Original Article

Outcomes of Clinical Practice Guideline for Sepsis Patients in Taksin Hospital

Supunnee Jirajariyavej MD[1], Apichot So-Ngern BSc[2], Terapong Tantawichien MD[3], Rapeepan Soomhirun RN[4]

[1] Department of Medicine, Taksin Hospital, Bangkok, Thailand

[2] Faculty of Pharmacy, Siam University, Bangkok, Thailand

[3] Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[4] Department of Nursing, Taksin Hospital, Bangkok, Thailand

Background: Sepsis is a serious disease with a high mortality rate.

Objective: To study the effect of a Clinical Practice Guideline [CPG] on mortality for sepsis patient management in Thailand.

Materials and Methods: The design was a retrospective study. The medical records of 472 severe sepsis or septic shock patients treated prior to and after the hospital sepsis CPG implementation in hospital were reviewed.

Results: Four hundred seventy-two patients were eligible for enrollment. The mortality rate was statistically significant different among studied patients in pre-implementation period (43.6%) and implementation period (13.1%) (p<0.001). There was statistically higher percentage of patients who received antibiotics within the first hours of being diagnosed with sepsis in implementation period (97.9%), compared with pre-implementation period (74.2%) (p<0.001). The significant higher numbers of patients in implementation period having enough volume replacement within the first six hours of severe sepsis or septic shock diagnosis compared with in pre-implementation period, as measured by an adequate urine output (≥0.5 ml/kg/hour) (84.6% versus 73.8%) (p = 0.018), and by an adequate central venous pressure (8 to 12 mmHg) (82.4% versus 43.3%) (p<0.001). In addition, there were significant difference in the percentages of patients having a reversal of septic shock in pre-implementation and implementation period (94.8% versus 88.4%) (p = 0.02).

Conclusion: An implementation of the sepsis CPG in secondary-care hospital led to increase appropriate management and decrease mortality among the severe sepsis patients.

Keywords: Severe sepsis, Septic shock, Clinical practice guideline for sepsis

J Med Assoc Thai 2018; 101 (8): 1115-20
Website: http://www.jmatonline.com

Sepsis is a serious disease with high mortality rate (44% to 54%)[1,2]. The present study showed early hemodynamic resuscitation after diagnosis with severe sepsis or septic shock led to lower organ dysfunction together with lower in-hospital mortality rates[3]. Delay in administering appropriate antibiotic also affected risk of death for these patients[4,5]. In 2012, the International Guidelines for Management of Severe Sepsis and Septic Shock has recommended hemodynamic resuscitation to be provided within the first six hours of diagnosis of severe sepsis or septic shock with administration of appropriate antibiotics for these patients within the first hour[6]. The goals of early hemodynamic resuscitation are to provide adequate central venous pressure (8 to 12 mmHg) with urine output of 0.5 ml/kg/hour or more, alongside reversal of shock (a mean arterial pressure greater than 65 mmHg), and adequate oxygenation measured by superior vena cava oxygenation saturation greater than 70% or mixed venous oxygen saturation greater than 65%[6]. Based on the previous studies published in 2014, there was no statistical difference in the mortality rate between patients receiving usual care and patients receiving protocol treatment for early hemodynamic resuscitation[7,8]. Moreover, it was found that there was no morality benefit from the early administration of appropriate antibiotics[9,10]. The recommended guideline for quality improvement of sepsis care has been implemented by many health-care institutions[11-13]. Castellanos-Ortega et al[13] reported that the implementation of a guideline for management of septic shock patients significantly lowered mortality

Correspondence to:

Jirajariyavej S. Department of Medicine, Taksin Hospital, 543 Somdet Chao Phraya Road, Khlong San, Bangkok 10600, Thailand.
Phone: +66-2-4370123
Email: jsupunee@yahoo.com

How to cite this article: Jirajariyavej S, So-Ngern A, Tantawichien T, Soomhirun R. Outcomes of clinical practice guideline for sepsis patients in Taksin Hospital. J Med Assoc Thai 2018;101:1115-20.

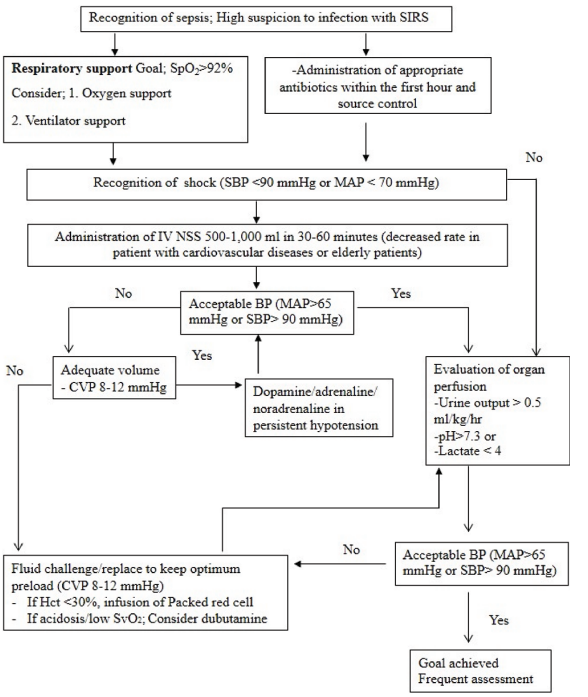
rate, however, this conclusion was controversial[11-13]. As mentioned above, the mortality benefit from compliance to the recommendation of the guideline has conflicting results. The authors' modified Clinical Practice Guideline [CPG] for Sepsis was implemented for management of sepsis and septic shock patients in our hospital in January 2014. This was a retrospective study aiming to compare the mortality rate between pre- and post-implementation of CPG for sepsis management in secondary-care hospital.

Materials and Methods

This retrospective study was conducted at the Taksin Hospital, a 461-bed hospital in Bangkok, Thailand. The medical charts of hospitalized patients aged more than 15 years who met criteria for severe sepsis or septic shock between January 2012 and August 2015 were reviewed. The data from the patient's medical records and an electronic database were collected for age, sex, source of infection, past medical history within three months, vital signs, laboratory tests, management of sepsis including time to diagnosis, initial antibiotic administration, adequate volume replacement, reversal of septic shock, and mortality at the end of treatment. Those patients who had incomplete data were excluded. The protocol for the present study was approved by Bangkok Metropolitan Administration Ethics Committee for Human Research (No. S018h/58_EXP).

The sepsis patients were divided into two groups. The first group was sepsis patients admitted between January 2012 and December 2013 treated with routine care, which was treatment by clinical decision of the physician (pre-implementation period). The second group was sepsis patients who received treatment with modified CPG for Sepsis (as shown in Figure 1) admitted between January 2014 and August 2015 (implementation period).

Sepsis was defined as a patient having systemic inflammatory response syndrome [SIRS] with or without presence of positive blood culture for bacteria. Those patients having SIRS met at least two criteria. SIRS criteria included body temperature lower than 36°C or greater than 38°C, heart rate greater than 90 bpm, respiratory rate greater than 20 bpm, white blood cell counts lower than 4,000 cells/mm³ or greater than 12,000 cells/mm³. Severe sepsis was defined as a patient with sepsis as defined previously, and with failure of at least one organ system. Septic shock was defined as a patient who met criteria for severe sepsis who had a low blood pressure that persisted despite



SIRS = systemic inflammation response syndrome, IV NSS = intravenous normal saline, SpO_2 = peripheral oxygen saturation, SBP = systolic blood pressure, mmHg = millimeter of mercury, MAP = mean arterial pressure, BP = blood pressure, CVP = central venous pressure, ml/kg/hour = milliliter per kilogram per hour, Hct = Hematocrit, SvO_2 = venous oxygen saturation

Figure 1. Clinical Practice Guideline [CPG] for Sepsis.

treatment with intravenous fluids. A low blood pressure was defined as a systolic blood pressure of less than 90 mmHg or a mean arterial pressure of less than 70 mmHg. All terms were defined by the International Guidelines for Management of Severe Sepsis and Septic Shock[6].

The primary outcome was in-hospital mortality. The secondary outcomes were the patient receiving appropriate the hemodynamic resuscitation within the first six hours of recognition of severe sepsis or septic shock and appropriate antibiotics being administered within the first hour of being diagnosed with sepsis. The goals of hemodynamic resuscitation were an adequate urine output (0.5 ml/kg/hour or more), an adequate central venous pressure (8 to 12 mmHg) and reversal of septic shock. The reversal of septic shock was defined as maintaining a systolic blood pressure of more than 90 mmHg or a mean arterial pressure of more than 65 mmHg.

Statistical analysis

The authors assumed a mortality rate of 44%

before implementation of the CPG[1]. The authors also had a goal of mortality rate after implementation of sepsis CPG of 31%[4]. The numbers of sepsis patients were calculated by a two-sided type 1 error (α) of 0.05 with a power of 80%. The authors allowed 10% for incomplete patient data. Therefore, 472 patients, randomized at 1:1 for before and after the implementation of sepsis CPG were recruited in the present study. Descriptive statistics were used to describe studied variables. Categorical variables were compared using the Pearson Chi-square test or Fisher's exact test. Continuous variables were compared using Student t-test or the Kruskal-Wallis test. To investigate the relationship between independent variables and mortality rate, univariate analysis was performed with the Pearson Chi-square test. Variables with a *p*-value of less than 0.05 on univariate analysis were included in the multivariate analysis Multivariate analysis was carried out using a logistic regression model. A *p*-value of less than 0.05 was considered statistically significant. SPSS for Windows (version 20 software package; SPSS Inc., Chicago, III) was used for statistical analysis.

Results

Of 472 patients, 56.8% were male and the mean age of patients was 66.6 years old. A summary of baseline characteristics is shown in Table 1. Most of sepsis patients (76.3%) had a community acquired infections. The three most common primary causes of sepsis were pneumonia (56.4%), urinary tract infection (24.6%), and intra-abdominal infection (13.3%). Twenty-four-point-eight percent of our patients had bacteremia at the time of sepsis diagnosis. Furthermore, the patients had a serum creatinine higher than 1.5 mg/dl (48.2%), acute respiratory failure (24.8%), and a platelet count of less than 150,000/microliter (23.8%). Pneumonia, urinary tract infection, and intra-abdominal infection were the common infections in sepsis patients before and after sepsis CPG implementation. However, pneumonia as a primary cause of sepsis was significantly more common in pre-implementation period (61.4% versus 51.3%; $p = 0.026$) and urinary tract infection was significantly more common in implementation period (33.1% versus 16.1%; $p<0.001$). There were significantly higher numbers of patients with hospital-acquired infection, septic shock, and acute respiratory failure in pre-implementation period than implementation period as shown in Table 1.

The outcomes of the present study are shown in Table 2. The mortality rates in implementation period of our CPG (13.1%) were significantly lower than pre-implementation period (43.6%) ($p<0.001$). There was statistically higher percentage of patients who received antibiotics within the first hour of being diagnosed with sepsis in implementation period (97.9%), compared

Table 1. Baseline characteristics

Baseline characteristics	Total (n = 472)	Pre-implementation period (n = 236)	Implementation period (n = 236)	*p*-value*
Male (%)	56.8	60.6	53.0	0.094
Age (year), mean (SD)	66.6 (16.4)	65.9 (17.0)	67.2 (15.8)	0.357
Bacteremia (%)	24.8	25.4	24.2	0.749
Diagnosis of patient (%)				
Severe sepsis	54.7	50.0	59.3	0.042
Septic shock	45.3	50.0	40.7	0.042
Type of infection (%)				
Community acquired infections	76.3	61.4	91.1	<0.001
Hospital acquired infections	23.7	38.6	8.9	<0.001
Primary diagnosis (%)				
Pneumonia	56.4	61.4	51.3	0.026
Urinary tract infection	24.6	16.1	33.1	<0.001
Intra-abdomen infection	13.3	15.3	11.4	0.223
Soft tissue and skin infection	4.4	4.7	4.2	0.823
Central nervous system infection	1.3	2.5	0.0	N/A
Status of patients at the time of diagnosis (%)				
Serum creatinine >1.5 mg/dl	48.2	50.9	45.3	0.557
Platelet <150,000/μl	23.8	28.8	18.3	0.169
Acute respiratory failure	24.8	33.5	16.1	<0.001

N/A = the variable cannot evaluate *p*-value; mg/dl = milligram per deciliter; μl = microliter

**p*-value compared between pre-implementation period of the Clinical Practice Guideline [CPG] and implementation period of the CPG

with pre-implementation period (74.2%) (p<0.001). A significant higher number of patients in implementation period received enough volume replacement within the first six hours of severe sepsis or septic shock diagnosis compared with the pre-implementation period, as measured by an adequate urine output (0.5 ml/kg/hour or more) (84.6% versus 73.8%) (p = 0.018), and by an adequate central venous pressure (8 to 12 mmHg) (82.4% versus 43.3%) (p<0.001). The authors also found that 94.8% of sepsis patients in CPG implementation period had a reversal of septic shock (maintain systolic blood pressure greater than 90 mmHg or a mean arterial pressure greater than 65 mmHg) compared with 88.4% of sepsis patients in pre-implementation period (p = 0.02). Of all sepsis patients, the authors investigated independent variables associated with mortality. The significant risk factors are shown in Table 3. On multivariate analysis, the risk factors significantly protective against death were patients having an adequate urine output within the first six hours of recognition of severe sepsis or septic shock (adjusted odds ratio [aOR] 0.108, 95% confidence interval [CI] 0.047 to 0.252; p<0.001), and patients who received appropriate antibiotics within the first hours of being diagnosed with sepsis (aOR 0.190, 95% CI 0.003 to 0.109; p<0.001).

Discussion

The present study revealed that the mortality rate in sepsis patients decreased after sepsis CPG implementation in hospital. The implementation of sepsis CPG in clinical practice led to an absolute mortality difference of 30.5%. The authors' results corresponded to previous studies that reported mortality decreased after implementation of the sepsis guideline[12-14]. Most of these studies had a high baseline mortality rate[12-14]. Moreover, the sepsis patients who were treated with our sepsis CPG received an appropriate management of sepsis (such as early appropriate antibiotic administration and adequate volume replacement within the first six hours) as standard care for sepsis. The authors know that inappropriate and delayed antibiotics administration in severe sepsis had high probability of leading to death[4,5]. In multivariate analysis, the findings showed that early appropriate antibiotics led to reduce mortality as in previous reports. Thus, the authors strongly recommend early appropriate antibiotics to all sepsis

Table 2. Clinical outcomes between pre-implementation period of the Clinical Practice Guideline [CPG] and implementation period of the CPG

Outcomes	Pre-implementation period (n = 236)	Implementation period (n = 236)	p-value*
In-hospital mortality (%)	43.6	13.1	<0.001
Administration appropriate antibiotic within the first hour of being diagnosed with sepsis (%)	74.2	97.9	<0.001
The goal of hemodynamic resuscitation within the first 6 hours of recognition of severe sepsis or septic shock (%)			
Patients having an adequate central venous pressure (8 to 12 mmHg)	43.3	82.4	<0.001
Patients having an adequate urine output (≥0.5 ml/kg/hour)	73.8	84.6	0.018
Patients having a reversal of septic shock	88.4	94.8	0.020

mmHg = millimeter of mercury; ml/kg/hour = milliliter per kilogram per hour

Table 3. Univariate and multivariate analysis of independent variables associated mortality rate

Independent variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Hospital acquired infections	3.259 (2.086 to 5.091)	<0.001	1.385 (0.521 to 3.684)	0.514
Patients having acute respiratory failure at the time of diagnosis	1.775 (1.138 to 2.767)	0.011	2.311 (0.943 to 5.661)	0.067
Patients having an adequate central venous pressure (8 to 12 mmHg) within the first 6 hours of recognition of diseases	0.531 (0.216 to 1.308)	0.165	-	-
Patients having an adequate urine output (≥0.5 ml/kg/hour) within the first 6 hours of recognition of diseases	0.079 (0.040 to 0.156)	<0.001	0.108 (0.047 to 0.252)	<0.001
Patients having a reversal of septic shock within the first 6 hours of recognition of diseases	0.226 (0.105 to 0.485)	<0.001	0.610 (0.202 to 1.844)	0.381
Patients who received appropriate antibiotic within the first hour of being diagnosed with sepsis	0.007 (0.002 to 0.027)	<0.001	0.190 (0.003 to 0.109)	<0.001

mmHg = millimeter of mercury; ml/kg/hour = milliliter per kilogram per hour

Diseases are severe sepsis or septic shock

patients. Hospital-acquired infections cause high mortality rate in sepsis patients and may impact the high mortality rate in pre-implementation period[15]. The multivariate analysis showed that hospital-acquired infection was not a risk factor associated with death.

In addition, the results found the factor associated with survival was patients who achieved adequate urine output (of 0.5 ml/kg/hour or more) within the first six hours of recognition of severe sepsis or septic shock. Other studies reported that delays in diagnosis and in initial hemodynamic resuscitation led to multiple organ failure and death[2,3]. Therefore, early hemodynamic resuscitation is an important strategy to reduce mortality rate in sepsis patients as reported in many studies[16,17].

The limitation was study design. Because the study design was a retrospective study, the outcome might have been affected by other confounding variables. Confounding variables were severity of disease, co-morbid conditions, or data of intensive care unit admission was not collected. Further study need to be a well-controlled study to investigate the outcome of a CPG on mortality. In conclusion, the implementation of a modified sepsis CPG significantly lowered mortality rate and improved the standard of care for sepsis patient in hospital.

What is already known on this topic?

The International Guidelines for Management of Severe Sepsis and Septic Shock has recommended hemodynamic resuscitation to be provided within the first six hours of diagnosis of severe sepsis or septic shock with administration of appropriate antibiotics for these patients within the first hour. Castellanos-Ortega et al[13] reported that the implementation of a guideline for management of septic shock patients significantly lowered mortality rate. However, Orford et al[11] reported implementation of the guideline for management of patients with severe sepsis and septic shock, failed to significantly lower mortality rate. As previously mentioned, the conclusions were controversial.

What this study adds?

Post-implementation of the CPG at hospital significantly decreased mortality rate. The CPG led to an absolute mortality difference of 30.5%. The authors' results corresponded to previous studies that reported mortality decreased after implementation of the sepsis guideline. Most of these studies had a high baseline mortality rate. The risk factors significantly protective against death were patients having an adequate urine output within the first six hours of recognition of severe sepsis or septic shock, and patients who received appropriate antibiotics within the first hour of being diagnosed with sepsis. The results support appropriate management of sepsis (such as early appropriate antibiotic administration and adequate volume replacement within the first six hours) as standard care for sepsis.

Acknowledgement

The authors would like to thank the physicians who cared for all the study patients as well as the patients themselves.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Degoricija V, Sharma M, Legac A, Gradiser M, Sefer S, Vucicevic Z. Survival analysis of 314 episodes of sepsis in medical intensive care unit in university hospital: impact of intensive care unit performance and antimicrobial therapy. Croat Med J 2006;47:385-97.
2. Blanco J, Muriel-Bombin A, Sagredo V, Taboada F, Gandia F, Tamayo L, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit Care 2008;12:R158.
3. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
4. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, 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;38:1045-53.
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. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

7. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
8. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.
9. Bloos F, Thomas-Ruddel D, Ruddel H, Engel C, Schwarzkopf D, Marshall JC, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care 2014;18:R42.
10. Yokota PK, Marra AR, Martino MD, Victor ES, Durao MS, Edmond MB, et al. Impact of appropriate antimicrobial therapy for patients with severe sepsis and septic shock--a quality improvement study. PLoS One 2014;9:e104475.
11. Orford NR, Faulkner C, Flintoff W, Eddey D, Lamb-Jenkins J, Henry M, et al. Implementation and outcomes of a severe sepsis protocol in an Australian tertiary hospital. Crit Care Resusc 2008;10:217-24.
12. Girardis M, Rinaldi L, Donno L, Marietta M, Codeluppi M, Marchegiano P, et al. Effects on management and outcome of severe sepsis and septic shock patients admitted to the intensive care unit after implementation of a sepsis program: a pilot study. Crit Care 2009;13:R143.
13. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Holanda MS, Ortiz F, Llorca J, et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Crit Care Med 2010;38:1036-43.
14. Barochia AV, Cui X, Vitberg D, Suffredini AF, O'Grady NP, Banks SM, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med 2010;38:668-78.
15. Sheng WH, Chie WC, Chen YC, Hung CC, Wang JT, Chang SC. Impact of nosocomial infections on medical costs, hospital stay, and outcome in hospitalized patients. J Formos Med Assoc 2005; 104:318-26.
16. Coba V, Whitmill M, Mooney R, Horst HM, Brandt MM, Digiovine B, et al. Resuscitation bundle compliance in severe sepsis and septic shock: improves survival, is better late than never. J Intensive Care Med 2011;26:304-13.
17. Permpikul C, Sringam P, Tongyoo S. Therapeutic goal achievements during severe sepsis and septic shock resuscitation and their association with patients' outcomes. J Med Assoc Thai 2014; 97(Suppl 3):S176-83.