study may provide important evidence to substantiate these recommendations for blood cultures. However, for patients with septic shock, there is almost no leeway in clinical practice to delay antibiotic administration for the purpose of drawing blood cultures. We believe that this affected the outcomes between the two subgroups.

The results of the present study indicate that the selection of the antibiotic agent and de-escalation on the basis of blood culture tests are beneficial for treatment outcomes of sepsis in the emergency domain. Therefore, further investigation of the utility of blood culture testing is warranted.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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