An updated view of hemostasis: mechanisms of hemostatic dysfunction associated with sepsis

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Abstract

Objective: To review the current understanding of mechanisms involved in normal hemostasis and to describe the changes associated with pro-inflammatory disease processes such as sepsis.

Data sources: Original research articles and scientific reviews.

Human data synthesis: Organ damage caused by sepsis is created in part by the interdependent relationship between hemostasis and inflammation. Markers of coagulation have been found to have prognostic value in human patients with sepsis and there are both experimental and clinical investigations of the therapeutic potential of modulating the hemostatic system in sepsis. Improvement of 28-day all-cause mortality in severe sepsis by treatment with recombinant human activated Protein C strongly supports the interdependence of hemostasis and inflammation in the pathophysiology of sepsis.

Veterinary data synthesis: Publications reporting clinical evaluation of the hemostatic changes occurring in septic dogs or cats are minimal. Experimental animal models of sepsis reveal significant similarity between human and animal sepsis and may provide relevance to clinical veterinary medicine until prospective clinical evaluations are published.

Conclusions: It is now apparent that inflammation and the coagulation system are intimately connected. Understanding this relationship provides some insight into the pathogenesis of the hemostatic changes associated with sepsis. This new updated view of hemostasis may lead to the development of novel therapeutic approaches to sepsis and disseminated intravascular coagulation in veterinary medicine.


Keywords: anti-thrombin, disseminated intravascular coagulation, fibrinolysis, protein C, tissue factor, tissue factor pathway inhibitor

Introduction

Hemostasis is the process of forming a blood clot to seal an injured vessel and the subsequent removal of this clot when it no longer serves a useful purpose. The clot prevents ongoing blood loss and also initiates tissue repair.1,2 Successful hemostasis can be separated into several phases, which include the formation of a platelet plug (primary hemostasis) and stabilization of the platelet plug with cross-linked fibrin (secondary hemostasis) followed by destruction of the clot by fibrinolysis.1

Secondary hemostasis requires the formation of the key element thrombin and ultimately, fibrin from the soluble pro-coagulant proteins. These serine proteases circulate as zymogens and form thrombin through a series of linked proteolytic enzyme reactions. Each reaction consists of one serine protease activating a downstream serine protease zymogen.2,3 A cascade is thereby formed allowing both amplification and numerous regulatory opportunities.

The traditional separation of secondary hemostasis into the intrinsic and extrinsic pathways (Figure 1) has been essential to our initial understanding of coagulation as well as the evaluation of hemostatic abnormalities. It was originally believed that the intrinsic coagulation pathway was the most important initiator of coagulation in health and disease.2,4 Several clinical situations were identified that forced investigators to question this original concept. For example, patients with factor XII deficiency have little or no evidence of clinical bleeding.5,6 Patients with factor VIII or IX deficiency have a significant coagulopathy despite the suggestion that an intact extrinsic pathway could ‘compensate’ for dysfunction of the intrinsic pathway.
Patients with factor XI deficiency have a variable degree of coagulopathy but it is never as severe as the bleeding issues seen in factor VIII or IX deficient individuals. It is now widely accepted that the extrinsic pathway is the most important initiator of in vivo coagulation and the extrinsic and intrinsic pathways can no longer be considered as separate entities.

An updated view of secondary hemostasis outlines the recently established interrelationship between the intrinsic and extrinsic coagulation pathways, dividing activation of coagulation into an initiation phase and a propagation phase. This modern view of hemostasis also characterizes anti-coagulant, fibrinolytic and anti-fibrinolytic mechanisms and emphasizes that these processes are as equally important to normal hemostasis as are the pro-coagulant mechanisms (Table 1).

Hemostasis and Sepsis

Sepsis, defined as the systemic inflammatory response to an infection, is associated with a high morbidity and mortality rate in human medicine. An evaluation of nearly 200,000 human septic patients in 1995 determined a mortality rate of 28.6%; this rate was 38.4% in children and patients greater than 85 years of age. There is limited information available regarding the morbidity and mortality of sepsis in veterinary medicine. One recent article reported a 50% mortality rate in a group of 20 dogs diagnosed with sepsis. Given the few published reports available and the similarity of this disease process with that seen in human medicine, it is likely that the morbidity and mortality of sepsis is also high in veterinary patients. Multiple organ dysfunction syndrome (MODS) can develop in patients with severe sepsis and is associated with increased mortality rates in humans.

Acute inflammation, as seen in association with sepsis, leads to systemic activation of the coagulation system. This inflammation-induced coagulation can result in intravascular fibrin formation; this phenomenon is called ‘disseminated intravascular coagulation (DIC)’. DIC may cause thrombotic occlusion of small blood vessels and it is believed to contribute to the development of MODS. Persistent activation of intravascular coagulation can lead to the consumption of platelets and coagulation factors and a coagulopathy may result. Just as acute inflammation can alter the coagulation system, changes in the coagulation system can also modify inflammatory pathways. More specifically, increased activation of coagulation promotes pro-inflammatory effects, including increased levels of pro-inflammatory cytokines and leukocyte activation. Similarly, activation of anti-coagulant processes tends to have anti-inflammatory effects such as reduced cytokine production and reduced leukocyte adhesion. This coagulation-dependent modulation of inflammation may play a significant role in the morbidity and mortality of the septic patient.

Initiation and Propagation

Tissue factor (TF), previously known as factor III of the extrinsic pathway, is the most important initiator of thrombin formation in both health and disease. Functionally active TF primarily exists as a transmembrane glycoprotein with both cytoplasmic and extracellular domains. Extravascular monocytes, macrophages and fibroblasts express TF constitutively, while intravascular leukocytes do not. There are high levels of TF 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. Circulating TF has also been identified in healthy human volunteers. This TF is found on microparticles, cell membrane fragments which arise from exocytotic budding of cells. The source of circulating TF is hypothesized to be activated endothelial cells or leukocytes. This intravascular TF is ‘encrypted’ such that it is functionally inactive. The role of ‘encrypted’ TF and the mechanisms behind its de-encryption are yet to be discerned.

### Table 1: Endogenous pro-thrombotic and anti-thrombotic pathways

<table>
<thead>
<tr>
<th>Pro-thrombotic systems</th>
<th>Anti-thrombotic systems</th>
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</thead>
<tbody>
<tr>
<td>Platelet activation</td>
<td>Tissue factor pathway inhibitor</td>
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<tr>
<td>Coagulation cascade</td>
<td>Anti-thrombin</td>
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<td>Anti-fibrinolysis</td>
<td>Protein C pathway</td>
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<td></td>
<td>Fibrinolysis</td>
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When exposed to blood, TF rapidly binds and activates FVII in the presence of calcium, forming a TF–VIIa–Ca$^{2+}$ complex. This membrane bound complex has 2 important functions: activation of FIX and activation of FX; and represents the initiation phase of the TF pathway (Figure 2). Factor Xa then leads to the generation of thrombin via the common pathway but because TF pathway inhibitor (TFPI) rapidly inactivates both TF–FVIIa and FXa, only traces of thrombin are produced from this initial reaction. Most of the thrombin generated from TF activation is produced via FXa acting on the common pathway, the propagation phase. This amplification is made possible by the activation of FV and FVIII by the trace levels of thrombin released in the initiation phase (Figure 3). Factors Va and VIIIa have co-factor roles in coagulation; they significantly enhance the function of factors Xa and IXa, respectively. The propagation of thrombin via the intrinsic pathway is essential; without it, TF initiation of coagulation would result in insufficient thrombin formation.

Pro-inflammatory mediators such as endotoxin, tumor necrosis factor-α (TNF-α), lipoproteins and growth factors can all stimulate TF expression on endothelial cells and circulating monocytes. The induction of intravascular TF expression is a primary mechanism of inflammation-induced coagulation activation. The potent pro-coagulant nature of TF has been demonstrated experimentally where infusion of recombinant TF can initiate DIC. Blockade of TF activity with neutralizing antibodies or TFPI administration prevents mortality in a lethal primate model of endotoxin infusion. Induced TF expression plays an essential role in numerous disease states including sepsis and atherosclerosis and is an extremely important link between the coagulation and inflammatory systems.

TF has functions beyond coagulation. It has important roles in both embryological and neoplastic angiogenesis. The importance of TF to angiogenesis is demonstrated by the in utero lethality of the TF knockout mouse model. The role of TF in atherosclerosis and cell metaplasia is currently an area of intense research. As a receptor molecule in the cytokine family, binding of the ligand, FVIIa, to TF alters the physiology of the TF expressing cell. Proposed regulatory functions of TF in the modulation of inflammation, cell proliferation and differentiation remain to be proven.

**Anti-Thrombotic Systems**

**TFPI**

There are three pools of TFPI in the body: within microvasculature endothelial cells, stored in platelets, and circulating bound to lipoproteins. The release of TFPI from endothelial cells by both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) may contribute to the efficacy of these drugs.

TFPI is an important endogenous anti-coagulant, inactivating both FXa and the TF–VIIa complex. Initially, TFPI complexes with and inactivates FXa. The TFPI–FXa complex then binds to the TF–FVIIa complex, forming a tetramer and subsequently inactivating TF–FVIIa.

Plasma levels of TFPI antigen have been reported to be low, normal or even elevated in septic patients. The specific role of TFPI in the development of DIC is unknown. In sepsis and the acute respiratory distress syndrome increases in plasma TF concentration without a corresponding increase in TFPI concentration have been reported.
Administration of recombinant TFPI (rTFPI) in animal models of sepsis significantly reduces mortality.\textsuperscript{46–48} Despite these findings, a large phase III human clinical trial of rTFPI in patients with severe sepsis failed to reduce 28-day all-cause mortality and the risk of adverse bleeding events was higher in treated patients.\textsuperscript{49} Additional investigations are underway to investigate the therapeutic potential of rTFPI in the treatment of severe sepsis.

**Anti-thrombin**

Anti-thrombin III, now known as anti-thrombin (AT), is a potent serine protease inhibitor produced by the liver and found in plasma and to a small extent, on the surface of endothelial cells and platelets.\textsuperscript{50} Its anti-coagulant strength is because of specific thrombin and FXa inhibition. In addition, AT can effectively inhibit the activity of factors VIIa, IXa, Xla, and XIIa. AT binds to and inactivates its target coagulation factor. This AT-factor complex is then removed by the reticuloendothelial system and as a result, the more active AT is, the faster it will be depleted.\textsuperscript{50,51}

The AT molecule contains a heparin-binding domain. Glycosaminoglycans (GAGs), including heparin, heparan sulfate and dermatan sulfate, contain repeating pentasaccharide sequences, which bind to this heparin-binding domain resulting in a conformational change and activation of the AT molecule.\textsuperscript{52} This allosteric activation of AT potentiates its enzymatic activity by more than a 1000 times.\textsuperscript{50} Heparan sulfate and other GAGs are found endogenously on endothelial cells of the microvasculature and will bind to AT in the absence of exogenously administered heparin.\textsuperscript{50,51}

To potentiate the inhibition of thrombin, the heparin molecule must be long enough to simultaneously attach to both thrombin and AT. This requires a heparin molecule containing at least 18 pentasaccharide units. This dual binding is not required for the inactivation of the other serine proteases.\textsuperscript{51} UFH is a heterogenous mix of molecules of varying molecular weights. A large proportion of these molecules contain more than 18 pentasaccharide sequences and as such can effectively mediate the AT inactivation of thrombin.\textsuperscript{52,53} In contrast, LMWH contains far fewer large molecules and as a consequence it has a limited ability to mediate thrombin inactivation. LMWH retains the ability to inactivate the other serine proteases, namely factor Xa.\textsuperscript{52,53} The increased FXa versus thrombin inhibitory effect explains how effective anti-coagulation with LMWH may not result in observable changes in the traditional coagulation tests such as the activated clotting time or activated partial thromboplastin time. In addition, at least in people, LMWH has a longer half-life and has far more predictable pharmacokinetics than UFH.\textsuperscript{52} As a result, a constant rate infusion of intravenous (IV) UFH in conjunction with continuous monitoring of coagulation tests can be replaced with intermittent subcutaneous administration of LMWH with minimal, if any, monitoring.\textsuperscript{53} LMWH was as effective and safe as UFH in several clinical human trials.\textsuperscript{54,55} Increased frequency of bleeding episodes is an adverse effect of LMWH administration and limits the use of this drug in patients at risk.\textsuperscript{52,53} There have been some investigations into the use of LMWH in veterinary medicine. There are reports of effective dosing of dalteparin sodium\textsuperscript{8} in dogs and horses, and there has been one investigation of dalteparin administration to cats.\textsuperscript{56–59} There have been numerous trials of several different types of LMWH in experimental animals.\textsuperscript{60–62} Each type of LMWH is unique in the composition of the heparin molecules and subsequently they have quite variable pharmacokinetics and biological properties.\textsuperscript{53} As a result, dosing information cannot be translated from one LMWH to another.

Thrombin and FXa are both pro-inflammatory in nature with wide ranging effects including increased cytokine release, leukocyte chemotaxis, and increased adhesion molecule expression.\textsuperscript{5} Hence, inhibition of thrombin and FXa by AT has significant anti-inflammatory consequences. In recent years, AT has also been found to have anti-inflammatory actions that are independent of its anti-coagulant activity.\textsuperscript{50,51} AT modulates the interaction between endothelial cells and leukocytes by reducing leukocyte activation and adhesion. AT-stimulated prostacyclin release from endothelial cells reduces platelet aggregation and decreases pro-inflammatory cytokine production.\textsuperscript{50,64,65} AT also directly inhibits interleukin-6 (IL-6) release and TF expression of endothelial cells.\textsuperscript{66} These anti-inflammatory effects rely on AT binding to endothelial cells of the microvasculature via GAGs and are virtually abolished by the administration of heparin.\textsuperscript{51,67,68} This creates a dilemma for the clinician treating a patient with heparin in order to maximize the anti-coagulant effects of AT, in doing so, the potentially important anti-inflammatory effects of AT may be lost.\textsuperscript{50,51}

Both septic humans and animals have been shown to have diminished plasma concentrations of AT and in human patients, the magnitude of this reduction has been correlated with the severity of illness and survival.\textsuperscript{10,32,69,70} AT therapy in animal models of sepsis is beneficial.\textsuperscript{71,72} Despite this benefit, the phase III human clinical trial of the administration of AT concentrate to patients with severe sepsis found no effect on all-cause 28-day mortality.\textsuperscript{73} There was some evidence of beneficial effects in a subgroup of patients that were not receiving concomitant heparin therapy, although this finding should be interpreted with caution as this trial...
was not designed for such subgroup analysis. Based on this evidence AT administration was not recommended in the treatment of severe sepsis and septic shock in the latest surviving sepsis campaign guidelines. 

Protein C (PC) pathway
PC and its co-factor, protein S, are vitamin K-dependent plasma proteins synthesized by the liver. The PC anti-coagulant pathway results in the inactivation of factors Va and VIIIa, enhanced thrombin inactivation, and has direct anti-inflammatory activity. PC requires activation by thrombomodulin (TM), an endothelial cell membrane protein. TM binds thrombin, preventing it from continuing to activate coagulation factors, platelets and endothelial cells. Thrombin bound to TM is more rapidly inactivated by inhibitors such as AT, than free thrombin. The TM–thrombin complex is approximately 1000 times more effective at activating PC than TM alone. The endothelial cell PC receptor (EPCR) binds PC and concentrates it around the TM–thrombin complex on the surface of the endothelial cell, enhancing PC activation approximately 20-fold. Once activated, PC dissociates from the EPCR, binds to protein S, and this complex inactivates FVa and FVIIa.

The complex interactions involved in PC activation are an essential aspect of normal hemostasis. The microvasculature has a very large endothelial cell surface area; as a result, almost all thrombin which escapes from local sites of coagulation into the systemic circulation will be rapidly bound by TM, enhancing thrombin inactivation and potentiating PC activation. At the local level, factors Va and VIIIa are vital in the propagation phase of TF-mediated coagulation; their inactivation by activated PC (aPC) is a potent AT mechanism. PC activation is largely dependent on the TM–thrombin interaction. This is an intriguing design because thrombin, one of the most pro-coagulant substances in the body, also participates in the formation of a primary anti-coagulant substance. This physiologic design is sometimes referred to as the ‘thrombin paradox’. The significance of the PC pathway is demonstrated by the severe and often fatal thrombosis (purpura fulminans) manifested in individuals with an inherited PC deficiency.

The aPC pathway has significant anti-inflammatory actions, indirectly by the inactivation of thrombin by TM and the inhibition of further thrombin generation, as well as directly. The EPCR has cell signaling functions and experimentally blocking the interaction between PC and EPCR has pro-inflammatory and pro-coagulant consequences. Soluble EPCR can be released from the endothelium in disease states such as sepsis and interferes with leukocyte–endothelium adherence. aPC has anti-apoptotic effects on endothelial cells via binding to EPCR and the subsequent initiation of cell signaling. aPC inhibits TNF release, nuclear factor-kB activation, leukocyte adhesion, and TF expression. The signaling pathways responsible for these actions of aPC are yet to be elucidated. In addition to these anti-inflammatory actions, aPC improves fibrinolysis in disease states by inhibition of plasminogen activator inhibitor-1 (PAI-1), an important mediator of impaired fibrinolysis.

Numerous human studies have documented that PC is consistently depleted in sepsis. Administration of aPC was associated with a reduction in relative risk of death in patients with severe sepsis. Depletion of PC during sepsis is thought to be the combined result of degradation by neutrophil elastases, consumption by increased pro-coagulant processes, inadequate hepatic biosynthesis, and possible acquired vitamin K deficiencies. The PROWESS trial, a phase III human clinical trial of recombinant aPC (Drotrecogin alfa) administration to patients with severe sepsis, resulted in a 6.1% absolute reduction in 28 days, all-cause mortality and a 19.4% reduction in the relative risk of death. There was an increased risk of serious bleeding found in the treated group, although serious bleeding occurred primarily in patients predisposed to hemorrhage (gastrointestinal ulceration, prolonged bleeding times, low platelet counts). Administration of aPC reduced the activation of thrombin and decreased inflammation, as determined by significant decreases in serum IL-6 concentrations in the treated patients. aPC is the first pharmacological agent proven to reduce mortality in severe sepsis. Administration of aPC was associated with a reduction in relative risk of death in patients regardless of the presence of an aPC deficiency prior to therapy. This result, in addition to the reduction in IL-6 levels, led to the conclusion that the effectiveness of aPC administration in septic patients is a consequence of its anti-inflammatory properties as much, if not more than its anti-coagulant properties. It serves as yet another example of the intimate relationship between the inflammatory and coagulation systems. The human recombinant aPC product has marked species specificity and requires a 15–20-fold higher dose in dogs to achieve a similar level of anti-coagulation in comparison with human subjects. In addition, drotrecogin alfa is rapidly eliminated in dogs and is antigenic in non-human species including primates and cannot be re-administered in animals for fear of anaphylaxis.
Fibrinolysis

The goal of the coagulation cascade is the formation of the stable fibrin clot to achieve hemostasis. Thrombin rapidly catalyses the conversion of fibrinogen to fibrin, the fibrin monomers then spontaneously associate to produce an initial clot. Under the influence of FXIIIa, covalent cross-links form between adjacent fibrin molecules, forming the final, stabilized clot. Factor XIII is found both in plasma and in the cytoplasm of platelets and is activated by thrombin, a reaction that is accelerated by the presence of fibrin itself.92

Fibrinolysis is the process of removal of intravascular fibrin clots and is an essential component of normal hemostasis. Plasminogen is cleaved by a plasminogen activator to form the enzyme plasmin, which subsequently digests the fibrin mesh.1 The 2 physiologic plasminogen activators are tissue plasminogen activator (tPA) and urokinase (uPA). Release of tPA from endothelial cells occurs in response to direct cell injury or following stimulation by thrombin. Urokinase is found in numerous cell types of the body and may have a greater role in extra-vascular fibrinolysis.86,92

Impairment of fibrinolysis has a prothrombotic effect. The hemostatic dysfunction associated with sepsis is characterized by both increased pro-coagulant processes and reduced fibrinolysis which can result in widespread microvascular thrombosis.14,94 PAI-1 is the primary physiologic inhibitor of tPA and uPA. This inhibitor of fibrinolysis is elevated in some human septic patients and both PAI-1 concentration and activity has been correlated with outcome in some studies.89,95,96

<table>
<thead>
<tr>
<th>Name</th>
<th>Coagulation effects</th>
<th>Inflammatory effects</th>
<th>Sepsis-associated changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF, Tissue factor</td>
<td>Pro-coagulant Initiation of coagulation</td>
<td>Pro-inflammatory</td>
<td>Elevated</td>
</tr>
<tr>
<td>TFPI, Tissue factor pathway inhibitor</td>
<td>Anti-coagulant Inhibition of FXa and TF–VIIa complex</td>
<td>Anti-inflammatory Variable</td>
<td></td>
</tr>
<tr>
<td>AT, Anti-thrombin</td>
<td>Anti-coagulant Inhibition of thrombin, Xa, VIIa, IXa, XIa, XIIa</td>
<td>Anti-inflammatory Reduced</td>
<td></td>
</tr>
<tr>
<td>PC, Protein C</td>
<td>Anti-coagulant Inhibition of FVa, FVIIIa Reduced fibrinolysis</td>
<td>Anti-inflammatory Reduced</td>
<td></td>
</tr>
<tr>
<td>TM, Thrombomodulin</td>
<td>Anti-coagulant Inhibits thrombin, activation of protein C and activates TAFI</td>
<td>Anti-inflammatory Reduced</td>
<td></td>
</tr>
<tr>
<td>EPCR, Endothelial cell protein C receptor</td>
<td>Anti-coagulant activation of protein C</td>
<td>Anti-inflammatory Reduced</td>
<td></td>
</tr>
<tr>
<td>PAI-1, Plasminogen activator inhibitor 1</td>
<td>Inhibits fibrinolysis Inhibits plasminogen</td>
<td>No known role Elevated</td>
<td></td>
</tr>
<tr>
<td>TAFI, Thrombin activatable fibrinolysis inhibitor</td>
<td>Inhibits fibrinolysis Reduces plasminogen activity</td>
<td>No known role Variable</td>
<td></td>
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</tbody>
</table>

Thrombin-activatable fibrinolysis inhibitor (TAFI), a plasma protein activated by high levels of thrombin or by thrombin–TM complexes, attenuates the conversion of plasminogen to plasmin. Plasmin can also activate TAFI, a negative feedback mechanism, this process is further stimulated by heparin.97,98 When thrombin is bound to TM, activation of TAFI, and hence, inhibition of fibrinolysis is increased 1250 times.92 Inflammatory processes such as sepsis are associated with increased oxidative damage. Oxidation of TM impairs its ability to activate PC but it retains its ability to activate TAFI. The result is the loss of the anti-coagulant effects of PC in the face of ongoing TAFI-mediated anti-fibrinolytic actions.92 This may further contribute to the prothrombotic coagulopathy associated with sepsis.

Summary of Hemostasis and Sepsis

Clinically, sepsis is a challenging disease process to treat successfully. Hemostatic abnormalities, collectively known as DIC, are commonly found in patients with severe sepsis. DIC produces a prothrombotic state, but because of consumption of coagulation factors and platelets, a unique situation can develop where a patient can have both thrombotic and hemorrhagic tendencies. In veterinary medicine, there remains a limited ability to recognize a prothrombotic state and the primary indication of the presence of DIC is the identification of a coagulopathy. As a result, DIC is often considered clinically as a bleeding disorder. Conceptually, DIC should be considered a prothrombotic process, reflecting the hemostatic system’s response to a pro-inflammatory
state. Important pro-coagulant changes in sepsis include the intravascular expression of TF in combination with a generalized reduction in endogenous anti-coagulant pathways (TFPI, AT, aPC). This overall pro-coagulant tendency is further aggravated by impaired fibrinolysis because of increased levels of PAI-1 and uninhibited activity of TAFI, the end result being widespread microvascular thrombosis (Table 2).

**Conclusions and Future Directions**

It is now apparent that the normal hemostatic response involves the interaction of multiple complex processes. Inflammation and the coagulation system are intimately connected; activation of one of these systems will invariably impact the activity of the other. Understanding this relationship provides some insight into the pathogenesis of the hemostatic changes seen during inflammatory disease processes such as sepsis. This new updated view of hemostasis has led to the development of novel therapeutic approaches to sepsis and DIC. In veterinary medicine, the challenge will be to determine which of these therapeutic options are beneficial as well as financially justifiable in our patient population.

**Footnotes**

a Fragmin, Pharmacia & Upjohn Company, Kalamazoo, MI.

b Xigris, Eli Lilly & Company, Indianapolis, IN.

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