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Inflammation, infection and coagulation disorders - Section 10

Disseminated intravascular coagulation – what can we do?

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Take home messages

Key goal: The aim is to converge increasing understanding of the cross-talk between coagulation, inflammation and innate immune activation pathways to inform new treatment strategies for patients with disseminated intravascular coagulation (DIC).

- DIC is the maladaptive response to injury that dysregulates thrombin generation in vivo.
- DIC can cause multi-organ dysfunction through micro-vascular thrombosis and bleeding due to loss of endothelial barrier integrity.
- Treating the cause and supporting the patient till DIC resolves is key to improving outcome.

Introduction

Disseminated intravascular coagulation (DIC) is a complication that arises in conditions associated with sustained cell damage.[*1] Its manifestation is as a result of increased and dysregulated thrombin generation in vivo, especially in the micro-circulation. Small blood vessels are particularly susceptible to the complex interactions between coagulation, fibrinolytic, inflammatory and innate immune responses.[2] This increases the likelihood of microvascular thrombosis, which can disrupt endothelial barrier integrity to increase vascular leakage and bleeding, especially because of thrombocytopenia and reduced coagulation factors.[*1] The difficulty in recognising this at an early enough stage contributes to poor outcome. In addition, the continued uncertainty of what to do also contributes to the high mortality rates in patients with DIC. This review focuses attention on recent advances in our understanding of DIC pathophysiology to inform how we might better care for such patients.

Current state of the art

Understanding the pathology in DIC

As DIC is a complication of diseases such as sepsis, trauma and obstetric calamities, there will be condition-specific pathogenic factors that influence both coagulation activation and the functional consequences. A major challenge in treating patients with DIC is to identify the predominant mechanism from the heterogeneous effects, which can also vary over time. Key aspects to consider include:

1. The multi-faceted role of thrombin generation in vivo. Understanding the diverse and often opposing thrombin-orchestrated effects on coagulation and fibrinolysis is important.[3] Thrombin is associated with pro-coagulant properties: converting fibrinogen into fibrin and also activating platelets. Conversely, thrombin also has anticoagulant properties through thrombomodulin (TM)-dependent protein C (PC) activation. Equally, thrombin affects opposing aspects of fibrinolysis; that is, promoting plasmin generation by inducing tissue-plasminogen activator release[4,5] but also inducing plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor activity.
2. Concomitant cellular dysfunction in the microcirculation. Cell surfaces and site-specific vascular endothelial features control the processes consequent to thrombin generation.[3] The microvasculature is particularly vulnerable due to its higher endothelial cell surface to blood volume ratios.[6] Receptors of the PC pathway; that is, the endothelial PC receptor (EPCR) and TM are among the most relevant as both have direct pleiotropic effects on coagulation, inflammation, endothelial barrier function through protease-activated receptor 1.[7]

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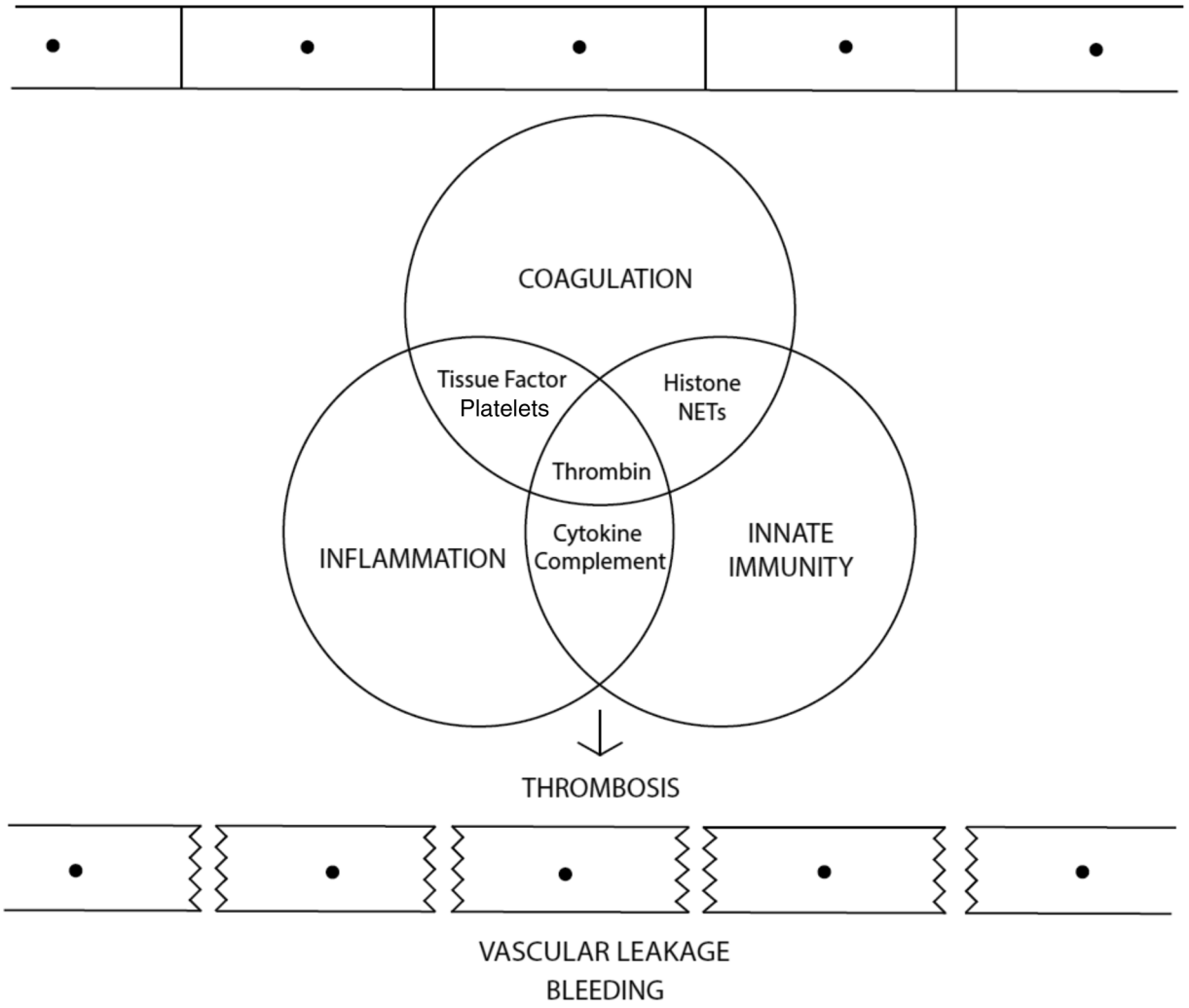

Figure 1. Pathogenic pathways and consequences in DIC. The cross-talk between coagulation, inflammation and innate immune activation increases thrombin generation, which is the hallmark of DIC. Through the interaction of various components, these processes potentiate microvascular thrombosis and endothelial barrier disruption to cause vascular leakage and bleeding.

3. The overlapping contribution of innate immune activation and inflammation. With cell damage and death common to all the causes of DIC, there is release of damage-associated molecular patterns, which can lead to thrombin generation. Extracellular DNA and histones occur in patients with DIC and histones are cytotoxic[8] with functional consequences that include thrombocytopenia, lysis-resistant thrombi, and vascular leakage as well as release of pro-inflammatory cytokines and extracellular traps, especially from neutrophils. Referred to as NETs, their release is affected by peptidyl-arginine deiminase 4 (PAD4).[9] NETs consist of extracellular DNA decorated with enzymes such as myeloperoxidase and elastase to kill bacteria.[*10] NETs also promote thrombosis by providing a scaffold for assembling clot components including tissue factor as well as through histone-dependent activity and platelet-polyphosphate release.[9,11]

Recognizing the patient with DIC

In general, physicians tend to consider the possibility of DIC when there is extensive and uncontrollable bleeding or from abnormalities in the platelet count or coagulation screen. The International Society on Thrombosis and Haemostasis (ISTH) scoring system of routine global coagulation tests provides a framework for diagnosing DIC with a cumulative score of 5 or more from increased prothrombin time, reduced platelets and fibrinogen together with elevated fibrin-degradation products forming the basis of diagnosis.[12,13] There are country-specific refinements, which similarly confirm the independent prediction of mortality by the ISTH Haemostasis DIC score and its added prognostic value to the Acute Physiology and Chronic Health Evaluation (APACHE) II system.[*14] A hybrid pathology with bleeding and thrombosis is characteristic of DIC although this may be subtle, especially with insidious micro-circulatory obstruction leading to organ dysfunction (Fig. 1).

Managing the patient with DIC

The management of DIC is challenging due to the heterogeneity of triggering causes, the diverse effects of thrombin generation and the lack of high-quality treatment trials. Its prompt recognition is emphasized by numerous guidelines[15] and the differential diagnosis has been well described recently.[*16]

The basic principles for treating DIC include[*1]:

1. Correcting the underlying condition causing DIC.
2. Inhibiting the effects of excess thrombin generation.

3. Supportive care, including with blood products when there is bleeding or if the patient is at high risk.
4. Regular clinical and laboratory surveillance with multi-specialty input.

Future perspectives

Improving patient outcome can only come from both better recognition and treatment of DIC. In terms of recognition, we will have to do better than the current reliance on the DIC score, which is a summation of individual coagulation tests that are routinely available. Although practical, they signify the phenomenon of coagulopathy rather than present a target for treatment advances. There is a long history of failed prognostic or mechanistic biomarker discovery work for the heterogeneous syndrome of DIC. If the emerging perspective on histones and NETs continue to be encouraging, there could be rationale for translational opportunities in developing new diagnostics and therapeutics. Assays will need to meet the challenge of being both robust but also practical in meeting the needs of the acute critical care setting.

Along the same lines, there would also be the potential for novel therapeutic approaches using modalities that neutralize histones (Activated PC,[*17] anti-histone antibodies,[8] recombinant soluble TM,[18] heparin[19]) and/or NETs (DNase,[*10] PAD4-targeted therapy[20]). These would require well-designed randomized control trials using appropriate DIC patient populations.

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