

Original Article

Galápagosization of sepsis management in Japan: a nationwide survey of current practices

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Aim: Sepsis treatment has been standardized in many countries worldwide. However, treatment of sepsis in Japan has developed independently, and how Japanese physicians actually treat sepsis patients nationwide remains uninvestigated. The aim of this study was to clarify the current practice for septic patients in Japan and how it differs from standard care throughout the world.

Methods: This study was designed as a prospective, cross-sectional, self-reported questionnaire- and Web-based electronic survey in Japan. The survey was undertaken to assess respondents' clinical practices and preferences regarding treatment strategies, sepsis assessment, and management in the setting of critical illness. An exploratory factor analysis and a hierarchical cluster analysis were carried out to identify the treatments distinctive to Japan, called "Galápagos therapies".

Results: The final analysis included 295 respondents. According to the factor analysis, we defined anticoagulant therapy for disseminated intravascular coagulation, antimediator renal replacement therapy, and others as Galápagos therapies. These Galápagos therapies were undertaken by approximately two-thirds of the Japanese physicians who responded. We classified Japanese physicians according to three patterns of clinical practice carried out for sepsis: (i) those who do not perform Galápagos therapies but do perform worldwide standardized care, (ii) those who perform Galápagos therapies on top of worldwide standardized care, (iii) those who do not perform worldwide standardized care.

Conclusion: On the basis of a nationwide questionnaire-based survey in Japan, we clarified distinctive sepsis treatments performed in Japan, such as antimediator renal replacement therapy and treatment for sepsis-induced disseminated intravascular coagulation.

Key words: Disseminated intravascular coagulation, professional practice, renal replacement therapy, sepsis, Surviving Sepsis Campaign

INTRODUCTION

SEPSIS IS A serious life-threatening syndrome affecting patients of all ages.¹ Due to worldwide activity since

the first Surviving Sepsis Campaign Guideline (SSC Guideline) was published in 2004,² sepsis treatment has been standardized in many countries. In that context, a measure called the SEP-1 (Sepsis CMS Core Measure) protocol³ was approved in the USA, and presently, it must be applied to all septic patients without exception. The obligation consists of so-called standard care including lactate checking, blood culture, treatment with antibiotics, fluid resuscitation, volume/perfusion assessment, and other care within the specific time periods for sepsis and septic shock. Levy *et al.* reported from the results of their survey that the SSC was associated with sustained, continuous quality improvement in sepsis care and that a reduction in reported hospital

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mortality rates was associated with participation in the campaign.⁴

However, there are no therapies for sepsis that are strongly supported by the evidence aside from the basic supportive ones that comprise standardized care, and this is why decision-making by physicians on the spot is of importance. Because only limited evidence exists on supportive care in sepsis, it is understandable that the methods of treating sepsis patients can differ from country to country, from facility to facility, and from physician to physician. Furthermore, in Japan, unlike in the USA,³ there are no measures enforcing physicians to follow any set protocols. Adjunctive interventional therapies on top of basic standardized care have tended to independently evolve in the islands around the Far East. For example, renal replacement therapy for non-renal indications⁵ is one of the major adjunctive interventions. Likewise, endotoxin removal with polymyxin B-immobilized fiber column is another adjunctive intervention developed in Japan.⁶ The concept of these therapies is based on the presumed elimination of the elevated inflammatory mediators, such as cytokines and endotoxins, by dialysis, hemofiltration, or adsorption. Also, anticoagulation therapies for sepsis-induced disseminated intravascular coagulation (DIC)⁷ are major adjunctive interventions. The concept of this therapy is inhibition of the overactivated coagulation cascade by natural anticoagulants such as antithrombin⁸ and recombinant thrombomodulin.⁹ Most of these therapies were developed in Japan, however, many of them are not supported by strong evidence. What is unique in Japan is that these therapies are both feasible and are covered by Japanese universal health insurance due to laws permitting the physician's choice of treatment.¹⁰

Thus, clinical practice for sepsis in Japan has developed independently from elsewhere in the world, but at present, no research has defined Japanese-specific treatments, nor investigated how Japanese physicians actually treat sepsis patients nationwide. We call these Japanese-specific treatments “Galápagos therapies” after the Galápagos Islands. In this research, we aimed to clarify current practice in the care of septic patients in Japan and how it differs from the standardized care practiced around the world.

METHODS

Study design

THIS STUDY WAS designed as a prospective, cross-sectional, self-reported questionnaire- and Web-based electronic survey in Japan. This quantitative survey was

undertaken as a part of a post-publication survey of the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSC Guidelines 2016).¹¹ The survey aimed to assess respondents' clinical practices and preferences with regard to treatment strategies, sepsis assessment, and management in the setting of critical illness.

Setting and participants

All surveys were completed over a 3-week period from 13 February, 2018 to 4 March, 2018. All members of the Japanese Society of Intensive Care Medicine ($n = 9295$) and the Japanese Association for Acute Medicine ($n = 9629$) were invited to participate in the survey by e-mail and the official homepages of the societies. The participants responded to the questionnaire anonymously by the Internet, and duplicate responses were avoided by IP address control. Following confirmation of eligibility, participants completed the online survey in approximately 20 min.

This study was exempt from institutional review board approval as the survey procedures did not elicit private, protected information or biological specimens, and responses were recorded in a way that did not link back to the physicians who completed the survey.

Questionnaire and data processing

A questionnaire (Table S1) was prepared to evaluate the management preferences and patterns of sepsis in Japan. The questions in the survey were designed to address management approaches to sepsis and sepsis-related conditions as described in both the SSC¹² and J-SSC Guidelines¹¹ and other conventional and unconventional approaches such as infection control, initial resuscitation for sepsis/septic shock, renal replacement therapy, adjunctive sepsis interventions such as i.v. immunoglobulins¹³ and anticoagulant therapies for DIC, and management of sedation and delirium. Responses were classified on a four-point Likert scale, according to the recommendation of the GRADE system¹⁴ applied in the SSC guidelines, with “almost always” indicating the situation selected more than 90% of the time, “most of the time” indicating approximately 70%, “sometimes” indicating approximately 30%, and “never” indicating less than 10% of the time. Demographic information (post-graduate year, department, board-certificated specialty, and the number of sepsis patients treated monthly) was also requested.

Statistical analysis

First, a descriptive analysis of the main variables of interest was undertaken. Then an exploratory factor analysis¹⁵ was

carried out using a maximum likelihood solution method with promax rotation.¹⁶ The latent root criterion¹⁷ was used to decide the number of factors extracted, and factors having eigenvalues greater than 1 were considered significant. The Kaiser–Meyer–Olkin (KMO) test was applied to measure the strength of the relationship between variables. The KMO values greater than 0.7 are acceptable, and values between 0.8 and 0.9 indicate a strong relationship.¹⁸ Factor loadings >0.3 were retained. If an item loaded equally on two factors, we dropped the item from the scales. Finally, means, standard deviations, and the internal consistency of the items were calculated for the factors that resulted from factor analysis. We also calculated interfactor correlations.

Following factor analysis, a hierarchical cluster analysis¹⁹ was applied using factor scores to identify the pattern of physicians' preferences. Visual inspection of the dendrogram was done to indicate the number of clusters that should be considered. The final number of clusters was determined by evaluating the characteristics of the physicians' preferences within the practical number of clusters. Bar charts were used to display characteristics of interest between clusters. All statistical analyses were

undertaken in SPSS version 25.0 (IBM, Armonk, NY, USA). A *P*-value of ≤ 0.05 was considered statistically significant.

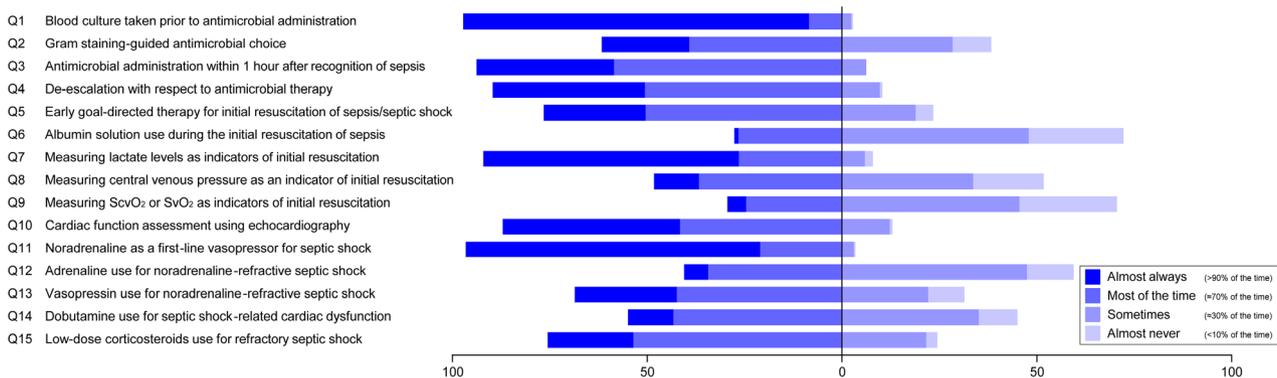
RESULTS

Descriptive statistics

A SUMMARY OF the demographic data of the 295 participants (1.6% of all members of the two societies) is shown in Table S2. The years of clinical experience ranged widely. The main department to which the participants belonged and their specialty was emergency medicine, followed by intensive care. The majority of participants (81%) reported caring for between ≤ 5 or 5–10 sepsis patients per month.

Figure 1 shows the treatment preferences of all participants. The response pattern varied for each question, for example, almost all respondents answered positively to question 1 (Q1; blood culture taken) but mainly negatively to Q6 (albumin use).

(A) Infection control and hemodynamic management



(B) Adjunctive management in sepsis

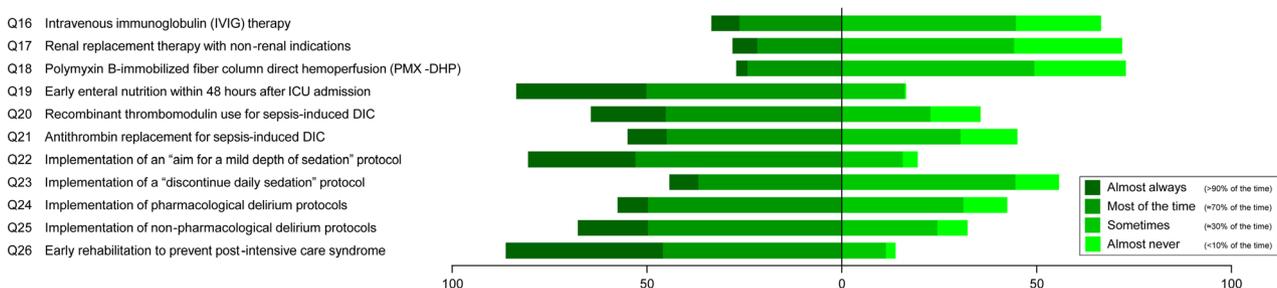


Fig. 1. Treatment preferences of all respondents in sepsis management. A, Preferences in infection control and hemodynamic management. B, Preferences in adjunctive management in sepsis. DIC, disseminated intravascular coagulation; ICU, intensive care unit.

Exploratory factor analysis

An exploratory factor analysis was carried out to explore the underlying structure of the physicians' preferences in sepsis management. The sample was appropriate for this analysis, as indicated by both the KMO measure of sampling adequacy of 0.759 and Bartlett's test of sphericity significance level ($\chi^2 = 1313.2$; $P < 0.001$). Finally, a five-factor solution with 20 items was chosen (Table 1).

Factor 1, consisting of five items, was named "Galápagos sepsis interventions in Japan". Similarly, factors 2–5, consisting of five, five, two, and three items, respectively, were named "Management of pain, agitation, and delirium", "Initial shock resuscitation with international consensus", "Old-fashioned hemodynamic assessment", and "Infection management under controversy", respectively. There was seldom interfactor correlation between factor 1 (Galápagos sepsis interventions) and factor 3 (initial shock resuscitation with international consensus) (Table 2). On the basis of this result, we interpreted the items in factor 1 to be the treatment options that evolved in the eastern islands of Japan independently from the world, as did the creatures living and evolving in the Galápagos Islands.

Cluster analysis and characteristics of each cluster

Three clusters were identified and contained between 36 and 192 participants. The preferences in representative sepsis managements in each cluster are shown in Figures 2 and 3. Cluster 1 consisted of 36 participants who did not have preferences against Galápagos sepsis interventions and tended to choose management methods with international consensus. In contrast, cluster 2, comprising 71% of all participants, chose treatment options of the Galápagos sepsis interventions and management with international consensus. Cluster 3 comprised the group who did not tend to perform or less frequently performed management with international consensus, suggesting that the participants in this group might not be familiar with sepsis management.

DISCUSSION

RENAL REPLACEMENT THERAPY for non-renal indications, endotoxin removal with polymyxin B-immobilized fibers, anticoagulation therapy for sepsis-induced DIC, i.v. immunoglobulin therapy, and other techniques

Table 1. Factor loadings for retained items using principal axis factoring and promax rotation

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Antithrombin replacement for sepsis-induced DIC	0.789	−0.209	0.200	0.001	0.007
Recombinant thrombomodulin use for sepsis-induced DIC	0.739	−0.139	0.025	−0.157	0.053
Polymyxin B-immobilized fiber column direct hemoperfusion	0.471	0.136	−0.242	0.152	0.045
Intravenous immunoglobulin therapy	0.466	0.025	−0.051	0.157	−0.239
Renal replacement therapy for non-renal indications	0.462	0.286	−0.199	0.220	0.004
Implementation of non-pharmacological delirium protocols	−0.100	0.667	−0.017	−0.070	−0.025
Implementation of pharmacological delirium protocols	0.068	0.608	−0.059	−0.040	−0.117
Implementation of a "discontinue daily sedation" protocol	−0.159	0.544	0.069	0.099	0.037
Early rehabilitation to prevent post-intensive care syndrome	0.013	0.482	−0.021	−0.078	0.216
Implementation of an "aim for a mild depth of sedation" protocol	0.071	0.402	0.296	−0.149	0.075
Measuring lactate levels as an indicator of initial resuscitation	−0.048	−0.106	0.648	0.125	0.019
Cardiac function assessment with echocardiography	−0.069	−0.038	0.589	0.140	−0.017
Low-dose corticosteroids use for refractory septic shock	−0.003	0.024	0.477	−0.079	−0.196
Vasopressin use for noradrenaline-refractive septic shock	0.032	0.145	0.475	−0.058	0.090
Noradrenaline as a first-line vasopressor for septic shock	0.156	0.132	0.334	−0.122	0.329
Measuring central venous pressure as an indicator of initial resuscitation	0.048	−0.124	0.109	0.770	−0.001
Measuring ScvO ₂ or SvO ₂ as an indicator of initial resuscitation	−0.002	−0.011	0.017	0.769	0.151
Albumin solution use during the initial resuscitation of sepsis	0.035	0.237	0.269	0.072	−0.642
De-escalation with respect to antimicrobial therapy	−0.043	0.103	0.160	0.263	0.487
Gram staining-guided antimicrobial choice	0.034	0.195	0.024	0.080	0.312

DIC, disseminated intravascular coagulation.

Table 2. Intersubscale correlations derived from the five-factor solution

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Factor 1: Galápagos sepsis interventions in Japan	1.000	0.007	0.003	0.444	-0.301
Factor 2: Management of pain, agitation, and delirium		1.000	0.435	0.078	0.144
Factor 3: Initial shock resuscitation with international consensus			1.000	-0.120	0.379
Factor 4: Old-fashioned hemodynamic assessment				1.000	-0.413
Factor 5: Infection management under controversy					1.000

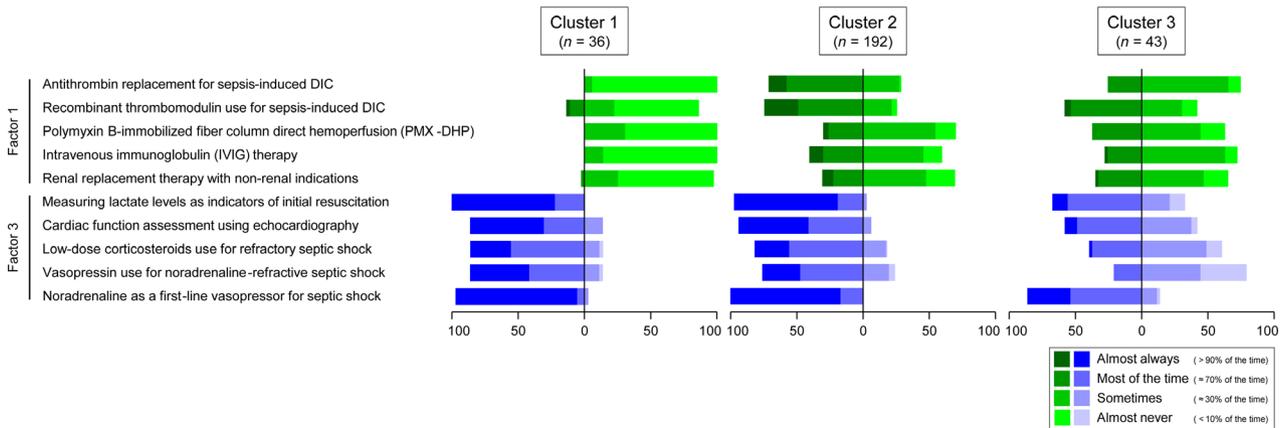


Fig. 2. Preferences on Galápagos sepsis interventions in Japan varied between clusters of physicians. DIC, disseminated intravascular coagulation.

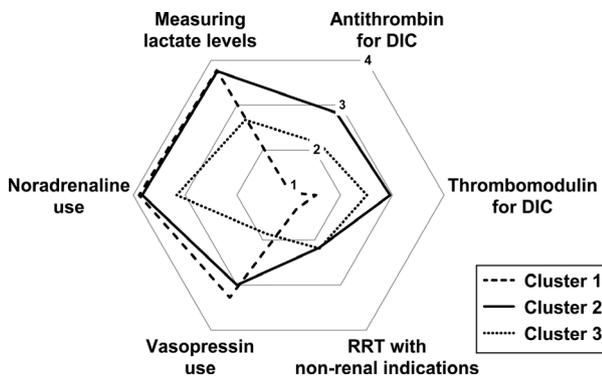


Fig. 3. Radar chart of three physicians' clusters for both Galápagos sepsis interventions and worldwide standardized sepsis care. Factor scores range from 1 point for the non-preferred to 4 points for the most preferred care. For each cluster, the mean scores of the six types of care are shown. DIC, disseminated intravascular coagulation; RRT, renal replacement therapy.

are actively used as adjunctive treatments of sepsis by approximately two-thirds of the physicians in Japan who responded to this survey. Although these interventions lack

strong evidence and, therefore, are not standard care around the world, they are referred to in the J-SSC Guidelines 2016. In fact, the direction of strength of the recommendations in the J-SSC Guidelines 2016 differs partly from those of the SSC Guidelines 2016. In this article, we defined them as Galápagos therapies and advocate their unique clinical concept.

The results on current practice in Japan indicate that three clinical preference patterns were recognized: the group that follows worldwide standardized care without Galápagos therapies (Fig. 2, cluster 1), the group that follows worldwide standardized care and also practices Galápagos therapies (Fig. 2, cluster 2), and the group that does not follow worldwide standardized care (Fig. 2, cluster 3). In particular, among those who follow worldwide standardized care, two distinctive groups were detected: those who prefer Galápagos therapies and those who do not undertake Galápagos therapies. This result implies that the decision to use Galápagos therapies, which do not have strong evidence showing that they improve outcome, is independent of properly carrying out the worldwide standardized care, which means that the

Galápagos therapies are thought to be culturally original to Japan.

Along with worldwide standardized care for sepsis, physicians in cluster 2 also carry out Galápagos therapies as a bundle, whereas physicians in cluster 1 never use these additional therapies. The clinical pattern of the physicians in cluster 1 is considered to be equivalent to standard worldwide clinical practice, whereas the clinical pattern of the physicians in cluster 2 is considered distinctively Japanese. According to epidemiological research, the treatment outcomes of sepsis in Japan are relatively good compared to those in other developed countries when taking the super-aging society of Japan into consideration;²⁰ however, the reason for this remains unclear. Performance of these Galápagos therapies as a bundle might be one of the reasons for the better outcomes. However, whether Galápagos therapies are beneficial cannot be evaluated solely from the results of the present analysis. Evaluation of the effectiveness of the Galápagos therapies will require detailed analysis of the data on a patient level. Thus, this research is intended only to clarify the current practice of treating patients with sepsis in Japan.

We acknowledge several limitations in this analysis. First, because this questionnaire was submitted through unidentifiable email, and thus not all facilities in Japan were comprehensively investigated, it is possible that the present results do not completely reflect the clinical practice in Japan. There is a possibility that volunteer bias has occurred. Second, the questionnaire does not cover some important questions on sepsis management, such as respiratory care, because the J-SSC Guideline does not cover such topics. Finally, the questionnaire response rate is quite small; only 1.6% of the targeted members of the two societies responded. Otherwise, this questionnaire-based analysis would appear to be the most feasible way of clarifying the current practice in Japan.

CONCLUSION

ON THE BASIS of the responses to a nationwide questionnaire-based survey in Japan, we defined distinctive Japanese sepsis treatments, such as antimediator renal replacement therapy and sepsis-induced DIC treatment, as Galápagos therapies. Although Galápagos therapies were preferred and carried out in a bundle by approximately two-thirds of the Japanese physicians who responded, those preferences were independent from whether they used worldwide standardized care. Future research to clarify the benefit of bundled Galápagos interventions is warranted.

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DISCLOSURE

Approval of the research protocol: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Study questionnaire translated into English. DIC, disseminated intravascular coagulation; ICU, intensive care unit; IVIG, i.v. immunoglobulin; PMX-DHP, polymyxin B hemoperfusion.

Table S2. Characteristics of the respondents.