

Overview of Inflammation and Coagulation

Brenda Lynn Morgan RN BScN MSc CNCC(C)

Inflammation and Coagulation: Review of Normal Responses

Inflammation is the body's immediate response to all types of cell injury. It is usually short in duration (hours to days). Within seconds of any tissue injury (e.g., hypoxia, trauma, infection), proinflammatory cytokines are released, activating a host of responses. Inflammation in turn will activate coagulation. Inflammation and coagulation are so vital to our survival that both responses are triggered by a number of different mediators. These multiple triggers promote amplification of the inflammatory and coagulation responses when a large or persistent stimulus is present.

Normally, homeostasis is achieved by the simultaneous release of anti-inflammatory cytokines and anticoagulants, and by initiating coagulation. Knowledge of the inflammatory and coagulation responses is needed to understand problems common in critical care (e.g. sepsis, Adult Respiratory Distress Syndrome, Acute Coronary Syndrome, Acute Brain Injury) and provides the basis for understanding common pharmacological interventions. This discussion will provide an overview of normal inflammation, coagulation and homeostasis.

Normal State

Endothelial cells make up the lining of all blood vessels (called endothelium). Capillary walls are made up of a single endothelial cell layer. Normally, tight junctions located between adjacent endothelial cells permit only small substances to pass across the capillary endothelium (e.g., oxygen, carbon dioxide, glucose). For every single white blood cell (leukocyte) in normal blood, there are approximately 700 red blood cells (erythrocytes). Only 1% of blood cells are white or platelets; RBCs make up 99%. During blood flow, the heavier red cell mass travels down the centre of the vessel lumen, pushing the platelets and leukocytes toward the endothelium. In normal states, leukocytes and platelets continue to flow without sticking to the blood vessel endothelium because non-activated endothelium releases substances that keep the vessel wall relaxed and non-adherent (e.g., prostacyclin, nitric oxide).

INFLAMMATION

Inflammation is the non-specific response of the microscopic circulation to tissue injury. Tissue injury causes mast cells to degranulate, leading to the release of dozens of inflammatory mediators, including histamine. Histamine augments blood flow to the affected area and increases blood vessel permeability. Proinflammatory substances stimulate neutrophil production and activate endothelial cells at the site of injury.

Neutrophils are the "first responders" of the leukocytes. They begin to increase in number within seconds of an inflammatory response. Neutrophils are phagocytes that "gobble up" pathogens and dead cells. Once trapped within the neutrophil, toxic substances that kill and digest the pathogen are released. When phagocytes die, their contents (dead bacteria and toxic agents) are released into surrounding tissue and appear as pus. The same substance that is toxic to invading bacteria can be injurious to surrounding healthy tissues, thus, persistent exudate can become a trigger for more inflammation.

Endothelial cells also become activated at the onset of inflammation. Activated endothelial cells contract, increasing the distance between endothelial cells. This increases the blood vessel permeability. Activated endothelial cells also express proteins onto their surface that are adhesive or "sticky". Recall that neutrophils and platelets are naturally pushed toward the endothelium during blood flow. If the endothelium has been activated, the neutrophils will begin to adhere to the endothelium. As neutrophils are pushed toward the activated endothelial surface, they begin to adhere to the vessel wall (margination) and roll along the surface. This causes a slowing of the neutrophil movement and increases the concentration of the neutrophils at the site of injury. This increased collection of neutrophils around the area where the endothelium has become more permeable facilitates the migration of large numbers of neutrophils toward the injured tissue (diapedesis). Water, protein and other cells also move across permeable endothelial membranes, causing an accumulation of tissue edema. Advancements in technology have enabled scientists to examine the microscopic circulation during inflammation, revealing that the largest area of increased permeability occurs on the venule side of the capillary.

When inflammation continues for days, or becomes persistent, the short life span and limited phagocytic capacity of the neutrophil may be inadequate. Monocytes are the next leukocytes to be activated. When monocytes are activated, they begin to migrate into injured tissues where they mature to become tissue macrophages. Macrophages are larger phagocytes, with longer survival times and more powerful killing capabilities than neutrophils. When inflammation persists, toxic contents released from dying neutrophils and macrophages can cause harm to healthy tissues, leading to increased or chronic inflammation.

Activated neutrophils, monocytes and macrophages all release substances called cytokines. Proinflammatory cytokines help to eradicate infection, remove dead cells and promote tissue repair. Examples of proinflammatory cytokines are tumour necrosis factor- α (TNF- α), interleukins 1, 2, 6 and 8 (IL-

1, IL-2, IL-6 and IL-8) and interferon- γ . To achieve homeostasis, the release of proinflammatory cytokines triggers the release of anti-inflammatory cytokines. Examples of anti-inflammatory cytokines are interleukins 4, 10, 11 and 13 (IL-4, IL-10, IL-11 and IL-13), soluble TNF- α and IL-1ra. When the inflammatory trigger subsides, proinflammatory cytokine release stops, allowing the anti-inflammatory cytokines to dominate and restore homeostasis.

Activated endothelial cells and various other proinflammatory mediators also trigger an increase in blood flow to the injured area. Initially, vasoconstriction of affected blood vessels and surrounding arteries occurs in order to decrease bleeding. This is followed by a vasodilatory response, most notably in the venules. The net effect is that blood flow increases in the direction of the permeable venules. This enhances the delivery of neutrophils, nutrients and water toward the injured tissue.

Prostaglandins and bradykinins also trigger pain receptors. Pain encourages the individual to attend to the injured tissue and immobilize the area of injury. Activated white blood cells will also release cytokines that increase the metabolic rate and trigger fever production. The higher rate of metabolism enhances blood flow delivery and facilitates oxygen extraction by the tissues. The net effect of the increased blood flow, increased metabolic rate and pain receptor stimulation is a warm, throbbing, painful area of inflammation.

COAGULATION

Coagulation can be divided into 3 distinct phases. Phase one is initiated when platelets begin to adhere to the surface of activated endothelium. Phase two is the creation of a platelet plug produced when platelets begin to aggregate or stick to each other. The final phase occurs when the coagulation cascade is activated, leading to the production of fibrin that will stabilize the clot by holding it in place. Endothelial cells play an important role in mediating adherence, aggregation and activation of the clotting cascade.

Homeostasis

Normal endothelium inhibits coagulation by producing substances such as nitric oxide and prostacyclin. Both of these substances promote vasodilation and platelet inhibition. Non-activated endothelium also expresses the protein thrombomodulin, which facilitates anticoagulant and fibrinolytic activity by converting Protein C to activated Protein C (discussed later). Additionally, normal endothelium expresses other anticoagulants such as glycosaminoglycans and heparinoids. Once formed, clots are removed from the vessel wall by a process called fibrinolysis. Fibrinolysis is the breaking down of a fibrin clot, a process that is triggered when tPA converts plasminogen to plasmin, the substance responsible for clot lysis. In the area of tissue injury, activated endothelial cells promote clot formation and inhibit clot lysis. In the uninjured areas, non-activated endothelium opposes clotting.

Platelet Activation

Normal blood contains a sufficient number of circulating platelets to achieve hemostasis when required. Following a break in the endothelial lining, platelets are exposed to subendothelial connective tissue. Circulating von Willebrand factor causes platelets to attach to the exposed collagen on injured endothelium. Platelet attachment to the endothelium is referred to as *adherence*. Once activated, platelets release granules, which contain: ADP, serotonin, fibrinogen, lysosomal enzymes and platelet factor 4. Activated platelets also stimulate the production of the prostaglandin thromboxane A₂ (TXA₂).

Platelet *aggregation* is the attachment of platelets to other platelets that are already bound to the endothelial wall. ADP and TX₂ both stimulate platelet adhesion and aggregation. In addition, platelet aggregation leads to the exposure of binding sites on the platelet surface known as Glycoprotein IIb and IIIa receptor sites (GPIIb/IIIa). These receptor sites facilitate platelet-to-platelet connections that enhance aggregation and increase the size of the platelet plug.

A number of drugs used in critical care influence platelet activity. For example, DDAVP (desmopressin) increases coagulation by enhancing the release of Factor VIII components, including von Willebrand factor. Aspirin blocks TXA₂, to decrease platelet adhesion. Because prostaglandins also stimulate inflammation and trigger pain receptors, aspirin also has anti-inflammatory and analgesic properties. Although heparin is used more commonly for its anticoagulant properties (preventing stabilization of the clot), heparin also inhibits platelet aggregation by blocking the thrombin binding sites on platelets. Clopidogrel (Plavix) blocks ADP receptors to decrease platelet adhesion and aggregation, whereas, drugs like abciximab (ReoPro) and eptifibatid (Integrilin) block the GP IIb/IIIa receptors. Multi-drug therapy is often used in acute coronary syndrome to ensure adequate platelet inhibition by using various drugs that each block a different platelet binding receptor.

Activation of Clotting Cascade

Activated or injured endothelium loses its natural anticoagulant property at the site of the tissue injury. Activated endothelium stops producing nitric oxide and prostacyclin, and decreases the expression of thrombomodulin. In addition, activated endothelial cells and monocytes express large amounts of Tissue Factor (TF), an important trigger of the coagulation cascade. Activation of the clotting cascade leads to the

generation of thrombin. Thrombin in turn stimulates additional ADP and TXA₂, increases platelet aggregation and triggers the conversion of fibrinogen to fibrin. Fibrin strands create a mesh-like structure to hold the platelet plug securely in place. Thrombin actually promotes more thrombin production by activating co-factors VIII and V of the coagulation cascade to stimulate additional thrombin production.

To ensure adequate coagulation occurs, the presence of TF and/or thrombin actually delays the onset of fibrinolysis. TF triggers the production of Plasminogen Activator Inhibitor (PAI 1), an endogenous inhibitor of tPA, whereas, thrombin mediates the production of Thrombin Activatable Fibrinolysis Inhibitor (TAFI). If the inflammatory trigger is large or persistent, platelet activation, TF generation and thrombin production will also persist, leading to ongoing clot production and fibrinolysis inhibition. A pro-coagulant state will remain until the inflammatory trigger is alleviated.

As previously mentioned, TF is an important activator of the coagulation cascade. The coagulation cascade consists of a series of enzymatic reactions that terminate in the development of a fibrin clot. Activation of each coagulation factor initiates the activation of the next factor in a sequential fashion. All of the coagulation factors except fibrinogen are either proenzymes or cofactors. Proenzymes are transformed into activated enzymes after hydrolysis of one or more of the peptide bonds. Cofactors include Factor III (Tissue Factor), V and VIII. Each acts as a catalyst to accelerate other enzymatic reactions. A Roman numeral is used to symbolize the various coagulation factors (listed in Table 1). When one of these coagulation factors becomes activated, a small letter "a" is added to the Roman numeral to denote the activated form of the coagulation factor (Figure 1).

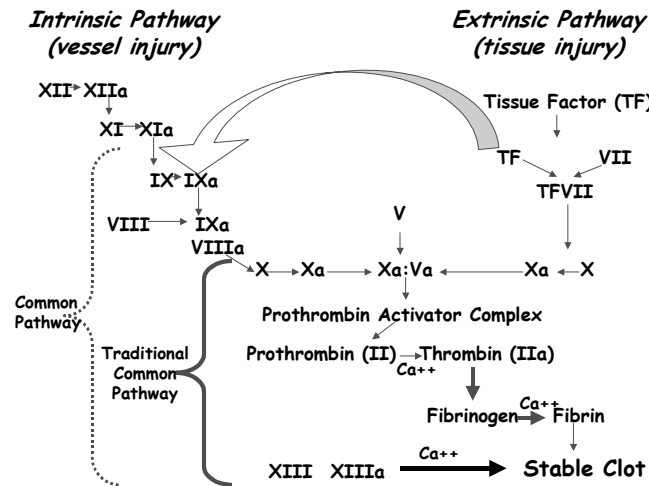


Figure 1.

Clotting Factors	Name	Cofactors (potentiates activation of other factors)
I	Fibrinogen	III
II	Prothrombin	VIII
III	Tissue factor (thromboplastin)	VII
V	Labile factor	
VII	Proconvertin	
VIII	Anti-haemophilic factor	
IX	Christmas factor	
X	Stuart-Prower factor	
XI	Plasma thromboplastin antecedent	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
	Prekallikrein	Mediators of XIIa
	High-molecular-weight kininogen (HMWK)	

Table 1.

Historically, the initiation of coagulation was believed to occur as a result of activation of either the intrinsic or extrinsic pathways. Both of these pathways converge to become one common final pathway when factor Xa and Va are combined (see Figure 1). The factor Xa:Va complex is responsible for the conversion of prothrombin to thrombin. Thrombin causes fibrinogen to become fibrin.

It is now believed that most coagulation is initiated when tissue factor expressed on injured endothelial cells and activated monocytes combines with Factor VIIa (refer to the extrinsic side of pathway). In addition to the activation of Factor Xa:Va, the complex of Tissue Factor:Factor VIIa simultaneously activates Factor IX (refer to the “intrinsic pathway” in Figure 1). Consequently, both sides of the coagulation cascade are activated under the influence of Tissue Factor, amplifying the amount of coagulation. This suggests that the common pathway likely begins at the point when Factor IX becomes activated. The role that the intrinsic pathway plays in the initiation of coagulation is not clearly known.

Clotting provides hemostasis, helps to wall off infection, traps leukocytes in the area of injury and initiates the repair of injured blood vessel walls.

Anti-inflammation

Anti-inflammatory cytokines are released from activated leukocytes, in response to the release of proinflammatory cytokines. Once the inflammatory trigger is removed and proinflammatory cytokine release subsides, anti-inflammatory cytokines can dominate. Corticosteroids also have anti-inflammatory properties. Activated Protein C is an important inhibitor of inflammation and will be examined below.

Anticoagulation:

Following activation of the clotting cascade, circulating antithrombin binds to thrombin, to weakly inactivate thrombin activity. Antithrombin also inactivates Factors Xa, IXa, XIa, and XIIa. Endogenous heparin binds with the antithrombin-thrombin complex to significantly enhance the antithrombin activity. Thrombin triggers the conversion of Protein C to activated Protein C, a potent anti-inflammatory, anticoagulant and pro-fibrinolytic agent. Pharmacological agents classed as anticoagulants work by inhibiting or de-activating steps within the coagulation cascade to delay or decrease the production of fibrin. Because anticoagulants block a different phase of coagulation than anti-platelet agents, both anti-platelet and anticoagulant agents may be used together when it is very important to prevent further clot formation (e.g., Acute Coronary Syndrome).

The administration of unfractionated heparin is believed to work the same way as endogenous heparin. Unfractionated heparin equally inhibits thrombin and Factor Xa on a 1:1 ratio. Heparin binds to the antithrombin-thrombin complex, to potentiate the antithrombin effect. When antithrombin levels are low (e.g., in procoagulant states such as septic shock), heparin resistance may develop.

Thrombin inhibition prolongs the aPTT. Low molecular weight heparins (LMWH) produce more anti Xa activity than antithrombin activity, because LMWH chains are not long enough to simultaneously link to antithrombin and thrombin. LMWHs have an antithrombin to anti Xa ratio of 1:2 – 1:4, with minimal effect on the aPTT. One advantage of LMWH therapy is the ease of use; monitoring is not required because weight based therapy produces consistent levels of anticoagulation. While unfractionated heparin has a shorter half-life, making it easier to reverse if bleeding occurs, it is often more difficult to titrate as many patient variables can influence an individual's response to a given weight-based dose of heparin.

Although the risk for developing heparin induced thrombocytopenia (HIT) is lowered when LMWHs are used, both unfractionated heparins and low molecular weight heparins are contraindicated if heparin induced thrombocytopenia (HIT) or heparin allergy develops.

Danaparoid is an anticoagulant that can be administered to patients with heparin allergy or HIT. Danaparoid has a 1:20 antithrombin to anti Xa activity, producing anticoagulation without prolonging the aPTT. Anti Xa levels must be measured to titrate danaparoid infusions. The long half-life of the drug (25-26 hours) is a concern; bleeding cannot be quickly reversed with danaparoid.

A newer alternative to danaparoid is argatroban. It is a synthetic direct thrombin inhibitor, with a shorter half-life than danaparoid (half-life is prolonged in hepatic failure). Because it is a thrombin inhibitor, it will prolong the aPTT. The aPTT is used to adjust the dose.

Fibrinolysis:

Tissue plasminogen activator (tPA) is released in response to fibrin generation. TPA converts plasminogen to plasmin. Plasmin causes fibrinolysis, or the dissolution of preformed clot. The dissolution of a clot causes an increase in the number of circulating fibrin degradation products. While anticoagulants prevent new clot from forming, fibrinolytics are responsible for the break down of clot that has already formed. The tPA-plasminogen-plasmin cascade is depicted in Figure 2.

In addition to the fibrinolytic activity of plasmin, endogenous activated Protein C also has important fibrinolytic effects.

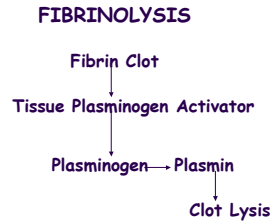


Figure 2.

The Role of Activated Protein C

As previously described, activated Protein C influences homeostasis by anti-inflammatory, anticoagulant and profibrinolytic actions. Protein C is an endogenous protein that circulates in the blood. When thrombin is produced, it circulates to areas where the endothelium is not in an activated state and combines with a protein called thrombomodulin that is located on the surface of the endothelial cells. The thrombin-thrombomodulin complex attaches itself to Protein C and Protein S, two other endogenous proteins. The formation of this thrombin:thrombomodulin:Protein C:Protein S complex causes the conversion of Protein C to activated Protein C.

Thrombomodulin is only generated on non-activated endothelium. In severe sepsis and septic shock, increased clotting can lead to Protein C depletion. In addition, when inflammation becomes systemic, the widespread activation of endothelial cells reduces the area available to convert Protein C to activated Protein C. Because the ability to convert activated Protein is limited, Protein C replacement must be given in the activated form. The administration of activated Protein C has been shown to reduce mortality associated with severe sepsis or septic shock.

Once activated, Protein C helps to restore homeostasis by causing the following 3 effects:

Anti-inflammatory: Activated Protein C inhibits further cytokine production (e.g. Tumour Necrosis Factor [TNF] and interleukin 1 and 6 [IL-1, IL-6] to decrease inflammation. A decrease in cytokine production will also reduce further production of TF (a mediator of clotting). Activated Protein C also decreases leukocyte rolling and adhesion to endothelial surfaces.

Anticoagulant: Activated Protein C deactivates factors VIIIa and Va, two cofactors that precipitate thrombin formation. Thus, Activated Protein C is an important anticoagulant.

Profibrinolytic: Activated Protein C blocks the formation of 2 antifibrinolytic substances that are produced during thrombin generation and endothelial injury (TAFI and PAI-1). By opposing these two inhibitors of fibrinolysis, clot lysis is facilitated.

TESTS OF THE INFLAMMATORY AND COAGULATION RESPONSES

INFLAMMATION

Leukocyte Count: The inflammatory response mounts quickly during an acute infection or tissue injury. If the inflammatory response is large and the neutrophils are no longer only localized to the site of injury, the leukocyte count will elevate, consisting primarily of elevated neutrophils. While infection will produce an acute inflammatory response, not all inflammation is caused by infection. For example, trauma, major surgery, Acute Coronary Syndrome and pancreatitis are examples of powerful inflammatory triggers. When a significant and persistent inflammatory response is present, the demand for neutrophils may exceed the ability to produce them. This can lead to the release of immature neutrophils into the circulation. This is identified on a blood smear or differential as a "left shift", or, as >10% bands. In persistent acute inflammation, the monocyte count can also be elevated.

An elevated leukocyte count that is mainly characterized by increased lymphocytes is not indicative of acute infection or inflammation. Lymphocytes are cells of the immune response (e.g. antibody complexes or helper/killer T cells). Lymphocytes are elevated in chronic or viral infection, and certain malignancies.

ESR or C Reactive Protein: An increase in the ESR (eosinophil sedimentation rates) or C reactive protein level indicates inflammation is occurring. These are both nonspecific indicators, therefore, neither provide any direction regarding the cause of the inflammatory response. ESR has little clinical value, as it will remain elevated for prolonged periods of time after inflammation has decreased. C reactive protein differs from the ESR because it declines quickly when the inflammatory response subsides. This makes C reactive protein useful in a variety of inflammatory conditions (e.g. Acute Coronary Syndrome, joint infection) as a marker of a patient's responsiveness to therapy.

Sometimes, particularly in research studies, proinflammatory cytokines are measured to identify the presence of ongoing or resolving inflammation. Examples include IL1 and 6 or TNF- α .

COAGULATION

Prothrombin Time (measured as INR): Measurements of both PT(INR) and PTT (aPTT) are done from a sample of whole blood that is collected in a tube that has a precise ratio of blood to citrate. Citrate prevents the blood from clotting by inactivating calcium ions. Calcium ions are important catalysts that precipitate clotting at several steps in the clotting cascade.

A prothrombin time is measured by calculating the time (seconds) it takes for a fibrin clot to form after the initiation of the extrinsic pathway. This is accomplished by adding calcium (to reverse the citrate) and thromboplastin (Tissue Factor) to the blood sample. Reporting of the PT has been standardized by conversion of the results to an International Normalized Ratio (INR). Each lab converts a normal PT to an INR of 1.0. This simplifies the adjustment of anticoagulant therapy and gives universal meaning to the INR value.

The PT measures the activity of clotting factors within the extrinsic (including Factor VII) and traditional common pathway (from Factor X to fibrin). It will be prolonged in a deficiency of Vitamin K or Vitamin K dependent clotting factors (e.g. VII, X, IX, Protein C and S). Coumadin or warfarin inhibit the synthesis of Vitamin K dependent clotting factors to prolong the PT. Because coumadin works by impairing production, its onset of action is much longer than heparin. When converting a patient from heparin to coumadin, it is important to maintain therapeutic levels of heparin (aPTT levels) until the coumadin has produced therapeutic effects (INR). Failure to do this will result in a period of inadequate anticoagulation.

Prolonged INR levels can be shortened by the administration of Vitamin K if the patient has received coumadin or has a low Vitamin K level. Fresh Frozen Plasma can be given to replace deficient clotting factors. Liver disease with hepatocyte destruction can prolong the INR by decreasing the uptake of Vitamin K from the GI tract and/or by impairing the ability to manufacture clotting factors. If the INR is prolonged due to Vitamin K deficiency, the INR will respond to one or two doses. Failure to respond indicates that hepatocyte damage is impairing clotting factor production; repeated doses of Vitamin K could lead to toxicity. Biliary obstruction can prolong the INR because bile salts are needed to absorb Vitamin K from the GI tract. Prolonged INR due to bile salt reduction should be responsive to Vitamin K.

Activated Partial Prothrombin Time (aPTT): Activated partial prothrombin time (aPTT) measures the time (seconds) that it takes for a fibrin clot to form after initiation of the intrinsic pathway. It measures the intrinsic and traditional common pathways (from Factor X to fibrin) and may become prolonged if there is a deficiency of any clotting factor EXCEPT Factor VII.

If the aPTT is prolonged and the INR is normal, Factor VII deficiency is excluded. The aPTT is most sensitive to antithrombin activity, therefore, heparin and argatroban therapy prolongs the aPTT. Because Activated Protein C deactivates VIIIa and Va, some prolongation of the aPTT may be seen with Activated Protein C administration. Activated Protein C should not have a significant impact on the INR. Prolongation of both the INR and aPTT in a patient receiving Activated Protein C for severe sepsis/septic shock indicates a coagulopathy is present.

Fresh frozen plasma will replace clotting factor deficits and correct a prolonged aPTT. If the prolongation is caused by intravenous heparin therapy, protamine sulphate can be administered to reverse the heparin (e.g. post bypass surgery). Protamine sulphate should not be administered if the aPTT prolongation is not due to exogenous heparin administration as it can precipitate more clotting.

If both the aPTT and the INR are prolonged, the problem is most likely occurring in the final common pathway or is due to significant reduction in multiple clotting factors. This can include deficiencies of Factors V, X or II (prothrombin), DIC or overanticoagulation with coumadin.

Thrombin Time (TT) and Fibrinogen Levels: The thrombin time is the time required for blood to clot following administration of thrombin. It tests the lower half of the common pathway and will be prolonged if the fibrinogen level is low. Because heparin potentiates antithrombin activity, heparin therapy also prolongs the thrombin time. Measurement of the fibrinogen level is a more specific indicator of fibrinogen deficiency than thrombin time, therefore, it is more common to measure the fibrinogen level than to measure TT. Fibrinogen levels can be low in DIC as a result of excessive consumption of coagulation factors, including fibrinogen. DIC is defined by a prolonged INR and aPTT, and decreased platelet count. Cryoprecipitate (Cryo) concentrate contains factor VIII, von Willebrand factor and fibrinogen. It is the only IV preparation available to correct fibrinogen deficiencies. Cryoprecipitate does not require compatibility testing.

Factor VII: Factor VII has begun to gain interest as an important treatment modality in severe trauma. Because most clotting is initiated when Tissue Factor combines with Factor VII, increased Tissue Factor can lead to depletion of Factor VII. Factor VII levels can be measured and Factor VII concentrate can be administered. It is being given at the roadside following massive trauma in war-torn regions of the world.

Fibrinogen Degradation Products (FDP) and D-Dimer: When a fibrin clot is broken down, fibrin degradation products increase in the bloodstream (measured as FDP or D-dimer). An elevated FDP or D-dimer is a non-specific indicator that increased clot lysis (and therefore clotting) has occurred. FDP only measures the byproducts of degradation, therefore, it only demonstrates the effects of plasmin. D-dimer is a much more specific indicator of DIC, measuring both thrombin and plasmin activity by detecting both newly formed and newly degraded fibrin.

Although elevated FDP and D-dimer levels indicate increased coagulation activities, levels are generally elevated in all critically ill patients for a variety of reasons (e.g. sepsis, intravascular lines, surgery). Consequently, these tests are of limited value during critical illness. It is generally more useful to measure the INR/PTT, platelets and specific clotting factors such as fibrinogen and/or Factor VII levels.

D-dimer can be useful as a means of *excluding* increased clotting in patients with no other reason for increased coagulation activity. For example, in the emergency room setting, a normal D-dimer can be useful as a means of ruling out DVT or pulmonary embolus, whereas, a positive test necessitates further investigation. A red D-dimer (or simply red) is a rapid method for measuring D-dimer using whole blood. It is available in some emergency room settings. D-dimer may also be useful when differentiating Thrombotic Thrombocytopenia Purpura (TTP) from DIC (D-dimer will be normal in TTP).

Anti Xa Levels

Although coagulation monitoring of LMWH is rarely indicated, anti Xa level monitoring would be the appropriate test. Danaparoid infusions should be adjusted to maintain a therapeutic anti Xa level. Normal anti Xa levels are 0, with a therapeutic goal of .5-.8 units/ml during systemic anticoagulation. Anti Xa levels are prolonged by unfractionated heparin, LMWH and danaparoid.

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Brenda Lynn Morgan RN BScN MSc CNCC(C)