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The Modern Coagulation Cascade and Coagulation Abnormalities Associated with Sepsis

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Traditional Coagulation Pathway:

Modern Coagulation:
In health the balance between pro and antithrombotic processes is such that vessel damage is repaired effectively without excessive bleeding or excessive coagulation. In disease there can be a loss of this balance leading to hemorrhage or thrombosis. (Table 1)

Table 1: Endogenous prothrombotic and antithrombotic pathways

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<thead>
<tr>
<th>Prothrombotic Systems</th>
<th>Antithrombotic Systems</th>
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<td>Platelet plug</td>
<td>Tissue factor pathway inhibitor</td>
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<tr>
<td>Coagulation cascade</td>
<td>Antithrombin</td>
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<td></td>
<td>Protein C system</td>
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<td>Fibrinolysis</td>
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The modern view of coagulation emphasizes the intricate connection between the coagulation system and inflammation. It is now clear that these pathways are intimately linked such that activation of one will always cause alterations in the other. In general pro-coagulant processes tend to have pro-inflammatory effects while anti-coagulant processes tend to have anti-inflammatory effects. This relationship is reciprocal, pro-inflammatory processes often have pro-coagulant effects etc.

Prothrombotic Systems:
1. Platelet Plug:
Platelet function will not be reviewed here.
Coagulation Cascade:

Tissue factor (TF), previously known as factor III of the extrinsic pathway is the primary initiator of coagulation in both normal and disease states. Tissue factor is the only membrane bound member of the coagulation cascade; it is an extremely pro-coagulant molecule that also has cell signaling actions and interacts with numerous pathways other than coagulation.

When TF comes into contact with blood it binds and activates FVII in the presence of calcium, this TF-VIIa-Ca\(^{2+}\) complex then activates factors IX and X (Figure 2); the initiation phase. Factor Xa leads to the generation of thrombin but tissue factor pathway inhibitor (TFPI) rapidly inactivates this part of the pathway such that only traces of thrombin can be produced. Activated FIX in addition to FVa and FVIIIa generated by the trace levels of thrombin allow amplification of the pathway. This 'propogation' of thrombin formation by the intrinsic pathway is an essential component of the secondary coagulation response in order to achieve effective hemostasis.

In the normal state TF is constitutively expressed in the extravascular tissues. There are high levels in the adventitia of blood vessels, fibrous capsules of organs and the epithelium of the skin and internal mucosal layers. This constitutive TF is found in close proximity to the vascular space where it is responsible for appropriate activation of coagulation in response to an interruption to vascular integrity. There are several cells which can be induced to express TF including endothelial cells, smooth muscle cells and circulating monocytes. Endotoxin, tumor necrosis factor alpha (TNF-a), lipoproteins and growth factors can all stimulate intravascular TF expression. Induced TF is present in the intravascular space where it can initiate pathologic coagulation. It is this induced TF expression that is believed to play a key role in numerous disease states including sepsis and atherosclerosis.

At the culmination of the coagulation cascade, thrombin cleaves fibrinogen into fibrin monomers which polymerize spontaneously but need to be cross linked to produce a stable clot. Factor XIII (plasma transglutaminase) is also activated by thrombin and stimulates the formation of covalent bonds between adjacent fibrin molecules completing the process of secondary coagulation.

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**The Modern Coagulation Cascade**

![Figure 2: The modern coagulation cascade](image)
ANTITHROMBOTIC SYSTEMS

1. Tissue Factor Pathway Inhibitor:
Tissue factor pathway inhibitor (TFPI) is a serine protease inhibitor produced primarily by endothelial cells of the microvasculature. It directly inhibits factor Xa and the factor VIIa – TF complex. It is the only endogenous inhibitor of TF-VIIa making it an extremely important component of normal hemostatic balance.

2. Antithrombin
Antithrombin (AT) is a broad spectrum serine protease inhibitor found in plasma and is produced by the liver. It has both anti-coagulant and anti-inflammatory effects.

Antithrombin inhibits the action of thrombin, VIIa, IXa, Xa, XIa and XIIa. The AT molecule binds the coagulation factor in a 1:1 ratio leading to factor inactivation, the complex is subsequently removed by the reticuloendothelial system. The anti-coagulant effects are potentiated 1000x by heparin.

There is increased consumption, increased destruction and reduced production of AT during sepsis leading to reduced levels of AT in septic patients.

3. Protein C System
Protein C and its cofactor protein S are vitamin K dependent serine proteases. Protein C has potent anticoagulant, profibrinolytic and anti-inflammatory actions.

Protein C is a plasma protein produced by the liver which circulates in an inactive form. Thrombomodulin (TM), an endothelial membrane bound protein complexes with and inactivates thrombin. The TM-thrombin complex can then rapidly bind and activate protein C. Another endothelial membrane bound protein the endothelial protein C receptor (EPCR) potentiates this process by concentrating protein C around TM. Once activated, protein C is then released back into circulation where it has anti-coagulant effects. The binding of thrombin to TM effectively converts thrombin from a potent pro-thrombotic factor to a potent anti-thrombotic factor.

Activated protein C in association with its cofactor protein S inactivates factors Va and VIIIa.

There is increased consumption, increased destruction and reduced production of Protein C leading to reduced levels of Protein C in septic patients. The administration of Protein C to human patients is the only pharmacological agent to date found to increase survival from severe sepsis.

4. Fibrinolytic pathway
Fibrinolysis is often forgotten when the normal coagulation cascade is considered but removal of fibrin is vital to maintaining hemostasis without producing thrombosis. Plasmin is responsible for the degradation of fibrin. Plasmin is cleaved from plasminogen (which is bound to fibrin within the clot) by tissue plasminogen activator (tPA) and/or urokinase. These are produced and released by endothelial cells in response to injury or thrombin. In addition to fibrin, plasmin also degrades FVa and FVIIIa.

There is an increase in production of fibrinolytic inhibitors leading to reduced fibrinolysis in septic patients.

Sepsis
- Increased pro-coagulant tendency
- Reduced anti-inflammatory mechanisms
- Reduced fibrinolysis

Overall septic patients have an increased likelihood of intravascular fibrin formation. When this is a clinical problem it is known as disseminated intravascular coagulation (DIC) and can lead to microvascular fibrin formation. If DIC is not controlled it may result in consumption of coagulation factors and a coagulopathy may develop. In veterinary medicine we are unable to identify a patient in a prothrombotic state and instead diagnose DIC in the coagulopathic stage, a very late stage of the disease. The diagnosis of DIC is not specific and is based on finding two or more suggestive laboratory abnormalities (Table 2) in a patient with a disease process believed to be likely to cause DIC.
Table 2: Laboratory findings supportive of the diagnosis of DIC

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>Platelet count</td>
<td>Reduced</td>
</tr>
<tr>
<td>Red blood cell morphology</td>
<td>Schistocytes</td>
</tr>
<tr>
<td>Coagulation times</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Reduced</td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>Elevated</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Elevated</td>
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Bibliography:


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