# Low-dose heparin for sepsis-associated disseminated intravascular coagulation and septic shock

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**Abstract**

***Background*: Sepsis and septic shock are severe clinical problems with high mortality rates, characterized by a systemic inflammation with substantial procoagulant elements and activating some clotting factors. Those are possible to develop the disseminated intravascular coagulation (DIC). Heparin is a well-known anticoagulant, which also provides anti-inflammatory properties. Nevertheless, the efficacy of heparin was limited by the potential risk of bleeding in critically ill patients. In this case report, we would like to explain the therapeutic effects of low-dose heparin on sepsis-associated DIC and septic shock.**

***Case report*: We report a case of a 60-year-old male with sepsis-associated DIC and septic shock caused by pneumonia. The patient had decreased consciousness for 10 hours before hospitalization. Standard intensive care and intravenous low-dose heparin (250 IU/h) were performed in the Intensive Care Unit (ICU). On day 12 of ICU admission, the patient's condition was fully conscious and clinically stable. Therefore, the patient discharged from ICU with no bleeding manifestation and no sequelae.**

***Conclusion*: Low-dose heparin successful treats patient with sepsis-associated DIC and septic shock.**

**Key words**: Disseminated intravascular coagulation (DIC), low-dose heparin, sepsis, septic shock.

## Introduction

Sepsis is an organ dysfunction caused by a dysregulated immune response to the infection. Sepsis can develop into septic shock with severe cardiovascular instability, multi-organ dysfunction syndrome (MODS), coagulopathy, and death. The mortality rate of sepsis is approximately 40% each year (about 660,000-750,000 death cases in the USA), whereas the mortality rates of septic shock between 40%-75% despite improvements in critical care standard therapy. (1-3)

Sepsis is an inflammatory disorder associated with coagulation abnormalities. Sepsis can promote mild coagulation to disseminated intravascular coagulation (DIC). (4) DIC is characterized by systemic activation of blood coagulation, which elevates intravascular thrombin and fibrin production. Long-term fibrin and thrombin elevation lead vascular thrombosis (small to medium-sized) MODS or severe hemorrhage. (5) The formation of MODS increases the mortality rates of sepsis. (6-8) Recent studies showed a complex correlation between inflammation and coagulation systems in sepsis. (1,8) Proinflammatory cytokines were capable to activates the coagulation system and downregulate the anticoagulant pathways. Otherwise, activated coagulation pathways may affect the inflammatory responses. An agent that capable to modulate the inflammation and coagulation are needed to treat sepsis patients. (9) Heparin is an inexpensive anti-

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coagulation drug that usually used in critical care patients. Several systematic reviews suggest that heparin doesn't only inhibit the coagulation system but also modulates the immune system. However, the efficacy of high dose heparin was limited by the potential risk of major hemorrhage in critically ill patients. (6,8,9) In this case report, we would like to present the therapeutic effects of low-dose heparin on sepsis-associated DIC and septic shock.

**Case report**

A 60-year-old male patient came to the emergency room with a decrease in consciousness. The patient has decreased consciousness for 10 hours before hospitalization. The patient had a history of fever and cough for 7 days before hospitalized and had been treated for 3 days but there was no improvement. The physical examination results were as follows: Glasgow Coma Scale (GCS) E3V3M4, respiratory rate 22 breaths/minutes, and there were rhonchi in the basal area of the lungs, oxygen saturation 98% with a 10 l non-rebreathing mask, blood pressure 120/80 mmHg, heart rate 130 bpm, and temperature 38.6 °C. The chest radiograph result was as follows: infiltrates in both basal of the lungs. Leukocytes 15,100/$mm^3$, platelets 52,000/µl, ureum 151 mg/dl, creatinine 3.52 mg/dl, C-reactive protein 354 mg/l, procalcitonin 55.26 ng/ml, total bilirubin 2.09 mg/dl, direct bilirubin 1.83 mg/dl, prothrombin time (PT) 10.9 seconds, international normalized ratio (INR) 1.01, activated partial thromboplastin time (aPTT) 57.6 seconds, and D-dimer level 10.51 ng/ml. The laboratory results fulfilled the diagnostic criteria of septic shock, sepsis-associated DIC, acute kidney injury (AKI) grade II, and pneumonia.

The patient was immediately transferred to the Intensive Care Unit (ICU). Following admission to ICU, the patient developed a decrease in GCS to E2V2M2, and increased respiratory rate to 28 breaths/minutes, requiring respiratory support by intubation and mechanical ventilation. The patient was given Adaptive Support Ventilation (ASV) mode breathing with positive end-expiratory pressure (PEEP) 10 and fraction of inspired oxygen (FiO2) 0.5. At this time, his blood pressure plummeted to 80/40 mmHg (mean arterial pressure [MAP] 50 mmHg), and his heart rate 110 bpm despite the administration of 500 ml of crystalloid. Hence, noradrenaline at 25 µg/minute was initiated to maintain his blood pressure 115/65 mmHg (MAP>65 mmHg). Two hours post intubation, his blood gas analysis was as follows: pH 7.331, pCO2 38.8 mmHg, pO2 113 mmHg, HCO3 20 mEq/l, base excess -5 mEq/l, SaO2 99%. The echocardiography revealed an ejection fraction of 76% with no ventricular wall motion abnormalities.

Patients received standard therapy in the ICU (feeding, analgesia, sedation, non-pharmacological thromboprophylaxis, head up position, ulcer prophylaxis, physiotherapy, and fluid therapy), broad-spectrum antibiotic therapy using meropenem, moxifloxacin, and micafungin while waiting the results of culture and antibiotic sensitivity tests. A low-dose intravenous heparin (250 IU per hour) was administered for 6 days to inhibit the hypercoagulable state that occurs in sepsis-associated DIC and septic shock.

During ICU admission, clinical and laboratory test showed an improvement day by day (**Table 1** and **Figure 1**). On day 7 of ICU admission, the results of the sputum culture test showed the presence of Acinetobacter baumannii, which was sensitive to tigecycline. Thus, meropenem and moxifloxacin administration were stopped. We performed an early tracheostomy to facilitate the weaning process. On day 12 of ICU admission, his condition was fully conscious and clinically stable. Therefore, the patient discharged from ICU with no bleeding manifestation or sequelae.

**Discussion**

Sepsis is an organ system dysfunction caused by a dysregulated inflammation. The untreated sepsis leads to the formation of septic shock, MODS, and death. Sepsis is commonly caused by respiratory and gastrointestinal infection. Sepsis affects almost 30 million people worldwide with a high mortality rate for up to 50%. The incidence of sepsis mostly affects people in the age range of 60-84 years old. In the last several decades the mortality rates of sepsis have decreased, but the morbidity rates significantly increase. (3,10,11) There are three critical phases of sepsis, including the presence of infection, the abnormal or dysregulated inflammation, and the organ system dysfunction. Sepsis triggers the organ system dysfunction with increasing of the Sequential Organ Failure Assessment (SOFA) score 2 points or more.

Septic shock is a subset of sepsis with circulatory and cellular-metabolic dysfunction associated with higher mortality rates, approaching 70%, especially in low and middle income countries. Septic shock also defined as circulatory and cellular-metabolic abnormalities with persistent hypotension, requiring vasopressors therapy to maintain MAP≥65 mmHg and serum lactate >2 mmol/l, despite the adequate volume of resuscitation. (1,10) Sepsis and septic shock are characterized by a systemic inflammation with substantial procoagulant

elements and activating some clotting factors. Coagulation is related to the inflammatory response and needed in the body defends against infection. However, the thrombocytopenia in coagulation process increases the risk of sepsis. The inflammatory mediators activate the coagulation system, make consumption of multiple clotting factors, and resulting in sepsis-associated DIC. (2,8)

The key factor of sepsis-associated DIC is the systemic inflammatory response to the infection. The causative microorganisms express unique cellular constituents called pathogen-associated molecular patterns (PAMPs) that recognized by the pattern recognition receptor (PRR) cells of the innate immune system. Other than that, the immune system also responses to the danger-associated molecular patterns (DAMPs), a molecular pattern caused by trauma, ischemia, and tissue damage. (7) PAMPs and DAMPs will trigger tissue factor (TF) expression on the neutrophil, macrophages, and monocytes through the toll-like receptor (TLR) signalling pathway. Bacterial-induced TLR signalling also may stimulate nuclear factor-κB (NF-κB) that leads to the production of the pro-inflammatory cytokines. The activated monocyte produces various pro-inflammatory cytokines including interleukin-1α (IL-1α), IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and high mobility group box-1 (HMGB1). HMGB1 promotes TF upregulation in endothelial cell (EC), expresses plasminogen activator inhibitor-1 (PAI-1) and thrombomodulin (TM) downregulation. The combination of pro-inflammatory cytokines, upregulation of pro coagulant pathways, and downregulation of physiological anticoagulant molecules cause microcirculation disorder and massive thrombin formation, which may contribute to localized venous thromboembolism, acute DIC and septic shock formations. (8,11,12)

In this case report, the patient was diagnosed with septic shock with SOFA score more than 2, needed vasopressors to maintain MAP≥ 65 mmHg despite adequate volume resuscitation, and had pneumonia (infiltrate on chest radiograph with fever, leukocytosis, and hypoxemia). He was also diagnosed with sepsis-associated DIC with the Japanese Association for Acute Medicine (JAAM)-DIC score ≥4. (13) We administered a low-dose of intravenous heparin (250 IU per hour) for 6 days to inhibit over-inflammation and hypercoagulation that occur in sepsis-associated DIC and septic shock. (1,6) Heparin is a common anticoagulant agent used in acute thrombosis due to the rapid onset and the availability of antidote. It has an effective anticoagulant mechanism by the indirect effect on antithrombin (AT). Heparin causes a conformational change of AT and increases the flexibility of its reactive site loop. The activated AT inactivates thrombin and other proteases, including factor Xa, XIa, and XIIa. Therefore, it reduces the production of excess thrombin and essential for DIC therapy. (8,11) Heparin also has a strong affinity for extracellular histones, a new class of DAMPs, that result from cellular destruction during sepsis. Histones are strongly associated with endothelial dysfunction, organ failure, and death during sepsis and septic shock. Several studies showed heparin has histone-neutralizing effects, which suggests heparin could prevent cytotoxicity and collateral organ damage from histones. Moreover, heparin directly affects pro-inflammatory mediators, such as NF-κB and pro-inflammatory cytokines (TNF-α, IL-6, IL-8, and IL-1), and attenuates EC dysfunction through the nitric oxide system. Several studies show that heparin was safe as there was no increased risk of bleeding. (6,8,11) So, heparin which is commonly available and inexpensive, could be an optimal therapeutic agent, targeted at both coagulation and inflammation in sepsis-associated DIC and septic shock.

The standard therapy for septic shock-associated DIC were fluid, vasopressor, antibiotic, surgical drainage at the infection site, and supportive treatment for abnormalities in the coagulation system. Surviving Sepsis Campaign (SSC) guidelines do not recommend any treatment associated coagulopathy such as anticoagulant. Heparin 1500 IU/day is only recommended in the prophylaxis venous thromboembolism if the heparin contraindication such as thrombocytopenia and bleeding are absence. (1)

The common therapy used for septic shock-associated DIC are antibiotic, fluid, vasopressor, and without anticoagulant. We performed a therapy using antibiotic, fluid, vasopressor, and anticoagulant (low dose heparin). We used low dose anticoagulant because it has an anti-inflammatory action by bind histones and prevent histone-mediated cytotoxicity. Low-dose heparin overcomes the hypercoagulation state that promotes the formation of thrombus, which leads the system organ dysfunction in the septic patient, without increase risk of bleeding. (14,15)

## Conclusion

We described successful treatment on a 60-year-old male patient with sepsis-associated DIC and septic shock caused by pneumonia. We used low-dose heparin (250 IU per hour) because it has anti-coagulant and anti-inflammatory properties. Hepa-

rin is providing an optimal therapeutic agent for sepsis-associated DIC and septic shock caused by pneumonia without bleeding. Low-dose heparin becomes a safe therapeutic agent of sepsis-associated DIC and septic shock.

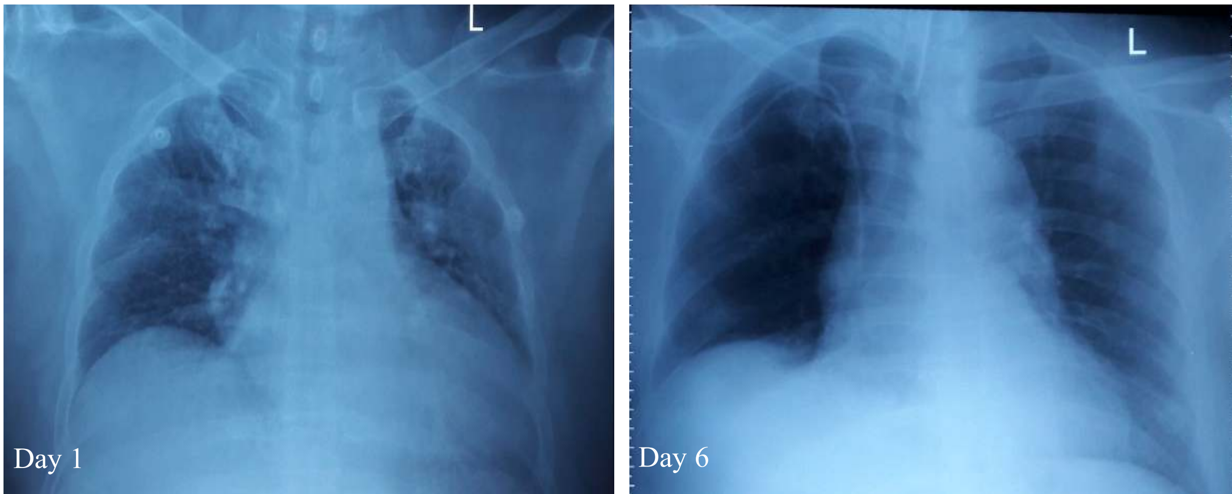
**Conflict of interest**
The authors declare there is no conflict of interest.

**Table 1**. Daily vital signs, vasopressors, and laboratory results of the patient

| | Day 1 | Day 2 | Day 4 | Day 6 | Day 9 | Day 11 |
|---|---|---|---|---|---|---|
| Blood pressure (mmHg) | 80/40 | 130/80 | 140/70 | 140/80 | 130/70 | 130/80 |
| Respiratory rate (breaths/minute) | 30 | 24 | 22 | 15 | 15 | 14 |
| Norepinephrine (µg/minute) | 24 | 20 | 10 | 0 | 0 | 0 |
| Leukocytes (/mm$^3$) | 15,100 | 21,570 | 20,160 | 11,490 | 12,721 | 6,000 |
| Platelets (/µl) | 52,000 | 55,000 | 128,000 | 182,000 | 151,000 | 141,000 |
| D dimer (ng/ml) | 10.51 | 9.6 | 8.32 | 3.69 | 1.8 | 1.5 |
| aPTT (seconds) | 57.6 | 50 | 47 | 30 | 43 | - |
| P/F ratio | 226 | 250 | 330 | 265 | 336 | 506 |
| Ureum (mg/dl) | 151 | 208 | 221 | 184 | 89 | 76 |
| Creatinine (mg/dl) | 3.52 | 4.33 | 3.09 | 2.17 | 1.2 | 1.03 |
| eGFR (ml/min/1.73 m$^2$) | 18.3 | 14.2 | 21.4 | 32.8 | 67.2 | 80.8 |

Legend: aPTT=activated partial thromboplastin time; P/F ratio=PaO2/FiO2 (Horowitz index for lung function); eGFR=estimated glomerular filtration rate.

**Figure 1**. Chest radiographs of the patient showed an improvement



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