Original Article

Efficacy of early administration of liposomal amphotericin B in patients with septic shock: A nationwide observational study

Masato Tashiro [a,b,*], Takahiro Takazono [a,c], Yuki Ota [d], Tomotaro Wakamura [e], Akinori Takahashi [f], Kumiko Sato [f], Taiga Miyazaki [a,c], Yoko Obata [d], Tomoya Nishino [d], Koichi Izumikawa [a,b]

[a] Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan
[b] Nagasaki University Infection Control and Education Center, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan
[c] Department of Respiratory Medicine, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan
[d] Department of Nephrology, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan
[e] Medical Affairs Division, Sumitomo Dainippon Pharma Co., Ltd, 1-13-1 Kyobashi, Chuo-ku, Tokyo, 104-8356, Japan
[f] Deloitte Tohmatsu Consulting LLC, Marunouchi Nijubashi Building, 3-2-3 Marunouchi, Chiyoda-ku, Tokyo, 100-8361, Japan

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ABSTRACT

Introduction: Liposomal amphotericin B (L-AMB), a broad spectrum anti-fungicidal drug, is often administered to treat invasive fungal infections (IFIs). However, the most suitable time to initiate treatment in septic shock patients with IFI is unknown.

Methods: Patients with septic shock treated with L-AMB were identified from the Japanese Diagnosis Procedure Combination national database and were stratified according to L-AMB treatment initiation either at septic shock onset (early L-AMB group) or after the onset (delayed L-AMB group) to determine their survival rates following septic shock onset and the shock cessation period.

Results: We identified 141 patients administered L-AMB on the day of or after septic shock onset: 60 patients received early treatment, whereas 81 patients received delayed treatment. Survival rates after septic shock onset were higher in the early L-AMB group than in the delayed L-AMB group (4 weeks: 68.4% vs 57.9%, $P = 0.197$; 6 weeks: 62.2% vs 44.5%, $P = 0.061$; 12 weeks: 43.4% vs 35.0%, $P = 0.168$, respectively). The septic shock cessation period was shorter in the early L-AMB group than in the delayed L-AMB group (7.0 ± 7.0 days vs 16.5 ± 15.4 days, $P < 0.001$), with a significant difference confirmed after adjusting for confounding factors with propensity score matching (7.1 ± 7.2 days vs 16.7 ± 14.0 days, $P = 0.001$).

Conclusion: Early L-AMB administration at septic shock onset may be associated with early shock cessation.

1. Introduction

Invasive fungal infections (IFIs) frequently occur in immunocompromised patients and critically-ill patients and are associated with high rates of morbidity and mortality [1–6]. Identifying the appropriate time to start antifungal treatment for IFI patients is thus crucial to improving the prognosis. For example, in candidemia, a significant reduction in crude mortality was observed if antifungal medication was initiated within 24 h of the date of positive blood culture [7,8]. Furthermore, a trend toward reduced crude mortality has been reported with the initiation of antifungal medication within 48 or 72 h of the onset of septic shock due to candidemia [9,10]. Conversely, prophylactic or empiric

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antifungal administration has been reported to reduce the incidence of IFIs but not improve crude mortality [11,12]. Additionally, in patients with septic shock caused by candidemia, the time from positive blood cultures to the start of antifungal medication did not differ between the survival and death groups [13]. As a result, the appropriate timing of treatment initiation for septic shock patients with IFI remains unclear.

Most clinical studies on the timing of antifungal drug initiation have been conducted in candidemia and only a few studies on empirical treatments have been performed. However, because the positive rate of fungal cultures, including blood cultures, is not high enough [14], empirical treatment is often used in actual clinical practice. Therefore, knowledge of the appropriate time to initiate empirical treatment with antifungal drugs is needed.

Liposomal amphotericin B (L-AMB) has a broad anti-fungicidal spectrum that covers most clinically relevant yeasts and molds that cause mycoses, such as candidiasis, aspergillosis, cryptococcosis, and mucormycosis [15]. L-AMB is used as a first-line drug in critically-ill IFI patients with candidiasis, aspergillosis, and mucormycosis who exhibit resistance to other antifungal drugs [16]. Thus, we aimed to clarify the effect of L-AMB administration timing on the outcome of septic shock patients requiring IFI treatment.

2. Patients and methods

2.1. Ethics

This study was conducted in accordance with the Declaration of Helsinki. The data herein were anonymously processed by the database provider (Medical Data Vision Co., Ltd) in accordance with the Act on the Protection of Personal Information of Japan and other related regulations. For the usage of unlinkable, de-identified data, ethical approval and informed consent were waived according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science, and Technology, and the Ministry of Health, Labour, and Welfare of Japan. The study received ethical approval from Nagasaki University School of Medicine Research Ethics Committee (approval number 18033038-5).

2.2. Study design and data source

This retrospective study was conducted with administrative claims data obtained from an electronic medical information database (Medical Data Vision Co., Ltd), which contains diagnosis procedure combination (DPC) hospital data and medical fee reimbursement claims from 345 facilities in Japan. Baseline patient information included age, sex, diagnosis, and comorbidities at admission, coded using the International Classification of Diseases, 10th Revision (ICD-10) codes. The database also contained all drug dosages and administration dates during hospitalization. All interventional procedures were decoded from the original Japanese codes. DPC is an administrative database containing inpatient information. Therefore, patient follow-up began on admission day and ended on discharge date, transferal to other hospitals, or death.

2.3. Patient selection

We identified patients administered L-AMB during hospitalization between April 2008 and January 2018. Patients with septic shock were defined as subjects treated with catecholamines. Septic shock onset was defined as the date of catecholamine treatment initiation. Patients that began L-AMB treatment on the day of or after septic shock onset and those administered carbapenems at septic shock onset were selected to avoid the effects that arise as confounders owing to antibiotics. Patients who met the following criteria were excluded: 1) <18 years old; 2) L-AMB daily dosing >6 mg/kg body weight; 3) <5 days of L-AMB treatment duration; 4) L-AMB administration before septic shock onset; 5) began L-AMB treatment four weeks after septic shock onset; 6) no fungal

infection tests such as culture, drug susceptibility tests of fungus, β-D-glucan, or antigens of *Aspergillus*, *Candida*, and *Cryptococcus* within seven days before the initiation of L-AMB administration; and 7) lacking required data, including body weight and outcome. The early L-AMB group included patients who initiated L-AMB treatment at septic shock onset, whereas the delayed group included patients who began treatment on and after the day following septic shock onset.

2.4. Variables and endpoints

We evaluated patient characteristics, including age, sex, IFI disease name, and antifungal drugs administered before L-AMB treatment initiation. Comorbidities were evaluated using the Charlson comorbidity index (CCI) [17]. CCI has been widely used by researchers to measure case mix and burden of disease. It includes 17 conditions that have a major impact on survival and are defined by the ICD-10 codes [18]. A higher CCI depicts the presence of severe comorbidities. The presence of malignant tumor, neutropenia treated with granulocyte colony-stimulating factor (G-CSF), corticosteroid treatment (≥0.3 mg/kg/day prednisolone conversion), diabetes treated with insulin, and T cell immunosuppressant therapy were assessed to evaluate the state of immunosuppression before and at septic shock onset. T cell immuno-suppressant therapy was defined as treatment with calcineurins, anti-TNFα inhibitors, anti-lymphocyte monoclonal antibodies, and purine and pyrimidine analogs the day of or within 90 days before septic shock onset [19]. The presence of a central venous (CV) catheter insertion and a history of gastrointestinal surgery were retrieved to evaluate the risk factors associated with the outcome of IFI treatment. Digestive tract surgery was defined as a surgery that incised the esophagus, stomach, duodenum, jejunum, ileum, cecum, appendix, colon, and rectum the day of or within 30 days before septic shock onset. The presence of interventions, including intensive care unit (ICU) admission, renal replacement therapy (RRT), mechanical ventilation, and CV catheter replacement, was assessed to evaluate the state of patients before and at septic shock onset. However, CV catheter removal was not evaluated as this was not included in the claims data. Initiation of IFI therapy before the onset of septic shock as well as oral and injected antifungal drug treatment before the initiation of L-AMB therapy were assessed to evaluate previous experience with antifungal treatment. IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval ≥2 days. This period includes the date of L-AMB therapy initiation. The attributes of clinicians were assessed to evaluate their experience with L-AMB dispensing or their capability to carry out patient management. Treatment departments were classified into four categories: hematology, which included clinicians with extensive experience in treating invasive pulmonary aspergillosis and pulmonary mucormycosis with L-AMB; internal departments, except the hematology department; surgical department; and other departments (e.g., emergency medicine). L-AMB or catecholamine treatment duration was defined as the time from treatment initiation to discontinuation, where treatment discontinuation was defined as an administration interval ≥8 or ≥2 days, respectively. Septic shock cessation was defined as catecholamine treatment termination. The following endpoints were assessed: 1) survival rates at 4, 6, and 12 weeks after septic shock onset, and 2) septic shock cessation period.

2.5. Statistical analysis

The survival rates after septic shock onset or during septic shock treatment were calculated using the Kaplan-Meier method and statistically evaluated with the log-rank test. Propensity scores were calculated using a logistic regression model and the following covariates: 14 variables related to prognosis of patients with septic shock from a clinical perspective, and variables with a significant difference between the early and delayed L-AMB groups in patient characteristics. Variables

associated with prognosis in patients with septic shock included those related to antifungal treatment (timing of L-AMB treatment initiation, daily average dosing of L-AMB, history of antifungal drug administration before the initiation of L-AMB administration, initiation of IFI therapy before septic shock onset), patient characteristics (age, sex, CCI, presence of neutropenia with G-CSF administration, treatment with corticosteroid, and T cell immunosuppressants), interventions (ICU admission, CV catheter replacement, and RRT), and clinician's attribute (hematology department). Using these propensity scores, early L-AMB cases were individually matched with delayed L-AMB cases at a 1-to-1 ratio using the nearest matching method within a 0.1 caliper distance. After matching, a paired Student's t-test was performed to compare the septic shock cessation period. Continuous variables were presented as the average ± standard deviation. Welch's t-test was used to compare two groups for continuous variables, while the Fisher's exact test was used for two categorical variables.

3. Results

3.1. Comparison of baseline characteristics

In total, 6640 patients administered L-AMB were selected. Thereafter, we identified 141 patients administered L-AMB on the day of or after septic shock onset: 60 patients received early L-AMB treatment at septic shock onset (early L-AMB group) whereas 81 patients received delayed L-AMB treatment on and after the day following septic shock onset (delayed L-AMB group) (Fig. 1).

The characteristics of patients in both groups are shown in Table 1. CCI and the proportion of immunosuppressed patients treated with corticosteroids or T cell immunosuppressants, patients with aspergillosis, and patients treated in the hematology department were higher in the early L-AMB group than the delayed L-AMB group. However, older patients, those requiring RRT, and those treated in the surgical department were more frequent in the delayed L-AMB group than the early L-AMB group. In the delayed L-AMB group, L-AMB treatment was initiated at 5.6 ± 6.1 days from septic shock onset. In both groups, over 60% of patients switched to L-AMB from other antifungal drugs, the majority of

which used echinocandins, such as micafungin and caspofungin, before L-AMB treatment initiation. The proportion of patients treated with voriconazole or itraconazole was higher in the early L-AMB group than the delayed L-AMB group (30% vs 15%, $P = 0.038$). This might be partly attributed to the higher presence of patients with aspergillosis in the early L-AMB group. In total, 35% of patients initiated IFI treatment before septic shock onset (early L-AMB group 47% of subjects; delayed L-AMB group 26% of subjects; $P = 0.013$). For patients administered IFI treatment before septic shock onset, no difference in the duration from IFI treatment initiation to septic shock was found between those in the early (12.9 ± 12.7 days, N = 28) and delayed L-AMB groups (9.7 ± 16.3 days, N = 21, $P = 0.478$).

3.2. Comparison of survival rates after septic shock onset

Survival rates at 4 weeks (68.4% vs 57.9%, $P = 0.197$), 6 weeks (62.2% vs 44.5%, $P = 0.061$), and 12 weeks (43.4% vs 35.0%, $P = 0.168$) after septic shock onset were higher in the early L-AMB group than the delayed L-AMB group, albeit without statistical significance (Fig. 2; Table 2). Sensitivity analysis revealed that survival rates did not significantly differ between patients whose L-AMB treatment was initiated within a day after septic shock onset and those whose treatment was initiated on and after two days following the onset; and patients whose L-AMB treatment was initiated within the two days after septic shock onset and those whose treatment was initiated on and after three days following the onset (Supplementary Table 1).

3.3. Comparison of septic shock cessation period

The septic shock cessation period was shorter in the early L-AMB group (7.0 ± 7.0 days, median: 4.5 days) than the delayed L-AMB group (16.5 ± 15.4 days, median: 12.0 days, $P < 0.001$) (Table 3). To balance the patient characteristics, propensity score matching was performed according to a multiple logistic regression model using 14 covariates related to prognosis in patients with septic shock and 3 covariates with a significant difference between the early and delayed L-AMB groups in patient characteristics (treatment with azoles for aspergillosis before the

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6,640 patients
Patients administered L-AMB during hospitalization between April 2008 and January 2018

Inclusion criteria	Exclusion criteria
• Patients with septic shock who were treated with catecholamine • L-AMB treatment initiation at or after the onset of septic shock • Carbapenems administration at the onset of septic shock	• Age <18 • Average daily dose of L-AMB >6 mg/kg body weight • Lack of required data (body weight/outcome) • <5 days of L-AMB duration • L-AMB administration before the onset of septic shock • L-AMB treatment initiation after 4 weeks of the onset of septic shock • No fungal infection test within 7 days before starting L-AMB treatment

141 study patients

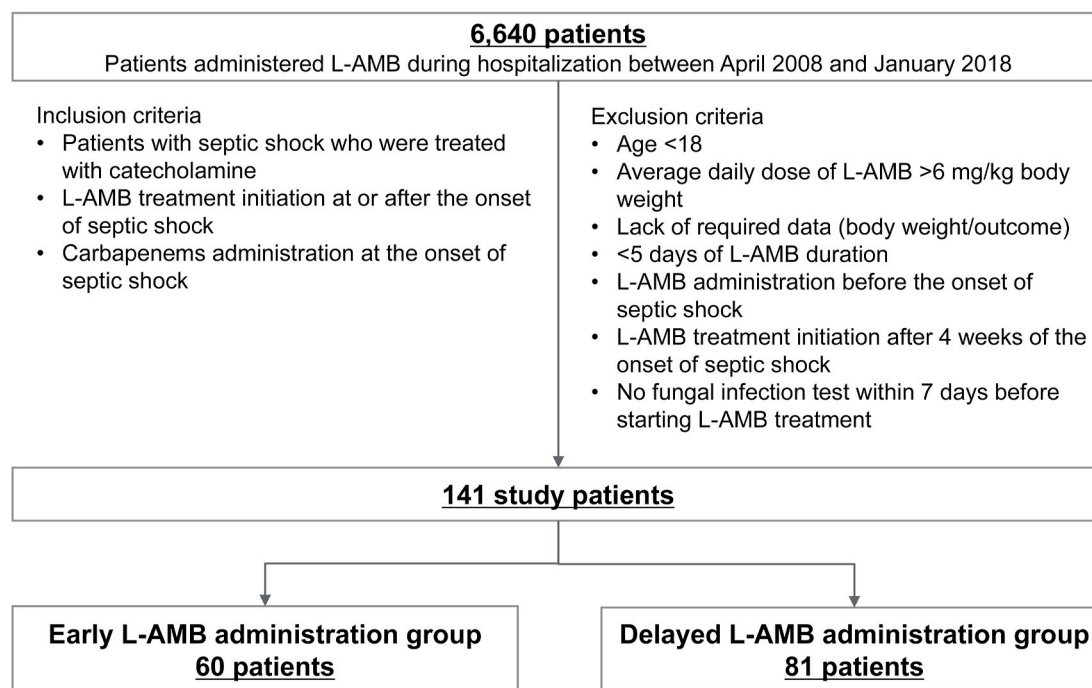| **Early L-AMB administration group** **60 patients**	**Delayed L-AMB administration group** **81 patients**

Fig. 1. Flow chart for patient selection.
L-AMB, liposomal-amphotericin B.

Table 1
Characteristics of septic shock patients administered early or delayed L-AMB.

Patient characteristics	Overall (N = 141)	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	P-value
Age (years)	68.4 ± 13.5	65.3 ± 13.5	70.7 ± 13.0	0.020
Sex, male (%)	90 (64%)	37 (62%)	53 (65%)	0.724
Preexisting comorbid conditions				
CCI	3.7 ± 3.1	4.4 ± 3.3	3.2 ± 2.9	0.035
Malignant tumor (%)	75 (53%)	36 (60%)	39 (48%)	0.176
G-CSF treatment for neutropenia (%)	29 (21%)	16 (27%)	13 (16%)	0.143
Corticosteroid (≥0.3 mg/kg/day Prednisolone) (%)	62 (44%)	33 (55%)	29 (36%)	0.027
T cell immunosuppressants	35 (25%)	21 (35%)	14 (17%)	0.019
Diabetes mellitus with insulin treatment (%)	32 (23%)	12 (20%)	20 (25%)	0.548
Gastrointestinal surgery within 30 days (%)	12 (9%)	2 (3%)	10 (12%)	0.071
CV catheter (%)	100 (71%)	47 (78%)	53 (65%)	0.133
Interventions				
ICU admission (%)	39 (28%)	14 (23%)	25 (31%)	0.348
Renal replacement therapy (%)	43 (30%)	12 (20%)	31 (38%)	0.026
Mechanical ventilation (%)	56 (40%)	24 (40%)	32 (40%)	1.000
CV catheter replacement within the following day (%)	22 (16%)	11 (18%)	11 (14%)	0.487
L-AMB administration				
Average daily dosing (mg/kg)	2.9 ± 1.0	2.9 ± 1.0	2.9 ± 1.0	0.919
Duration (days)	15.7 ± 13.9	18.2 ± 16.6	13.8 ± 11.2	0.081
L-AMB administration initiation after the onset of septic shock (days)	3.2 ± 5.4	0.0 ± 0.0	5.6 ± 6.1	NA
Initiation of IFI therapy before the onset of septic shock[a]	49 (35%)	28 (47%)	21 (26%)	0.013
Antifungal drug treatment before the initiation of L-AMB therapy (%)[b]				
Overall	90 (64%)	39 (65%)	51 (63%)	0.860
Echinocandin (micafungin, caspofungin)	69 (49%)	27 (45%)	42 (52%)	0.496
Azole not for Aspergillosis (fluconazole)	17 (12%)	8 (13%)	9 (11%)	0.795
Azole for Aspergillosis (itraconazole, voriconazole)	30 (21%)	18 (30%)	12 (15%)	0.038
Treatment department (%)				
Hematology	46 (33%)	27 (45%)	19 (23%)	0.011
The internal department (except for Hematology)	63 (45%)	26 (43%)	37 (46%)	0.864
The surgical department	27 (19%)	5 (8%)	22 (27%)	0.005
Others[c]	2 (1%)	0 (0%)	2 (2%)	0.508
Unknown	3 (2%)	2 (3%)	1 (1%)	0.575
Diagnosis (%)				
Aspergillosis	31 (22%)	19 (32%)	12 (15%)	0.023
Candidiasis	17 (12%)	9 (15%)	8 (10%)	0.436
Others[d]	29 (21%)	9 (15%)	20 (25%)	0.207
Unknown[e]	65 (46%)	24 (40%)	41 (51%)	0.235

Abbreviations: CCI, Charlson comorbidity index; CV, central venous; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit; L-AMB, liposomal-amphotericin B, NA, not analyzed.
Categorical variables were presented as frequencies and proportions (%), while continuous variables were expressed as mean ± standard deviation. Welch's *t*-test was employed to compare two groups for continuous variables, while Fisher's exact test was used for two categorical variables.

[a] IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval of ≥2 days. This period included the date of L-AMB therapy initiation.

[b] Oral and injection antifungal drugs were evaluated.

[c] Other treatment department included anesthesiology and emergency medicine.

[d] Other diagnoses included cryptococcosis, zygomycosis, coccidioidomycosis, blastomycosis, maduramycosis, and unclassified or unspecified mycoses.

[e] Unknown diagnosis included patients without any mycosis diagnosis and those with neutropenia.

initiation of L-AMB therapy, surgical department, and aspergillosis) (Table 1). Following propensity score matching, no difference was observed in patient characteristics between the early and delayed L-AMB groups (Supplementary Table 2). We confirmed shorter septic shock cessation period in the early L-AMB group (7.1 ± 7.2 days, median: 3.0 days, N = 36) than in the delayed L-AMB group (16.7 ± 14.0 days, median: 12.5 days, N = 36; P = 0.001) (Table 3). Sensitivity analysis demonstrated that the septic shock cessation period was significantly shorter in patients administered early L-AMB treatment within a day after septic shock onset or within two days after the onset than in patients administered late treatment (Supplementary Table 3).

4. Discussion

Herein, we found early initiation of L-AMB treatment at septic shock onset was associated with short septic shock cessation period. However, this association may not imply causation, because patients with shock caused by non-IFI causes, such as bacterial infections or hypovolemic shock, might be included in subjects analyzed in the study. Importantly, the timing of L-AMB treatment was not associated with mortality during septic shock treatment: survival rates during septic shock treatment were similar between the early and delayed L-AMB groups (Fig. S1). This finding may imply that a risk of mortality during septic shock treatment increases regardless of the timing of L-AMB administration as duration of septic shock treatment is prolonged. Therefore, early L-AMB treatment at septic shock onset, which is associated with short septic shock cessation period, as a consequence might be linked to decreased mortality during septic shock treatment.

Patients analyzed in this study may include patients with various IFIs and those without IFIs. However, cases that were not tested for fungus were excluded, and patients without the possibility of IFI were not included. Several studies have revealed that early initiation of antifungal drug administration improves the outcome of patients with candidiasis [7,8]. Our findings demonstrate that the timing of L-AMB administration may affect the prognosis of septic shock in a population with confirmed cases and empirical situations. The impact of such results on clinical practice is significant as the diagnosis cannot be confirmed in clinical practice in many situations.

Because the backgrounds of patients in the early and delayed L-AMB groups differed markedly in this study, we carefully conducted propensity score matching to adjust for confounding factors. For example, the proportion of patients treated in the hematology department was higher in the early L-AMB group, whereas the proportion of patients treated in the surgical department was higher in the delayed L-AMB group. We were mainly concerned that the difference in the overall management ability for IFIs between hematologists accustomed to treating IFIs and surgeons unfamiliar with IFIs may have influenced the difference in the septic shock cessation period between the two groups. Therefore, we calculated propensity scores using the covariates related to the attribute (hematology), immunosuppression state (e.g., neutropenia treated with G-CSF), and risk factors of poor treatment outcome of candidiasis (e.g., CV catheter replacement). Collectively, we revealed the association between early L-AMB initiation and short septic shock cessation period.

However, the difference in survival rates four weeks after septic shock onset did not reach statistical significance between the groups. These results align with prior findings: crude mortality at 30 days following positive blood culture is associated with age, RRT, intubation, and primary source, but not with prompt proper antifungal treatment [10]. As the septic shock cessation period was 9 days (median) in all patients, septic shock might have already improved in many patients within four weeks after septic shock onset. However, these patients may have died from primary diseases that were unaffected by L-AMB treatment, as many patients with IFI have a serious background illness and often have a poor prognosis.

If early L-AMB administration improves the prognosis of IFI-induced
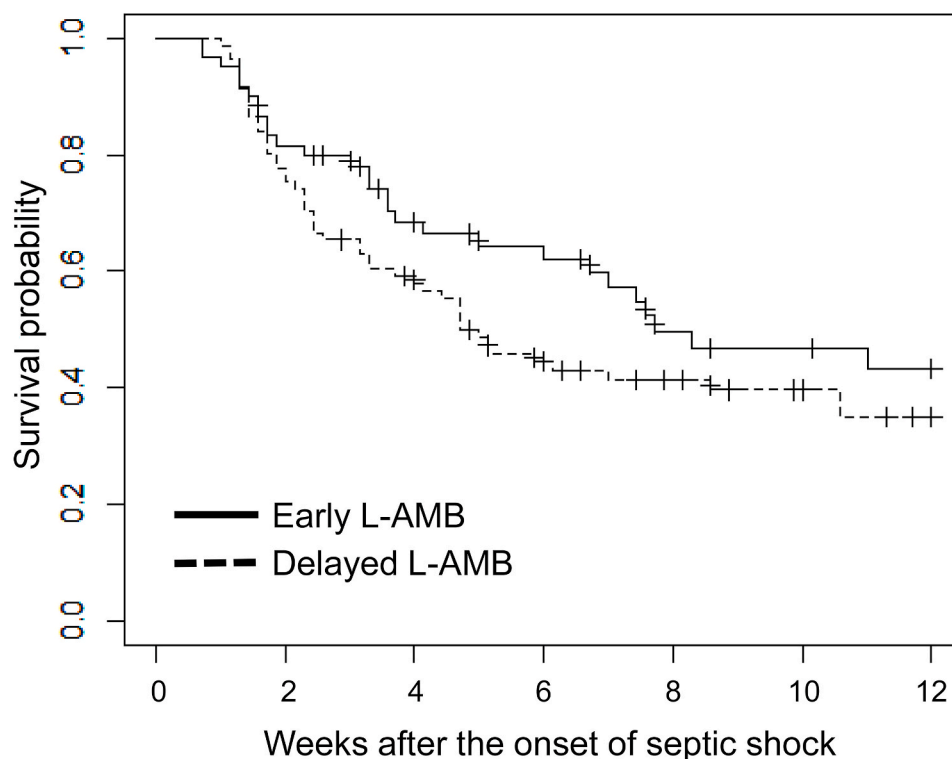
Fig. 2. Kaplan-Meier survival curve for septic shock patients administered early or delayed L-AMB.
L-AMB, liposomal-amphotericin B.

Table 2
Survival rates for patients administered early or delayed L-AMB after septic shock onset.

Weeks after the onset of septic shock	Survival rates (%, 95% CI)		P-value
	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	
4 weeks	68.4% (57.2–81.7%)	57.9% (48.0–69.7%)	0.197
6 weeks	62.2% (50.5–76.6%)	44.5% (34.8–57.0%)	0.061
12 weeks	43.4% (30.7–61.2%)	35.0% (25.1–48.7%)	0.168

Abbreviations: CI, confidence interval; L-AMB, liposomal-amphotericin B.

Table 3
Septic shock cessation period for patients administered early or delayed L-AMB before and after propensity score matching.

	No adjustment			After propensity score matching		
Septic shock cessation period (days)	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	p-value	Early L-AMB (N = 36)	Delayed L-AMB (N = 36)	p-value
AVE ± SD	7.0 ± 7.0	16.5 ± 15.4	<0.001	7.1 ± 7.2	16.7 ± 14.0	0.001
Median	4.5	12.0		3.0	12.5	

Abbreviations: AVE, average; L-AMB, liposomal-amphotericin B; SD, standard deviation.
The septic shock cessation period was presented as average ± standard deviation. Welch's *t*-test was used to compare two groups without adjustment, while paired Student's *t*-tests were performed to compare two groups after propensity score matching.

septic shock, early administration of other antifungal drugs could also improve the prognosis. In the delayed L-AMB group, although 38% (31/81) of patients were treated with antifungal drugs except for L-AMB at septic shock onset, the septic shock cessation period in those patients (19.1 ± 17.3 days) was longer than in patients administered L-AMB at septic shock onset (7.0 ± 7.0 days, P < 0.001). These results suggest that early L-AMB initiation may be particularly important.

Sixty four percent of patients were switched from other antifungal drugs to L-AMB, suggesting that a switch to L-AMB is effective even for septic shock antifungal treatment. This switching might be partly attributed to insufficient treatment outcomes of other antifungal drugs. Echinocandin-resistant *Candida* has been reported [20]; echinocandins are not used as first-line drugs against invasive pulmonary aspergillosis and are ineffective for pulmonary mucormycosis [21]. Therefore, early

L-AMB initiation might be beneficial, especially for septic shock patients whose target fungus has not been identified or in patients infected with a drug susceptibility-unconfirmed fungus.

Clinicians in the hematology department, but not the surgical department, may initiate L-AMB administration at septic shock onset, suggesting that sufficient experience with L-AMB treatment is required for prompt treatment initiation. Both hematologists and physicians who are familiar with the use of L-AMB are infectious disease specialists. In cases of septic shock with possible IFI, physician intervention for an

infectious disease on the day of onset may improve prognosis.

This study had several limitations. First, several data could not be obtained from the database. Indicators of infectious severity, such as acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA), were not evaluated because respiratory or cardiovascular parameters were not included in the database. Alternatively, we opted to calculate the propensity score using variables related to ICU admission, RRT, and detailed patient characteristics to validate the reliability of our results. As source control was not evaluated using CV catheter removal, we opted to evaluate replacement instead of CV catheter removal. As the results of fungal infection tests or blood culture tests could not be obtained, we could not distinguish definitive or presumed antifungal infection or could not exclude patients with blood stream infections caused by bacteria to avoid the influence of bacterial infections on outcome. Second, owing to the retrospective nature of this analysis, prospective studies are required to verify the results. A retrospective analysis might be suitable for evaluating the efficacy of early L-AMB initiation in septic shock patients owing to the difficulty involved in conducting a prospective study. Finally, because a comparative study with non-L-AMB treatment cases was not carried out, the characteristics of septic shock cases that should be treated with L-AMB were not captured. Further studies are needed to further identify patients requiring L-AMB treatment.

In conclusion, early L-AMB administration at septic shock onset may be associated with early shock cessation.

Author contributions

Study conception and design: M.T. Data analysis: A.T. Interpretation of data: all authors. Manuscript drafting: M.T. and A.T. Study supervision: all authors. Final approval for submission: all authors.

Declaration of interest

K.I. received honorarium and research grant from Sumitomo Dainippon Pharma Co., Ltd. T.W. is a full-time employee of Sumitomo Dainippon Pharma Co., Ltd. A.T. and K.S. are full-time employees of Deloitte Tohmatsu Consulting LLC. Deloitte Tohmatsu Consulting LLC receives consulting fees from Sumitomo Dainippon Pharma Co., Ltd.

Authorship statement

All authors meet the ICMJE authorship criteria.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.06.013.

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