Coagulopathies – Diagnosis and Therapy

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Coagulopathies, or bleeding disorders, affect hemostasis. This article provides a brief review of the physiological mechanisms of hemostasis, hemorrhagic diathesis signs and symptoms, coagulopathy classifications, and therapeutic options for patients.

Bleeding in Patients

Coagulopathy is a bleeding disorder characterized by impaired blood clotting. Determining the underlying cause when a patient presents with a coagulation disorder requires a thorough history and physical. For example, coagulopathy may be due to an underlying medical condition or a complication of surgical or dental procedures.
Physiology and Pathophysiology of Hemostasis

**Hemostasis** refers to the fluid state of blood within the circulatory system and the prevention of bleeding by compression or ligation. Processes affecting hemostasis include vasoconstriction, platelet aggregation, thrombin and fibrin generation, and fibrinolysis. Hemostasis is divided into primary and secondary subtypes.

### Primary hemostasis

Primary hemostasis consists of **vasoconstriction and the formation of a “white” thrombus** with platelets (also known as thrombocytes) aggregating to form a plug. An injury to or irritation of the vascular wall leads to the release of adenosine triphosphate (ATP), which, in conjunction with the von Willebrand factor, allows platelet adherence.

The platelets synthesize thromboxane from the arachidonic acid in their membranes through cyclooxygenase (COX), where the COX enzyme converts arachidonic acid to prostaglandin.

Platelets also transport and release serotonin. While the exact role of serotonin remains to be elucidated, it is involved in platelet adherence; it constricts injured blood vessels and enhances platelet aggregation to minimize blood loss.

### Secondary hemostasis

Secondary hemostasis is a time-delayed process that aims for thrombus stabilization after platelet aggregation. The plasma coagulation cascade leads to the formation of the prothrombin activator complex, either intrinsically (factors XII, XI, IX, VIII, X, and V) or extrinsically (factors III, VII, X, and V), which converts **prothrombin to thrombin** (activated factor II). The activated thrombin splits fibrinogen, and the soluble fibrin eventually forms a firm meshwork using the fibrin-stabilizing factor XIII.

### Dissolving fibrin

Plasmin dissolves fibrin via fibrinolysis during the wound healing process. Various plasminogen activators convert inactive plasminogen into active plasmin, which in turn eventually splits fibrin, allowing small wounds, bleeding, or microthrombosis to heal.
This process may become unbalanced because of disturbances that are congenital, pathological, or influenced by iatrogenic mechanisms that dissolve blood clots or prevent their formation.

**Definition of Hemorrhagic Diathesis**

Diathesis refers to a tendency to bleed or bruise easily. It can manifest itself in the forms of thrombotic, plasma, or vascular disorders. Hemorrhagic diatheses may be divided into three groups according to their clinical signs:

1. **Platelet disorders**, which broadly refer to any platelet hemostasis disorder, account for approximately 70% of all cases. Causes include kidney or renal disease, chemotherapy, diminished immunity, and radiation.
2. **Coagulopathies** caused by plasma irregularities account for approximately 20% of hemorrhagic diatheses. It is caused by fibrinolysis disorders triggered by anticoagulant and fibrinolytic drugs, or conditions such as hemophilia.
3. There are also **combined hemostasis disorders** with platelet and plasma components caused by von Willebrand’s disease or radiation exposure.

**Diagnosing Coagulation Disorders**

The first step is taking the patient’s medical history and performing a physical examination. Important factors are a family history of bleeding or easy bruising and whether the patient is taking an anticoagulant. The physician should also rule out malignancy.

Clinically categorizing blood frequently reveals the hemostasis disorder’s location.

- **Coagulopathies** frequently manifest themselves as large, extensive hematomas accompanied by unexplained and easy bruising. This extensive bleeding is usually sharply defined. Affected organs may be, for instance, muscles, joints, or the skin.

![Intermediate magnification micrograph of fetal thrombotic vasculopathy. H&E stain. Histopathologically, it is characterized by clustered fibrotic chorionic villi without blood vessels; thrombi in fetal vessels. Clinically, it is associated with cerebral palsy and stillbirth.](Image)
Petechiae are a sign of thrombotic or vascular bleeding. Extensive petechiae are referred to as purpura, but there may also be ecchymosis, which is bruising caused by damaged blood vessels. Both symptoms may appear in combined hemostasis disorders.

Should you suspect a coagulation disorder, you may be able to narrow down the causes using different tests:

- **The blood count** will provide evidence of platelet count changes. **Prolonged bleeding points** toward a disorder of the platelet function or a vascular disorder.

- **Partial thromboplastin time (PTT)** indicates the amount of time needed for blood coagulation. The normal range is 20-35 seconds. PTT may be prolonged with defective or decreasing coagulation factors II, V, VIII, IX, X, XI, and XII.

- **Prothrombin time** (thromboplastin time) is the amount of time required for blood plasma to clot. In many cases, assays of Factor VIII and IX are indicated. It is measured in percentages; results lower than 70% are signs of defective or decreased coagulation factors II, VII, IX, and X. The test result can be used to calculate the INR (international normalized ratio), which is used to monitor patients taking anticoagulants.

- **Thrombin time (TT)** is a test to determine the common pathway for blood clot formation after thrombin is added. Active thrombin activates fibrinogen. In cases of fibrinogen deficiency, TT is prolonged, indicating disseminated intravascular coagulation.

- Another option to detect fibrinogen deficiency is to measure **reptilase time**. Reptilase is a snake venom that may split fibrinogen. In cases of fibrinogen deficiency, reptilase time is prolonged.

**Note:** If the patient is on heparin, the reptilase time will help detect fibrinogen deficiency. Thrombin activity is directly affected by heparin or hirudin therapy, but reptilase is not. If PTT is abnormal, it indicates a definite history of bleeding. However, an abnormal PT, with or without abnormal PTT, indicates abnormal levels of vitamin K coagulation factors (II, VII, IX, and X).
Furthermore, there are other specific tests for different indications:

- Measuring **factor Xa** activity may be used to monitor therapy in cases of low-molecular-weight heparin therapy (LMWH). PTT is not suitable for LMWH. Therefore, if therapy is to be evaluated, the anti-factor Xa levels should be monitored 3–4 hours after injecting LMWH. This is indicated for underweight or overweight patients, for patients with renal insufficiency, or if bleeding occurs after LMWH administration.
- **D-dimer** tests are often done to rule out thrombosis or a pulmonary embolism. D-dimers are fibrin by-products whose levels are elevated during fibrinolysis, indicating the formation of fibrin intravascularly. Elevated d-dimer levels may have many causes. Normal d-dimer levels, however, rule out thrombosis or pulmonary embolism for the most part.

**Definition and Classification of Coagulopathies**

Coagulopathies describe coagulation disorders that impact secondary hemostasis. They are disorders of the coagulation factors.

Coagulopathies may be subdivided into four large groups, each requiring different therapeutic measures:

- Coagulation defects
- Consumption coagulopathies
- Immune-mediated coagulopathies
- Hyperfibrinolysis

**Coagulation defects**

Coagulation defects describe various deficient or defective coagulation factors. These disorders may be acquired or congenital. For example, congenital coagulation defects include von Willebrand syndrome or hemophilia.

Vitamin K deficiency is often associated with acquired coagulation-factor deficiencies and is known to be involved in the synthesis of factors II, VII, IX, and X. Liver disease and vitamin K antagonists, such as Coumarin, may affect absorption.

**Consumption coagulopathies (disseminated intravascular coagulation, DIC)**

**DIC** is diagnosed by an elevation in PTT, PT, plasma D-dimers, and decreased fibrinogen levels. Disseminated intravascular activation of the coagulation system occurs slowly, via various processes, along with the formation of multiple microthrombi. It leads to increased production of thrombin and fibrin.

This systemic coagulation activation hyperstimulates the hemostasis system, leading to excessive consumption of coagulation factors, antithrombin, and platelets. This results in an increased bleeding tendency that may lead to bleeding complications or even shock—the disseminated microthrombi increases fibrinolysis along with proteolysis of other coagulation factors.
Immune-mediated coagulopathies

Many immune-mediated diseases, such as systemic lupus erythematosus, produce different autoantibodies. These autoantibodies may target the coagulation system components, thus creating coagulopathy.

Hyperfibrinolysis

As previously mentioned, plasminogen regulates fibrinolysis. Different mechanisms may increase fibrinolysis through excessive plasminogen activation, which, in turn, increases the consumption of coagulation factors. This results in more fibrinolytic activity than fibrin formation and severe bleeding.

Genetically, there may be a deficiency of alpha-2 antiplasmin, but malignant diseases and chronic liver disease are other common causes of fibrinolysis.

Cardiopulmonary bypass surgery or removal of the thrombus in arterial or venous thromboembolism can trigger hyperfibrinolysis by using fibrinolytic agents.

Consumption coagulopathy may cause secondary increased reactive fibrinolysis and exaggerate the consumption of coagulation factors via proteolysis. Reactive fibrinolysis means that increased fibrinolysis is only activated after preceding thrombus formation. Fibrinolytic therapy is used for vascular occlusions.

Therapy for Secondary Hemostasis Disorders

The goal of therapy is to restore the normal coagulation balance. In cases of mild disorders, close monitoring may be appropriate. However, pending surgeries or relevant bleeding must be dealt with more urgently.

- An underlying disease should be treated first. Administering coagulation factors will have minimal benefit if antibody production continues. In this case, immunotherapy should be considered.
- Intrinsic system disorders (i.e., hemophilia) are typically treated with factor replacement therapy.
- Extrinsic system disorders may be balanced like intrinsic system disorders. Patients on vitamin K antagonist therapy (warfarin) should temporarily discontinue treatment and take vitamin K. This may pose a therapeutic dilemma for which there are no clear recommendations. The indication for individual oral anticoagulation must be weighed against the risk of bleeding, calculated as an INR. The INR should be <5.
- Hyperfibrinolysis may be stopped by administering tranexamic acid, which inhibits plasmin formation.

Increased Tendency to Clot

Hypercoagulopathy, or the increased tendency of blood to clot, can cause certain diseases, such as antithrombin deficiency, protein C and S deficiency, and resistance to activated protein (APC resistance/factor V Leiden mutation). Prothrombin mutations or increased levels of factor VIII are also possible.

Individuals with these diseases frequently suffer from thrombophilia early in life. Young people who present with phlebothrombosis, pulmonary artery thrombosis, or cerebral...
Infarction should be evaluated for thrombophilia.

References

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