

Sepsis Induced Coagulopathy – Bringing Science to the Bedside

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Sepsis and septic shock have been twin enigmas for both clinicians and researchers alike. Over several decades, a standard definition, a definite pathophysiological pathway, a clinching diagnostic test, and an all-encompassing therapeutic solution have all remained elusive. The most recent definition of sepsis considers it as a dysregulated host immune response to infection.¹ Organ dysfunction has been the main consequence of such a dysregulated immune response. Dysfunction of major organs such as the brain, heart, liver, and kidneys, in the context of sepsis, have been well recognized and described. But, the most consistent accompaniment of the sepsis syndrome seems to be the failure of coagulation. The clinical manifestations of sepsis-induced coagulopathy (SIC) range from isolated thrombocytopenia through mild derangements of coagulation to florid disseminated intra-vascular coagulation (DIC).² Coagulation may be a natural defense mechanism operating in the initial phase of sepsis.³ However, it could manifest as impairment of fibrinolysis and suppression of anti-coagulant mechanisms in severe forms of sepsis. Patients with sepsis could therefore be either prothrombotic or coagulopathic depending on the predominance of the mechanism active at a particular point of time. Assessment of the coagulation pattern, therefore, is an integral part of the organ function assessment among patients with sepsis. Conventionally, the assessment has been carried out using standard tests such as platelet count, prothrombin time (PT), international normalised ratio (INR), and fibrin degradation products (FDPs) like D-Dimer and fibrinogen.⁴ The availability of tests evaluating the anticoagulant proteins and visco-elastic properties of blood has strengthened the armamentarium for the diagnostic workup of coagulation status in sepsis.

The most important aspect to consider while discussing the coagulation abnormalities in Sepsis is the potential cross-talk between the inflammatory process and the hemostatic mechanisms. It is well recognized that there is a bidirectional interplay between inflammation and coagulation during the septic process.⁴ This seems to be a self-sustaining cycle and is driven by high levels of pro-inflammatory mediators such as tumour necrosis factor α (TNF- α) and interleukin-6 (IL-6). In addition, the interaction of coagulation proteins with cell receptors, results in the modification of the inflammatory pathways.⁵ This interaction is mediated by the protease activated receptors (PARs).⁶ The interaction between complement and hemostasis also seems to play an important role in the genesis of DIC.⁷ It is also now well understood that there is a significant cross-talk between mediators of inflammation and anti-coagulant factors.⁵ This discussion, would therefore, imply that assessment of the coagulation system in sepsis is a complex exercise. It is also likely that derangements of coagulation could be

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markers of sepsis in the early stages and could help us in prioritizing therapeutic strategy.

The role of conventional tests of coagulation such as PT and FDPs, in assessing the severity of sepsis is well documented. Thrombocytopenia is a common occurrence in sepsis and is known to predict adverse outcomes.^{8,9} However, thrombocytopenia can be a manifestation of an infective process (e.g. tropical disease) and is not a phenomenon exclusive to sepsis. Assessment of FDPs like D-dimer has often been used to identify the presence of DIC among septic patients. However, FDPs can be associated with or elevated in several non-infectious conditions (e.g. trauma), and mortality in Sepsis is known to occur among those with normal FDPs.^{10,11} Tests of anticoagulation such as PT and INR traditionally assess the hemostatic system. The key factor is that these tests tend to become abnormal fairly late in the temporal course of sepsis and do not assess the cellular components of the coagulation cascade.

The emergence of visco-elastic tests – the thrombo elasto graph (TEG) and rotational thrombo elastometry (ROTEM) – as bedside tests for the comprehensive evaluation of the hemostatic process, has added an informative tool in evaluating patients with sepsis.^{12,13} These methods assess the role of both cellular and plasma components of the hemostatic process. These tests have the potential to identify hemostatic derangement among septic patients, even when the standard tests for coagulation are normal.¹⁴ The other feature of these tests is that they can identify both hyper- and hypo-coagulable states associated with sepsis.¹⁵ Kim et al. evaluated the role of TEG in predicting DIC early among patients with septic shock.¹⁶ In an analysis of close to 900 patients presenting with septic shock to an emergency department, TEG values were shown to be different between DIC and non-DIC groups. The authors also identified the maximum amplitude (MA) as the TEG parameter with the highest discriminating power for DIC. An MA value of <60 mm was noted to identify DIC with a specificity of 73%. The TEG was performed at

the time of recognition of shock. This discriminating power of the MA value was comparable to the ability of age, initial lactate level, and sequential organ failure assessment (SOFA) score in predicting DIC. The same authors evaluated the role of TEG in evaluating patients with septic shock who had normal PT and activated partial thromboplastin time (APTT) time.¹⁷ In this analysis, the authors identified certain TEG profiles (α angle $<53^\circ$, MA <50 mm) that predictive of mortality among septic patients who had normal PT and APTT. These tests are traditionally viewed as functions of fibrinogen. However, the authors did not find any statistical difference in the fibrinogen levels between the survivors and non-survivors. This probably implies that the TEG parameters are deranged well before the plasma markers of coagulopathy show abnormality. Similarly, the MA value which is considered to be reflective of the platelet function, also showed derangement even when the absolute platelet counts were normal. Similar findings were reported in a retrospective study among septic patients from China.¹⁸ Chen et al. attempted to review the role of TEG in predicting SIC by comparing the TEG values among septic and non-septic patients. The authors found lower fibrinogen levels in the septic group which was not statistically significant. They also found that septic patients had higher R and K values on TEG with a lower MA and α angle, along with prolonged PT and higher DIC scores. They also established a negative correlation between MA and α angle with the SOFA score. Based on their findings, the authors suggested that the K value of TEG is highly predictive of SIC while α angle and MA of TEG are helpful in excluding SIC.

In this edition of the journal, Mohapatra and Gupta¹⁹ report the results of their prospective observational study evaluating the effect of sepsis and septic shock on the visco-elastic properties of clot quality and mass using TEG. They evaluated the TEG profiles among 50 patients each with sepsis and septic shock and compared it with the corresponding profile among 30 non-septic subjects. This evaluation included patients who had a diagnosis of either sepsis or septic shock made within the preceding 24 hours of administering the TEG test. The SOFA score of the septic shock cohort was three points higher than in the septic cohort. In this single-centre study, the R time, the K time, α angle and the MA value were all significantly prolonged among patients with septic shock, while the derangement was not very pronounced among those with sepsis alone. On the other hand, the authors report that TEG values consistent with a hypercoagulable state were consistently seen among those with sepsis without shock. A negative correlation was shown between TEG markers and fibrinogen. They could not show a significant association between TEG markers and platelet count.

It seems quite plausible from the preceding discussion that derangements of the coagulation cascade can be picked up earlier by visco-elastic testing than with conventional markers of coagulation. Platelet counts and PT-INR seem to be deranged a little later in the course of sepsis and more specifically septic shock. Point-of-care testing has already made its presence felt in the emergency room for evaluating sepsis and septic shock (Lactate, Base Excess). Application of the principles of TEG to identify those in the hypercoagulable phase of sepsis as well as those in the hypo-coagulable phase might help in strategizing the therapeutic plans. This could also provide us with a reliable prognostic tool for sepsis which has remained elusive so far.

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