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Pathogenesis of Sepsis

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Abstract

Sepsis is a clinical condition caused by the body's immune response to infection and manifests as SIRS. Systemic inflammatory response syndrome is a state of systemic inflammatory response characterized by two or more of the following conditions. Etiology Sepsis can be caused by various microorganisms and the most etiology of sepsis is bacterial. Gram-negative bacteria cause sepsis about 60% - 70% in developing countries, but in the United States the causes of infection by Gram-positive bacteria begin to increase. This may be due to the large number of uses of invasive procedures, increased hospital acquired pneumonia (HAP) and antibiotic resistance. The body also has anti-inflammatory mechanisms including increased levels of anti-inflammatory cytokines and glucocorticoid hormones. The hormone inhibits the synthesis of cytokines by monocytes and decreases the ability of neutrophils to attach to the vascular endothelium. The inflammatory process in sepsis is not controlled leading to the occurrence of excessive discharge of inflammatory mediators over a long time and goes beyond the anti-inflammatory mechanisms of the body. This leads to various organ dysfunctions including cardiovascular, liver, pulmonary and renal dysfunctions

Keywords— Sepsis, SIRS, organ dysfunctions

Abstrak

Sepsis adalah kondisi klinis yang disebabkan oleh respon imun tubuh terhadap infeksi dan bermanifestasi sebagai SIRS. Sindrom respon inflamasi sistemik adalah keadaan respon inflamasi sistemik yang ditandai oleh dua atau lebih kondisi berikut. Etiologi Sepsis dapat disebabkan oleh berbagai mikroorganisme dan etiologi terbanyak dari sepsis adalah bakteri. Bakteri gram negatif menyebabkan sepsis sekitar 60% - 70% di negara berkembang, namun di Amerika Serikat penyebab infeksi oleh bakteri gram positif mulai meningkat. Ini mungkin karena banyaknya penggunaan prosedur invasif, peningkatan pneumonia yang didapat di rumah sakit (HAP) dan resistensi antibiotik. Tubuh juga memiliki mekanisme anti-inflamasi termasuk peningkatan kadar sitokin anti-inflamasi dan hormon glukokortikoid. Hormon tersebut menghambat sintesis sitokin oleh monosit dan menurunkan kemampuan neutrofil untuk menempel pada endotel vaskular. Proses inflamasi pada sepsis yang tidak terkontrol menyebabkan terjadinya pelepasan mediator inflamasi yang berlebihan dalam waktu yang lama dan melampaui mekanisme anti inflamasi tubuh. Hal ini menyebabkan berbagai disfungsi organ termasuk disfungsi kardiovaskular, hati, paru dan ginjal

Katakunci — Sepsis, SIRS, disfungsi organ

I. INTRODUCTION

Sepsis is a clinical condition caused by the body's immune response to infection and manifests as SIRS. Systemic inflammatory response syndrome is a state of systemic inflammatory response characterized by two or more of the following conditions (Carvalho & Trotta, 2003; Munford, 2011):

If > temperature of 38 °C or < 36°C the heart rate > 90 times per minute of exhalation > 20 times per minute or PaCO2 < 32 mmHg leukocytes > 12,000/mm3 or < 4,000/mm3 or found > 10% of stem neutrophils

The severity of sepsis depends on organ dysfunction and hemodynamic disorders. A condition is expressed as severe sepsis if there is sepsis with at least one of several signs of hypoperfusion or organ dysfunction, for example capillary filling time > 2 seconds, urine production < 0.5 mL / kg / hour or requires dialysis, lactate levels > 4 mmol / L, sudden changes in mental status, the presence of disseminated intravascular coagulation (DIC) and the presence of acute distress respiratory syndrome (ARDS) (Neviere, 2009; Munford, 2011).

Severe sepsis can continue into MODS and sepsis shock. Multiple organ dysfunction syndrome is a state of alteration of organ function so that intervention needs to be carried out to maintain homeostasis, characterized by the failure of more than one organ that occurs simultaneously or gradually (Hamzaoui & Carlet, 2009). Sepsis shock is severe sepsis with one of the circumstances below (Neviere, 2009; Munford, 2011): hypotension (systolic blood pressure < 90 mmHg or 40 mmHg less than the blood pressure of the previous patient) for at least 1 hour even with adequate administration of fluid. vasosresors are required to maintain systolic blood pressure ≥ 90 mmHg or average arterial pressure ≥ 70 mmHg.

II. EPIDEMIOLOGY SEPSIS

Sepsis is a worldwide health problem both economically and socially. The number of sepsis cases in the United States at the end of 1970 was 164,000 per year. This number is increasing rapidly to reach 650,000 cases per year. As many as 2% of patients in hospitals and almost 75% of intensive care unit (ICU) patients experience sepsis with a mortality rate of 20% to 50%. The number of severe sepsis cases and sepsis shock is also increasing by nearly 300,000 cases per year. The mortality rate increased according to the severity of sepsis, which was 16% for sepsis, 20% for severe sepsis and 46% for sepsis shock. The increase in the incidence of sepsis is associated with the large number of the population with old age, the increase in patients with chronic diseases and patients with immunocompromised (Moss, 2005; Neviere, 2009; Munford, 2011).

The average number of severe sepsis cases per year in the UK is currently 51 per 100,000 population, in France it is 95 per 100,000 population and Australia is 77 per 100,000 population. The average age of sufferers is 60 years and about more men than women. Sepsis is more prevalent in African American and other non-white races (Moss, 2005). The incidence of sepsis for the last 5 years in Indonesia is also still high, namely 8.7% to 30.29% with a mortality rate of 11.56% to 49.9%. The number of incidences of sepsis in rs. Dr. Sarjito Yogyakarta in 2002 as many as 275 cases and in the hospital. Dr. M. Djamil Padang from January to July 2006 as many as 71 cases. Other epidemiological data on the incidence of sepsis remain unclear (Soebronto & Soebagyo, 2003; Erza, 2007; Nelly, 2012).

Etiology Sepsis can be caused by various microorganisms and the most etiology of sepsis is bacterial. Gram-negative bacteria cause sepsis about 60% - 70% in developing countries, but in the United States the causes

of infection by Gram-positive bacteria begin to increase. This may be due to the large number of uses of invasive procedures, increased hospital acquired pneumonia (HAP) and antibiotic resistance. The number of incidences of sepsis caused by fungi has also begun to increase in the last decade although it is still lower than sepsis by bacteria (Guntur, 2009; Reade & Angus, 2009).

III. PATHOGENESIS AND PATHOPHYSIOLOGY

The body's defense mechanism against bacterial infections is influenced by the structure and pathogenicity of the bacteria. Gram-negative bacteria have an outer layer consisting of lipids which are important components because they are usually sensitive to the mechanism of lysis by complement. Complement activation can kill bacteria and also produce chemotaxis factors (Morse, 2004; Boedina, 2010). Gram-negative bacteria that are lysis will release lipopolysaccharides (LPS), bind to LPS-binding protein (LBP) and stimulate monocyte cells, macrophages and neutrophils to remove mediators, namely tumor necrosis factor (TNF) α, as shown in Figure 7.1. The cell will also secrete reactive oxygen / nitrogen species and metabolites resulting from activation of the arachidonic acid pathway which eventually causes vascular disorders in the form of changes in tone and increased vascular permeability. Peptidoglycan bacteria, lipotemycoic acid, deoxyribo nucleic acid (DNA), polysaccharides and fimbriae also produce (Guntur, 2009; Munford, 2011).

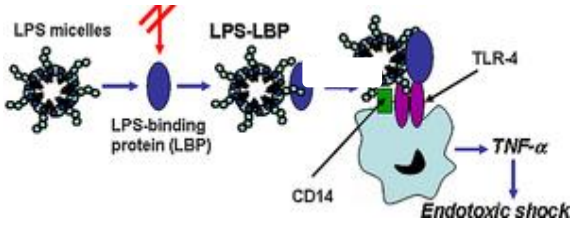

FIGURE 1. MECHANISM OF LPS STIMULATES THE SECRETION OF INFLAMMATORY MEDIATORS (MARCO, 2011)

Lipopolysaccharides and inflammatory mediators cause endothelial damage. The endothelial membrane has molecules with anticoagulant properties, but when endothelial sepsis becomes procoagulant through several mechanisms including increasing the transcription of tissue factor molecules, downregulation of anticoagulant molecules such as thrombomodulin, lowering tissue plasminogen activator activator and increasing plasminogen activator inhibitor 1 (PAI-1). Activated endothelium will increase the expression of adesy molecules including intercellular adhesion molecule 1 (ICAM-1), E-selectectin and stimulate the migration of leukocytes and their adesi to the endothelium (Hamzaoui & Carlet, 2009; Munford, 2011). Lipopolysaccharides activate factor XII, initiate a coagulation cascade and convert fibrinogen into fibrin. The inhibition pathways of protein C and protein S are disrupted and antithrombin decreases. All of these circumstances cause microvascular disorders and coagulopathy occurs (Guntur, 2009; Munford, 2011). The pathophysiology of sepsis appears in Figure 2.

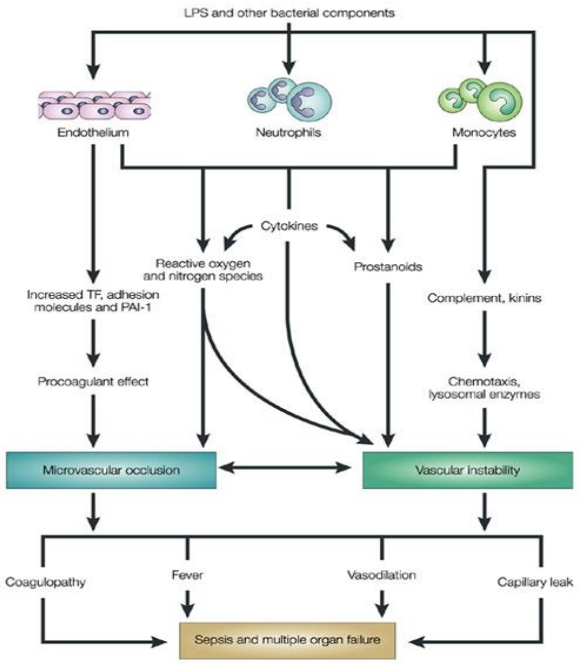

FIGURE 2. PATHOPHYSIOLOGY OF SEPSIS (LOLIS & BUCALA, 2003)

The body also has anti-inflammatory mechanisms including increased levels of anti-inflammatory cytokines and glucocorticoid hormones. The hormone inhibits the synthesis of cytokines by monocytes and decreases the ability of neutrophils to attach to the vascular endothelium. The inflammatory process in sepsis is not controlled leading to the occurrence of excessive discharge of inflammatory mediators over a long time and goes beyond the anti-inflammatory mechanisms of the body. This leads to various organ dysfunctions including cardiovascular, liver, pulmonary and renal dysfunctions (Hamzaoui & Carlet, 2009; Munford, 2011).

IV. CLINICAL MANIFESTATIONS

The clinical manifestations of sepsis are difficult to distinguish from the underlying disease or its primary infection. The process of developing such symptoms and signs differs between patients in that there are individual variations, depending on the inflammatory process, the severity of the infection and the affected organ system. Symptoms of sepsis are more severe in elderly people, cancer, diabetes and granulocytopenia patients (Pohan, 2005; Munford, 2011). Clinical manifestations of sepsis are not specific, usually preceded by fever, chills, malaise and restlessness. The places of infection are most often the tract of the digestivus, the pulmonary, the tract of the urinarius, the skin, soft tissues and the central nervous system. Gastrointestinal disorders that can be found include nausea, vomiting and diarrhea. Jaundice indicates the presence of hepar disorders. Skin disorders can be found if bacteria or their toxins spread to the skin (Hamzaoui & Carlet, 2009; Guntur, 2009).

V. EFFECTS OF SEPSIS ON ORGANS

5.1 Cardiovascular Dysfunction

Cardiovascular dysfunction includes cardiac and vascular dysfunction. Cardiac dysfunction leads to a decrease in the volume of the sekuncup, cardiac output (CO), the ejection fraction of the left ventricle and an increase in the volume of the systolic end as well as the diastolic end. This is associated with impaired left ventricular ability due to a decrease in the contractility of the myocardium. The causes are twofold, namely (Jones & Puskarich, 2009; Hamzaoui & Carlet, 2009):

a. Intrinsic factors
   Intrinsic factors that play a role include: a decrease in the number of L-type calcium channels so as to reduce the flow of calcium. increased production of nitric oxide (NO) associated with inducible nitric oxide synthase (iNOS). Nitric oxide causes heart dysfunction either directly or indirectly through peroxynitrite. the presence of apoptosis and structural abnormalities (myocyte necrosis, intersciial edema).
b. Extrinsic factors
   Extrinsic factors that play a role include: there are myocardial depressant factor (MDF) compounds that cause negative inotropic effects. the endothelial cells

surrounding the myocytes secrete various mediators that affect the functioning of the myocytes.

Vascular dysfunction is due to dilatation of blood vessels and increased permeability leading to the transfer of intravascular volume to the third cavity. Other factors that decrease intravascular volume are dehydration of the underlying disease, insensible water loss, vomiting and diarrhea. This situation will decrease the preload of the left ventricle as well as CO (Hamzaoui & Carlet, 2009; Jones & Puskarich, 2009; Munford, 2011). Vasodilation that occurs in sepsis is associated with excessive production of NO by cytokine-stimulated iNOS. Nitric oxide stimulates the relaxation of smooth muscle cells by stimulating the change of guanosine triphosphate (GTP) to guanosine monophosphate (GMP). Nitric oxide can stimulate damage to the central nervous system in the area that regulates autonomic control. Sepsis patients often have a decrease in vasoconstrictor response to catecholamines. This loss of sensitivity is due to downregulation of adrenergic receptors and an increase in NO levels (Neviere, 2008; Hamzaoui & Carlet, 2009; Munford, 2011).

5.2 Hepar Dysfunction

The cause of hepar disorder in sepsis is microvascular damage to hepar caused by (Backer, 2006; Hamzaoui & Carlet, 2009) : release of cytokines by Kupfer cells that have a cytotoxic effect on hepatocyte cells decreases portal blood flow due to the effect of NO secreted by intestinal cells

5.3 Pulmonary Dysfunction

Endothelial damage to the pulmonary blood vessels leads to impaired capillary blood flow and increases permeability. Neutrophils trapped in the microvascular lungs aggravate this damage. This gives rise to alveolar and intersciial edema, decreases pulmonary compliance, interferes with gas exchange, perfusion ventilation discrepancies occur thereby lowering the PO2 of the arteries. Frequent lung damage in sepsis is associated with the vastness of the microvascular surface of the lungs (Neviere, 2008; Munford, 2011).

5.4 Renal Dysfunction

Renal impairment is usually caused by acute tubular necrosis induced by a state of hypotension. Other circumstances that can be found include oliguria, azotemia, and proteinuria (Neviere, 2008; Munford, 2011).

VI. DIAGNOSIS

Diagnosis of sepsis is quite difficult to do because of the clinical manifestations that are less pronounced and similar to other non-infectious causes. Septic screen criteria can be used for rapid diagnosis of sepsis, namely positive sepsis when two or more criteria are found as follows (NNF Teaching Aids, 2009; Wynn, 2010):

1. *Leukopenia (total leukocyte count (TLC) < 5000/mm3)*
2. *Neutropenia (absolute neutrophil count (ANC) < 1800/mm3)*
3. *Immature neutrophil to total neutrophil ratio (IT) > 0.2*
4. *Blood sedimentation rate with westergreen pipettes (men > 10 mm/hour, women > 15 mm/h) CRP > 0.5 mg/dLInternational sepsis definition conference* (2001)

issuing a list containing a number of clinical manifestations of sepsis to aid the diagnosis of sepsis as shown in Table 1.

TABLE 1. SEPSIS DIAGNOSIS CRITERIA

It was found or estimated that there was an infection and some of the manifestations below:	
1	Common variables
	Fever (temperature > 38.3°C)
	Hypothermy (temperature < 36°C)
	Heart rate > 90 x/min or 2 standard deviations (SD) above normal values according to age
	Takipneu
	Changes in mental status

	Noticeable edema
	Hyperglycemia in patients not diabetes mellitus
2	Inflammatory variables
	Leukocytosis (leukocytes > 12,000/mm3)
	Leukopenia (leukocytes < 4,000/mm3)
	The number of normal leukocytes with an immature form > 10%
	CRP > 2 SD above normal values
	Procalcitonin > 2 SD above normal values
3	Hemodynamic variables
	Hypotension (systolic blood pressure (SBP) / systolic blood pressure < 90 mmHg, mean arterial pressure (MAP) / average arterial pressure < 70 mmHg or a decrease in blood pressure > 40 mmHg in adults or < 2 SD below normal values according to age
	Mixed venous oxygen saturation (SvO2) > 70%
	Heart index > 3.5 l/min/m2
4	Variable dysfunction of organs
	Hypoxemia (PO2/ fraction of inspired oxygen (FIO2) < 300)
	Acute oliguria (urine production < 0.5 ml/kg/hour)
	Increased creatinine > 0.5 mg/dL
	Coagulation disorders [(international normalized ratio) INR > 1.5 or [activated partial thromboplastin time (aPTT) > 60 seconds]
	Ileus
	Thrombocytopenia (platelet count < 100,000/mm3)
	Hyperbilirubinemia (total bilirubin > 4 mg/dL)
5	Variable perfusion of organs
	Hyperlactitation
	Decrease in capillary filling

(Carvalho & Trotta, 2003)

VII. LABORATORY OVERVIEW

Abnormalities that occur at the beginning of the course of sepsis include leukocytosis with a shift to the left, thrombocytosis, hyperglycemia, an increase in acute phase proteins such as CRP and PCT. Neutrophils may contain toxic granules, Dohle bodies and vacuums. Abnormalities found during sepsis that continue in the form of leukopenia, decreased fibrinogen, the presence of D-dimer, azotemia, and increased aminotransferase levels (Pohan, 2005; Thunder, 2009; Munford, 2011). Active hemolysis can occur in infection by microorganisms such as malaria. Analysis of blood gases indicates the presence of hypoxemia. Hyperventilation causes respiratory alkalosis at the beginning of the sepsis state then lactic accumulation and respiration muscle fatigue causes metabolic acidosis. Albumin levels initially within the normal range will then decrease as sepsis continues (Munford, 2011; Guntur, 2009).

The causes of sepsis are known by the isolation of microorganisms from the blood or local places of infection. Positive results are obtained from the culture or gram staining of samples e.g. blood, sputum, urine or body fluids. Positive blood cultures for bacteria or fungi were found in 20% to 40% of severe sepsis cases and 40% to 70% of sepsis shock cases. Blood samples for cultures of at least two pieces were obtained from different places of phlebotomy of 10 ml each. Some cases show a negative culture result caused by the previous use of antibiotics, the presence of slow-growing bacteria or no invasion of microorganisms into the blood. Gram staining or sample culture of the place of primary infection is carried out at the state (Neviere, 2009; Munford, 2011).

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