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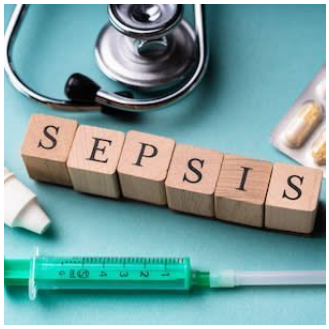
Venous Thromboembolism in Sepsis



Septic patients are often affected by coagulation disorders. Hence, they are at a high risk of thrombotic complications, ranging from widespread microvascular involvement, such as disseminated intravascular coagulation, to venous thromboembolism, arising as deep vein thrombosis or pulmonary embolism.

Over the years, knowledge about the interconnected and reciprocal influence of immune and coagulation systems has emerged. This phenomenon is called immunothrombosis. It indicates an effective response where immune cells and the coagulation cascade cooperate to limit pathogen invasion and endothelial damage.
In sepsis, this network becomes dysregulated due to systemic inflammatory activation. This can cause pathological thrombosis. The main elements involved in this process include the endothelium, platelets, neutrophils and the TF and coagulation cascade that play a critical role in the host defense and thrombogenesis.

Heparin is the primary therapeutic response to this phenomenon. However, the use of heparin is not always effective. There is a need to better understand this relationship to identify more effective clinical instruments to establish thrombotic risk and treatments that address the connection between coagulation and inflammation. However, no effective alternatives have been found so far.

This review discusses the role of sepsis-related inflammation in the development and resolution of venous thromboembolism and its clinical implications. Researchers identified keywords to explore the association between sepsis and venous thromboembolism, such as sepsis, thromboembolism, venous thrombosis, deep
vein thrombosis, thromboinflammation and coagulopathy. They performed literature and selected articles from the last ten years. Studies related to COVID-19 infection, which presents an elevated incidence of VTE, were also included in the analysis.

In sepsis, the chemical or physical vascular damage due to infectious pathogens can interrupt the integrity of the endothelial barrier with the exposure of collagen and tissue factor (TF) to the bloodstream. This TF expression can be considered the initiating event in the coagulopathy of acute sepsis. Sepsis inflammation stimulates the release of platelet-activating factor (PAF), which accelerates platelet activation. This contributes to the upregulation of TF and leads to thrombin generation.

Immune cells play an important role in response to pathogens and in the genesis of thrombotic processes during sepsis. In particular, neutrophils are the first line of defense during sepsis. Hence, neutrophils can be considered an interesting target for therapeutic interventions. However, their systemic modulation or depletion could comprise the entire host defence system, so it may not be a sustainable therapeutic option.

COVID-19 also presents an increased risk for micro and macrovascular thrombosis. The process starts from the downregulation of angiotensin-converting enzyme 2 (ACE-2) activity. The activation of ACE-2 results in reduced conversion of angiotensin II into angiotensin 1–7, which has important anti-inflammatory and antithrombotic functions.

Overall, coagulation disorders are a major cause of death during sepsis. However, the lack of effective diagnostic instruments and strategies continues to be a challenge. There is a need for clinical instruments that address the connection between coagulation and inflammation. Similarly, the Surviving Sepsis Guidelines recommend only VTE prophylaxis and favour low molecular weight heparin. But the use of heparin and other anticoagulant agents does not take into account the correlation between the immune system and coagulation factors. The best dosages of heparin to use are still unclear. Thus, a clearer understanding of the crosstalk between inflammation and coagulation is needed to stimulate the discovery of new therapeutic targets.

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