Disorders of Hemostasis: “Causes of Bleeding”

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Introduction to Hemostasis

Normal blood flow through the arterial and venous systems requires blood to be in a fluid rheologic state so that cardiac output can freely deliver oxygen and nutrients to vital organs. This is ensured by a finely *balanced* hemostatic system that includes proteins and cells in the blood as they interact with the endothelium to ensure fluidity. This “balance” that exists in normal hemostasis also enables formation of a clot at sites where the endothelium may need repair, for example during vascular injury. This physiologic system has positive and negative feedback mechanisms that ensures blood remains liquid to facilitate circulation but can rapidly respond to vascular injury to prevent excessive blood loss. Pathophysiologic disruption in this balance can lead to either excessive hemorrhage or thrombosis. Understanding the normal process and physiology of hemostasis is helpful in order to understand why bleeding and clotting can occur at times when they are not desired. We will review the normal process, the coagulation cascade models, and the various inherited and acquired disorders affecting each step.

Physiology of Normal Hemostasis

When blood vessel injury occurs, the primary goal of treatment is to prevent hemorrhage using transfusions and pharmacologic agents, while avoiding pathologic thrombosis. Endothelial cells play a critical role by releasing anticoagulant factors thereby preventing clot formation on intact vessel walls. Upon injury or trauma, the subendothelial matrix is exposed and expresses such factors as tissue factor and collagen. Together with circulating blood cells and platelets, these factors start to form a plug, to seal the injury. Concurrently, a complex coagulation cascade further stabilizes this plug. Coagulation results in fibrin formation, which strengthens the forming clot. After clot formation and during healing, fibrinolysis is a negative feedback mechanism that dissolves clots so that the process does not proceed unchecked.

Coagulation Cascade Models

Historically, two main models explain coagulation: the cascade model and the cell-based model.

- The **cascade model** conceptualizes coagulation as two pathways—extrinsic and intrinsic—that converge to activate factor X, the final common pathway leading to thrombin generation and fibrin clot formation. The extrinsic pathway (factor VII and tissue factor) and the intrinsic pathway (factors XII, XI, IX, and VIII) are useful in understanding laboratory testing. Test such as the prothrombin time (PT), international normalized ratio (INR), and the activated partial thromboplastin time (aPTT) are easy to interpret using the cascade modeling.
- However the **cell-based model** more accurately describes physiological coagulation, emphasizing the critical role of the platelet surface and its interactions with the coagulation cascade factors. The phases of initiation, amplification, and propagation are described. The cell-based model takes into account the importance of thrombin in activation and amplification of clot formation. This model underscores the importance of cell surface interactions and local regulation in vivo, clarifying the mechanisms behind certain bleeding disorders.

Disorders Affecting Coagulation

Disorders of coagulation may be inherited or acquired. Many of the inherited disorders are classified based on the phase of coagulation they affect. Various congenital deficiencies of coagulation factors such as Factor II, V, VII, X are considered disorders of clot initiation. Treatment would include replacement of the deficient clotting factors such as with recombinant Factor VII, prothrombin complex concentrates, or plasma transfusion. When administering factor concentrates or any procoagulant therapy, one must recognize that over-treatment may cause indiscriminate clotting, an undesirable consequence.

Inherited disorders of hemophilia A and B, and fibrinogen disorders are considered propagation phase disorders. These disorders can be diagnosed early in life and often present with severe bleeding, depending on the magnitude of the defect. Factor replacement therapy in Hemophilia has been the mainstay of treatment but newer

therapies including mimicking antibody treatments are now available. Fibrinogen replacement in the form of cryoprecipitate or fibrinogen concentrates is used to treat fibrinogen deficiency or dysfunction.
Congenital platelet abnormalities are a frequent cause of a bleeding diathesis. Congenital thrombocytopenia exists when a reduced platelet production occurs. More commonly platelet-related bleeding is due to the production of abnormal platelets via mutated receptors or as a result of abnormal platelet adhesive or aggregatory capacity. In certain disease states, increased destruction or sequestration of platelets may be the culprit. Certain inherited platelet disorders are characterized by a normal platelet count, but disordered function of platelets, or a qualitative defect. This usually manifests as an increased risk of bleeding. Treatment can be very nuanced and must be defined by platelet function testing. Certain disease states of abnormal platelet function may also place patients at risk for thrombosis.

Von Willebrand Disease (vWD) is the most common inherited bleeding disorder. It results from deficiency or dysfunction of von Willebrand factor (vWF), which mediates platelet adhesion and stabilizes factor VIII. Types range from mild quantitative deficiency (Type 1) to qualitative defects (Type 2), and near absence in Type 3. Clinical features include mucocutaneous bleeding, easy bruising, and heavy menses.

The aforementioned coagulation defects due to inherited disease must be considered, in bleeding patients, but the role of acquired hemorrhagic risk must not be underestimated. Many hemostasis defects are acquired either due to medical conditions or as a result of medication ingestion. Medical conditions that can result in acquired platelet production defects can be caused by bone marrow damage from chemotherapy, radiation, malignancies, or nutritional deficiencies. More commonly, patients may be prescribed anti-platelet medication (aspirin, clopidogrel (Plavix®, and others) and the ingestion of these medications renders the platelets less able to promote clot formation. The disease states for which these anti-platelet medications are prescribed include coronary artery disease, peripheral arterial vascular disease, and stent management, in which the formation of clot within these diseased arteries would cause a blockage and a devastating occlusion.

Disorders of the coagulation cascade are also frequently a result of medication ingestion, as these anticoagulants are commonly prescribed drugs. Many anticoagulant pharmaceuticals such as warfarin and thrombin inhibitors are prescribed for venous occlusive disease. The novel oral anticoagulant medications that inhibit factor Xa are now the preferred anticoagulant agents for prophylaxis against clot formation in patients with atrial fibrillation. These medications are a common cause for excessive bleeding in patients with simple injuries or trauma.

Hypercoagulable (Thrombophilic) Disorders

Conditions that predispose individuals to thrombosis are of genetic or acquired origin. Genetic or heritable conditions for thrombosis include antithrombin deficiency, protein C and S deficiencies, Factor V Leiden mutation, and prothrombin gene mutations. Anti-phospholipid antibody syndrome is also a known condition predisposing to thrombosis. Acquired conditions that can predispose to thrombotic events can be due to innumerable disease states or physiologic conditions. Some of these include malignancies, nephrotic syndrome, myeloproliferative disorders, autoimmune conditions, and pregnancy. Medication ingestion such as estrogens or oral contraceptive drugs has also been associated with thrombotic risk.

Conclusion

Disorders of hemostasis encompass a wide spectrum of inherited and acquired abnormalities affecting platelet production, function, and coagulation factors at various phases of clotting. Accurate diagnosis relies on a combination of clinical history, laboratory testing, and understanding of underlying pathophysiology. Management strategies are tailored to the specific disorder, aiming to correct deficiencies, prevent bleeding, yet mitigate thrombosis risk. Accurate diagnosis using the proper testing and appropriate intervention remain critical for optimal patient care.