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Septic Shock In A Patient With Diabetic Ulcer Complicated By Acute Kidney Failure

Ade Laksono[1], Agrietia[2]
[1,2] RS Tasik Medika Citratama Kota Tasikmalaya

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Email :
laksono_ade@yahoo.com

ABSTRACT

Sepsis is the main cause of death in critically ill patients treated in intensive care units and inpatient rooms. Sepsis is defined as a life-threatening organ dysfunction caused by an uncontrolled host response due to infection. The principles of sepsis therapy consist of fluid resuscitation and hemodynamic support, antibiotics and source control, and a series of adjunctive measures. Inadequate initial treatment of sepsis and septic shock will increase the mortality rate.

1. INTRODUCTION

The term "sepsis" originates from the Greek word "sepo," which means to decay, and was first mentioned in a poem by Homer (18th century BC). In 1914, Hugo Schottmuller formally defined "septicaemia" as a disease caused by microbial invasion into the bloodstream [1]. For several decades, sepsis was considered as the systemic spread of infection involving damage to multiple organs and systems, with high morbidity and mortality [2]. According to a consensus meeting in 2003, sepsis was defined as a systemic inflammatory response syndrome (SIRS) caused by infection [3]. In 2016, sepsis was defined as a serious, potentially fatal, organ dysfunction caused by a dysregulated host response to infection, and septic shock can occur when the underlying circulatory and cellular/metabolic abnormalities are significant enough to increase mortality rates [4]. Sepsis is a leading cause of death among critically ill patients in intensive care units and general hospital wards [5]. The management of sepsis incurs high costs during hospitalization and recovery, making it a major healthcare issue [6]. Sepsis is defined as a life-threatening organ dysfunction caused by an uncontrolled host response to infection [4]. Septic shock itself is a serious response of the body to infection involving circulatory and cellular metabolic disturbances, which can result in increased morbidity and mortality rates. Patients with septic shock and acute kidney injury (AKI) have a poor prognosis, including prolonged hospitalization, increased risk of ICU and hospital admission, chronic kidney failure, and increased mortality [7].

2. METHOD

A 57-year-old female patient presented to the emergency department with complaints of fever for approximately 3 days, accompanied by pain in her legs and right hand. The patient also reported loss of appetite, nausea, and the presence of pus-filled wounds on her hand and right leg. The wounds initially felt like boils and had burst approximately 2 weeks before admission to the hospital. The patient stated that the wounds had been progressively getting larger and filled with pus. The patient had a history of uncontrolled type 2 diabetes mellitus (DM). On physical examination, the patient was found to have apathetic consciousness (GCS E3M5V5), blood pressure of 70/37 mmHg, heart rate of 108 beats per minute, respiratory rate of 30 breaths per minute, oxygen saturation of 99%, and a temperature of 38°C. Wounds were observed on the patient's right hand and leg, with muscle involvement and the presence of pus.

Laboratory examination revealed a hemoglobin level of 8.9 g/dL, leukocytes of 27,210/mm3, platelets of 548,000/mm3, hematocrit of 28%, random blood glucose of 334 mg/dL, fasting blood glucose of 185 mg/dL, urea of 107 mg/dL, and creatinine of 5.9 mg/dL.

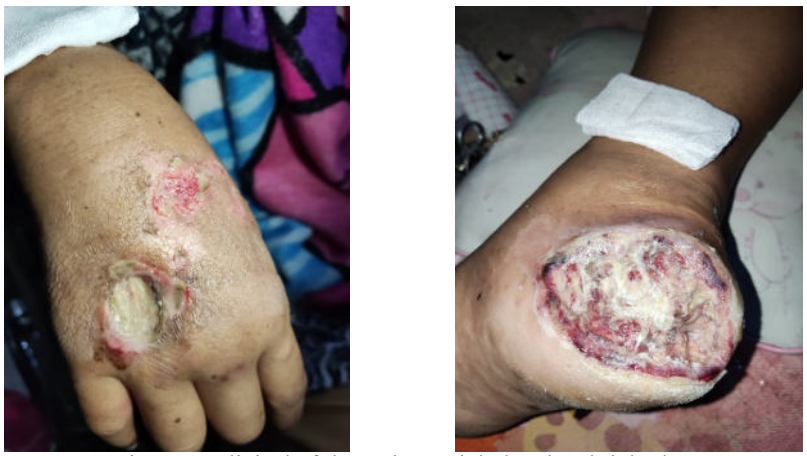

Figure 1. Clinical of the patient's right hand and right leg

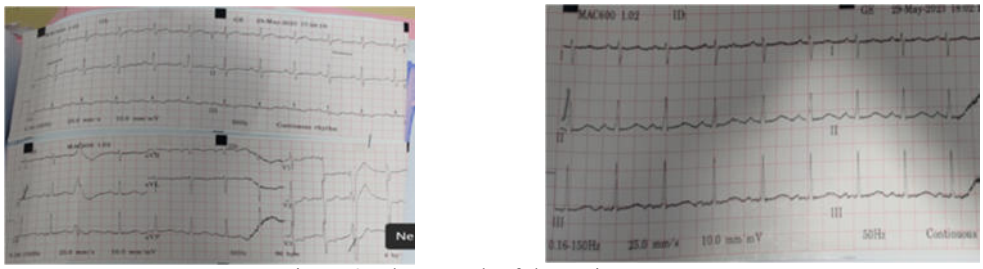

Figure 2. Photograph of the patient's ECG

On the EKG examination, the patient was found to have normal sinus rhythm, the patient was diagnosed with septic shock, diabetic ulcers in the right hand and foot region, type 2 diabetes mellitus (DM), and acute kidney injury (AKI) possibly due to chronic kidney disease (CKD). The patient received initial management with a rapid infusion of 1000 cc lactated Ringer's solution, a drip infusion of 1 gram paracetamol, and urinary catheter placement.

The patient's vital signs were re-evaluated, showing a blood pressure of 85/40 mmHg, heart rate of 100 beats per minute, respiratory rate of 24 breaths per minute, temperature of 36°C, and urine output of 300 cc. The patient was given norepinephrine drip therapy starting at 0.2 mcg/kg/min, titrated up to 0.5 mcg/kg/min, ranitidine injection twice daily, paracetamol drip infusion three times daily, meropenem injection three times daily, 10 units of Ryzodeg, and daily wound toileting with normal saline and 1 ampule of gentamicin. After 5 days of treatment with stable vital signs and without vasoconstrictive drugs, the patient's random blood glucose level was 112 mg/dL. The patient was referred to a surgeon for debridement of the right hand and foot ulcers, which was performed in the operating room.

3. RESULTS AND DISCUSSION

Sepsis is a systemic response to an infection within the body that can develop into septic shock [5]. Septic shock is defined as sepsis with refractory hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, or a decrease of >40 mmHg from baseline systolic blood pressure that is unresponsive) [8].

Screening reduces mortality in sepsis. Risk factors for sepsis include being 65 years of age or older, younger than 1 year, or having concomitant chronic conditions such as lung disease, heart failure, cirrhosis, diabetes, cancer, kidney disease, or immune disorders [9].

Table 1. SOFA (Sequential Organ Failure Assessment) score [4].

	Score				
	0	**1**	**2**	**3**	**4**
Respiration					

PaO2/FIO2, mmHg (kPa)	≥400 (53,3)	<400 (53,3)	<300 (40)	<200 (26,7) with respirator	<100 (13,3) with respirator
Coagulation					
Platelets, ×103/µL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/L)	<1,2 (<20)	1,2-1,9 (20-32)	2,0-5,9 (33-101)	6,0-11,9 (102-204)	≥12,0 (≥204)
Cardiovascular					
Blood preasure	MAP ≥70 mmHg	MAP <70 mmHg	Dopamin ≤5 or dobutamin (all dose)*	Dopamin 5,1-15 or epinefrin ≤0,1 or norepinefrine ≤0,1*	Dopamin >15 or epinefrin >0,1 or norepinefrine >0,1*
Central nerve system					
Score *Glasgow Coma Scale*c	15	13-14	10-12	6-9	<6
kidney					
Creatinin, mg/dL (µmol/L)	<1,2 (110)	1,2-1,9 (110-170)	2,0-3,4 (171-299)	3,5-4,9 (300-440)	>5,0 (440)
	Urine output, mL/day			<500	<200

*Catecholamine doses are administered in mcg/kg/minute over at least 1 hour

There are assessment systems used to identify sepsis, such as qSOFA (quick Sequential Organ Failure Assessment) and SOFA score (Sequential Organ Failure Assessment). The qSOFA score utilizes three criteria: systolic blood pressure ≤100 mmHg, respiratory rate ≥22 breaths per minute, and GCS<15. If the qSOFA score is ≥2, it indicates an increased risk of deterioration [4]. On the other hand, the SOFA score consists of six variables (Table 1).

On physical examination, this patient was found to have apathetic consciousness (E3M5V5), blood pressure of 70/37 mmHg, and respiratory rate of 30 breaths per minute, with an infection focus in the patient's hand and foot. When applied to the qSOFA criteria, this patient's score is greater than 2, indicating a high risk of deterioration. When applied to the SOFA score criteria, the patient has a score of 6, which means that the higher the patient's SOFA score, the higher the risk of mortality or deterioration. The condition experienced by this patient is not only sepsis but also septic shock caused by the infection. Septic shock can be clinically identified as sepsis accompanied by persistent hypotension requiring vasopressors to maintain a mean arterial pressure ≥65 mmHg and blood lactate concentration >2 mmol/L (>18 mg/dL), despite adequate fluid resuscitation. The mortality risk for patients requiring treatment is >40% [4].

Pathophysiology

The coagulation (procoagulant) and inflammation responses to infection are closely related. Several inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin-1 activate the coagulation or clotting system by stimulating the release of tissue factor from the endothelium and monocytes, leading to thrombin formation and fibrin clot formation [10]. Cytokines and thrombin can disrupt the endogenous fibrinolytic process by stimulating the release of plasminogen activator inhibitor-1 (PAI-1) from platelets and endothelium. PAI-1 is a potent inhibitor of plasminogen activation in tissues, which is an endogenous pathway for fibrin clot dissolution [10].

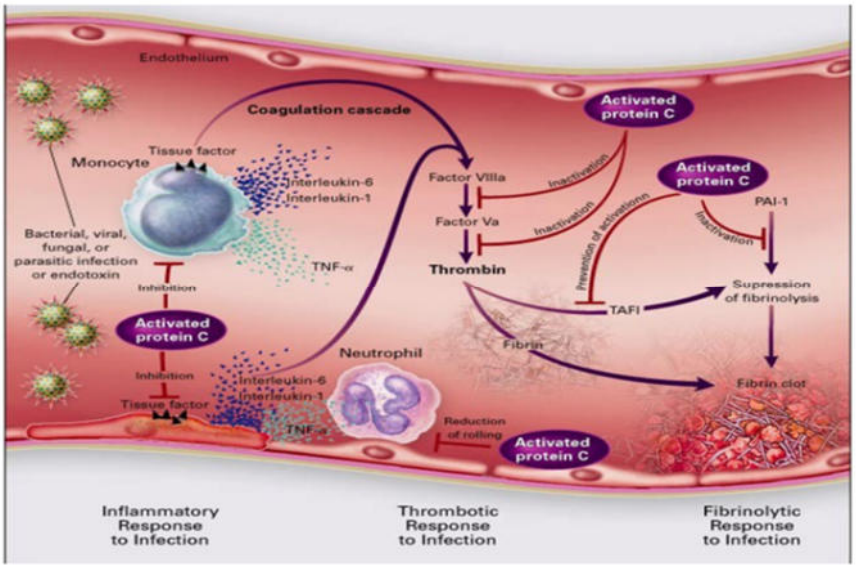

Figure 3. Clotting mechanism through inflammatory response, thrombosis, and fibrinolysis to infection

Another effect of procoagulant thrombin is its ability to stimulate several inflammatory pathways and suppress the endogenous fibrinolytic system by activating Thrombin Activatable Fibrinolysis Inhibitor (TAFI). Another mechanism is through the activation of activated protein C, which is associated with the systemic response to infection. Protein C is an endogenous protein that is involved in the body's systemic response to infection. It aids in fibrinolysis, inhibits thrombosis and inflammation, and serves as an important modulator in coagulation and sepsis-related inflammation [10].

This condition provides antithrombotic effects by inhibiting the activation of factor Va and VIIIa, thus inhibiting thrombin formation. The decrease in thrombin has an impact on the processes of inflammation, procoagulation, and antifibrinolysis. According to in vitro data, activated protein C has anti-inflammatory effects by inhibiting the production of inflammatory cytokines (TNF-α, interleukin-1, and interleukin-6) by monocytes and limiting the adherence of neutrophils and monocytes to damaged/injured endothelium by binding to selectins [10]. The end result of tissue response to infection includes the development of diffuse endovascular injury, microvascular thrombosis, organ ischemia, multiorgan dysfunction, and death [10].

Table 2. Differences of 6 hours bundle, 3 hours bundle and 1 hour bundle 9

Bundle	Measurement
6 hours bundle	Apply a vasopressor (for unresponsive hypotension initial fluid resuscitation) to maintain mean arterial pressure (MAP) ≥65 mm Hg
3 hours bundle	Measure lactate, obtain blood culture before antibiotics, give antibiotics, start fast 30 ml/kg crystalloid if lactate >4 mmol/l or hypotension
1 hours bundle	Measure lactate, obtain blood culture before antibiotics, give antibiotics, start fast 30 ml/kg crystalloid if lactate >4 mmol/l or hypotension, start vasopressor for maintain MAP > 65

The purpose of this change is to expect a change in early resuscitation management, especially in addressing hypotension in septic shock [11].

For adults with sepsis or septic shock, it is recommended to use crystalloids as the first-line fluid for resuscitation. (Strong recommendation, moderate-quality evidence).

Fluid therapy is an essential part of sepsis and septic shock resuscitation. Crystalloids have the advantage of being inexpensive and widely available. There is no clear difference between the use of

crystalloid and colloid solutions in resuscitating patients with sepsis and septic shock. For several decades, the administration of normal saline solution (0.9% NaCl) has been widely used, but it carries the potential side effects, including hyperchloremic metabolic acidosis, renal vasoconstriction, increased cytokine secretion, and the risk of acute kidney injury (AKI).

For patients with hypoperfusion or sepsis-induced septic shock, it is recommended that at least 30mL/kg of intravenous crystalloid fluid be given within the first 3 hours of resuscitation. (Weak recommendation, low-quality evidence).

Effective fluid resuscitation is crucial for stabilizing tissue hypoperfusion caused by sepsis in sepsis and septic shock. Previous guidelines recommended initiating appropriate resuscitation immediately upon recognizing sepsis or septic shock. Although the evidence comes from observational studies, this recommendation is considered best practice, and there is no new data suggesting a need for change. The recommendation is to use a minimum of 30 mL/kg (ideal body weight) of intravenous crystalloid in early fluid resuscitation. The recommended initial resuscitation volume is based on observational evidence.

One of the most important principles in managing complex septic patients is the need for detailed initial assessment and ongoing reevaluation of the response to treatment. To avoid both under-resuscitation and over-resuscitation, the administration of fluids after initial resuscitation should be guided by careful assessment of intravascular volume status and organ perfusion.
Several techniques for assessing fluid responsiveness are [12]:

Passive leg raising test.

This assessment is used to determine whether a septic patient is a responder or non-responder, with a sensitivity of 97% and specificity of 94%. If the pulse pressure increases by >10% from the baseline, the patient is considered a responder. The aim of this assessment is to evaluate the increase in cardiac output with volume addition [12].

Fluid challenge test

It measures the significance of changes in stroke volume or arterial systolic pressure or pulse pressure. Fluid administration can restore oxygen distribution in the blood and perfusion to vital organs to prevent organ damage [12].

Stroke Volume Variation (SVV).

Assessment of the variation in stroke volume due to changes in intrathoracic pressure when the patient is on mechanical ventilation. The criteria for assessing fluid responsiveness with this method are: Patient under full mechanical ventilation control, Tidal volume of 8-10 mL/kg body weight (predicted body weight), No arrhythmia. The patient is categorized as a responder if SVV is ≥12% [12]. In addition to SVV, Pulse Pressure Variation (PPV) can also be used to assess fluid responsiveness [12]. For adults with septic shock, it is recommended to use norepinephrine as the first-line vasopressor agent over other vasopressors (Strong recommendation) [13].

Early resuscitation management aims to restore tissue perfusion, particularly perfusion of vital organs. If blood pressure does not increase after fluid resuscitation, the administration of vasopressors should not be delayed. Vasopressors should be given within the first hour to maintain a mean arterial pressure (MAP) >65 mmHg [11].

Norepinephrine is recommended as the first-line vasopressor. Norepinephrine is a potent agonist of α-1 and β-1 adrenergic receptors, resulting in vasoconstriction and increased MAP with minimal effects on heart rate [13]. If norepinephrine is not available, epinephrine or dopamine can be used as alternatives, with special attention given to patients at risk of arrhythmias when using dopamine and epinephrine [11]. Dopamine, as an alternative vasopressor to norepinephrine, is only recommended for specific patients, such as those at low risk of tachyarrhythmias and relative bradycardia [12] [14]. The use of low-dose dopamine for renal protection is no longer recommended [12]. Dobutamine is recommended for persistent hypoperfusion despite adequate fluid and vasopressor therapy.

For adults with suspected or highly likely septic shock, immediate administration of antimicrobials is recommended, ideally within one hour of recognition. (Strong recommendation, low-quality evidence)[13].

Early appropriate antimicrobial administration is one of the most effective interventions to reduce mortality rates in patients with sepsis. Antibiotics should be initiated as soon as possible, within the first hour if feasible, after obtaining microbiological samples [9]. Broad-spectrum antibiotic therapy is highly recommended in the initial management. The choice of antibiotics should be tailored to the empirically identified bacteria [11]. Antibiotic treatment for 7 to 10 days is usually sufficient for most severe infections. A shorter duration may be appropriate if the patient shows improvement, while a longer duration may be necessary for specific pathogens or persistent infection focus [9].

Blood Cultures (Researcher's best experience) [11]

Blood cultures should be obtained promptly to optimize antibiotic administration and identify pathogens. Blood cultures should ideally be taken in two sets, especially for aerobic and anaerobic organisms. Culture testing can also rule out the cause of sepsis, and if no pathogenic infection is found, antibiotic therapy can be discontinued [11].

For adults with sepsis or septic shock, initiating insulin therapy is recommended when glucose levels are ≥180 mg/dL (10 mmol/L). (Strong recommendation; moderate-quality evidence)[13].

Hyperglycemia (glucose levels >180 mg/dL), hypoglycemia, and increased glycemic variability are associated with increased mortality in critically ill patients. The American Diabetes Association, in its latest recommendations for glycemic control in critically ill patients, suggests initiating insulin therapy for persistent hyperglycemia with glucose levels >180 mg/dL and targeting a glucose range of 140-180 mg/dL [13].

4. CONCLUSION

Sepsis remains a leading cause of increased mortality. There are criteria that can be used, such as qSOFA and SOFA scores. These criteria can be used for immediate management in cases of sepsis and septic shock. Early intervention within the first hour is crucial for patients with sepsis and septic shock. In these patients, fluid management, vasopressor therapy, antibiotic administration, glucose control, and further management of the underlying infection that caused sepsis have been implemented. Inadequate initial management of sepsis and septic shock will increase mortality rates.

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