



## Inflammation, Coagulation Process in Sepsis and LMWH Role in it

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### ABSTRACT

Despite advances in antibiotic treatment, mechanical ventilation, fluid resuscitation, and blood glucose control, sepsis continues to be a leading cause of death in critical care units. To present, no effective treatment regimens for the routine management of septic patients exist. The core pathophysiology of sepsis is influenced by the substantial interaction between inflammation and coagulation. As a result, medicines that reduce the activation of both inflammation and coagulation may help to improve sepsis outcomes. Heparin, in addition to its well-known anticoagulant properties, also has immunomodulatory capabilities and prevents glycocalyx from shedding. As a result, heparin appears to be such an agent. Anticoagulant therapy should be given at the right time, as immunothrombosis plays an important role in the initial host defense against bacterial growth. We explore the scientific and clinical evidence that supports the use of heparin in sepsis. Heparin's usage in the treatment of sepsis is currently debatable. Future heparin treatment trials for sepsis should focus on the most critically ill subjects, where benefit is most likely to be shown.

**Keywords:** Heparin, Sepsis, Inflammation, Coagulation, LMWH.

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### INTRODUCTION

Sepsis is a systemic illness characterised by a systemic inflammatory response syndrome triggered by pathogenic microorganisms, most commonly bacteria<sup>1,2</sup>. Sepsis is a disrupted immune response to infection that sets off a chain reaction of interrelated systems<sup>3</sup>. The pathophysiological transition process is difficult. Various pathological alterations, including as inflammation, coagulation function, immunological function, and microcirculation, occur throughout the course of the disease<sup>4</sup>. One or more of the following symptoms may occur as a result of sepsis: Breathing and heart rate are both quite fast. Breathing problems, Confusion or disorientation are two words that come to mind when people think of confusion. Fever, shivering, or feeling extremely cold, clammy or damp skin Severe sepsis can result in septic shock, which causes your blood pressure to drop dangerously low and many organs to fail<sup>5</sup>.

Inflammation of the vascular endothelium causes loss of integrity and increased permeability, allowing fluid and protein to escape into the perivascular tissues and lymphatics, exacerbating hypotension in sepsis. Long-term

hypotension causes hypoperfusion, which leads to Sepsis shock. Cardiogenic, hypovolemic, obstructive, or distributive/vasodilatory aetiologies cause it to develop. The most prevalent type of distributive/vasodilatory shock is septic shock, which is caused by the release of vasoactive mediators such as prostacyclin and nitric oxide (NO). These mediators cause vasodilation and eventually hypotension by suppressing autoregulation of blood flow and perfusion in central, regional, and microcirculatory beds. As a result, septic shock resembles hypovolemic shock. Because of the myocardial depressive effects of a variety of circulating mediators, septic shock can also have cardiogenic symptoms<sup>6</sup>.

### Immune response to infection

Depending on the microenvironment and most likely the timing of the process, the immune response to infection includes a complex array of cellular and chemical mediators that flow in cascades, activating or inhibiting other components (Figure 1)<sup>7</sup>. Homeostasis is easily restored after infection or injury if the balance of these counter-regulatory systems is maintained. The implications of a considerable dysregulation of the process might be severe, resulting in increasing inflammation and MODS.

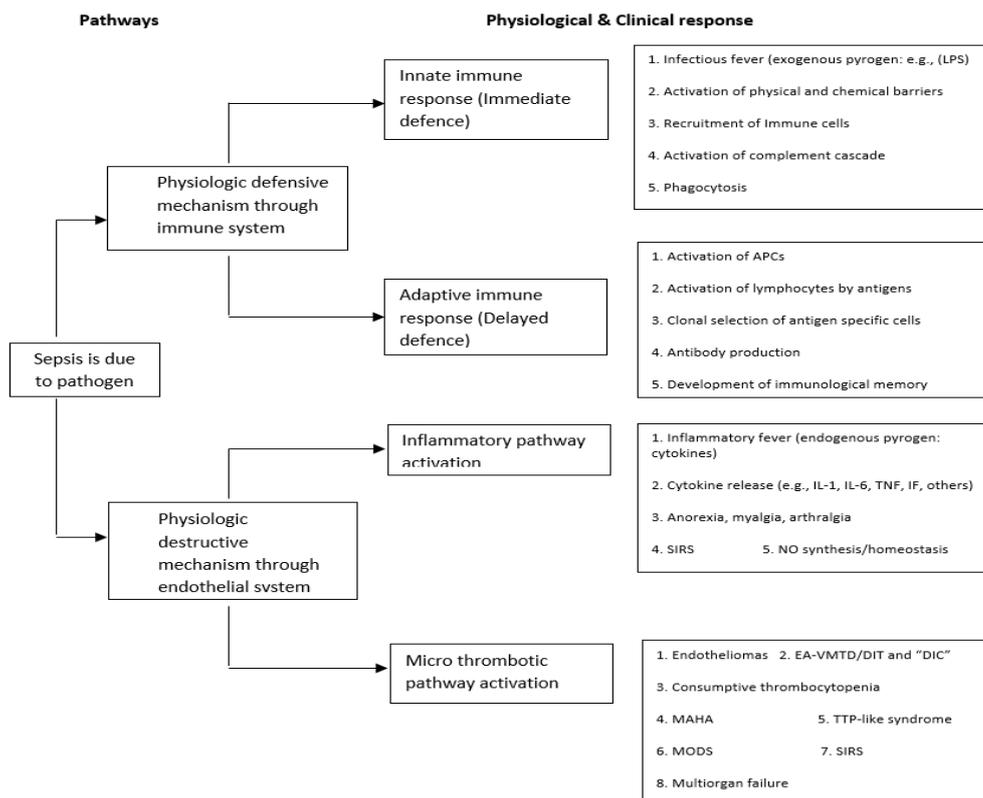
Following the invasion of pathogens, the human body's hemostatic function is stimulated to fight infection, resulting in the formation of thrombin and fibrin, both of which encourage the onset of inflammation<sup>8</sup>. Furthermore, the fibrinolytic process is inhibited. Thrombocytopenia, disseminated intravascular



coagulation, micro thrombosis, and multiple organ dysfunction syndrome (MODS) can all be caused by excessive procoagulant and antifibrinolytic reactions<sup>9</sup>.

The coagulation system becomes diffusely activated in severe illness, leading to the consumption of several

clotting factors, creating Disseminated Intravascular Coagulation (DIC). When DIC is present, a greater death rate is predicted. The development of therapeutic approaches will be aided by a better understanding of the pathways that link inflammation with diffuse thrombosis<sup>10</sup>.



**Figure 1:** Illustration of the many potential pathways and responses in sepsis<sup>7</sup>. In sepsis, host response is characterized by 2 mechanisms: a physiologic defensive mechanism mounted through immune system and a pathologic destructive mechanism mounted through the endothelial system. The physiologic response and pathologic clinical syndromes are notated in this figure. It is now known that the complement system, while protecting the host through activation of its innate immune system, could trigger harmful endothelial pathogenesis. This dual role of the complement system can be viewed as similar to normal hemostasis, which protects humans in the event of external bodily injury but also may cause harm in the form of intravascular injury through thrombogenesis. APC indicates antigen presenting cell; DIC, disseminated intravascular coagulation; DIT, disseminated intravascular micro thrombosis; EA-VMTD, Endotheliopathy-associated vascular micro thrombotic disease; MAHA, microangiopathic hemolytic anemia; MODS, multiorgan dysfunction syndrome; MOF, multiorgan failure; NO, nitric oxide; IF, interferon; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor; TTP, thrombotic thrombocytopenic purpura<sup>3</sup>.

Acute Sepsis Coagulopathy is a dynamic process that is time and illness burden dependent. Coagulation whole blood testing may provide more clinically valuable information than traditional tests. In sepsis, natural anticoagulants that control thrombosis are downregulated. When there is systemic inflammation and hypercoagulopathy, patients may benefit from coagulation system regulation. Anticoagulant medication administered at the right time may reduce the risk of multisystem organ dysfunction (MODS)<sup>10</sup>.

Sepsis is characterised by cytokine production, an imbalance of pro-inflammatory and anti-inflammatory reactions, immune system overactivation, and immunological dysfunction. The synthesis of TNF- α and IL-1 together initiates an inflammatory response in the early stages, and a significant number of inflammatory mediators

rises. TNF- is one of these inflammatory mediators that causes body damage from bacterial endotoxins, and its blood level has a direct impact on the prognosis of patients with severe sepsis<sup>11</sup>. The two cytokines mentioned above cause IL-6 to be produced. Under the influence of IL-6, T cells multiply and B lymphocytes generate and release immunoglobulin. The phagocytosis process of ageing neutrophils will slow down as a result of IL-6, resulting in a significant rise in the concentration of inflammatory mediators. As a result, IL-6 can be utilized to evaluate the severity and prognosis of patients with sepsis. The patient's prognosis is frequently poor if the concentration of IL-6 rises sufficiently<sup>12</sup>.

Platelets, which should be in a quiet state in normal blood circulation, are activated immediately once the vascular endothelium of septic patients is injured, bind to the

damaged sections of the vascular endothelium, and release numerous coagulation factors. Platelet activation factors are produced at the same time, resulting in continuous platelet activation, coagulation dysfunction, severe microthrombosis, enormous platelet and coagulation factor depletion, and the formation of disseminated intravascular coagulation<sup>13</sup>. Platelets that have been activated can generate leukocyte and neutrophil aggregation and activation, encourage platelet aggregation, and release cytokines and coagulation factors, all of which exacerbate the body's inflammatory response and vascular damage. At the same time, the patient's physiological anticoagulation pathway is disabled. Although tissue plasminogen activator generated by endothelial cells can activate the fibrinolytic system in the early stages, the level of plasminogen activator inhibitor-1 in the blood increases with the progression of the disease, and the plasminogen system's action is also reduced<sup>14</sup>. In septic patients, platelet counts frequently drop.

### The Importance of Coagulation Abnormalities Caused by Inflammation

There's evidence that coagulation activation combined with inflammatory activation might cause microvascular thrombosis, which can lead to multiple organ failure in people with severe sepsis<sup>15</sup>. Several reports of postmortem findings in septic patients with coagulation disorders and DIC have been reported<sup>16,17</sup>. Diffuse bleeding, hemorrhagic necrosis of tissue, micro-thrombi in small blood vessels, and thrombi in mid-size and larger arteries and veins are among the postmortem findings. Ischemia and necrosis were shown to be related with fibrin accumulation in small and medium-sized vessels of several organs<sup>18</sup>. Importantly, the development of these intravascular thrombi appears to be directly linked to the onset of organ dysfunction. In the kidneys, lungs, liver, brain, and other organs, experimental bacteremia or endotoxemia promotes intravascular and extravascular fibrin deposition. In some, but not all, cases, improving the hemostatic deficit with various therapies appears to enhance organ failure and mortality in these experimental models<sup>19-22</sup>. Surprisingly, some research suggests that improving systemic coagulation activation will have a significant positive impact on the resolution of local fibrin deposition and the alleviation of organ failure<sup>23,24</sup>. Finally, clinical investigations back up the idea that coagulation is a key driver of clinical outcome. DIC has been found to be a reliable predictor of organ failure and death<sup>25,26</sup>.

Patients with DIC had a 43 percent mortality rate compared to 27 percent for those without DIC in a group of patients with severe sepsis. In septic patients, mortality was likewise linked to the severity of the coagulopathy<sup>27</sup>. Coagulatory disorders can cause a variety of problems, including microvascular thrombosis and organ failure. Thrombocytopenia, for example, increases the risk of bleeding in individuals with sepsis<sup>28</sup>. Critically ill individuals with a platelet count of 50 x 10<sup>9</sup>/L, in instance, have a four- to five-fold increased risk of bleeding than those with a

higher platelet count<sup>29,30</sup>. The incidence of intracerebral haemorrhage in patients in the intensive care unit (ICU) is modest (0.3 percent to 0.5 percent), yet platelet counts of 100 x 10<sup>9</sup> /L are seen in 88 percent of patients with this problem<sup>31</sup>. In multivariate analysis, thrombocytopenia is an independent predictor of ICU mortality, with a relative risk ranging from 1.9 to 4.2 in distinct studies<sup>29,30,32</sup>. A four-fold to six-fold increase in mortality is related with sustained thrombocytopenia more than four days after ICU admission or a 50% fall in platelet count during ICU hospitalisation<sup>29,33</sup>. Platelet count was found to be a better predictor of ICU mortality than composite grading systems like the APACHE II score or the Multiple Organ Dysfunction Score (MODS). Low levels of coagulation factors, as seen by longer global coagulation times, may also be a risk factor for bleeding and mortality in patients with sepsis. In critically unwell patients, a prothrombin time or partial thromboplastin time ratio of 1.5 was observed to predict severe bleeding and higher death<sup>34,35</sup>.

### How Does Inflammation Lead to Coagulation Activation?

Tissue factor-mediated thrombin production and an imbalance or impairment of the usual physiologic anticoagulant mechanisms, such as the antithrombin system and the protein C system, are the principal mechanisms of coagulation derangement during systemic inflammatory activity<sup>15,36</sup>. In addition to increased fibrin production, fibrin clearance is hampered by the fibrinolytic system's depression.

### The mechanism of anticoagulant activity

Coagulation is a complex process that involves platelets, soluble proteins, and cellular components such monocytes and endothelial cells, and haemostasis is maintained by a balance of clotting factors and coagulation inhibitors<sup>37</sup>. Heparin is a glycosaminoglycan that has both anticoagulant and anti-inflammatory properties. It has been widely utilised in clinical practise for many indications, particularly for the prevention and treatment of venous thromboembolism (VTE) from its discovery in 1916 and early clinical use in the late 1930s<sup>38,39</sup>.

AT is the most common plasma coagulation inhibitor, and it works by inhibiting active coagulation factors including XIIa, XIa, Xa, IXa, VIIa, and thrombin. Heparin interacts with the coagulation system in a variety of ways, but its interaction with AT to block thrombin and factor (F) Xa action is unique. An arginine-reactive region on the AT molecule clearly inhibits the active core serine of thrombin and other coagulation enzymes. Heparin works as an anticoagulant by binding to the lysine site on AT and causing a non-reversible conformational modification at the arginine-reactive site, inhibiting thrombin by up to 1000 times<sup>40</sup>.

Given that a ternary complex must be formed simultaneously between heparin, AT and thrombin, thrombin inhibition necessitates a heparin chain with at least 18 saccharide units. As a result, unfractionated heparin (UFH) but not low-molecular-weight heparin (LMWH) can cause it<sup>41</sup>. Furthermore, UFH binds to heparin





(factor II), and calcium, resulting in the formation of thrombin (factor IIa). The conversion of fibrinogen to fibrin is one of thrombin's most important actions. The tissue factor-factor VIIa complex can also activate factor IX, resulting in the formation of a tenase complex with activated factor IX and factor X, which generates more factor Xa, constituting an important amplification loop.

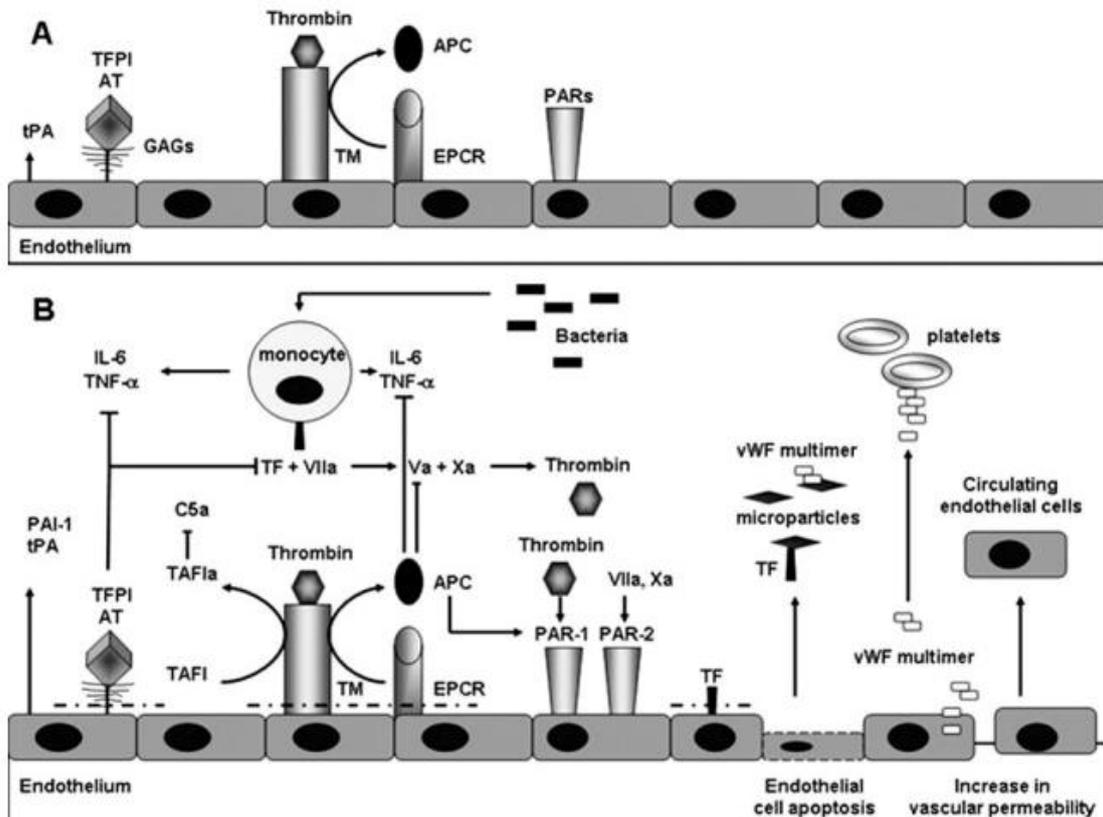
If an adequate phospholipid surface is available, ideally presented by active platelets, the assembly of the prothrombinase and tenase complex is greatly enhanced. Platelets can be activated directly by endotoxin or indirectly by proinflammatory mediators such as platelet activating factor in the context of inflammation-induced coagulation activation. In vivo, thrombin is one of the most powerful platelet activators.

Platelet activation may also enhance fibrin production through another route. The presence of platelets and

granulocytes stimulates tissue factor expression on monocytes in a P-selection-dependent reaction<sup>55</sup>. This action could be caused by active platelets attaching to neutrophils and mononuclear cells, which activates nuclear factor kappa B<sup>56</sup>. This cellular contact also boosts IL-1b, IL-8, monocyte chemoattractant protein-1, and tumour necrosis factor (TNF)-alpha production<sup>57</sup>. Platelet adhesion to endothelial cells and leukocytes is mediated by P-selection expression on the active platelet membrane.

**Physiologic Anticoagulant Pathways are Down-Regulated During Inflammation**

Antithrombin (AT), the protein C system, and tissue factor pathway inhibitors (TFPI) are three major anticoagulant pathways that control procoagulant activity. The function of all three routes can be affected during inflammation-induced coagulation activation<sup>58</sup>. (Fig.3).



**Figure 3:** The role of the endothelium in normal situations and in sepsis. (A) In normal situations, the endothelial layer provides for an anticoagulant surface to prevent the blood from clotting by expressing thrombomodulin (TM) and endothelial PC receptor (EPCR), which support thrombin in generating activated PC (APC), by having TF pathway inhibitor (TFPI) and antithrombin (AT) attached to their surface and by secreting tissue-type plasminogen activator (tPA), which promotes fibrinolysis. (B) When in infection bacteria invade the bloodstream, systemic activation of inflammation leads to cytokine release and endothelial activation and dysfunction, resulting in release of MPs, apoptosis, detachment of ECs, and loss of barrier function. Coagulation is activated by induction of TF on monocytes and MPs and possibly on endothelium and by release of von Willebrand factor (vWF), which adds to platelet adhesion to the subendothelial surface and platelet aggregation. Production of glycosaminoglycans (GAGs) is down-regulated, and the anticoagulant proteins TFPI, AT, EPCR, and TM are cleaved from the EC surface and are impaired in action. Moreover, APC and AT are consumed. Fibrinolysis is impaired as a result of a rise in the main inhibitor of the PA (PAI-1), which outweighs a rise in tPA, and complement activation is enhanced by loss of activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which normally inhibits complement factor C3a and C5a and bradykinin activity. Anticoagulant proteins in turn modulate cytokine-release: tissue factor-factor VIIa (TF-FVIIa), factor (F) Xa, and thrombin exert proinflammatory activity by cleaving mainly PAR-1 and PAR-2. APC cleaves PAR-1 in an EPCR-dependent manner and hereby modulates inflammation and apoptosis<sup>59</sup>.

Antithrombin, a serine protease inhibitor, is the primary inhibitor of thrombin and factor Xa. AT neutralises coagulation enzymes in a slow, progressive manner without heparin<sup>60</sup>. AT undergoes structural changes in response to heparin, resulting in a 1000-fold increase in AT activity. Heparin's clinical effectiveness is thus related to its interaction with AT. Endogenous glycosaminoglycans on the vascular wall, such as heparan sulphates, also facilitate AT-mediated thrombin and other coagulation enzyme inhibition. AT levels are considerably reduced during severe inflammatory responses due to poor synthesis (as a result of a negative acute phase response), elastase destruction by activated neutrophils, and quantitatively most critically consumption as a result of continuing thrombin generation<sup>61</sup>.

### Heparin and the inflammatory response

Heparin has been known to reduce certain components of the allergic inflammatory response since the 1920s. Heparin and related glycosaminoglycans have been shown to alter the activity of a variety of inflammatory cells, including T-cells and neutrophils, in recent investigations. In a concentration-dependent manner, heparin suppresses the respiratory burst of neutrophils activated with N-formyl-methionyl-leucyl-phenylalanine. In vitro, dermatan sulphate and low molecular weight dermatan sulphate had significantly lower inhibitory activity, although heparin derivatives with low anticoagulant activity prevented superoxide anion production to varying degrees. The inhibitory activity of a 2-O-desulphated heparin derivative was equivalent to that of heparin, although it was much more effective than N-desulphated heparin. Heparin and a low molecular weight heparin (2 kDa) inhibited the release of neutrophil enzymes from azurophilic granules as well as neutrophil homotypic aggregation. The efficacy of heparin derivatives, such as 2-O-desulphated heparin and N-desulphated heparin, to block enzyme release was also investigated. The ability of these heparin derivatives to block this process was correlated with a rise in total sulphate concentration.

Heparin's connection with superoxide dismutase-L allows it to neutralise harmful substances such as superoxide radicals produced by active leukocytes. These findings suggest that heparin can protect endothelium and tissue parenchyma against neutrophil damage through a variety of mechanisms. Heparin can also reduce mast-cell activation mediated by non-immunological and immunological stimuli. Heparin is thought to block the endoplasmic reticulum's inositol 1,4,5-trisphosphate receptors, preventing the release of intracellular Ca<sup>2+</sup> along with the downstream signals required for mast-cell degranulation. Heparin also suppresses the cytotoxicity of eosinophil-derived cationic proteins such as major basic protein and regulates the activity of mast-cell tryptase.

Heparin and related compounds can reduce leukocyte adhesion to the vascular endothelium and subsequent trafficking of these cells into tissues, according to a growing body of evidence. On monocyte and neutrophil adherence

to endothelium, as well as lymphocyte adhesion to endothelium, a well-reviewed paradigm has been established. Activated endothelium interacts with these cells first via carbohydrate-selectin interactions. Selectins are a family of C-type (Ca<sup>2+</sup>-dependent) lectin receptors that are expressed on activated endothelium (E-selectin), platelets (P-selectin), and leukocytes (L-selectin) and are (the endothelium contains both E- and P-selectins). Second, rolling leukocytes engage with particular chemoattractants, which are presented on the cell surface by the heparan sulphate proteoglycan. Third, integrins, which are increased on leukocytes, firmly bind to their corresponding locations on the endothelium (members of the immunoglobulin superfamily). The cells pass through the endothelium and move to the inflamed area along a chemoattractant gradient<sup>62</sup>.

### Low-Molecular-Weight Heparin

Standard supportive therapy for sepsis includes low-molecular-weight heparin (LMWH), however clinical studies on anticoagulant therapy is still debated. From UFH, LMWH is degraded and refined. Heparin acts as an anticoagulant by increasing antithrombin activity and inactivating Xa and IIa (thrombin) factors, according to studies. Because thrombin is strongly linked to inflammation, inhibiting it is similar to inhibiting inflammation. As a result, heparin is thought to have an anti-inflammatory action separate from its anticoagulant effect, and there is no link between the two. It has a rapid and long-lasting antithrombotic action, and it is commonly employed in clinical settings. LMWH has the following advantages over UFH: (I) it has a stronger anti-factor Xa effect and does not require close monitoring of factor Xa; (II) it has a high bioavailability and a long half life; (III) it requires less antithrombin III; and (IV) it has a low risk of thrombocytopenia and less spontaneous haemorrhage<sup>63</sup>.

According to the findings of a meta-analysis, the LMWH group can reduce APACHE II score, 28-day mortality rate, and MODS incidence rate by statistically significant amounts. With statistically significant differences, the LMWH group can considerably lower serum TNF- $\alpha$  and IL-6 cytokine levels, raise platelet count, and lower PT and serum D-dimer levels. However, the findings of the sensitivity analysis suggest that these two indicators are not as strong as they appear to be, which may be due to the sample size and must be confirmed with a larger sample size. As a result, more research is needed to establish the finding that LMWH dramatically lowers PT when compared to standard treatment<sup>63</sup>.

### CONCLUSION

Increased understanding of the molecular mechanisms underlying the intimate link between inflammation and coagulation could lead to the discovery of new therapeutic targets for modifying excessive activation or dysregulation of these systems. In the medical literature, the findings on heparin therapy in septic patients have sparked numerous debates. UFH has considerable immunomodulatory effects in addition to its well-known anticoagulant properties.



Heparin is still unknown as a critical supplementary medication in the treatment of sepsis. Future heparin treatment for sepsis clinical trials may focus on the most critically ill patients with the highest predicted mortality, as this is the group where benefit is most likely to be demonstrated. Each of the studies mentioned has helped us take a modest step ahead. Heparin investigations will undoubtedly pave the way for breakthroughs in the treatment of sepsis in the long run. Hopefully, by implementing all of these strategies at the same time, the death rate of this deadly disease will be significantly reduced.

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