

Analysis of sepsis and septic shock 3- and 6-hour management at resuscitation room in Dr. Soetomo General Hospital

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Abstract

Objective: To provide a record of the implementation and outcome of surviving sepsis campaign 2016 at Dr. Soetomo General Hospital, Surabaya, Indonesia, such as 3- and 6-hour sepsis bundle compliance as a baseline and the Sepsis-related Organ Failure Assessment (SOFA) score after 48 hours of treatment. SOFA values were used to predict mortality in the hospital.

Design: This was an observational experimental study that used cross sectional design.

Setting: Resuscitation room in Dr. Soetomo General Hospital.

Patients and participants: A purposive sample was taken of patients older than 17-year-old suspected with sepsis or septic shock according to diagnosis criteria from Surviving Sepsis Campaign (SSC) 2016. Thirty-two patients, consist of 24 male and 8 female patients were included.

Interventions: After patients were suspected of sepsis or septic shock according to diagnosis criteria from SSC 2016, they were treated with 3- and 6-hour sepsis bundle, then the data were collected with questionnaire.

Measurements and results: We found 75% of patients received a 3-hour sepsis bundle in <3 hours, and 50% of patients had 6-hour sepsis bundle in <6 hours. The compliance rate of 3- and 6-hour sepsis and septic shock bundles reached 46.88%. SOFA scores before and after 48-hour management of sepsis had a significant increase with $p=0.001$ ($p<0.05$).

Conclusions: There were significant decreasing of SOFA values in baseline and 48 hours after the management of sepsis and septic shock in 81.25% patients ($n=26$). This result suggests that management of sepsis based on SSC 2016 contribute to the improvement of the patient's condition and better prognosis.

Key words: Sepsis, SOFA, 3-hour sepsis bundle, 6-hour sepsis bundle, compliance, Dr. Soetomo General Hospital.

Introduction

Infection is one of the most three common causes of death from all over the world. Most of the infections become septic. (1-3) Sepsis is defined by So-

ciety of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) as life-threatening organ dysfunction that caused by dysfunction of body response to infection. (4,5) The third international definition of sepsis (Sepsis-3) provides a new definition of sepsis diagnosis using quick Sepsis-related Organ Failure Assessment (qSOFA), which is used to indicate suspected infection in adult patients. (4) qSOFA is a simple criterion and does not use any laboratory tests, so it can be used widely in various departments, including emergency and pre-hospital areas, if possible, but serum lactate examination is still determined as a marker of results in patients with sepsis. (4) Patient with suspected infection may experience longer ICU stay or death in hospital. This patient should be identified faster with qSOFA (Table 1). (4,5)

Septic shock is part of sepsis with circulatory and cellular/metabolic disorders associated with a high-

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er risk of mortality, which can be identified by clinical enforcement of sepsis accompanied by persistent hypotension that requires vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg, and serum lactate value > 2 mmol/l (18 mg/dl) despite adequate fluid resuscitation. While wider organ dysfunction can be known as an acute disorder with SOFA score ≥ 2 points due to infection. The SOFA score ≥ 2 shows an estimated overall mortality risk of 10% in the general hospital population suspected of infection (**Table 2**). (4)

Administering fluids with a volume of 30 ml/kg gives clinicians the opportunity to resuscitate while obtaining more information about patients, including specific conditions in septic patients and while waiting for a more appropriate measurement of hemodynamic status. Interventional studies have described this in daily practice in the early stages of resuscitation, and observational evidence supports this practice. (6,7) As recommendation, the usage of vasopressors in the latest guidelines is norepinephrine to achieve the average target of arterial blood pressure. If norepinephrine is inadequate, epinephrine can be added, or vasopressin for the reduction of norepinephrine. Vasoactive administration is mostly (56% of septic shock patients) through peripheral access at first, because to achieve the expected MAP target until central venous catheter (CVC) is installed.

The use of central venous pressure (CVP) as a single guide for fluid resuscitation is no longer reliable because of its limited ability to estimate responses to fluid administration tests. This also applies to static measurements of other right and left heart pressures and volumes. (8,9) Dynamic measurements have been proposed to estimate whether patients need additional fluid in an attempt to improve fluid management by increasing stroke volume. (8,9) These techniques include passive leg raising, fluid response tests to measure stroke volume, or variations in systolic pressure, pulse pressure, or stroke volume values to change in intrathoracic pressure that are affected by mechanical ventilation. (9) However, if cardiac output monitor or echocardiography is not available, changes in CVP values can be considered, although accuracy is not as good as the two methods. (9)

Broad-spectrum antibiotics are advised to be given within the first hour of diagnosis of sepsis and septic shock. Every hour delay of up to 6 hours is associated with a 7.6% decrease in survival. A 2-hour delay since the onset of persistent/recurrent hypotension correlates with the mortality rate increased relatively significantly compared with those receiving therapy in the first hour. (10)

Further management of sepsis includes empirical antibiotics. Empirical antibiotic therapy consists of one or more drugs that can fight all pathogens (bacteria and fungi/viruses) and are able to penetrate the source of sepsis in sufficient concentration. Patients with sepsis and septic shock should be given broad-spectrum antibiotic therapy for the organisms and undergo antimicrobial sensitivity. Furthermore, immediately after the pathogen has been identified, de-escalation must be carried out. (7) Type of organism that causes severe sepsis is a factor that is closely related to the prognosis. Gram-negative organisms is still the most common pathogen. (11)

Based on the infection site, pneumonia are the most frequent infection source causing sepsis with the highest mortality rates. (10,12,13) Esper et al found that sepsis mostly caused by respiratory infections (33%) followed by genitourinary infections (32%), gastrointestinal infections (23%), bone and joint infections (7%), soft tissue and skin infections (5%), other infections (3%), and with more than one source of infections (3%). (13)

Serum lactate is not a direct measurement of tissue perfusion. (11) Increased serum lactate can reflect tissue hypoxia, acceleration of aerobic glycolysis due to excessive beta-adrenergic stimulation, or other causes, such as liver failure. Whatever the cause, the increase in lactate is related to worse outcome. (14) There was a significant reduction in mortality while resuscitation is done with lactate outcome as guideline compared with resuscitation without lactate monitoring. (15)

In addition to the availability of good guidelines and facilities, good human resources are needed, which can be compliant in conducting resuscitation. Many studies have proved the existence of an association between adherence to SSC bundle with a reduction in mortality in septic patients. Extensive research in Europe, the United States, and South America showed significantly lower mortality rates in groups with high adherence to SSC bundles. The overall hospital mortality decreased by 0.7% with 3 months participation in SSC, and associated with a 4% reduction in hospital stay for every 10% improvement in compliance with bundles. (16)

Sepsis management still pose great challenges to be implemented based on diagnosis and compliance to sepsis bundles.

Material and methods

The present study was approved by Komite Etik Penelitian Kesehatan Dr. Soetomo General Hospital, Surabaya, Indonesia. A cross-sectional - obser-

vational study was held in Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia from December 2017 to February 2018. A purposive sample was taken of patients older than 17-year-old suspected with sepsis or septic shock according to diagnosis criteria from SSC 2016. Diagnosis was made from suspicion of infection, qSOFA score, and SOFA score in resuscitation room. Patients that had been diagnosed and treated in resuscitation room with sepsis or septic shock before study duration were excluded.

In the hospital data were collected using questionnaires consisting of 3-hour sepsis bundle (serum lactate, blood culture, administration of antibiotics, administration of crystalloid fluids) and 6-hour sepsis bundle (vasopressor administration, central venous oxygen saturation [ScvO₂] target, re-examination of lactate serum) (**Table 3**), and initial SOFA score assessment and 48 hours after sepsis management. SOFA assessment after 48 hours was required as a prediction. If the SOFA score <2 then the prognosis was good, but if the SOFA score was >2 the prognosis would be poor. Data were analyzed by chi-square and t-test using SPSS 18.

Results

A total of 32 patients, 24 male patients and 8 female patients, ranged from 37- to 81-year-old were observed in resuscitation room. The most common source of infection during this study was lung infection (n=20), followed by abdominal infection (n=8), bone-soft tissue-dermal infection (n=2), and neurological infection (n=1). During further observation we found that most lung infection caused by community acquired pneumonia (CAP) with *Staphylococcus aureus* as the most common pathogen.

Then after further examination we found 16 patients were diagnosed with sepsis and 16 others were diagnosed with septic shock. All patients were scored by SOFA score and the score ranged from 2 to 17 with mean 6.63 ± 4.513 . The majority of patient received complete 3-hour sepsis bundle treatment within 3 hours (75%) and septic shock patients mostly received complete 6-hour sepsis bundle within 6 hours (50%) (**Table 4**).

We also collected further data about the completion of each component of 3-hour and 6-hour bundle of sepsis (**Table 5**) in which we found that most patients received serum lactate level measurement within 3 hours (96.8%, 15 septic patients and 16 septic shock patients). All patient serum lactate levels were then measured. We found that most septic patients had serum lactate levels <4 (n=15, 93.8%), while patients with septic shock

mostly had serum lactate levels >4 (n=10, 62.5%), with $p=0.002$ ($p < 0.05$), and an odd ratio of 25 (**Table 6**). Blood cultures in this study were carried out within 3 hours in most patients (n=23, 71.87%), while 4 blood cultures were taken afterwards due to patients' resuscitation and proxy approval needed. Due to financial problems, 5 patients did not undergo blood culture examinations.

Most patients received broad-spectrum antibiotics in 3 hours (n=30, 93.75%). Patients with hypotension or lactate >4 received 30 ml/kgBW crystalloids (n=28, 100%). Most patients achieved MAP>65 mmHg in 60 minutes (n=25, 78.1%). Eleven from 16 patients (68.75%) with septic shock received norepinephrine. Nine patients (56.2%) with septic shock achieved ScvO₂ targets $\geq 70\%$ in the first 6 hours, while others still needed resuscitation for more than 6 hours.

Patients with elevated serum lactate level in initial measurement were examined again within 6 hours. This measurement was done in 11 patients (68.7%). Five other patients were not examined because 2 of them died before 6 hours, and 3 of them had unstable hemodynamic condition, and while resuscitated died in 7 and 8 hours after initial treatment. Besides 3- and 6-hour sepsis bundle, we also did supportive components such as blood glucose control, which was applied in all patients (n=32, 100%) and steroid treatment in patients who didn't achieve target MAP despite vasopressor therapy, in which we used methylprednisolone instead of hydrocortisone because of its availability limitation (n=4, 66%) (**Table 7**).

This study found that there were 15 patients (46.8%) which received full 3- and 6-hour sepsis bundle components, followed by 11 patients (34.37%) received more than 50% sepsis bundle components, and 18.75% received less than 50% sepsis bundle components. In this study 7 patients were assessed with >11 initial SOFA score, 5 of them died within 48 hours after initial treatment.

Discussion

This study aims to provide and analyze the data of management of patients with sepsis and septic shock in the resuscitation room of Dr. Soetomo General Hospital in the first 3 hours and 6 hours based on Surviving Sepsis Campaign 2016, and provide data of the compliance of sepsis and septic shock management to the SSC 2016 guidelines.

Initial lactate examination was performed in 31 patients (96.8%). Examination of serum lactate is very important because it can describe the occurrence of tissue hypoxia or other causes, since an increase in lactate correlates with the worse out-

come. (17) Thus, the management of sepsis with lactate evaluation is necessary. This is consistent with previous studies, which found a significant reduction in mortality in resuscitation with lactate outcome guidelines. (4)

Compliance with the implementation of blood culture before antibiotics administration in the first 3 hours was 71.9% (23 patients). The obstacle to perform this culture was the very severe condition of the patients who were resuscitated because the blood pressure and pulse were very low, followed by the patients' death within <8 hours. The next obstacle was due to the public financing that required family approval.

Administration of broad-spectrum antibiotics within the first 3 hours could be achieved in 30 patients with 93.75% adherence. Obstacle in this area was caused by doubt about the source of the sepsis. For example, 1 patient was not given antibiotics because the patient was suspected of having tuberculosis disease, still waited for the result of sputum examinations.

The most common cause of sepsis in resuscitation room of Dr. Soetomo General Hospital was pneumonia. This supports previous studies by Esper, et al in 2006 and by Vincent, et al in 2009. (13,18) Other causes of infection found in the study were based on the most subsequent sequences, namely abdominal, urinary tract, skin, bone and soft tissue infections, and nervous system.

Fluid administration is the key to managing sepsis. Of the 32 patients diagnosed with sepsis, 16 patients were categorized as sepsis without shock. Of these 16 samples, there were 12 patients eligible for crystalloid due to hypotension or lactate ≥ 4 , and all 12 samples were given crystalloid 30 ml/kg. Whereas all septic shock patients received initial fluid resuscitation 30 ml/hour (100% compliance).

Fluid therapy given to patients in addition to the SSC guidelines was 30 ml/kg to achieve the MAP target. Sixteen patients experienced septic shock. Thirteen of them had a fluid challenge test and 3 people did not (two patients due to no CVC installed because of the cost constraints mentioned earlier, and one patient because of MAP has reached 70 after initial fluid administration and low-dose vasopressor. As for the ScvO₂ target, 9 ScvO₂ results were met $\geq 70\%$ within <6 hours, 5 patients were examined but did not meet the criteria for achieving the target, and 2 patients were not examined by ScvO₂ because of unstable hemodynamic condition and still under resuscitation.

Based on the data of 16 septic shock patients who needed vasopressor drugs to achieve MAP ≥ 65

mmHg, the drugs used in most patients were norepinephrine (in eleven patients), a combination of norepinephrine+dopamine (two patients), a combination of norepinephrine+adrenaline (one patient), and dobutamine (without combination) (two patients with high systemic vascular resistance and poor cardiac contractility based on echocardiographic evaluation). This was in accordance with SSC 2016 guidelines that the first choice of vasoactive drugs use to increase blood pressure is norepinephrine, and the use of adrenaline as an addition, as well as the use of dopamine in patients with relative or absolute bradycardia, or patients who have difficulty to becoming tachyarrhythmia. (4) To achieve the expected MAP target, the provision of vasoactive at the beginning was mostly (56% of patients with septic shock) through peripheral access because CVC has not been installed. This would actually increase the risk of local tissue damage or extravasation of vasopressors through peripheral access. However, based on research from Loubani, et al in 2015, in emergency or emergency situations, the administration of vasopressors through peripheral access for a short time (<2 hours) is believed not to cause damage to local tissues. This is done temporarily until CVC is installed, to support stable hemodynamic achievement in a faster time. (19)

Hydrocortisone administration in septic shock cannot be performed because of the unavailability of this preparation in Indonesia, but can be substituted by methylprednisolone according to the equivalent dose of substitution. As per the guidelines for handling sepsis, the dose of steroids given is in a low dose of <300 mg, equivalent to methylprednisolone <60 mg. In septic shock treatment in this study, there were four patients, from six septic shock patients, who were given steroids because they did not respond to fluid and vasoactive administration (66% compliance). Three of them died before 48 hours. The patients, who were given steroids, were given a dose of 62.5-125 mg, which meant the dose was greater than the dose based on the guidelines for handling sepsis. There were six patients who underwent echocardiography, of which four were found to have left ventricular dysfunction, and two with diastolic dysfunction. This data are also needed, because if septic patients have myocardial dysfunction, especially diastolic dysfunction, according to Patil, et al, this could be a mortality predictor and output of patients with severe sepsis and septic shock. (20)

Overall adherence to the bundle handling initial sepsis that must be met within the first 3 hours was 75% and adherence to the septic shock bundle in

the first 6 hours was 50%. While the number of samples that met the criteria of 100% compliance with all components of the sepsis bundle and septic shock were 15 samples (46.88%), with the constraints of each component causing non-compliance as described previously. This compliance rate was still low, as in previous study by Lie KC, et al. (21)

This study found full compliance of sepsis bundle in 46.88% patients and 15.62% mortality within 48 hours. Five patients who died within the span of 48 hours of the study were evaluated with a high initial SOFA score (>11). This supported previous research by Acharya SP, et al (2007), who examined SOFA scores as predictor of end-conditions in 50 patients with systemic inflammatory response syndrome (SIRS) who underwent ICU treatment. They were studied with an initial SOFA values after 48 hours and after 96 hours. The initial SOFA value in the group of patients who died was higher than the group of patients who were still alive. The initial value of $SOFA > 11$ had a 90% prediction of mortality, while the average value of $SOFA > 7$ had a 73.9% prediction of death. (18) Five patients who died in this study had SOFA values > 11 . These patients also had lactate values ≥ 4 , similar with previous statement that the higher lactate value predicted worse outcome. (17) However, in terms of management, the five patients who died within 48 hours of the study had received $> 50\%$ components of the sepsis bundle, so that we predicted the cause of death of these patients was the very weak baseline condition of the patients. In these patients, the compliance of sepsis bundle components were quite high at 85.7%, where the obstacle for one component caused by the difficulty of achieving $ScvO_2 > 70\%$ in 6 hours, not because of the slow handling of each component of the bundle.

Based on the results of the T test statistical analysis, there were significant differences between ini-

tial SOFA values and SOFA values after 48 hours of treatment of sepsis and septic shock based on SSC 2016. There was significant difference between initial SOFA average scores and SOFA average scores after 48 hours with $p=0.001$ ($p < 0.05$). So, it is expected that if the treatment of sepsis and septic shock based on SSC 2016 is carried out with a high level of adherence, can improve SOFA values, which can improve multi-organ damage and ultimately reduce mortality.

Conclusion

From this study we found compliance to 3- and 6-hour sepsis bundle according to SSC 2016 correlated with clinical improvements signified by decrement from baseline SOFA score to 48 hours post treatment SOFA score. Continuous and comprehensive education on detection, diagnosis, and management of sepsis is needed. The research needs to be done on periodic management of sepsis. Further research needs to be done with more sample size and longer period. Research needs to be done to determine the relationship of compliance and mortality. Research on the effect of education on compliance and mortality is needed. Evaluate sepsis management by taking into account the progress on medical science and the local condition. There are many factors that may affect compliance such as stakeholder, government policy, standard of operational procedures, health care provider, facility that we need to improve to increase compliance.

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Table 1. Quick Sequential Organ Failure Assessment (qSOFA)

Criteria	Score
Respiratory rate ≥ 22 x/min	1
Altered mental status	1
Systolic blood pressure ≤ 100 mmHg	1

Table 2. Sequential (sepsis-related) Organ Failure Assessment score

Score	0	1	2	3	4
Respiration: PaO ₂ /FiO ₂ ratio	≥ 400	< 400	< 300	< 200	< 100
Cardiovascular (listed doses are in $\mu\text{g}/\text{kg}/\text{min}$)	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine	Dopamine > 5 or (nor) epinephrine ≤ 0.1	Dopamine > 15 or (nor) epinephrine > 0.1
Thrombocyte (x $10^3/\mu\text{l}$)	≥ 150	< 150	< 100	< 50	< 20
Glasgow Coma Scale (GCS)	15	13-14	10-12	6-9	< 6
Creatinine (mg/dl) or urine output	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9 or < 500 ml/day	> 5.0 or < 200 ml/day
Bilirubin (mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	12.0

Adapted from Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine. (4)

Table 3. 3- and 6-hour sepsis bundle

3-hour sepsis bundle in sepsis and septic shock patients
<ul style="list-style-type: none"> • Serum lactate level measurement • Blood culture sampling before antibiotic treatment • Administer broad spectrum antibiotic treatment • Administer crystalloid fluid 30 ml/kg in hypotensive or lactate conditions ≥ 4 mmol/l
6-hour sepsis bundle in septic shock patients
<ul style="list-style-type: none"> • Administer vasopressor to maintain mean arterial pressure (MAP) ≥ 65 mmHg • Target central venous oxygen saturation (ScvO₂) $\geq 70\%$ • Repeat serum lactate level measurement if there is elevation in initial examination
Supportive component
<ul style="list-style-type: none"> • Blood glucose control • Steroid treatment

Table 4. Demographic information

Categories	Number (%)
Diagnosis	32 (100%)
- Sepsis	16 (50%)
- Septic shock	16 (50%)
Gender	32 (100%)
- Male	24 (75%)
- Female	8 (25%)
Source of infection	32 (100%)
- Lung	20 (62.5%)
- Abdomen	8 (25%)
- Urinary tract	1 (3.125%)
- Skin-soft tissue-bone	2 (6.25%)
- Neurological system	1 (3.125%)
3-hour sepsis bundle completion	32 (100%)
- Incomplete	5 (15.6%)
- Completed in ≤ 3 hours	24 (75%)
- Completed in > 3 hours	3 (9.4%)
6-hour sepsis bundle completion	16 (100%)
- Incomplete	7 (43.75%)
- Completed in ≤ 6 hours	8 (50%)
- Completed in > 6 hours	1 (6.25%)

Table 5. Compliance of 3-hour sepsis bundle components

3-hour sepsis bundle components		Sepsis bundle compliance (%)		
		Achieved within allocated time	Achieved > allocated time	Not done
Serum lactate level examination (n=32)	Sepsis	15 (93.8%)	1 (6.2%)	0 (0%)
	Septic shock	16 (100%)	0 (0%)	0 (0%)
Blood culture sampling before antibiotic treatment (n=32)	Sepsis	10 (62.5%)	2 (12.5%)	4 (25%)
	Septic shock	13 (81.25%)	2 (12.5%)	1 (6.25%)
Broad spectrum antibiotic treatment (n=32)	Sepsis	15 (93.8%)	0 (0%)	1 (6.2%)
	Septic shock	15 (93.8%)	1 (6.2%)	0 (0%)
Crystalloid fluid 30 ml/kg administration in hypotension or lactate >4 mmol/l (n=28)	Sepsis (n=12)	12 (100%)	0 (0%)	0 (0%)
	Septic shock (n=16)	16 (100%)	0 (0%)	0 (0%)

Table 6. Serum lactate level measurement

Serum lactate levels (mmol/l)	Sepsis (n=16)	Septic shock (n=16)	p value	OR	95% CI
<4	15 (93.8%)	6 (37.5%)	0.002	25	2.6-240
≥4	1 (6.2%)	10 (62.5%)			

Table 7. Compliance of 6-hour sepsis bundle components

6-hour sepsis bundle components	Sepsis bundle compliance (number, %)		
	Achieved within allocated time	Achieved > allocated time	Not done
Vasopressor administration to maintain mean arterial pressure (MAP) >65 mmHg (n=16)	16 (100%)	0 (0%)	0 (0%)
Target central venous oxygen saturation (ScvO2) ≥70% (n=16)	9 (56.2%)	5 (31.3%)	2 (12.5%)
Repeated serum lactate level measurement if there is elevation in initial examination (n=16)	11 (68.7%)	0 (0%)	5 (31.3%)
Supportive components			
- Blood glucose control (n=32)	32 (100%)	0 (0%)	0 (0%)
- Steroid treatment (n=6)	4 (66.67%)	0 (0%)	2 (33.33%)

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