Original Article

JHSMR Journal of Health Science and Medical Research

Efficacy of a Modified Sepsis System on the Mortality Rate of Septic Shock Patients in the Emergency Department of Siriraj Hospital

Natvadee Rakpraisuthepsiri, B.S.[1], Usapan Surabenjawong, M.D.[2], Chok Limsuwat, M.D.[2], Ploylarp Lertvipapath, M.Sc.[3]

[1]Outpatient Pharmacy Division, Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Bangkok Noi, Bangkok 10700, Thailand.
[2]Department of Emergency Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Noi, Bangkok 10700, Thailand.
[3]Adverse Drug Reaction Unit, Division of Academic Affairs, Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Noi, Bangkok 10700, Thailand.

Received 31 October 2021 ● Revised 21 December 2021 ● Accepted 27 December 2021 ● Published online 21 February 2022

Abstract:

Objective: To compare the 28-day mortality rate between pre- and post-implementation of a modified sepsis fast-track system.

Material and Methods: A cross-sectional cohort study was conducted at the Emergency Room (ER) of Siriraj Hospital, Bangkok. All patients who were diagnosed with septic shock and who received antimicrobial treatment at admission in the ER were included.

Results: In total, 420 patients were included in the study, split into 210 patients in the pre-protocol group and 210 patients in the post-protocol group. Comparing between pre- and post-modified sepsis fast-track system implementation, the patients who received antimicrobials within 1 hour numbered 140 (66.7%) and 175 (83.3%), respectively (OR 2.5, 95% CI 1.57–3.97, p-value<0.001). The 28-day mortality rates of the pre- and post-protocol groups were 44.8% vs. 34.8% (p-value=0.036). According to the multivariate analysis, the factors that were significantly related to 28-day mortality in patients with septic shock were age greater than 75 years, diabetes mellitus, and initial SOFA score ≥9.

Conclusion: Implementation of a modified sepsis program improved the time to first antimicrobial administration and decreased the 28-day mortality for patients with septic shock in the ER.

Keywords: antimicrobials, sepsis program modification, septic shock

Contact: Ploylarp Lertvipapath, M.Sc.
Adverse Drug Reaction Unit, Division of Academic Affairs, Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Noi, Bangkok 10700, Thailand.
E-mail: ploylarpl@gmail.com

J Health Sci Med Res 2022;40(5):543-550
doi: 10.31584/jhsmr.2022865
www.jhsmr.org

Introduction

Sepsis is a potentially life-threatening condition that causes multi-organ dysfunction through the dysregulated host response to infection. Organ dysfunction can be defined by the Sequential Organ Failure Assessment (SOFA) score, in which a higher score is associated with a greater in-hospital mortality rate.[1] Sepsis remains one of the major global health burdens in terms of morbidity, mortality, and resource utilization. In 2017, an estimated 48.9 million incident of sepsis were recorded worldwide and 11.0 million sepsis-related deaths were reported, representing 19.7% of all global deaths.[2] In Thailand, the mortality rate of sepsis and septic shock are 34.3% and 52.6% that higher than the global data.[3]

Early resuscitation and hemodynamic support, especially the early initiation of appropriate antimicrobials, are important strategies to improve the outcome of sepsis patients.[4] The administration of antimicrobials should be done as soon as possible after diagnosis.[1] Each hour of delayed administration of antimicrobials increases the risk of death. One study reported that the mortality rate among patients who received antimicrobials within 1 hour post-diagnosis was statistically significantly lower than in patients who had antimicrobial therapy initiated 6 hour or more post-diagnosis (24.6% and 33.1%, respectively, p-value< 0.001).[5]

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] The Surviving Sepsis Campaign's 2021 international guidelines for management of sepsis and septic shock recommend that appropriate antimicrobial therapy should be administered immediately, ideally within 1 hour post-diagnosis to septic shock or possible septic shock patients.[6,7]

Despite strong evidence suggesting that the early initiation of appropriate antimicrobial treatment within 1 hour is associated with a lower mortality rate, in our setting, data on the initiation of appropriate antibiotic treatment within 1 hour post-diagnosis are quite limited. Indeed, the time lapsed from diagnosis to initiation of appropriate antimicrobial treatment can often be several hours due to the complicated drug-ordering system in our institution. When a patient was diagnosed with septic shock, the doctor prescribed an antimicrobial and sent the prescription to a pharmacist. Then, the pharmacist would complete the prescription, take payment, and dispense the medicine before the drug could be administered to the patient. For the purpose of reducing the drug administration time, the researchers implemented a new fast-track sepsis system with an aim to shorten the process and time, as shown in Figure 1. To ensure the quality of this system, the researchers conducted a study at Siriraj Hospital where this new system was tried in order to assess the reduction, if any, in 28-day mortality after the system implementation.

Material and Methods

The study design was a cross-sectional cohort study which aimed to measure the impact of a modified sepsis protocol on the mortality rate in an ER from septic shock and sepsis. The study was conducted at ER of Siriraj Hospital in Bangkok, Thailand. The modified protocol (Figure 1) was implemented in December 2018. Participants were enrolled from the ER. Relevant data were obtained from the medical records and computerized system of the hospital for patients diagnosed with septic shock. The inclusion criteria were patients aged at least 18 years who were diagnosed with septic shock and who received antimicrobials in the ER. The exclusion criteria were patients who received antimicrobials before entering the ER. This study was approved by the Siriraj Institutional Review Board. After treatment and discharge from the ER, our study collected hospital outcomes including mortality in hospital and 28-day mortality.

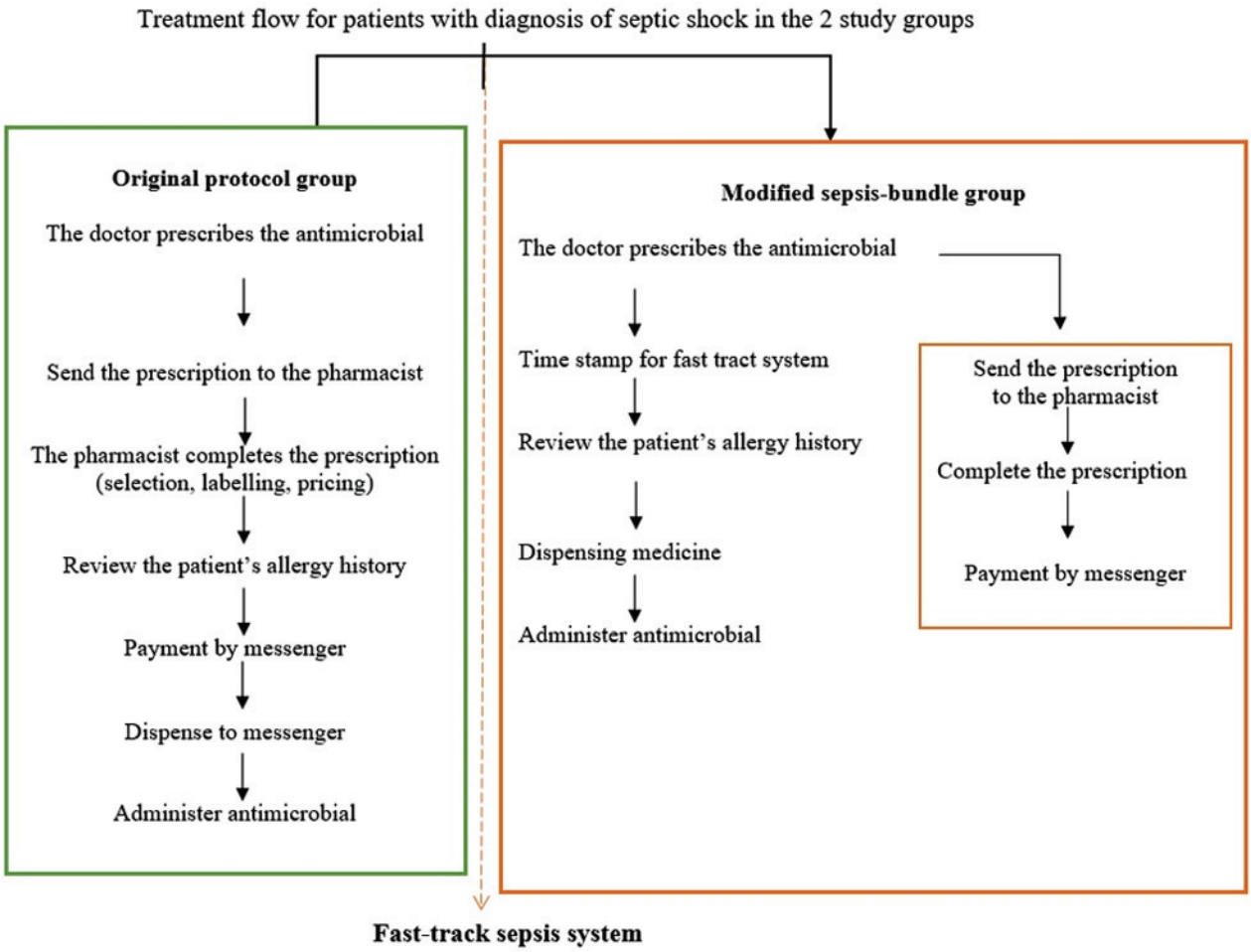

Figure 1 Fast-track sepsis system modification compare with previous sepsis

The modified sepsis protocol is a new dispensing system which is aimed to reduce the antimicrobials administration time. To shorten the process, the new protocol cut off and payment process by using the parallel track. After the fast track is stamped, the attending staff would carefully order for empirical antimicrobials and send the prescription to the pharmacist. The allergy reviewing and antimicrobial prescribing would be done immediately. At the same time, the parallel payment process would be done by the relatives of the patient.

Septic shock was defined as persistent hypotension requiring a vasopressor to maintain mean arterial pressure ≥65 mmHg despite adequate volume resuscitation.

Appropriate empirical antimicrobial therapy was defined based on the following parameters:

1. Empirical antimicrobial therapy was administered within the time limit of 1 hour.

2. First empirical antimicrobial dosage was delivered as a full dose.

3. The dose and frequency of the empirical antimicrobial administration were adjusted in patients with renal insufficiency.

4. De-escalating antimicrobial was administered at a certain dose, and then possible the dose was lowered.

Mortality rate referred to all-cause mortality. We collected this data from the in-patient and follow up documentation.

The primary outcome was the 28-day mortality rate compared between the two study periods (pre- and post-protocol implementation). The secondary outcomes were the appropriateness of antimicrobial use, the in-hospital mortality rate, the rate of systemic inflammatory response syndrome (SIRS) resolution, and factors associated with the 28-day mortality.

The sample size was calculated based on the mortality rate, as reported in 2018 in Siriraj Hospital. The researchers predicted that the sepsis program modification would reduce the mortality rate by 10.0%. After calculation, the sample size of 420 patients was considered sufficient for achieving 80.0% power, with a significance level (alpha) of 0.05.

Descriptive data, which are the categorical data, are reported by number and percentage. The continuous data are presented as median and interquartile range (IQRs). Chi-square and Mann–Whitney U test were used to compare differences between the groups. SPSS® version 22.0 for Windows® was used for the statistical analysis, descriptive analysis, and inferential analysis. The statistical significance level was defined as p-value<0.050.

Results

In total, 420 patients were included in this study, comprising 210 patients in the pre-protocol period group and 210 in the post-protocol period. The baseline characteristics of the overall patients are shown in Table 1. The median age was 73±21 years and 51.4% were male. Most of the patients were from a community setting. When comparing between the 2 groups, although the patients who were in the post-protocol group, i.e., post-implementation of the fast-track sepsis system, had a lower median SOFA score, they had higher numbers of patients with renal disease, respiratory and cardiovascular failure (Table 1). The most common source of infection in both groups was pneumonia. The post-implementation group had higher rates of urinary tract and intra-abdominal infections. In addition, we found no differences in specimen blood culture data between the previous and modified systems (35.9% vs 39.7%, p-value=0.463). The utilization of a vasopressor for shock resuscitation was not different between the 2 groups (139 vs 134 cases in the pre- and post-protocol groups, respectively). Moreover, we found no differences in vasopressor usage between the previous and modified systems. When specific name of vasopressor, norepinephrine and epinephrine showed different between pre-protocol and post-protocol (66.5% vs 63.5%, p-value =0.562). In the subgroup of intra-abdominal infection, we found no difference in the numbers of patients requiring surgery between the previous and modified systems (13.4% vs 23.1%, p-value=0.181).

For the primary outcome, the 28-day mortality rate was 34.8% in the post-protocol group against 44.8% in the pre-protocol group, which was significantly lower (p-value= 0.036). The in-hospital death in the post-protocol group was also lower than in the pre-protocol group (p-value= 0.011), although the SIRS resolution was not statistically different between the 2 groups (Table 2).

Regarding the appropriateness of the antimicrobial administration in the study, the researchers found that

success in achieving antibiotics administration within 1 h was 83.3% in the post-protocol group, which was significantly higher (OR 2.5, 95% CI 1.57–3.97, p-value<0.001) than in pre-protocol group. We found that the loading antimicrobial dose administered in the post-protocol group was higher than in the pre-protocol group (OR 3.05, 95% CI 1.26–7.38, p-value=0.010). The adjusted renal dose was also higher number of patients in the post-protocol group (70.5 vs. 82.4%, p-value=0.004). Only the results from de-escalation of the antimicrobial administration were higher in the pre-protocol sepsis group (Table 3).

The univariate analysis factors associated with 28-day mortality were age >75 years, liver disease, diabetes mellitus, SOFA score ≥9, Fast-track Sepsis Program administration, adjusted renal dose, and de-escalation of antimicrobial administration (Table 4).

Table 1 Baseline characteristics of the study patients

Characteristic	Total No. (%) (n=420)	Previous system No. (%) (n=210)	Modified system No. (%) (n=210)	p-value
Male	216 (51.4)	117 (55.7)	99 (47.1)	0.079
Age (median±IQR)	73±21	73±24	73±20	
<65	145 (34.5)	85 (40.5)	60 (28.6)	
65–80	171 (40.7)	85 (40.5)	86 (41.0)	0.007
>80	104 (24.8)	40 (19.0)	64 (30.5)	
Habitation				
Home	385 (91.7)	205 (97.6)	183 (87.1)	<0.001
Nursing care	35 (8.3)	5 (2.4)	27 (12.9)	
Underlying disease				
DM	148 (35.2)	71 (33.8)	77 (36.7)	0.540
Cardiovascular disease	115 (27.4)	51 (24.3)	64 (30.5)	0.155
Renal disease	108 (25.7)	42 (20.0)	66 (31.4)	0.007
Liver disease	68 (16.2)	35 (16.7)	33 (15.7)	0.791
Immunosuppressive drug				
Corticosteroids	14 (3.3)	4 (1.9)	10 (4.8)	0.103
Immunoglobulin suppressant	5 (1.2)	0 (0.0)	5 (2.4)	0.204
Vasopressor	273 (65.2)	139 (66.5)	134 (63.5)	0.562
Norepinephrine	261 (95.6)	128 (49.0)	133 (50.1)	
Dopamine	3 (1.1)	2 (1.4)	1 (0.7)	
Epinephrine	9 (3.3)	9 (6.5)	0	
Source of infection				
Respiratory tract	141 (33.6)	66 (31.4)	75 (35.7)	0.352
Urinary tract	106 (25.2)	40 (19.0)	66 (31.4)	0.003
Intra-abdominal	121 (28.8)	82 (39.0)	39 (18.6)	<0.001
Specimen blood culture	135 (38.1)	52 (35.9)	83 (39.7)	0.463
qSOFA score ≥2	309 (73.6)	166 (79.0)	143 (68.1)	0.011
SOFA score (median+IQR)	5±2	6±2	3.5±2	
SOFA ≥9	54 (12.9)	42 (20.0)	12 (5.7)	<0.001
Organ failure				
Renal	46 (11.0)	19 (9.0)	27 (12.9)	0.271
Respiratory	18 (4.3)	3 (1.4)	15 (7.1)	0.004
Cardiovascular	16 (3.8)	3 (1.4)	13 (6.2)	0.011
Liver	15 (3.6)	6 (2.9)	9 (4.3)	0.430

DM=diabetes mellitus, qSOFA=quick Sequential Organ Failure Assessment, SOFA=Sequential Organ Failure Assessment, IQR=interquartile range

Table 2 Association between the fast track sepsis system and the clinical outcomes

Clinical outcome	Total No. (%) (n=420)	Previous system No. (%) (n=210)	Modified system No. (%) (n=210)	OR (95% CI)	p-value
28-day mortality	167 (39.8)	94 (44.8)	73 (34.8)	0.658 (0.444-0.974)	0.036
In-hospital death	147 (35.0)	86 (41.0)	61 (29.0)	0.59 (0.394-0.888)	0.011
Resolution of SIRS					
No	97 (23.1)	53 (25.2)	44 (21.0)	1.27	0.297
Yes	323 (76.9)	157 (74.8)	166 (79.0)	(0.808-2.008)	

SIRS=systemic inflammatory response syndrome

Table 3 Appropriateness of the antimicrobial therapy in the study

Antimicrobial criteria	Total No. (%) (n=420)	Previous system No. (%) (n=210)	Modified system No. (%) (n=210)	OR (95% CI)	p-value
Antimicrobial within 1 hour	315 (75.0)	140 (66.7)	175 (83.3)	2.5 (1.57-3.97)	<0.001
Loading dose administration	393 (93.6)	190 (90.5)	203 (96.7)	3.053 (1.26-7.38)	0.010
Adjusted renal dose					
No	99 (23.6)	62 (29.5)	37 (17.6)	1.959	0.004
Yes	321 (76.4)	148 (70.5)	173 (82.4)	(1.23-3.11)	
De-escalation of antimicrobial use	280 (79.1)	157 (96.3)	123 (64.4)	0.69 (0.03-0.17)	0.001

Table 4 Univariate analysis of the factors associated with 28-day mortality

Factor	Total (%) (n=420)	Death (%) (n=167)	Univariate logistic regression	
			OR (95% CI)	p-value
Age >75 years	186	89 (47.8)	1.84 (1.24-2.73)	0.003
Liver disease	68	40 (58.8)	2.53 (1.49-4.29)	0.001
Diabetes	148	73 (49.3)	1.84 (1.23-2.77)	0.003
SOFA score ≥9	54	33 (61.1)	2.72 (1.51-4.89)	0.001
Fast-track sepsis program				
Pre	210	94 (44.8)	0.66	0.037
Post	210	73 (34.8)	(0.44-0.97)	
Adjusted renal dose	198	80 (40.4)	0.53 (0.34-0.84)	0.007
De-escalation of antimicrobial use	280	81 (28.9)	0.45 (0.27-0.77)	0.003

SOFA=Sequential Organ Failure Assessment

Table 5 Multivariate analysis of factors associated with clinical outcomes on 28-day mortality

Factor	Total (%) (n=420)	Survived (%) (n=253)	Deceased (%) (n=167)	OR (95% CI)	p-value
Age >75 years	186	97 (52.2)	89 (47.8)	2.08 (1.36-3.19)	0.001
Diabetes	148	75 (50.7)	73 (49.3)	2.02 (1.32-3.11)	0.001
SOFA score ≥9	54	21 (38.9)	33 (61.1)	3.73 (1.94-7.19)	<0.001

SOFA=Sequential Organ Failure Assessment

Following multivariate analysis, the factors that were related to the 28-day mortality were age >75 years, diabetes mellitus, and SOFA score ≥9 (Table 5).

Discussion

The modified sepsis system that the researchers helped introduce in Siriraj Hospital to attempt to increase the rate of within 1 hour antimicrobial administration decreased the 28-day and in-hospital mortality rates significantly. The results are compatible with previous studies which found that appropriate antimicrobial therapy were associated with a survival rate of 50.0-80.0%.[7,8] Our data strongly support the findings of these studies, that the initiation of antimicrobial administration within 1 hour was associated with a substantially decreased mortality rate in patients with septic shock.

Other than the Surviving Sepsis Campaign international consensus guideline recommendation of beginning effective antimicrobial therapy within the first hour[9], a previous study also found that each hour of delayed antimicrobial therapy after a patient developed hypotension was associated with an average decrease in survival of 7.6%.[7] In addition, Gaieski et al. found that antimicrobial administration within 1 hour showed a statistically significant associated decrease in the mortality rate of 13.7% and the time from qualification for early goal-directed therapy to antimicrobial administration within 1 hour showed a statistically significant associated decrease in mortality rate of 13.5%.[10]

The intervention of the fast-track sepsis program is a new method in our institution, which aims to improve the pharmacist service to make it more lean and able to hasten the speed of delivery of antimicrobial administration. This modification has lead to better treatment and fewer delays. After the intervention, the achievement rate of meeting the target time of within 1 hour antimicrobial administration was 83.3%, which was higher than with the previous system. Besides improved clinical outcomes, the 28-day mortality was also significantly decreased. This could imply that the availability of this fast-track sepsis system led to better clinical outcomes in patients with septic shock.

According to the multivariate analysis, the factors pertaining to a higher mortality rate were age greater than 75 years, diabetes mellitus, and SOFA score greater than 9. These findings are similar to previous studies, which reported that higher age, more underlying diseases, and higher SOFA scores were related to poor outcomes[1]. However, the modified fast-track system is not the only direct factor that leads to better survival, as a patient may receive the antimicrobial therapy faster, there are many factors that are important for survival, for example, the severity of their disease.

The strength of this study is its prospective design. There were no missing data in the outcomes that we were interested in studying. The other benefit is its generalizability. Although the data were from a single center, the study was conducted in the Emergency Department, which has a population of both medical and surgical patients. These are the same types of patients which can be found in other hospitals in Thailand. Thus, they could apply this system to their hospitals too.

A limitation of this study to note is the absence of resuscitation data, which is be an important factor relating to the survival of septic shock patients. However, Siriraj Hospital is a high-quality university hospital and we believe that the standard of treatment was not different between our 2 groups. Another limitation of this study is that the post-protocol group had lower SOFA scores when compared with the pre-protocol group, which could have impacted the mortality of the primary outcome. Further investigations with larger populations are needed to identify the power of the new protocol.

Conclusion

This study illustrates the potential advantages of implementing a fast-track sepsis program modification. A fast-track sepsis had the effect of decreasing the initiation time of antimicrobial therapy, resulting in decreased in-hospital and 28-day mortality rates of septic shock patients in our study. However, further studies are needed to prove these clinical benefits.

Acknowledgement

The authors are grateful to the patients of the Emergency Department, Siriraj Hospital, who participated in this study.

Conflict of interest

There are no potential conflicts of interest to declare.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:801-10.
2. Rudd KE, Johnson SC AK, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. Lancet 2020;395:200-11.
3. Angkasekwinai N, Rattanaumpawan P, Thamlikitkul V. Epidemiology of sepsis in Siriraj Hospital 2007. J Med Assoc Thai 2009;92:S68-78.
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy collaborative group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
5. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749-55.
6. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181–247.
7. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.
8. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.
9. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit Care Med 2018;46:997-1000.
10. Gaieski DF, Pines JM, Band RA, Mikkelsen ME, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38:1-9.