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Sepsis-Induced Coagulopathy

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ABSTRACT

Sepsis, a life-threatening condition resulting from the body's response to an infection, remains a major global health concern. One of the critical complications associated with sepsis is coagulopathy, characterized by dysregulated blood clotting and a heightened risk of both thrombosis and bleeding. This abstract aims to provide a concise overview of the intricate interplay between sepsis and coagulopathy, shedding light on the underlying mechanisms and clinical implications.

Keywords: Sepsis, Coagulopathy, Critical care

INTRODUCTION

Humanity's struggle with sepsis is as old as humanity itself. The word "sepsis" originates from the Greek word "sepo," which was introduced by Homer in the 8th century BC and means "I rot." Sepsis continues to constitute a major burden of morbidity and mortality worldwide. As per the global burden of disease study 2107, sepsis accounted for 20% of all deaths worldwide.[1] Sepsis remains the most common reason for admission and death in the intensive care unit.[2]

Despite all the advances in the medical field, mortality in critically sick septic patients continues to remain high, and as per one global report on epidemiology and burden of sepsis by the World Health Organization, the mortality is as high as 42%.

In our opinion, the extremely complex and profound nature of the pathogenesis of sepsis, including the dysregulated host response (which is difficult to detect in early stages and, even if detected, may not be amenable to effective and rapid correction always), is responsible for high mortality in sepsis.

COAGULOPATHY IN SEPSIS

Coagulopathy has been recognized as an important part of the pathology of sepsis. The coagulopathy that happens in septic patients is quite similar to disseminated intravascular coagulopathy (DIC), and as per one report by Saito *et al.*, up to 61% and 29% of septic patients were diagnosed as having DIC by the Japanese Society for Acute Medicine (JAAM) and International Society of Thrombosis and Hemostasis (ISTH) criteria, respectively. Another remarkable finding in this investigation was that patients with DIC had higher in-hospital mortality compared with those without DIC (33% vs. 20% in JAAM and 38% vs. 24% in ISTH).[3]

Similarly, Gando *et al*. also reported that among the septic patients, those with coagulopathy were more seriously ill. They had a higher prevalence of multiple organ dysfunction syndrome (32.0% vs. 13.1%) on day 0 and a higher mortality rate (24.8% vs. 17.5%). They also had a lower survival probability than non-DIC patients (Log-rank $P = 0.028$).[4]

The importance of coagulopathy in the pathogenesis and prognosis of sepsis has been recognized, and as a matter of fact, coagulopathy (platelet counts) is part of the sequential organ failure assessment (SOFA) score for sepsis.

PATHOGENESIS

Pathogenesis of coagulopathy in sepsis has three major components:

- Upregulation of procoagulant pathways
- Down-regulation of anticoagulant pathways
- Suppression of fibrinolysis.

Pathogen-associated molecular pattern derived from microorganism and danger-associated molecular pattern (DAMP) host-derived microorganism agents activate the pattern recognition receptors on monocytes-macrophages, platelets, and endothelial cells and activate specific intracellular signal-transduction pathways leading to up-regulation of procoagulant molecules and proinflammatory cytokines such as phosphatidylserine and tissue factor (TF). TF is a pivotal procoagulant in the setting of sepsis and endotoxemia. Neutrophils release-neutrophil extracellular traps are composed of procoagulant DNA, histones, and DAMPs.

Healthy endothelial cells produce multiple anti-thrombogenic molecules such as nitric oxide, up-regulation of prostacyclin (pg12), thrombomodulin (TM), endothelial protein C receptor, protein S, TF pathway inhibitor, heparin such as proteoglycan, heparan sulfate glycocalyx, and antithrombin. Antithrombin provides 80% of activity against thrombin. It inhibits X, IX, VII, XI, and XII and binds glycocalyx to endothelium. This leads to protection of endothelium and anti-thrombogenic effect. The endothelium also plays a pivotal role in the fibrinolysis process and regulates the synthesis and release of tissue plasminogen activator, urokinase-type plasminogen activator, and PAI-1—any increase in levels of PAI-1 leads to fibrinolytic shutdown.

Endothelial dysfunction and injury, which happen in sepsis, lead to deficiency of antithrombotic molecules, increased release of ultra-long von Willebrand factor and TF, and sustained increase in plasma PAI-1 levels. Decreased production, consumption, and degradation by neutrophil elastase during sepsis lead to decreased levels and activity of antithrombin.[5] All these changes contribute to a prothrombotic state, encourage platelet aggregation and decrease fibrinolysis.

All of this coagulation disruption not only leads to fibrin deposition and thrombosis in small blood vessels, resulting in hampering of microcirculation and subsequent organ dysfunction, but also depletion of platelets and coagulation factors with increased risk of bleeding.

DIC VERSUS SEPSIS-INDUCED COAGULOPATHY (SIC) AND SIC SCORE

Although coagulopathy in sepsis or SIC is very similar to DIC, there exist certain notable differences. SIC is characterized by a greater degree of suppression of fibrinolysis and overproduction of plasminogen, more prominent organ dysfunction, and a lesser degree of hypofibrinogenemia.[6-8]

A separate and simpler (as compared to DIC criteria) scoring system for recognition of SIC has been proposed consisting of prothrombin time, platelet count, and SOFA score using four parameters (respiratory, cardiovascular, hepatic, and renal). SIC is diagnosed if the total score is greater than or equal to 4, with the sum of coagulation and SOFA criteria exceeding 2.[9]

This score has been shown to perform well, it has been shown to have higher sensitivity in detected coagulopathy (approximately twice as much as that of overt DIC), and patients met SIC criteria earlier than ISTH criteria for overt DIC.[10]

ROLE OF THROMBOELASTOGRAPHY (TEG) AND ROTATIONAL THROMBOELASTOMETRY (ROTEM)

The use of TEG to detect and follow SIC has been studied. One such investigation reported that with an increase in SOFA scores, R value and K value increased, and α angle, maximum amplitude (MA) value, and confidence interval (CI) decreased significantly ($P < 0.05$). TEG also detected a decrease in platelet function in coagulopathy group, which was not possible using traditional coagulation parameters.[11]

Similarly, point of care test ROTEM has also been investigated for SIC. In one such report, it was found that a hypercoagulability profile at admission was helpful for the early detection of sepsis, and lower maximum lysis was reported to predict greater severity of organ failure.[12]

MANAGEMENT OF SIC

Cornerstone management of SIC consists of treatment of sepsis – (the underlying cause) and supportive measures (hemodynamic, ventilation, renal replacement therapy, and transfusion).

The role of heparin has been studied in sepsis. One such meta-analysis reported that low molecular weight heparin (LMWH) significantly reduced APACHE II score (Mean deviation [MD] −2.50; 95% CI −3.55–−1.46) and 28-day

mortality (risk ratio [RR] 0.72; 95% CI 0.57–0.91), but it also significantly increased the bleeding events.[13]

TM forms a reversible bond with the anion-binding exosite-I of thrombin, and by doing so, it prevents the binding of thrombin to its procoagulant substrates such as fibrinogen, protease-activated receptors and coagulation factors V and VIII. TM also binds the anticoagulant zymogen – protein C, thereby enhancing the activation of protein c by thrombin. Due to these properties, its use in SIC has been studied by a number of investigators. Two recently conducted meta-analyses reported that recombinant TM was associated with a trend in reduction of mortality at 28–30 days in SIC patients and a decline in the mortality rate by 13% (relative risk [RR]: 0.87, 95% CI, 0.74–1.03, $P = 0.10$), respectively.[14,15]

Antithrombin is a glycoprotein produced by the liver that inactivates Xa, Ixa, XIa, XIIa, (thrombin) (Iia), VIIa, kallikrein, and plasmin. In septic patients, the plasma levels of antithrombin are usually very low. Low antithrombin level has been reported to be independent predictor of the clinical outcome in septic patients.[16,17] A meta-analysis published in 2018 reported a beneficial effect of antithrombin in septic patients on the mortality (risk ratio, 0.85; 95% CI, 0.69–0.99; $I^2 = 0\%$).[18]

The Japanese clinical practice guidelines for sepsis and septic shock 2016 have even suggested the use of antithrombin replacement therapy in patients with sepsis-associated DIC with ≤70% fall in antithrombin activity (rate of agreement, 68.4%).[19]

The American Society of Hematology has published an algorithm for the management of coagulopathy in sepsis. For active bleeding, it recommends Vitamin K if prothrombin time (PT) is elevated, fresh frozen plasma (FFP) 10 mL/kg if activated partial thromboplastin time (APTT) is increased, cryoprecipitate if fibrinogen is <1.5 g/dL, platelet transfusion to keep platelet level >20000 in the absence of active bleeding, and >50000 in the presence of active bleeding. In case manifestation of thrombosis is present. It recommends a treatment dose of anticoagulation/anti-thrombin/plasma exchange.[20,21]

CONCLUSION

Coagulopathy is a very important component of sepsis-related morbidity and mortality. Early recognition and management of coagulopathy may improve the outcome in septic patients. Heparin is only recommended for deep vein thrombosis prophylaxis, while TM and antithrombin have been given the status of optional choice when available. Hopefully, targeted therapy using precision medicine will provide the solution to dealing with SIC in the coming future.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

Yatin Mehta is the member of the editorial board of the Journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, *et al.* Global, Regional, and National Sepsis incidence and Mortality, 1990-2017: Analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.
2. Chatterjee S, Bhattacharya M, Todi SK. Epidemiology of Adult-population Sepsis in India: A Single Center 5 Year Experience. Indian J Crit Care Med 2017;21:573-7.
3. Saito S, Uchino S, Hayakawa M, Yamakawa K, Kudo D, Iizuka Y, *et al.* Epidemiology of Disseminated Intravascular Coagulation in Sepsis and Validation of Scoring Systems. J Crit Care 2019;50:23-30.
4. Gando S, Shiraishi A, Yamakawa K, Ogura H, Saitoh D, Fujishima S, *et al.* Role of Disseminated Intravascular Coagulation in Severe Sepsis. Thromb Res 2019;178:182-8.
5. Iba T, Levy JH. Sepsis-induced Coagulopathy and Disseminated Intravascular Coagulation. Anesthesiology 2020;132:1238-45.
6. Koyama K, Madoiwa S, Nunomiya S, Koinuma T, Wada M, Sakata A, *et al.* Combination of Thrombin-antithrombin Complex, Plasminogen Activator Inhibitor-1, and Protein C Activity for Early Identification of Severe Coagulopathy in Initial Phase of Sepsis: A Prospective Observational Study. Crit Care 2014;18:R13.
7. Hack CE. Fibrinolysis in Disseminated Intravascular Coagulation. Semin Thromb Hemost 2001;27:633-8.
8. Engelmann B, Massberg S. Thrombosis as an Intravascular Effector of Innate Immunity. Nat Rev Immunol 2013;13:34-45.
9. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New Criteria for Sepsis-induced Coagulopathy (SIC) Following the Revised Sepsis Definition: A Retrospective Analysis of a Nationwide Survey. BMJ Open 2017;7:e017046.
10. Iba T, Arakawa M, Di Nisio M, Gando S, Anan H, Sato K, *et al.* Newly Proposed Sepsis-Induced Coagulopathy Precedes International Society on Thrombosis and Haemostasis Overt-

Disseminated Intravascular Coagulation and Predicts High Mortality. J Intensive Care Med 2020;35:643-9.
11. Zhou W, Zhou W, Bai J, Ma S, Liu Q, Ma X. TEG in the Monitoring of Coagulation Changes in Patients with Sepsis and the Clinical Significance. Exp Ther Med 2019;17:3373-82.
12. Prakash S, Verghese S, Roxby D, Dixon D, Bihari S, Bersten A. Changes in Fibrinolysis and Severity of Organ Failure in Sepsis: A Prospective Observational Study Using Point-of-care Test-ROTEM. J Crit Care 2015;30:264-70.
13. Fan Y, Jiang M, Gong D, Zou C. Efficacy and Safety of Low-molecular-weight Heparin in Patients with Sepsis: A Meta-analysis of Randomized Controlled Trials. Sci Rep 2016;6:25984.
14. Yamakawa K, Aihara M, Ogura H, Yuhara H, Hamasaki T, Shimazu T. Recombinant Human Soluble Thrombomodulin in Severe Sepsis: A Systematic Review and Meta-analysis. J Thromb Haemost 2015;13:508-19.
15. Yamakawa K, Murao S, Aihara M. Recombinant Human Soluble Thrombomodulin in Sepsis-Induced Coagulopathy: An Updated Systematic Review and Meta-Analysis. Thromb Haemost 2019;119:56-65.
16. Mesters RM, Mannucci PM, Coppola R, Keller T, Ostermann H, Kienast J. Factor VIIa and Antithrombin III Activity During Severe Sepsis and Septic Shock in Neutropenic Patients. Blood 1996;88:881-6.
17. Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, *et al.* Septic Shock, Multiple Organ Failure, and Disseminated Intravascular Coagulation. Compared Patterns of Antithrombin III, Protein C, and Protein S Deficiencies. Chest 1992;101:816-23.
18. Wiedermann CJ. Antithrombin Concentrate Use in Disseminated Intravascular Coagulation of Sepsis: Meta-analyses Revisited. J Thromb Haemost 2018;16:455-7.
19. Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, *et al.* The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016). J Intensive Care 2018;6:7.
20. Levi M, Scully M. How I Treat Disseminated Intravascular Coagulation. Blood 2018;131:845-54.
21. Iba T, Levy JH, Raj A, Warkentin TE. Advance in the Management of Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. J Clin Med 2019;8:728.

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